Metal-Organic Frameworks as Potential Drug Carriers

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Summary of Recent Advances

Nanoparticle-based therapeutics have received increasing attention, as these systems can alleviate many drawbacks of conventional therapy. Metal-organic frameworks (MOFs), a new class of hybrid materials composed of metal ions and organic bridging ligands, have emerged as a promising platform for drug delivery, owing to their high drug loadings, biodegradability, and versatile functionality. The bulk MOF materials can absorb and release large amounts of therapeutics including ibuprofen, procainamide, and nitric oxide. Scale-down of MOFs to the nano-regime yields nanoscale metal-organic frameworks (NMOFs) which are more applicable as delivery vehicles, such as selective delivery of cisplatin prodrugs. Although progress has been made in utilizing NMOFs for drug delivery, many improvements must occur before they can become viable nanotherapeutics.

Introduction

Despite remarkable progress in our understanding of the fundamental biology behind many diseases, we have yet to observe comparable advances in the treatment of these diseases. Current therapeutics are limited by their nonspecific distribution throughout the body leading to high doses, rapid clearance, poor pharmacokinetics, and high side effects [1,2]. While a number of different strategies have been developed to improve the efficacy of conventional drugs, nanoparticle-based therapeutics have received an increasing amount of attention over the past 20 years. Many of the drawbacks of small molecule drugs can be alleviated through use of these novel systems. Typically, a nanoparticle therapeutic is composed of an active agent incorporated within the nanoparticle carrier; a variety of nanocarriers have been used for this purpose, such as polymeric nanoparticles, micelles, liposomes, iron oxide, and gold [3,4]. Some of the key properties of nanomaterials are small size, high drug loading, surface properties, drug release kinetics, improved pharmacokinetics, and biocompatibility [5–8]. Additionally, nanoparticles can be specifically targeted to diseased tissues (e.g., tumor regions) by conjugation with targeting ligands and can be engineered to contain multiple agents (e.g., imaging and therapeutic agents for both imaging and therapy), both of which are much harder to achieve with conventional therapeutics. The clinical success of nanoparticle therapies such as Abraxane and Doxil illustrates the power of this approach. A large number of promising nanoparticle-drug conjugates are currently in different stages of clinical development [1,3,4].

Metal-organic frameworks (MOFs) are a new class of highly tunable hybrid materials crafted from metal connecting points and organic bridging ligands [9]. They are typically synthesized

under mild conditions via coordination-directed self-assembly processes (Figure 1), and are also called coordination polymers or coordination networks[10–14]. Known for their large porosity with tunable pore sizes, shapes, and functionalities, MOFs are well studied among the scientific community for many applications such as nonlinear optics, gas storage, catalysis, and chemical sensing [9,10,13–20]. MOFs exhibit many desired characteristics as drug carriers, including exceptionally high surface areas and large pore sizes for drug encapsulation, intrinsic biodegradability as a result of relatively labile metal-ligand bonds, and versatile functionality for postsynthetic grafting of drug molecules. Over the past three years, MOFs have been investigated for applications in loading and release of several drug molecules. MOFs can be scaled down to the nano-regime to form nanoscale metal-organic frameworks (NMOFs) by using a variety of different techniques that have been developed for inorganic and organic polymeric nanoparticles. NMOFs are potential nanovectors for delivering therapeutic agents to targeted areas of the body, as they are able to control drug release with their large surface areas, high porosity, and presence of functional groups to interact with loaded moieties. Our group has recently reported MOFs as important delivery devices for contrast enhancement agents for magnetic resonance imaging, computed tomography, and optical imaging [21–25]; however, this review will focus on applications of MOFs and NMOFs as potential drug carriers. Although still at its infancy, NMOFs exhibit many desired characteristics as nanocarriers; intrinsic tunability and biodegradability as well as exceptionally high drug loading capacity of this emerging class of hybrid nanomaterials should make them a promising candidate for further development as nanotherapeutics.

Proof of Concept: Drug Release with MOFs

In developing MOFs for drug delivery, the goal is to design carriers that show little toxicity in the body; biocompatibility of both the metal and bridging ligand must be considered. While chromium and other metals are highly toxic, some metals exist in appreciable amounts in the body. For example, iron is a component in hemoglobin and is approximately 22 μM in blood plasma. Tissue also contains various metals, such as copper (68 μM), manganese (180 μM), nickel (2 μM), and zinc (180 μM) [26]. Since this is an emerging class of drug carriers, there is very limited data on the biological fate of these systems. Iron oxide nanoparticles are clinically approved as MRI contrast agents, and *in vitro* assays have shown that these particles do not exhibit toxicity [27].

