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Two-Photon-Induced CO-Releasing Molecules as Molecular Logic Systems in Solution, Polymers, and Cells

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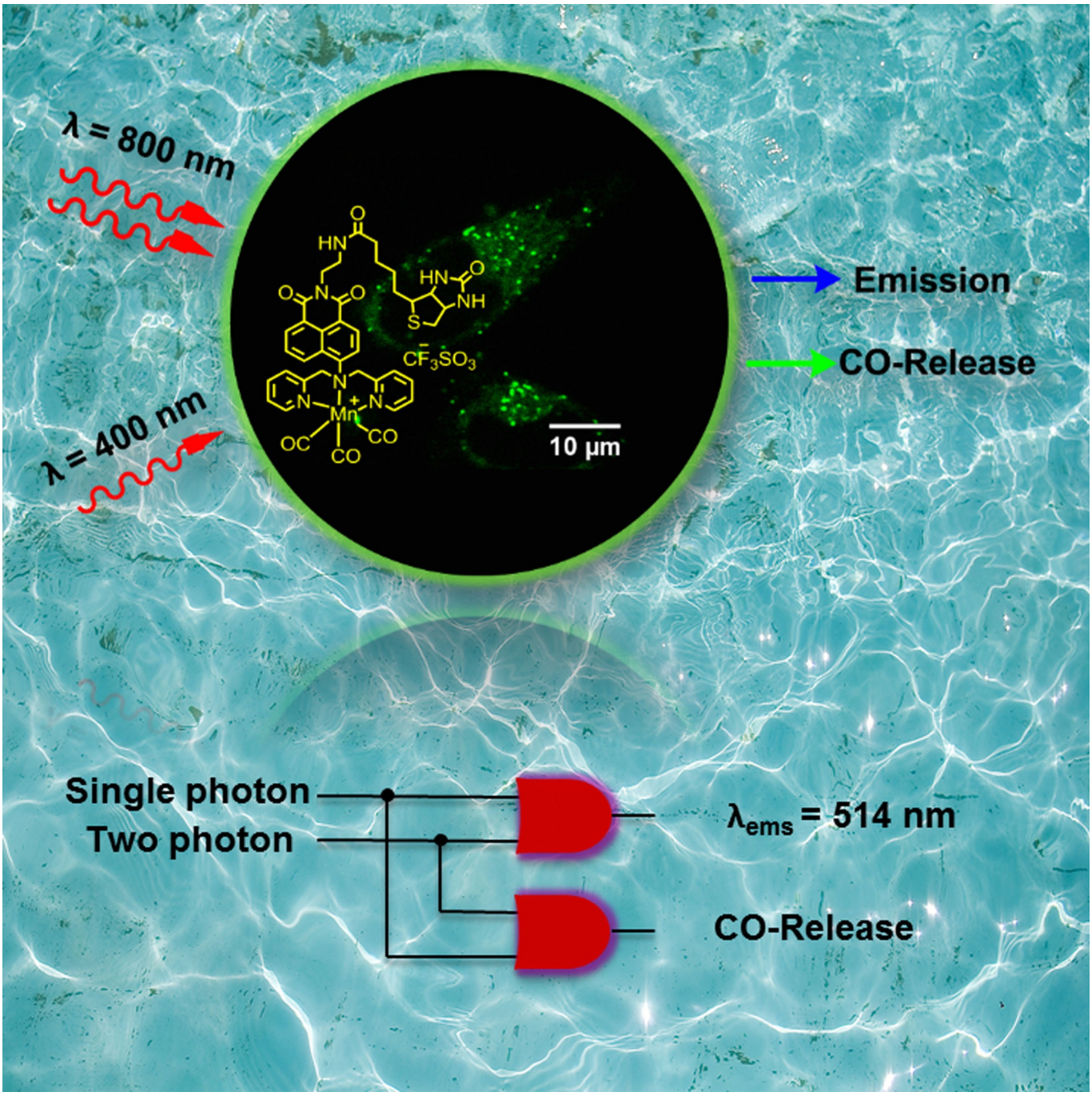
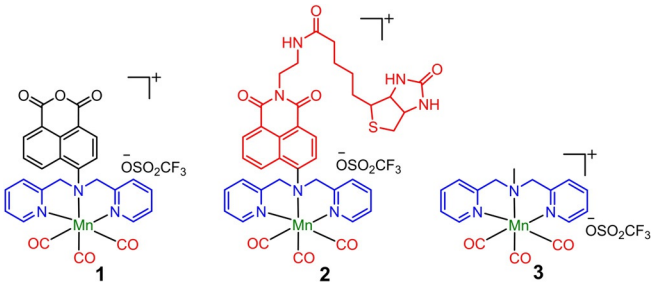


