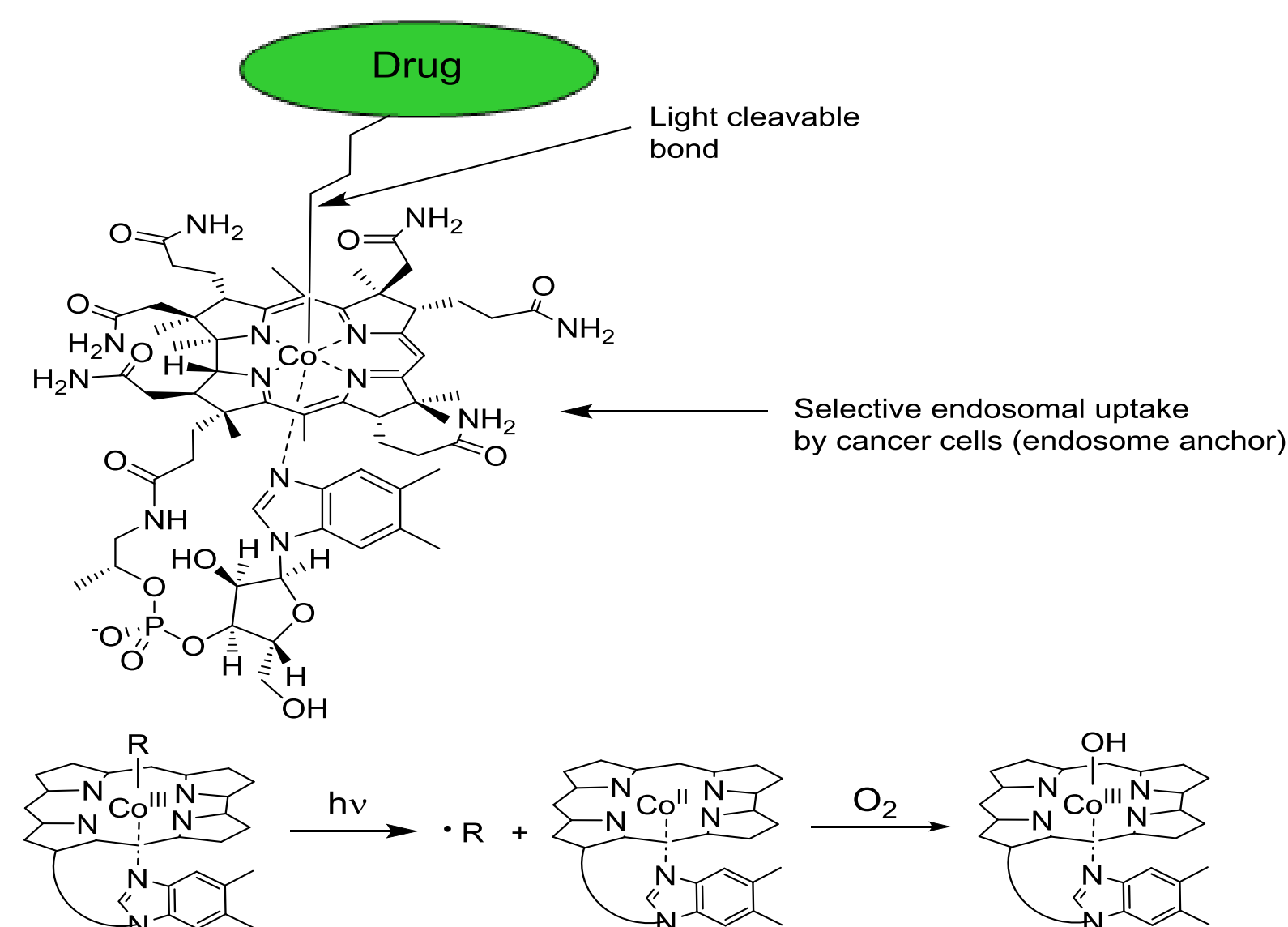


Introduction

- Traditional light-activated compounds require high energy, short wavelength light.
- Biological molecules easily absorb this type of light rendering it unable to penetrate skin.
- Alkylcobalamins, which are structurally related to vitamin B₁₂, that respond to light wavelengths within the skin's "optimal window" (600-900 nm) have been developed.
- The general concept involves coordinating a drug to the cobalamin, introducing the cobalamin-drug conjugate into the body and then exposing specific areas of interest to light
- This offers a therapeutic approach which limits side effects and extends the timeframe for treatments.
- Alkylcobalamins are useful for studying DNA structure via footprinting experiments due to the ability to produce radicals that cleave DNA when exposed to long wavelength light that does not damage DNA.

Alkylcobalamin-Drug Conjugate Structure



