Single-Pot Self-Assembly of Heteroleptic Mn(I)-Based Aminoquinonato-Bridged Ester/Amide-Functionalized Dinuclear Metallastirrups: Potential Anticancer and Visible-Light-Triggered CORMs

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Supporting Information

ABSTRACT: Multicomponent self-assembly of Mn₂(CO)₁₀, a bis-chelating aminoquinonato (ON\(\text{ON}\)) bridge (L), and an ester/amide-functionalized flexible neutral ditopic linker (L') has resulted into the formation of Mn₂LL'-type manganese(I)-based dinuclear metallastirrups of general formula \([\{(CO)₃Mn(μ-η²-L)Mn(CO)₃\}μ-L']\) (1–10). Compounds 1–10 were accomplished via orthogonal bonding of the aminoquinone ligand (2,5-bis(n-butylamino)-1,4-benzoquinone/2,5-bis(phenethylamino)-1,4-benzoquinone) and ditopic pyridyl ligand to manganese carbonyl. The resultant metallastirrups were characterized using elemental analyses and IR, UV–vis, \(^1\)H NMR, and electrospray ionization-mass spectroscopic techniques. The molecular structure of 6 was confirmed by single-crystal X-ray diffraction methods. Furthermore, molecular recognition capabilities of 1, 5, 7, and 9 were evaluated with aromatic compounds containing hydroxy/amine functionalities. Anticancer activities of compounds 1–3, 5–7, 9, and 10 were investigated against three cancer cell lines, that is, lung (A549), colon (HCT-15), and cervical (HeLa) as well as on normal cells (HEK 293). Compound 9 showed a broad-spectrum inhibition toward these cancer cells upon exposure to visible light. The myoglobin assay was performed using UV–vis absorption spectroscopy to investigate the visible-light-triggered CO release from 5 and 9 that could be related to their ability to effectively inhibit cancer cells. In addition, morphological studies confirmed the induction of autophagy due to the treatment of cancer cells using compound 9.

INTRODUCTION

Coordination-driven self-assembly is widely employed for the construction of topologically significant and aesthetically appealing supramolecules.¹ The synthetic principles for the generation of self-assembled nanoscale coordination architectures are now well established. Metallasupramolecules thus developed have garnered a great deal of interest due to their ease of construction from simple complementary metal–ligand precursors and functionality offered by the building blocks.² It is well-known that the ligating topologies of the organic ligands used in metal-mediated self-assembly play a key role in determining the binding abilities, size, geometry, and functionality of resulting metallasupramolecular objects.³ It is a continuous endeavor to diversify the choice of chelating linkers and to functionalize the resulting complexes to achieve supramolecular architectures with interesting properties.⁴ Recently, researchers have focused on developing different varieties of fac-Re(CO)₅ and fac-Mn(CO)₃-based compounds for their probable utility as CO releasing molecules and studied their related antiproliferative properties.⁵,⁶ A survey on the literature related to photo-carbon monoxide releasing molecules (photo-CORMs) disclosed that the photo-CORMs requiring high-energy UV light to initiate the CO release process have been well explored and the mechanism of photo-triggered CO release is also understood.⁷ However, considering the harmful effects of UV light on biological tissues, molecules requiring UV light activation for CO release might have limited applicability in therapeutic use.⁸ Therefore, designing of photo-CORMs that can be stimulated with visible light for controlled release of CO is highly desirable and is also a key challenge.⁹

We envisioned that incorporation of an organic bridge with more conjugation, in the design of Mn-based compounds, could result in a red shift of the metal–ligand charge transfer (MLCT) band. The choice of aminoquinonato bridge for this purpose was driven by the fact that some of our previous examples based on Re–aminoquinonato complexes showed

ABSTRACT: Multicomponent self-assembly of Mn₂(CO)₁₀, a bis-chelating aminoquinonato (ON\(\text{ON}\)) bridge (L), and an ester/amide-functionalized flexible neutral ditopic linker (L') has resulted into the formation of Mn₂LL'-type manganese(I)-based dinuclear metallastirrups of general formula \([\{(CO)₃Mn(μ-η²-L)Mn(CO)₃\}μ-L']\) (1–10). Compounds 1–10 were accomplished via orthogonal bonding of the aminoquinone ligand (2,5-bis(n-butylamino)-1,4-benzoquinone/2,5-bis(phenethylamino)-1,4-benzoquinone) and ditopic pyridyl ligand to manganese carbonyl. The resultant metallastirrups were characterized using elemental analyses and IR, UV–vis, \(^1\)H NMR, and electrospray ionization-mass spectroscopic techniques. The molecular structure of 6 was confirmed by single-crystal X-ray diffraction methods. Furthermore, molecular recognition capabilities of 1, 5, 7, and 9 were evaluated with aromatic compounds containing hydroxy/amine functionalities. Anticancer activities of compounds 1–3, 5–7, 9, and 10 were investigated against three cancer cell lines, that is, lung (A549), colon (HCT-15), and cervical (HeLa) as well as on normal cells (HEK 293). Compound 9 showed a broad-spectrum inhibition toward these cancer cells upon exposure to visible light. The myoglobin assay was performed using UV–vis absorption spectroscopy to investigate the visible-light-triggered CO release from 5 and 9 that could be related to their ability to effectively inhibit cancer cells. In addition, morphological studies confirmed the induction of autophagy due to the treatment of cancer cells using compound 9.
increased absorptivity with a concomitant red shift of the MLCT band. To the best of our knowledge, compounds 1–10 are the first report of heteroleptic \((\text{M}_2\text{LL'})\) Mn(I)-based dinuclear metallastirrups comprising an aminoquinonato bridge and ester/amide-functionalized flexible tectons. Herein, we present the self-assembly of Mn(I)-based ester/amide-bridge and ester/amide-functionalized dinuclear metallastirrups comprising an aminoquinonato bis(4-pyridinecarboxamide)-1,2-ethane (bpce), and 1,2-phenylene diisonicotinate (pdi), carboxylate (etdp), 4-pyridinecarboxylic acid diethylene glycol cleating bispyridyl ligands \([\text{L}']\), and ester/amide-functionalized dinuclear bispyridyl ligands \([\text{L}']\). The synthesis of these compounds was achieved via an orthogonal assembly approach. A typical one-pot self-assembly process involved the reaction of an equimolar mixture of \(\text{Mn}_2(\text{CO})_{10}\) bis-chelated aminoquinonato ligands \([\text{L} = 2,5\text{-bis(n-butylamino)}\text{-}1,4\text{-benzoquinone (bbpq)}, 2,5\text{-bis(phenethylamino)}\text{-}1,4\text{-benzoquinone (bbpq)}, \text{and ester/amide-functionalized dinucleating bispyridyl ligand \([\text{L} = 2,5\text{-bis(4-pyridinecarboxamidine)}\text{-}1,2\text{-ethane (bpce)}, and 1,2-phenylene diisonicotinamide (pda)}\)]) in the presence of \(\text{Me}_2\text{NO}\) in dichloromethane at \(25\)–\(30\) °C for \(35\)–\(40\) h under dark conditions (Scheme 1). The products obtained were stable toward air and moisture but sensitive to exposure of light. Compounds 1–10 were soluble in polar organic solvents and have been characterized by elemental analysis and IR, UV–vis absorption, NMR, and ESI-mass spectroscopic techniques. The molecular structure of compound 6 was confirmed using single-crystal X-ray diffraction methods.

