Razuvaev Institute of Organometallic Chemistry of RAS

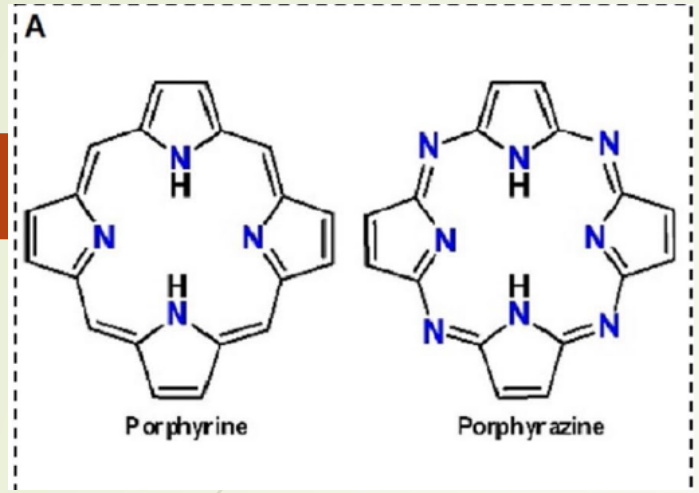
Lobachevsky State University of Nizhny Novgorod, Russia

Новые фотоактивные органические молекулы, содержащие биполярные D-π-A фрагменты, как уникальные неинвазивные сенсоры локальной вязкости и полярности

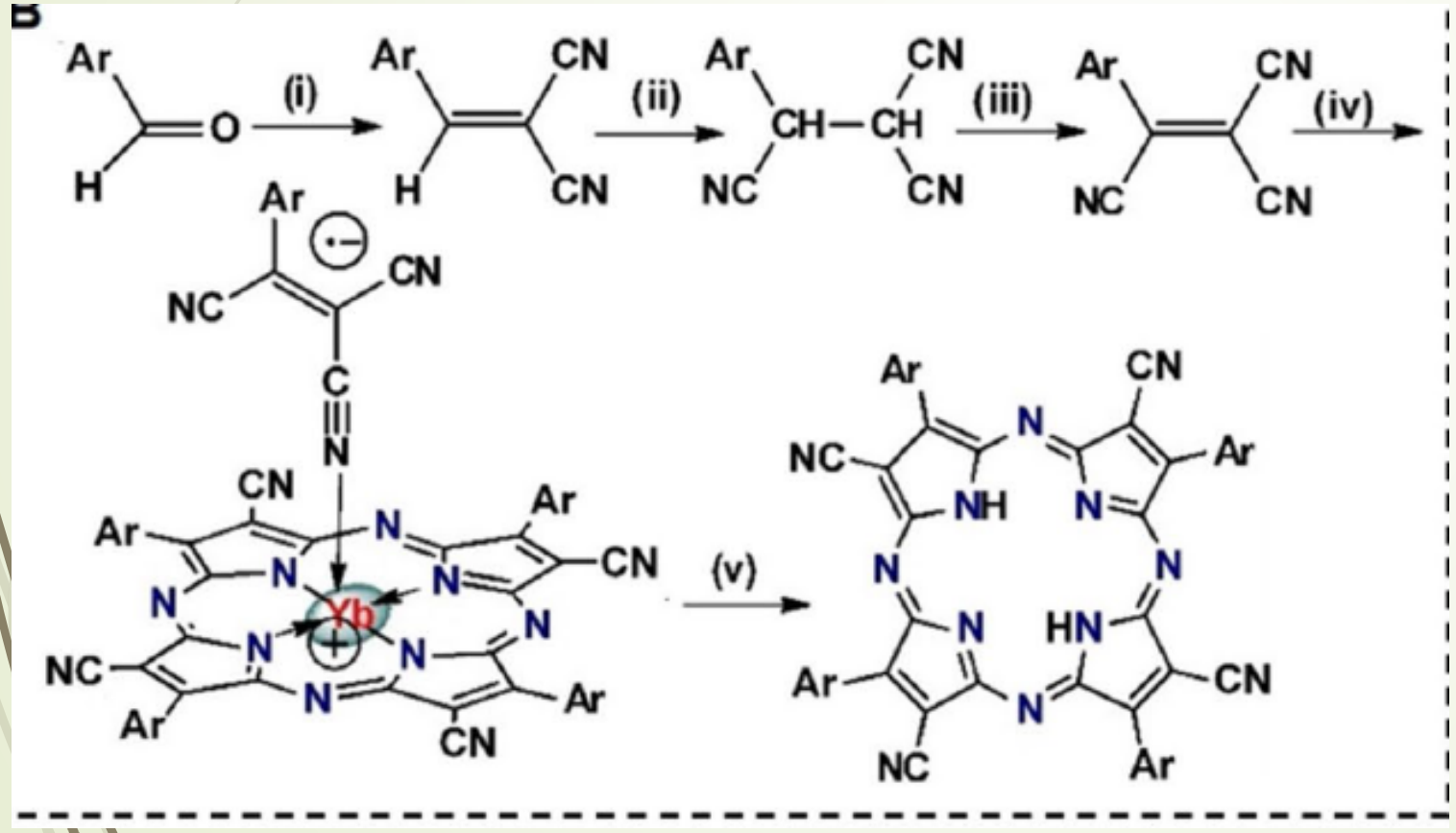
Nizhny Novgorod State Medical Academy, Russia

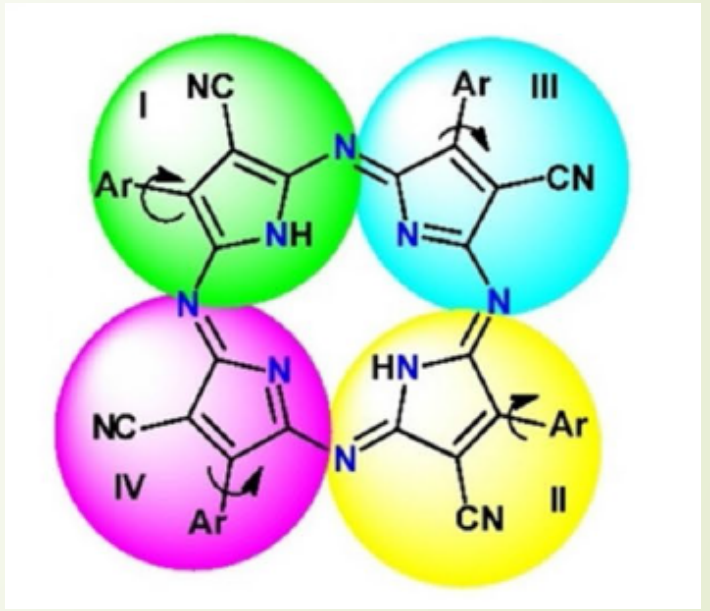
Imperial College, London, UK

Institute of Applied Physics of RAS

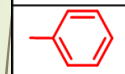
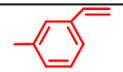
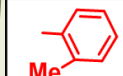
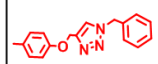
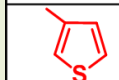
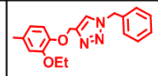
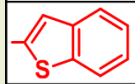
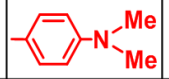
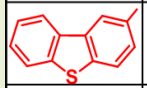
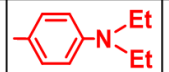
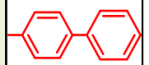
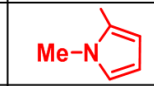
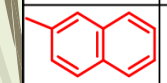
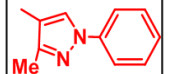
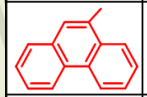
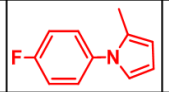
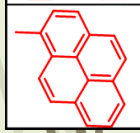
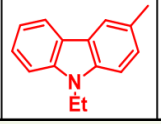


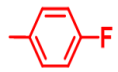
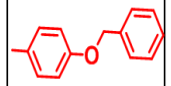
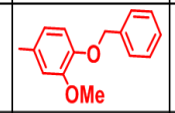
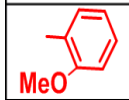
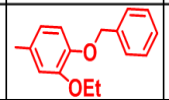
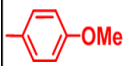
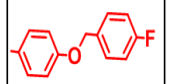
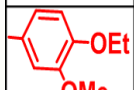
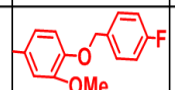
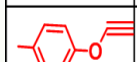
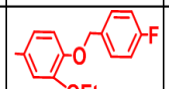
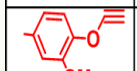
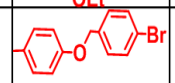
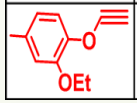
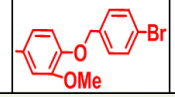
Cyanoaryl porphyrazines synthesis





