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Research Article

RECENT DEVELOPMENT OF FLUOROGENIC PROBES FOR CARBON MONOXIDE IMAGING IN LIVING CELLS

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The identification as well as detection of small endogenously produced gaseous molecules, carbon monoxide (CO), as signal transmitters in living systems has discovered that these gases perform essential biological functions and are associated with various diseases in human. It is now recognised that chronic exposure to low levels of CO also poses a significant health risk. Thus the selective monitoring and detection of low levels of CO remains challenging for researchers. Although some traditional methods, e.g. gas chromatography, electrochemical analysis, and colorimetric detection, have been established for sensing CO but these methods are not able to selectively detect CO in living systems in a non-invasive manner. In contrast, detection by fluorescence techniques is highly attractive due to its high sensitivity and real-time detection approach in a non-destructive way. This review article covers the design of fluorogenic probes, mechanistic behaviour with CO and their application to CO sensing in living cells.

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INTRODUCTION

Carbon monoxide (CO) is a well-known toxic pollutant because of its strong affinity to bind with hemoglobin that could lead to fatal consequences.[1,2] CO is often called the "silent killer" due to tasteless, colourless, odourless and particularly hard to sense nature.[3,4] The presence of CO in environment is due to the incomplete combustion of gas, oil or solid fuels. Confusion and tiredness as well as migraine-like symptoms and dizziness can arise from long term exposures even at low levels of CO (30–50 ppm). Death can occur after a few minutes at extreme exposure to the gas (2000 ppm). It is important to note that these symptoms are often misdiagnosed as those of common viral infections. It has also been reported in literature that chronic exposure to carbon monoxide may often have a significant impact on the central nervous system, leading to depression and memory loss.[5]

Despite the deadly nature of CO, it is obvious from various research that CO is continuously produced in our human body *via* endogenous degradation of heme by a family of inducible (HO-1) and constitutive (HO-2) heme oxygenase enzymes.[6-9] Thus CO, a gasotransmitter molecules, was considered to be an important versatile signaling bio-molecule with significant therapeutic potential protecting from inflammatory, vascular or even cancer diseases.[10,11]

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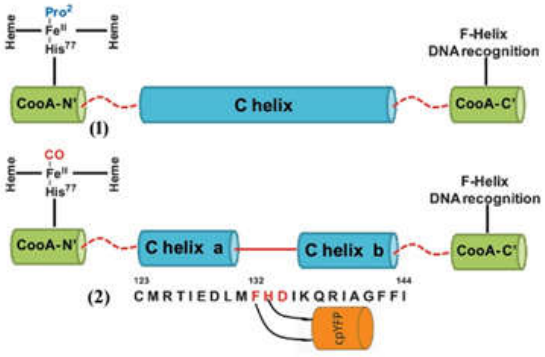
CO gas is known to accelerate potent anti-inflammatory effects in the concentration rang 10 to 500 ppm.[12] It plays an essential role in a variety of physiological and pathophysiological processes within the nervous, cardiovascular and immune systems.[13] CO generated in the vessel by heme oxygenase enzyme has been discovered to prevent both acute and chronic hypertension. And also it helps to avoid vasoconstriction through the stimulation of soluble guanylate cyclase.[14,15] Endogenous CO inhibits human airway smooth muscle cell proliferation,[16] prevents endothelial cell apoptosis[17,18] and protects against hyperoxic as well as ischemic lung injury.[19] Also, it seems to regulate sinusoidal tone in the hepatic circulation.[20] These have fascinated unparalleled attention for developing research of CO in biology. Many chemical and biological aspects of CO remain indescribable owing to having the lack of ways for selective monitoring of this transient small molecule. Thus the development of the selective method for direct tracking of this small molecule in living systems is of great scientific interest.

