Electronic Supplementary Information For

Tantalum Oxide Nanoparticles as Versatile Contrast Agents for X-ray Computed Tomography

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1. Synthetic Details for Tantalum Oxide Nanocrystals (TaO_x NCs).

1.1. General Information

All reactions, unless otherwise stated, were performed with oven-dry glassware. All other reagents and solvents were obtained from commercial suppliers and used without further purification. Centrifugation to isolate NCs were performed on a Sorvall LYNX 4000 Superspeed centrifuge.

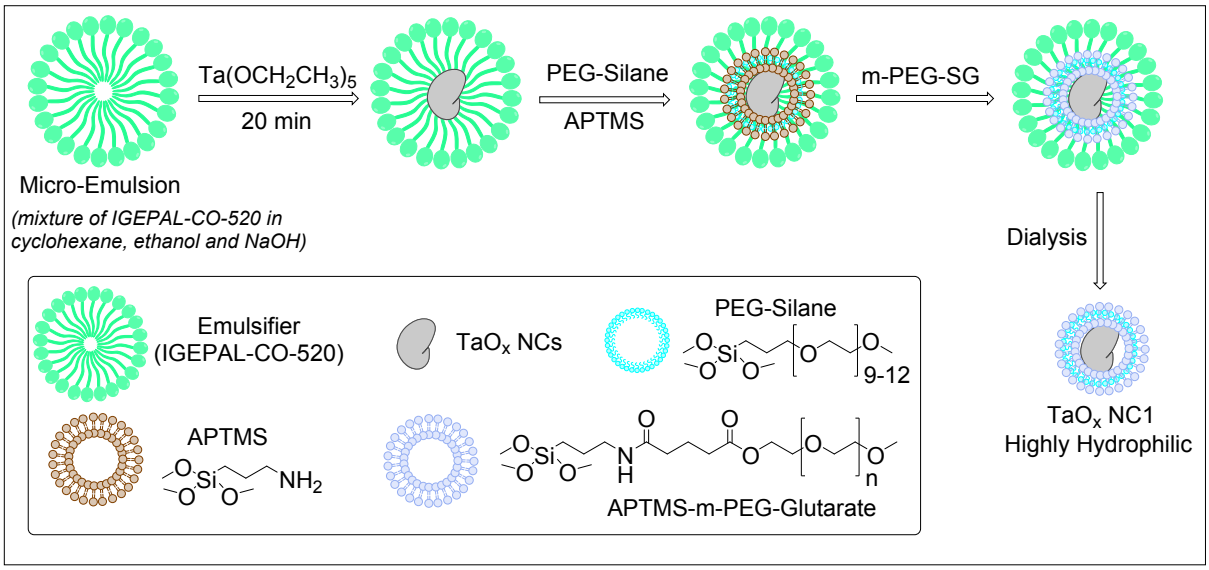
1.2. Synthesis of Tantalum Oxide NCs.

Typical Procedure: In a 250 mL, one neck round bottom flask, fitted with a septa, IGEPAL®-CO-520 (poly(oxyethylene)nonylphenyl ether); average M_n 441, ALDRICH, 23.0 g), Cyclohexane (≥99%, A.C.S. spectrophotometric grade, SIGMA-ALDRICH, 200 mL) and Ethanol (200 Proof, Anhydrous, KOPTEC USP, 2.5 mL), were added and the contents were stirred to obtain a clear solution. To this stirring mixture, a solution of Sodium Hydroxide (100 mM, 2.5 mL) was added and the micro-emulsion so obtained was sonicated in a water bath to ensure homogeneity. Next, Tantalum (V) ethoxide, (Ta_2O_5, 99.98% trace metal basis, ALDRICH, 0.5 mL) was added in one portion and the contents so obtained were stirred at ambient

temperature for 20 minutes. On addition of Ta_2O_5, the otherwise clear solution gave way to slight turbidity, indicating the formation of uncoated NCs. At this stage of the reaction, different silane end group reactants were added to form NCs with varying degree of hydrophilicity/hydrophobicity or to append fluorescent tags to the NC surface, as per requirement.

1.2.1. Synthesis of Extremely Hydrophilic Tantalum Oxide NCs (TaO_x NC1).

To the micro-emulsion mixture containing uncoated TaO_x NCs, 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 3.0 mL), quickly followed by (3-Aminopropyl)trimethoxysilane (APTMS, 97%, ALDRICH, 0.028 mL) were added. The resulting milky white suspension solution was stirred at room temperature for 16 h. The addition of reactants with silane end groups ensures a condensation reaction with the hydroxyl groups on the bare surface of TaO_x NCs and ensures a protective coating around it so that a well-dispersed collection of NCs is obtained. On absence of any PEG-Silane, agglomerated NCs are obtained (**Figure S1**). After 16 h, the reaction mixture is diluted to three times volume using a 1:1 mixture of Ethyl Ether (Anhydrous, Certified ACS, Fisher Scientific, 110 mL) and Hexane (meets ACS specifications, VWR Chemicals, 110 mL) and the NCs were isolated via centrifugation (15,000 rpm, 10 minutes, 10 °C) as white oily residue. This residue was suspended in ethyl ether and washed using a similar centrifugation procedure twice. The supernatants were discarded and the residue pellet so obtained was suspended in 100 mL Ethanol and Methoxy-poly(ethylene-glycol)-succinimidyl glutarate (m-PEG-SG-2000, Average MW 2000, LAYSAN BIO INC., 50 mg) was added to it.



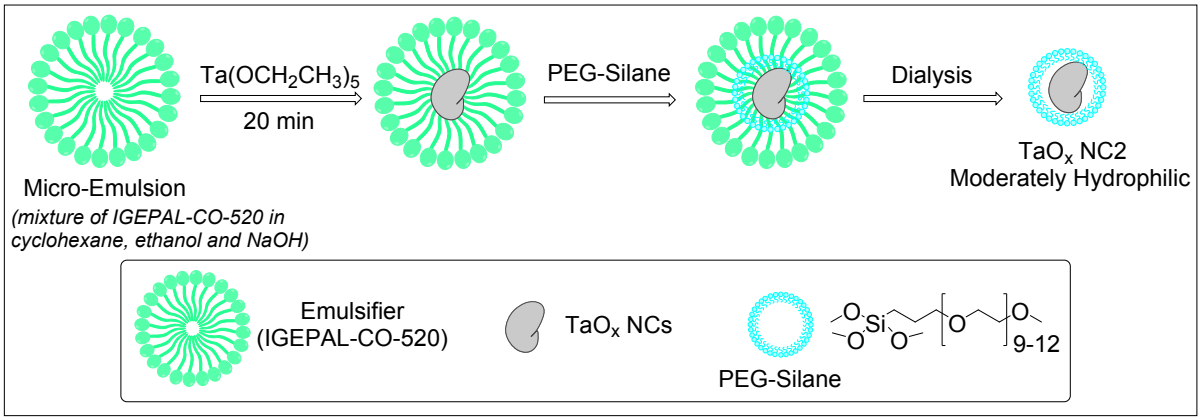
Scheme S1. Synthesis of Extremely Hydrophilic TaO_x NC1.

The contents so obtained were stirred at RT in dark for 16 h. After the aforementioned time, the solvent was removed on a rotary evaporator to reduce the volume to about 5 mL. This final residual solution was dissolved in water (10 mL) and transferred to Dialysis Membrane bags (SPECTRA/POR® 3 Dialysis Membrane, Standard RC Tubing, MWCO: 3.5 kD), clipped at both ends and dialyzed against water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the

dialysis bags were lyophilized to obtain the TaO_x NC1 as a white fluffy powder. Product Yield: 940 mg. Ta% = 73% (calculated from ICP-OES).

1.2.2. Synthesis of Moderately Hydrophilic Tantalum Oxide NCs (TaO_x NC2).

To the micro-emulsion mixture containing uncoated TaO_x NCs, 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 3.0 mL) was added. The resulting milky white suspension solution was stirred at room temperature for 16 h. After 16 h, the reaction mixture is diluted to three times volume using a 1:1 mixture of Ethyl Ether (Anhydrous, Certified ACS, Fisher Scientific, 110 mL) and Hexane (meets ACS specifications, VWR Chemicals, 110 mL) and the NCs were isolated via centrifugation (15,000 rpm, 10 minutes, 10 °C) as white oily residue. The residual oily pellet was dissolved in water (10 mL) and transferred to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the dialysis bags were lyophilized to obtain the TaO_x NC2 as a white sticky powder. Product Yield: 840 mg. Ta% = 78% (calculated from ICP-OES).

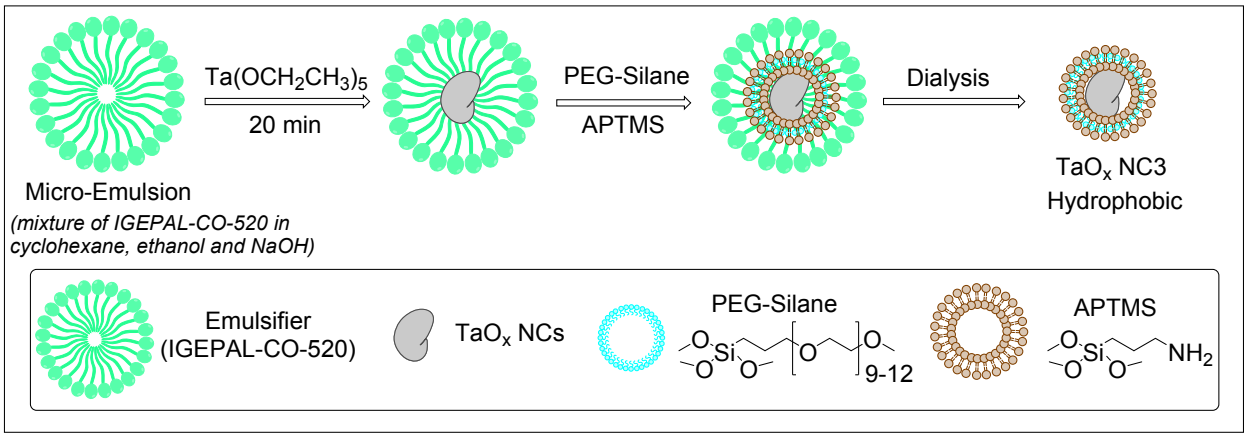


Scheme S2. Synthesis of Moderately Hydrophilic TaO_x NC2.

1.2.3. Synthesis of Hydrophobic Tantalum Oxide NCs (TaO_x NC3).

To the micro-emulsion mixture containing uncoated TaO_x NCs, 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 1.0 mL) followed by (3-Aminopropyl)trimethoxysilane (APTMS, 97%, ALDRICH, 6.0 mL) were added in rapid succession. The resulting milky white suspension solution was stirred at room temperature for 16 h. After 16 h, the reaction mixture is diluted to three times volume using a 1:1 mixture of Ethyl Ether (Anhydrous, Certified ACS, Fisher Scientific, 110 mL) and Hexane (meets ACS specifications, VWR Chemicals, 110 mL) and the NCs were isolated via centrifugation (15,000 rpm, 10 minutes, 10 °C) as white oily residue. This residue was suspended in ethyl ether and washed using a similar centrifugation procedure twice. This residual oily pellet was dissolved in water (10 mL) and transferred to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the

contents in the dialysis bags were lyophilized to obtain the TaO_x NC3 as a white free flowing powder. Product Yield: 900 mg. Ta% = 69% (calculated from ICP-OES).



Scheme S3. Synthesis of Hydrophobic TaO_x NC3.

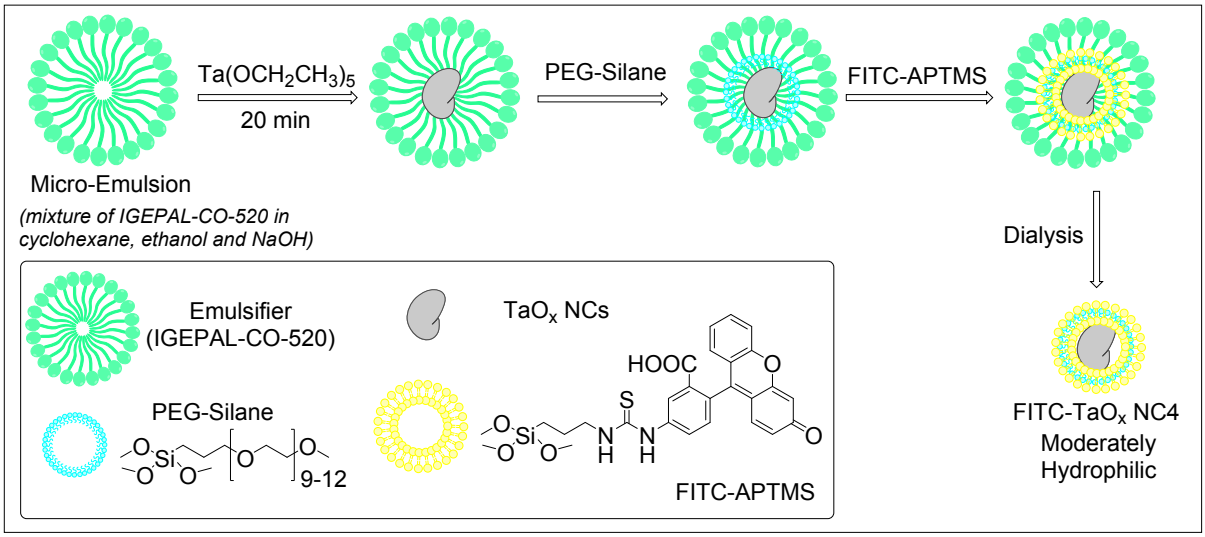
1.3. Synthesis of Fluorescently labeled Tantalum Oxide NCs.

Typical Procedure: In a 4 dram vial, Fluorescein Isothiocyanate (FITC, Isomer I, ≥90%, SIGMA, 20.0 mg) and (3-Aminopropyl)trimethoxysilane (APTMS, 97%, ALDRICH, 0.040 mL) were taken and Ethanol (200 Proof, Anhydrous, KOPTEC USP, 10.0 mL) was added to it. This reaction mixture was stirred at room temperature in the dark for 12 h. Separately, in a 250 ml, one neck round bottom flask, fitted with a septa, IGEPAL®-CO-520 (average M_n 441, ALDRICH, 23.0 g), Cyclohexane (≥99%, A.C.S. spectrophotometric grade, SIGMA-ALDRICH, 200 mL) and Ethanol (200 Proof, Anhydrous, KOPTEC USP, 2.5 mL), were added and the contents were stirred to obtain a clear solution. To this stirring mixture, a solution of Sodium Hydroxide (100 mM, 2.5 mL) was added and the micro-emulsion so obtained was sonicated in a water bath to ensure homogeneity. Next, Tantalum (V) ethoxide, (Ta_2O_5, 99.98% trace metal basis, ALDRICH, 0.5 mL) was added in one portion and the contents so obtained were stirred at ambient temperature for 20 minutes. On addition of Ta_2O_5, the otherwise clear solution gave way to slight turbidity, indicating the formation of uncoated NCs. At this stage of the reaction, different silane end group reactants were added to form NCs with varying degree of hydrophilicity/hydrophobicity or to append fluorescent tags to the NC surface, as per requirement.

1.3.1. Synthesis of FITC labeled Hydrophilic Tantalum Oxide NCs (FITC-TaO_x NC4).

To the micro-emulsion mixture containing uncoated TaO_x NCs, 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 3.0 mL) followed by the mixture of APTMS-FITC prepared beforehand were added to it in quick succession. The resulting yellow colored suspension solution was stirred at room temperature for 16 h in the dark. After 16 h, the reaction mixture is diluted to three times volume using a 1:1 mixture of Ethyl Ether (Anhydrous, Certified ACS, Fisher Scientific, 110 mL) and Hexane (meets ACS specifications, VWR Chemicals, 110 mL) and the NCs were isolated via centrifugation (15,000 rpm, 10 minutes, 10 °C) as a yellow colored oily residue. The residual oily pellet was dissolved in water (10 mL) and transferred to Dialysis Membrane bags (SPECTRA/POR® 4

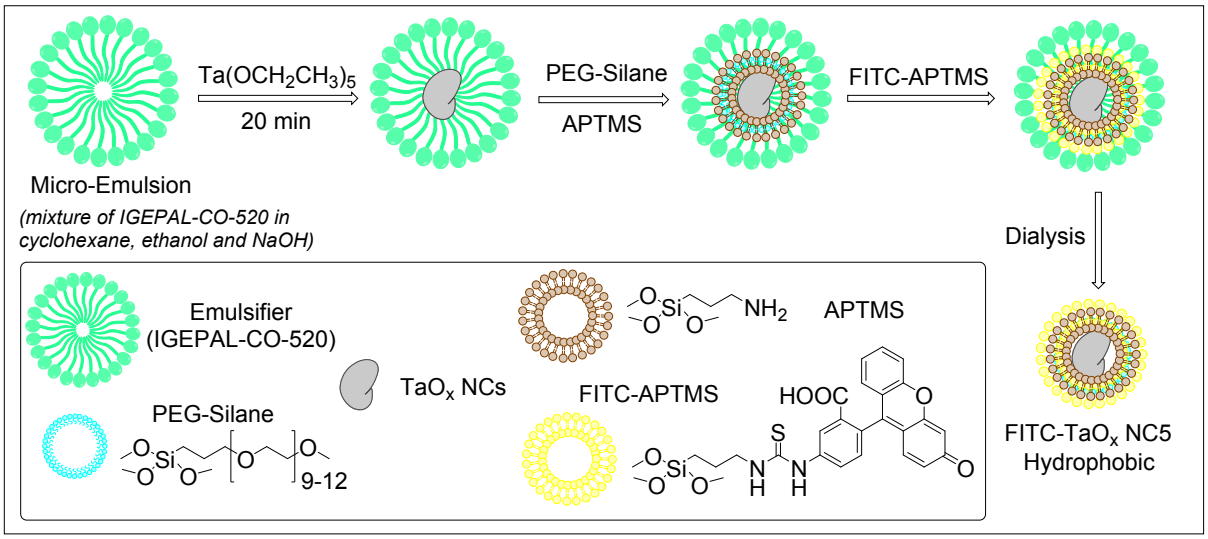
Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the dialysis bags were lyophilized to obtain the FITC-TaO_x NC4 as a yellow orange colored sticky powder. Product Yield: 800 mg. Ta% = 61% (calculated from ICP-OES).



Scheme S4. Synthesis of FITC-labeled moderately hydrophilic FITC-TaO_x NC4.

1.3.2. Synthesis of FITC-labeled Hydrophobic Tantalum Oxide NCs (FITC-TaO_x NC5).

To the micro-emulsion mixture containing uncoated TaO_x NCs, 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 3.0 mL), (3-Aminopropyl)trimethoxysilane (APTMS, 97%, ALDRICH, 6.0 mL) and the mixture of APTMS-FITC prepared beforehand were added in quick succession. The resulting yellow colored suspension solution was stirred at room temperature for 16 h in the dark. After 16 h, the reaction mixture was diluted to three times volume using a 1:1 mixture of Ethyl Ether (Anhydrous, Certified ACS, Fisher Scientific, 110 mL) and Hexane (meets ACS specifications, VWR Chemicals, 110 mL) and the NCs were isolated via centrifugation (15,000 rpm, 10 minutes, 10 °C) as yellow oily residue. The residual oily pellet was dissolved in water (10 mL) and transferred to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the dialysis bags were lyophilized to obtain the FITC-TaO_x NC5 as a yellow-orange colored free flowing powder. Product Yield: 740 mg. Ta% = 56% (calculated from ICP-OES).



Scheme S5. Synthesis of FITC-labeled hydrophobic FITC-TaO_x NC5.