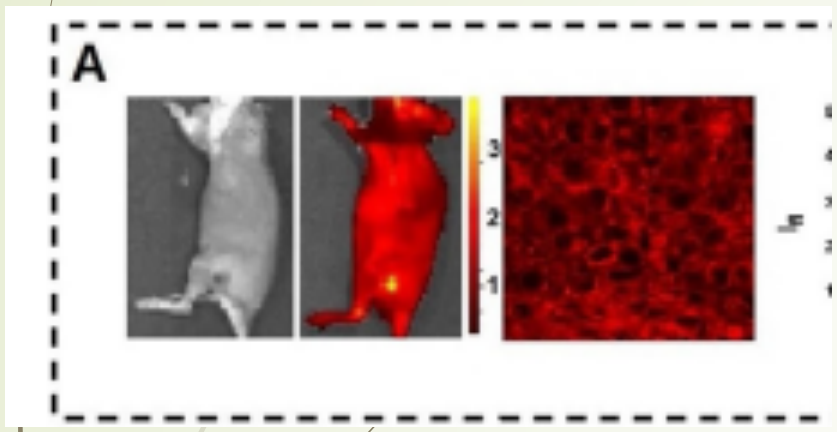
The aromatic groups variation as the efficient tool for a fine tuning of the porphyrazine photophysical and cytoxic properties

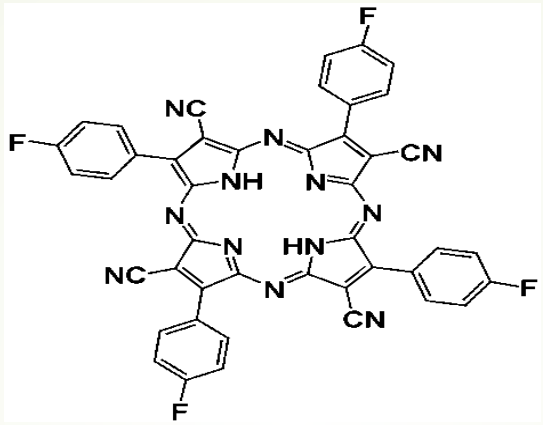
R	Q-band, nm	IC_{50} light, mol/l	IC_{50} dark, mol/l	IC_{50} dark / IC_{50} light	R	Q-band, nm	IC_{50} light, mol/l	IC_{50} dark, mol/l	IC_{50} dark / IC_{50} light
	575	$3.7 \cdot 10^{-6}$	$1.1 \cdot 10^{-5}$	3.3		593	$1.1 \cdot 10^{-6}$	$1.3 \cdot 10^{-5}$	12
	580	$3 \cdot 10^{-6}$	$1.4 \cdot 10^{-5}$	4.7		593	$2.7 \cdot 10^{-6}$	$3 \cdot 10^{-5}$	11
	580	$3.8 \cdot 10^{-6}$	$1.3 \cdot 10^{-5}$	3.4		591	$3.5 \cdot 10^{-6}$	$2.5 \cdot 10^{-5}$	7
	610	$1.5 \cdot 10^{-7}$	$6.8 \cdot 10^{-6}$	45			$4.6 \cdot 10^{-6}$	$8.5 \cdot 10^{-5}$	18
	600	$1.9 \cdot 10^{-6}$	$8.5 \cdot 10^{-5}$	45		590	$4 \cdot 10^{-7}$	$2.5 \cdot 10^{-5}$	62.5
	594	$4 \cdot 10^{-7}$	$2.3 \cdot 10^{-5}$	57.5		594	$4.3 \cdot 10^{-6}$	$1.1 \cdot 10^{-5}$	2.6
	592	$1.4 \cdot 10^{-7}$	$9.5 \cdot 10^{-6}$	68		580	$2.8 \cdot 10^{-7}$	$3.7 \cdot 10^{-5}$	132
	608, 580	$1.1 \cdot 10^{-6}$	$2 \cdot 10^{-4}$	182		610	$1.5 \cdot 10^{-7}$	$1 \cdot 10^{-5}$	67
	630	$1 \cdot 10^{-6}$	$1.5 \cdot 10^{-4}$	150		585	$2.2 \cdot 10^{-6}$	$8.2 \cdot 10^{-5}$	37

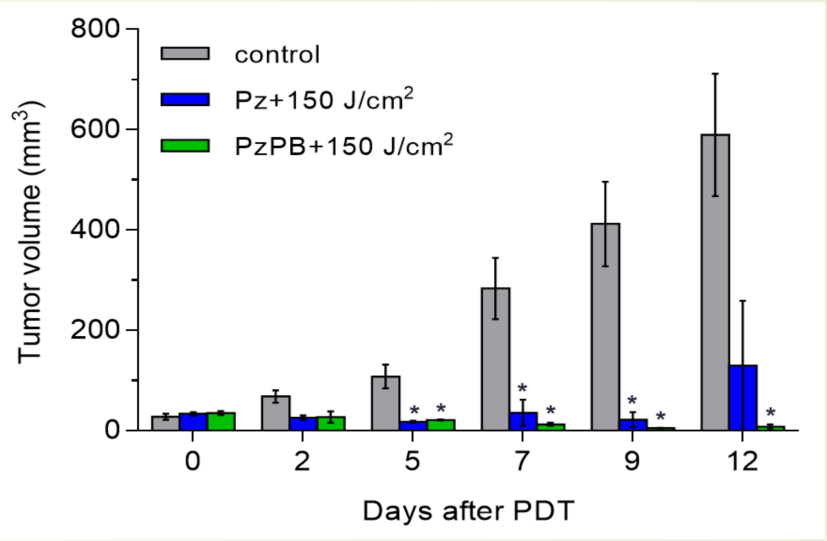
R	Q-band, nm	IC_{50} light, mol/l	IC_{50} dark, mol/l	IC_{50} dark / IC_{50} light	R	Q-band, nm	IC_{50} light, mol/l	IC_{50} dark, mol/l	IC_{50} dark / IC_{50} light
	579	$8 \cdot 10^{-7}$	$6.9 \cdot 10^{-6}$	8.6		595	$1 \cdot 10^{-6}$	$4.5 \cdot 10^{-5}$	45
	604	$9 \cdot 10^{-7}$	$3.6 \cdot 10^{-6}$	4		587	$4.9 \cdot 10^{-7}$	$2.9 \cdot 10^{-5}$	59.2
	586	$2.4 \cdot 10^{-6}$	$1.1 \cdot 10^{-5}$	4.6		592	$2.7 \cdot 10^{-7}$	$1 \cdot 10^{-5}$	37
	576	$1.3 \cdot 10^{-6}$	$2.1 \cdot 10^{-5}$	16.2		594	$1.2 \cdot 10^{-6}$	$5.2 \cdot 10^{-5}$	43
	576	$2.4 \cdot 10^{-6}$	$1.2 \cdot 10^{-5}$	5		593	$1.7 \cdot 10^{-6}$	$4.1 \cdot 10^{-5}$	24.1
	580	$2 \cdot 10^{-6}$	$1.1 \cdot 10^{-5}$	5.5		591	$3.6 \cdot 10^{-6}$	$4.3 \cdot 10^{-5}$	11.9
	579	$2.5 \cdot 10^{-6}$	$2 \cdot 10^{-5}$	8		594	$5.9 \cdot 10^{-6}$	$3.4 \cdot 10^{-5}$	5.8
	577	$8.8 \cdot 10^{-7}$	$6.6 \cdot 10^{-6}$	7.5		596	$8 \cdot 10^{-6}$	$1.9 \cdot 10^{-4}$	23.8

Porphyrazines as photosensitizers for PDT in animal tumor model (mice Balb/c) .