Acknowledgements

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References

- Shell, T. A.; Shell, J. R.; Rodgers, Z. L.; Lawrence, D. S. Tunable Visible and Near IR Photoactivation of Light Responsive Compounds by Using Fluorophores as Light-Capturing Antenna. *Angew. Chem. Int. Ed.* 2014, 53, 875-878.

Background

- Vitamin B₁₂ derivatives accumulate in high concentrations within cancerous cells due to an increased requirement for the vitamin.
- Therefore, cobalamin-drug conjugates should target cancerous cells.
- Cells uptake cobalamin-drug conjugates in endosomes preventing the drug from interacting with cellular environment.
- Photolysis of the cobalamin-drug conjugate will release the drug from the endosomes.

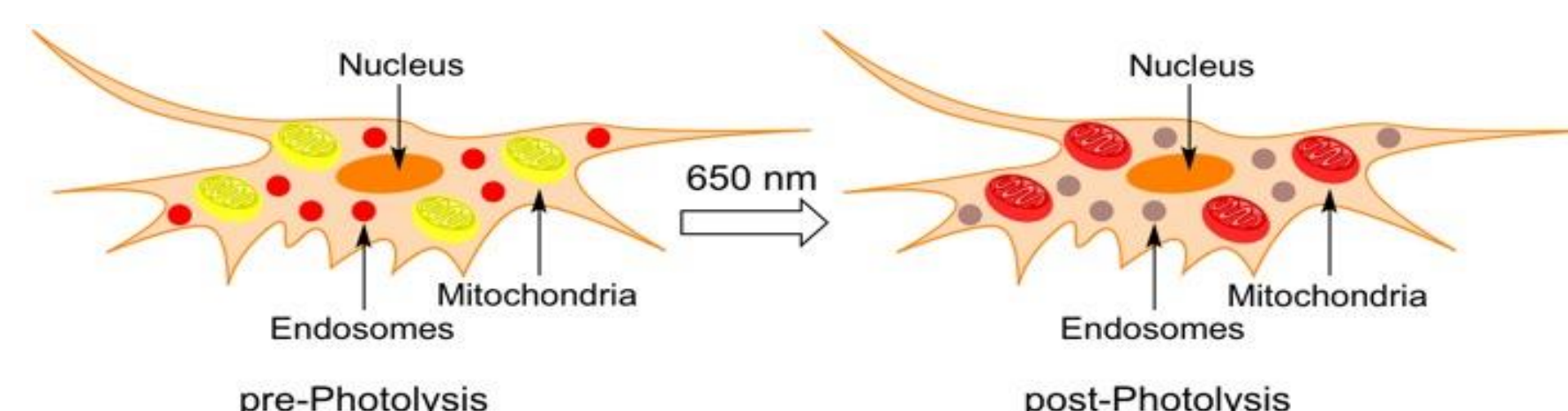


Fig. 1. A cartoon of BoDipy 650 translocation from endosomes to mitochondria due to photolysis of a cobalamin-BoDipy 650 conjugate.