2. Characterization Details for TaO_x NCs.

2.1. General Information-Physicochemical Characterization (for NCs and NPs).

The TaO_x NCs and NPs were characterized using a variety of techniques. The surface morphology was determined using Scanning Electron Microscopy (SEM; JEOL 7500F with a cold field emission emitter). For the TaO_x-doped MCS, surface morphology was determined by SEM carried out using a Hitachi S-3500N, operating at 20 keV and a working distance of 10 mm. Encapsulation of TaO_x NCs within PLGA and mesoporous silica was observed using Transmission Electron Microscopy (TEM; JEOL, 2200FS, JEOL, USA). The hydrophobic TaO_x NCs, size was determined by analyzing corresponding TEM images using Image J software. For each batch, 200 NCs were analyzed in triplicates with images taken from different portions of a TEM grid. For hydrophilic TaO_x NCs and TaO_x NP formulations, hydrodynamic radii (D_h, nm), polydispersity index (PDI) and zeta potential (ζ, mV). were determined using Dynamic Light Scattering, carried out on a Zetasizer instrument (Malvern, USA). Fourier Transform Infrared (FTIR) spectroscopy was performed on a Mattson Genesis 3025 FTIR spectrometer. FTIR was used to verify the surface coating of silyl groups and PEG chains on the TaO_x NCs as well as to ascertain the presence of PLGA, Silica and FITC in the different TaO_x NP formulations. Energy Dispersive Spectroscopy (EDS; TEM-EDS, JEOL, 2200 FS, JEOL, USA) was used to confirm the presence of Ta and Si in the NPs. For EDS, INCA software program was employed to carry out analysis of samples prepared on a TEM grid. BET surface area and porosity analysis was performed on a ASAP 2020 Accelerated Surface Area and Porosimetry System (Micromeritics, USA). For the MCS, White light interferometry was conducted on dry 1 cm^2 sample, using a Zygo New View 5000. The microstructure was imaged at 640 x 640 μm^2 area, showing a rough surface indicative of a porous structure. To determine the molecular state of TaO_x, X-ray Photoelectron Spectroscopy (XPS) of the NCs was performed using a Perkin Elmer Phi 5600 ESCA system with a Mg Kα X-ray source at a take-off angle

of 45°.For the Inductively Coupled Optical Emission Spectroscopy (ICP-OES) was performed to analyze the Ta content in various NCs and NP formulations.

Sample Preparation for TEM and EDS: To carry out TEM analysis, square mesh, carbon support film on copper grids (CF300-Cu, 300 mesh, standard thickness, Electron Microscopy Sciences, USA) were used. For hydrophobic NCs, a homogenous, semi-transparent suspension in hexane was prepared and 10 µL was dropped on the grid. The suspension was allowed to stand for 2 minutes to allow for the crystals to settle down, following which the residual solvent was blown off and the grid was air dried prior to imaging on the electron microscope. For NPs and hydrophilic NCs, a homogenous aqueous suspension was prepared and 10 µL was gently placed on the grid. The particles were allowed to settle down over a period of 30 minutes and the residual aqueous drop was absorbed using a kimwipe. The resulting grid was air dried prior to imaging.

Sample Preparation for SEM: For SEM analysis, freeze-dried NPs were mounted on aluminum stubs using high vacuum carbon tabs. The solid samples were placed on the carbon tabbed aluminum stubs and pressed lightly using a spatula to seat the particles. The stubs were gently tapped to remove any loose particles, thus forming a thin uniform layer of particles. For the liquid samples, NP dispersions were placed on 10 mm x 10 mm silicon wafers attached on top of aluminum stubs. The solution was then allowed to dry in air. Finally, both the type of sample stubs were coated with Iridium with an approximate thickness of 2.7 nm. This coating was performed in a Quorum Technologies/Electron Microscopy Sciences Q150T turbo pumped sputter coater (Quorum Technologies, Laughton, East Sussex, England BN8 6BN) purged with argon. Finally, these sample stubs were dried in vacuum for 48 h prior to imaging. For the TaO_x-doped MCS, hydrated scaffolds were frozen in liquid nitrogen and sectioned with a razor blade before being placed on an aluminum stub. All samples were sputter coated with gold for 4 minutes at 40 mA and imaged subsequently.

Sample Preparation for FTIR: For FTIR analysis, 1 mg of the solid sample was mixed with 150 mg of dry Potassium Bromide (KBr, Uvasol®, Millipore Sigma) and crushed to a fine powder using a mortar pestle. About 100 mg of the ground mixture was made into a transparent or translucent disc using a die assembly and a hydraulic press. The disc so obtained was transferred to a sample holder and analyzed for signals in the IR spectrum range. For samples that were in liquid state or as an oil, a diluted sample was prepared in chloroform as the solvent. A drop of this solution was put on a sodium chloride disc for analysis in the IR spectrum range.

Explanation of peaks observed in FTIR for TaO_x NCs: Typically, silanes are characterized by one or more strong infrared bands in the region of 1300–1000 cm^{-1} corresponding to the Si-O-Si stretching vibration. The presence of a silane coating on all the TaO_x NC variants was evident from strong IR bands centered at 1100 cm^{-1}. FTIR spectra of various TaO_x NCs also contain peaks that are in concordance with various surface functional groups such as a network of H-bonded hydroxyl groups (broad bands centered at 3380 cm^{-1}), repeating PEG units (broad band centered about 1100 cm^{-1}, corresponding to the asymmetric C-O-C stretching of the repeating *-O-CH_2-O-CH_2-O-* groups; superimposed with the Si-O-Si stretching vibration) and amine groups (IR peaks centered around 1634 cm^{-1} corresponding to the N-H bend).

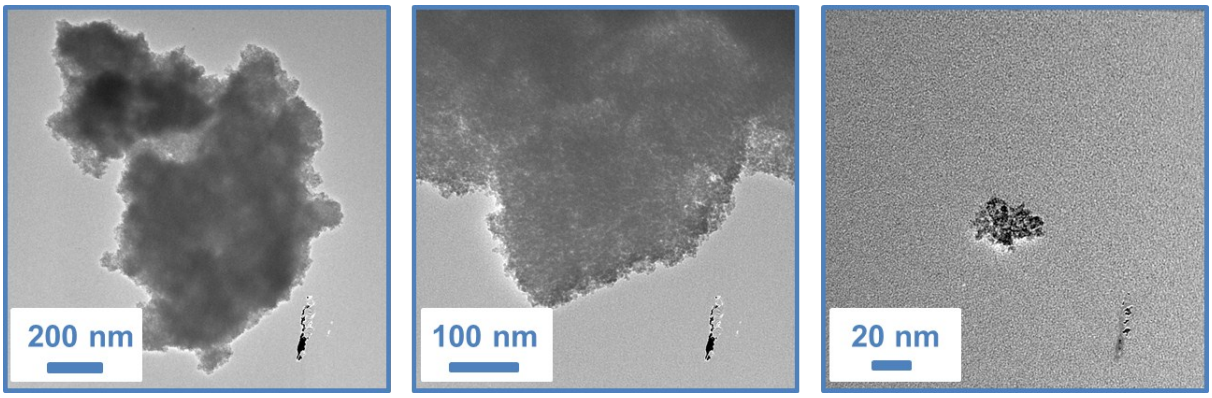


Figure S1. Transmission Electron Microscopy (TEM) images of bare TaO_x NCs prepared without addition of any surface coating PEG-Silane. The agglomeration of NCs is very evident.

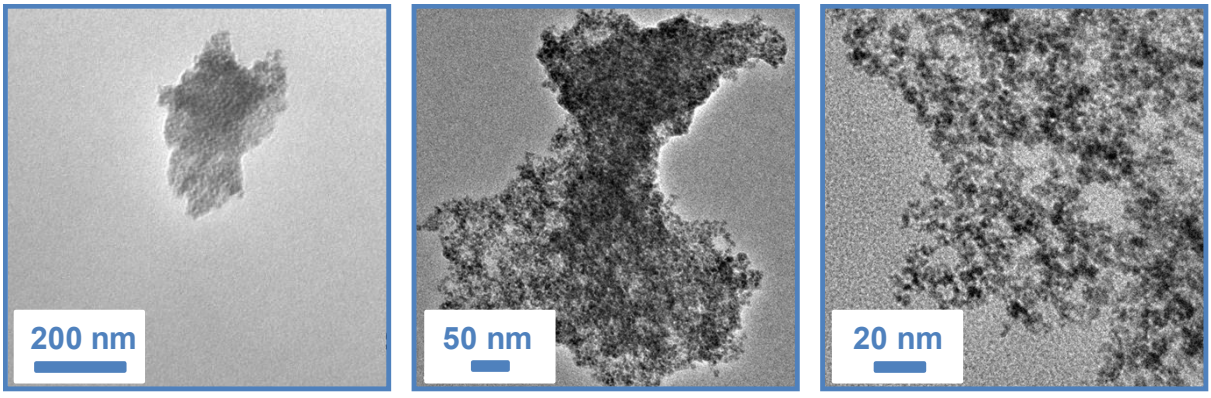


Figure S2. Transmission Electron Microscopy (TEM) images of bare TaO_x NCs synthesized using APTMS as a singular surface coating agent. No PEG-Silane was used. The agglomeration of the resulting NCs signifies the exclusivity of a PEG based agent required to form a well dispersed collection of TaO_x NCs.

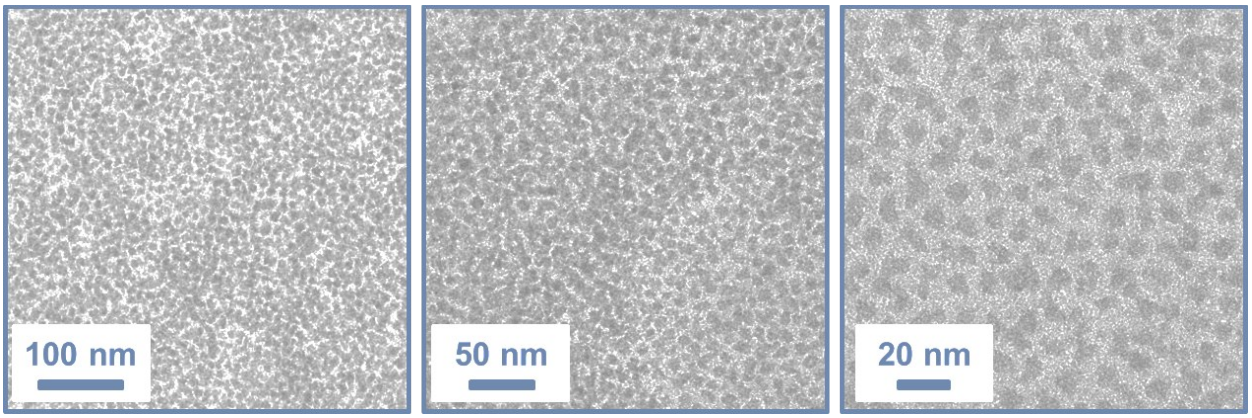


Figure S3. Transmission Electron Microscopy (TEM) images of TaO_x NC1. The left, center and right panels correspond to TaO_x NC1 obtained from three different batches and show excellent homogeneity in size and morphology.

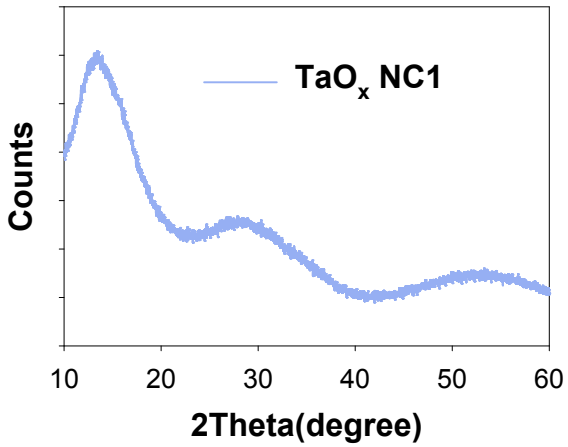


Figure S4. X-ray diffraction (XRD) pattern of TaO_x NC1. XRD patterns were obtained on Bruker D8 DaVinci diffractometer equipped with Cu X-ray radiation operating at 40 kV and 40 mA. Peak intensities were obtained by counting with the Lynxeye detector every 0.02° at sweep rates of 1.2° 2θ /min. The sample was place in a PVMA sample holder. The sample was rotated at 5 degrees per minute.

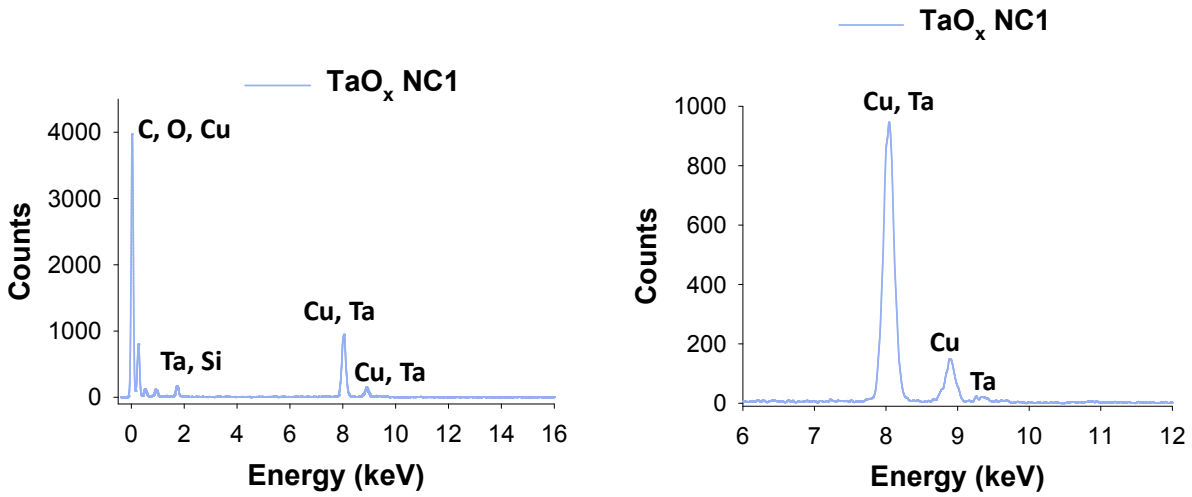


Figure S5. Energy Dispersive Spectroscopy (EDS) for TaO_x NC1, showing the presence of Ta and Si in the NCs. The Cu peaks can be ascertained to the grid used for TEM. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

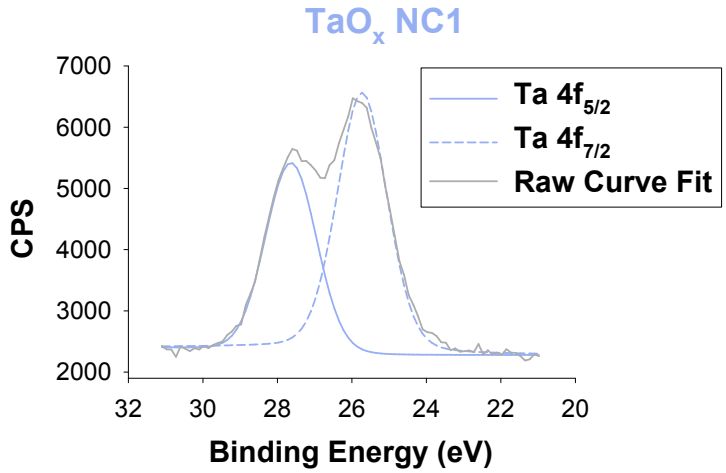


Figure S6. The narrow scan X-ray Photoelectron Spectroscopy (XPS) for TaO_x NC1, showing Ta $4f_{7/2}$ and Ta $4f_{5/2}$ that are close to characteristic Ta^{2+} in TaO, as reported in literature.

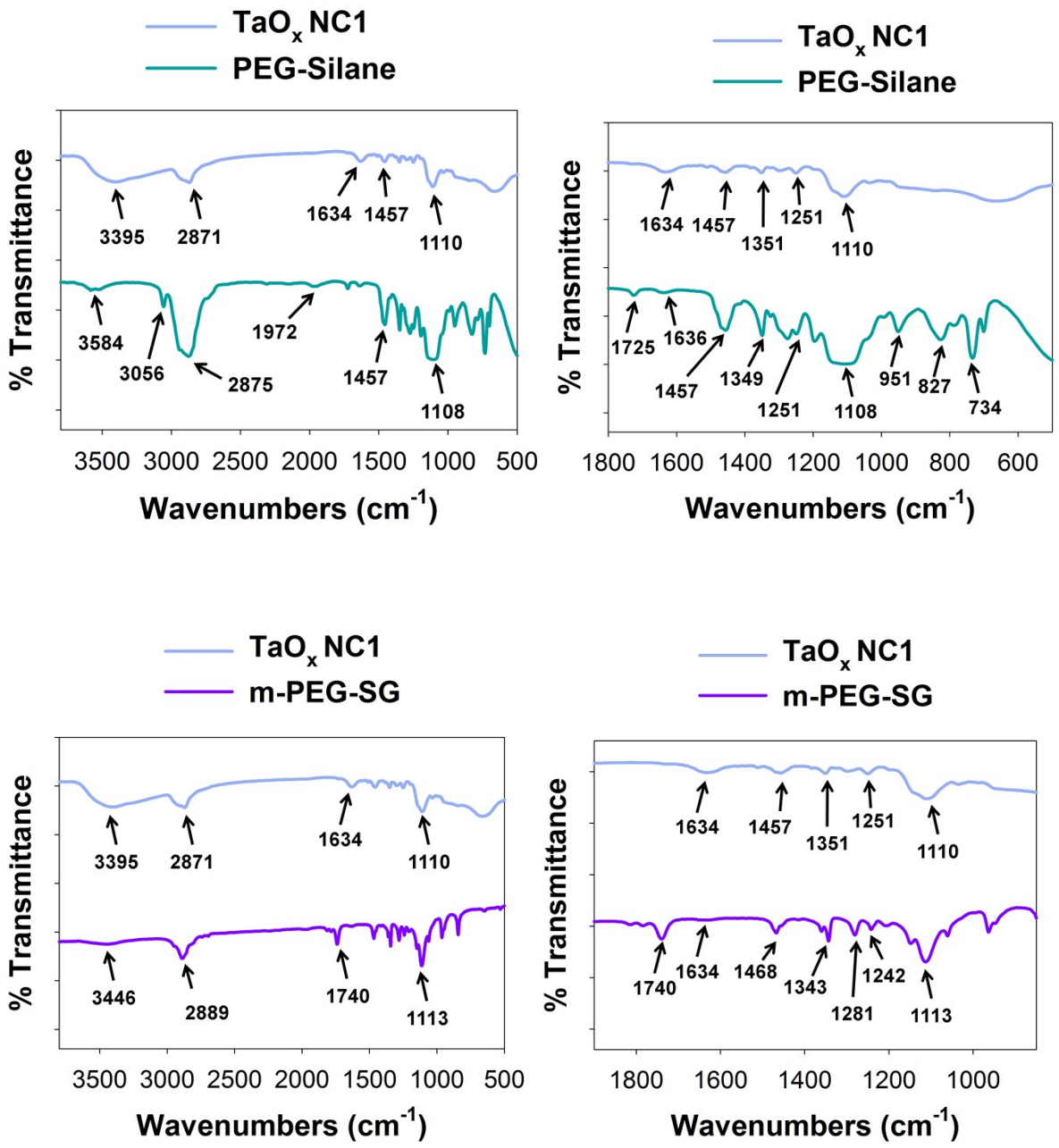


Figure S7. FTIR Spectra showing the surface coating of PEG-Silane (*top panel*) and Methoxy-PEG-succinimidyl glutarate (m-PEG-SG) (*bottom panel*) on the as synthesized TaO_x NC1. Prominent and common transmittance peaks are pointed out.

