One- and Two-Photon Uncaging of Carbon Monoxide (CO) with Real-Time Monitoring: On Demand Carbazole based Dual CO-Releasing Platform to Test over Single and Combinatorial Approaches for the Efficient Regression of Orthotopic Murine Melanoma *In Vivo*

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Abstract: Real-time monitored controlled delivery of carbon monoxide (CO) has recently emerged as a promising strategy for effective cancer therapy. However, it remains a challenge to develop CO releasing molecules (CORMs) that enable a dose dependent spatio-temporal release of CO in the "phototherapeutic window" with real time monitoring ability.

To address this deficiency, we report here three new metal-free, photochemically active CORMs (photoCORMs) based on a carbazole fused 1,3-dioxol-2-one moiety. Here, the designed single, dual, and combinatorial photoCORMs were able to release one equiv of CO, two equiv of CO, and combination of one equiv of each CO and anticancer drug, chlorambucil (cbl) upon one and two-photon excitation, respectively. We have demonstrated the detection of CO release under one and two-photon excitation both qualitatively and quantitatively by a fluorescein-based "turn on" probe and the standard myoglobin assay. Results suggest that dual photoCORM releases a quantitative amount of CO at a low dosage compared to single and combinatorial photoCORMs. The photorelease mechanism for the CO involves simple "cheletropic extrusion" upon light irradiation, and a sequential stepwise CO release was observed for the dual photoCORM. The important aspect of this current work was the real-time monitoring ability of CO uncaging by changing the fluorescent color from blue to green, which is achieved through the "internal charge transfer" (ICT) process between the donor and acceptor units. To exhibit the utility of newly developed photoCORMs, we evaluated the *in vitro* anticancer properties of photoCORMs on B16F10 cancerous cells and the results demonstrated that dual photoCORMs showed enhanced anticancer efficacy by its superior capability to release quantitative amount of CO at lower dosage over single and combinatorial models. In agreement with the *in vitro* results, the *in vivo* study of dual photoCORM on C57BL/6J mice model showed significant regression in tumor volume along with enhanced overall survivability by the resultant of dual CO uncaging at 730 nm.

Therefore, we envisioned that dual photoCORM system developed in this study provides a promising platform to use in ongoing cancer research and profound understanding of the therapeutic benefits of CO molecule.

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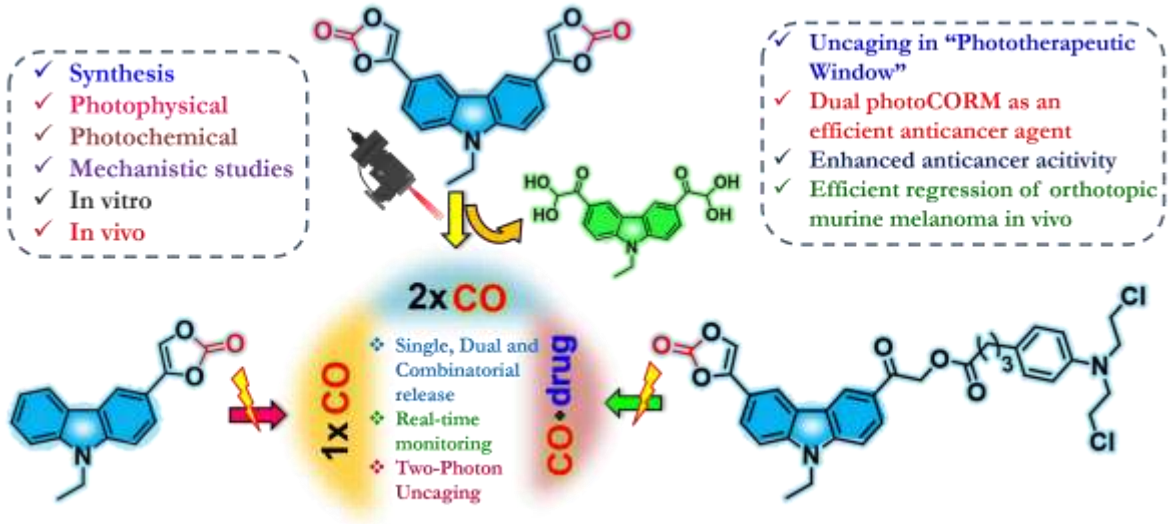
Figure:

Scheme:



References and Notes:

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Bio-Sketch of Speaker

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