Supporting Information for

Cargo Delivery on Demand from Photodegradable MOF Nano-Cages

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1. Instrumentation and Reagents

Materials: The 4-nitrobenzoic acid (98 %), sodium hydroxide (≥ 98%), D-glucose (≥ 98 %), $ZrCl_4$ (anhydrous, 99.99 %),$MgCl_2$ (anhydrous, 99 %) and Nile red (technical grade) were purchased from Sigma Aldrich and used without further purification. Glacial acetic acid (certified ACS),NaCl (99 %), KCl (99 %), $CaCl_2$ (93 %), HEPES sodium salt (99 %), dimethylsulfoxide (DMSO) and dimethylformamide (DMF, Spectrophotometric grade ≥ 99.8 %) were used as received from Fisher Scientific.Phosphate buffered saline (PBS), Dulbecco's Modified Eagle Medium (DMEM), and (3-(4,5-Dimethylthiazol-2-yl)-2,5,Diphenyltetrazolium bromide (MTT) were used as received from Thermo Fisher Scientific.

Powder X-ray Diffraction (PXRD): For X-ray diffraction analysis, a 600 W RigakuMiniFlex powder diffractometer operating with a Cu (K_α = 0.15418 nm) radiation source was used, with asweeping range of 3-50° in continuous scanning mode. Data was collected in 0.1° increments at a scanning rate of 1°/min, andpatterns were generated with PDXL software.

Scanning Electron Microscopy (SEM): A Leo (Zeiss) 1550 field-emission scanning electron microscope, equipped with an in-lens detector and operating at 5.0 kV, was used to collect SEM images. NPs were prepared for SEM imaging by first dispersing them in ethanol (0.1 mg/mL) via sonication. The resulting solution was then deposited via drop casting, with a short stem Pasteur pipette (1 drop), onto precut 5 mm x 5 mm glass slides. After room temperature drying, slides were mounted onto an SEM sample peg using double sided Cu tape and the sides of the slides were painted with carbon paint. A Cressington 208 High Resolution Sputter Coater with a Au/Pd target (80/20) was used to deposit a conductive layer on the surface of the slides in order to allow for imaging. Samples were coated for 60 seconds.

Transmission Electron Microscopy (TEM): TEM images and diffraction patterns were obtained using a JEOL 2100 transmission electron microscopewith an accelerating voltage of 200kV. Samples were prepared by depositing 10 μL of UiO-AZB nanoparticles on a 300 mesh carbon coated copper grid (EM Science) and left to dry overnight.

Dynamic Light Scattering (DLS): The size distribution of the UiO-AZB nanoparticles was measured using a Malvern ZetasizerNano-ZS, with five measurements taken per trial. Nanoparticles were suspended in ethanol via sonication and passed through a 0.45 μm filter prior to measurement.

Thermogravimetric Analysis (TGA): A Q-series TGA from TA instruments was used to analyze thermal stability of materials. 10 mg of sample in an aluminum pan or a high temperature platinum pan were heated under nitrogen from 25-40 °C up to 600 or 800 °C (respectively with pans) with a heating rate of 10 °C/min.

Gas Sorption Isotherms: The N_2 sorption isotherm measurements were collected on a Quantachrome Autosorb-1 at 77 K. The samples were placed in a 6 mm large bulb sample cell, which was degassed under vacuum for 24 h at 120 °C. The surface areas of the materials were determined by fitting the adsorption data within the 0.05-0.3 P/P_0 pressure range to the BET and Langmuir equations.

White Light Sources: 1000 W white light was generated witha Newport LCS-100 solar simulator (AM 1.5G spectrum) equipped with a detachable IR filter. A commercial clamping desk lamp with a 100 W bulb was used to generate 100 W white light. In the case of the 100 W lamp, the IR filter was removed from the solar simulator and mounted between the light source and the sample.

UV-Vis Spectroscopy: Absorbance measurements were taken using a Cary 5000 UV-Vis-NIR spectrometer controlled with Cary WinUV software. Single point measurements at 392 nm were taken using the Simple Reads application for the degradation of UiO-AZB. The Scan application was used to collect spectra from 200-800 nm to observe the release of NR from the UiO-AZB nanoparticles.

High Performance Liquid Chromatography (HPLC): An Agilent 1100 series HPLC equipped with a G1367A autosampler, quaternary pump, column heater set at 40°C and DAD detector set at 254 nm was used to measure the release of IBU. Separations were obtained through the C_{18}XBridge column (4.6 mm x 25 mm with 5µm spherical packing) using H_2O/ACN (85%:15%) as the isocratic elution solvent. The flow rate was set to 1 mL/min and each run was 6 min.

Confocal Laser Scanning Microscope: A Zeiss LSM 880 confocal microscope was used to obtain images of HeLa cells. Images were collected using the red channel (550-700 nm) at 0.52 µm intervals and stacked in the Z axis. The image was prepared using Zen imaging software.

