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A Structurally-Tunable 3-Hydroxyflavone Motif for Visible Light-Induced Carbon Monoxide-Releasing Molecules (CORMs)**

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Molecules that can be used to deliver a controlled amount of carbon monoxide (CO) have the potential to facilitate investigations into the roles of this gaseous molecule in biology and advance therapeutic treatments. This has led to the development of light-induced CO-releasing molecules (photoCORMs). A goal in this field of research is the development of molecules that exhibit a combination of controlled CO release, favorable biological properties (e.g., low toxicity and trackability in cells), and structural tunability to affect CO release. Herein, we report a new biologically-inspired organic photoCORM motif that exhibits several features that are desirable in a next-generation photoCORM. We show that 3-hydroxyflavone-based compounds are easily synthesized and modified to impart changes in absorption features and quantum yield for CO release, exhibit low toxicity, are trackable in cells, and can exhibit both O_2-dependent and -independent CO release reactivity.

Carbon monoxide (CO)-releasing molecules (CORMs) are of significant current interest due to the potential of CO as a therapeutic molecule.[1] The vast majority of CORMs developed to date are based on a metal carbonyl unit as the CO-releasing moiety.[2] Many molecules of this type, including protein-bound derivatives of [RuCl(glycinato)$(CO)_3$] (CORM-3) and analogues, release CO spontaneously through ligand exchange in an aqueous environment.[3]

The lack of temporal control of CO release in such systems has led to the use of metal carbonyl complexes that release CO only when triggered.[4,5] Examples of such complexes include photoCORMs, which release CO from a metal carbonyl unit upon illumination with UV or visible light.[4] Recent advances in the field of metal carbonyl photoCORMs demonstrate that CO release can be tuned to occur upon illumination with low-energy red or near infrared (NIR) light through modification of supporting ligands or through approaches using nanoparticles.[4] However, a concern associated with some metal-carbonyl-based photoCORMs are side effects related to the metal-containing photoproducts.[6] A limited number of organic photoCORMs (**1**–**3**, Figure 1) have also been recently reported.[7] However, these molecules also have limitations. For example, **1** and **2** are derived from relatively low-yield, multistep synthetic routes that have not been shown to be amenable to structural modification for the tuning of physical properties or biological targeting. Diels–Alder product **3** can be generated in good yield and subsequently undergoes CO release. However, this compound cannot be isolated and stored.

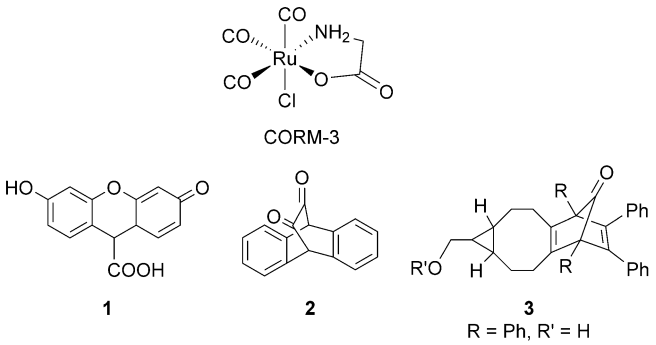

Figure 1. Structural motifs of selected previously reported CORMs

Desirable features in a next-generation organic photoCORM motif include: 1) a high-yield synthesis that enables the preparation of gram quantities of analytically pure compound; 2) solubility in water or aqueous dimethyl sulfoxide (DMSO); 3) thermal stability in aerobic, aqueous environments; 4) controllable, triggered CO release, preferably using light at wavelengths that do not have the potential to impart cellular damage; 5) low toxicity of the photoCORM and its post-CO-release byproducts; 6) ease of structural modification to modulate aqueous solubility, photochemical properties (e.g., light absorption properties), and biocompatibility; and 7) exhibits fluorescence so as to enable tracking of the localization and CO-release reactivity of the molecule within cells.[8] In the results reported herein, we describe a new class of biologically inspired photoCORMs that exhibit all of the desirable features noted above.