CT26 murine colon carcinoma cell line was used to obtain the tumor model. Irradiotion with a 640-nm LED light source,dose 150 J/cm2 (**A)**

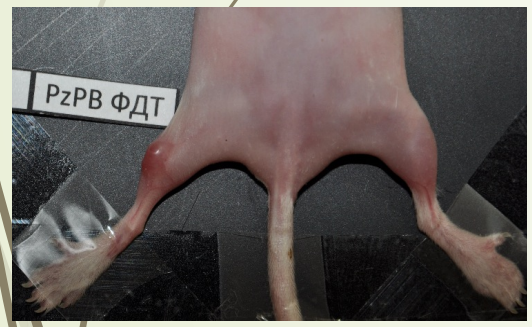






A histogram of growth dynamics of the tumour node volume *in vivo* in mouse models subjected to PDTtreatment in control and experimental groups

B



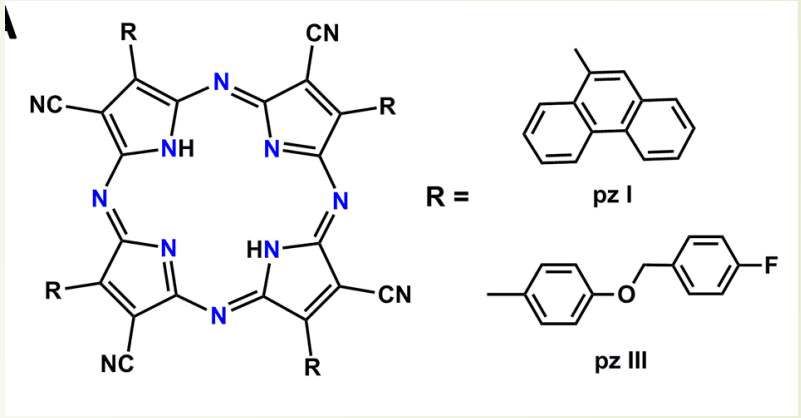
B – animal tumor model before PDT with porphyrazine

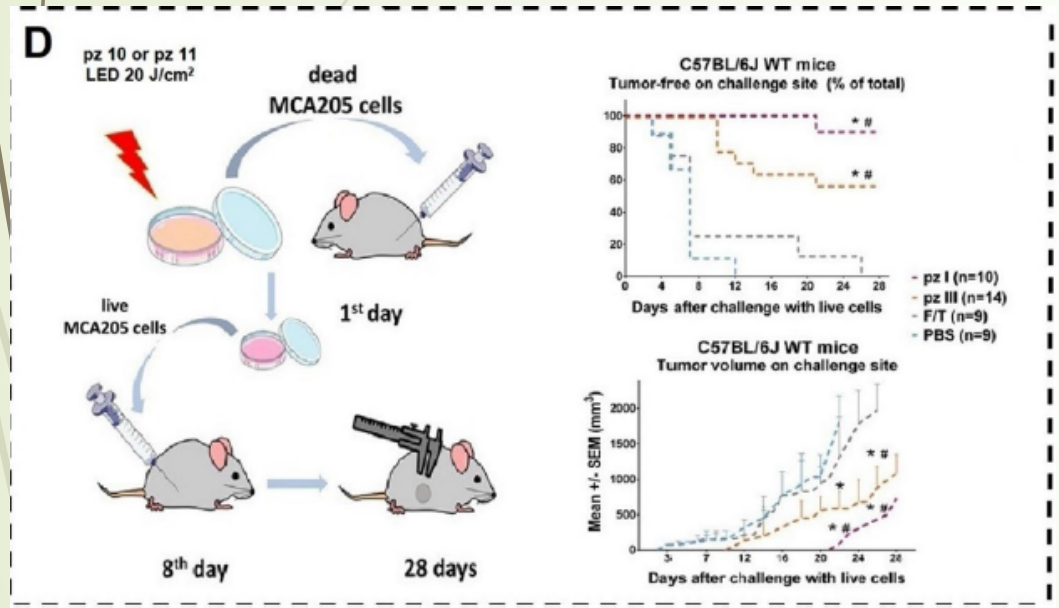
C

C– animal tumor model in 8 days after PDT with porphyrazine

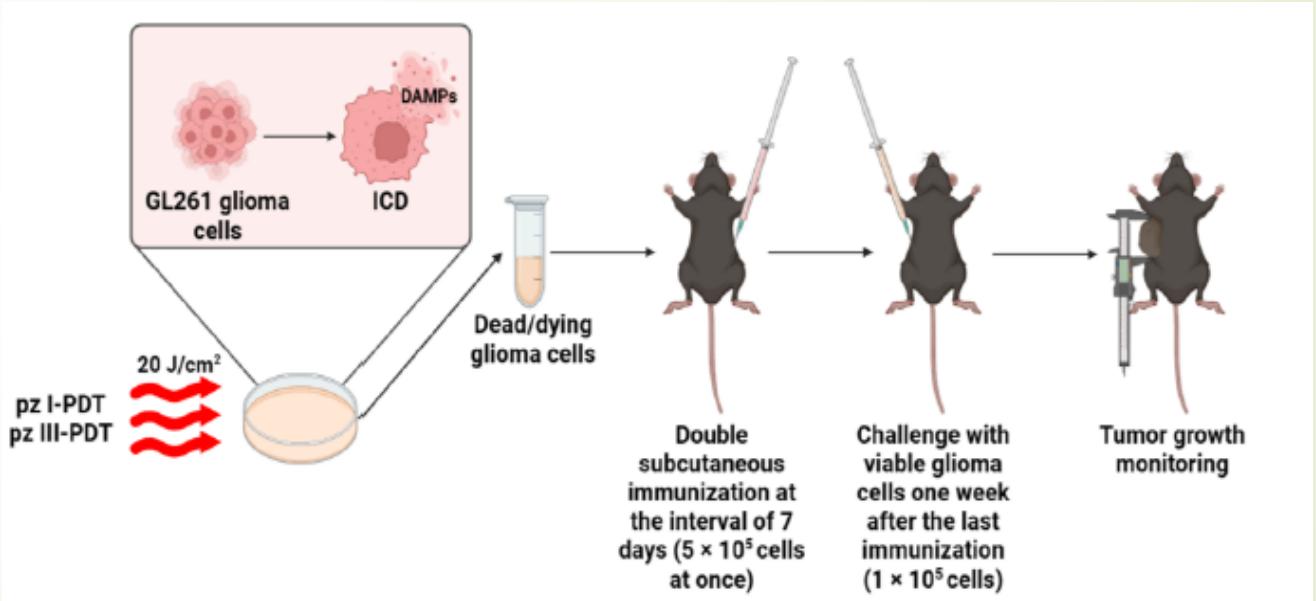
Novel porphyrazine-based photodynamic anti-cancer therapy induces immunogenic cell death

Effective prophylactic vaccines that activated anti-tumor immunity, significantly reduced the rate of tumor growth, prolonged mouse survival,





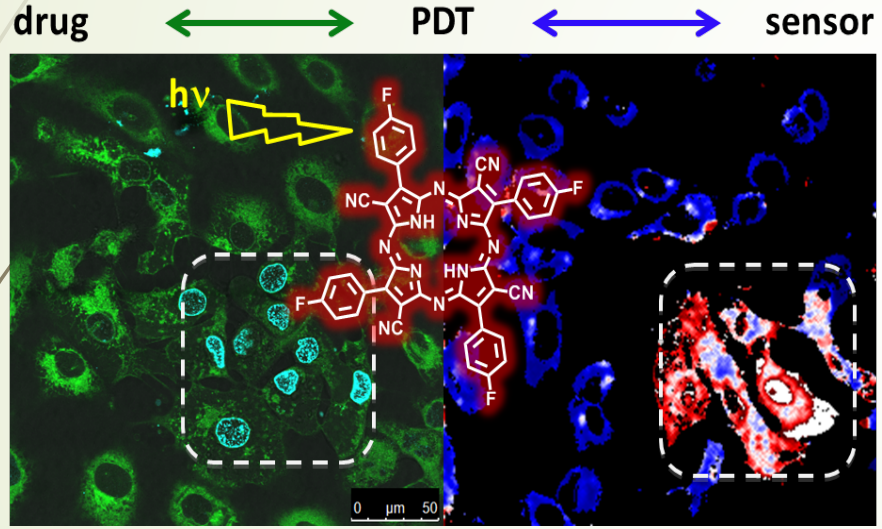
Turabanova VD, et al *«Novel porphyrazine-based photodynamic anticancer therapy induces immunogenic cell death.»* **Sci Rep** 2021 Mar 30;11(1):7205.