Abstract: Phototherapeutic applications of carbon monoxide (CO)-releasing molecules are limited because they require harmful UV and blue light for activation. We describe two-photon excitation with NIR light (800 nm)-induced CO-release from two Mn^{I} tricarbonyl complexes bearing 1,8-naphthalimide units (**1**, **2**). Complex **2** behaves as a logic OR gate in solution, nonwovens, and in HeLa cells. CO release, indicated by fluorescence enhancement, was detected in solution, nonwoven, and HeLa cells by single- (405 nm) and two-photon (800 nm) excitation. The photophysical properties of **1** and **2** have been measured and supported by DFT and TDDFT quantum chemical calculations. Both photoCORMs are stable in the dark in solution and noncytotoxic, leading to promising applications as phototherapeutics with NIR light.

The toxic effects of large amounts of carbon monoxide (CO) cause the death of many people every year.[1] However, CO is also known to be produced in small amounts naturally and in healthy individuals, where it is involved in cell signaling. It is also recognized as a potential therapeutic agent since it can exhibit positive effects on wound healing and during heart[2,3] or kidney[4] transplantations. CO can finally act as an anticancer or anti-inflammatory agent.[5] Practically, the delivery of CO for therapeutic purposes requires careful control of dosage and localized delivery, which is very challenging. Therefore, gaseous CO in therapy is not advisable. Instead, the delivery of CO from CO-releasing materials and molecules (CORMs) is preferable, as it is controllable, highly tissue specific, and can be triggered by local light irradiation.[6,7] The research groups of Motterlini, Mascharak, Ford, or Schatzschneider, for example, thoroughly investigated the use of CORMs and photoCORMs based on transition-metal complexes.[2,8–14] Most of these photoCORMs require UV or blue light for efficient CO release.[2,15] Light in this region is not only toxic to cells and tissues, but its penetration length through human skin and tissues is limited.[16] This issue prevents the development of most clinical applications of photoCORMs, for which activation should occur preferentially in the phototherapeutic window (600–950 nm).[17,18] Researchers have partially addressed this problem by extending the π system of the ligands,[19] by conjugation of the photoCORM to upconverting nanoparticles,[20] or by mixing the photoCORM with a red-light-sensitive photosensitizer.[21] Another alternative that does not require any molecular modification or physical mixing of the photoCORM is to trigger CO release by two-photon absorption (2PA).[22] 2PA processes involve the simultaneous absorption of two NIR photons; they can trigger efficient photochemistry while minimizing photodamage and maximizing tissue penetration.[23] 2PA is a nonlinear optical process that finds applications in 3D microscopy,[24] fluorescence microscopy,[25] optical data storage, nanofabrication,[26] and photodynamic therapy.[27] Herein, we propose to also analyze 2PA-induced CO release as a new form of molecular logic gates. The optically activated, cancer-targeted CORMs presented in this work display excellent properties as molecular logic devices since they can process concomitantly electromagnetic, chemical, and environmental information.[28–30]

Herein, photoCORMs compounds **1**–**2** (Scheme 1) combine a $[Mn^{I}(CO)_3]$ CO-rich fragment with a potentially emissive dipicolylamine-1,8-naphthalimide ligand, while **2** also integrates a biotin tether. The turn-on fluorescent chromophore 1,8-naphthalimide has a large 2PA cross-section[31–34] and can be excited between λ_{exc} = 600–950 nm.[35–38] Biotin is required to sustain the natural growth of eukaryotic cells.[36] Standard HeLa cancer cells over-expressing biotin receptors to sustain their rapid proliferation.[39] Biotin has been used as a tumor-targeting ligand for tumor imaging and targeted drug delivery.[40] Compound **2** thus includes five features for processing concomitantly electromagnetic, chemical, and environmental information: It can be excited at 400 (1PA) or 800 nm (2PA), increases fluorescence intensity after CO-release, and targets biotin receptors.



Scheme 1. Structures of complexes **1**, **2**, and **3** used in this study.