2. Synthesis of 4,4´-azobenzenedicarboxylic acid (AZB)[1]

4-nitrobenzoic acid (13 g) and 250 mL of 5 M NaOH were heated to 50 °C in a 500 mL round bottom flask. An aqueous solution of 3.7 M D-glucose (150 mL) was added slowly (30 mL/min) to the flask with vigorous stirring.The reaction was allowed to stir for 10 minutes and then cooled to room temperature. The solution was aerated for 12 h and 5 M (200 mL) aqueous acetic acid was added to precipitate the AZB. The pink solid was collected via vacuum filtration and dried in a 100 °C oven for 18 h. (9.6 g, ~91 %) ^{1}HNMR (500 MHz, basic D_2O, δ, ppm) trans: 7.94, 7.92 (d, 2H, J= 10 Hz), 7.82, 7.80 (d, 2H, J = 10 Hz), cis: 7.68, 7.66 (d, 2H, J=10 Hz), 6.91, 6.89 (d, 2H, J = 10 Hz), (Predicted m/z= 270.2; M-H$^-$= 269 m/z).

3. Synthesis of UiO-AZB nanoparticles

The synthesis described here was adapted from a previous report by changing the identity and concentration of the modulator.[2] In order to control particle sizes, the acetic acid (AA) modulator was varied from 30-70 molar equivalents to Zr^{4+} (30 mol AA: 1 mol Zr^{4+}, Figure SI). For example, a 30 equivalent synthesis follows: to a 20 mL vial, $ZrCl_4$ (0.0234 g, 0.1 mmol), glacial acetic acid (172 µL, 3 mmol), water (10 µL), and DMF (5 mL) were added and the mixture sonicated for 5-10 min. H_2AZB (0.0270 g, 0.1 mmol) was then added and the solution sonicated for ~5 min to give an orange suspension. The mixture was placed in a 100 °C oven for 24 h. While still warm, the contents of the vial were transferred to a 15 mL centrifuge tube and the particles collected via centrifugation (4,000 rpm for ~15 min). After decanting the supernatant, 5 mL fresh DMF was added and the particles redispersed with sonication for 10

minutes. Particles were allowed to soak in the fresh DMF for 0.5-1 h. Particles were again collected via centrifugation and the supernatant decanted. This washing process was repeated for a total of 1 x 5 mL DMF and 5 x 5 mL EtOH. Upon removal of the final supernatant, the particles were dried in a vacuum oven at 50 °C for 24 h.

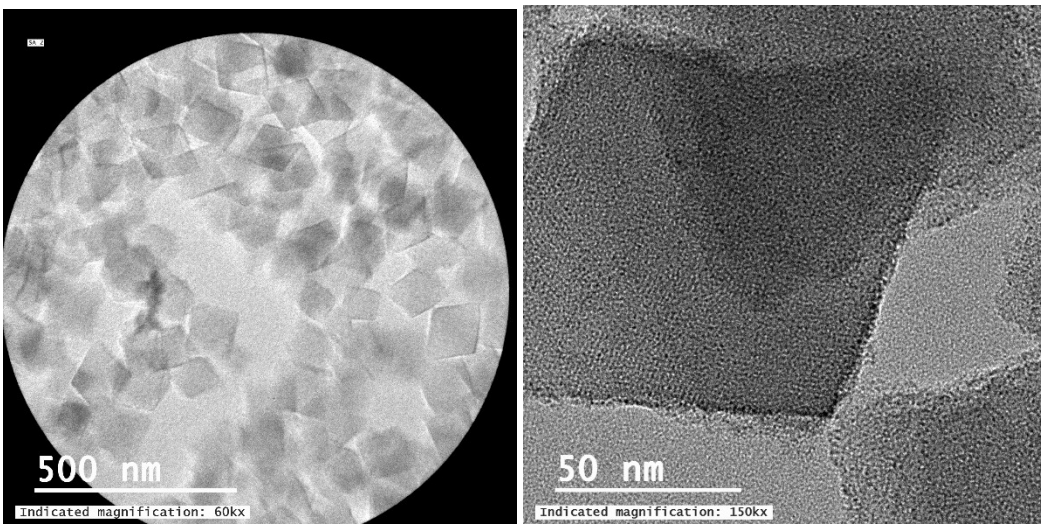

Figure S1. Left: High-resolution TEM image showing area selected for selected area diffraction. Right:Additional high-resolution TEM image of UiO-AZB nanoparticles showing sharp defined edges.

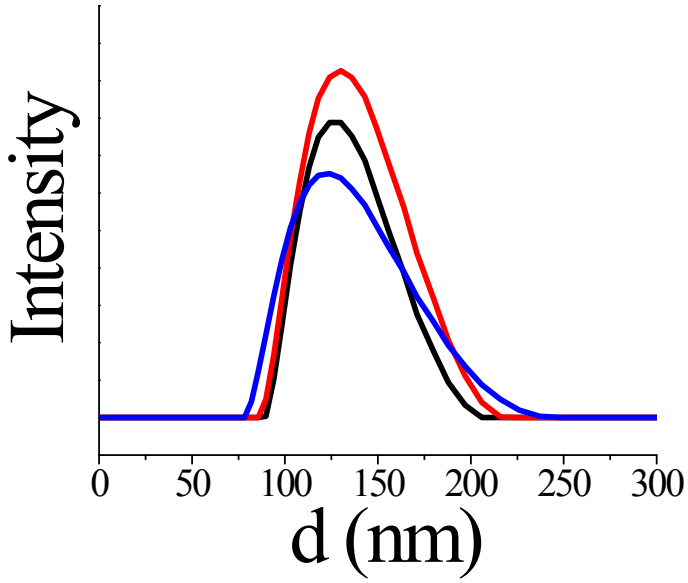

Figure S2. The DLS of UiO-AZB nanoparticles indicates an average particle size of 128 ± 3 nm.