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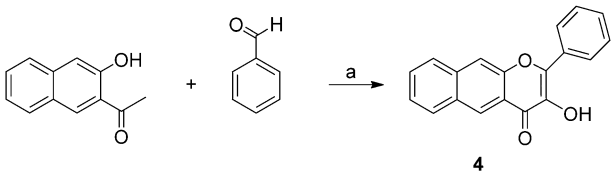
The parent structure contains a 3-hydroxyflavone (3-HflH) motif, which is found in naturally occurring molecules that are already known to exhibit several types of biological activity, including antioxidant, anti-inflammatory, and anticancer activity, as well as protection against cardiovascular disease.[9] The new flavones reported herein all exhibit visible-light-induced CO-release in O_2-containing environments, with one derivative also exhibiting O_2-independent CO-release reactivity.

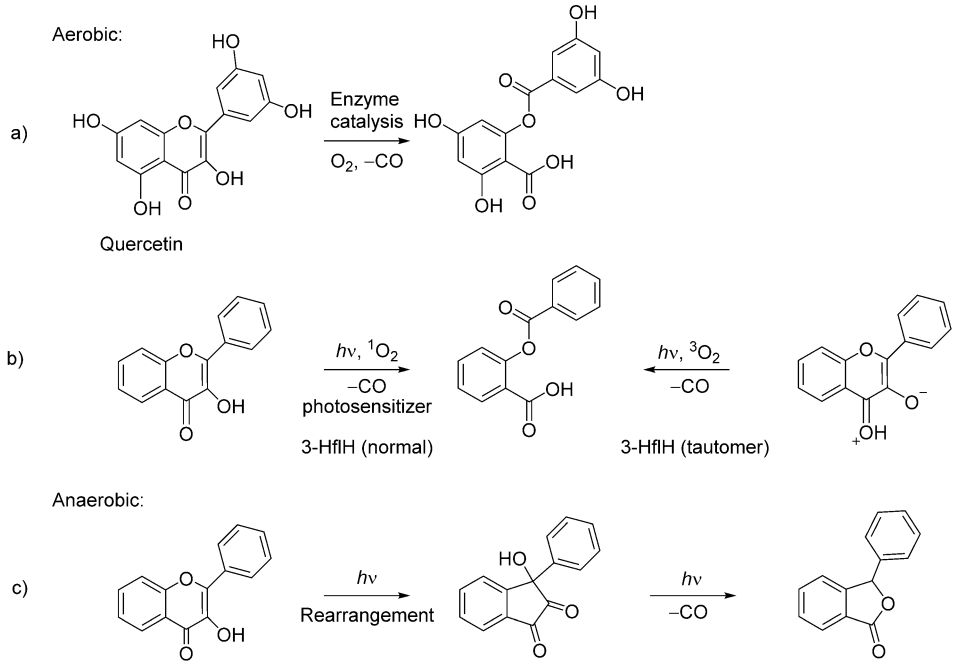
Naturally occurring 3-HflH derivatives, such as quercetin (Scheme 1 a), are known to undergo O_2-dependent, enzyme-catalyzed degradation to produce CO in bacteria and fungi.[10] In the absence of enzyme, quercetin is known to undergo various types of oxidative reactions, including UV-light-induced reactions, which can result in CO release.[11] It is known that unsubstituted 3-HflH will undergo incorporation of both atoms of O_2 and expulsion of CO in the presence of a photosensitizer, or via direct illumination using UV light (Scheme 1 b).[12] These reactions are proposed to proceed from the normal and tautomeric excited-state forms of 3-HlfH, respectively. We have re-examined the photoinduced ($\lambda = 300$ nm) reactivity of 3-HflH under O_2 and found that while a near-quantitative amount of CO is generated (0.95 equiv), multiple organic products are detected by gas chromatography–mass spectrometry (GC–MS). Finally, 3-HflH is also known to undergo UV-light-induced rearrangement resulting in CO release under anaerobic conditions (Scheme 1 C).[13] These combined results indicate that 3-HflH derivatives have multiple reaction pathways by which light-induced CO release can occur.