The synthesis and characterization of photoCORMs **1**[41] and **2** was achieved by standard synthetic methods (see the Supporting Information).[19,42] Compound **3**, a known analogue deprived of chromophore and biotin tether, was used as a nega-

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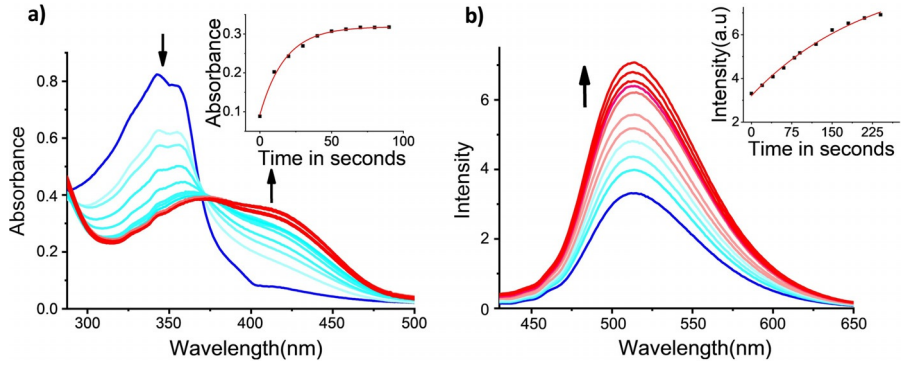


Figure 1. Changes in the absorption and emission spectra of **2** upon photochemical release of CO using 405 nm light (10 mW cm^{-2}) in acetonitrile. Spectra of 3 mL solution of [**2**] = 10 μM were measured at 10 seconds intervals. Inset: absorbance at 405 nm or emission at 514 nm as a function of irradiation time.

tive control.[42] Initially, single-photon excitation experiments were performed. The alterations of the absorption and emission spectra were recorded upon irradiation at $\lambda_{exc} = 405$ nm (10 mW cm^{-2}, Figure 1). For both **1** and **2** the initial absorption band at 340 nm—assigned by TD-DFT calculations to S_7, a local excitation of the naphthalimide moiety—gradually decreased, to be replaced by a new absorption band at 420 nm. A subsequent color change from colorless to yellow was observed. The prominent isosbestic point at 370 nm indicates the formation of a single photoproduct species.[19] Concomitantly to irradiation, the emission intensity for **1** (Figure S15b, Supporting Information) and for **2** (Figure 1 b) gradually increased. Under dark conditions, no changes in the absorption or emission spectra were observed, thus confirming the dark stability of **1** and **2** (Figure S16, Supporting Information).

Secondly, since the naphthalimide unit possesses a large 2PA cross-section, we investigated the two-photon-induced CO-releasing properties of **1** and **2**. Acetonitrile solutions of **1** or **2** were photolyzed with a two-photon laser beam (800 nm, 50 mW cm^{-2}) as described in Figure S17, Supporting Information. The amount of CO release was measured using a portable CO gas sensor (Drager Pac 7000) in a closed desiccator.[15] From the graph shown in Figure S18, Supporting Information, one could observe that the nonbiotin conjugated photoCORM **1** released a higher amount of CO (220 ppm) than **2** (145 ppm), while none of the compounds released any CO in the dark. Of fundamental importance for the light-induced CO release is the initial absorption. The present experiments were performed upon excitation at 400 (1PA) and 800 nm (2PA), respectively. As evident from the measured and simulated absorption spectra, the absorption profiles of **1** and **2** feature distinct differences between 400 and 450 nm. In particular, the red-sided shoulder of the main absorption feature in the UV-region features is more prominent for complex **2**. This band is associated with intraligand states, thus the population of the desired metal-centered states of Mn–associated with CO release—compete with the population of undesired intraligand states. These intraligand states do not contribute to CO release as the electronic environment around the manganese center is unchanged, thus decreasing the CO release of **2** in comparison to **1**. To the best of our knowledge, compounds **1** and **2** are the first described 2PA photoCORMs without the involvement of an external stimuli like H_2O_2. The release of CO at the given excitation wavelength is accounted for the low-lying ligand field states S_1 and S_2 found between approximately 465 and 335 nm by TDDFT. These states feature—in contrast to the ground state—anti-bonding interactions between the manganese d-orbitals and CO ligands, thus leading to CO release. Details on the simulated photophysical properties of **1** and **2** are collected in Figure S30, Supporting Information, as well as in Tables S4 and S5, Supporting Information.