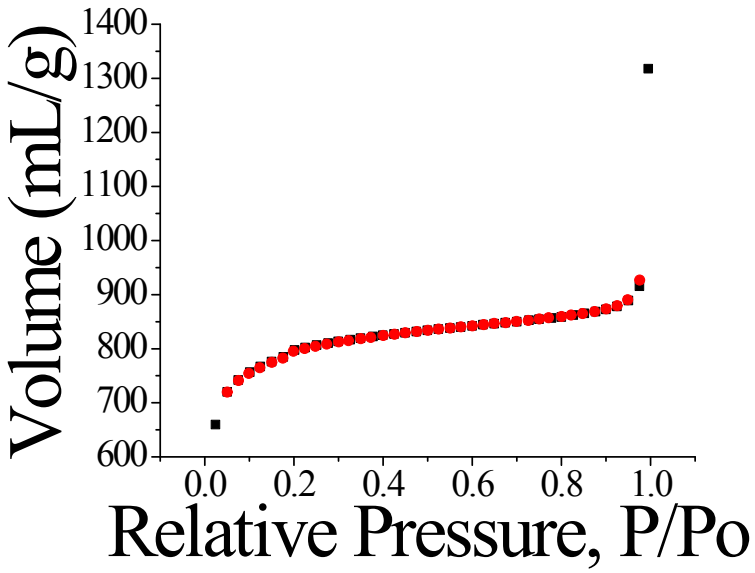

Figure S3. N_2 adsorption (black) and desorption (red) isotherms used to calculate BET surface area of 2465 m^2/g. The shape is indicative of a type II isotherm which is characteristic of macroporous materials.

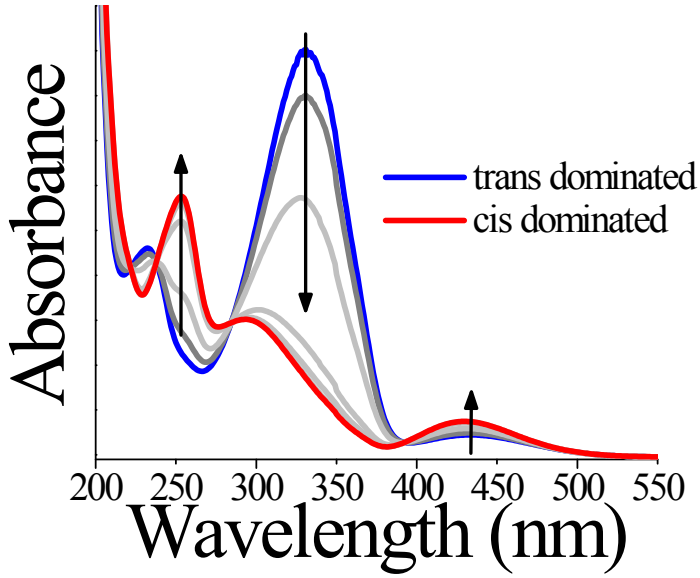

Figure S4. Isomerization of trans-AZB (blue) to cis-AZB (red) upon irradiation with a 355 nm laser as measured in a 0.3 mM solution of AZB in basic water.

4. Simulated Cerebrospinal Fluid (SCF)

Simulated cerebrospinal fluid (SCF) was made following a Cold Spring Harbor Laboratory Press protocol.[3] The solution consists of 135 mMsodium chloride (NaCl), 5.4 mMpotassium chloride (KCl), 5 mM4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid sodium salt (Na-HEPES buffer), 1.8 mMcalcium chloride ($CaCl_2$), and 1 mMmagnesium chloride ($MgCl_2$). The pH of the solution was adjusted to 7.3 by adding concentrated (~12 M) hydrochloric acid.

5. Degradation studies

The degradation of the UiO-AZB was monitored by submersing 0.5 mg into 3 mL of a 1:1 (v/v) solution of ethanol and SCF in a 24/40 jointed quartz cuvette. The cuvette was capped with a rubber septum and either wrapped in tin foil (dark conditions) or placed in front of the light source (irradiated conditions). The absorbance at 392 nm (isosbestic point) of the supernatant solution was measured as a function of time. Experiments were replicated 3 times.

