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Meso-methyl-BODIPY conjugate with cabozantinib as a red-light-activated prodrug for anticancer therapy

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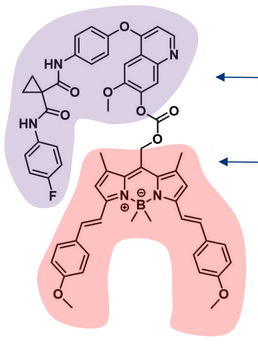
INTRODUCTION & AIM

Photoactivated chemotherapy is a new strategy for the development of anticancer drugs in which the activity of a chemotherapeutic drug is controlled by light irradiation. This avoids systemic toxicity and reduces side effects.. The aim of this work was to evaluate the therapeutic potential of the light-activated prodrug BODIPY-Cab.

METHOD

The tested compound



Cabozantinib suppresses metastasis, angiogenesis, and oncognesis by inhibiting receptor tyrosine kinases (AXL, VEGFR2, MET).

Meso-methyl-BODIPY plays a dual role acting as photosensitizer and photoremovable protective group for cytostatic simultaneously.

Solvent: deionized water and 1% Tween 80

Cell lines

- Human breast adenocarcinoma **MDA-MB-231** (AXL++/VEGFR2+/MET+);
- Human epidermoid carcinoma **A-431** (AXL+/VEGFR2-/MET+);
- Human embryonic kidney cells **HEK293** (AXL-/VEGFR2-/MET-).

The cells were exposed to light irradiation (655-675 nm, 20 J/cm2) using an LED light source.

Methods

- The photochemical and photophysical properties of the compound were evaluated using **a spectrophotometer-spectrofluorometer**;
- **A laser scanning confocal microscope** was used to study cellular uptake of conjugate BODIPY-Cab and reference hydroxyl-BODIPY;
- The effect of compounds on cell viability was estimated using **the microculture tetrazolium test (MTT);**
- A two-way ANOVA with Tukey's test for multiple comparisons was used for statistical analysis.

RESULTS & DISCUSSION

Photophysical measurements

The BODIPY-Cab conjugate absorbs light within the phototherapeutic window (λ = 650-900 nm), enabling enhanced light penetration depth.

Table 1. Photophysical characterization of compounds in DMSO

BODIPY derivative	λ_{abs}, nm	λ_{em}, nm	Φ_{Fl}, %	Φ_{Δ}, %
hydroxyl-BODIPY	364; 638	656	9	13
BODIPY-Cab	368; 662	678	16	17

Cytotoxicity study

The conjugate showed greater toxicity than cabozantinib, indicating the role of BODIPY in the total conjugate activity. On the other hand, the conjugate was less phototoxic than free hydroxyl-BODIPY.

Table 2. *In vitro* light and dark cytotoxic activity

Tested compound	Cell line	IC_{50}-light, μM (95% confidence intervals)	IC_{50}-dark, μM (95% confidence intervals)
BODIPY-Cab	MDA-MB-231	2.04# [1.5−2.7]	33.74** [29.75−38.25]
	A-431	3.4# [2.9−4.02]	33.47** [28.85−38.82]
	HEK293	1.7# [1.5−1.98]	12.89 [11.17−14.88]
hydroxyl-BODIPY	MDA-MB-231	1.2″ [0.88−1.6]	32.47* [29.16−36.15]
	A-431	0.88″ [0.7−1.1]	34.97* [33.37−36.65]
	HEK293	0.77″ [0.66−0.9]	2.8 [1.8−4.3]
Cabozantinib derivative	MDA-MB-231		48.75** [43.64−54.47]
	A-431		57.17** [50.5−64.72]
	HEK293		13.58 [10.26−17.96]

Statistically significant difference from HEK293 cell line in each group (*p < 0.01; **p < 0.0001), from BODIPY-Cab in dark conditions (#p < 0.0001), from hydroxyl-BODIPY in dark conditions (″p < 0.0001).

Study of cellular uptake of the tested compounds

Qualitative analysis of the confocal images demonstrated a more selective conjugate accumulation in tumor cells with receptors compared to cells without them. The compounds are localized in mitochondria and the endoplasmic reticulum.