IR spectra of 1–10 in \(\text{CH}_2\text{Cl}_2/\text{THF}\) showed strong bands for the \(\text{fac-Mn(}\text{CO})_3\) core in the range of \(\nu = 2031\)–\(1890\) cm\(^{-1}\). Compounds 1–10 have a formal local symmetry lower than \(\text{Cs}\) and displayed two overlapping high-energy and two overlapping low-energy bands. These four infrared stretching frequencies were indicative of the lowering of symmetry, which resulted into the completely nondegenerate modes \(4A\). The amide \(\text{C}=\text{O}\) stretching frequency of the bis-chelated aminoquinonato moiety appeared as a weak band at around \(\nu = 1536\)–\(1531\) cm\(^{-1}\), whereas the corresponding \(\text{C}=\text{O}\) stretching frequency of free aminoquinone ligands \((\text{H}_2\text{L})\) appeared at \(\nu = 1553\) cm\(^{-1}\). The shift in the \(\text{C}=\text{O}\) stretching frequency toward the lower-energy side and the disappearance of the NH band of aminoquinone ligands in 1–10 indicated the coordination of aminoquinone ligands with two manganese centers. The ester \(\text{C}=\text{O}\) stretching band in 1–6 appeared as a medium band in the range \(\nu = 1761\)–\(1729\) cm\(^{-1}\), and the amide \(\text{C}=\text{O}\) stretching frequency of the bipyrilid linker in 7–10 appeared as a medium band in the range of 1681–1611 cm\(^{-1}\) (Figure S1, Supporting Information). UV–vis absorption spectra of 1–10 indicated the coordination of aminoquinone ligands with two manganese centers. The ester \(\text{C}=\text{O}\) stretching band in 1–6 appeared as a medium band in the range \(\nu = 2031\)–\(1890\) cm\(^{-1}\), and the amide \(\text{C}=\text{O}\) stretching frequency of the bipyrilid linker in 7–10 appeared as a medium band in the range of 1681–1611 cm\(^{-1}\) (Figure S1, Supporting Information). UV–vis absorption spectra of 1–10 displayed intense bands in the higher-energy regions at \(\lambda_{\text{max}} = 228\)–\(311\) and 324–344 nm due to ligand-centered transitions and intraligand charge transfer (ILCT) transitions, respectively. In addition, toward the lower-energy region, intense broad bands were observed in the range \(\lambda_{\text{max}} = 465\)–\(486\) nm, whereas the free ligands were transparent in the corresponding window. The appearance of these new bands in the complexes was assigned to ILCT transitions (Figure S2, Supporting Information).

\(^1\text{H}\) NMR spectra of compounds 1–10 showed appropriate signals for the ester/amide-functionalized dipyrilid linkers, and...
the spectral data are given in the Experimental Section. The signals corresponding to the bispyridyl linker were downfield-shifted (Figures S4–S10, Supporting Information). The formation of compounds 1–10 was further confirmed by the ESI-mass spectroscopic technique. The experimental isotopic distribution pattern was distinctly observed and isotopically resolved. The observed pattern matched well with the theoretical isotopic distribution pattern. Further, the appearance of molecular ion peaks for 1–10 at the expected value (Experimental Section) supported the intact existence of the compounds in solution (Figures S11–S20, Supporting Information). The elemental compositions for compounds 1–10 were ascertained by elemental analyses, and the obtained results were satisfactory.