The first group of MOFs to be investigated as a potential drug delivery system is the MIL (Materials of Institut Lavoisier) family, pioneered by Férey and co-workers [28]. This investigation occurred at about the same time as the Lin group first explored the applications of NMOFs as potential MRI contrast agents [22]. The MIL family of MOFs is crafted from trivalent metal centers and carboxylic acid bridging ligands. The MIL family holds great promise in drug delivery for their attractive characteristics: large pores (25–34 Å), outstanding surface areas (3100–5900 m^2/g), and the ability to incorporate functional groups into the framework.

Férey and co-workers studied the storage and release of Ibuprofen with chromium-based MIL-101 (Figure 2) and MIL-100 [29]. Both materials showed high Ibuprofen loading, with 0.347 g Ibuprofen/g MOF for MIL-100 and 1.376 g Ibuprofen/g MOF for MIL-101. The drastic difference in drug loading between the two materials is attributed to the pore sizes of the materials; MIL-101 has larger pore volumes of 12700 and 20600 Å (8200 and 12700 Å for MIL-100). The kinetics of Ibuprofen release was investigated by suspending the Ibuprofen-loaded materials in simulated body fluid (SBF) at 37 °C. There is an initial release of weakly-bound drug molecules within the first 2 h for MIL-100, and the entire cargo is released within 3 days. For MIL-101, steady release is observed for the first 8 h with complete release after 6 days. These MOFs contain toxic chromium, and thus, the use of these materials for drug

delivery is very limited. A less-toxic analog, MIL-101(Fe) has been developed as a biocompatible alternative [30], and should be much more appropriate drug carriers.

The Férey group has also reported controlled drug release for MIL-53, a more flexible MOF in the MIL family [31]. Both MIL-53(Cr) and the less toxic MIL-53(Fe) achieved loadings of 0.220 g Ibuprofen/g MOF and 0.210 g Ibuprofen/g MOF, respectively. The delivery kinetics was investigated in SBF at 37 °C. Complete drug delivery occurred in 3 weeks, a long release time attributed to the flexibility of the MIL-53 framework and the strong drug-framework interactions. The prolonged drug release gives MIL-53 the potential of being used for sustained release and drug delivery. The drug loadings achievable with the MIL family are much higher than any material previously studied for drug encapsulation (i.e., through non-covalent interactions). Given the ability to construct highly porous MOFs with tunable hydrophobicity from practically any metal centers, we foresee many more porous MOFs will be examined as potential drug carriers.

The MOFs with hydrophobic pores such as the MIL family are ideal for encapsulating drug molecules that have poor aqueous solubility. MOFs can also be designed to have hydrophilic pores that can carry either positive or negative charges, and such MOFs can be used to encapsulate drugs that contain opposite charges to the MOFs. Rosi and co-workers recently developed an anionic MOF composed of zinc(II) ions, adenine, and *para*-biphenyldicarboxylic acid that can be cationically-triggered to release its cargo.[32] The MOF is anionic, so its use for storage and release of cationic drugs via exchange with cations in biological fluid was investigated. The MOF was loaded with 0.22g/g of hydrochloride salt of procainamide, an antiarrythmia drug. Procainamide therapy is currently limited by its rapid clearance from the body, requiring dosing every 3–4 hrs. The drug release behavior of the MOF was monitored by HPLC; complete release was observed at 72 h in phosphate buffered saline (PBS). In contrast, the drug-loaded MOF was also dialyzed against pure water, with only 20% of the drug released, suggesting that the majority of procainamide is released by the cations present in PBS. In addition, the authors demonstrated that the framework remained intact under these conditions.

MOFs have also been studied as carriers for gaseous therapeutics which represent a significant challenge for drug delivery. Nitric oxide (NO) has several applications in therapy, including antibacterial, antithrombotic, and wound-healing applications.[33,34] The storage and release of nitric oxide (NO) in a MOF was investigated by Morris and co-workers [35]. Two MOFs were synthesized by a previously reported procedure [36], from either cobalt or nickel and 2,5-dihydroxyterephthalic acid. These MOFs can absorb 7 times the amount of NO than any previously reported material on a per gram basis via ligation to coordinatively unsaturated metal centers, with little background release [37]. Figure 3 depicts the activation, loading, and release of NO by these MOFs. The effect of the NO-loaded MOFs on precontracted pig coronary arteries was investigated. The MOFs resulted in more vessel relaxation than the NO-free control. While Ni and Co are too toxic to be used for biological applications, the work discussed thus far shows the ability of MOFs to absorb and release large amounts of therapeutic cargo. The ability to deliver significant doses of NO is also relevant to cancer therapy since NO has shown anticancer activity in high concentrations, but shows tumorigenic properties at lower concentrations. The concentration at which this switch occurs is unknown [38,39].