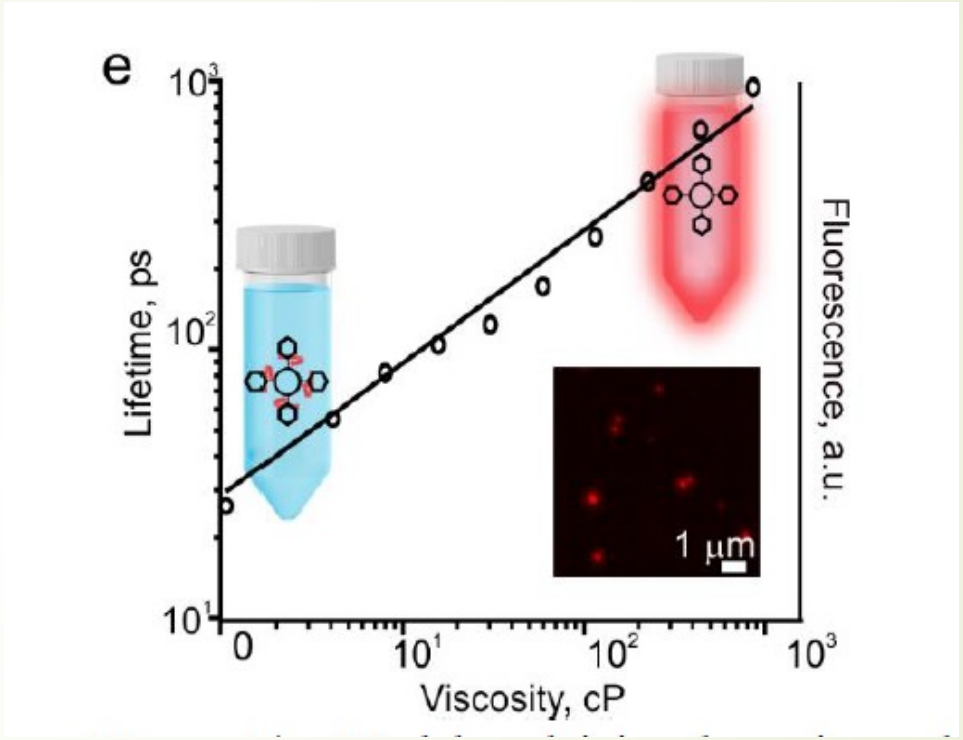


T.S.Redkin *et al "Dendritic Cells Pulsed withTumor Lysates InducedTetracyanotetra(aryl)porphyrazines-Based Photodynamic Therapy Effectively Trigger Anti-Tumor Immunity in an OrthotopicMouse Glioma Model"* **Pharmaceutics** 2023, 15, 2430. https://doi.org/10.3390/pharmaceutics15102430
"

CYANO-ARYL PORPHYRAZINES (pz) AS THE NEW FLUORESCENT MOLECULAR ROTORS

$$\log \phi = z + \alpha \log \eta$$
$$\log \tau = z + \alpha \log \eta$$
Förster-Hoffman equations

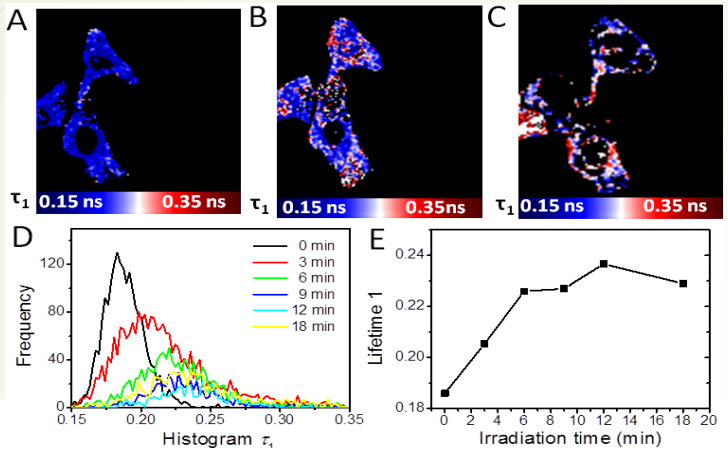


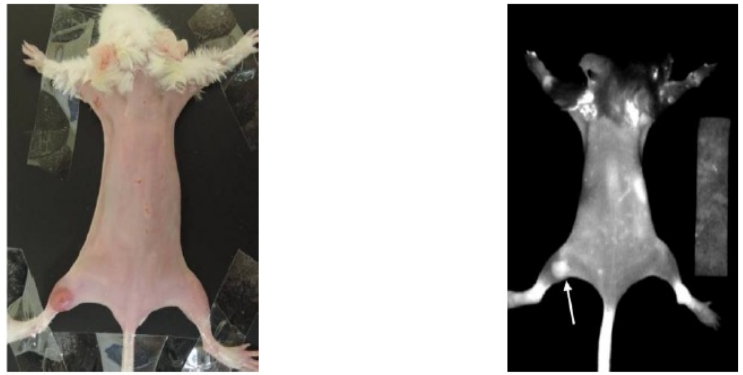


Plot of the pz fluorescence lifetime (left *y*-axis) and intensity (right *y*-axis) versus solution viscosity. Left and right insets illustrate pz solution in a tube exhibiting faint (low viscosity media) and bright (high viscosity media) fluorescence upon the excitation in low- and high-viscosity micro-environments, respectively.

M. A. Izquierdo, A. Vyˇsniauskas, S. A. Lermontova, I. S. Grigoryev, N. Y. Shilyagina, I. V. Balalaeva, Larisa G. Klapshina and M. K. Kuimova. Dual use of porphyrazines as sensitizers and viscosity markers in photodynamic therapy // J. Mater.Chem B, 2015, 3, 1089-1096]

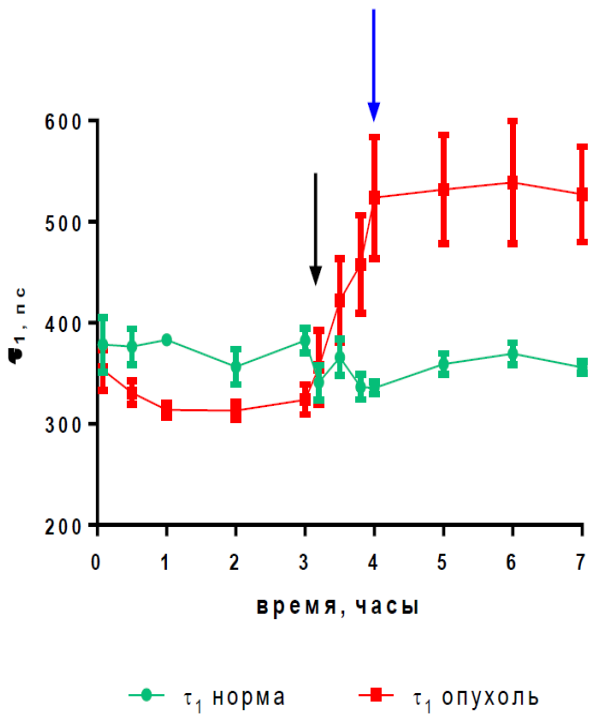
Real time monitoring of PDT *in vitro* and *in vivo* with porphyrazine as photosensitizer and optical viscosity sensor