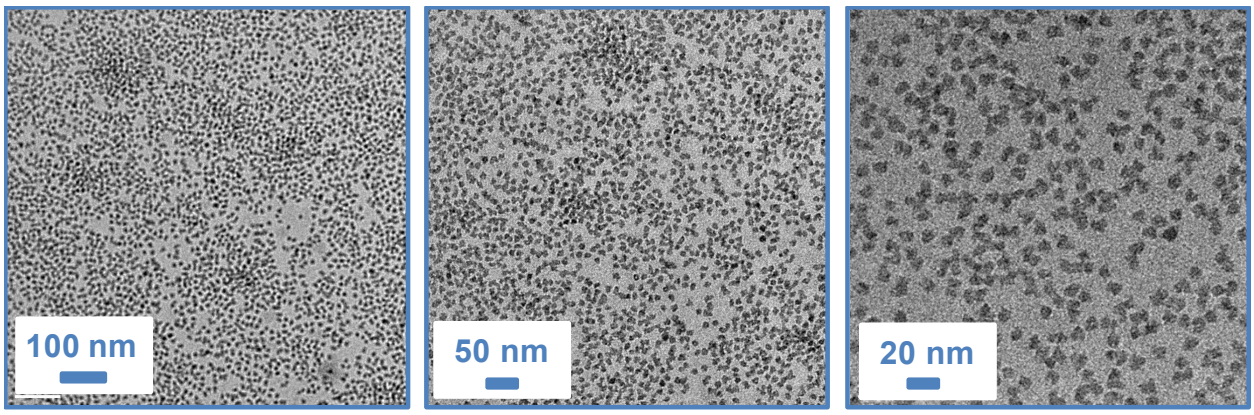


Figure S8. Transmission Electron Microscopy (TEM) images of TaO_x NC2. The left, center and right panels correspond to TaO_x NC2 obtained from three different batches and show excellent homogeneity in size and morphology.

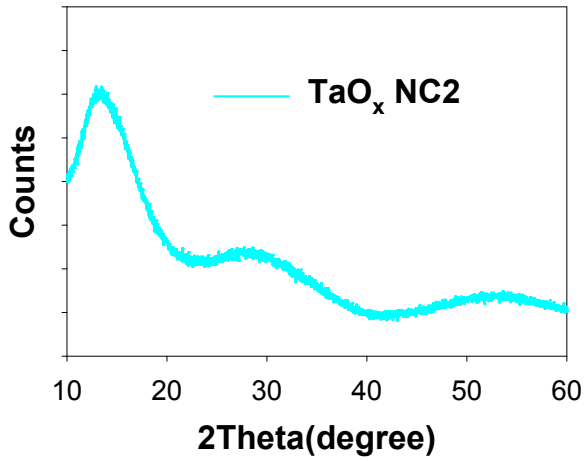


Figure S9. X-ray diffraction (XRD) pattern of TaO_x NC2. XRD patterns were obtained on Bruker D8 DaVinci diffractometer equipped with Cu X-ray radiation operating at 40 kV and 40 mA. Peak intensities were obtained by counting with the Lynxeye detector every 0.02° at sweep rates of 1.2° 2θ /min. The sample was place in a PVMA sample holder. The sample was rotated at 5 degrees per minute.

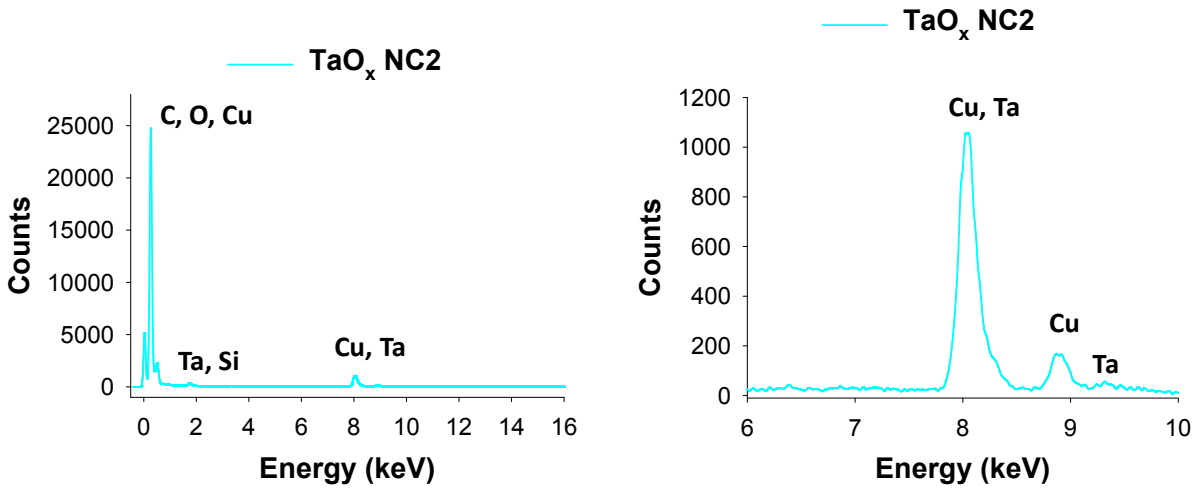


Figure S10. Energy Dispersive Spectroscopy (EDS) for TaO_x NC2, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

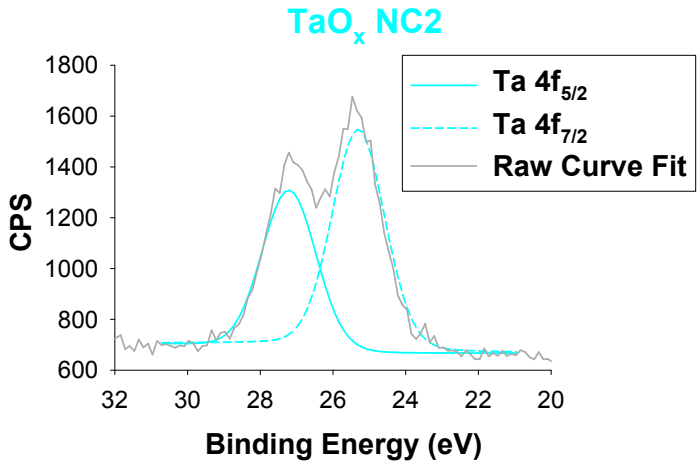


Figure S11. The narrow scan X-ray Photoelectron Spectroscopy (XPS) for TaO_x NC2, showing Ta $4f_{7/2}$ and Ta $4f_{5/2}$ that are close to characteristic Ta^{2+} in TaO, as reported in literature.

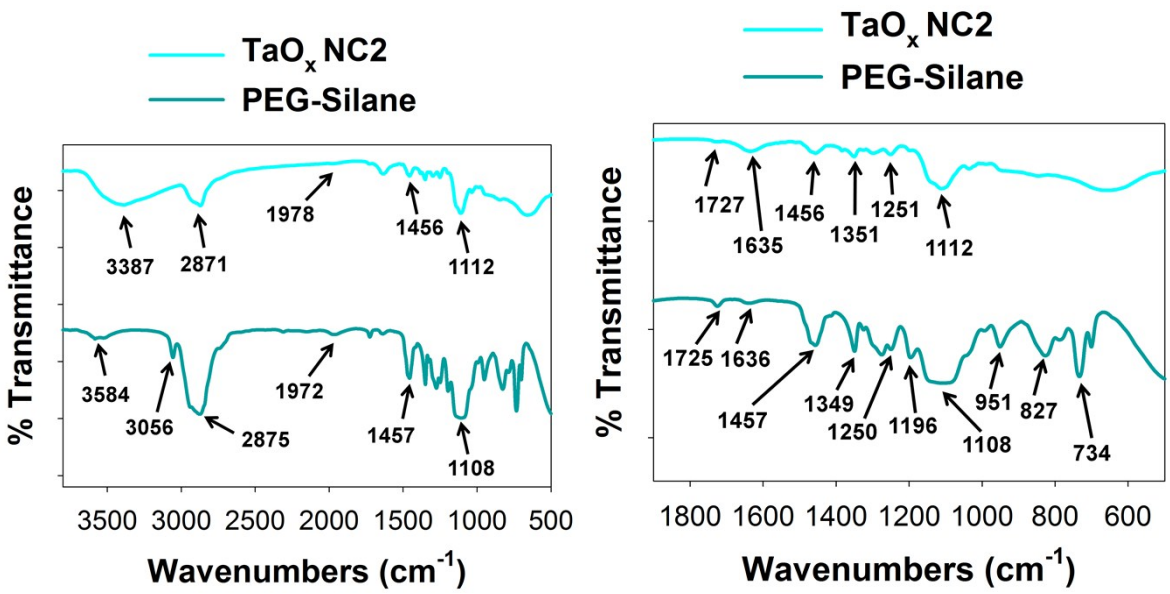


Figure S12. FTIR Spectra showing the surface coating of PEG-Silane on the as synthesized TaO_x NC2. Prominent and common transmittance peaks are pointed out.

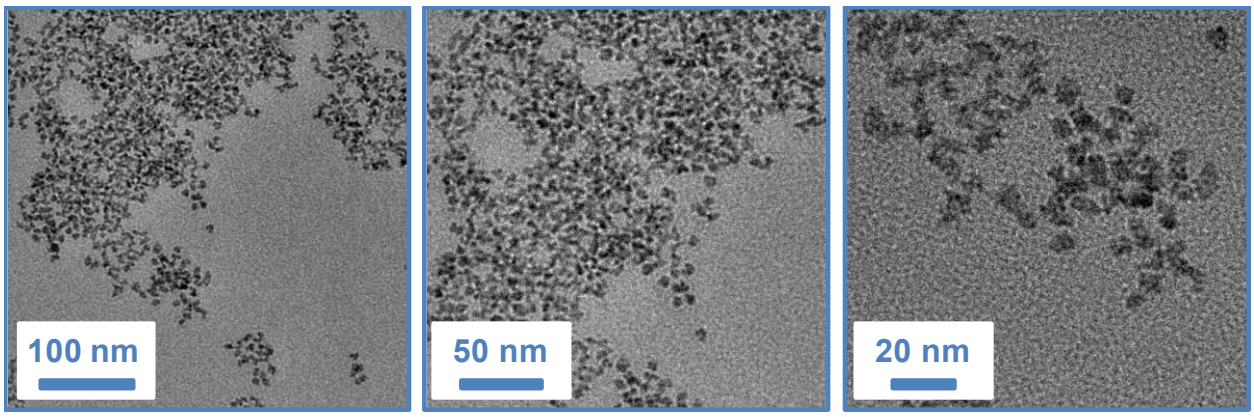


Figure S13. Transmission Electron Microscopy (TEM) images of TaO_x NC3. The left, center and right panels correspond to TaO_x NC3 obtained from three different batches and show excellent homogeneity in size and morphology.

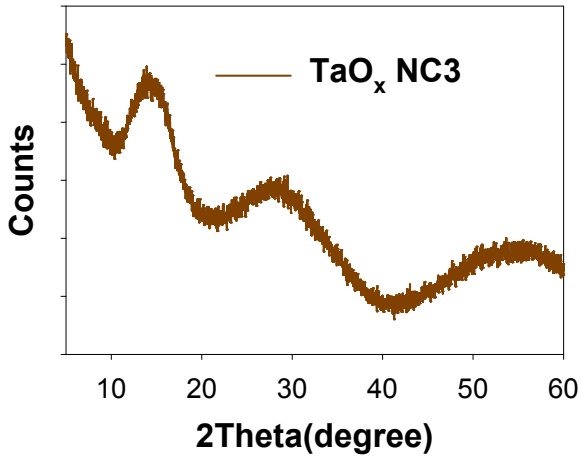


Figure S14. X-ray diffraction (XRD) pattern of TaO_x NC3. XRD patterns were obtained on Bruker D8 DaVinci diffractometer equipped with Cu X-ray radiation operating at 40 kV and 40 mA. Peak intensities were obtained by counting with the Lynxeye detector every 0.02° at sweep rates of 1.2° 2θ /min. The sample was place in a PVMA sample holder. The sample was rotated at 5 degrees per minute.

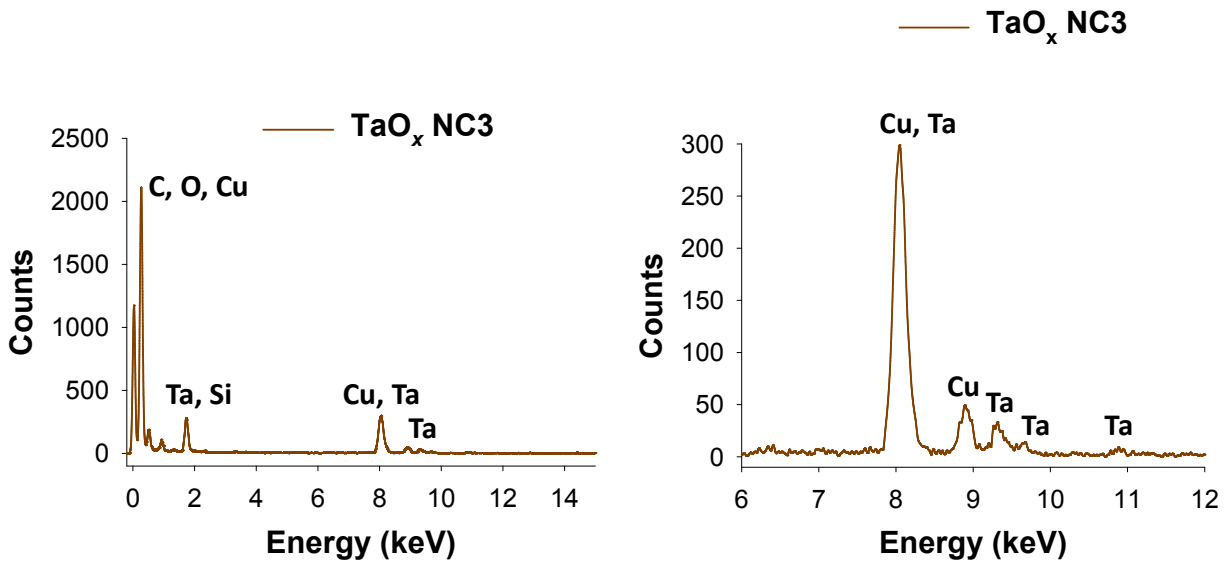


Figure S15. Energy Dispersive Spectroscopy (EDS) for TaO_x NC3, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

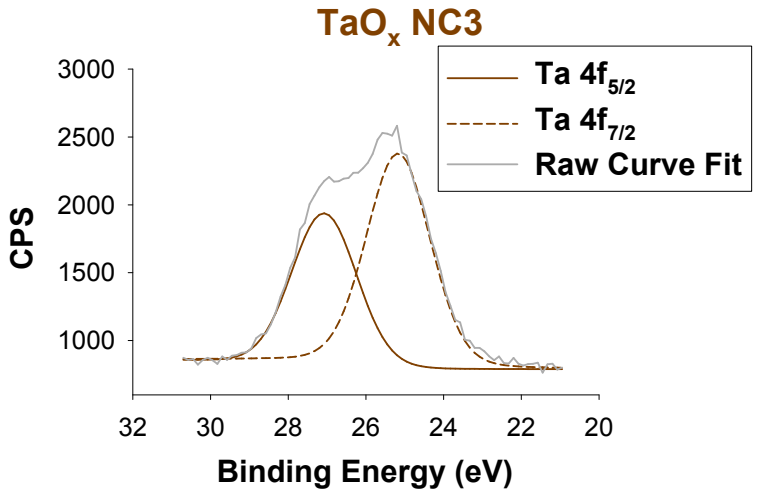


Figure S16. The narrow scan X-ray Photoelectron Spectroscopy (XPS) for TaO_x NC3, showing Ta $4f_{7/2}$ and Ta $4f_{5/2}$ that are close to characteristic Ta^{2+} in TaO, as reported in literature.

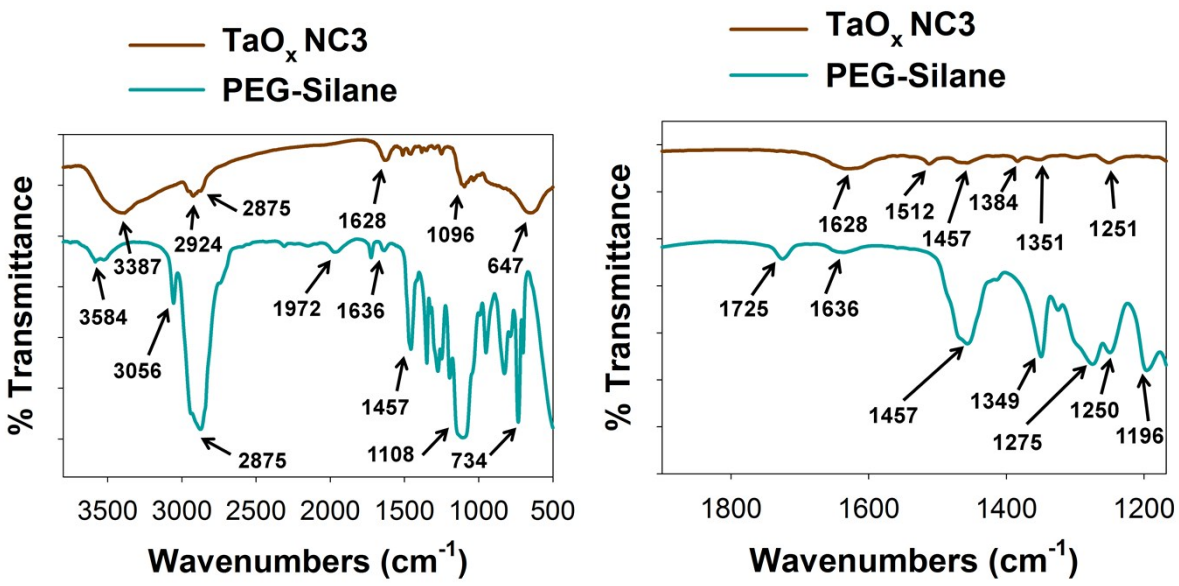


Figure S17. FTIR Spectra showing the surface coating of PEG-Silane on the as synthesized TaO_x NC3. Prominent and common transmittance peaks are pointed out.

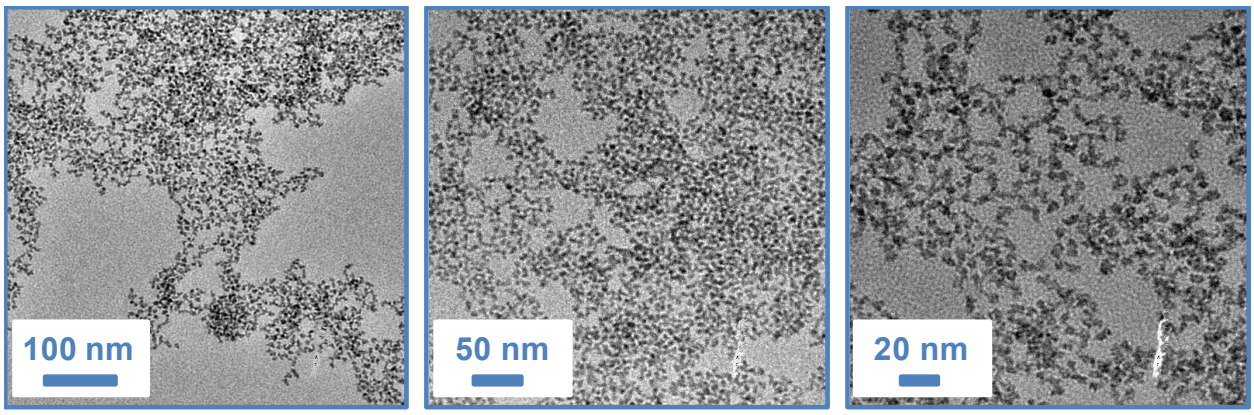


Figure S18. Transmission Electron Microscopy (TEM) images of FITC-TaO_x NC4. The left, center and right panels correspond to FITC-TaO_x NC4 obtained from three different batches and show excellent homogeneity in size and morphology.