We hypothesized that the 3-HflH structural motif could be tuned to undergo visible-light-induced CO release. With this strategy in mind, **4** was designed and prepared using Alger–Flynn–Oyamada methodology (Scheme 2).[14] X-ray-quality crystals of **4** were obtained via slow evaporation of a dichloromethane solution. Compound **4** was additionally characterized by elemental analysis, spectroscopic methods, and mass spectrometry (see Figures S1–S5 in the Supporting Information). Compound **4** is readily soluble in organic solvents and is also soluble in aqueous DMSO at concentrations suitable for spectroscopic measurements (H_2O/DMSO, 1:1) and biological experiments (1% DMSO). Compound **4** crystallizes in the monoclinic space group *C*2/*c*.[15] A representation of the molecular structure of **4** is shown in Figure 2. In the solid state, the 3-hydroxy-4-pyrone units from two molecules form centrosymmetric hydrogen-bonded dimers with two identical intermolecular O–H···O hydrogen bonds (O···O: 2.69 Å and 145.3°).[16] The naphthyl-fused 3-hydroxy-4-pyrone ring structure is nearly planar, and the phenyl appendage twists only slightly out of this plane. This overall structure favors conjugation of the two electronic systems. Compound **4** has bond lengths and angles very similar to those of 3-HflH.[16]

The extended conjugation in **4** produces a red-shift of the absorption features relative to those found for 3-HflH in aceto-



Scheme 2. Synthetic route for the preparation of **4**. *Reagents and conditions*: a) 1. 5 M aq. NaOH (4 equiv), EtOH, 5.5 h, RT; 2. H_2O_2, 0 °C→RT, o/n; 3. 0.5 M aq HCl (to pH 6), 62% yield. Complete experimental protocols and characterization data are given in the Supporting Information.



Scheme 1. O_2-dependent CO-release reactivity of a) quercetin and b) 3-hydroxyflavone (3-HflH); C) O_2-independent, UV-light-induced isomerization of 3-HflH.

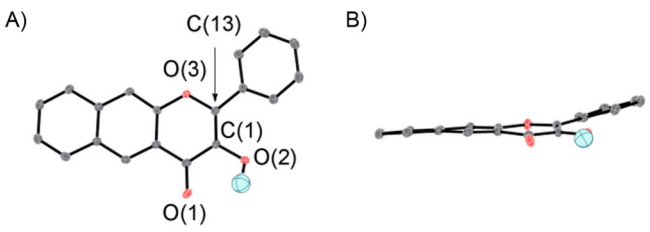
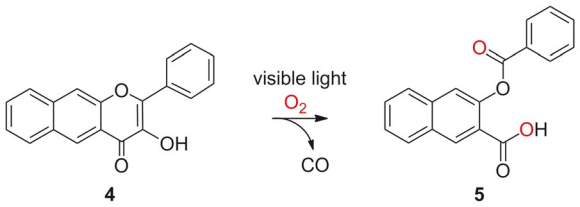


Figure 2. A) Representation of the molecular structure of **4** as determined by X-ray crystallography; B) side-on structural view.

nitrile (Figure S3 in the Supporting Information).[13] The lowest energy band for **4** is found in the visible region with maximum intensity at 409 nm ($\varepsilon = 16{,}600\ M^{-1}\,cm^{-1}$) in acetonitrile, whereas there is no absorption feature above 400 nm for 3-HflH. In 1:1 aqueous DMSO, compound **4** exhibits similar absorption features but with overall lower intensity (Figure S3 in the Supporting Information). Excitation into any of the absorption features exhibited by **4** in acetonitrile produces a single broad emission feature centered at 582 nm (Figure S4 in the Supporting Information). Based on literature precedent for 3-HflH, the large Stokes shift ($\geq$177 nm) suggests the formation of an excited state tautomeric form wherein intramolecular proton transfer has occurred to give a zwitterionic species.[17] When dissolved in 1:1 aqueous DMSO and excited in the lowest energy absorption band, compound **4** exhibits two emission bands: 475 and 582 nm (Figure S5 in the Supporting Information). The former is of relatively low intensity and likely represents emission from an excited state normal form of the molecule, whereas the latter matches the emission feature produced in organic solvent.[17]