Drug Delivery with Nano-MOFs

While the systems discussed above illustrate the promise of MOFs as drug delivery vehicles, *in vivo* applications of the bulk MOFs are however limited because they are not suitable for systemic circulation. The bulk MOFs thus need to be scaled down to the nano-regime so that the resulting NMOFs can circulate systemically while maintain the advantageous properties

of bulk MOFs for drug delivery. NMOFs can improve the pharmacokinetic properties of the encapsulated drugs [1,5,7].

The Lin group was able to fabricate an NMOF (designated as **NCP**-1) from Tb^{3+} ions and *c*,*c*,*t*-(diamminedichlorodisuccinato)Pt(IV) (disuccinatocisplatin, DSCP), a cisplatin prodrug [40]. The **NCP**-1 nanoparticles were 58.3±11.3 nm in diameter, and were encapsulated with silica to enhance stability (half-life of 9 h in HEPES buffer at 37°C, compared to 1 h for uncoated). Silica-coated **NCP**-1 particles were further functionalized with c(RGDfk), a cyclic peptide that targets the $\alpha_v\beta_3$ integrin, which is overexpressed in many cancers. The cytotoxicity of the nanoparticles was investigated against HT-29 human colon adenocarcinoma cells. These particles displayed a lower IC_{50} (Inhibitory Concentration, 50%) than that of cisplatin (9.7 μM vs. 13.0 μM for cisplatin), while the untargeted particle did not exhibit significant cell death. The improved cytotoxicity of the c(RGDfk)-functionalized particles suggests that these particles are taken up by receptor-mediated endocytosis, followed by reduction to the active Pt(II) species by the reducing environment inside the cell (Figure 4). The ability to switch from a relatively nontoxic prodrug to a highly potent anticancer drug in such a delivery scheme is very attractive since it facilitates selective delivery of anticancer drugs to cancerous cells, which can in turn lower the dose-limiting side effects that plague most anticancer chemotherapeutics.

Recently, the Lin group reported loading and release of biomedical agents in nanoMIL-101 (Fe).[41] This is the first report of the synthesis of an NMOF and subsequent loading of a fluorophore and anticancer agent via post-synthetic modification (Figure 5). The NMOF particles of MIL-101(Fe) were octahedral particles about 200 nm in diameter with impressive porosity, a Langmuir surface area of 3700–4535 m^2/g. Amino-functionalized nanoMIL-101 was synthesized by incorporating 2-aminoterephthalic acid in the synthesis. A Bodipy fluorophore was grafted on the NMOF through a covalent amine bond with up to 11 wt% loading. Confocal microscopy of the Bodipy-loaded particles with HT-29 cells showed fluorescent signal only with those cells incubated with the particles, indicating that the particles are able to cross the cell membrane and release their fluorescent cargoes. Additionally, a platinum(IV) prodrug, *c*,*c*,*t*-[PtCl$_2$(NH$_3$)$_2$(OEt)(O$_2$CCH$_2$CH$_2$CO$_2$H] (ethoxysuccinato-cisplatin, ESCP) was grafted on amino nanoMIL-101, with an overall drug payload of 12.8 wt %. The particles were coated with silica to enhance stability *in vitro*, giving a half-life of 14 h in PBS at 37°C, compared to 1.2 h for the uncoated particles. Silica-coated particles were grafted with c(RGDfk) and studies with the functionalized particles against HT-29 cells showed that the particles had comparable cytotoxicity to that of cisplatin (IC_{50} = 21 μM for the particles, IC_{50} = 20 μM for cisplatin, IC_{50} = 29 μM for silica-coated particles only). Grafting of both an optical imaging agent and a cisplatin prodrug into the nanoMIL-101 system suggests the potential of using such a platform for theranostic applications that allow real-time monitoring of therapeutic responses of an anticancer drug.