The interest in detecting this gas (lower than 50 ppm) is therefore becoming important to avoid its toxicity from its presence as a chronic poison. The majority of sensors used for the detection of CO in air are based on electrochemical cells and on semiconducting metal oxides (typically tin dioxide).[21] However, significant progress has been made recently towards the development of new, inexpensive CO sensors using different technologies. In this context, colorimetric and fluorometric probes for carbon monoxide, that exhibit striking optical changes visible to the 'naked eye' at low

concentrations of the analyte, are seen as a powerful alternatives to the established systems. Since the discovery of the benign role of carbon monoxide, a whole new research field, focused on the real-time detection of CO in living cells and tissues, has emerged. The growth of these fields has led to attempts to develop luminescent chemosensors capable of quantifying the production of endogenous CO or the generation of CO by CORMs in cells. However, despite this attention, few systems capable of the fluorogenic detection of CO in cells and tissues have been reported. This review covers the recent developments to date in the design of fluorogenic probes for the detection of carbon monoxide in living cells including our own contribution in the area. The review deals mainly with the fluorescence behaviour as sensing response and within each section, structural features, the response observed and details of the sensing mechanism used by the probe are highlighted.

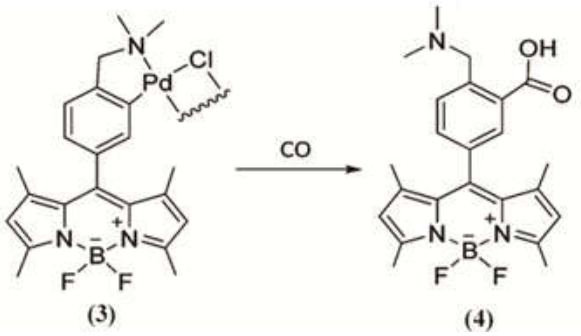
Fluorogenic Probes

He and co-workers[22] were the first to describe a genetically encoded fluorescent protein (probe) (**1**) that is capable of selectively imaging CO in living cells. Although the probe is very complex in nature, the sensing mechanism is comparatively simple and is based on the affinity of iron(II) centre of the haem cofactor situated in the binding domain towards CO (Scheme 1). The quaternary structure of this type of protein normally involves two major domains (the haem effector-binding domain and a DNA-binding domain). Here a genetically encoded system, as a new domain (yellow fluorescent protein), is introduced to make the fluorogenic response towards CO. Upon reaction of CO with the haem–iron(II) system, it forms the new entity **2** and simultaneously the encoded protein undergoes a conformational change that exposes the yellow fluorescent protein. This phenomenon results a 2-fold fluorescence enhancement at 528 nm. This new probe fulfils the urgent need for monitoring CO production and signalling in biological systems.



Scheme 1 Changes in the long C helix of CooA (a dimeric CO-sensing haem protein from *Rhodospirillum rubrum*) after CO binding (probe 1).

After this contribution, Chang and co-workers[23] reported a palladium based BODIPY complex (**3**) for Co detection in biological system. The CO-sensing mechanism was based on a selective palladium-mediated carbonylation reaction under mild conditions (**Scheme 2**). The presence of palladium (in case of **3**) would quench the fluorescence of the BODIPY moiety via heavy atom quenching effects and that upon binding of CO, a carbonylation reaction would concomitantly release reduced Pd(0) and a more fluorescent species **4**. The fluorescence properties and reactivity towards CO of **3** were examined in aqueous buffered of physiological pH. The addition of 50 μM of [RuCl(glycinate)$(CO)_2$] (an easily handled CO source, CORM-3) resulted in a 10-fold increase in fluorescence within 60 min of reaction. The detection limit was reported as low as 1 μM (~28 ppb CO). 3 shows a robust turn-on fluorescence response to CO that is selective over a variety of reactive nitrogen, oxygen, and sulfur species and can be used to image CO in living cells. Upon incubation of HEK293T cells with CORM-3 and treated with 3, a significant and also dose-dependent increase in the intracellular fluorescence was recorded (Figure 1).