Good-quality single-crystals of 6 were obtained by slow evaporation of the mixture of acetone and dimethylformamide (2:1) solutions at ~40 °C. Compound 6·acetone crystallized in the monoclinic space group C2/c. Details about data collection, solution, and structure refinement are given in Table S1, Supporting Information. The Oak Ridge thermal ellipsoid plot (ORTEP) diagram of 6·acetone is depicted in Figure 1. The single-crystal X-ray structure of 6 showed a metastacyclic structure, wherein two manganese centers are bridged by a bis-chelated bpbq unit and further linked by the pdi unit. The coordination geometry around Mn(1) centers was found to be a distorted octahedron, with facially disposed three terminal carbonyl groups, one nitrogen atom, an oxygen atom from the aminquinonato pdi linker, and one nitrogen atom from the pyridyl unit of the pdi linker. The dianionic bis-chelating bpbq ligands are in a nearly planar arrangement, and phenethyl groups of aminquinonato bridge are positioned in an opposite manner with respect to each other. Two ester C==O groups are oriented anti with respect to each other. The distance between the Mn⋯Mn centers along the aminquinonato pillar is ~7.86 Å. The centroid–centroid distance between pyridyl moieties of the pdi unit was found to be 5.62 Å and that between the central phenyl moiety of the pdi unit and the central benzoquinone moiety of bpbq is 9.166 Å. An acetone molecule was trapped outside of the crystal lattice. The crystal packing diagram of 6·acetone along the b axis displayed various soft intramolecular and intermolecular interactions, as shown in Figure 2. Compound 6 showed intermolecular hydrogen-bonding interactions between (i) the acetone carbonyl group and phenyl group of the bpbq unit, i.e., C==O⋯H–C with a distance of 2.658 Å, (ii) the acetone methyl group and ethereal linkage of the ester groups present in the pdi unit, i.e., –CH3⋯OC==O with a distance of 2.715 Å, and (iii) the terminal manganese carbonyl group and the phenyl group of the bpbq unit, i.e., C==O⋯H–C with a distance of 2.673 Å. Notably, two different weak mutual CH⋯π interactions were observed between (i) the methyl group present in the acetone moiety and the phenyl group present in the pdi unit with a distance of 3.657 Å and (ii) the pyridyl group present in the pdi unit and the phenyl group present in the bpbq unit with a distance of 3.674 Å.

Figure 1. ORTEP diagram of [(CO)3Mn(μ-η¹-bpbq)Mn(CO)3] (6·acetone) with thermal ellipsoids drawn at 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (deg) are as follows: Mn(1)–N(1) 2.034(2), Mn(1)–N(2) 2.103(3), Mn(1)–O(4) 1.999(2), Mn(1)–C(1) 1.803(4), Mn(1)–C(2) 1.794(4), Mn(1)–C(3) 1.815(4), N(1)–Mn(1)–N(2) 85.25(9), O(4)–Mn(1)–N(1) 79.14(9), O(4)–Mn(1)–N(2) 81.93(9), C(1)–Mn(1)–N(1) 91.12(13), C(1)–Mn(1)–C(2) 172.33(14), C(1)–Mn(1)–O(4) 90.76(13).

The assemblage of different functional groups in the metallastirrups and the observance of various soft interactions in the X-ray crystal structure of 6 induced us to study the molecular recognition capability of the aminquinonato-bridged metallastirrups with aromatic compounds in its solution state. Absorption and emission spectrophotometric titration methods were adopted for quantitative evaluation of the binding affinity of Mn(I)-based compounds, and 4,4′-dihydroxybiphenyl and benzidine were used as guest species in the titration experiments. In a typical experiment, the concentration of guest [G] was maintained constant, while the concentration of the host [H] (1, 5, 7, and 9, respectively) was varied. In the UV–vis absorption spectrum, the intensity of bands corresponding to guests enhanced upon addition of hosts, due to formation of a host–guest charge transfer complex. A linear correlation resulted from a Benesi–Hildebrand double-reciprocal plot of change in intensity of guest absorption (1/ΔA taken along the Y axis) at a given wavelength versus change in host concentration (1/[H] taken along the X axis).

$$[G]/ΔA = (1/[H]) \left(1/eK_{sv}\right) + (1/e)$$

To further support the formation of a host–guest complex, emission titration experiments were performed. In these experiments, the intensity of emission bands owing to guests was quenched upon incremental addition of respective host metallastirrups. The Stern–Volmer constants, $K_{sv}$, were calculated from the linear plot of $I_0/I$ versus concentration of host [H], where $I_0$ and $I$ are fluorescent intensities of the guest in the presence and absence of the host. The following Stern–Volmer equation was adapted for the calculations.

$$I_0/I = 1 + K_{sv}[H]$$

The binding and Stern–Volmer constants furnished in Table 1 indicated efficient binding of guest molecules by the metallastirrup hosts. The observed spectral patterns for the titration experiments are given in Figures S21–S28, Supporting Information.
normal human embryonic kidney cells (HEK 293). The cancer cells were exposed to the compounds 1–3, 5–7, 9, and 10, and the ability of cancer cells to survive in the presence of these compounds at variable concentrations was investigated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The above-mentioned compounds were inactive against the cancer cells under dark conditions, whereas upon exposure to visible light, they showed significant inhibition of cancer cells in a differential and dose-dependent manner (Figures S29–S44, Supporting Information). As shown in Figures S29, S31, S33, S35, S37, S39, S41, and S43, the dose-dependent inhibition of the compounds with cancer cells was observed. The percentage reduction in cell viability were found to be approximately 83, 92, 77, and 34% at a maximum concentration of 50 μM on lung (A549), colon (HCT-15), cervical (HeLa), and normal human embryonic kidney cells (HEK 293) for compound 1 (Figures S30, S32, S34, S36, S38, S40, S42, S44, and Table 3). Among the compounds screened, 7 and 9 were more potent in inhibiting the proliferation of lung, colon, and cervical cancer cells with IC50 values of 2.89 ± 0.12, 4.43 ± 0.62, 0.98 ± 0.38 μM and 2.34 ± 0.1, 2.58 ± 0.57, 0.78 ± 0.03 μM, respectively (Table 2). The inhibitory potency grade of the dinuclear metallastirrup series increased as 3 < 5 < 6 < 2 < 1 < 7 < 9 < 10 as assessed in cancer cell lines. Indeed, compound 9 showed broad-spectrum activity with significantly low IC50 values toward lung, colon, and cervical cancer cells lines in comparison to cisplatin.