It is worth noting that several related inorganic nanoparticle systems have also been developed as potential anticancer therapeutics. O'Halloran and co-workers were able to improve efficacy of the leukemia agent, As_2O_3 by formation of insoluble metal-arsenate complexes inside liposomes [42,43]. As_2O_3 is a potent therapy for leukemia, limited by its severe side effects and poor pharmacokinetics. Salts of nickel, cobalt, copper, and zinc were incorporated into liposomes, followed by loading of As(OH)$_3$ to form insoluble M(II) complexes of As_2O_3. Folate-targeted liposomes with nickel/As_2O_3 showed high cytotoxicity against HeLa cells with an IC_{50} of 1.8±0.6 μM (IC_{50} = 4.3±0.3 μM for As_2O_3). Recently, O'Halloran and co-workers were able to coencapsulate As_2O_3 and a cisplatin-based drug (acetate salt of diaqua-cisplatin) inside a liposome using the same strategy [44]. This formulation exhibited comparable cytotoxicity to As_2O_3 and diaqua-cisplatin alone, with several different cell lines. Adair and coworkers were able to successfully encapsulate organic fluorophores and hydrophobic chemotherapeutics within calcium phosphate nanoparticles [45,46]. Calcium phosphate

nanoparticles provide a pH-tunable way to deliver encapsulated molecules to targeted cells with minimal background release. Ceramide, an apoptosis inducer, was encapsulated into the nanoparticles during synthesis. Preliminary *in vitro* cell assays against breast cancer and melanoma cell lines revealed that the nanoparticle conjugate showed highly effective induction of apoptosis, while the nanoparticle carrier displayed little toxicity. Additionally, the Ceramide-calcium phosphate conjugate showed activity in resistant cell lines. Although these systems are not NMOFs, they share some of the same design principles as NMOF-based nanotherapeutics.

Conclusion

Significant progress has been made in adapting MOFs and NMOFs for drug delivery. With these hybrid systems, an immense number of metal centers and organic building blocks can be pieced together and specifically tailored to form new materials with desirable characteristics as drug carriers. Since NMOFs represent an infinitely tunable material platform, many other drugs will be incorporated into them in a foreseeable future. The ability to carry both imaging and therapeutic agents in NMOFs should greatly facilitate the efficacy studies of this promising class of nanotherapeutics. The future for MOFs and NMOFs in drug delivery is bright, although many more improvements are needed before they can be considered for clinical applications.