Scheme 2 Reaction of palladium complex **3** with CO in physiological pH

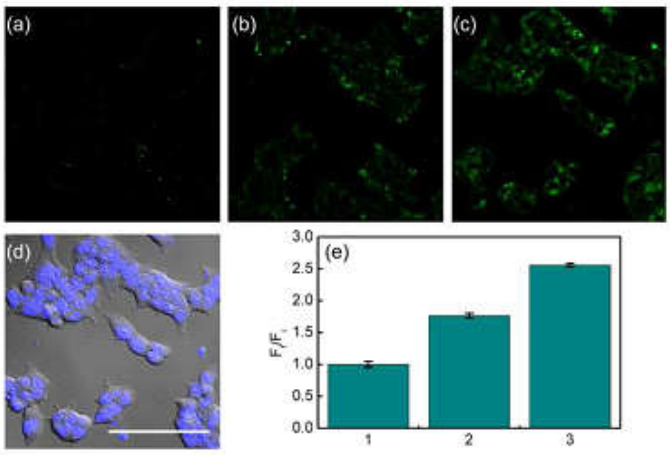
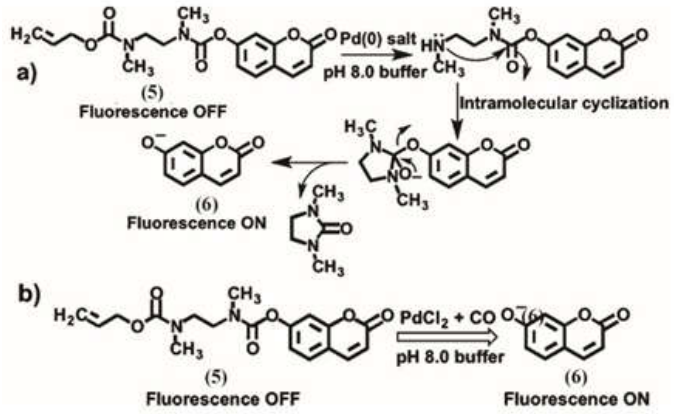


Figure 1 Confocal images (microscopy) of CO detection in live HEK293T cells using **3**. (a) HEK293T cells incubated with **3** for 30 min at 37 °C. (b) HEK293T cells incubated with 5 μM CORM-3 for 45 min at 37 °C and 1 μM **3** for the final 30 min. (c) HEK293T cells incubated with 50 μM CORM-3 for 45 min at 37 °C and 1 μM **3** for the final 30 min. (d) Bright-field image of the cells in (c) overlaid with images of 1 μM Hoescht 33342-stained cells. The scale bar represents 100 μM. (e) Mean fluorescence intensities of representative images with (1) 1 μM **3**, (2) 1 μM **3** and 5 μM CORM-3, and (3) 1 μM **3** and 50 μM CORM-3.

Although these fluorescent probes (**1** and **3**) display the detection of CO in living systems, performance should be improved in terms of response time, signal-to-noise etc. Keeping this in mind, work in our own laboratories has produced a fluorogenic probe **5** to investigate the selective detection of CO in aqueous media.[24] The probe **5** was designed based on coumarin moiety which undergoes intramolecular cyclisation and elimination reactions in the presence of palladium(0) species (**Scheme 3**). The fluorescence behaviour of the probe **5** is initially quenched due to the introduction of the carbamate bond. However, when probe **5** was incubated with palladium(II) species (e.g. $PdCl_2$, $Pd(OAc)_2$, Na_2PdCl_4)

and CO as a reducing agent in aqueous buffer, the highly fluorescent 7-hydroxycoumarin (**6**) was generated through the intramolecular cyclisation and elimination reactions, resulting in a strong emission at 460 nm. The probe **5** triggered a 'turn-on' fluorescence response to CO with a concomitant increase of fluorescence intensity by 150 times. The response is selective over a variety of relevant reactive nitrogen, sulfur and oxygen species. Here we have used CORM-3 as source of CO in aqueous buffer medium. The highest fluorescence response was found at pH 8 when the 7-hydroxycoumarin is deprotonated since the p*Ka* of that species is ~7.8. To visualize CO levels in live cells we examined a fluorescence microscopy experiment with probe **5** (**Figure 2**). A549 human lung carcinoma cells were incubated with 10 μM **5** and CORM-3 (10, 20 and 50 μM) in the presence of 10 μM $PdCl_2$ at 37 ^{0}C. In addition to that, 10 μM of **5** did not show any significant cytotoxic effect on A549 human lung carcinoma cells for at least up to 4 h of its incubation. Although there was significant cytotoxicity for higher doses after 4 h onward. These results indicated that the fluorogenic probe, **5**, is an efficient candidate for monitoring changes in intracellular CO.