Furthermore, live cell imaging and AO/EB staining were employed to study the morphology of cancer cells treated with compound 9. The morphological analysis of control and compound 9-treated cells showed vacuolization, cell shrinkage, and floating dead cells (Figure 3a). The distinct vacuoles and cell shrinkage indicate that the nature of cell death might be due to autophagy.15 The AO/EB fluorescence staining showed uniform green color, indicating live cells, while the dead cells were stained orange due to ethidium bromide (Figure 3b).16a

The probable reason behind the antiproliferative effect of these metallastirrup compounds is due to the CO release and the formation of photoproducts upon exposure to light.5a,b,i,16b,c Although suppression of cancer cells subsequent to CO delivery using light stimulus (such compounds are called photo-CORMs) is documented in the literature, photo-CORMs that can be activated with visible light are relatively rare. Our earlier work involving photo-CORMs required UV light (λmax = 365 nm) to trigger CO release, whereas inclusion of the aminoquinonato bridge in the metallastirrup compounds presented here has resulted in a considerable red shift of the MLCT band (λmax = 486 nm), which allowed activation of the photo-CORMs using visible light. The red shift in the MLCT band can be attributed to the conjugation present in the aminoquinonato bridge.

The anticancer efficacy of metallastirrup compounds 1–3, 5–7, 9, and 10 was studied against a series of cancer cell lines, namely, lung (A549), colon (HCT-15), cervical (HeLa), and

Table 1. Binding Constants (Kb) and Stern–Volmer Constants (KSV) for Host–Guest Systems of 1, 5, 7, and 9 with 4,4′-Dihydroxybiphenyl and Benzidine

|        | 4,4′-dihydroxybiphenyl | benzidine |
|--------|-------------------------|-----------|
|        | Kb (M⁻¹) | KSV (M⁻¹) | Kb (M⁻¹) | KSV (M⁻¹) |
| 1      | 4.65 × 10⁴ | 2.47 × 10⁵ | 1.19 × 10⁵ | 5.48 × 10⁴ |
| 5      | 2.53 × 10² | 1.58 × 10⁶ | 2.76 × 10⁶ | 7.93 × 10⁴ |
| 7      | 1.13 × 10² | 1.73 × 10⁵ | 7.43 × 10⁵ | 2.26 × 10⁵ |
| 9      | 4.74 × 10⁶ | 1.32 × 10⁸ | 2.11 × 10⁸ | 1.82 × 10⁸ |

Figure 2. Supramolecular interactions of 6•(Acetone) viewed along the b axis showing (a) C=O···H−C hydrogen-bonding interaction, (b) C≡O···H−C hydrogen-bonding interaction, and (c) C≡O···H−C hydrogen-bonding and CH···π interactions.
These compounds are generally stable at room temperature in both solid and solution states under dark conditions. For example, compounds 5 and 9 remained stable even after 24 and 12 h in dimethyl sulfoxide (DMSO)/H2O (8:2) under dark conditions. The LED green-light-triggered CO release by compounds 5 and 9 was then studied using the standard myoglobin (Mb) assay by the UV–vis absorption spectroscopic method. In addition, the stability of compounds 5 and 9 in phosphate-buffered saline (PBS, pH = 7.4) under the reduced conditions of the myoglobin assay was monitored using the UV–vis absorption spectroscopic method. Compounds 5 and 9 showed negligible spectral changes over 24 and 12 h, respectively. Four different wavelengths, namely, λmax = 510, 540, 556, and 577 nm, were chosen to observe the stability of the compounds. This indicates that no CO release occurred during this time under dark conditions, suggesting that these compounds may be suitable for photoactivatable CO release (photo-CORM) (Figures 4 and S45).

To ascertain CO release from the metallastirrups, compound 9 was chosen for myoglobin assay experiments. Compound 9 was added to a buffered aqueous solution of equine heart myoglobin (MbFe(II)) that was freshly reduced with excess sodium dithionite under a nitrogen atmosphere. Compound 9 was stable in the absence of light, whereas CO release was found to be photochemically triggered, upon exposure to LED green light (λ = 520–560 nm, 220–240 V, 0.5 W). The spectral variations in the Q-band region of MbFe(II) upon

**Table 2. Antiproliferative Activity Profile of Compounds 1–3, 5–7, 9, and 10 in Normal Cells and Different Cancer cells”**

| compound | A549 | HCT-15 | HeLa | HEK 293 |
|----------|------|--------|------|---------|
| 1        | 2.18 ± 0.57 | 3.99 ± 0.63 | 11.6 ± 4.58 | >50 |
| 2        | 1.51 ± 0.35 | 2.03 ± 0.27 | 17.32 ± 1.14 | >50 |
| 3        | 6.87 ± 0.42 | >50 | 1.74 ± 0.15 | 45.25 ± 5.13 |
| 5        | 5.55 ± 0.4 | 7.88 ± 0.85 | 30.91 ± 2.32 | >50 |
| 6        | 2.29 ± 0.46 | 3.13 ± 0.41 | 31.88 ± 2.63 | >50 |
| 7        | 2.89 ± 0.12 | 4.43 ± 0.62 | 0.98 ± 0.38 | 45.36 ± 6.38 |
| 9        | 2.34 ± 0.1 | 2.58 ± 0.57 | 0.78 ± 0.03 | >50 |
| 10       | 2.67 ± 0.89 | 1.97 ± 0.19 | 2.51 ± 0.36 | na |
| cisplatin | 15.78 ± 4.8 | 16.78 ± 4.8 | 17.56 ± 5.7 | 17.62 ± 2.87 |