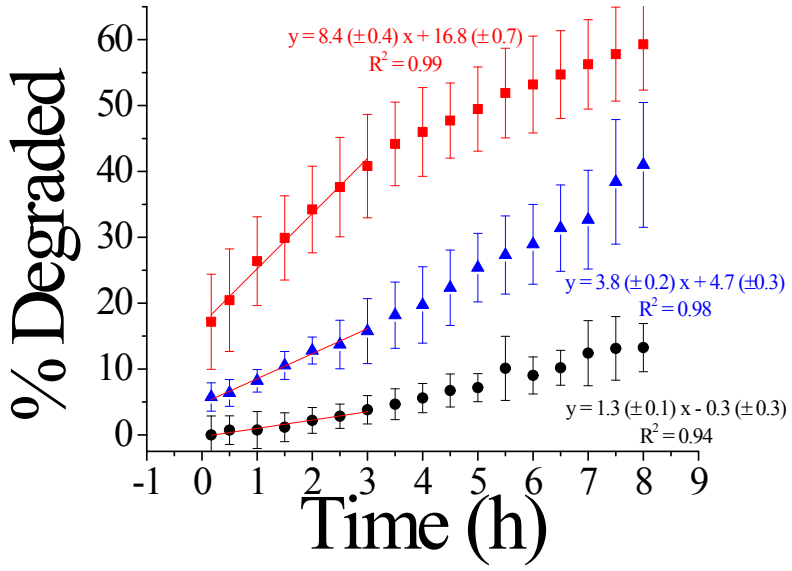

Figure S5. Initial degradation rates of the UiO-AZB nanoparticles in the dark (black), under irradiation with 1000 W light (red), and with 100 W light (blue).

6. Drug loading

IBU loading:50 mg UiO-AZB was suspended into a solution of 150 mg IBU in 30 mL hexane following an impregnation method previously reported.[4]The solution was allowed to stir for 5 h and the nanoparticles were collected via centrifugation of 15 mL aliquots. After decanting the final supernatant, 15 mL hexane was added and the nanoparticles were re-suspended via brief (< 1 min) sonication. Nanoparticles were then centrifuged again for ~5 min and the supernatant decanted. IBU loaded particles were then dried in a vacuum oven for 24 h at 50 °C.

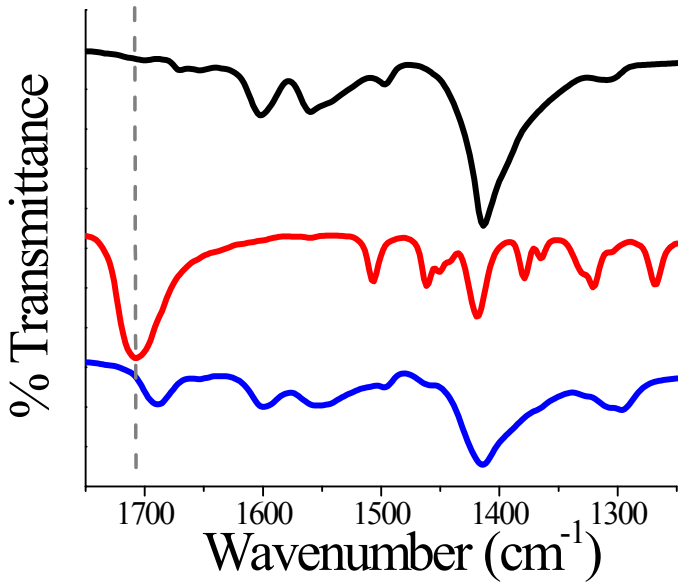

Figure S6. FTIR of UiO-AZB (black), IBU (red), and IBU loaded UiO-AZB (blue). The peak from the C=O stretch of pure IBU at 1706 cm^{-1} shifts to 1690 cm^{-1} when loaded into the UiO-AZB nanoparticles, indicative of IBU binding to the metal nodes.

Caffeine loading: 50 mg UiO-AZB was suspended into a solution of 150 mg caffeine in 30 mL ethanol following an impregnation method previously reported.[4] The solution was allowed to stir for 24 h and the nanoparticles were collected via centrifugation of 15 mL aliquots. After decanting the final supernatant, 5 mL ethanol was added and the nanoparticles were re-suspended via brief (< 1 min) sonication. Nanoparticles were then centrifuged again for ~5 min and the supernatant decanted. IBU loaded UiO-AZB particles were then dried in a vacuum oven for 24 h at 50 °C.

NR loading: 50 mg UiO-AZB was suspended into 15 mL 48 μM NR in ethanol. Beyond this concentration the structural integrity of the nanoparticles was compromised as evidenced by PXRD (Figure S6). The solution was allowed to stir for 24 h and the nanoparticles were collected via centrifugation. After decanting the supernatant, 5 mL ethanol was added and the nanoparticles were re-suspended via brief (< 1 min) sonication. Nanoparticles were then centrifuged again for ~5 min and the supernatant decanted. NR loaded UiO-AZB particles were then dried in a vacuum oven for 24 h at 50 °C.