Scheme 3 (a) Proposed mechanistic routes of probe **5** for the detection of Pd(0) through intramolecular cyclization–elimination reaction. (b) Proposed sensing mechanism of CO by the in situ generation of Pd(0).

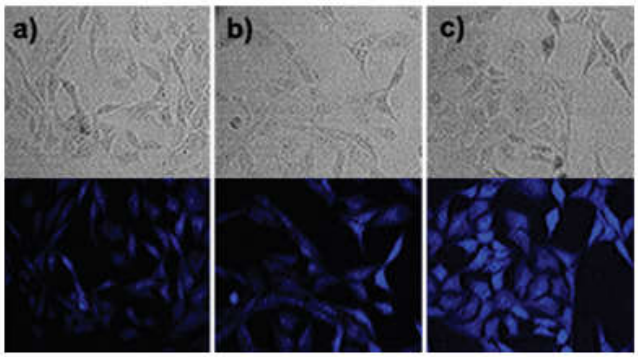
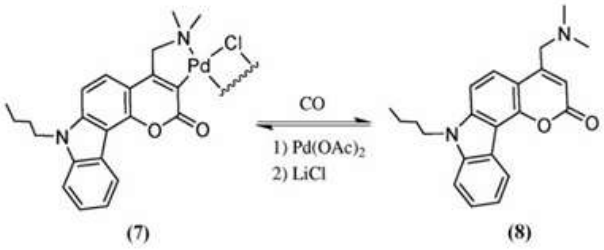


Figure 2 Fluorescence microscopy images of A549 cells for CO detection using the probe **5** (10 μM) in the presence of 10 μM $PdCl_2$ with the incubation of (a) 10 μM, (b) 20 μM and (c) 50 μM of CORM-3 in the reaction buffer at 37 ^{0}C (ex: ~340 nm). The first and second rows represent the phase contrast and fluorescence images respectively.

Inspired by the revolutionary work of Chang, a carbazole–coumarin-fused cyclometallated palladium complex (**7**) has been reported for imaging carbon monoxide in living tissues (**Scheme 4**). Lin group developed a unique family of carbazole–coumarin (CC) derivatives by fusing carbazole with coumarin, which displayed favourable two-photon properties due to a push–pull character i.e. carbazole electron-donor group as well as a carbonyl electron-acceptor group.[25] Upon the treatment of CO the probe produce highly fluorescent metal free CC derivative (**8**) due to have two-photon fluorescence property. The functionalisation of the coumarin derivative at the 4'-position allows the facile (re)generation of the cyclometallated palladium probe **7** from **8**. A solution of the probe **7** in PBS buffer and DMSO (9 : 1 v/v) at pH 7.4 at 37 ^{0}C displays a very weak one-photon fluorescence (□ = 0.07) and a negligible two-photon emission due to the heavy atom effect of the palladium. However, after the addition of $[Ru_2Cl_4(CO)_6]$ (CORM-2), a remarkable emission is detected due to production of **8**. The compound 8 showed strongly fluorescence having a one-photon fluorescence spectrum at 477 nm (□ = 0.51) and a high two-photon cross section at 740 nm. Further studies at different pH values indicated that the probe is sufficiently stable with a maximum fluorescence response in the pH range of 7.0–9.0. The detection limit was reported as low as 0.653 μM which proves the high sensitivity towards CO. The authors demonstrated that other biologically relevant species such as anions, reactive oxygen, nitrogen and sulfur species induced no emission changes indicating that the probe is highly selective towards CO. Further, the incubation of the probe **7** in the presence of CORM-2 with HeLa, MCF-7 and MKN-28 cells was performed and found a strong fluorescence response toward CO (**Figure 3**). Also, probe **7** was effective to detect CO in living tissue slices of liver incubated with CORM-2 when subjected to two-photon fluorescence microscopic analysis.