Table 3. Cell Viability Profile of Compounds 1–3, 5–7, 9, and 10 in Normal Cells and Different Cancer Cells

| compound | A549 | HCT-15 | HeLa | HEK 293 |
|----------|------|--------|------|---------|
| 1        | 83   | 92     | 77   | 34      |
| 2        | 89   | 92     | 61   | 35      |
| 3        | 69   | 54     | 78   | 48      |
| 5        | 72   | 83     | 53   | 42      |
| 6        | 87   | 88     | 55   | 45      |
| 7        | 93   | 95     | 89   | 47      |
| 9        | 90   | 90     | 76   | 68      |
| 10       | 75   | 65     | 96   | 21      |

These compounds are generally stable at room temperature in both solid and solution states under dark conditions. For example, compounds 5 and 9 remained stable even after 24 and 12 h in dimethyl sulfoxide (DMSO)/H2O (8:2) under dark conditions. The LED green-light-triggered CO release by compounds 5 and 9 was then studied using the standard myoglobin (Mb) assay by the UV–vis absorption spectroscopic method. In addition, the stability of compounds 5 and 9 in phosphate-buffered saline (PBS, pH = 7.4) under the reduced conditions of the myoglobin assay was monitored using the UV–vis absorption spectroscopic method. Compounds 5 and 9 showed negligible spectral changes over 24 and 12 h, respectively. Four different wavelengths, namely, λmax = 510, 540, 556, and 577 nm, were chosen to observe the stability of the compounds. This indicates that no CO release occurred during this time under dark conditions, suggesting that these compounds may be suitable for photoactivatable CO release (photo-CORM) (Figures 4 and S45).

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**Figure 3.** (a) Morphological observations of the lung, colon, and cervical cells treated with respective IC50 concentrations of 9, showing floating dead cells in live cell imaging (left) and (b) the presence of dead cells (violet arrows) in acridine orange/ethidium bromide (AO/EB) staining (right) after 48 h.
exposure to LED green light are shown in Figure 5. The photoirradiation was carried out at a 30 min interval. The intensity of the band at $\lambda_{\text{max}} = 557$ nm gradually decreased, whereas two bands at $\lambda_{\text{max}} = 542$ and 577 nm increased in intensity. These changes in bands were due to formation of the MbFeCO complex. The formation of the MbFeCO complex completed in 4 h, beyond which there were no changes in the spectral pattern. The myoglobin assay carried out for compound 5, which is different from 9 only in terms of the ester-based flexible linker, also displayed CO releasing characteristics upon exposure to LED green light ($\lambda = 520$–$560$ nm, 220–240 V, 0.5 W). However, in the presence of compound 5, formation of MbFeCO was complete only in 10 h, indicating a slower kinetics for CO release. The structural difference between 5 and 9 is only the ester/amide functionality, although it is not clear, at this stage, if this could be the reason for difference in their CO releasing abilities. However, this observance does indicate that there could be opportunities for temporally controlled release of CO for a specific duration by structural modifications (Figure 5).

When 4 $\mu$M compounds 5 and 9 were added to 66 $\mu$M deoxymyoglobin, the CO release profiles of 5 and 9 were accomplished upon exhaustive photoactivation. The concentration of MbCO was obtained from the absorption data, which indicates that approximately two CO molecules, i.e., $1.73 \pm 0.21$ and $1.87 \pm 0.05$, were released per molecule of 5 and 9 with half-life ($t_{1/2}$) values of $9.21 \times 10^2$ and $3.27 \times 10^2$ min, respectively (Figures 6 and S46 and Table 4). In this study, $t_{1/2}$ is defined as the time taken by the compounds 5 and 9 to release 50% of CO per molecule. The values of the apparent rate of CO release by 5 and 9 determined by the logarithmic plot of absorption of 5 and 9 against irradiation time were found to be $7.53 \times 10^{-4}$ and $2.12 \times 10^{-3}$ s$^{-1}$, respectively (Figures 7 and S47 and Table 4).

**Figure 4.** UV–vis absorption spectral changes at a selected wavelength with increasing incubation time under dark conditions for a solution of reduced equine heart myoglobin and compound 5 in phosphate buffer.

**Figure 5.** UV–vis absorption spectral changes in the Q-band region of a solution of reduced equine heart myoglobin and compounds 5 and 9 in phosphate buffer under LED green light exposure observed for every (a) 1 h and (b) 30 min.

**Figure 6.** Amount of MbCO formed (in $\mu$M) with increasing irradiation time at $\lambda = 520$–$560$ nm for a solution of compound 5 in reduced equine heart myoglobin as determined by UV–vis absorption spectroscopy.

**Figure 7.** $k_{\text{CO}}$ rate plot from the logarithmic plot of absorption of 5 vs time in minutes.
The photolytic CO release by compounds 5 and 9 was further confirmed by the solution IR spectroscopic method. The IR spectra of compounds 5 and 9 (in DMSO) upon irradiation with LED green light (λ = 520–560 nm) exhibited strong CO stretching modes for the terminal CO groups between ν 2031 and 1890 cm⁻¹ under dark conditions. A remarkable reduction in the intensity for the terminal CO groups of 5 was observed progressively. However, beyond 10 h, no further changes were observed. However, for compound 9, a dramatic change happened very quickly (4 h), beyond which there were no changes in the spectral pattern (Figures 8 and S48).