Next, the myoglobin assay was used to detect CO release upon two-photon irradiation of **1** and **2** in aqueous solution.[43] Changes in the Q-band of the myoglobin absorption spectrum at 540 nm was followed upon irradiation (Figure S19, Supporting Information). The decreased intensity of the absorption band of myoglobin at 556 nm and two increased bands at 541 nm and 578 nm demonstrated the formation of carboxymyoglobin and thus CO-release from **1** and **2**. Furthermore, a small but visible band at 628 nm was also found due to the formation of metmyoglobin for which conversion of Fe^{II} to Fe^{III} takes place.[43] The one-photon irradiation of the myoglobin solution in the presence of both the photoCORMs **1** and **2** also resulted in similar changes when photolyzed at 405 nm light. As the sodium dithionite present in the solution may also initiate CO release, dark controls were recorded for 30 min; they showed no spectroscopic changes (Figure S20, Supporting Information), demonstrating that CO release was solely photochemical. The known photoCORM **3**—lacking the naphthalimide unit—was used as a control[42] and showed no changes in the myoglobin absorption spectrum upon irradiation for 30 min (Figure S21, Supporting Information) under similar conditions to **1** and **2**. This experiment establishes that the two-photon-induced CO-release in **1** and **2** is due to the presence of the naphthalimide chromophore unit.

As both complexes, **1** and **2** hold a 1,8-naphthalicanhydide moiety that increases two-photon absorption, the relative 2PA cross-sections (σ_s) were determined for **1** (0.2 GM) and **2** (4.5 GM) by the two-photon excited fluorescence measurement technique in methanol by taking rhodamine B as a reference compound.[44] As shown in Figure S22, Supporting Information, both **1** and **2** could be excited with NIR light (two-photon excitation between 760–810 nm). The peak positions and spectral shapes of spectra with two-photon excitation are in agreement

Table 1. CO release, cell viability, and logP values of photoCORMs **1** and **2**.

photoCORM	Log*P*	IC_{50} [μmol]	CO release in acetonitrile [ppm]	CO release from PLA fabric [ppm]
1	-0.5 ± 0.2	≥ 500	200	20
2	1.5 ± 0.1	≥ 250	145	10

with the fluorescence detected upon one photon excitation (Figure S23, Supporting Information). These σ_s values suggested that both **1** and **2** could serve as two-photon CORMs.

As photoCORMs may also be used in the scope of photoactivated chemotherapy, the cytotoxicity of both compounds was evaluated in LX-2 and HeLa (Figure S24a, Supporting Information) cancer cell lines. After 24 h incubation, both **1** and **2** were found to be nontoxic even at high concentrations (Table 1). Further, confocal laser scanning microscopy (CLSM) imaging studies were conducted to investigate the cellular uptake and compartmentalization of both photoCORMs (Figure 2). The confocal images of HeLa cells treated with **1** or **2** were captured by one-photon excitation as well as two-photon excitation. As anticipated from previous reports,[45] the presence of long aliphatic chain in biotin structure could increase the overall lipophilicity of **2** when compared to nonbiotin conjugated **1** (Table 1). The lipophilicity (log*P*) values for both the photoCORMs were calculated using octanol/water shake flask method.[46] It is not just noticeable that the biotin-conjugate **2** shows higher uptake with brighter emission, but also reveals the characteristic feature of a biotin-receptor-mediated endocytosis in the form of additional clearly visible intracellular vesicle-like particles (Figure 2c). These observations suggest, that the enhanced uptake of **2** compared to its pendant **1** is not simply caused by higher lipophilicity of biotin's aliphatic chain of compound **2** (Figure 2a).[47] As photoCORM **2** has a higher lipophilicity than **1** (log$P = +1.5$ and -0.5, respectively), one could anticipate that **2** has higher cellular uptake. From the one-photon fluorescence images in Figure 2c, it is clear that **2** localized not only in the cell membrane,[48] but also in the cytoplasm. The fluorescence intensity profile plot (Figure 2d) suggested that the emission intensity for **2** was increased after 2PA irradiation in HeLa cells.