Scheme 4 Synthesis of the palladium complex **7** and its reaction with CO.

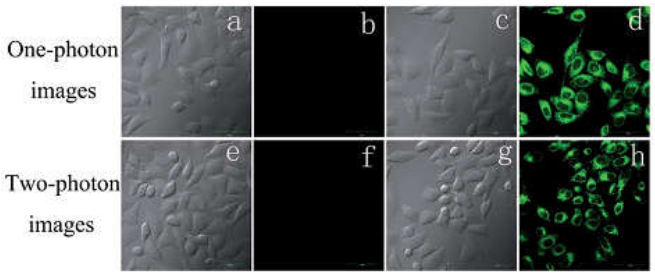


Figure 3 One-photon fluorescent images: (a) bright-field image of live HeLa cells incubated with only **7** (5.0 μM) for 30 min; (b) fluorescence image of (a); (c) Bright-field image of live HeLa cells incubated with CORM-2 (200 μM) for 30 min, then with **7** (5.0 μM) for 40 min; (d) fluorescence image of (c). Excitation at 405 nm. Two photon fluorescent images: (e) bright-field image of live HeLa cells incubated with only **7** (5.0 μM) for 30 min, (f) fluorescence image of (e); (g) bright-field image of live HeLa cells incubated with CORM-2 (200 μM) for 30 min, then treated with **7** (5.0 μM) for 40 min; (h) fluorescence image of (g). Excitation at 740 nm. Scale bar = 50 μm.

Feng and co-workers reported a readily available fluorescein-based fluorogenic probe for rapid detection of CO.[26] This structure of the probe **9** system uses an allyl chloroformate functionalized fluorescein as the CO signaling moiety and $PdCl_2$ as an additive to trap CO (**Scheme 5**). The author choose the fluorescein as a signaling unit because it is a well-known fluorophore with excellent photophysical properties such as high absorption coefficient, high fluorescence quantum yield (Φ = 0.92, 0.1 M NaOH), high photostability, good water solubility etc. The strategy of this probe system based on the in situ generation of Pd^{2+} to Pd^0 by CO. This reaction undergoes the elimination of the allyl group and the main structure of the highly fluorescent fluorescein molecule was generated. The probe **9** showed that this probe system has the following properties: (1) it is readily available and can be used in almost wholly water solution; (2) it exhibits near-zero background fluorescence, but shows a rapid, colorimetric and remarkable fluorescent turn-on response for CO, which allows a convenient visual and sensitive fluorescent detection for CO. The probe also shows high selectivity and sensitivity for CO with a detection limit as low as 37 μM. It was used to image both exogenous and heme stimulation produced CO in living cells using a very low dose of the probe **9** (1 μM dose) (**Figure 4a,b**). It is important to note that this study was the first time of showing a fluorescent probe capable of imaging heme stimulation produced CO in living cells.

Scheme 5 Detection of CO by a mixture of the probe **9** and $PdCl_2$.

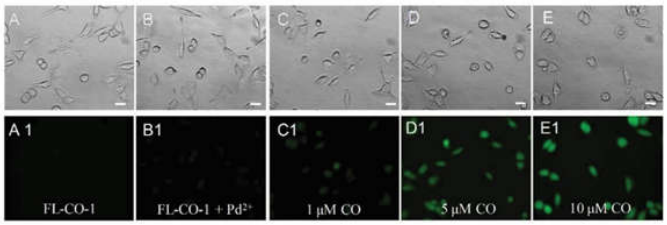


Figure 4a. Fluorescent imaging of CO in A549 cells by the probe **9** and $PdCl_2$ (1 μM each). Top row A-E: bright field images. Bottom row A1-E1: fluorescent images of A-E, respectively, with excitation wavelength at 450-480 nm. A and A1: The cells were incubated with **9** (1 μM) for 30 min. B and B1: The cells were incubated with the probe system (**9** + $PdCl_2$, 1 μM each) for 30 min. C and C1, D and D1, and E and E1: cells were pre-incubated with 1, 5 and 10 μM of CORM-3 for 30 min, then with the probe system for 30 min, respectively. Scale bar = 20 μm.