**EXPERIMENTAL SECTION**

**General Methods.** All reactions were carried out under an oxygen-free, N₂ atmosphere using standard Schlenk line techniques. The starting materials were purchased from Alfa-Aesar and Sigma-Aldrich Chemicals. Mn₂(CO)₁₀, trimethylamine-N-oxide, isonicotinoyl chloride hydrochloride, 1,2-ethanediol, 1,2-dihydroxybenzene, diethylene glycol, 1,2-ethylamine, and phenethylamine were used as received. The aminoquinone ligands (etdp, pcadgd, pdi, bpce, and pdia) were synthesized as reported in the literature.¹⁷ Dichloromethane, ethanol, methanol, tetrahydrofuran, and other solvents were dried using standard methods and freshly distilled prior to use.¹⁸ IR spectra were recorded on a Nicolet iS10 Fourier transform infrared spectrometer. Electronic absorption spectra were obtained on a Shimadzu UV-2450 spectrophotometer. Emission spectra were recorded on a Fluoromax-4 spectrofluorometer. Solvents used for UV–vis and emission titration experiments were of spectral grade.¹⁹ ¹H NMR spectra were obtained on a Bruker Avance 400 MHz NMR spectrometer with tetramethylsilane as the internal reference. Elemental analyses were performed using a Thermo Scientific Flash 2000 CHNS analyzer. ESI-mass spectra were taken on an Agilent 6530B Q-TOF mass spectrometer.

Synthesis of [(CO)₃Mn(µ-η²-L)Mn(CO)₃(µ-L')] (1–10).

A mixture of Mn₂(CO)₁₀ (0.1 mmol), aminoquinone ligand (L) (0.1 mmol), and ester/amide-functionalized bispyridyl ligand (L') (0.1 mmol) was taken in a Schlenk flask with a magnetic pellet. The system was evacuated and purged with nitrogen. To this, freshly distilled dichloromethane (10 mL) was added under a positive pressure of nitrogen gas using a vacuum Schlenk line. The reaction mixture was stirred by a magnetic stirrer at room temperature (25–30 °C) for 35–40 h. The color of the reaction mixture changed from dark red to dark maroon. The solvent was removed under vacuum and washed with hexane to remove unreacted Mn₂(CO)₁₀. The reaction mixture was filtered through a silica gel column using dichloromethane to remove unreacted trimethylamine-N-oxide. The products were isolated as a maroon solid of [(CO)₃Mn(µ-η²-L)Mn(CO)₃(µ-L')] and dried under vacuum.

**Table 4. CO Release and Kinetic Data of Compounds 5 and 9**

| compounds | equivalents of CO released per molecule | percentage of CO released (%) | half-life, t₁/₂ (min) | rate constant, k_CO (s⁻¹) |
|-----------|----------------------------------------|-----------------------------|----------------------|--------------------------|
| 5         | 1.73 ± 0.21                           | 28.83                       | 9.21 × 10⁻¹          | 7.53 × 10⁻¹              |
| 9         | 1.87 ± 0.05                           | 31.17                       | 3.27 × 10⁻¹          | 2.12 × 10⁻¹              |

Synthesis of [(CO)₃Mn(µ-η²-bbbq)Mn(CO)₃(µ-etdp)] (1).

A mixture of Mn₂(CO)₁₀ (40 mg, 0.1 mmol), 2,5-bis-(butylamino)-1,4-benzoquinone (25 mg, 0.1 mmol), and ethane diyl di-4-pyridine carboxylate (etdp) (27 mg, 0.1 mmol) and trimethylamine-N-oxide (0.2 mmol) were taken in a Schlenk flask equipped with a magnetic stirring bar. The system was evacuated and purged with nitrogen using a vacuum Schlenk line. To this, freshly distilled dichloromethane (12 mL) was added, and the reaction mixture was stirred at room temperature for 40 h. The color of the reaction mixture changed to dark maroon from dark red. The solvent was removed by vacuum distillation, and the reaction mixture was washed with hexane and filtered through a short silica gel column. The product was isolated as a dark maroon solid of [(CO)₃Mn(µ-η²-bbbq)Mn(CO)₃(µ-etdp)] and dried under vacuum. Yield: 61 mg, 74% [based on Mn₂(CO)₁₀].²³ ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.53 (d, J = 8.0 Hz, 4H, H², py, etdp), 7.61 (d, J = 8.0 Hz, 4H, H³, py, etdp), 5.46 (s, 2H, quinone-H), 4.87 (q, 2H, H¹, alkoxy CH₂, etdp), 4.62 (q, 2H, H², alkoxy CH₂, etdp), 3.70 (t, 4H, H¹, C H², Bu), 1.89 (m, 2H, H², C H₂, Bu), 1.69 (m, 2H, H², C H₂, Bu), 1.43 (m, 4H, H³, C H₂, Bu), 1.00 (t, 6H, H⁴, C H₂, Bu). UV–vis (CH₂Cl₂): λₘₐₓ(ab) (nm) 232 (LIG), 335 (ILCT), 479 (MLCT). Anal. Calcd for C₃₂H₂₃N₂O₆Mn₂: C, 51.14; H, 4.04; N, 7.02. Found: C, 51.12; H, 3.99; N, 6.96. IR (CH₂Cl₂, cm⁻¹): ν CO (s) 2030 (m), 2022 (s), 1937 (s), 1907 (s, ν CO), 1737 (m, ν(CO); ν(COO)), 1533 (s, ν(aminoquinone C=O)). High-resolution mass spectrometry (HRMS): for C₃₂H₂₃N₂O₆Mn₂ [M + H]⁺ calcd: 799.0856, m/z; found: 799.0873, m/z.

Synthesis of [(CO)₃Mn(µ-η²-bbpq)Mn(CO)₃(µ-etdp)] (2).