Solutions of **4** in acetonitrile, 1:1 aqueous DMSO, or cell culture media (RPMI-1640; pH 7.4) are stable in the presence of ambient O_2 for $>$2 weeks when protected from light. Exposure of an aerobic acetonitrile solution of **4** to visible light (419 nm) results in quantitative CO release (0.96(2) equiv) as determined by GC headspace analysis and the formation of 3-(benzoyloxy)-2-naphthoic acid (**5**, Scheme 3; see also Figures S6–S8 in the Supporting Information). This organic product is pale yellow in color and does not exhibit any emission features in the visible region (Figure S9 in the Supporting Information). The quantum yield for the CO-release reaction of **4** is 0.007(3). The same reaction occurs in methanol (Figure S10 in the Supporting Information) and 1:1 aqueous DMSO as determined by ^{1}H NMR and GC head space gas analysis. Control reactions indicate that both O_2 and visible light are needed for the CO release reaction of **4**. An $^{18}O_2$-labeling experiment demonstrates that both oxygen atoms from O_2 are incorporated into the organic photoproduct.



Scheme 3. Photoinduced CO-release reactivity of **4**.

Compound **4** exhibits several features that suggest that it could be a useful CO-release agent in biological systems. First, it exhibits minimal toxicity, as determined by MTT cell viability assays using A549 cells ($IC_{50} = 41.5\ \mu M$; Figure S11 in the Supporting Information), and the organic product remaining following CO-release is nontoxic. Importantly, the fluorescent nature of **4** makes it trackable in cells prior to CO release. The cellular uptake properties of **4** were evaluated in A549 cells, which were exposed to Hoechst stain for 10 min (to enable visualization of nuclei), followed by incubation with **4** for 1 h in the dark. Fluorescence microscopy images of the cells were collected after 30 s, 3 min, and 10 min of visible light exposure (Figure 3; see also Figure S12 in the Supporting Information).[18]

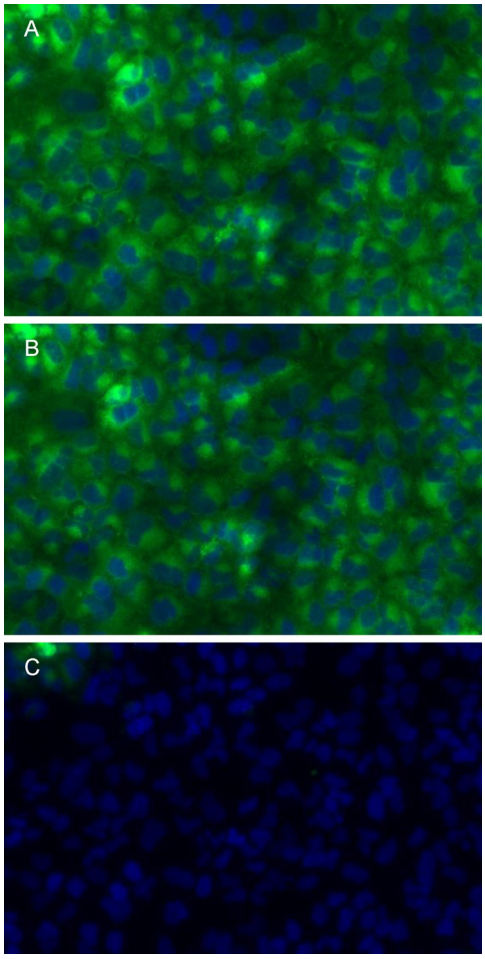
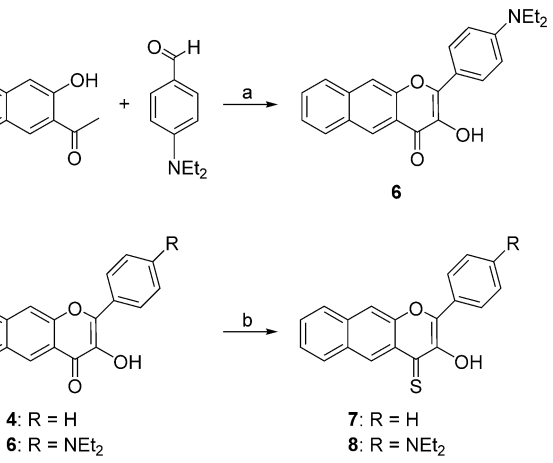