Acknowledgments

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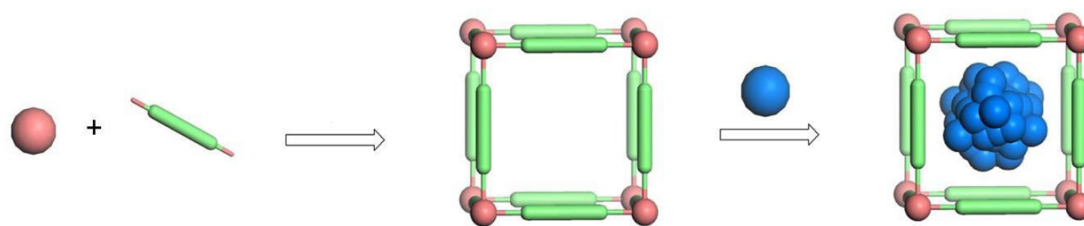
Figure 1.
Formation of MOFs by coordination-directed self-assembly processes and the loading of drugs into MOFs via physical encapsulation. Only one unit of an infinite MOF framework is shown for clarity.
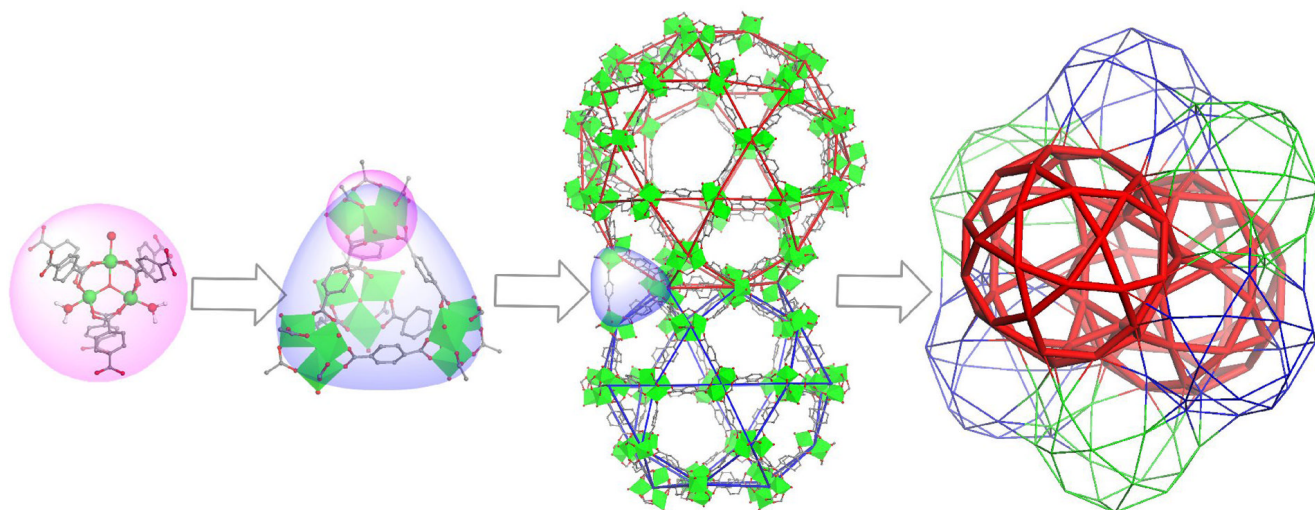
Figure 2.
The structure of MIL-101. The tetrahedra are assembled from trivalent metal centers (Cr or Fe) and 1,4-benzenedicarboxylate. MIL-101 possesses larger cages than MIL-100, which facilitates Ibuprofen loading.
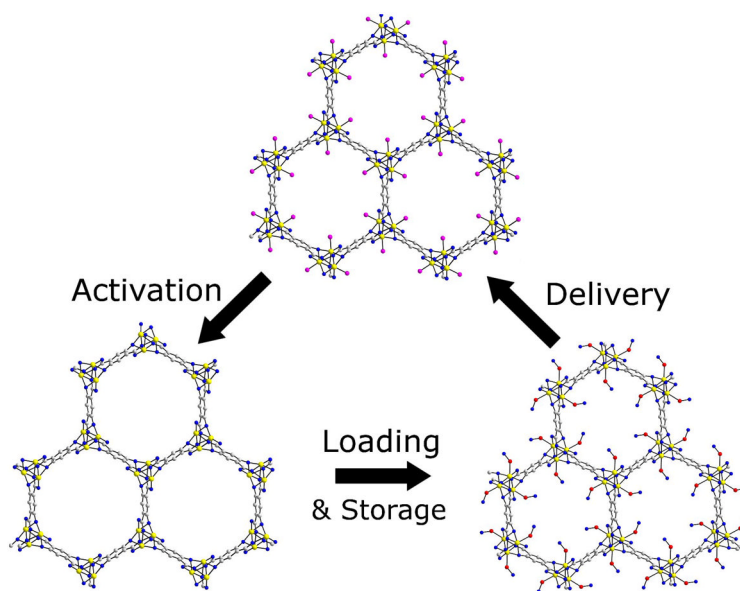
Figure 3.
Absorption, storage, and release of nitric oxide (NO) in a Co or Ni MOF. Activation occurs by dehydration of the MOF at 110 °C, followed by NO loading at room temperature. Finally, delivery (release) of NO is triggered when the MOF was exposed to 11% relative humidity. (Pink spheres indicate water molecules, red and blue spheres indicate nitric oxide.)