In order to determine the amount of NR loaded into the nanoparticles, 1.93 mg of loaded material was placed into a vial and digested using 3 mL 50 mM Na_2HPO_4 via sonication for ~1 h. A UV-Vis spectrum of the digestion solution was compared to a calibration curve to determine the concentration of NR in the solution and to calculate the amount of NR present in the sample (Figure S10).

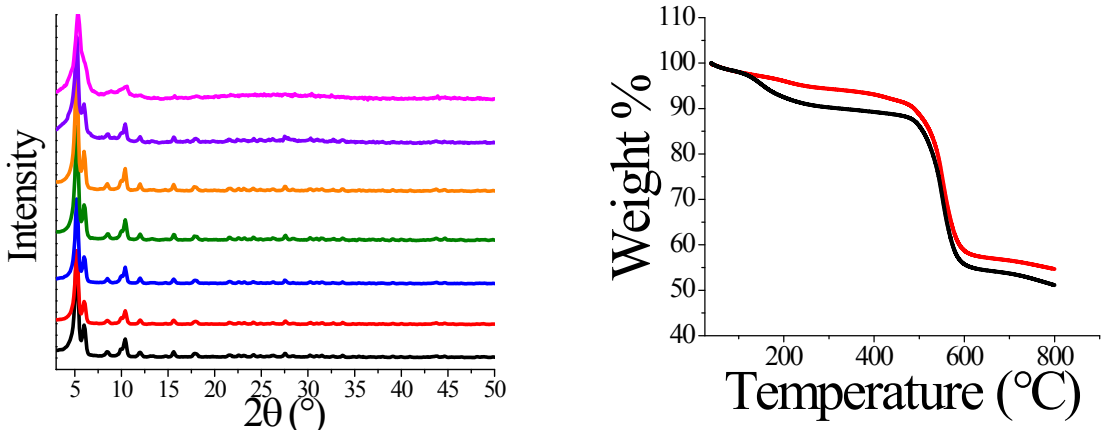

Figure S7. Left: PXRD taken of the NR loaded UiO-AZB with increasing concentrations of NR in the loading solution (black, 29 µM; red, 34 µM; blue, 38 µM; green, 43 µM; orange, 48 µM; purple, 60 µM; magenta, 72 µM). Right: TGA of NR loaded UiO-AZB (red) compared with UiO-AZB (black). Therefore, TGA could not be used to accurately determine NR loading.

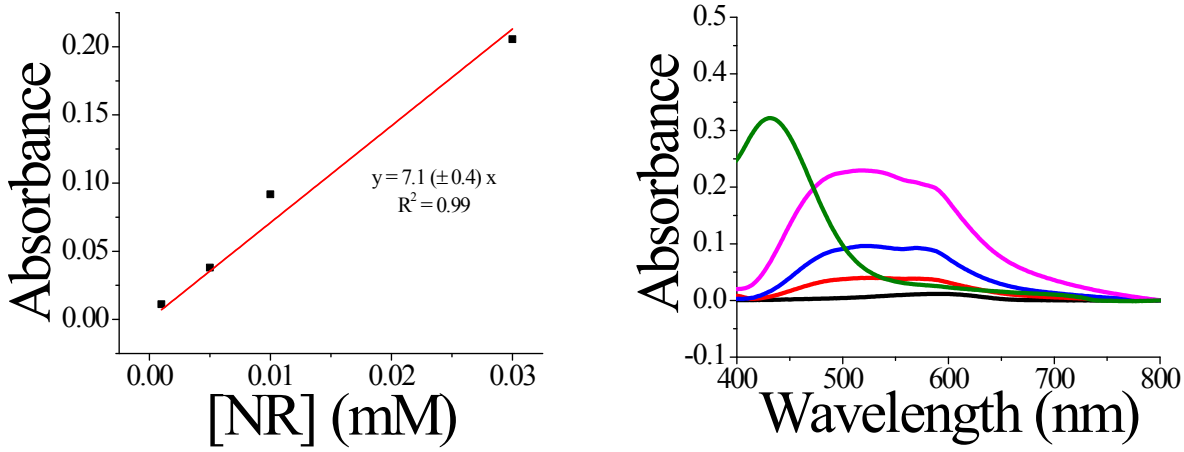

Figure S8. Left: Calibration curve of NR in 50 mM NaH_2PO_4at 575 nm. Right: UV-Vis spectra of the standard solutions of NR (black, 0.001 mM; red 0.005 mM; blue, 0.01 mM; magenta, 0.03 mM) and the digested NR loaded UiO-AZB nanoparticles (green).

7. Drug release studies

IBU release: The release of IBU from the IBU loaded UiO-AZB nanoparticles was measured using HPLC. 2.7 mg of the IBU loaded UiO-AZB nanoparticles were submersed into 5 mL 1:1 (v/v) ethanol/SCF in a 24/40 jointed quartz cuvette. The cuvettes were capped with a rubber septum and kept either wrapped in tin foil (dark conditions) or placed in front of a 1000 W white light source (irradiated conditions). 100 µL aliquots were removed over time from the cuvettes and placed into a glass LC/MS vial. Aliquots were diluted with 900 µL ethanol/SCF (1:1 v/v)

and analyzed using HPLC as described *vide supra*. The 100 µL was replaced with fresh ethanol/SCF solution after the removal of each aliquot. A calibration curve was made by analyzing the peak area as a function of standard concentrations of 0.005, 0.01, 0.02, 0.05 mg/mL IBU in ethanol/SCF (1:1 v/v). Experiments were repeated in triplicate. Figure S11 provides the calibration curve as well as the release profile of IBU from UiO-AZB nanoparticles.