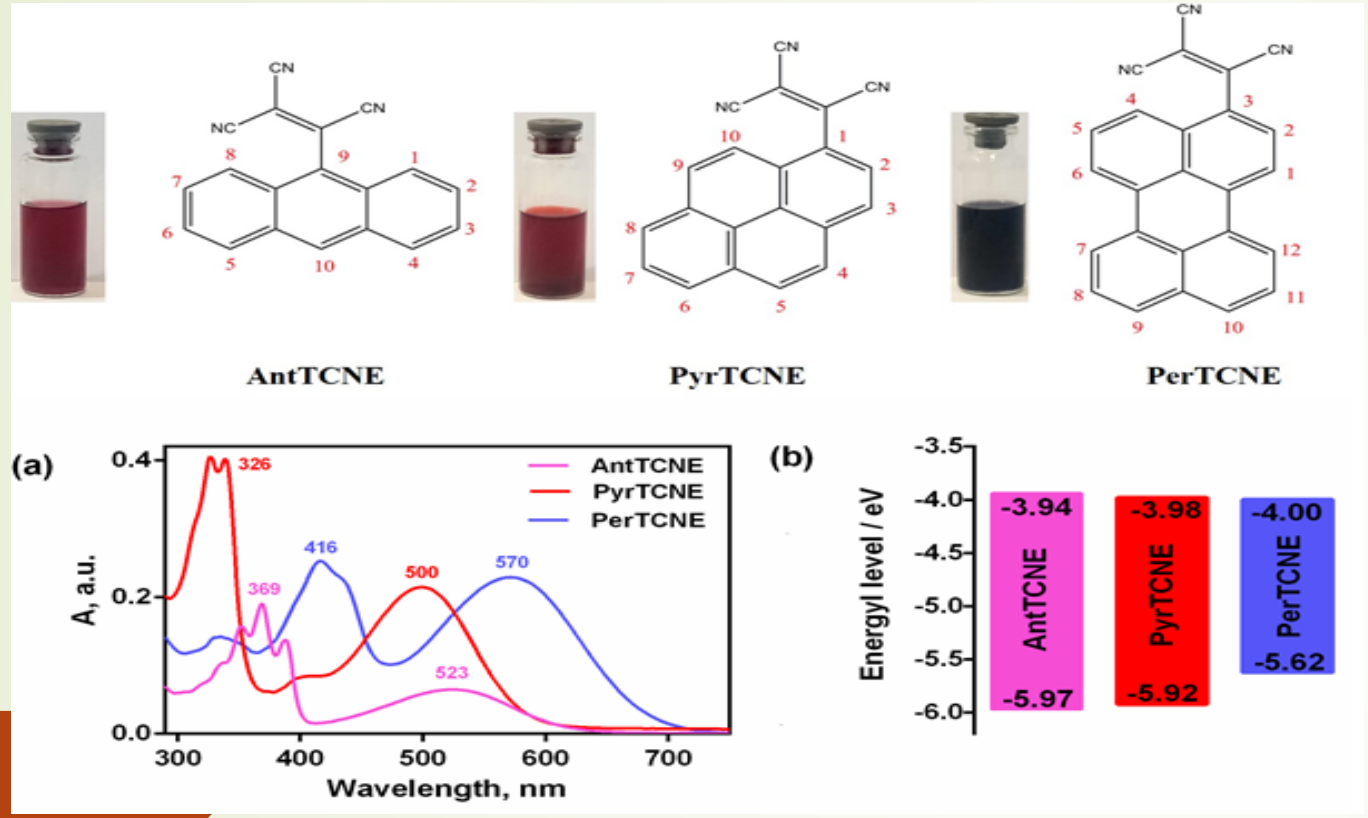
А Б

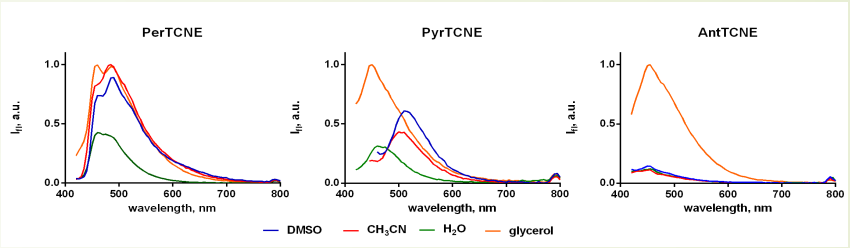
СПОСОБ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ С КОНТРОЛЕМ ЭФФЕКТИВНОСТИ В РЕЖИМЕ РЕАЛЬНОГО ВРЕМЕНИ



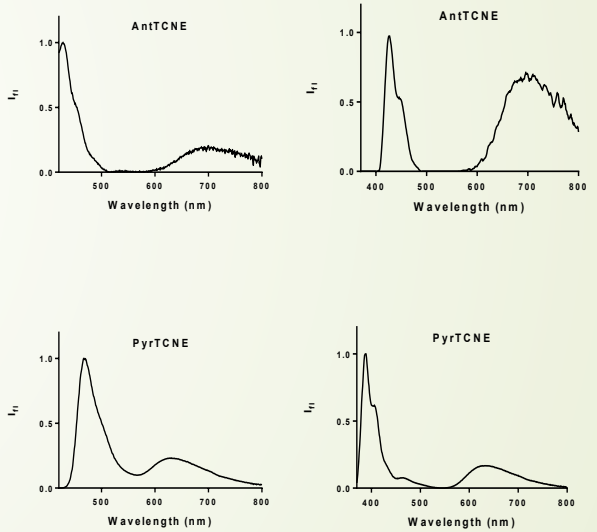
Plot of porphyrazine fluorescence lifetime (τ_1) *VS* observation time in normal tissue (green line) and tumor tissue (red line).

New pigments based on aromatic polycyclic hydrocarbons substituted with tricyanoethylene fragments

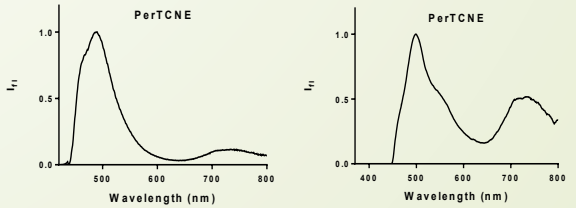




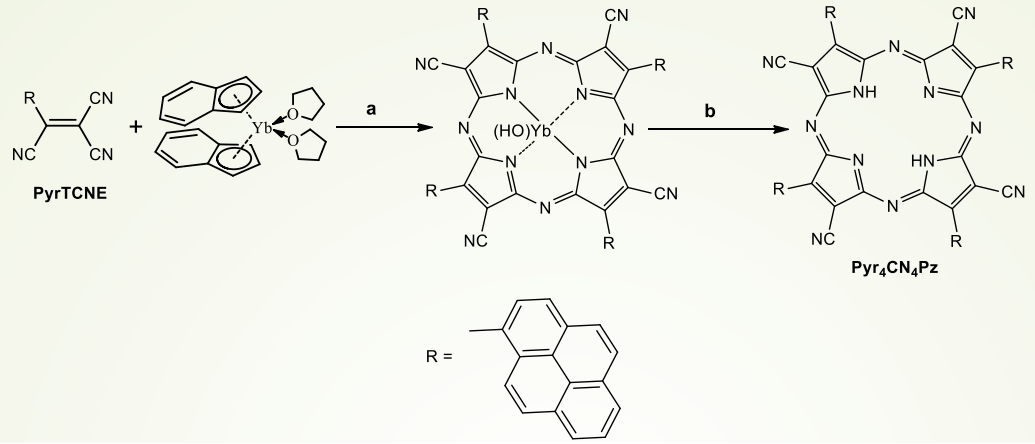
Emission spectra in the different solvents **AntTCNE**, **PyrTCNE** and **PerTCNE** (10^{-3} mol/L), λ_{exc} = 350 nm (**b**), λ_{excit} = 400 nm (**c**).

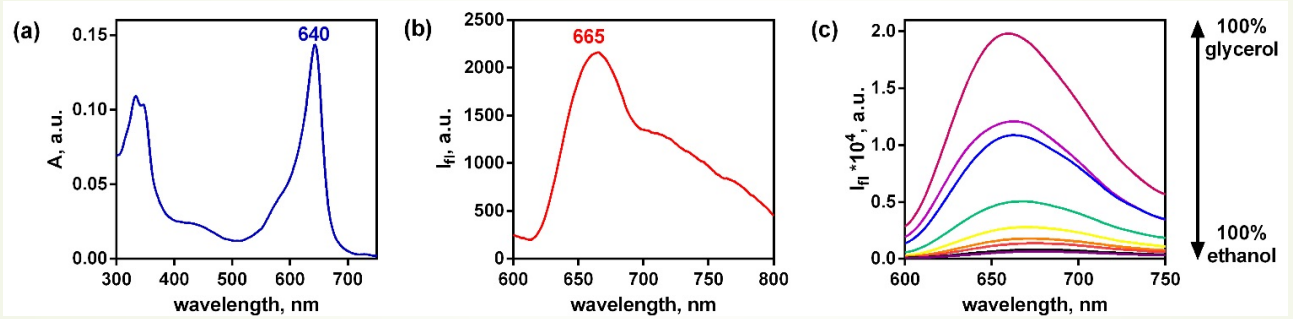


Emission spectra of **AntTCNE**, **PyrTCNE** and **PerTCNE** in non-polar low viscosity solvent (toluene) (10^{-3} mol/L), λ_{excit} = 350 nm (on the right) , λ_{excit} = 400 nm (on the left).



Template assembling of the new cyanoaryl porphyrazine framework based on PyrTCNE as the structural unite of a tetrapyrrople macrocycle

