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Conjugates of Photosensitizers and Doxorubicin with Cleavable Linkers for Controlled Release

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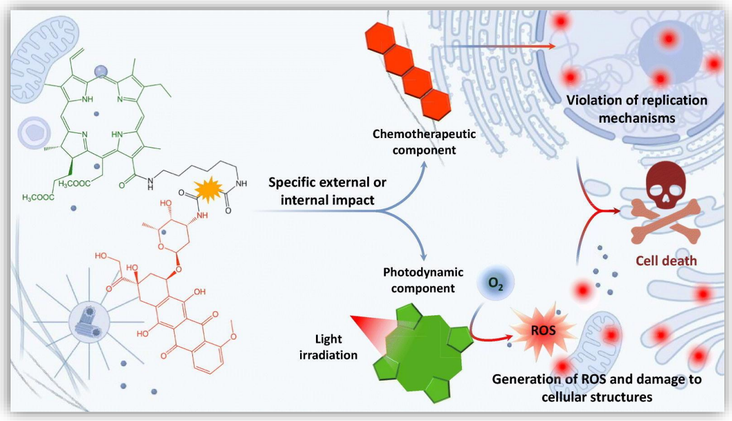
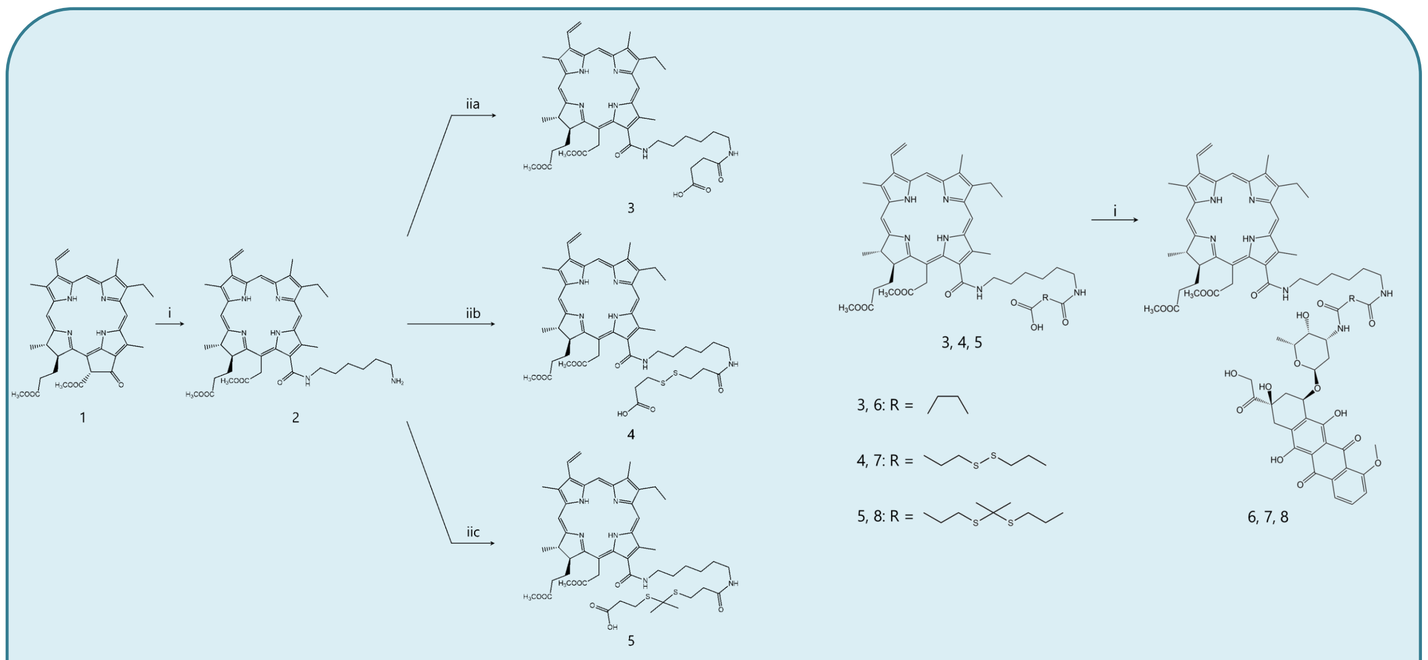
Introduction and aim of research

Chemotherapy, as a method of fighting cancer, has a number of significant limitations, so the search for new drugs to increase its effectiveness and reduce side effects is relevant. Another therapeutic approach, photodynamic therapy, is less invasive with minimal side effects; however, its spectrum of action does not go beyond the treatment of superficial tumors due to the low depth of light penetration into tissues. The objective of this work was to synthesize and study the biological activity of conjugates of derivatives of natural chlorines and doxorubicin containing thioketal (ROS-sensitive) and disulfide (GSH-sensitive) linkers designed for the controlled release directly into tumor cells and the tumor microenvironment.