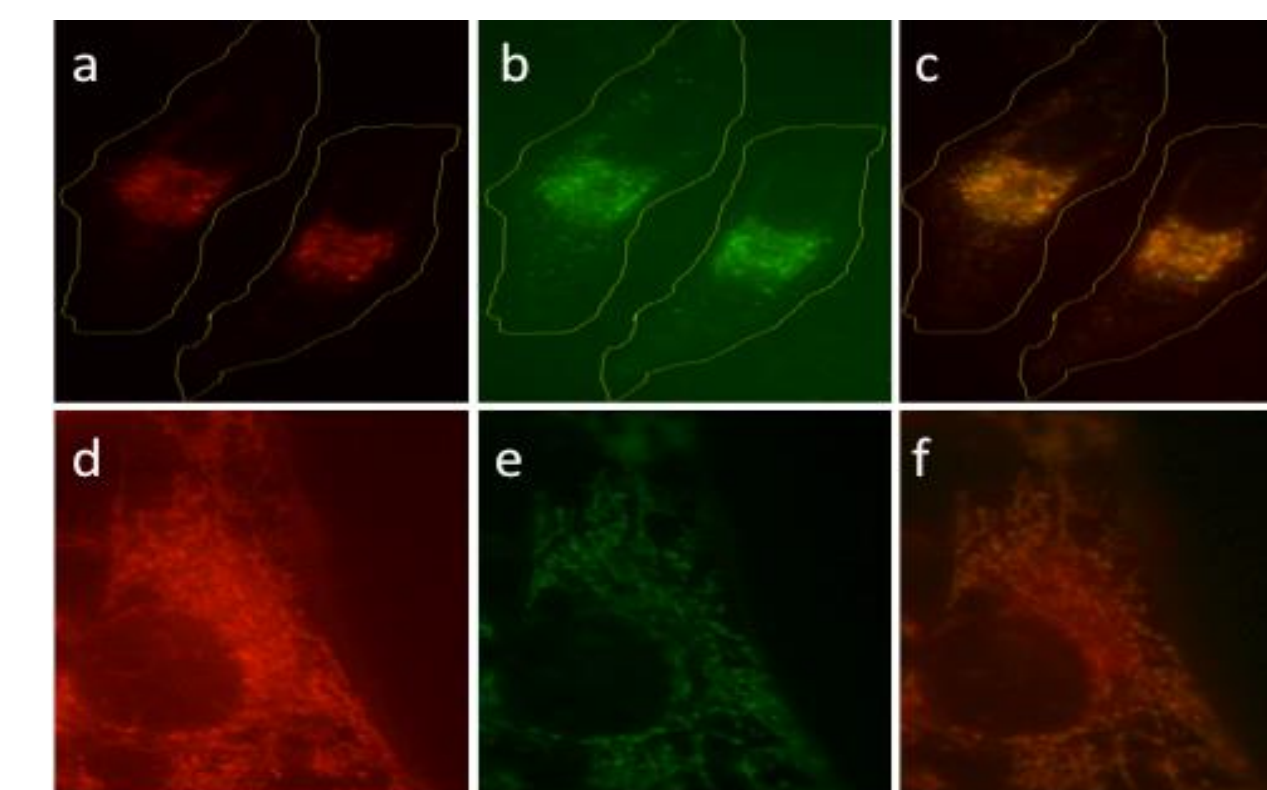
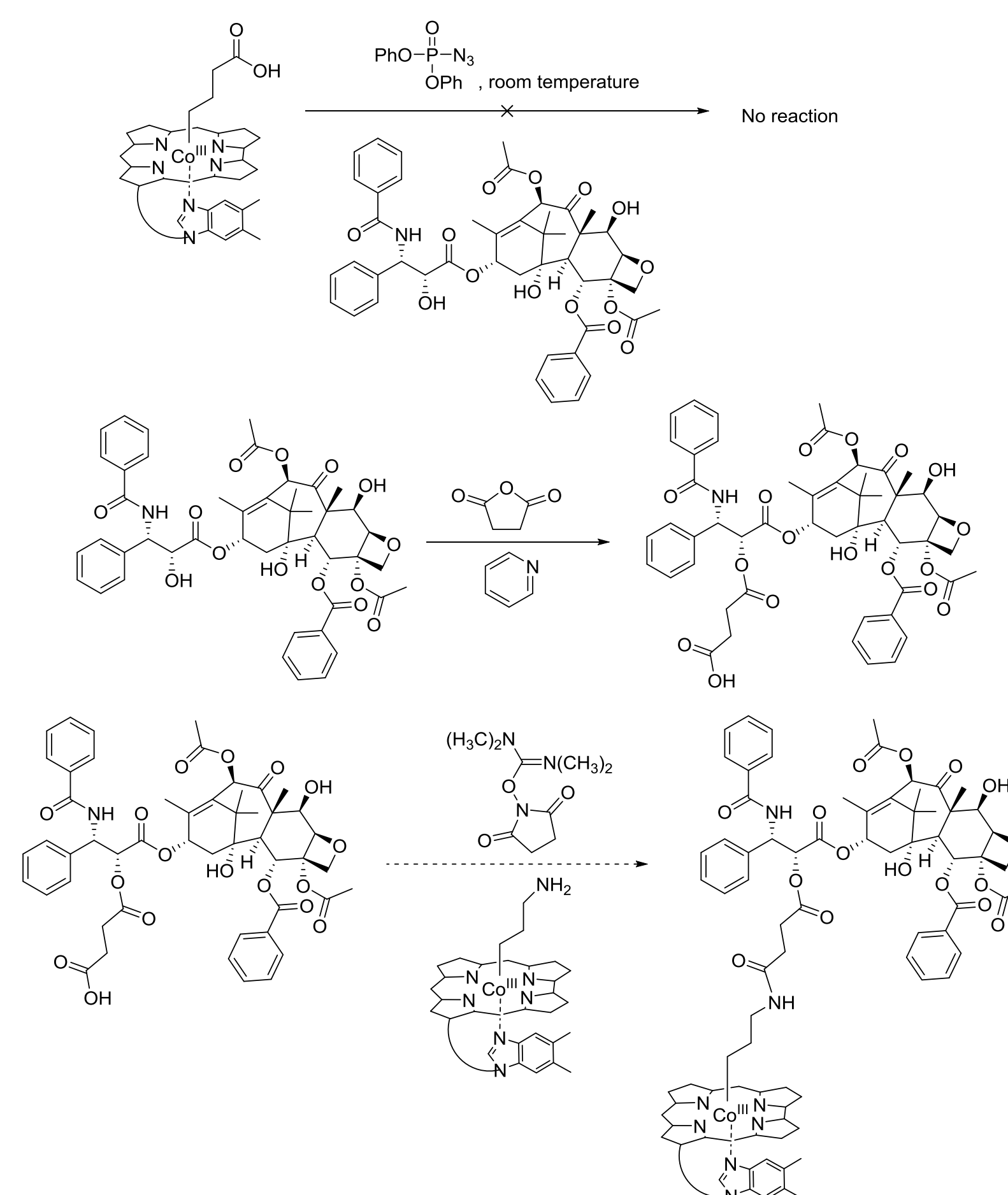