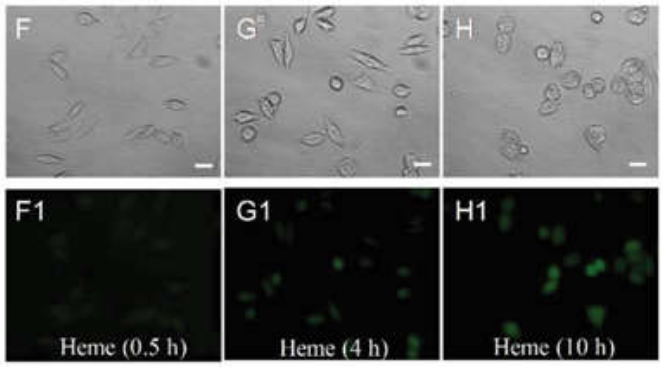
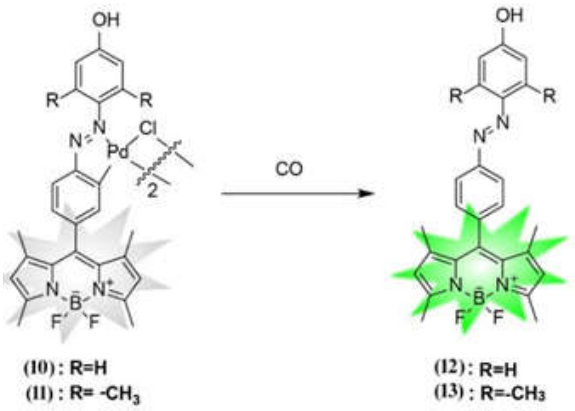


Figure 4b. Fluorescent imaging of CO produced via heme stimulation in A549 cells using the probe system (**9** + $PdCl_2$). Top row F-H and bottom row F1-H1 are bright field images and the corresponding fluorescent images, respectively, with excitation wavelength at 450-480 nm. The cells were pre-incubated with 100 μM of heme for 0.5 h (F and F1), 4 h (G and G1) and 10 h (H and H1), then with the probe system (**9** + $PdCl_2$, 1 μM each) for 30 min, respectively. Scale bar = 20 μm.

Again inspired by the revolutionary work of Chang, Tang and co-workers developed two new organic fluorescent probes, **10** and **11,** which are specific for CO detection.[27] The probes were designed by combining a unique CO recognition group, azobenzene-cyclopalladium, and boron-dipyrromethene (BODIPY) fluorophore. In the absence of CO, **10** and **11** manifested relatively low fluorescence because of the heavy atom quenching effect of Pd(II). In the presence of CO, Pd(II) was released based on the catalytical reaction between CO and azobenzene-cyclopalladium. And thus the heavy atom quenching effect was eliminated resulting in fluorescence enhancement (**Scheme 6**) and the corresponding compound **12** and **13** were formed. Among the two probes, **11** showed much improved sensitivity towards CO and was selected to fluorescently monitor endogenous CO detection in HepG2 cells (**Figure 5**).



Scheme 6.The chemical structure of **10** and **11** and their detection mechanism towards CO.

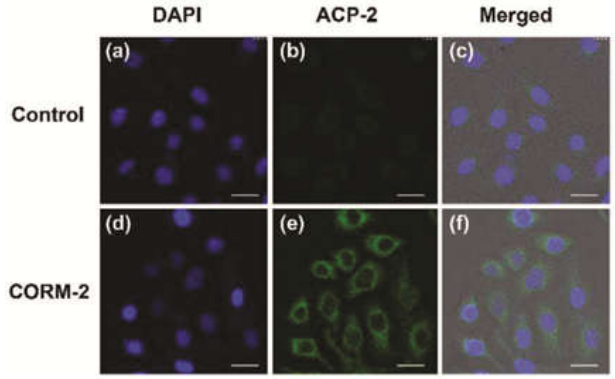
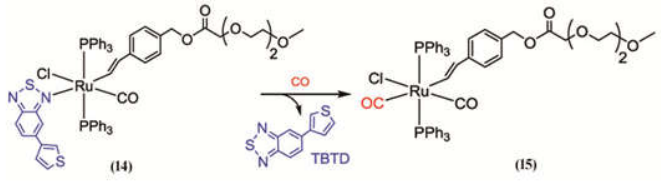