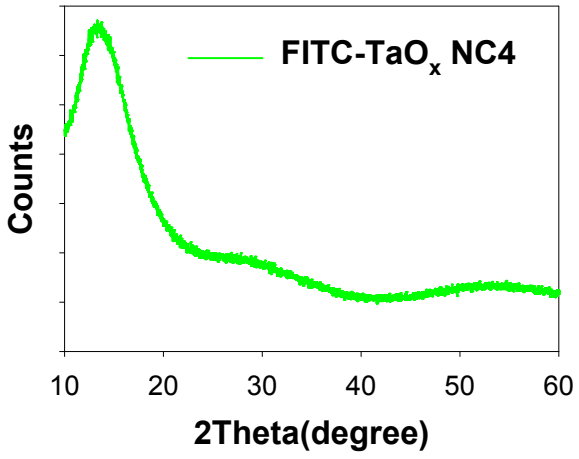


Figure S19. X-ray diffraction (XRD) pattern of TaO_x NC4. XRD patterns were obtained on Bruker D8 DaVinci diffractometer equipped with Cu X-ray radiation operating at 40 kV and 40 mA. Peak intensities were obtained by counting with the Lynxeye detector every 0.02° at sweep rates of 1.2° 2θ /min. The sample was place in a PVMA sample holder. The sample was rotated at 5 degrees per minute.

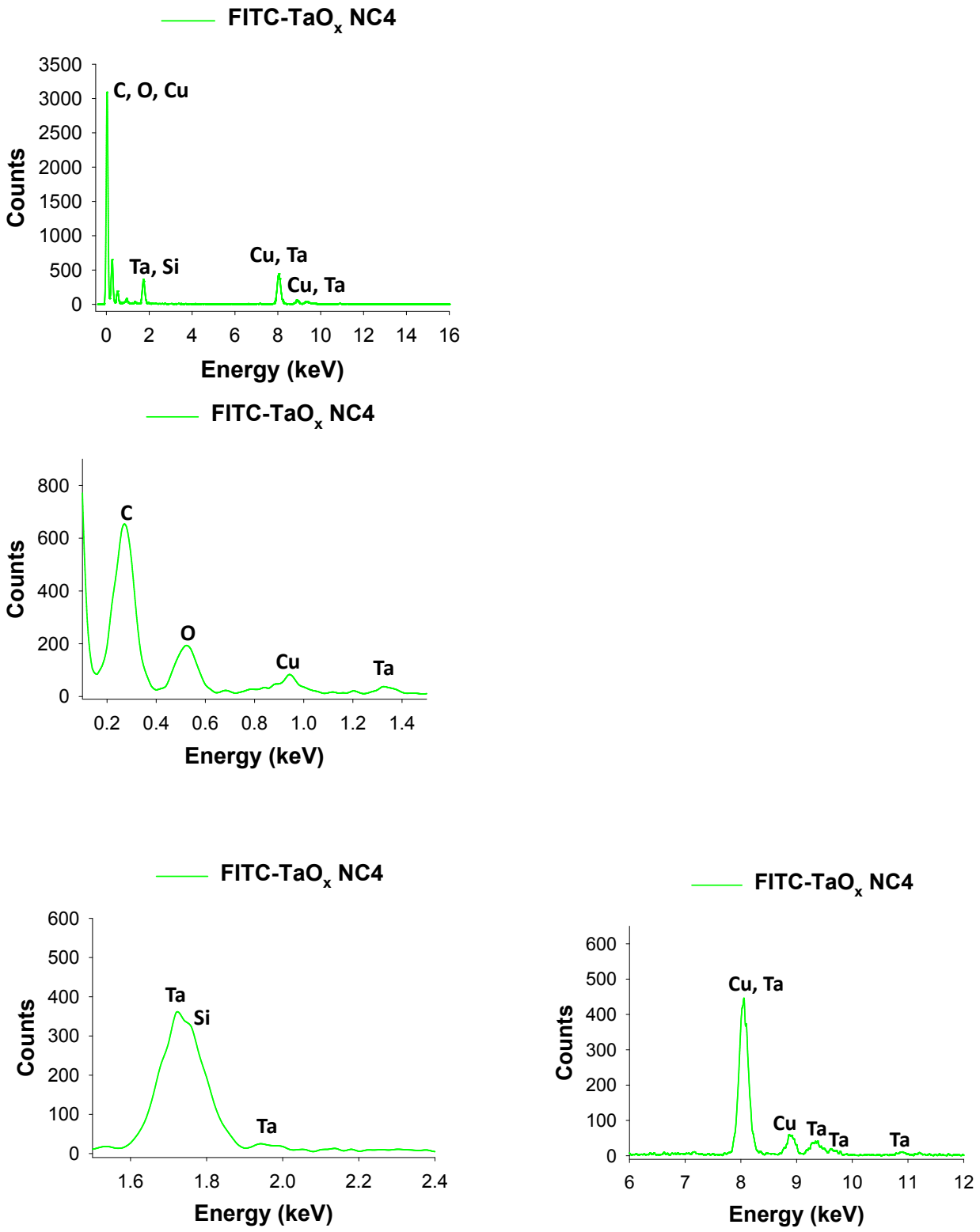


Figure S20. Energy Dispersive Spectroscopy (EDS) for FITC-TaO$_x$ NC4, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

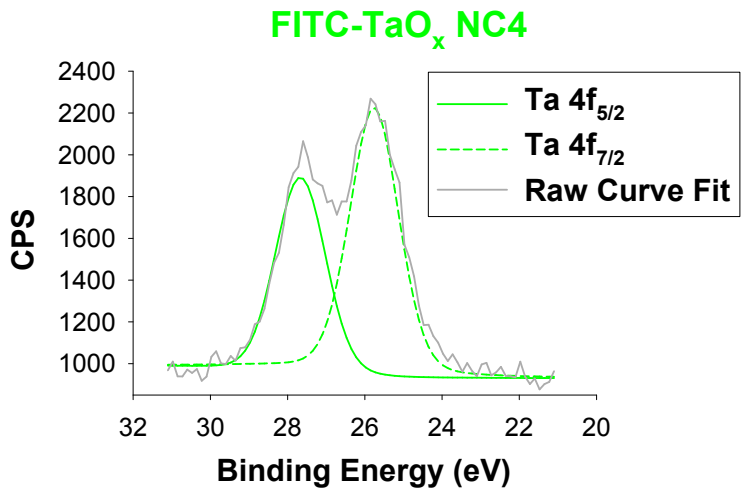
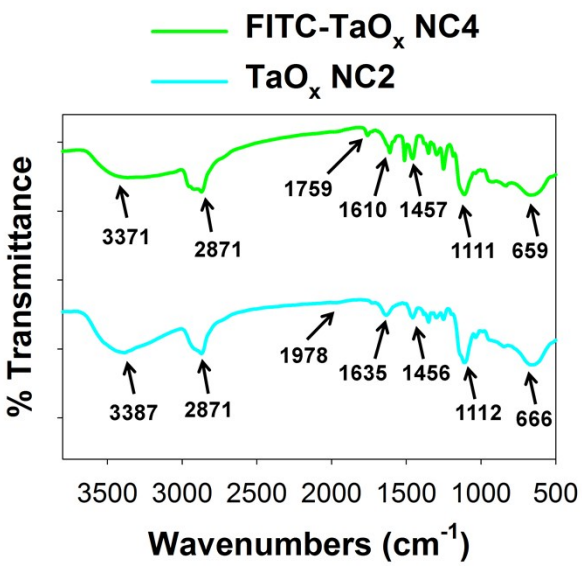
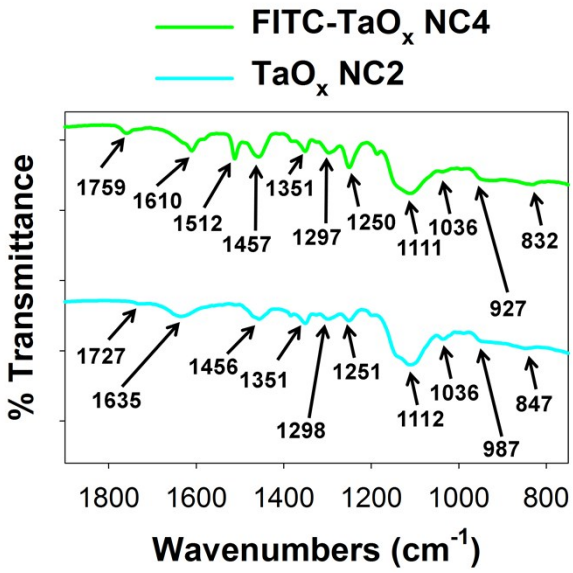
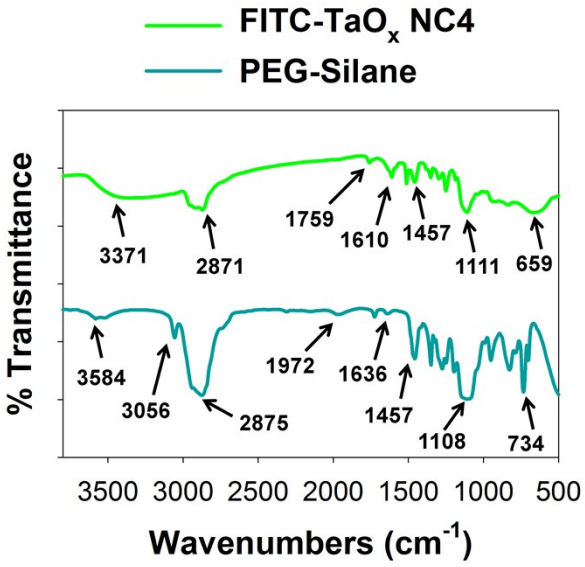


Figure S21. The narrow scan X-ray Photoelectron Spectroscopy (XPS) for FITC-TaO_x NC4, showing Ta $4f_{7/2}$ and Ta $4f_{5/2}$ that are close to characteristic Ta^{2+} in TaO, as reported in literature.


FITC-TaO$_x$ NC4
TaO$_x$ NC2
% Transmittance
3371
2871
1759
1610
1457
1111
659
3387
2871
1978
1635
1456
1112
666
3500 3000 2500 2000 1500 1000 500
Wavenumbers (cm^{-1})


FITC-TaO$_x$ NC4
TaO$_x$ NC2
% Transmittance
1759
1610
1512
1457
1351
1297
1250
1111
1036
832
927
1727
1635
1456
1351
1298
1251
1112
1036
847
987
1800 1600 1400 1200 1000 800
Wavenumbers (cm^{-1})


FITC-TaO$_x$ NC4
PEG-Silane
% Transmittance
3371
2871
1759
1610
1457
1111
659
3584
3056
2875
1972
1636
1457
1108
734
3500 3000 2500 2000 1500 1000 500
Wavenumbers (cm^{-1})

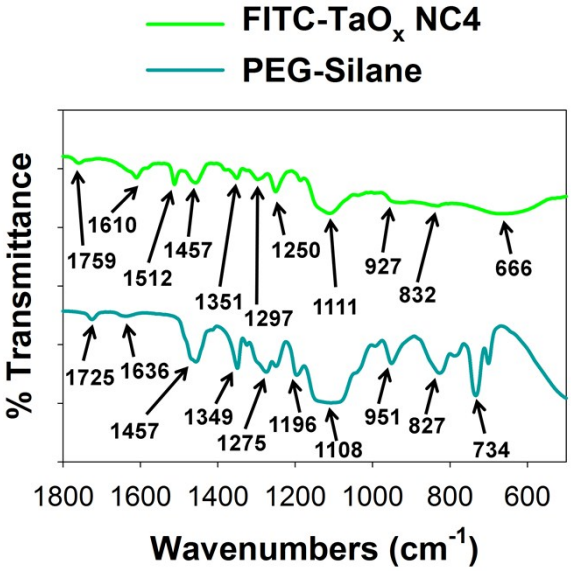

FITC-TaO$_x$ NC4
PEG-Silane
% Transmittance
1610
1759
1512
1457
1351
1297
1250
1111
927
832
666
1725
1636
1457
1349
1275
1196
1108
951
827
734
1800 1600 1400 1200 1000 800 600
Wavenumbers (cm^{-1})

Figure S22. FTIR Spectra comparing the as synthesized FITC-TaO_x NC4 with the starting TaO_x NC2 (*top panel*), and the surface coating of PEG-Silane (*bottom panel*) on the as synthesized FITC-TaO_x NC4. Prominent and common transmittance peaks are pointed out.

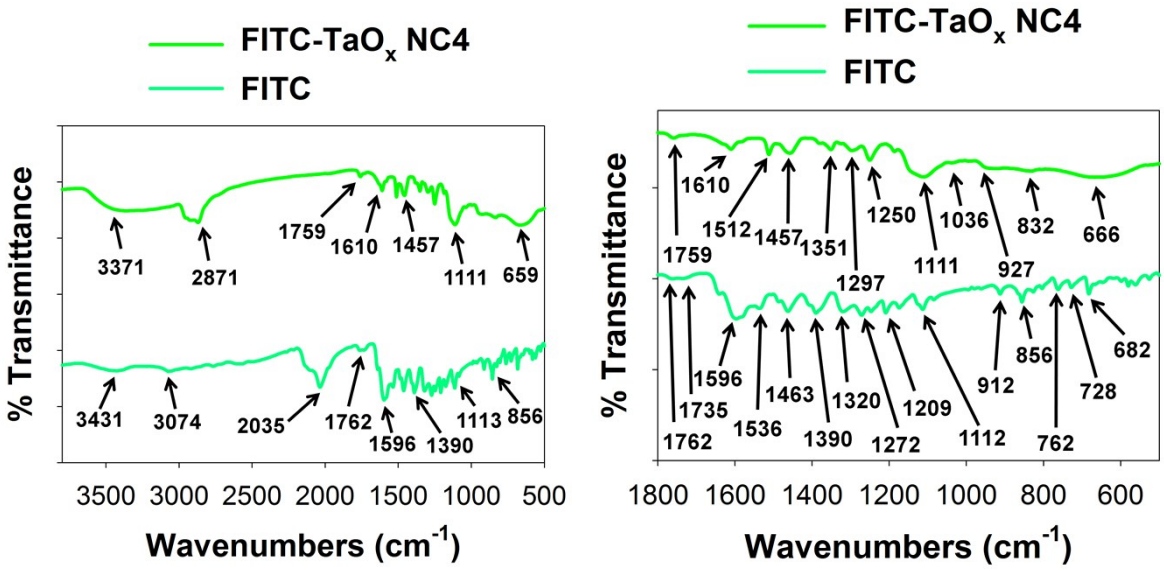


Figure S23. FTIR Spectra comparing the as synthesized FITC-TaO_x NC4 with Fluorescein Isothiocyanate (FITC). The peak at 2035 cm^{-1} in FITC corresponds to the isothiocyanate group that undergoes reaction with APTMS to generate a linker for subsequent reaction with TaO_x NC2 surface silane groups and is consequently absent in the product spectrum. Prominent and common transmittance peaks are pointed out.

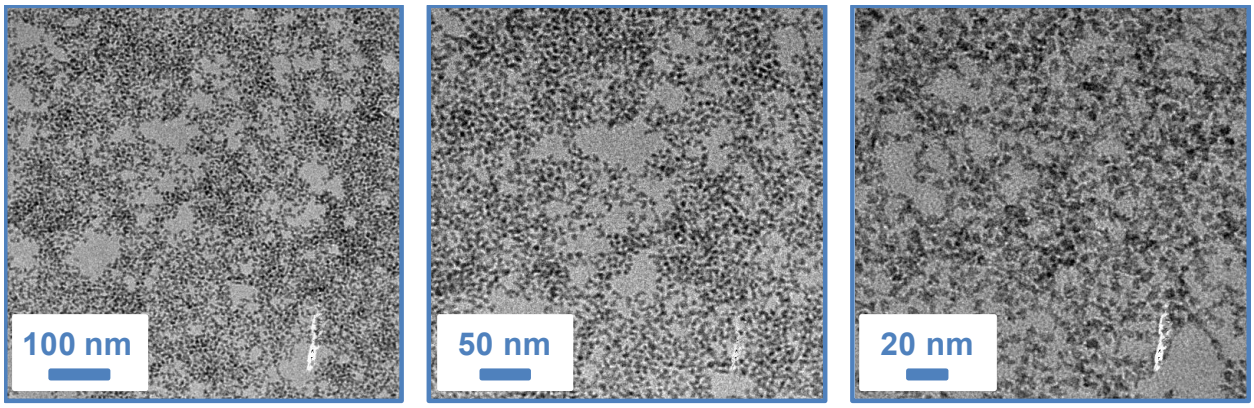


Figure S24. Transmission Electron Microscopy (TEM) images of FITC-TaO_x NC5. The left, center and right panels correspond to FITC-TaO_x NC5 obtained from three different batches and show excellent homogeneity in size and morphology.

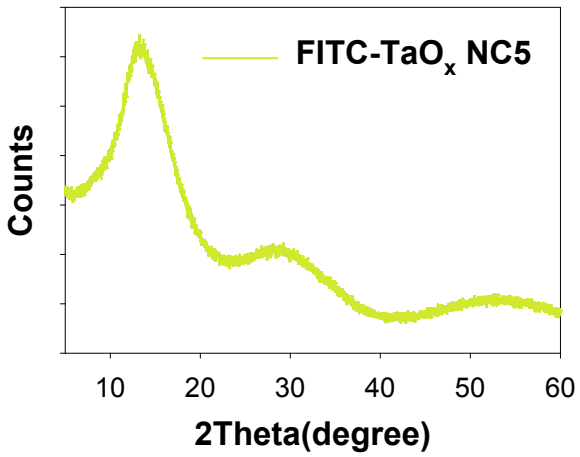


Figure S25. X-ray diffraction (XRD) pattern of TaO_x NC5. XRD patterns were obtained on Bruker D8 DaVinci diffractometer equipped with Cu X-ray radiation operating at 40 kV and 40 mA. Peak intensities were obtained by counting with the Lynxeye detector every 0.02° at sweep rates of 1.2° 2θ /min. The sample was place in a PVMA sample holder. The sample was rotated at 5 degrees per minute.