The concept of the proposed approach



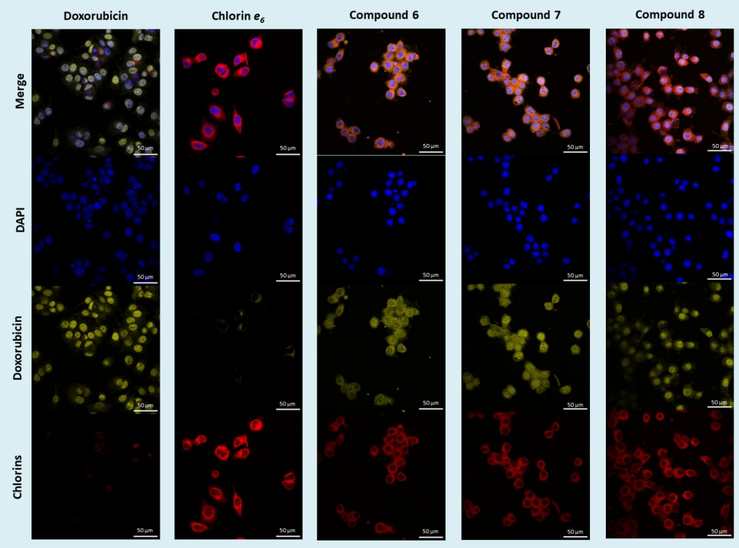
Synthesis of the obtained conjugates



Scheme A – Preparation of pheophorbide *a* methyl ester derivatives with linkers: (i) 1,6-diaminohexane, TEA, DCM, 16 h; (iia) succinic anhydride, TEA, DMF, 24 h; (iib) 3,3'-dithiodipropionic acid, HBTU, TEA, DMF, 24 h; (iic) 3,3'-(propane-2,2-diylbis(sulfanediyl))dipropionic acid, HBTU, TEA, DMF, 24 h.

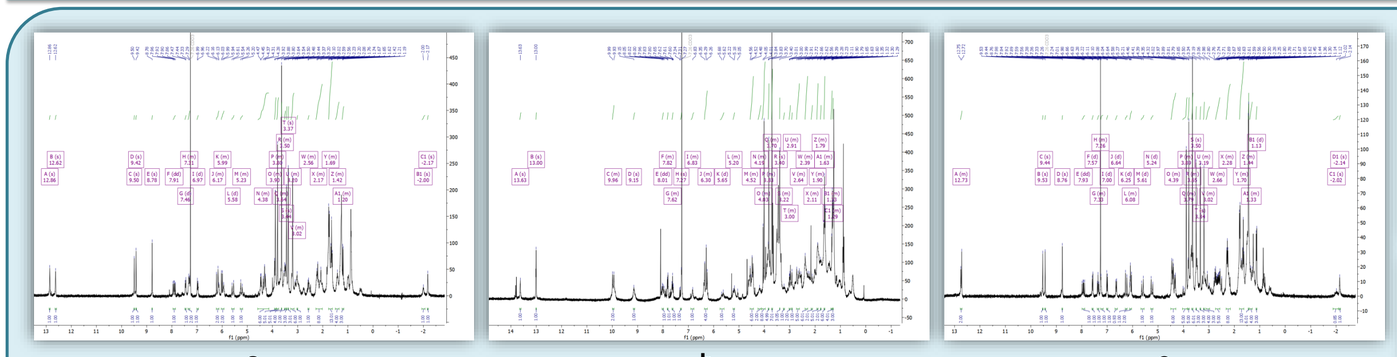
Scheme B – Preparation of conjugates of pheophorbide *a* methyl ester derivative with doxorubicin: (i) doxorubicin hydrochloride, HBTU, TEA, DMF, 3 h.