Figure 5 Confocal fluorescence microscopic imaging of CO in HepG2 cells. (a-c) HepG2 cells co-incubated with **11** (10 μM) and DAPI (10 μg/mL) for 15 min. (d-f) HepG2 cells were incubated with CORM-2 (100 μM) for 30 min, then treated with **11** and DAPI for 15 min. DAPI was imaged in blue channel with λ_{ex}=405 nm and emission collection in 430-480 nm. The probe **11** was imaged in green channel with λ_{ex}=488 nm and emission collection in 500-550 nm. Scar bar=25 μm.

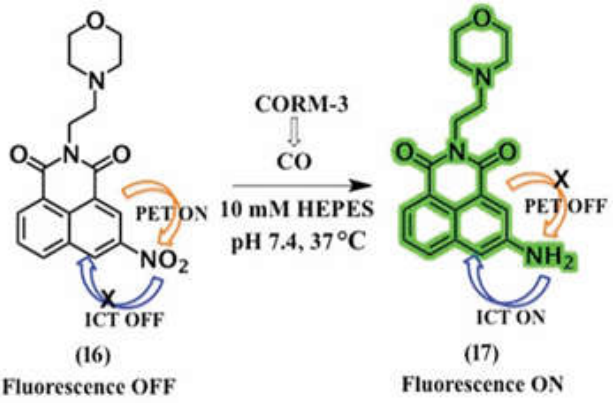
Recently Martínez-Máñez and co-workers reported a interesting and novel molecular probe **14** for the two-photon

fluorogenic detection of CO in biological environments.[28] The probe **14** was designed based on the 5-(3-thienyl)-2,1,3-benzothiadiazole (TBTD), as a signaling unit, which is coordinated directly to the metal center. The design strategy was employed to introduce hydrophilic groups to the vinyl substituent for the betterment of water solubility of the probe. The fluorogenic behavior of probe **14** in aqueous medium was investigated in the absence and in the presence of CO. The weak nature of this emission of **14**, centered at 500 nm was ascribed to quenching of the TBTD fluorescence by the Ru(II) center due to heavy atom effect (upon excitation at 355 nm). The probe **14** induced a progressive enhancement of the emission at 500 nm after the passing of CO gas into the aqueous solution (**Scheme 7**). The observed emission enhancement was attributed to the dissociation of TBTD from the complex upon CO binding. The replacement of the labile TBTD ligand by CO was found to disrupt the quenching behaviour of the Ru(II) center and accounted for the emission enhancement observed. The product **15** was formed as the final product for the reaction of **14** and CO. Further, the imaging of CO in living cells was investigated using probe **14**. The mouse macrophage RAW 264.7 cell line was selected as it can induce HO-1 and generate CO under different physiological conditions RAW 264.7 cells were incubated with probe **14** (10 μM) for 30 min, leading to no significant emission. However, when the cells were pre-incubated with the CO source, CORM-3, and then treated with **14** (10 μM), a dose- dependent intracellular two-photon fluorescence response was clearly observed.



Scheme 7 The reaction of the probe **14** with CO to produce the compound **15**.