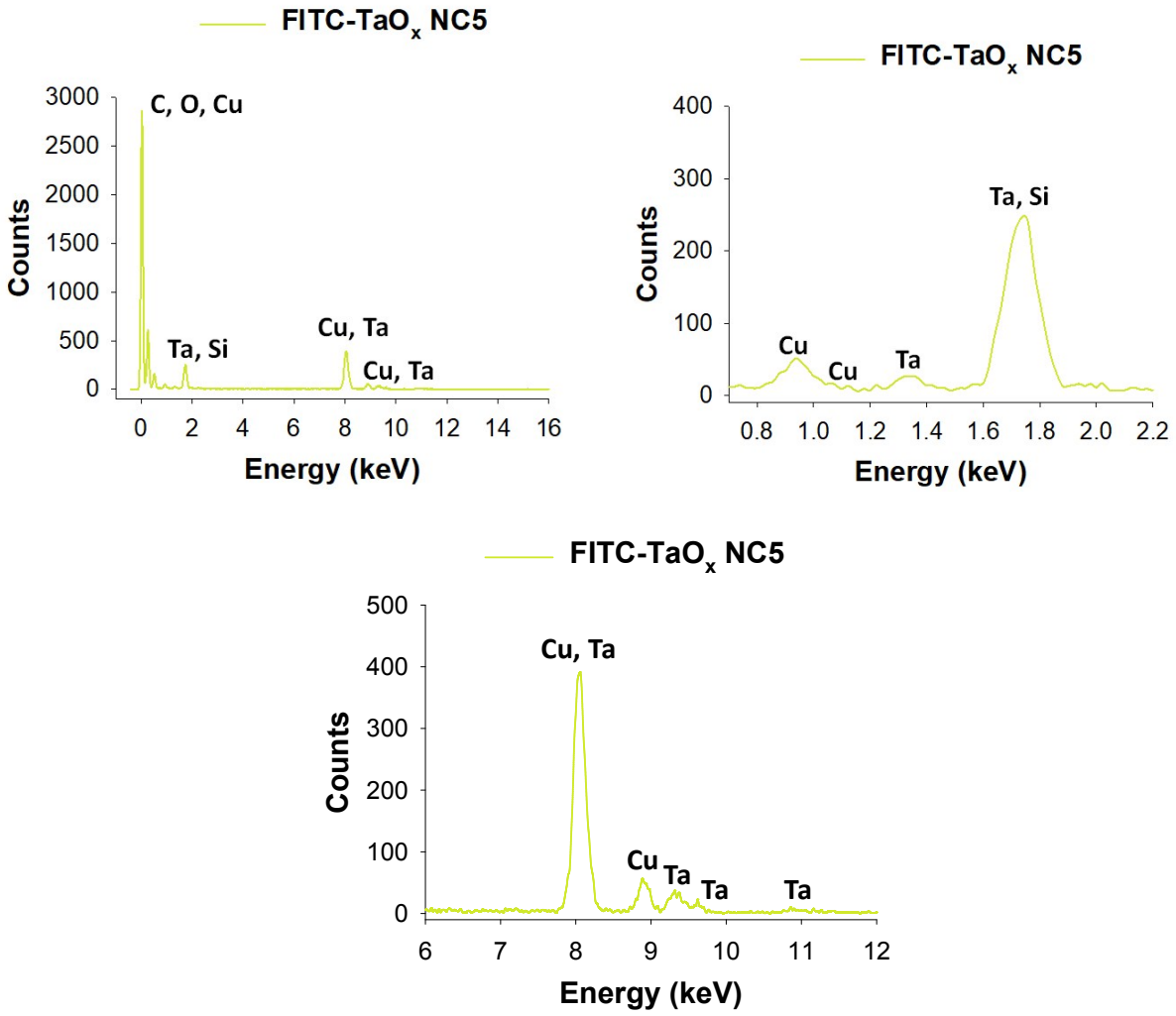


Figure S26. Energy Dispersive Spectroscopy (EDS) for FITC-TaO_x NC5, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

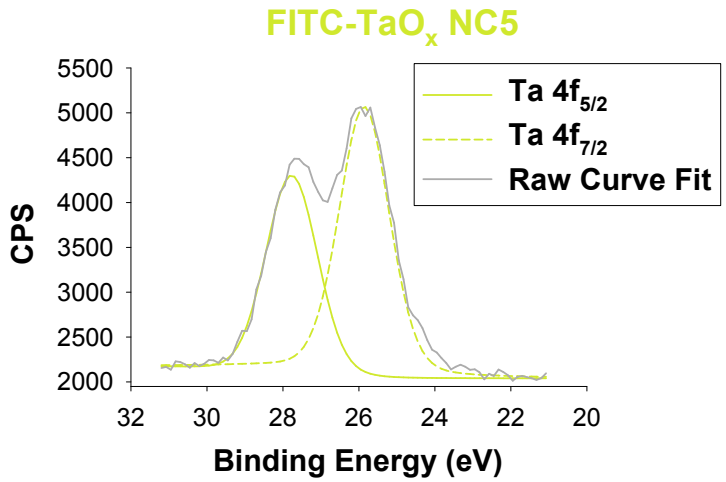


Figure S27. The narrow scan X-ray Photoelectron Spectroscopy (XPS) for FITC-TaO$_x$ NC5, showing Ta 4f$_{7/2}$ and Ta 4f$_{5/2}$ that are close to characteristic Ta^{2+} in TaO, as reported in literature.

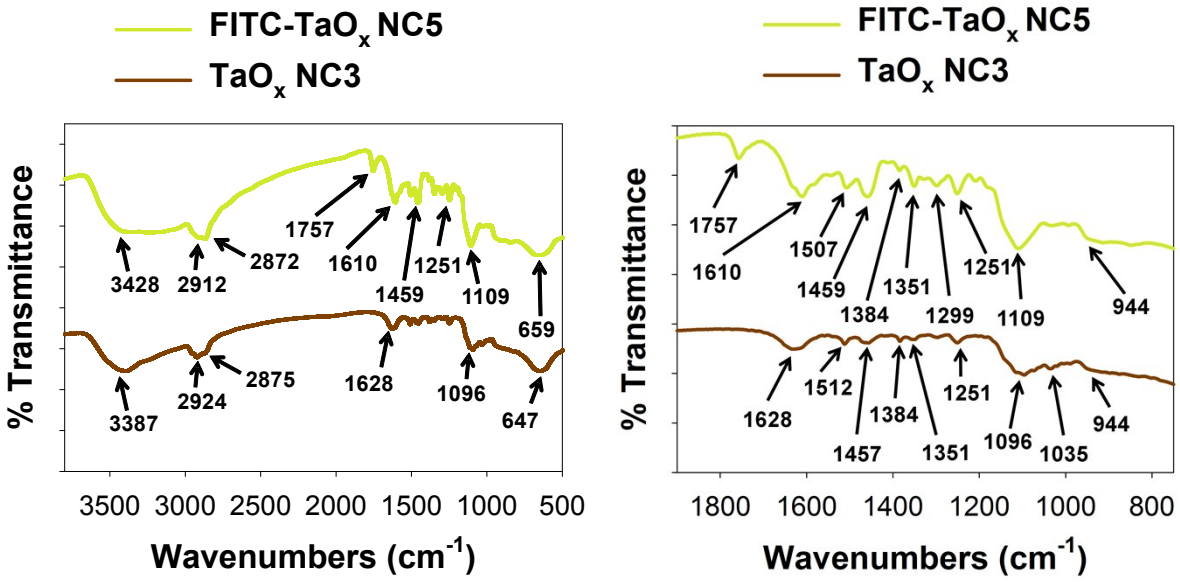


Figure S28. FTIR Spectra comparing the as synthesized FITC-TaO$_x$ NC5 with the starting TaO$_x$ NC2. Prominent and common transmittance peaks are pointed.

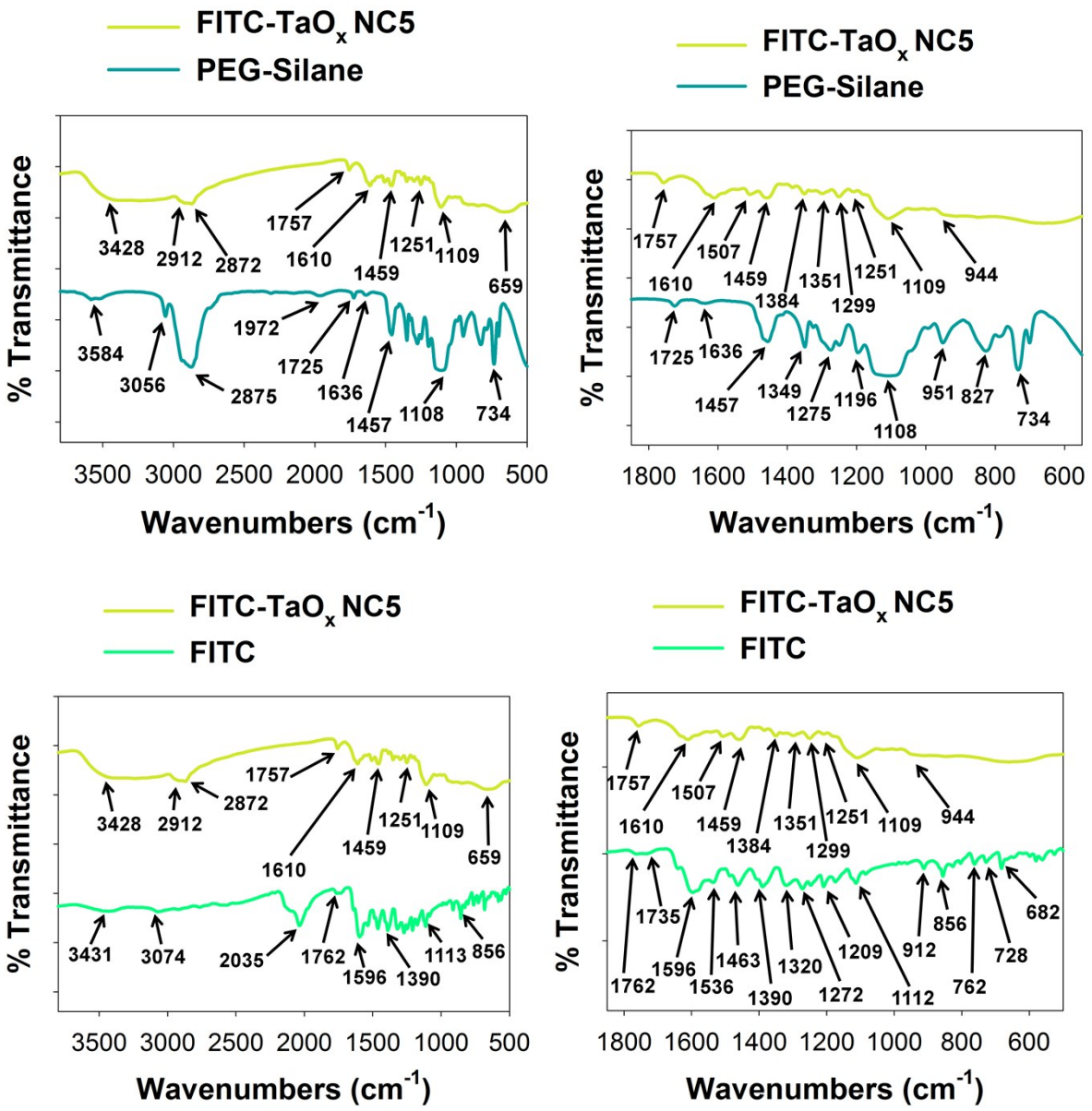


Figure S29. FTIR Spectra comparing the as synthesized FITC-TaO$_x$ NC5 with the starting materials, PEG-Silane (*top panel*) and Fluorescein Isothiocyanate (FITC) (*bottom panel*). Prominent and common transmittance peaks are pointed out.

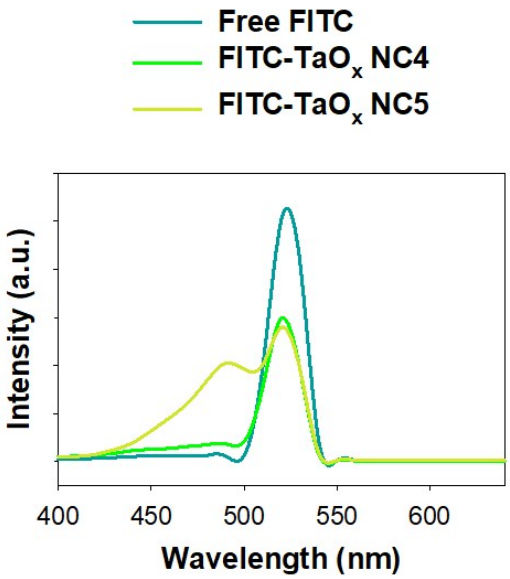


Figure S30. Fluorescence Spectra for free FITC and FITC-labeled TaO_x NCs.

3. Estimation of Ta content and Ta dissolution from TaO_x NCs.

3.1. Ta content estimation using ICP-OES:

To estimate the Ta content in various TaO_x NCs, each dry sample was analyzed using ICP-OES. For each sample, weighed portions (~ 5 mg) of various TaO_x NCs were suspended in a 4:1 mixture of HNO_3 (concentrated, 69%)and HF (concentrated, 48%). The resulting solution was stored at RT until complete dissolution was observed. Once a clear and transparent solution with no visible debris was obtained, the solutions were diluted to a final concentration of 2% HNO_3 and 0.01 % HF to prepare samples that were directly analyzed for Ta content using ICP-OES using a Varian 710-ES, ICP-OES instrument. All measurements were carried out in triplicates and the mean concentration have been reported.

3.2. In vitro Ta dissolution:

To analyze the dissolution of various TaO_x NCs in lysosomal media, an *in vitro* dissolution study was carried out. In a typical experimental set up, 5 mg of each variety of NCs were taken in separate 1.8 mL centrifuge vials and suspended separately in 1 mL each of PBS (Phosphate Buffer Saline, pH 7.4) and sodium citrate (NaCit, 50 mM, pH 5.5). The resulting suspensions were transferred to a rotor maintained in an oven at 37 °C. After various time points (1 h, 4 h, 8 h, 20 h, 24 h, 48 h, Day 3, 4, 5, 7, 8, 9, 10, 11, 14, 21 and 28) the tubes were centrifuged and the supernatant was collected. The residue were re-suspended in the respective media and the experiment was continued. After 4 weeks, the supernatant liquid was evaporated and the residue so obtained was digested by adding 0.8 mL concentrated Nitric Acid (HNO_3, 69%) and 0.2 mL concentrated Hydrofluoric acid (HF, 48%) and leaving the suspension so obtained till a clear yellow solution was obtained (48 h).

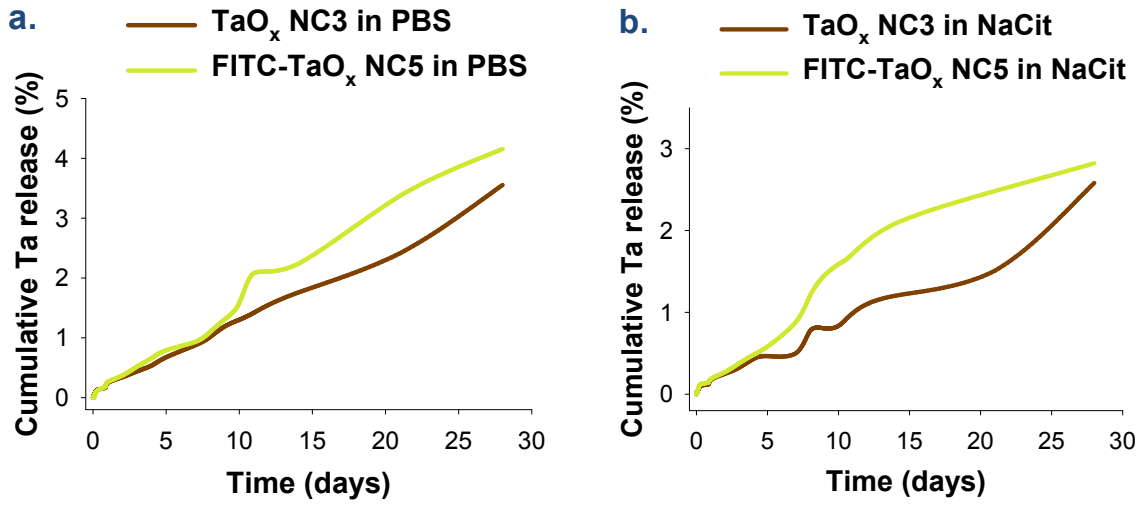


Figure S31. Ta dissolution from TaO_x NC3 and FITC-TaO_x NC5 in (**a.**) PBS (pH 7.4) and (**b.**) sodium citrate (NaCit, pH 5.5) over 4 weeks using ICP-OES (n = 3, S.D. < 0.5).

After 48 h, each sample was diluted to a final concentration of 2% HNO_3 and 0.01% HF the Ta content in the digested samples was analyzed using ICP-OES. Each sample was analyzed in triplicate and each study

was repeated thrice. For both NC types, minimal Ta dissolution was observed during the first week. During the second week, dissolution ranged between 0.8 - 1.2%; for the third week, dissolution within 1.5 - 1.8% was observed while for the fourth week, a total of 2.6 - 2.9% Ta dissolution was recorded (**Figure S31**).

4. Cellular Studies.

4.1. Cellular Viability using RAW 264.7 and HEK 293 Cells

To test the cytocompatibility of various TaO_x NCs, MTT assay using RAW 264.7 macrophage cells and HEK 293 cells was performed. Briefly, respective cells (100 µL, 100, 000 cells per mL) suspended in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FBS (Fetal Bovine Serum) and 1% antibiotic Pen Strep (Penicillin Streptomycin) were seeded in multiple 96-well plates and incubated for 24 h (37 °C, 5% CO_2). Next, 100 µL each of TaO_x NP formulation suspensions in DMEM media were added to the respective wells in a range of concentrations (0.0001 to 2.4 mg per mL Ta concentration) and the plates were incubated for another 24 h. After incubation for the desired period, supernatant media from the wells were aspirated out and each well was washed with 100 µL PBS (Phosphate Buffer Saline, pH 7.4) thrice, following which 100 µL of fresh DMEM media was added to each well. The final MTT assay was done as described by the manufacturer's protocol.

5. *In vitro* micro-CT Experiments for TaO_x NCs.

For *in vitro* phantom measurements, solutions of TaO_x NC1 in saline were prepared at various concentrations (0, 20, 50, 80 and 100 mM Ta). Phantom CT images were acquired on a Perkin Elmer Quantum GX micro-CT scanner operating at 90 kVp and 88 µA.

6. *In vivo* micro-CT Experiments for TaO_x NCs.

6.1. General Information:

We used micro-CT for quantifying the efficacy of TaO_x NCs when used as a high Z-value radiopaque contrast agent in an *in vivo* model.

BALB/c mice (Charles River Laboratories, Inc.; sex, male; age, ~ 3 months; body weight, ~ 25g) were randomized into experimental groups and received either a single intravenous dose of formulated TaO_x NCs in sterile saline (0.9% Sodium Chloride for Injection, USP) at 100 mM (n = 2) (296 mg kg^{-1}) or 200 mM (n = 3) TaO_x NCs (592 mg kg^{-1}). Animals were serially imaged via micro-CT at 0 h (baseline), immediate Post-Injection, 1 h, 3 h, 24 h, and 72 h post-injection using the PerkinElmer Quantum GX micro-CT. The following image acquisition scan parameters were used at each scan interval time point: scan mode, high resolution; gantry rotation time, 14-minutes; power, 90 kVp/88 µA; Field of View (FOV), 72 mm; number of slices, 512; slice thickness, 144 µm; voxel resolution, 144 $µm^3$.

Animals were housed in MSU Small Animal Vivarium, with standard 12 h light cycle (6 am – 6 pm) at ~ 30-40 foot candles of light intensity; ~ 72 °F Room Temperature; ~ 45% Relative Humidity (RH). Animals received water and standard rodent diet (Envigo Teklad®) *ad-libitum*, and were fasted for ~ 4-6 h prior to each scan interval to reduce micro-CT image hyperintensity anomalies found in the GI tract.

On study Day 0, animals were anesthetized via inhalant isoflurane (3-4% isoflurane in 0.8-1 LPM oxygen for induction) and maintained via inhalant isoflurane during imaging (1-3% isoflurane in 0.8-1 LPM oxygen). A lateral tail vein catheter was placed for I.V. injection, and the TaO_x NC formulation was administered as a single, slow bolus injection (25 µL min^{-1}). Animals were fully recovered from anesthesia following each scan interval time point. On Day 3, following the 72 h post-injection scan time point, animals were euthanized via CO_2 inhalation overdose, with cervical dislocation as a secondary physical method to confirm death.

6.2. ICP-OES for Ta content, H&E Staining and Clinical Chemistry:

For ICP analysis, organ sections from heart, liver, kidneys and spleen were weighed to record their wet weight and then drying them over a heating block. The weight of the dry tissue sections were recorded and next these were digested using a 4:1 mixture of HNO_3 (concentrated, 69%) and HF (concentrated, 48%). The resulting solution was stored at RT until complete dissolution was observed. Once a clear and transparent solution with no visible debris was obtained, the solutions were diluted to a final concentration of 2% HNO_3 and 0.01% HF to prepare samples that were directly analyzed for Ta content using ICP-OES using a Varian 710-ES, ICP-OES instrument. The Ta content in various organs of mice injected with 100 mM TaO_x NC1 and 200 mM TaO_x NC1 are shown in **Figure S32**.