Figure 3. Fluorescence microscopy images of human lung cancer (A549) cells treated with **4** for 1 h, then exposed to visible light (X-Cite 120 LED light source (Lumen Dynamics) with a 120 W lamp used at 18% power ($\sim 4\times10^{16}$ photons s^{-1}) and a 38HE filter) for a) 30 s, b) 3 min, and c) 10 min.[18] Pictures represent overlay images for fluorescence detection of **4** (green) and the nuclear Hoechst stain (blue). Loss of fluorescence with increasing length of exposure to visible light is consistent with photoinduced CO release from **4**. See Figure S12 in the Supporting Information for separate images of each detection channel and the complete field of view observed.

The observed green emission at the first two time points provides evidence that **4** is taken up by almost all cells. The compound is not associated with the plasma membrane but is distributed throughout the cytoplasm and appears to concentrate around the nucleus. Importantly, continued exposure of the cells to visible light results in a decrease in the observed green fluorescence of the compound after 3 min, with complete loss after 10 min. This observation provides strong evidence for the photoinduced cleavage of the 3-hydroxy-4-pyrone ring and

CO-release reactivity within the cell as the photoproduct does not display any emission. It should be noted that use of the intracellular CO Probe 1 (COP-1) is not feasible in this system because the emission of **4**, which disappears upon CO release, overlaps with the emission feature of CO-incorporated COP-1.[19]

A key feature of the structural motif of **4** that distinguishes it from all previously described organic photoCORMs is the ease with which structural modifications can be introduced to tune its physical properties. For example, a dialkylamino substituent can be incorporated on the phenyl ring or the carbonyl oxygen can be substituted with sulfur to red-shift absorption features toward the therapeutic window. Dialkylamino-substituted flavonols have been previously used as environment-sensitive probes in biological systems.[20] However, neutral flavonols of this type have *not* been previously shown to exhibit photoinduced CO-releasing reactivity. Flavothiones, have been reported to undergo O_2-dependent photodegradation to give nontoxic byproducts, but these reactions have *not* been fully explored in terms of product identification.[21] Molecules **6**–**8** were easily prepared using standard synthetic methods (Scheme 4) and were isolated in analytically pure forms via precipitation. Each compound was characterized by elemental analysis, UV-vis, fluorescence and IR spectroscopy, and mass spectrometry (Figures S13–S21 in the Supporting Information). These molecules exhibit red-shifted absorption features and higher molar absorptivity values than were observed for **4** (Figure 4). Quantitative CO release occurs when aerobic acetonitrile solutions of **6**–**8** are exposed to visible light (**6** and **7**: 419 nm; **8**: >546 nm; Table 1). For compounds **6** and **7**, O_2-incorporated organic products akin to that found in the reaction of **4** were identified by ^{1}H NMR and IR spectroscopy, and mass spectral analysis (Figures S22–S25 in the Supporting Information). The quantum yield associated with the reaction of **7** is significantly enhanced relative to that found for **4** (Table 1). The reaction involving **8** is noteworthy in that, while a full equivalent of CO is released under aerobic conditions, significant light-induced CO-release reactivity (0.32(7) equiv) also occurs under anaerobic conditions. Both the aerobic and anaerobic pathways for CO release from **8** result in the production of a mixture of products, including some that appear to result from photoisomerization reactivity (Figures S26–S27 in the Supporting Information). Photoinduced CO-release also occurs when **6**–**8** are dissolved in other solvents, including DMSO and 1:1 aqueous DMSO.