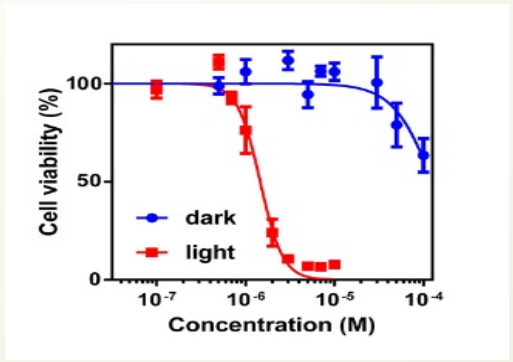


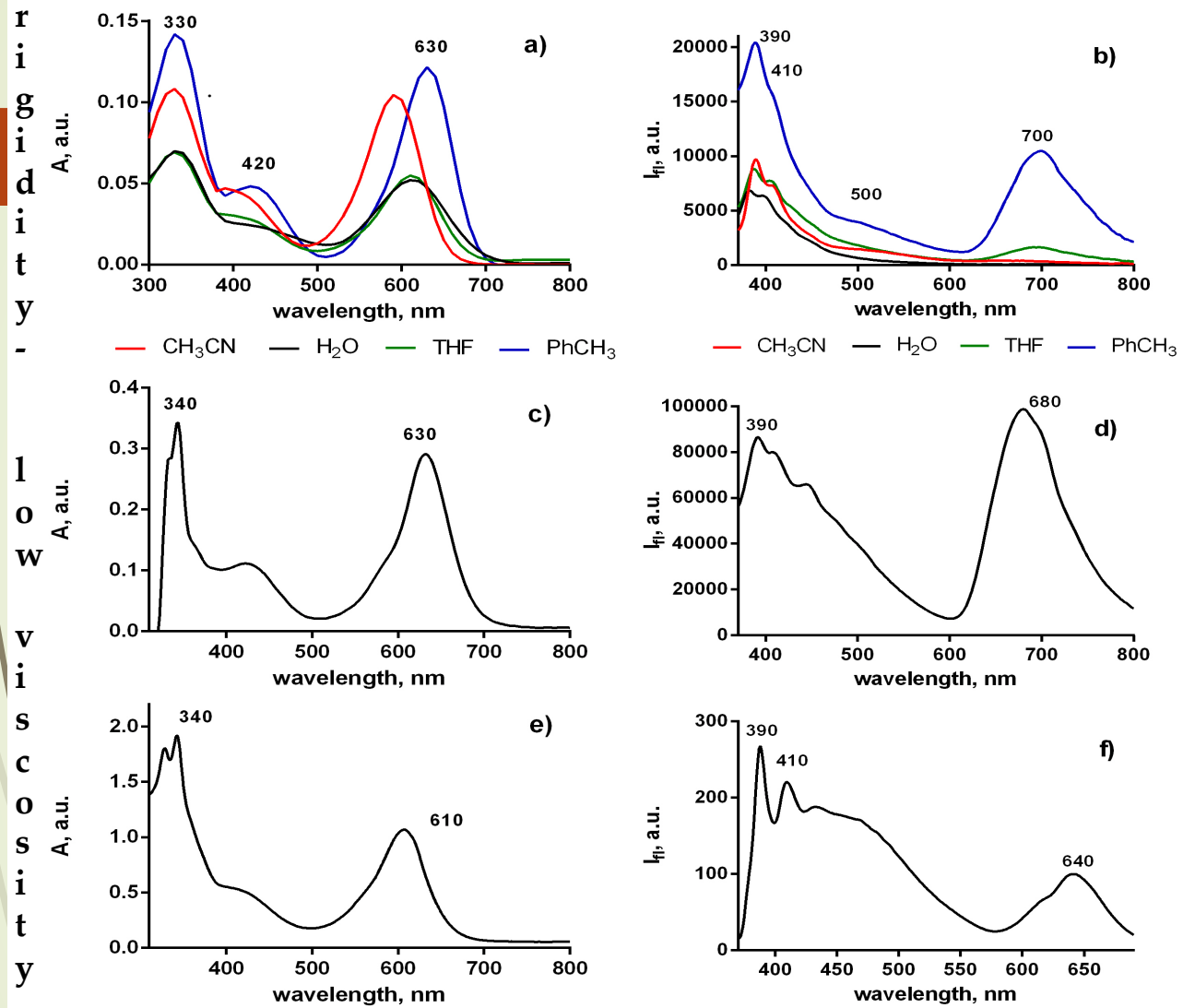


Absorption (a), fluorescence (b) spectra of **Pyr_4CN_4Pz** (λ_{excit} = 580 nm) in water (5 x 10^{-6} mol/L). Emission of **Pyr_4CN_4Pz** (10^{-6}mol/L) in the mixtures of ethanol and glycerol (c).

IC_{50} light =1.0x 10^{-6} mol/l
IC_{50} dark=1.5x10^{-4} mol/l
IC_{50} dark/ IC_{50} light = 130

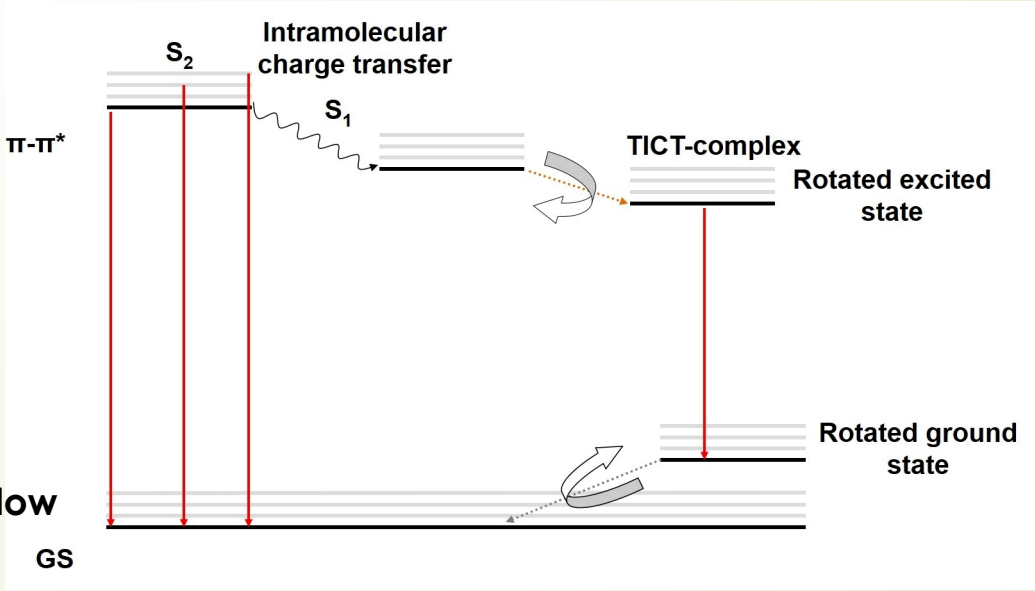
-



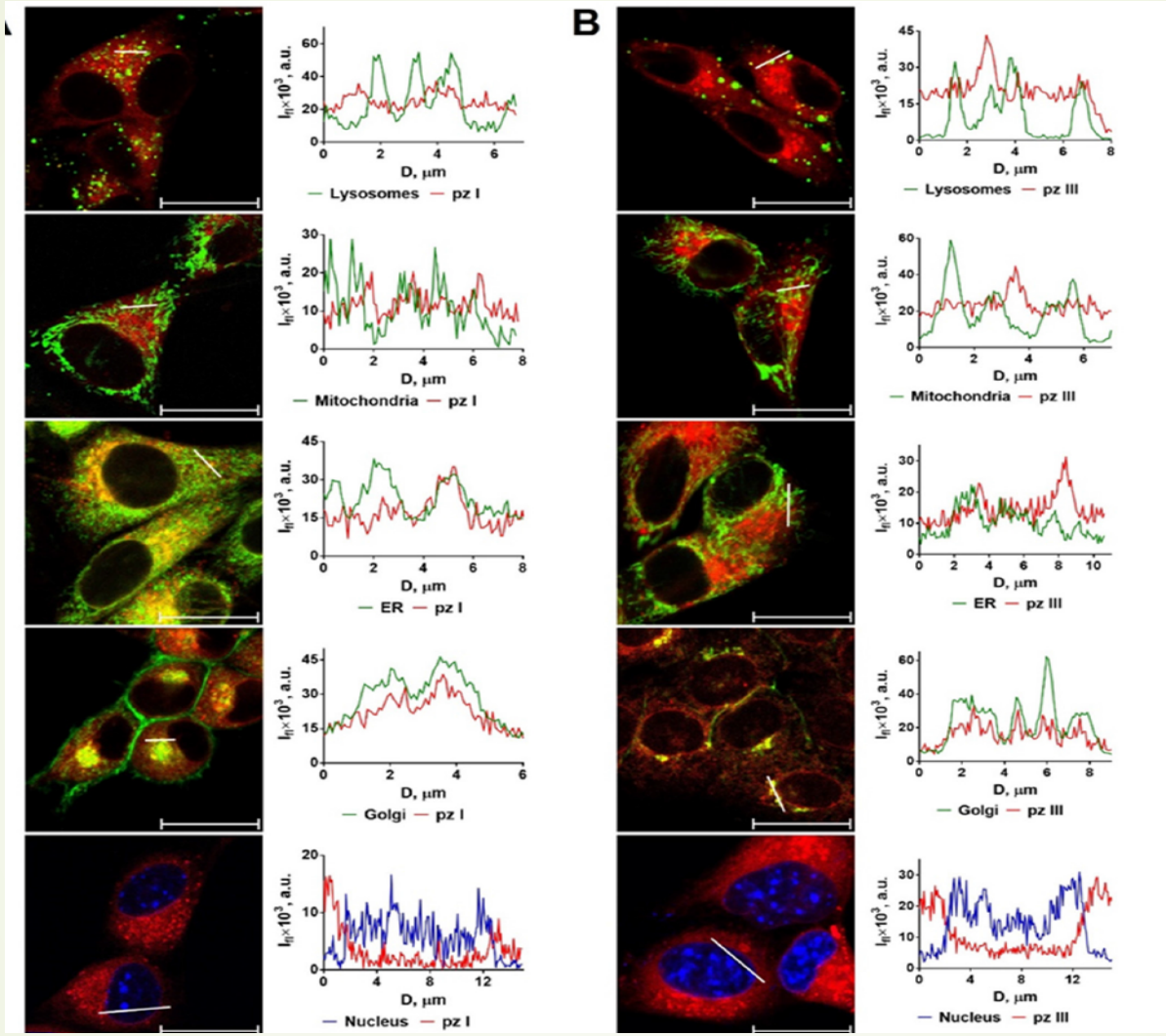


Fuorescence quantum yeald of **Pyr_4CN_4Pz** in the different solvents (η - viscosity, ε - dielectric constant **LW**-long wave, **SW**- short wave