Compound 2 was prepared by following the procedure adopted for 1 using Mn₂(CO)₁₀ (40 mg, 0.1 mmol), 2,5-bis(phenethylamino)-1,4-benzoquinone (34 mg, 0.1 mmol), ethane diyl di-4-pyridine carboxylate (etdp) (27 mg, 0.1 mmol), and trimethylamine-N-oxide (0.2 mmol). The product [(CO)₃Mn(µ-η²-bbpq)Mn(CO)₃(µ-etdp)] (2) was isolated as a maroon solid. Yield: 63 mg, 69% [based on Mn₂(CO)₁₀].²⁵ ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.67 (dd, J = 8.0 Hz, 4H, H², py, etdp), 7.73 (dd, J = 8.0 Hz, 4H, H³, py, etdp), 7.45 (d, 4H, H⁴, Ph, phenethyl), 7.38 (t, 4H, H⁵, Ph, phenethyl), 7.21 (d, 2H, H⁶, phenethyl), 7.17 (d, 2H, H⁷, phenethyl).
7.29 (t, 2H, H°, Ph, phenethyl), 5.54 (s, 2H, quinone-H), 4.91 (q, 2H, H°, alkoxyl CH₂, etdp), 4.64 (q, 2H, H°, alkoxyl CH₂, etdp), 3.96 (m, 4H, H°, CH₂, phenethyl), 3.21 (m, 2H, H°, CH₂, phenethyl), 2.98 (m, 2H, H°, CH₂, phenethyl). UV–vis (CH₂Cl₂): λ_max (nm) 232 (LIG), 329 (ILCT), 486 (MLCT). Anal. Calcld for C₄₂H₃₄N₄O₁₂Mn₂: C, 56.39; H, 3.72; N, 6.65. Found: C, 55.94; H, 3.72; N, 6.46. IR (CH₂Cl₂, cm⁻¹): ν 2031 (m), 1938 (s), 1906 (s, v(CO)), 1739 (m, νester ≈C=O), 1532 (s, ν aminoquinonato ≈C=O). HRMS: for C₄₂H₃₄N₄O₁₂Mn₂ [M + H⁺] calcld: 847.0856, m/z; found: 847.0887, m/z.

Synthesis of [(CO)₅Mn(μ-η⁴-bbbq)Mn(CO)](μ-pcadgd) (3). Compound 3 was prepared by following the procedure adopted for 1 using Mn₂(CO)₁₀ (40 mg, 0.1 mmol), 2.5-bis(butylalino)-1,4-benzoquinone (25 mg, 0.1 mmol), 4-pyridinecarbonic acid diethylen glycol diester (pcadgd) (31 mg, 0.1 mmol), and trimethylamine-N-oxide (0.2 mmol). The product [(CO)₅Mn(μ-η⁴-bbbq)Mn(CO)](μ-pcadgd) (3) was isolated as a maroon solid. Yield: 72 mg, 73% [based on Mn₂(CO)₁₀]. ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.73 (dd, J = 8.0 Hz, 4H, H°, Ph, pcadgd), 7.82 (dd, J = 8.0 Hz, 4H, H°, py, pcadgd), 7.45 (d, 4H, H°, Ph, phenethyl), 7.37 (t, 4H, H°, Ph, phenethyl), 7.27 (t, 2H, H°, Ph, phenethyl), 5.72 (s, 2H, quinone-H). 4.55 (m, 2H, H°, alkoxy CH₂, pcadgd), 4.47 (m, 2H, H°, alkoxy CH₂, pcadgd), 3.81 (t, 4H, H°, CH₂, phenethyl), 3.19 (m, 2H, H°, CH₂, phenethyl), 2.98 (m, 2H, H°, CH₂, phenethyl). UV–vis (CH₂Cl₂): λ_max (nm) 232 (LIG), 327 (ILCT), 485 (MLCT). Anal. Calcld for C₃₈H₃₂N₄O₁₀Mn₂: C, 58.50; H, 3.90; N, 5.94. IR (CH₂Cl₂, cm⁻¹): ν 2030 (m), 1938 (s), 1906 (s, v(CO)), 1729 (m, νester ≈C=O), 1531 (s, ν aminoquinonato ≈C=O). HRMS: for C₃₈H₃₂N₄O₁₀Mn₂ [M + H⁺] calcld: 843.1118, m/z; found: 843.1133, m/z.

Synthesis of [(CO)₅Mn(μ-η⁴-bbbq)Mn(CO)](μ- pcadgd) (4). Compound 4 was prepared by following the procedure adopted for 1 using Mn₂(CO)₁₀ (40 mg, 0.1 mmol), 2.5-bis(phenethylamino)-1,4-benzoquinone (34 mg, 0.1 mmol), 4-pyridinecarbonic acid diethylen glycol diester (pcadgd) (31 mg, 0.1 mmol), and trimethylamine-N-oxide (0.2 mmol). The product [(CO)₅Mn(μ-η⁴-bbbq)Mn(CO)](μ-pcadgd) (4) was isolated as a maroon solid. Yield: 72 mg, 73% [based on Mn₂(CO)₁₀]. ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.73 (dd, J = 8.0 Hz, 4H, H°, Ph, pcadgd), 7.45 (d, 4H, H°, Ph, phenethyl), 7.37 (t, 4H, H°, Ph, phenethyl), 7.27 (t, 2H, H°, Ph, phenethyl), 5.72 (s, 2H, quinone-H). 4.55 (m, 2H, H°, alkoxy CH₂, pcadgd), 4.47 (m, 2H, H°, alkoxy CH₂, pcadgd), 3.81 (t, 4H, H°, CH₂, phenethyl), 3.19 (m, 2H, H°, CH₂, phenethyl), 2.98 (m, 2H, H°, CH₂, phenethyl). UV–vis (CH₂Cl₂): λ_max (nm) 232 (LIG), 327 (ILCT), 485 (MLCT). Anal. Calcld for C₃₈H₃₂N₄O₁₀Mn₂: C, 58.50; H, 3.90; N, 5.94. IR (CH₂Cl₂, cm⁻¹): ν 2030 (m), 1938 (s), 1906 (s, v(CO)), 1729 (m, νester ≈C=O), 1531 (s, ν aminoquinonato ≈C=O). HRMS: for C₃₈H₃₂N₄O₁₀Mn₂ [M + H⁺] calcld: 843.1118, m/z; found: 843.1133, m/z.