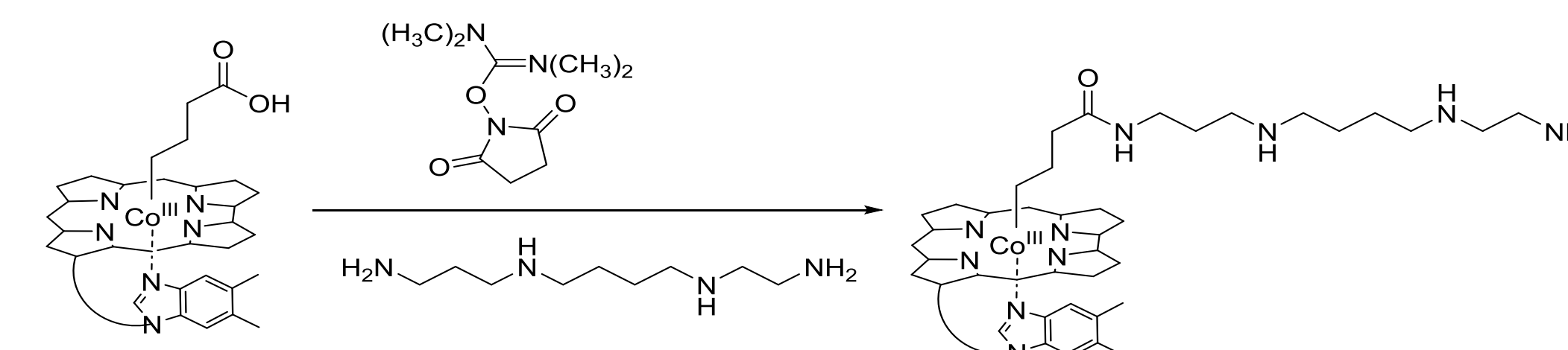