Solvent	η (cP)	ε	Φf	
			LW	SW
Castor oil	1079	4.7	0.360	0.480
CH_3Ph	0.59	2.4	0.066	0.129
THF	0.55	7.5	0.030	0.168
CH_3CN	0.37	37.0	0.002	0.043
Water	1.00	80.0	0.007	0.398



Jablonski diagram demonstrating proposed photophysical mechanism of DE for Pyr_4CN_4Pz and PerTCNE in a non-polar low viscosity medium. GS –ground state, π - π* - high lying transition state. ICT – intramolecular charge transfer, TICT- twisted intramolecular charge transfer.



Confocal images of the intracellular spatial distribution of pz I (A) and pz III (B) in glioma GL261 cells. Pz I and pz III are localized predominantly in the Golgi apparatus and partially in the Figure 1. GL261 cells. Pz I and pz III are localized predominantly in the Golgi apparatus and partially in the ER after 4 h of incubation. Importantly, pz I and pz III were not detected in mitochondria, lysosomes, or nucleus.

Заключение

1.Открыта принципиальная возможность быстрой темплатной сборки порфиразинового макроцикла при комнатной температуре;

2. Полученные цианоарильные порфиразины демонстрируют:
(а) высокую эффективность в качестве фотосенсибилизаторов ФДТ и тригеров иммуногенного механизма смерти раковых клеток;
(б) сочетание возможностей эффективных терапевтических агентов с уникальными для тетрапиррольных макроциклов сенсорными способностями- высокой чувствительностью флуоресцентных свойств к локальной вязкости и полярности среды

3. Цианоарилпорфиразины как потенциальные неинвазивные флуоресцентные сенсоры представляют значительный интерес в широком диапазоне практических приложений от оптоэлектроники и фотоники до биомедицины и дианостикию

Потенциальное применение порфиразинов с D-π-A структурой обрамления макроцикла в

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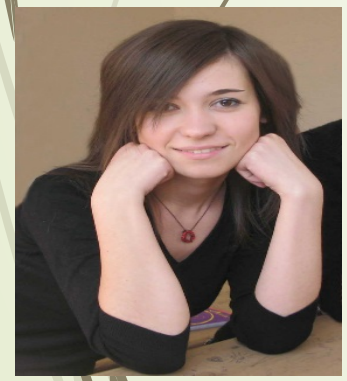

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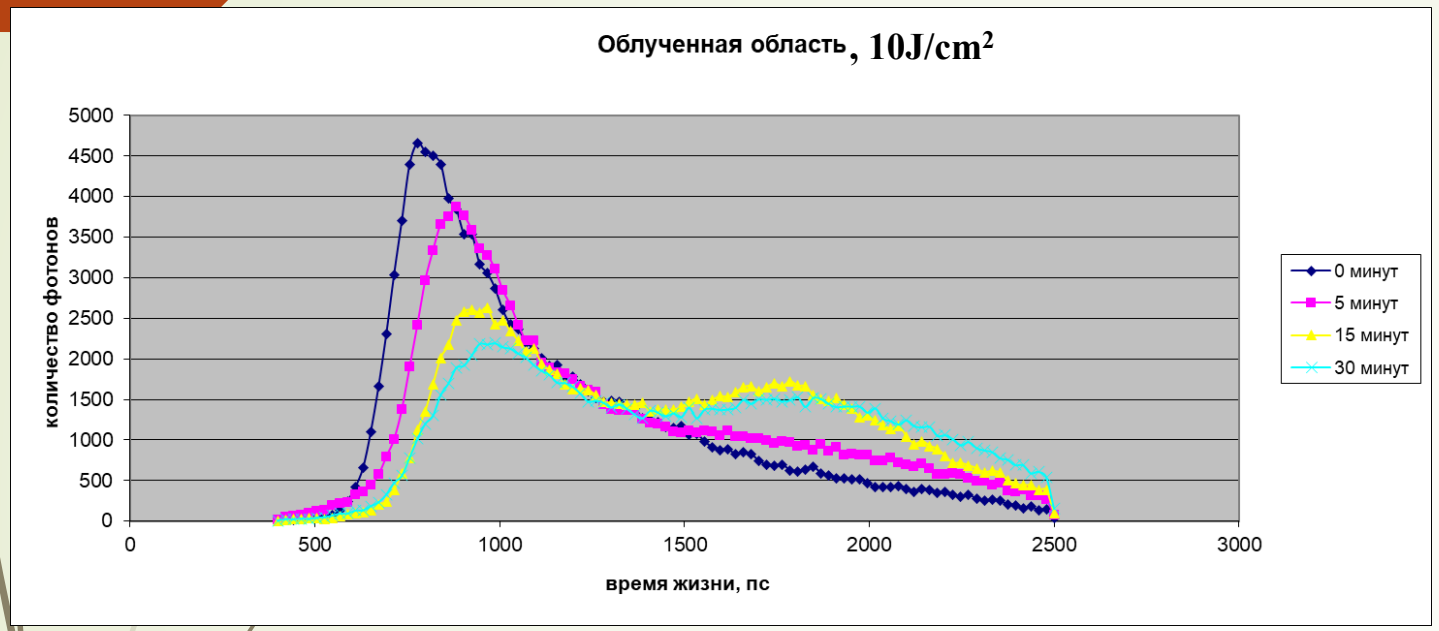
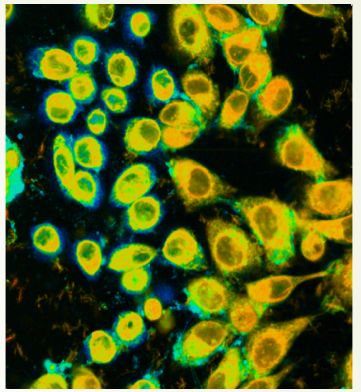
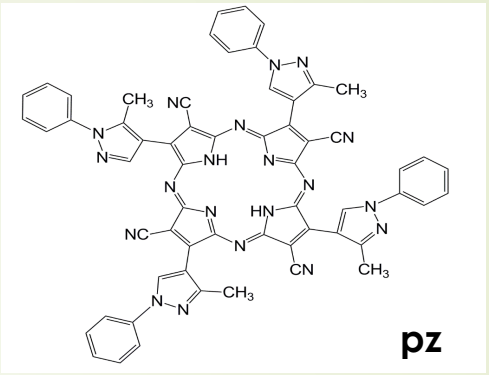
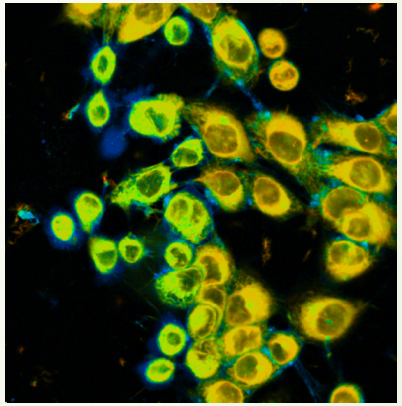
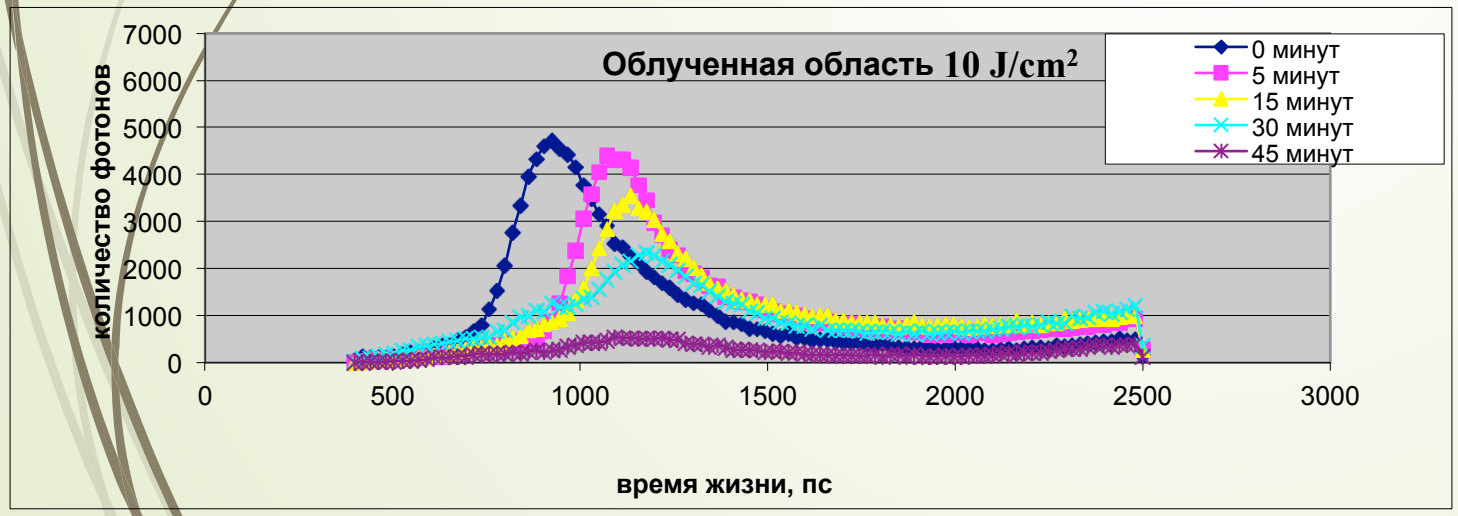
Время-разрешенный имиджинг (FLIM) для pz в процессе ФДТ in vitro (A 431)