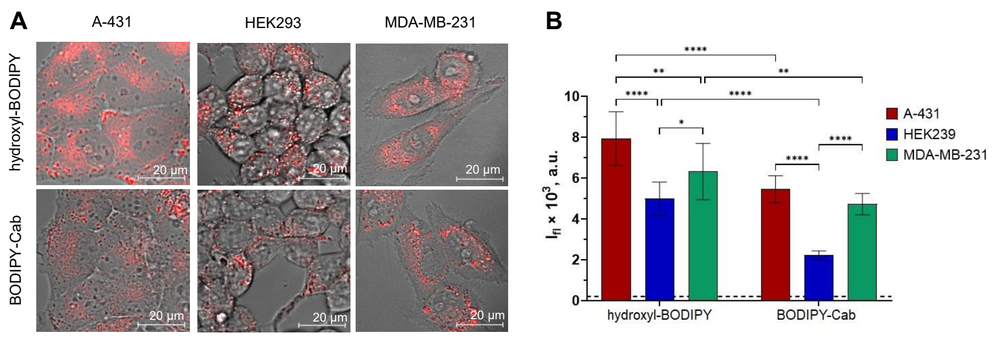


Figure 1. Cellular uptake study of compounds by cells: (A) confocal images of the living cells after 24 h incubation with a tested compound (C = 5 μM); (B) results of the qualitative analysis of the cellular fluorescence signal; means ± SD. Statistically significant differences in relative fluorescence (*p < 0.1; **p < 0.01; ****p < 0.0001)

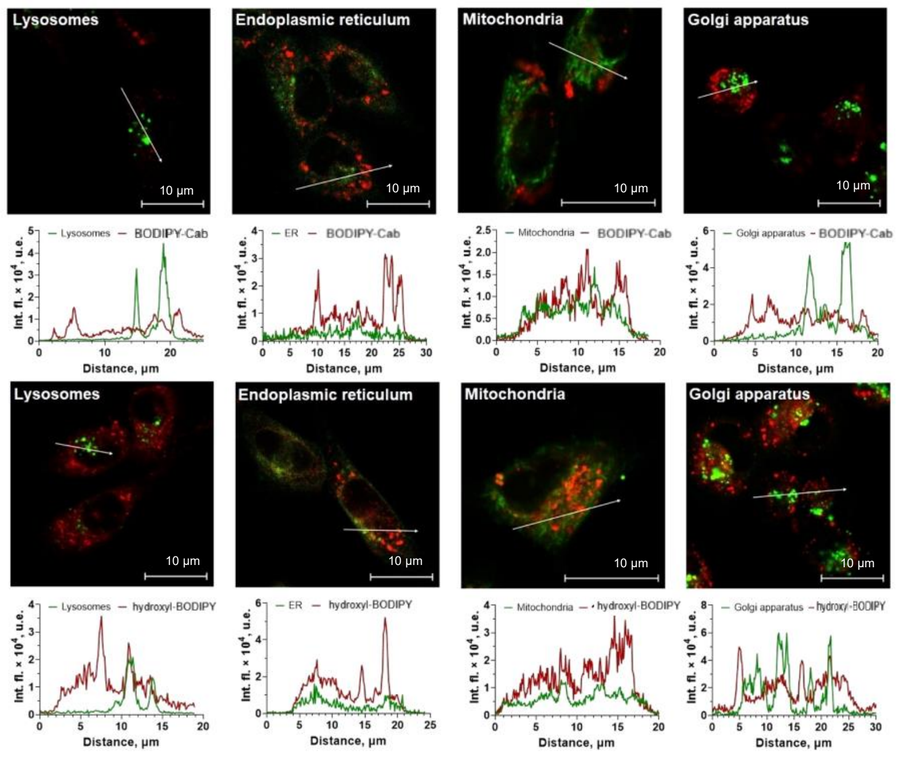


Figure 2. Analysis of intracellular localization of compounds in MDA-MB-231 cells; the merged fluorescent channels for the organelle dyes (green) and the compounds (red) are presented

CONCLUSION

The therapeutic potential of the light-activated prodrug BODIPY-Cab was investigated. The photophysical properties of the conjugate make it possible to use it for photodiagnosis to clarify the localization and size of the tumor focus. The BODIPY-Cab showed a predominantly photosensitizing effect with minimal cytostatic contribution of cabozantinib, which may be due to the low rate of photoinduced release of conjugate fragments.

FUTURE WORK / REFERENCES

We plan to optimize the design of BODIPY-based prodrugs to fast activation kinetics and improve the selectivity in order to ensure their further practical use.

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