After 72 h scanning and following euthanasia, blood samples were collected for clinical chemistry blood serum analysis, and tissue samples (spleen, liver, heart, kidneys, and bladder) were harvested for histopathology and ICP analysis for Ta content. Various tissue sections from respective organs as heart, liver, kidneys, spleen and bladder were collected and stained with hematoxylin and eosin (H&E). The

representative histological sections for mice injected with 200 mM Ta in saline are shown in Figure S40 and clearly indicate multifocal areas of necrosis. Such sections within the spleen are characterized by pyknotic cells and karyorrhectic debris surrounded by macrophages. Sections of liver from two of the three mice in the 200 mM Ta dose group had coagulative necrosis with one mouse having few small randomly distributed foci, while the other mouse had large confluent areas of random midzonal necrosis. These areas were characterized by swollen, hypereosinophilic cells that had lost their nuclear detail and there was accumulation of karyorrhectic debris. One mouse had multiple acute renal cortical infarcts characterized by sharply demarcated, wedge-shaped areas of coagulative necrosis extending from the beneath the renal capsule into the outer cortex causing slight indentations. These areas were surrounded by tubules lined by swollen epithelial cells and few infiltrating mononuclear cells. Arterioles at the tip of these infarcts were thrombosed. The histological analysis of the tissues from the bladder, kidney and heart from mice injected with 200 mM TaO_x NC1 were unremarkable. For mice injected with 100 mM TaO_x NC1, no adverse observation was noted on histological analysis of tissue sections of various organs such as the liver, spleen, kidney, heart and bladder.

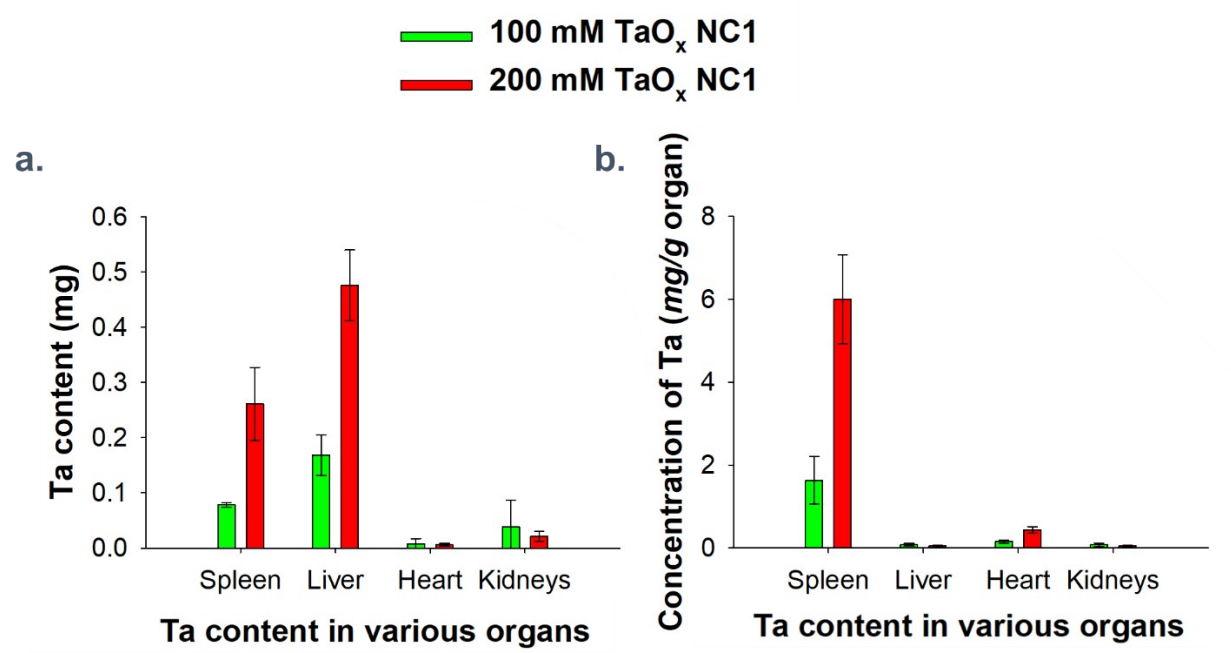


Figure S32. Ta content in various organs of mice injected with 200 mM TaO_x NC1 as analyzed by ICP-OES (n = 3, S.D. < 0.5).

Extensive clinical pathological analysis for all the set of mice (control and test groups) was performed using a Beckman Coulter AU680U chemistry analyzer and Beckman Coulter reagents. No clinically significant differences were observed in control (saline group) and treated mice (100 mM and 200 mM TaO_x NC1 groups) across a number of parameters such as albumin, total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (ALP), alanine aminotransferase (ALT)

and aspartate aminotransferase (AST). These findings are summarized in **Figure S33**. Minor elevation in blood glucose levels were observed in the control and treated groups, however the differences were not clinically relevant. Further, wide range of values is typical and is affected by factors like stress associated with collection and length of fasting prior to sample collection. However, the elevated ALT and AST activity in the 200 mM TaO_x NC1 dose group as compared to the control group (saline) and 100 mM TaO_x NC1 dose group supports hepatocellular damage and is consistent with the histologic findings of liver necrosis.

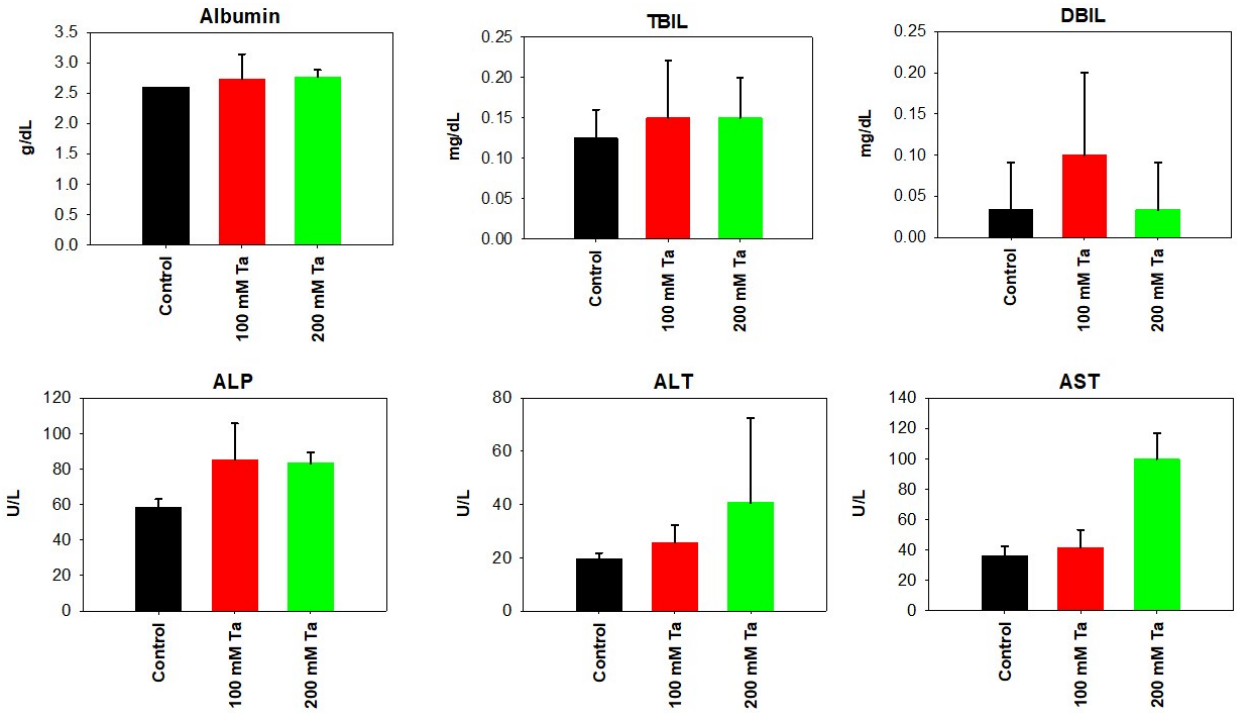


Figure S33. Detection results of liver and kidney function in terms of Albumin, TBL, DBL, ALP, ALT and AST index for mice injected with saline (control group), 100 mM TaO_x NC1 and 200 mM TaO_x NC1.

7. **Synthetic Details for Tantalum Oxide PLGA NPs (TaO_x @PLGA NPs).**

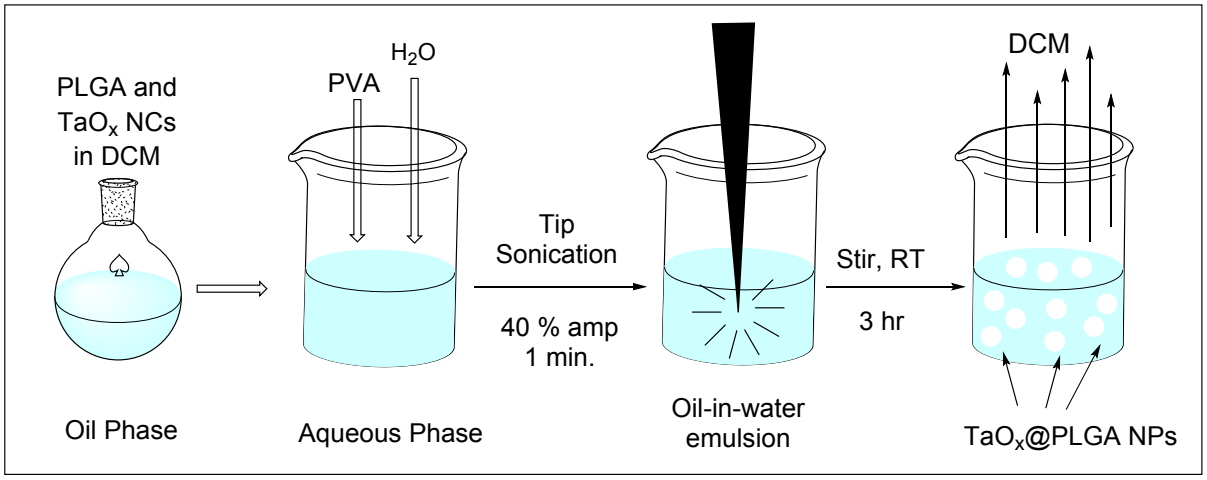
7.1. General Information.

All reactions, unless otherwise stated, were performed with oven-dry glassware. Poly(*DL*-Lactic-co-Glycolic Acid) (or *PLGA*), [LG 50:50, *acid terminated* (nominal), Inherent viscosity range 0.95 – 1.20 dL g^{-1} in HFIP, 20.0 g) was purchased from LACTEL Absorbable Polymers, DURECT Corporation, AL, USA and stored at -20 °C prior to use. All other reagents and solvents were obtained from commercial suppliers and used without further purification. For NP formulation, tip sonication was performed using a QSonica microtip sonicator probe with a tip diameter of 3 mm. at varying amplitudes. Centrifugation to isolate NPs from reaction mixture was performed on a Sorvall LYNX 4000 Superspeed centrifuge.

7.2. Synthesis of PLGA NPs Encapsulating TaO_x NCs (TaO_x@PLGA NPs).

Prior to encapsulation in PLGA, the hydrophobic TaO_x NC3 were suspended in Dichloromethane (DCM). The resulting white suspension (25 mg TaO_x NCs per mL DCM) was sonicated for 20 min. with periodic vortex to form a homogenous suspension of TaO_x NCs in DCM. This suspension was further utilized for NP formulation. A stock solution of 4% Poly(vinyl alcohol) (PVA) in DI water (w/w) was prepared by dissolving 8.0 g PVA (22 kDa, 88% hydrolyzed, SIGMA ALDRICH) in 900 mL DI water by continuous stirring at 50 °C for 2 h. Once a clear solution was obtained with no visible residue, the volume of the solution was increased to 1000 mL by adding DI water to it. This final solution was allowed to cool down to RT, filtered (using a coarse filter paper) and stored at 4 °C prior to use. A stock solution of PLGA in DCM was prepared (50 mg PLGA polymer per mL DCM) and stored at sub-zero temperatures.

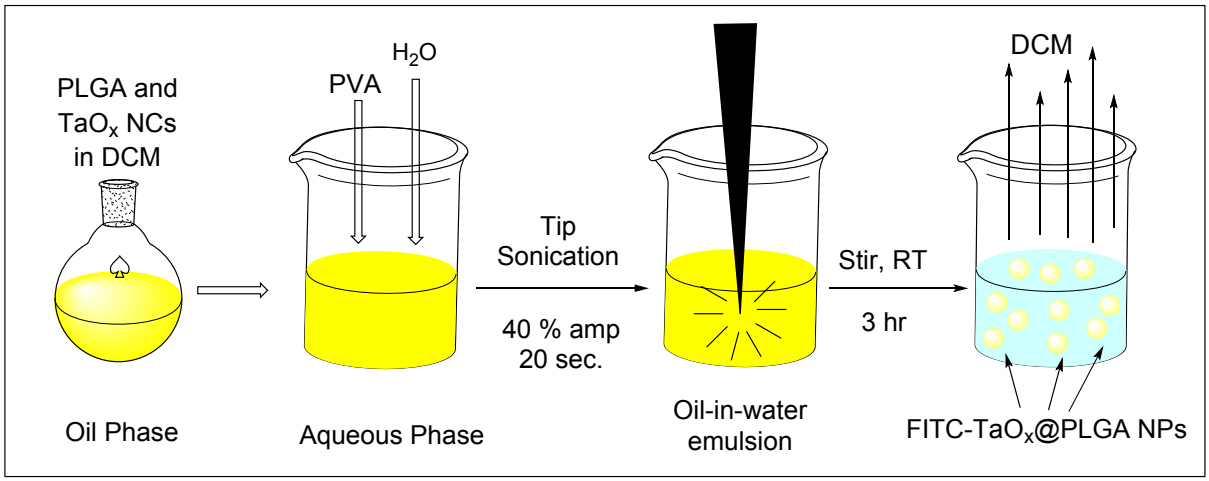
Typical Procedure: In a 50 mL falcon tube, 4% PVA (3 mL) was taken. In a separate 15 mL falcon tube, 1.0 mL of the TaO_x NC suspension in DCM was taken and 0.5 mL PLGA stock solution in DCM (25 mg TaO_x NC : 25 mg PLGA polymer) was added dropwise to it with continuous vortex. The resulting white colored suspension was sonicated for 5 min. with periodic vortex to make it homogenous. This solution was next added dropwise to the 4% aqueous PVA solution (3 mL) in the falcon tube with rigorous and continuous vortex. Once addition was complete, the resulting white suspension was tip sonicated at 40% amplitude for 20 sec. and then transferred to an ice bath for 10 sec. This process of tip sonication, followed by rapid cooling in an ice bath was repeated six times. After the final cycle, the white suspension was added to 10 mL 4% PVA and diluted further using 10 mL ultra-pure water. The resulting reaction mixture was stirred at RT for 3 h to remove DCM, resulting in particle hardening and consequent NP formulation. After 3 h, the NPs were isolated by centrifugation at 15,000 rpm for 10 min. The white NPs so obtained were cleaned again by repeated dispersion in aqueous media and centrifugation to isolate the NPs, until the supernatant was clear (3 times). Dry NPs were isolated by lyophilization of the NP pellet. Product Yield: 34 mg, Ta% = 56% (ascertained from ICP-OES).



Scheme S6. Synthesis of Non-Fluorescent TaO_x@PLGA NPs.

For FITC labeled FITC-TaO_x@PLGA NPs: The reaction sequence for the fluorescent, FITC loaded variant of the TaO_x@PLGA NPs is shown in Scheme S7 and is similar to the one previously discussed. The only variation lies in using the previously prepared hydrophobic FITC-TaO_x NC5, instead of TaO_x NC3 in the oil phase, together with PLGA polymer. The rest of the steps were exactly identical. In order to protect the reaction from light, all the reaction beakers and falcon tubes were covered with aluminium foil. The work up for this reaction was also identical to the non-fluorescent TaO_x@PLGA NPs. Dry NPs were isolated by lyophilization of the NP pellet. Product Yield: 34 mg, Ta% = 45% (ascertained from ICP-OES).

In all, two different types of TaO_x@PLGA NPs were prepared, viz., TaO_x NC3@PLGA and FITC-TaO_x NC5@PLGA (with fluorescent FITC tag). These have been characterized by TEM, SEM, EDS, IR and ICP. As shown below by the TEM images, a homogenous and efficient packing of the hydrophobic TaO_x NCs in PLGA was observed (Figure S25, S28 *TEM inset*) for both NP types.This can be easily explained by the virtue of the procedure used for NP formation that entails the encapsulation of hydrophobic TaO_x NCs within a similarly hydrophobic PLGA shell.



Scheme S7. Synthesis of Fluorescent, FITC labeled FITC-TaO_x@PLGA NPs.

8. Characterization Details for TaO_x@PLGA NPs.

General considerations for physicochemical characterization of the NPs are identical to that of the NCs. Please refer to Section 2 for specific details.

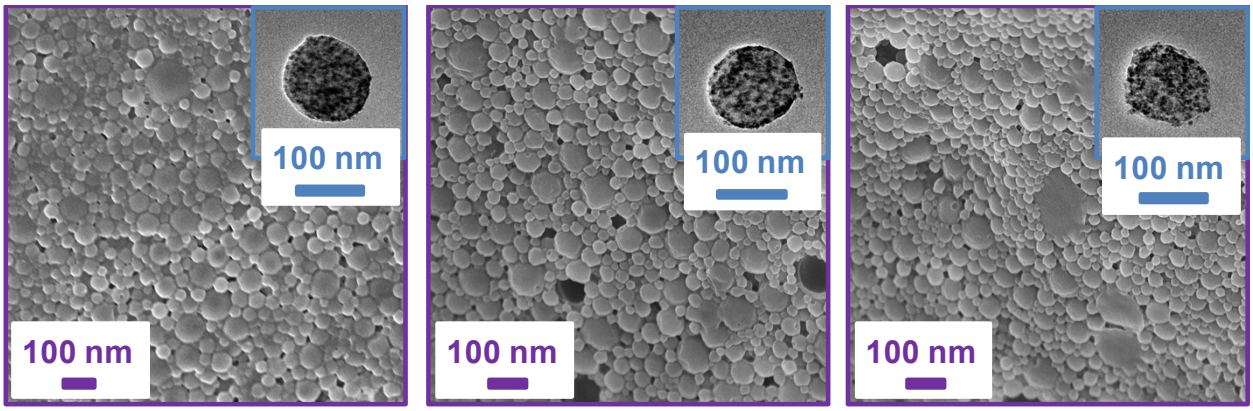


Figure S34. TEM (*inset*) and Scanning Electron Microscopy (SEM) images of TaO_x@PLGA NPs. The left, center and right panels correspond to TaO_x@PLGA NPs obtained from three different batches that quite clearly show the homogeneity in size and the efficiency in packing of TaO_x NC3 within the PLGA polymer.