Fig. 2. Red-light induced translocation of BoDipy 650 in HeLa cells. a) Cbl-Bodipy 650 before photolysis b) rhodamine B-dextran endosomal marker c) an overlay of a and b demonstrating that the cobalamin conjugate is endosomal d) Cbl-Bodipy 650 after photolysis e) Mito-Tracker Green mitochondria tracker f) an overlay of d and e demonstrating the translocation of the BoDipy 650 fluorophore to the mitochondria.

Results



Scheme 1. Synthesis of cobalamin-taxol conjugate.



Scheme 2. Synthesis of cobalamin-spermine conjugate that is useful for damaging DNA.

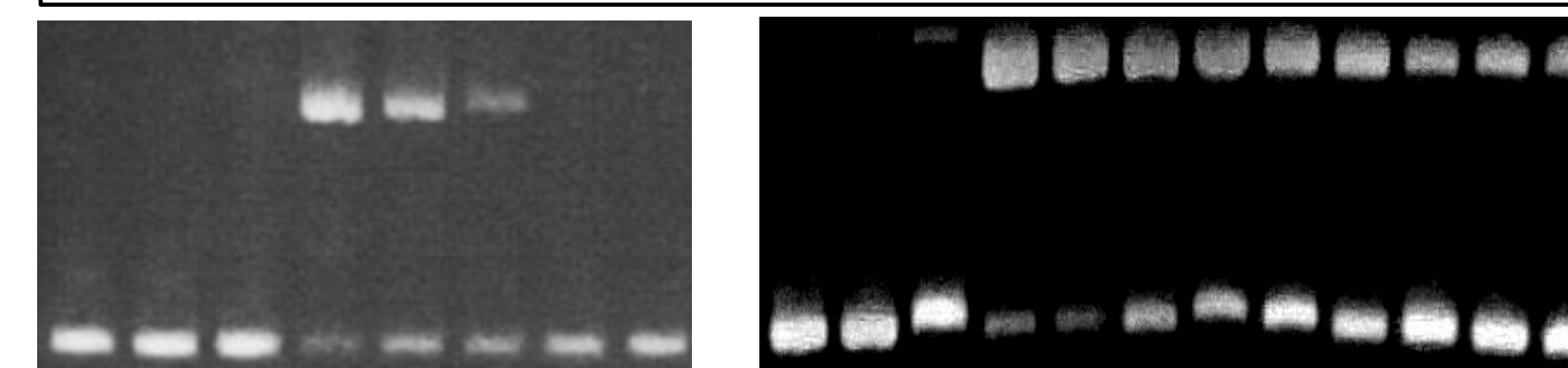


Fig. 3 & 4. Gels demonstrating the difference in ability to cleave DNA between methylcobalamin (left) and spermine cobalamin-conjugate (right).

Lane	1	2	3	4	5	6	7	8	9	10	11	12
Methylcobalamin (μM)	0	0	1000	750	563	423	316	237				
Spermine-cobalamin (μM)	0	0	250	250	175	122	85	60	42	29	20	14
Light Exposure	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table 1. Concentrations of compounds for experiments of Fig. 3 & 4