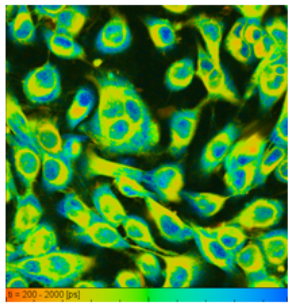




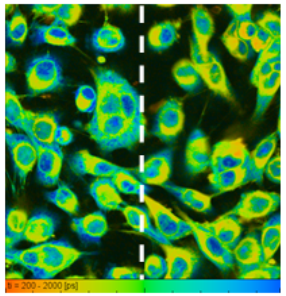
Время-разрешенный имиджинг (FLIM) для pz в процессе ФДТ in vitro (A 431)

para-fluorine phenyl pyrrole substituted Pz

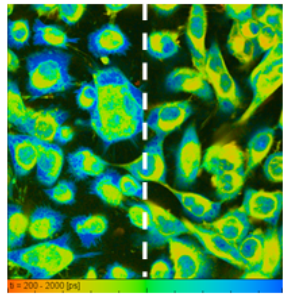
10 Дж/см^2



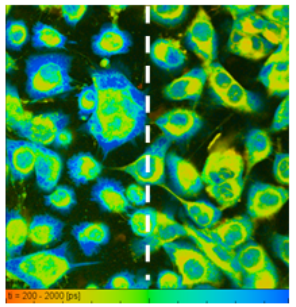
до облучения



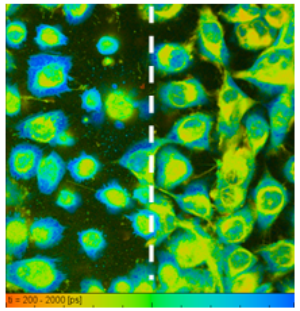
1 минута



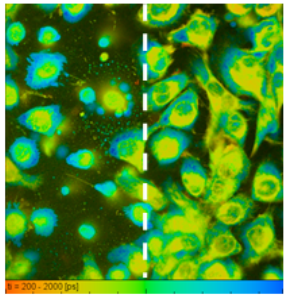
5 минут



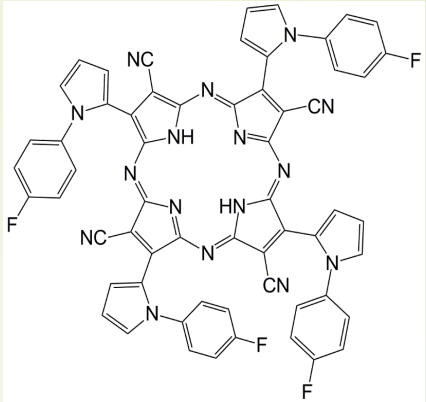
15 минут

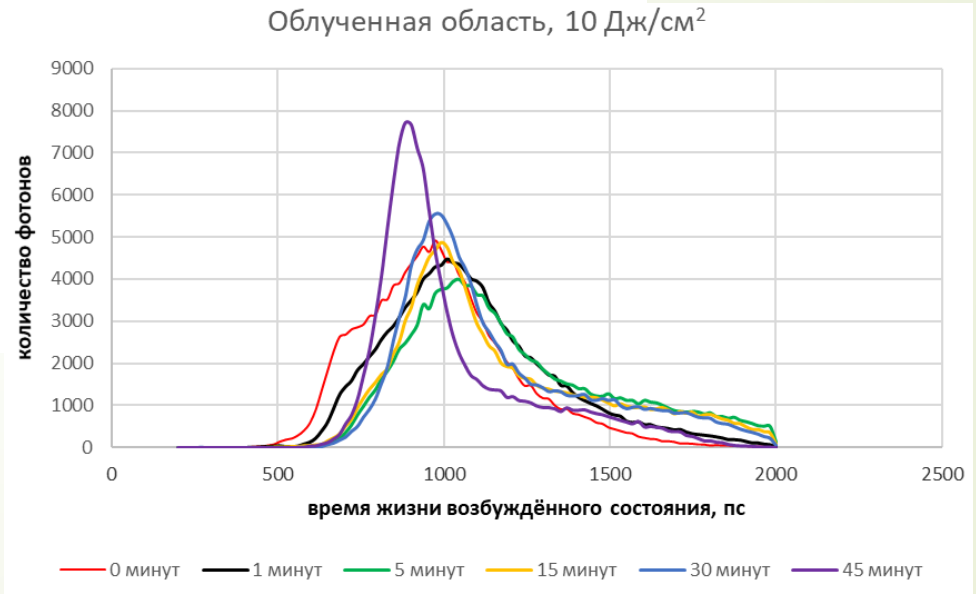


30 минут



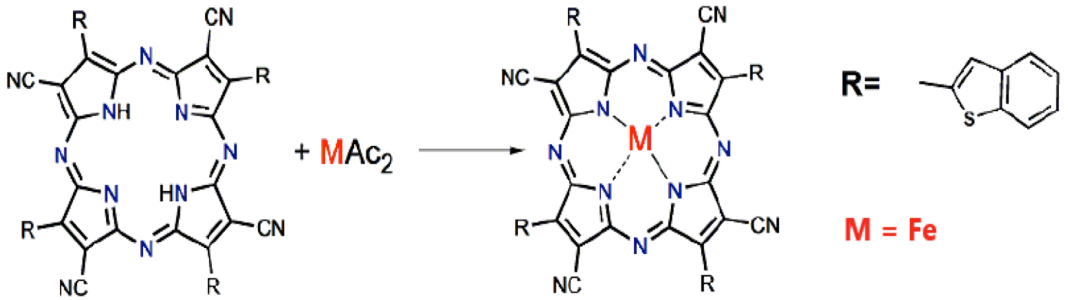
45 минут





Исследование влияния центрального катиона металла с переменной валентностью (FeII) на фотофизические свойства цианоарил порфиразинов

Оценка темновой и световой (10 и 20 Дж/см2) токсичности металлокомплекса порфиразина - тетра(бензотиофен-2-ил)тетрацианопорфиразинат железа (FepzBenzoThioph).



Значения IC_{50} для FepzBenzoThioph

Число клеток в лунке	IC_{50}, М, темнота	IC_{50}, М, 10 Дж/см^2	IC_{50}, М, 20 Дж/см^2	IC_{50} темнота/ IC_{50} 10Дж/см^2	IC_{50} темнота/ IC_{50} 20Дж/см^2
4000	~10^{-4}	3.4*10^{-8}	4.4*10^{-8}	2941	2273

FepzBenzoThioph, 20 Дж/см

Таблица 1. Распределение **FepzBenzoThioph** в клетках A431 по времени жизни возбужденного состояния. Метод FLIM. Длина волны возбуждения 800 нм, диапазон регистрации сигнала 640–710 нм. Показаны изображения до и после облучения части области зрения в дозе 20 Дж/см^2, обозначенной пунктиром. Псевдоцветная палитра представлена в диапазоне от 400 до 1200 пс