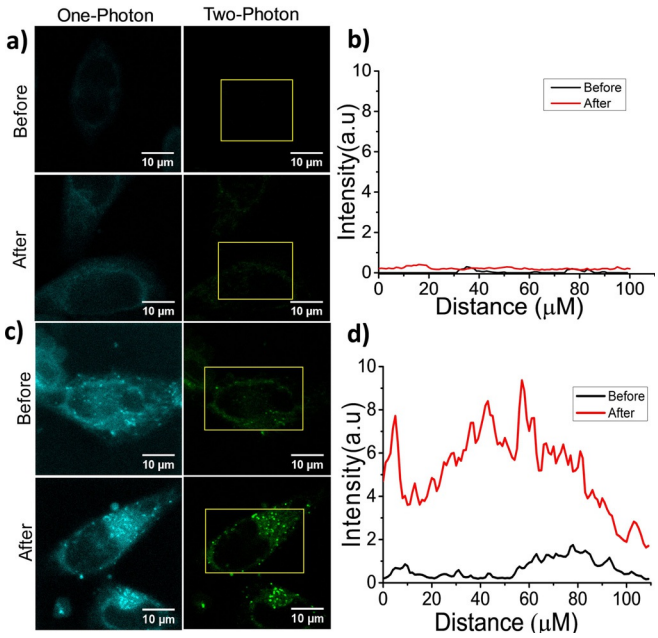


Figure 2. CLSM images of HeLa cells treated with a) **1** and b) **2** (50 μM, 60 min) shows the fluorescence enhancement change upon irradiation with one- and two-photon excitation. Fluorescence intensity measured before and after two-photon irradiation for b) **1** and d) **2**. The intensity was measured using ImageJ software from the yellow color rectangular boxes.

Based on these results, we proposed an innovative approach to construct a second layer in logical gates to this biological aspect. We used one and two-photon excitations as inputs and the concomitant fluorescence enhancement upon CO release as an output for **2** in HeLa cells. Considering the fluorescence enhancement from cells treated with **2** upon one and two photon irradiations, we constructed the logical co-registered OR gate (Figure 4a). Due to the poor cellular uptake with almost no fluorescence enhancement, compound **1** (Figure 2b) could not be used for the construction of such an OR gate in HeLa cells.

In this present contribution, we did not study in-depth the post-irradiation products generated upon CO release, as the main focus of this work was to thoroughly investigate the (quantitative) release of CO upon two-photon excitation. However, according to the literature addressing the irradiation of structurally analogous complexes, the vacant coordination sites at the manganese center are coordinated by solvent molecules after irradiation.[42] To determine whether all carbonyls were released upon two-photon-irradiation, **1** and **2** were photolyzed in the solid state while following the changes of CO stretch vibrational modes between 1800 and 2200 cm^{-1} using IR spectroscopy (Figure 3 and Figure S25, Supporting Information). Within the first 15 min of irradiation, the typical signals of CO stretch at 2047 and 1938 cm^{-1} vanished, thus confirming the quantitative release of CO from both photoCORMs.

Many potential therapeutic applications of photoCORMs require immobilization on a carrying material. Nonwovens represent exciting new materials for tissue bioengineering and nanotechnology.[49] Embedding photoCORMs into nonwoven materials represents one way to prevent the release of toxic metal fragments after CO release.[21] Hence, **1** and **2** were embedded in poly(L-lactide-co-D/L-lactide) (PLA) nonwoven fabric material by electrospinning techniques.[5,15,21] The resulting materials were named as **PLA-1** and **PLA-2**. The CO-releasing properties of both **PLA-1** and **PLA-2** were studied by irradiation with the two-photon laser at 800 nm, and simultaneous recording of the IR spectral changes. **PLA-1** released higher amounts of CO (≈22 ppm) than **PLA-2** (≈10 ppm) as evident from Figure 3c. Approximately the same amount of CO was released upon one-photon irradiation experiments performed

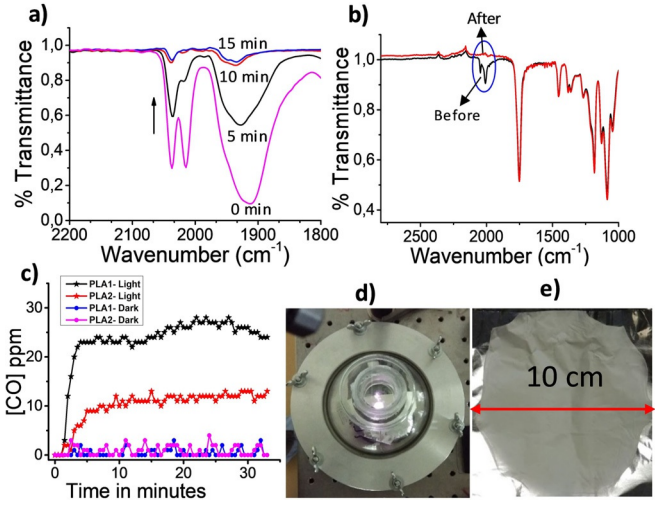
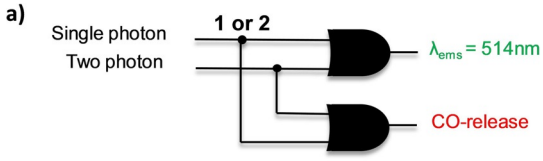