Scheme 4. Synthetic procedures for **6**–**8**. *Reagents and conditions*: a) 1.5 M aq. NaOH (4 equiv), EtOH, 24.5 h, RT; 2. H_2O_2, 0 °C→RT, overnight; 3. 0.5 M aq HCl (to pH 6), 42% yield; b) Lawesson's reagent, toluene, reflux, 4 h, 61% (**7**) and 60% (**8**) yield. Complete experimental protocols and characterization data are given in the Supporting Information.

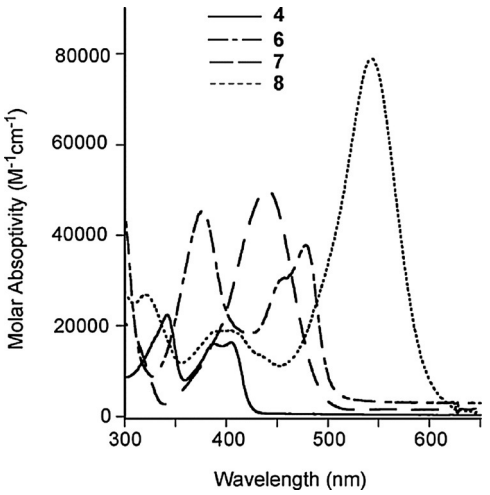


Figure 4. Absorption spectra of **4** and **6**–**8** in acetonitrile.

Table 1. Carbon monoxide quantification (equiv CO released) and quantum yields (Φ) for the reactions of **4** and **6**–**8** in acetonitrile with O_2 upon illumination with visible light.

Compd	equiv CO[c]	Φ[c]
4[a]	0.96(2)	0.007(3)
6[a]	0.99(1)	0.006(1)
7[a]	1.00(1)	0.426(3)
8[b]	1.00(1)	_[d]
8[b]	0.32(7)[e]	_[d]

[a] Measured using 419 nm light. [b] Measured using >546 nm light. [c] Reported values are the average of three independent trials; values in parentheses represent standard errors. [d] Not reported due to mixture of products. [e] Reaction performed under anaerobic conditions.

The use of a 3-HflH-based structural motif offers many advantages in terms of photoCORM design. Compounds of this type can be prepared and isolated in analytically pure form using simple organic chemistry. Compounds **4** and **6**–**8** are soluble in organic solvents as well as aqueous DMSO. Solutions of these compounds are stable with respect to O_2 for weeks when protected from light. CO release is triggered under aerobic conditions by the introduction of visible light, the wavelength of which can be tuned through structural modification of the molecule. A representative example of this family of compounds (**4**) exhibits minimal toxicity and its organic byproduct following CO release is nontoxic. The fluorescent nature of **4** and analogues makes these molecules trackable in

cells up to the point of CO release. The observed photoinduced reactivity of **6**–**8** demonstrates that structural modifications can be made without loss of CO-release reactivity, and that both aerobic and anaerobic CO-release reaction pathways can be accessed. Overall, this family of compounds thus meets the key criteria set forth for next-generation photoCORMs. Further evaluation of the applications of these novel molecules and analogues for CO-release in biological systems is in progress.

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Keywords: carbon monoxide · CORMs · flavonols · fluorescence · photochemistry · synthesis design

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[18] Light intensity for fluorescent microscope source with 38HE filter: 3.67×10^{16} photons s^{-1}. This is similar to the photon flux (1.58×10^{17} photos s^{-1}) delivered by the Rayonet photoreactor used in the CO-release studies of **4**. The absorption spectrum of the fluorescence microscope source under the conditions described above overlaps with the low-energy portion of the visible absorption band of **4**. Notably, a solution of **4** in 1:1 aqueous DMSO was found to undergo visible-light-induced CO-release reactivity upon illumination with the fluorescence microscope source under identical conditions.

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