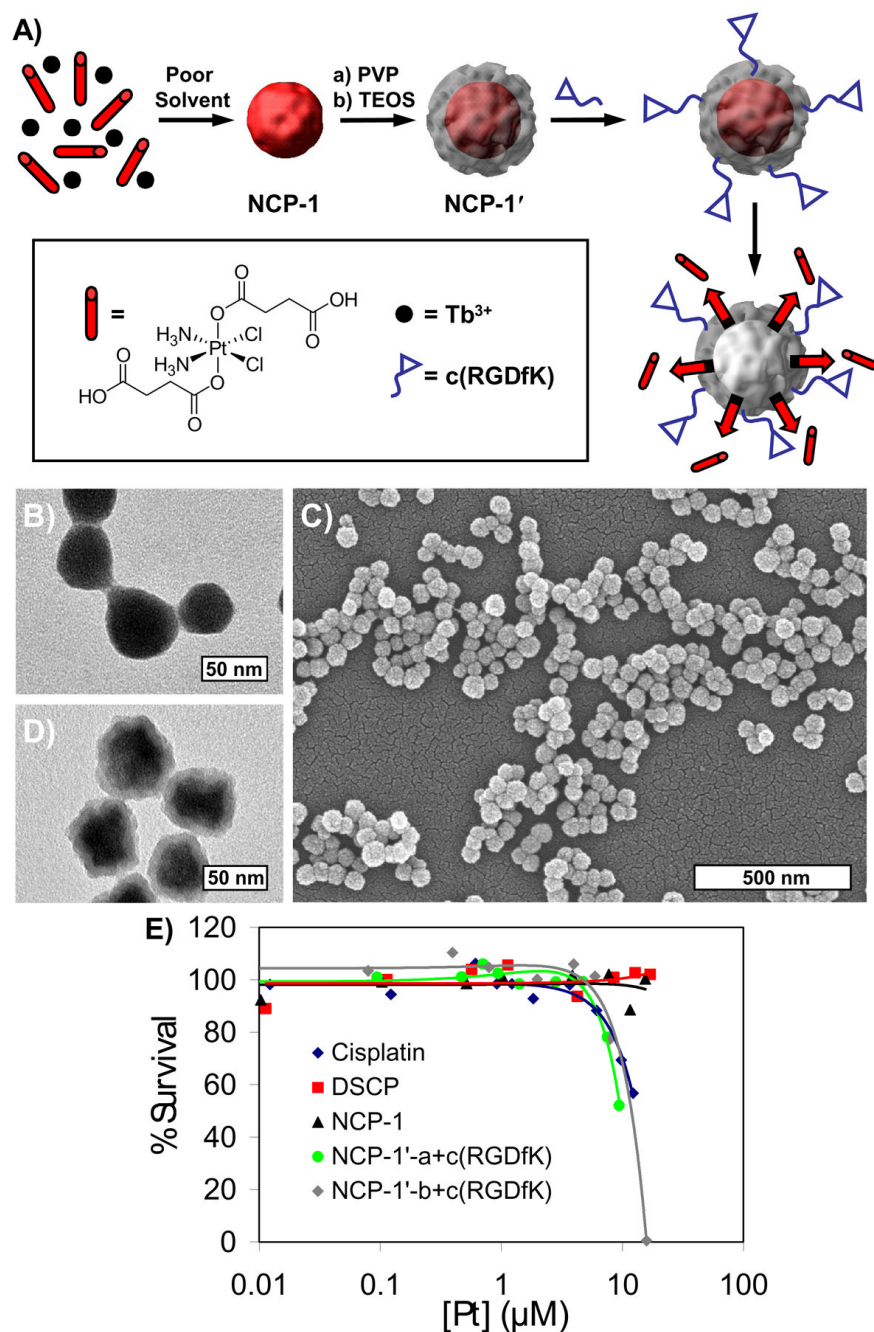
Figure 4.
A) Schematic showing the synthesis of Tb-DSCP NMOF (designated as **NCP**-1) and its subsequent coating with silica shell (**NCP**-1′) and conjugation with cyclic peptide. (PVP = polyvinylpyrollidone, TEOS = tetraethylorthosilicate) B) TEM micrograph for as-synthesized **NCP-1**. C) TEM and D) SEM micrographs for **NCP-1′**. E) *In vitro* cytotoxicity assay curves for HT-29 cells obtained by plotting the % cell viability against the Pt concentration of various samples and cisplatin control.
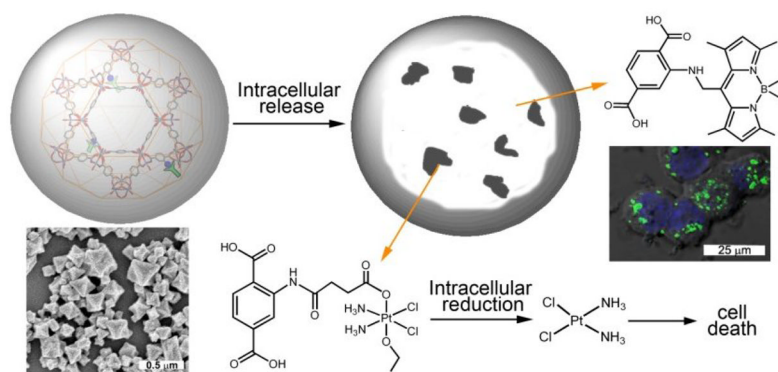
Figure 5.
NanoMIL-101 can be loaded both with an optical imaging agent and cisplatin prodrug.
Simultaneous release of the fluorophore and cisplatin prodrug allows real-time monitoring of
the drug delivery by optical imaging.