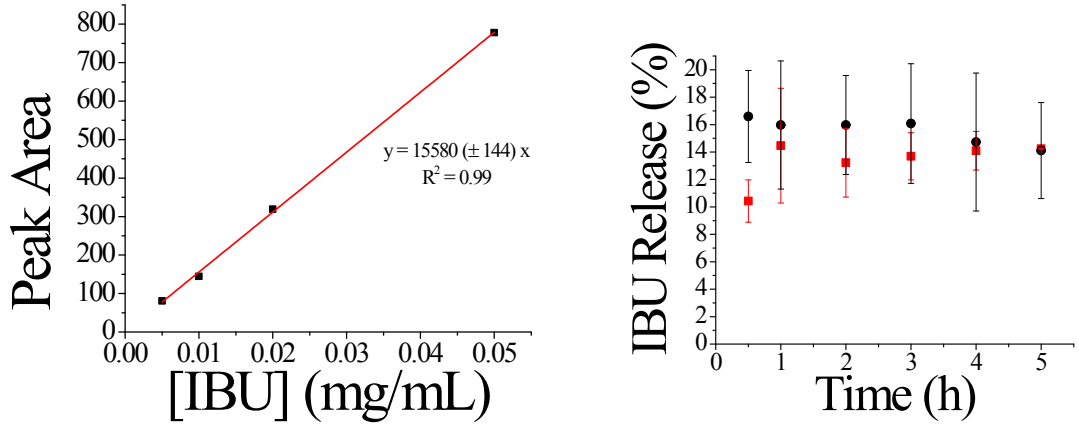

Figure S9. Left: Calibration curve of IBU. Right: IBU release from UiO-AZB in the dark (black circles) and upon irradiation with 1000 W white light (red squares) indicating rapid diffusion from the material and no release dependence on irradiation.

Caffeine release: The release profiles of caffeine from the IBU loaded UiO-AZB nanoparticles were measured using HPLC. 2.4 mg of the caffeine loaded UiO-AZB nanoparticles were submersed into 5 mL 1:1 (v/v) ethanol/SCF in a 24/40 jointed quartz cuvette. The cuvettes were capped with a rubber septum and kept either wrapped in tin foil (dark conditions) or placed in front of a 1000 W white light source (irradiated conditions). 100 µL aliquots were removed over time from the cuvettes and placed into a glass LC/MS vial. Aliquots were diluted with 900 µL ethanol/SCF (1:1 v/v) and analyzed using HPLC as described *vide supra*. The 100 µL was replaced with fresh ethanol/SCF solution after the removal of each aliquot. A calibration curve was made by analyzing the peak area as a function of standard concentrations of 0.0005, 0.001, 0.002, 0.005 mg/mL caffeine in ethanol/SCF (1:1 v/v). Experiments were repeated in triplicate. Figure S12 provides the calibration curve as well as the release profile of caffeine from UiO-AZB nanoparticles.

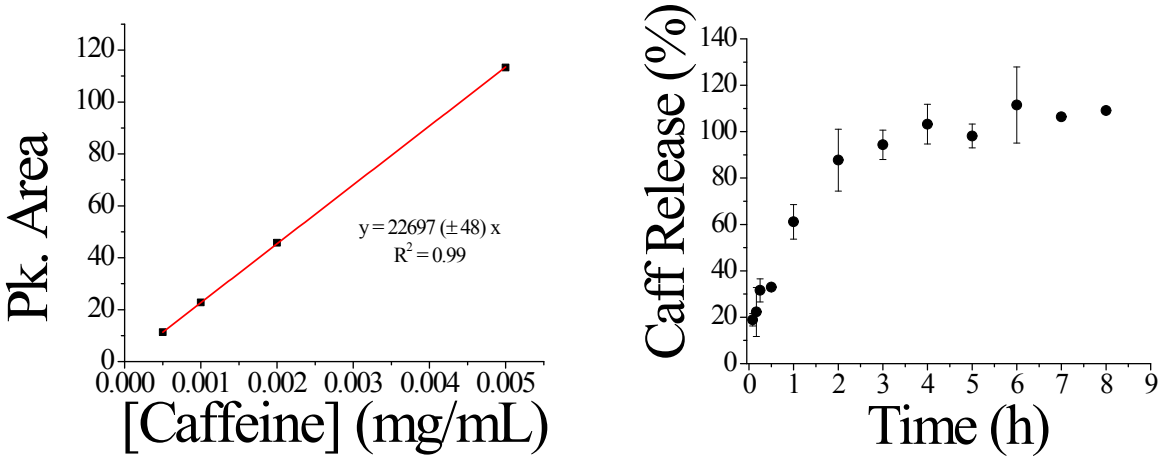

Figure S10. Left: Calibration curve for caffeine. Right: caffeine release from UiO-AZB in the dark (black circles) indicating rapid diffusion of caffeine from the material in the dark.