Very recently, our group has produced a simple and small fluorogenic probe **16** for the detection of CO in a lysosome-targetable manner.[29] To the best of our knowledge, to date, there has been no report on any targetable fluorogenic probe that can selectively detect lysosomal CO in living cells. It is important to note that this probe **16** work with CO without the help of any costly heavy metals e.g. Pd, Rh etc. We have designed and developed a simple and effective lysosome-targetable fluorogenic probe, **16**, with 3-nitro naphthalimide as a fluorophore moiety, where the nitro group behaves as a CO responsive unit, and the tagged morpholine fragment behaves as the lysosome-targetable entity. The probe **16** displayed very weak fluorescence emission in aqueous buffer at pH 7.4. This nonemissive (Φ_F = 0.0016) nature is due to the photoinduced electron transfer (PET) process from the naphthalimide fluorophore to the nitro group. After the probe was treated with 100 μM CORM-3, the intensity enhanced with the progress of time and finally achieved its highest value with a quantum yield, Φ_F = 0.1025, after incubation for 45 min at 37 °C in reaction buffer. The mechanistic behaviour of probe **16** was described in **Scheme 8**. The enhanced fluorescence can be achieved by the transformation of the 3-nitro moiety of the probe into a possible highly fluorescent amino-functionalized 1,8-naphthalimide moiety (**compound 17**), whereas the analyte, CO, can be oxidized into carbon dioxide. The probe is also efficient in detecting lysosomal CO in living cells. The cells were coincubated with the probe **16** along with the addition of 100 μM CORM-3 and LysoTracker Blue (50 nM). As shown in **Figure 6**, the fluorescence patterns in the green channel of the probe **16** signal manifested and specifically localized in lysosomes due to the sensing of CO. Moreover, the blue fluorescence signal in the blue channel due to the staining of the lysosomes by LysoTracker Blue was obtained (**Figure 6c**). The merged image signified that the green fluorescence overlaps very well with the blue fluorescence (**Figure 6d**). These results demonstrate that the newly designed probe **16** could display a brilliant lysosome-targetable property and detect CO in the lysosomes. In addition to that, 10 μM of **16** did not display any significant cytotoxic effect on the HEPG2 human liver cancer cell line for at least up to 5 h of its treatment. It represents a unique chemical tool that features a selective "turnon" response to CO over reactive, nitrogen, oxygen, and sulfur species, and thus, it can be applied to detect this gasotransmitter molecule in an aqueous buffer medium.



Scheme 8 Possible mechanistic route of the probe **16** for CO detection through the transformation of nitro group into the amino-functionalized molecule (**17**).

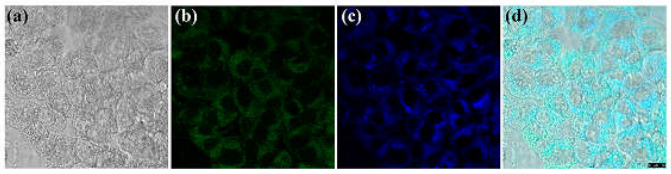


Figure 6 Images of the living MCF7 cells coincubated with the probe 10 μM **16**, 100 μM CORM-3, and LysoTracker Blue (50 nM). (a) Bright-field image of the MCF7 cells treated with **16** (10 μM) and LysoTracker Blue; (b) fluorescence image of the green channel due to the probe sensing CO; (c) fluorescence image of the blue channel due to the known LysoTracker Blue; and (d) the merged image of a, b, and c. Scale bar: 10 μm.

CONCLUSIONS

The approaches discussed above in this review provide examples of the designing aspects of recently reported fluorogenic probes for CO detection in in living cells. Most of the reported probes are based on metal complexes (e.g. palladium) or the addition of Pd^{2+} metal ion that act as suitable centres for CO coordination. In this cases, palladium metal ion was used to quench the fluorescence of the fluorogenic systems. Then the sensing response can arise from the displacement of palladium ion in the respective fluorogenic systems by CO through the reduction process of Pd^{2+} to Pd^0. Only one example that was reported by our group, was based on the simple organic transformation of fluorophore -NO_2 group to the respective -NH_2 group upon reaction with CO.

This work introduced a new approach for CO detection by a fluorescence method in aqueous buffer medium in a targetable way (here lysosome). The responses of above fluorogenic probes were selective over a variety of relevant reactive nitrogen, oxygen, and sulfur species. Also, the probes were able to monitor the changes in intracellular CO by fluorescence microscopy. Recently reported probe, by our group, was capable to detect CO in living cells in such a way that the fluorescence signals specifically localize in lysosomes compartment. The biological detection of carbon monoxide is still urgently needs probes with an improved fluorescence response over a shorter timeframe in order to monitor the role of endogenous CO in cells and tissues. This will help to understand the fascinating role of carbon monoxide in further.

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