Figure 3. IR spectral changes for a) **2** and b) **PLA-2** upon irradiation with the two-photon laser in the solid state. c) CO concentration vs. time during the two-photon irradiation of **PLA-1** and **PLA-2**. d) Setup for the two-photo-irradiation and CO-releasing measurements. e) Photograph of **PLA-2**.



b)

Input		Output	
λ_{Ex} = 405nm	λ_{Ex} = 800nm	λ_{Em} = 514nm	CO-release
0	0	0	0
1	0	1	1
0	1	1	1
1	1	1	1

Figure 4. a) Diagram of the logic circuit for the co-registered logic OR gate. b) Truth table based on input-output signal correlation pattern, indicating that excitation of **1** and **2** with one or two-photons could induce the CO-release.

with **PLA-1**, **PLA-2** at 405 nm (Figure S26). To test their stability, **PLA-1** and **PLA-2** were stored under dark conditions at low temperature (+8 °C) for one month. The CO stretching bands were still observed between 1950 and 2050 cm^{-1} (Figure S27, Supporting Information), which demonstrated the good dark stability of **1** and **2** when embedded in PLA fabric. To closely investigate the morphological changes of **PLA-1**, **PLA-2** fibers upon two-photon laser irradiation, SEM images were captured (Figure S28, Supporting Information). Notably, the fibers have a smooth surface and no porosity was observed due to the release of CO during the electrospinning process which proved the stability of **1** and **2** under the electrospinning conditions. These SEM images also revealed that there was no damage or morphological alterations to the PLA fiber at the laser power used for the two-photon excitation and consequent CO-releasing studies.

On the other hand, logic gates can be used to selectively screen a particular analyte in a certain region of the body/cell by processing the information related to the analyte of interest.[50] The first application of molecular logic gates in biological media was biosensing.[51] This type of sensing allows the screening of more than one analyte simultaneously and using the multiple outputs of a gate and can exclude false results by taking multiple diagnostic parameter at once, hence, improving the accuracy of the diagnosis.[52] Considering the overall results, we have constructed a molecular "OR" gate for photoCORMs **1** and **2** (Figure 4a). We assigned one- and two-photon excitations as two inputs and the associated fluorescence and CO release as outputs. The truth table shown in Figure 4b discloses the necessary combinations of an "OR" gate. "OR" gates are logic functions in full adders for the construction of computers.[53,54] Both the photoCORMs **1** and **2** upon excitation with 1PA and 2PA can be used as co-registered "OR" gate; fluorescence enhancement indicates a visible output, whereas the simultaneous output CO-release can be used as an input for a concatenated chemical logic gate.[42] Logic gate behavior was also demonstrated in HeLa cancer cell lines as shown in Figure 4a. Overall the photoCORMs displayed the behavior of two OR gates in the solutions, nonwovens as well as in the HeLa cells.

In conclusion, we proposed a novel method for CO release using two-photon excitation of photoCORMs **1** and **2**. Compared to one-photon excitation, the ambitious approach of two-photon excitation signifies a dramatic improvement in the field of CORMs. As of our knowledge, the direct two-photon induced CO-release without the involvement of any external stimuli like H_2O_2 in the literature is scarce. The two-photon induced CO-release from **1** and **2** occurred not only in solution state but also in the electrospun polymeric nonwoven fabric and found to be stable up to(at least) one month. These NIR photoCORMs feature potentially low cytotoxicity and allowed CO-release monitoring by confocal microscopy in HeLa cells through fluorescence enhancement. Furthermore, we developed different co-registered OR gates with structural modifications in the ligands and also expanded the logic gate concept into the biological context. Due to the lower cytotoxicity levels of **1** and **2**, they may enable CO delivery for anti-inflammatory and wound healing therapeutic applications.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: immobilization · logic gates · low cytotoxicity · nonwoven fabric materials · two-photon CORMs

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