NR release: The release of NR from the NR loaded UiO-AZB was measured using UV-Vis spectroscopy. 2.0 mg of the NR loaded UiO-AZB nanoparticles were submersed into 3 mL 1:1 (v/v) ethanol/SCF in a 24/40 jointed quartz cuvette. The cuvettes were capped with a rubber septum and kept either wrapped in tin foil (dark conditions) or placed in front of a white light source (irradiated conditions). The absorbance spectra from 200-800 nm of the supernatant solutions were measured over time. From the spectra, the absorbance at 575 nm was plotted as a function of time for each light exposure condition. Figure S13 confirms that only NR absorbs at this wavelength. Experiments were repeated in triplicate.

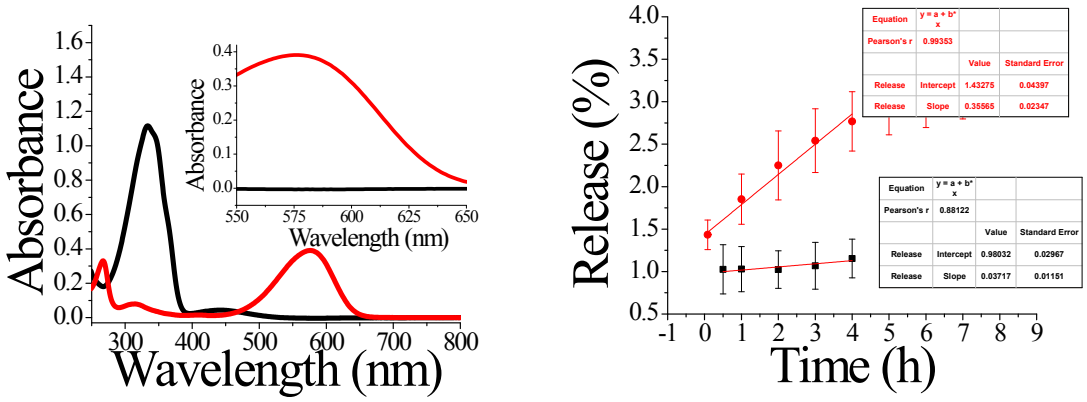

Figure S11. Left: Absorbance of AZB (black, 0.05 mM) and NR (red, 0.01 mM) demonstrating that AZB does not absorb at 575 nm where NR absorbance is monitored for release studies (inset). Right: Release of NR (%) in the dark (black) and under irradiation with 1000 W light (red).

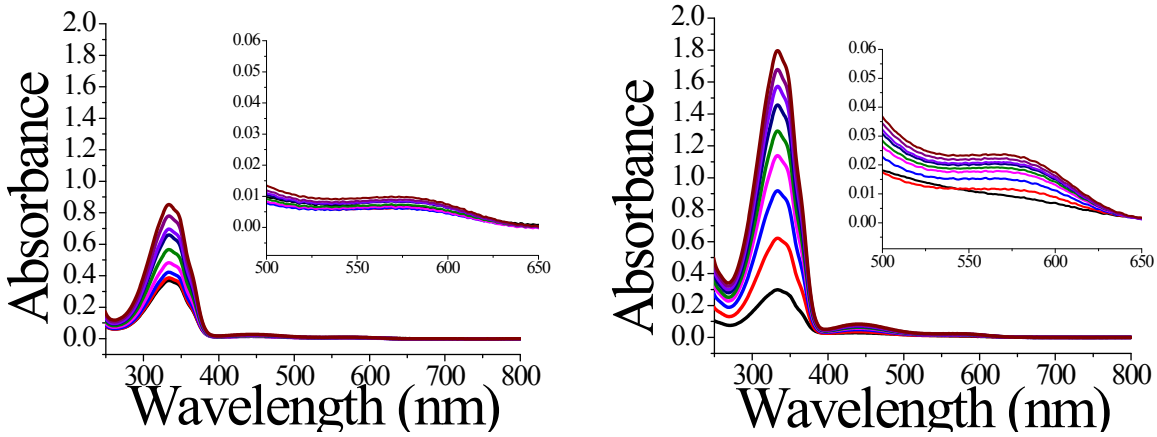

Figure S12.Left: Example of absorbance scansfor the release of NR (monitored at 575 nm, inset) under dark conditions (black, 30 min; red, 1 h; blue, 2 h; magenta, 3 h; green, 4 h; indigo, 5 h; light purple, 6 h; dark purple, 7 h; maroon, 8 h). Right: Example of absorbance scans for the release of NR (monitored at 575 nm, inset) under irradiation with 1000 W white light (black, 5 min; red, 1 h; blue, 2 h; magenta, 3 h; green, 4 h; indigo, 5 h; light purple, 6 h; dark purple, 7 h; maroon, 8 h).