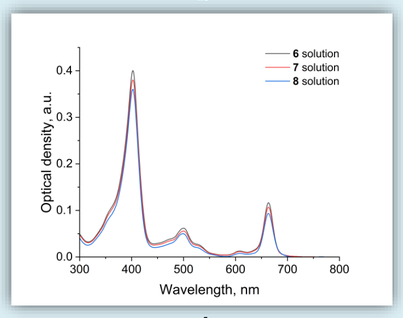
Confocal microscopy results



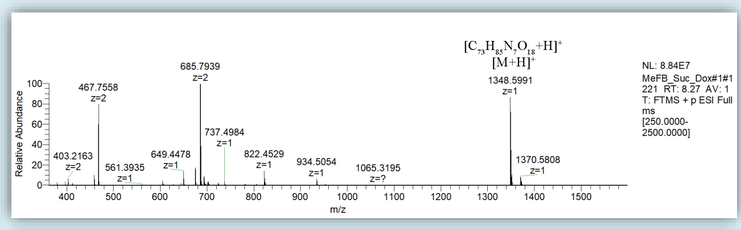
Fluorescent images of MCF-7 cells preincubated with synthesized compounds and DAPI: blue fluorescent signal corresponds to the nucleus (DAPI), yellow fluorescent signal corresponds to doxorubicin localization, and red fluorescent signal corresponds to chlorin localization. Laser scanning confocal microscopy, scale bar 50 um.

Analysis of the structure and physicochemical properties of the obtained compounds

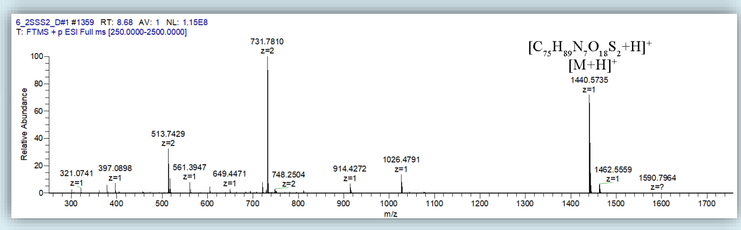




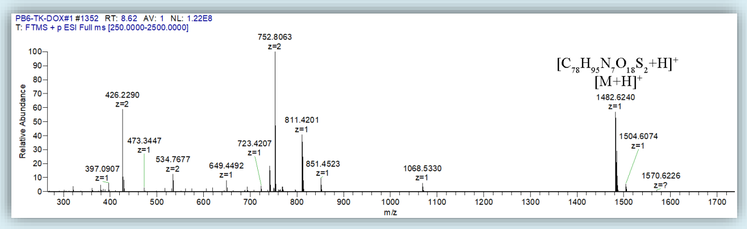
a - ^{1}H NMR spectrum of compound **6** in $CDCl_3$;
b - ^{1}H NMR spectrum of compound **7** in $CDCl_3$;
c - ^{1}H NMR spectrum of compound **8** in $CDCl_3$;
d - UV-Vis spectra of conjugates **6**, **7** and **8** in DCM solutions;
e - Mass spectrum (ESI/FTMS) of compound **6**;
f - Mass spectrum (ESI/FTMS) of compound **7**;
g - Mass spectrum (ESI/FTMS) of compound **8**.



e $[M+H]^+$ calculated for $[C_{73}H_{85}N_7O_{18}+H]^+$ – 1348.6024; found – 1348.5991



f $[M+H]^+$ calculated for $[C_{75}H_{89}N_7O_{18}S_2+H]^+$ – 1440.5778; found – 1440.5735



g $[M+H]^+$ calculated for $[C_{78}H_{95}N_7O_{18}S_2+H]^+$ – 1482.6248; found – 1482.6240

Photoinduced cytotoxicity *in vitro*

Compound	IC_{50}, nM			
	Photoinduced activity	Combined activity	Cytotoxic activity	
	4 h incubation of compounds with cells → Irradiation at 10 J/cm^2 → MTT after 24 h	4 h incubation of compounds with cells → Irradiation at 10 J/cm^2 → MTT after 72 h	24 h incubation of compounds with cells → MTT	72 h incubation of compounds with cells → MTT
MCF-7 – human breast adenocarcinoma				
6	645 ± 23	205 ± 11	7323 ± 31	2617 ± 19
7	386 ± 14	223± 12	6629 ± 26	1635 ± 26
8	377 ± 15	145 ± 14	6044 ± 27	1910 ± 24
Chlorin e_6	1191 ± 25	1132 ± 20	13095 ± 29	12988 ± 27
Doxorubicin	-	-	23620 ± 41	4699 ± 13

Conclusion

A strategy for the synthesis of chlorin–doxorubicin conjugates containing various linker molecules was proposed and developed. Studies of photoinduced and cytotoxic activity *in vitro* on human MCF-7 cells have demonstrated the high efficiency of the synthesized compounds. The confocal microscopy results demonstrated that conjugates with labile linkers showed chlorin internalization in the cytoplasm and doxorubicin in the nucleus, which indicates the effectiveness of the chosen strategy.

More information about this work can be found in the article: Ostroverkhov P. et al. New conjugates of natural chlorins with doxorubicin featuring controlled release for combined photodynamic and chemotherapeutic treatment // Journal of Photochemistry and Photobiology B: Biology. 2026. Vol. 278. p. 113404.

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