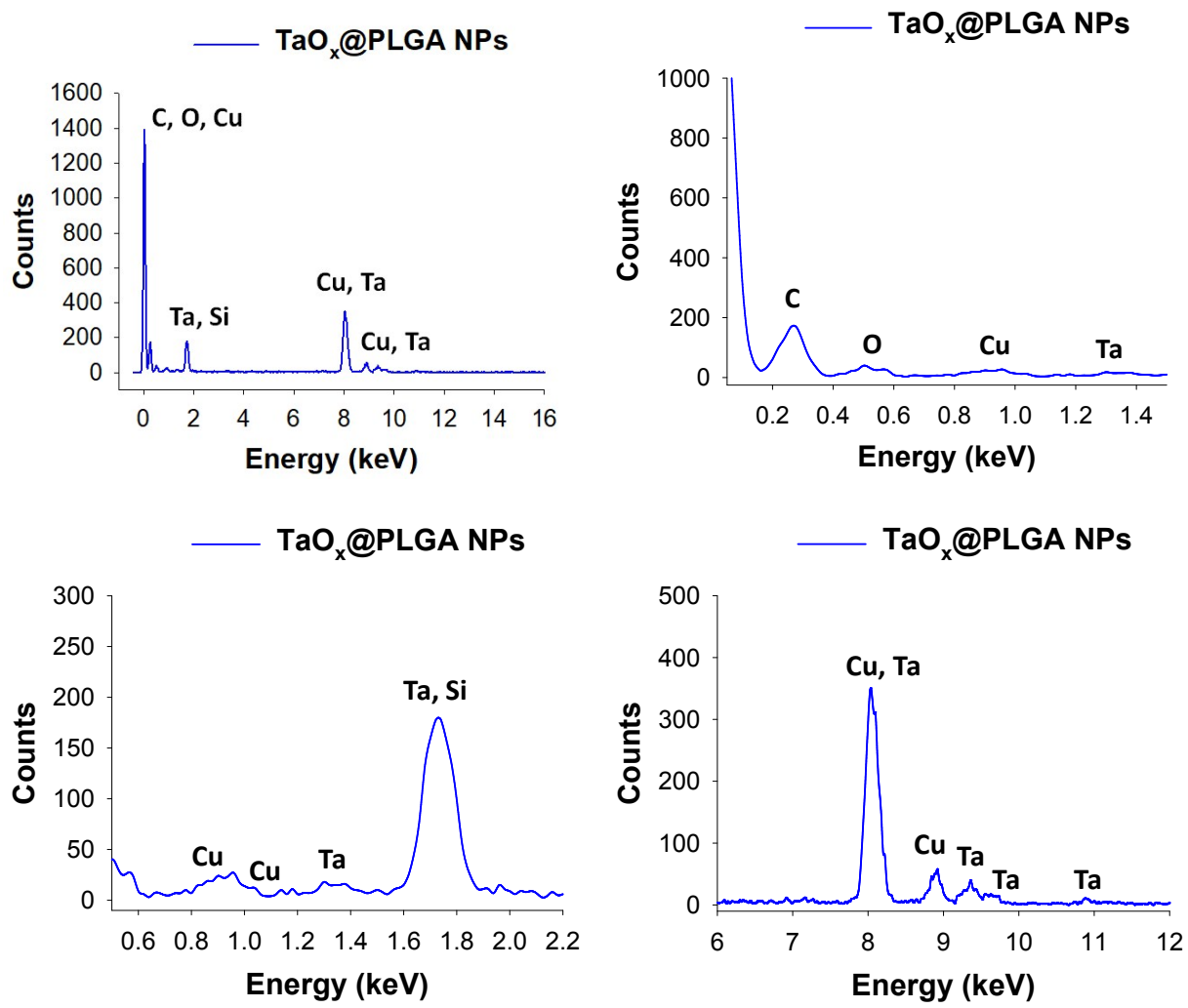


Figure S35. Energy Dispersive Spectroscopy (EDS) for TaO_x@PLGA NPs, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

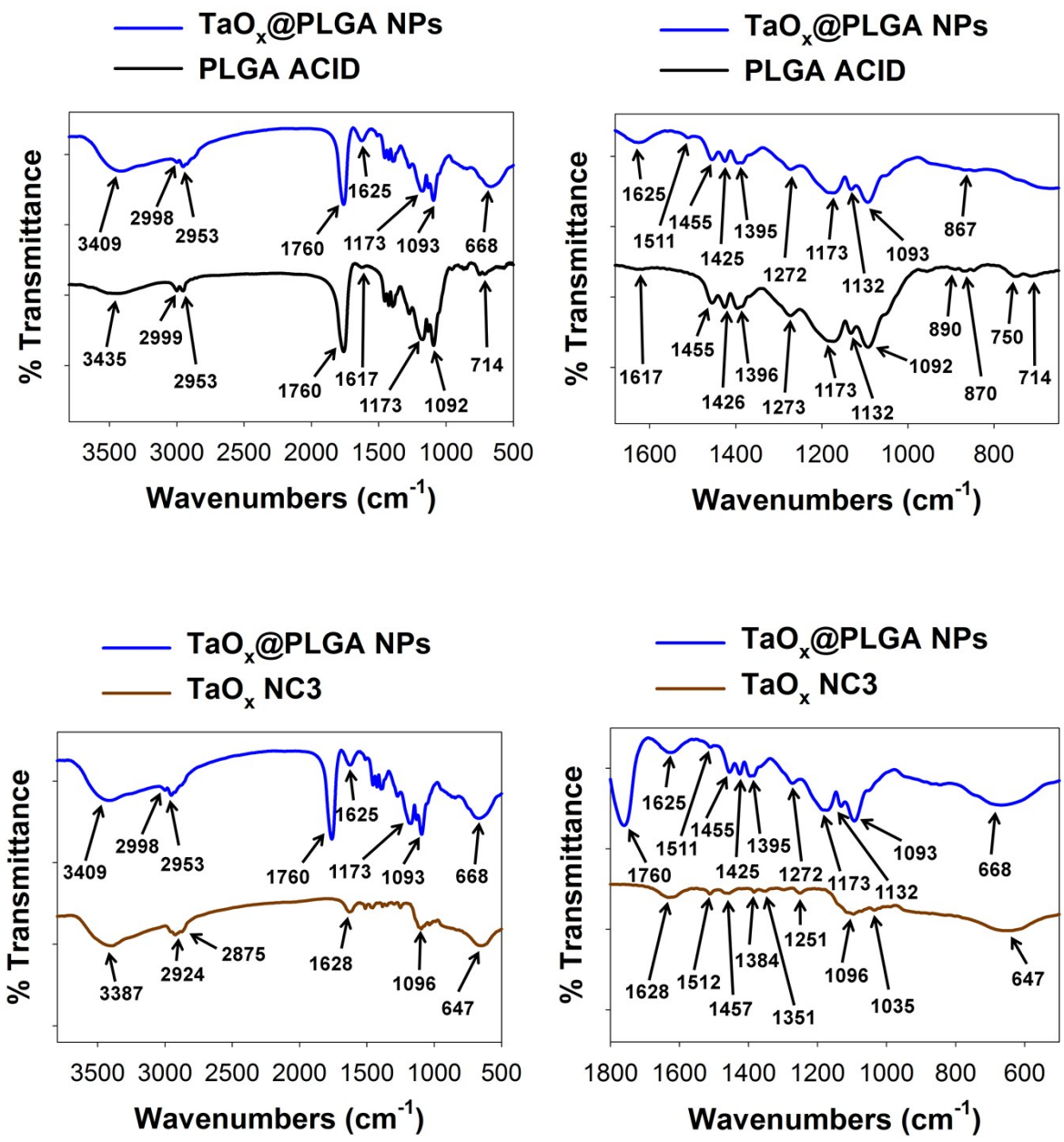


Figure S36. FTIR Spectra comparing the as synthesized TaO_x@PLGA NPs with the starting materials, PLGA ACID (*top panel*) and TaO_x NC3 (*bottom panel*). Prominent and common transmittance peaks are pointed out.

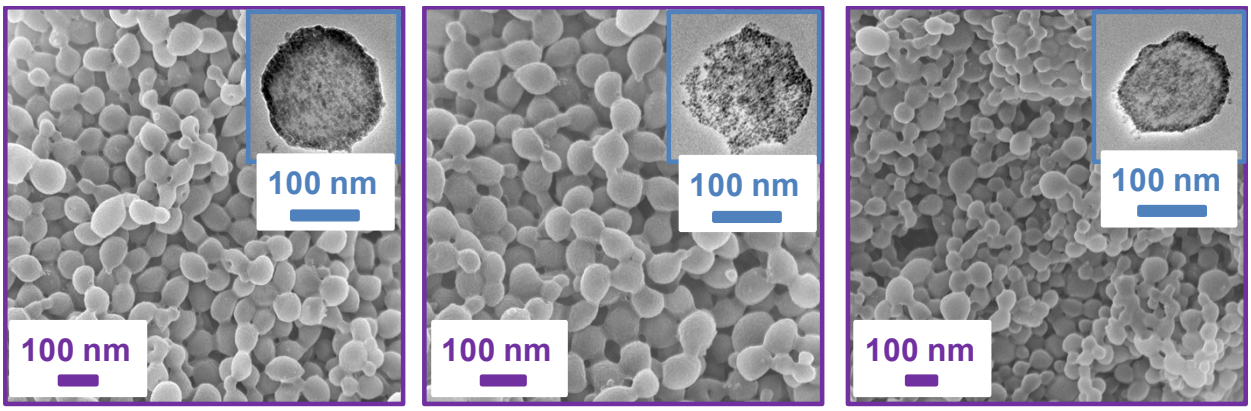


Figure S37. TEM (*inset*) and Scanning Electron Microscopy (SEM) images of FITC-TaO_x@PLGA NPs. The left, center and right panels correspond to FITC-TaO_x@PLGA NPs obtained from three different batches that quite clearly show the homogeneity in size and the efficiency in packing of FITC-TaO_x NC5 within the PLGA polymer.

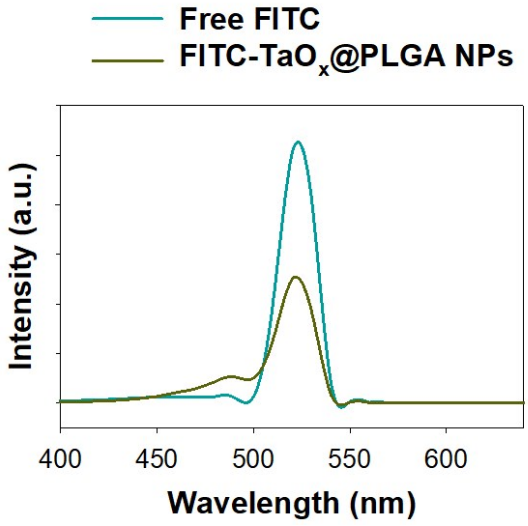
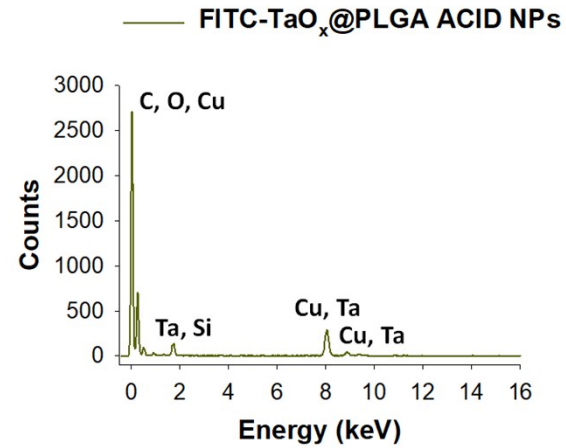
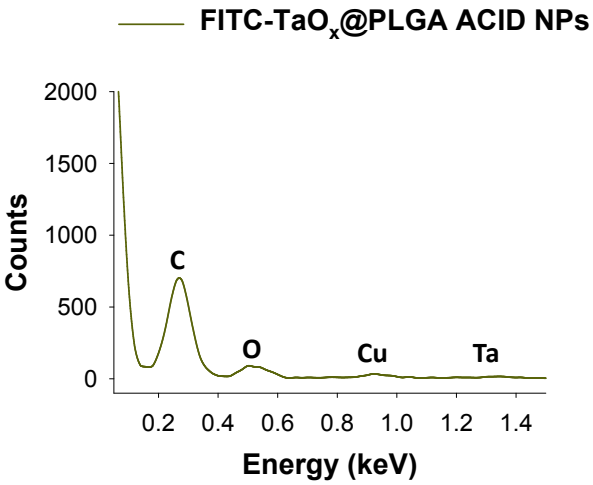


Figure S38. Fluorescence spectral comparison for free FITC and the FITC-TaO_x@PLGA NPs in PBS.


FITC-TaO$_x$@PLGA ACID NPs
Counts
Energy (keV)
C, O, Cu
Ta, Si
Cu, Ta
Cu, Ta


FITC-TaO$_x$@PLGA ACID NPs
Counts
Energy (keV)
C
O
Cu
Ta

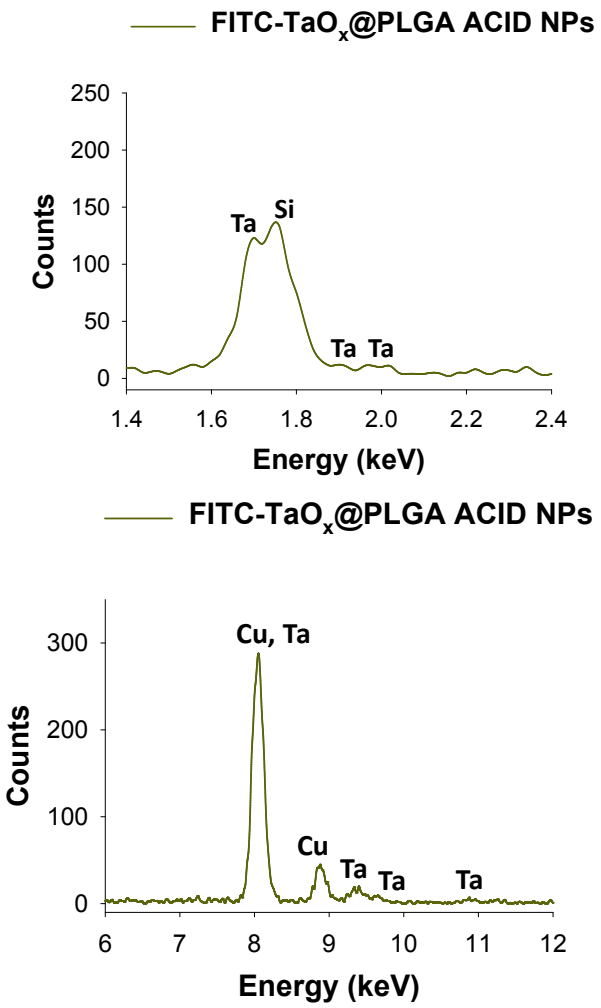


Figure S39. Energy Dispersive Spectroscopy (EDS) for FITC-TaO$_x$@PLGA NPs, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

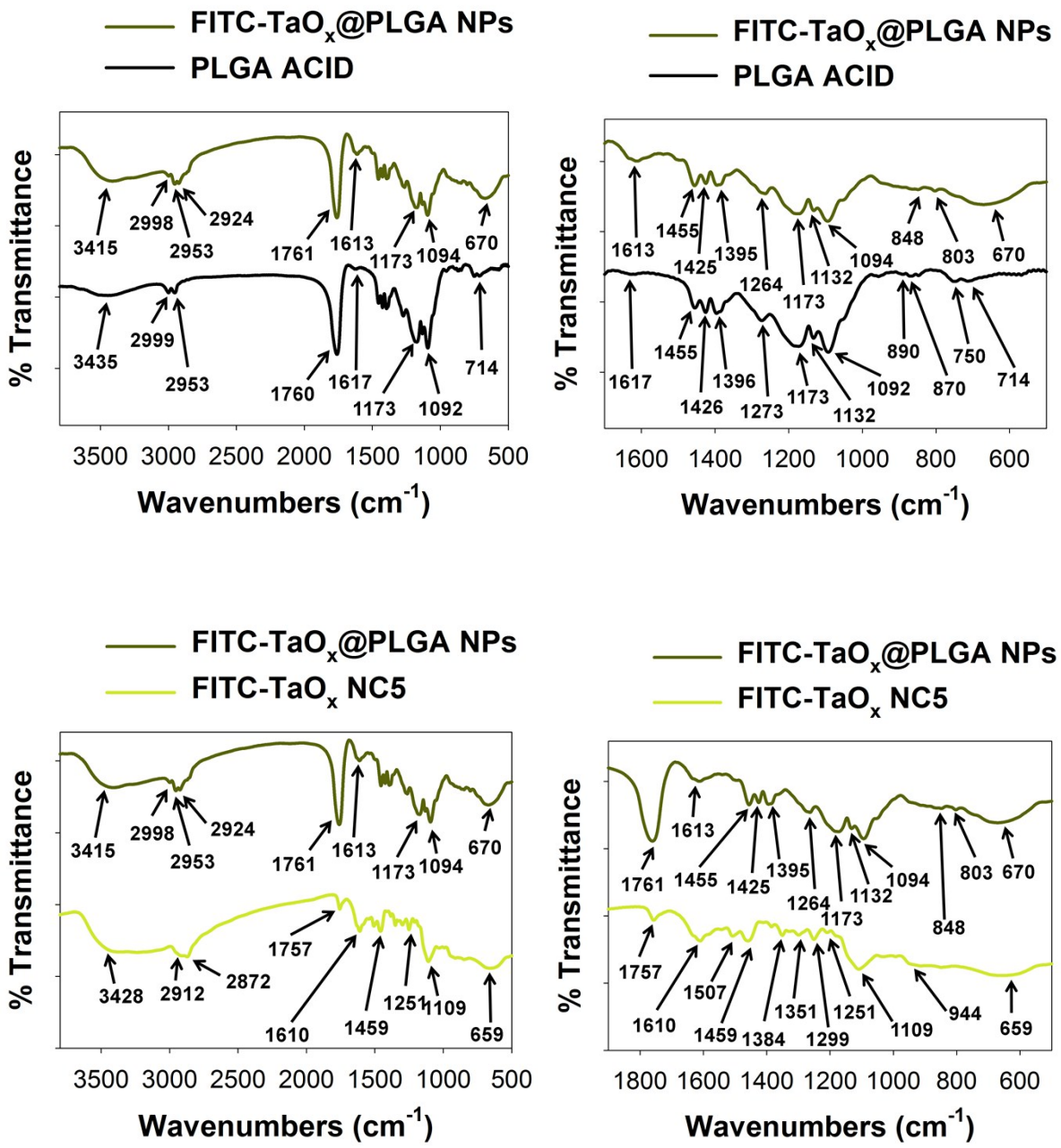


Figure S40. FTIR Spectra comparing the as synthesized FITC-TaO$_x$@PLGA NPs with the starting PLGA ACID (*top panel*) and FITC-TaO$_x$ NC5 (*bottom panel*). Prominent and common transmittance peaks are pointed out.

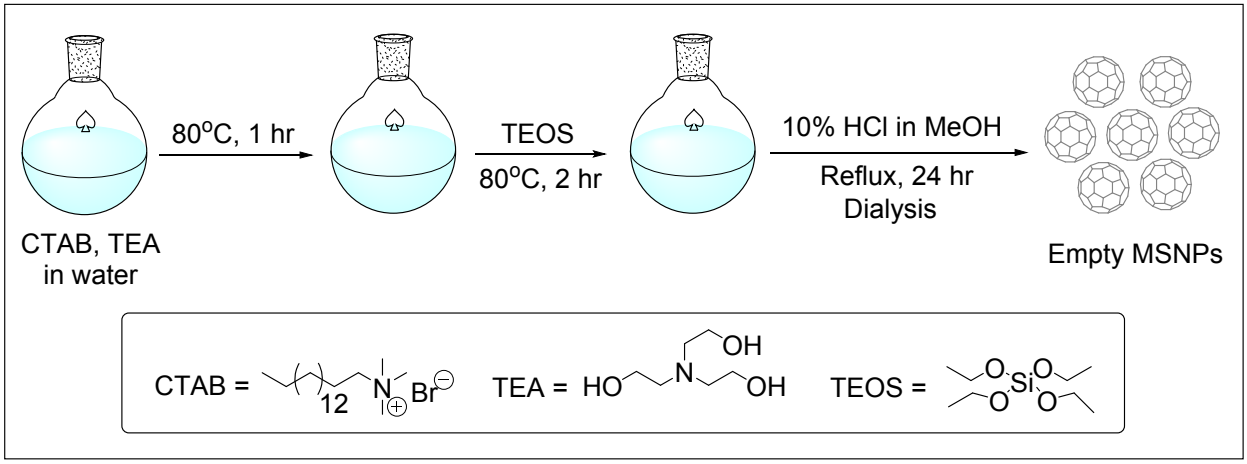
9. **Synthetic Details for Tantalum Oxide Mesoporous Silica NPs (TaO_x @MSNPs).**

9.1. General Information.

The synthesis of MSNPs is straightforward and involves a template assisted sol-gel reaction using a silica precursor. This procedure is carried out in an aqueous reaction media and henceforth the moderately hydrophilic TaO_x NC2 were employed. Empty MSNPs were also synthesized.