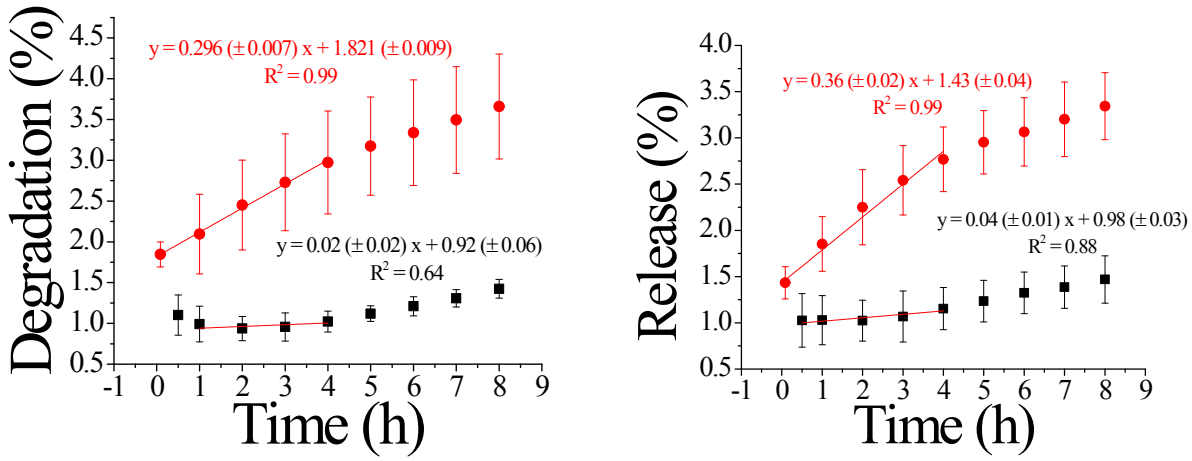

Figure S13. Left: Degradation (%, measured at 392 nm from the absorbance scans above) as a function of time in the dark (black squares) and under irradiation with 1000 W white light (red circles). The initial rates of degradation have been fitted to a linear profile to estimate how the material would behave in continuous flow conditions. Right: NR release (%, measured at 575 nm from the absorbance scans above) as a function of time in the dark (black squares) and under irradiation with 1000 W white light (red circles).

8. Cellular Studies

Cellular Uptake: HeLa cells were seeded in 35 mm glass bottom petri dishes (MatTek) at 10,000 cells per well and cultured for 24 h at 37 °C and 5% CO_2. To each dish 300 µL of 0.5 mg/mL UiO-AZB loaded with Nile red was added. After 30 min incubation at 37 °C the solution was removed and the cells were washed three time with PBS. Images were acquired using a confocal laser scanning microscope.

Cellular Toxicity: HeLa cells were seeded at 5,000 cells per well in a 96-well plate and cultured for 24 h at 37 °C and 5% CO_2. Solutions of UiO-AZB (2, 5, 10, 25, 50 µg/mL) in DMEM were added to the wells. After 72 h incubation the media was removed and cells were washed three times with PBS. To each well 10 µL of 5 mg/mL MTT and 90 µL of DMEM were added and incubated at 37 °C. After 4 h the media was removed and the formazan crystals were dissolved in 100 µL DMSO. The absorbance at 570 nm was measured using a microplate reader. Percent viability of the cells was calculated as the ratio of mean absorbance of triplicate readings with respect to mean absorbance of control wells.

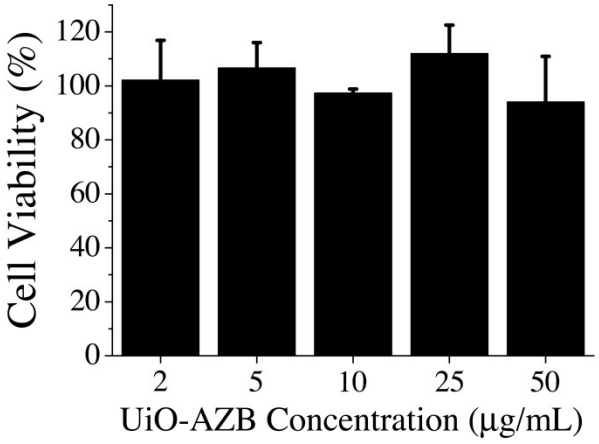

Figure S14. *In vitro* cytotoxicity of UiO-AZB against HeLa cells at different concentrations of UiO-AZB. Untreated cells were used as a control. Each data point is the average of three independent experiments.

9. References

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(2) Schaate, A.; Dühnen, S.; Platz, G.; Lilienthal, S.; Schneider, A. M.; Behrens, P. *Euro. J. Inorg. Chem***2012**, *2012*, 790.
(3) *Cold Spring Harbor Protocols***2011**, *2011*, pdb.rec066696.
(4) Horcajada, P.; Serre, C.; Vallet-Regí, M.; Sebban, M.; Taulelle, F.; Férey, G. *Angew. Chem. Int. Ed.***2006**, *45*, 5974.