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Reduced using CrysAlisPro RED software. The structures were solved by direct methods (SHELXS) and refined by full-matrix least-squares calculations on \( F^2 \) (SHELXL). The positions on all of the atoms were obtained by direct methods. All nonhydrogen atoms were refined anisotropically. The hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally 1.2 \( x U_{eq} \) of their parent atoms.

**Cell Culture.** Cancer cell lines A549 (lung), HCT-15 (colon), and HeLa (cervical) and HEK 293 normal cells were obtained from the National Centre for Cell Sciences, Pune, India. Lung, cervical, and normal HEK 293 cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotic–antimycotic solution (1X), and colon cancer cells were maintained in Roswell Park Memorial Institute (RPMI) supplemented with 10% FBS and antibiotic–antimycotic solution (1X). The cells were maintained as a monolayer, passaged on reaching 80% confluency, and incubated at 37 °C in a 5% CO\(_2\) incubator.

**Antiproliferative Activity Studies.** The cytotoxicity of the complexes was analyzed using the MTT assay. Cancer cells (lung and cervical) and normal cells were suspended in DMEM supplemented with 10% FBS at a density of 10 000 cells per well in a 96-well plate and incubated overnight. Colon cancer cells were suspended in RPMI supplemented with 10% FBS and plated as mentioned above. The compounds were irradiated with common household LED light of \( \lambda \geq 560 \) nm for 1 h. Different concentrations of the photolyzed compounds 1–3, 5–7, 9, and 10 (2, 5, 10, 25, 50 \( \mu \)M) were treated in triplicates and incubated for 48 h at 37 °C in a 5% CO\(_2\) incubator. Then, 10 \( \mu \)L of MTT (5 mg/mL) was added to the wells and incubated for 3 h. The medium was discarded, and the formazan product was dissolved in 100 \( \mu \)L of DMSO. The plates were read at \( \lambda = 595 \) nm using a Dynex multimode plate reader. The IC\(_{50}\) values were calculated using nonlinear regression fit from GraphPad prism 5.0 software. Data were represented as the average and standard error of three independent assays.

**Morphological Observations.** The cancer cells were seeded at a density of 50 000 cells/mL and incubated overnight in a CO\(_2\) incubator. The cells were treated with IC\(_{50}\) concentration of 9 and incubated for 48 h. After incubation, the cells were observed for any morphological changes under a phase contrast microscope. Further, the cells were trypsinized, washed with PBS, further stained with acridine orange/ethidium bromide at a final concentration of 1 \( \mu \)g/mL, and viewed under a Nikon eclipse 80i fluorescent microscope for cell death.

**Myoglobin Assay.** The CO release by the compounds 9 and 9 was studied using the myoglobin assay. Equine heart myoglobin (66 \( \mu \)M) was obtained by dissolving in 890 \( \mu \)L of phosphate-buffered saline (pH 7.4). Then, 0.1% of 100 \( \mu \)L of freshly prepared sodium dithionite dissolved in PBS was added to reduce the myoglobin to its deoxy form. The deoxy-myoglobin curve was recorded using a UV–vis spectrophotometer (Shimadzu UV-2450) at room temperature using a quartz cuvette at a range of \( \lambda = 500–600 \) nm. Then, 10 \( \mu \)L of 9 in DMSO was added to give a final concentration of 4 \( \mu \)M. When compound 9 was added to deoxyhemoglobin under dark conditions, it remained stable and therefore the solution was exposed to LED green light. The system was positioned in a cardboard box to protect from any unwanted lights, and the
quartz cuvette containing the solution was placed in front of the light source (LED green light (λ = 520–560 nm, 220–240 V, 0.5 W)) with a distance of 10 cm. After irradiation, there was a substantial change observed in the deoxyMb absorption band. The absorption spectra were recorded for 10 h at regular intervals of 1 h and subjected to LED green light exposure until the saturated curve was observed. When compound 9 was added to deoxymyoglobin under dark conditions, it remained stable and therefore the solution was subjected to LED green light exposure and there was a change observed in the deoxyMb absorption band. The absorption spectra were recorded at regular intervals of 30 min of visible light exposure up to 4 h.

**CONCLUSIONS**

In conclusion, we have demonstrated and successfully synthesized a series of functionalized neutral Mn(1)-based aminquinonato-bridged dinuclear metallastirrups with flexible pyridyl ligands. The manganese(1)-based dinuclear compounds were obtained in a one-pot reaction condition via the orthogonal bonding approach. The compounds were characterized by IR, UV−vis, 1H NMR, and ESI-mass spectroscopic techniques. The molecular structure of 6 was ascertained by single-crystal X-ray diffraction methods. The molecular recognition capabilities of compounds 1, 5, 7, and 9 were studied with aromatic compounds containing ester and amide functionalities. The cytotoxicity studies were performed for the compounds 1−3, 5−7, 9, and 10 against lung, colon, and cervical cancer cells as well as normal cells. Compound 9 showed better cytotoxic activity in comparison with cisplatin. Visible light-triggered CORMs were identified by the myoglobin assay for the compounds 5 and 9. Compound 9 released CO much faster than the compound 5 probably due to the amide functionality.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01438.

Structure refinement details, and packing diagram of 6; overlay IR spectra, overlay UV−vis absorption spectra, 1H NMR, and ESI-MS isotopic distribution patterns; Benesi−Hildebrand and Stern−Volmer linear regression plots of 1, 5, 7, and 9 with aromatic guest molecules; graphical representation of cytotoxicity of compounds 1−3, 5−7, 9, and 10 and images showing the dose-dependent inhibition and cell viability of cancer cells; graphical representations of dark stability, rate of CO release, and rate constant of compound 9; the photolytic CO release and IR spectra of compound 9 (PDF)

Crystallographic data for 6 (CIF)

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**Notes**

The authors declare no competing financial interest.

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