9.2. Synthesis of Empty MSNPs.

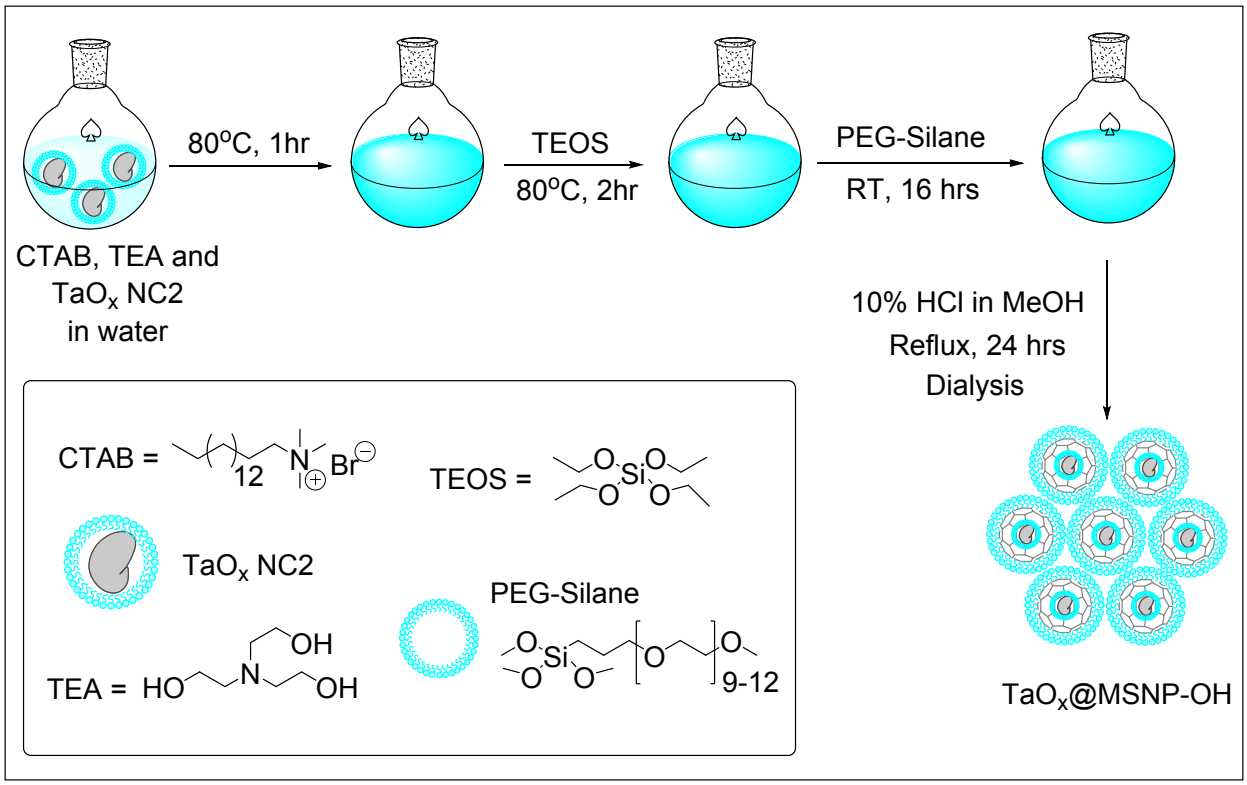
In a 100 mL four neck round bottom flask, fitted with three rubber septa and a screw top temperature probe, Hexadecyl trimethylammonium bromide (CTAB, ≥99%, SIGMA, 383 mg) and Triethanolamine (TEA, Anhydrous, SIGMA, 0.060 mL) were taken and water (DI, 50 mL) was added to it. The flask was placed on a heating mantle and temperature of the reaction mixture was increased to 80 °C. On reaching the aforementioned temperature, heating was continued for 1 h. and a clear solution was obtained. After 1 h, Tetraethyl orthosilicate (TEOS, ≥99%, ALDRICH, 2.0 mL) was added and heating was continued for another 2 h. Next, the reaction mixture was diluted to three times its volume using Methyl Alcohol (MeOH, anhydrous, ACS grade, MACRON, 200 mL) and the MSNPs were collected via centrifugation (15,000 rpm, 10 min.) as a white colored pellet. This pellet was re-suspended in a solution of Hydrochloric acid (HCl, ACS grade, MACRON) in MeOH (10% v/v, 100 mL) and this suspension was heated at reflux for 24 h. After 24 h, the reaction mixture was concentrated to a final volume of ~ 2 mL using a rotary evaporator and diluted to ~ 10 mL using DI water. This suspension was next transferred to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against DI water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the dialysis bags were lyophilized to obtain empty MSNPs as a white powder. Product Yield: 430 mg.



Scheme S8. Synthesis of Empty Mesoporous Silica Nanoparticles (Empty MSNPs).

9.3. Synthesis of MSNPs embedded with TaO_x NC2 (TaO_x@MSNP-OH).

In a 500 mL four neck round bottom flask, fitted with three rubber septa and a screw top temperature probe, Hexadecyl trimethylammonium bromide (CTAB, ≥99%, SIGMA, 800 mg) and Triethanolamine (TEA, Anhydrous, SIGMA, 0.5 mL) were taken and water (DI, 190 mL) was added to it. To this mixture was added a previously prepared suspension of TaO_x NC2 in water (200 mg in 10 mL). The flask was placed on a heating mantle and temperature of the reaction mixture was increased to 80 °C. On reaching the aforementioned temperature, heating was continued for 1 h to obtain a white colored solution with slight turbidity. After 1 h, Tetraethyl orthosilicate (TEOS, ≥99%, ALDRICH, 2.0 mL) was added and heating was continued for another 2 h. Next, the reaction mixture was allowed to cool down to ambient temperatures and following the addition of 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 2.0 mL), the contents was stirred overnight.



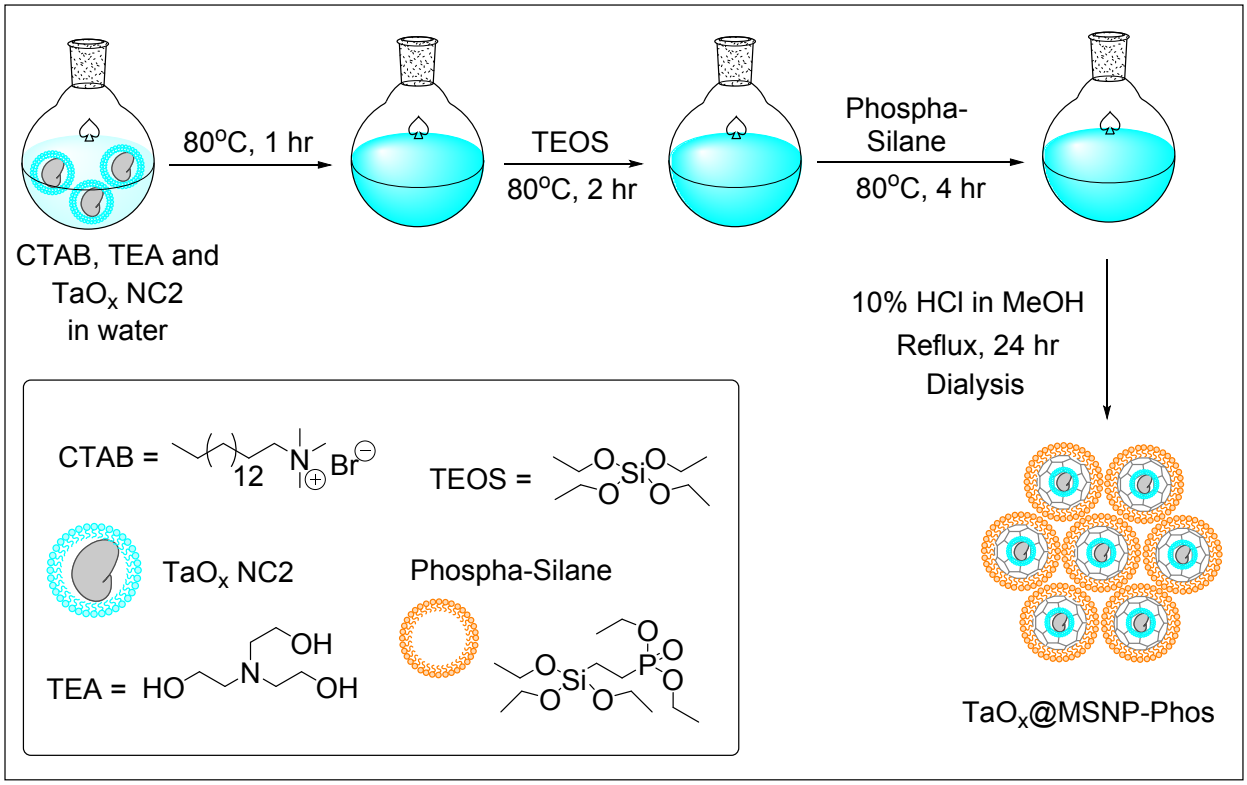
Scheme S9. Synthesis of MSNPs embedded with TaO_x NC2 (TaO_x-MSNP-OH).

Next, the reaction mixture was diluted to three times its volume using Methyl Alcohol (MeOH, anhydrous, ACS grade, MACRON, 200 mL) and the TaO_x@MSNPs were collected via centrifugation (15,000 rpm, 10 min.) as a white colored pellet. This pellet was re-suspended in a solution of Hydrochloric acid (HCl, ACS grade, MACRON) in MeOH (10% v/v, 200 mL) and this suspension was heated at reflux for 24 h. After 24 h, the reaction mixture was concentrated to a final volume of ~ 2 mL using a rotary evaporator and diluted to ~ 10 mL using DI water. This suspension was next transferred to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against DI water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive

dialysis, the contents in the dialysis bags were lyophilized to obtain TaO_x@MSNP-OH as a white powder. Product Yield: 460 mg, Ta% = 43% (ascertained from ICP-OES).

9.4. Synthesis of MSNPs embedded with TaO_x NC2 (TaO_x@MSNP-Phosphate).

In a 500 mL four neck round bottom flask, fitted with three rubber septa and a screw top temperature probe, Hexadecyl trimethylammonium bromide (CTAB, ≥99%, SIGMA, 800 mg) and Triethanolamine (TEA, Anhydrous, SIGMA, 0.5 mL) were taken and water (DI, 190 mL) was added to it. To this mixture was added a previously prepared suspension of TaO_x NC2 in water (200 mg in 10 mL). The flask was placed on a heating mantle and temperature of the reaction mixture was increased to 80 °C. On reaching the aforementioned temperature, heating was continued for 1 h to obtain a white colored solution with slight turbidity. After 1 h, Tetraethyl orthosilicate (TEOS, ≥99%, ALDRICH, 2.0 mL) was added and heating was continued for another 2 h Next, (2-Diethylphosphatoethyl)triethoxysilane (Phospha-Silane, tech-95, GELEST INC., 2.0 mL), was added to the reaction mixture and heating was continued for another 4 h.



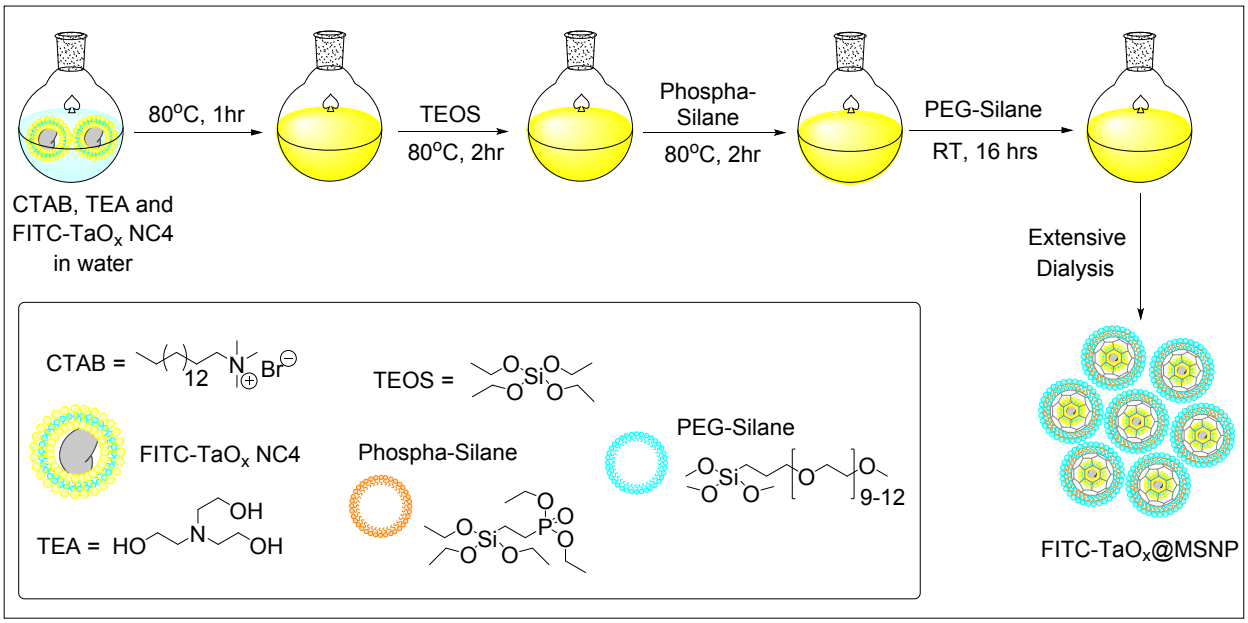
Scheme S10. Synthesis of MSNPs embedded with TaO_x NC2 (TaO_x@MSNP-Phos).

Next, the reaction mixture was allowed to cool down to RT, diluted to three times its volume using Methyl Alcohol (MeOH, anhydrous, ACS grade, MACRON, 200 mL) and the TaO_x@MSNPs were collected via centrifugation (15,000 rpm, 10 min.) as a white colored pellet. This pellet was re-suspended in a solution of Hydrochloric acid (HCl, ACS grade, MACRON) in MeOH (10% v/v, 200 mL) and this suspension was heated at reflux for 24 h. After 24 h, the reaction mixture was concentrated to a final volume of ~ 2 mL using a rotary evaporator and diluted to ~ 10 mL using DI water. This suspension was next transferred

to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at both ends and dialyzed against DI water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the dialysis bags were lyophilized to obtain TaO_x@MSNP-Phos as a white powder. Product Yield: 450 mg, Ta% = 45% (ascertained from ICP-OES).

9.5. Synthesis of MSNPs embedded with FITC-TaO_x NC4 (FITC-TaO_x@MSNP).

In a 500 mL four neck round bottom flask, fitted with three rubber septa and a screw top temperature probe, Hexadecyl trimethylammonium bromide (CTAB, ≥99%, SIGMA, 500 mg) and Triethanolamine (TEA, Anhydrous, SIGMA, 0.6 mL) were taken and water (DI, 190 mL) was added to it. To this mixture was added a previously prepared suspension of hydrophilic FITC-TaO_x NC4 in water (250 mg in 10 mL). The flask, covered with an aluminum foil, was placed on a heating mantle and temperature of the reaction mixture was increased to 80 °C. On reaching the aforementioned temperature, heating was continued for 1 h to obtain a yellow colored solution with slight turbidity. After 1 h, Tetraethyl orthosilicate (TEOS, ≥99%, ALDRICH, 1.5 mL) was added and heating was continued for another 2 h. Next, (2-Diethylphosphatoethyl)triethoxysilane (Phospha-Silane, tech-95, GELEST INC., 1.5 mL), was added to the reaction mixture and heating was continued for another 2 h.



Scheme S11. Synthesis of MSNPs embedded with FTIC-TaO_x NC4 (FITC-TaO_x@MSNP)

Next, the reaction mixture was allowed to cool down to RT and following the addition of 2-[Methoxy (polyethyleneoxy)-9-12-propyl]trimethoxysilane (PEG-Silane, tech-90, MW 591-723, GELEST INC., 2.0 mL), the contents was stirred overnight. All these procedures were carried out in the dark to protect from light. Next, the reaction mixture was diluted to three times its volume using Methyl Alcohol (MeOH, anhydrous, ACS grade, MACRON, 200 mL) and the FITC-TaO_x@MSNPs were collected via centrifugation (15,000 rpm, 10 min.) as a white colored pellet. This pellet was re-suspended in DI water and transferred to Dialysis Membrane bags (SPECTRA/POR® 4 Dialysis Membrane, Standard RC Tubing, MWCO: 12-14 kD), clipped at

both ends and dialyzed in two stages. For the first stage, dialysis was carried out against a 1:1:0.01 mixture of water:ethanol;glacial acetic acid with regular change of media after 24 h. This cycle was repeated thrice and ensured the removal of the surfactant CTAB. Next, the dialysis bags were transferred for extensive dialysis against DI water with regular change of external media after 2, 4, 16, 4, 4 and 16 h. After extensive dialysis, the contents in the dialysis bags were lyophilized to obtain FTIC-TaO_x@MSNP-Phos as a yellow colored free flowing powder. Product Yield: 430 mg, Ta% = 39% (ascertained from ICP-OES).

10. Characterization of TaO_x@MSNPs.

General considerations for physicochemical characterization of the MSNPs are identical to that of the NCs. Please refer to Section 2 for specific details.

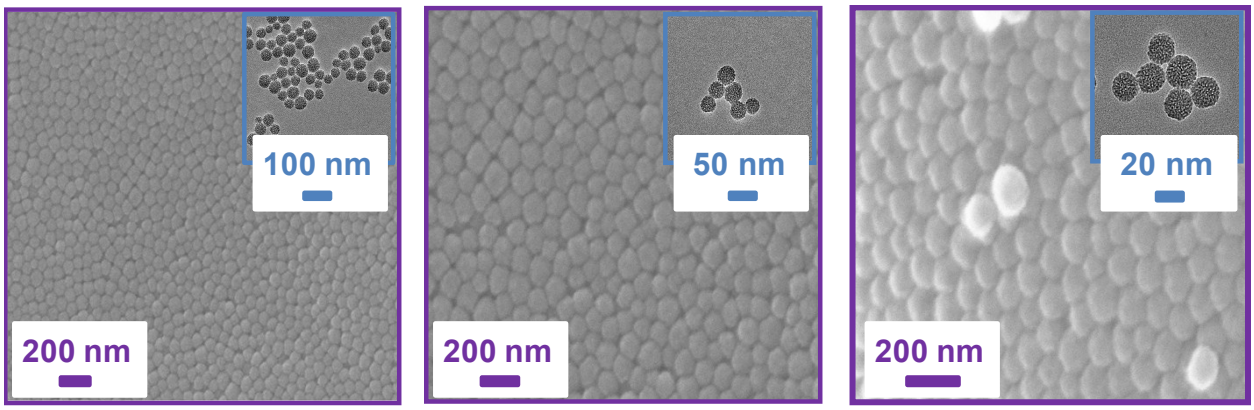


Figure S41. TEM (*inset*) and Scanning Electron Microscopy (SEM) images of Empty MSNPs. The left, center and right panels correspond to MS NPs obtained from three different batches that quite clearly show the homogeneity in size.

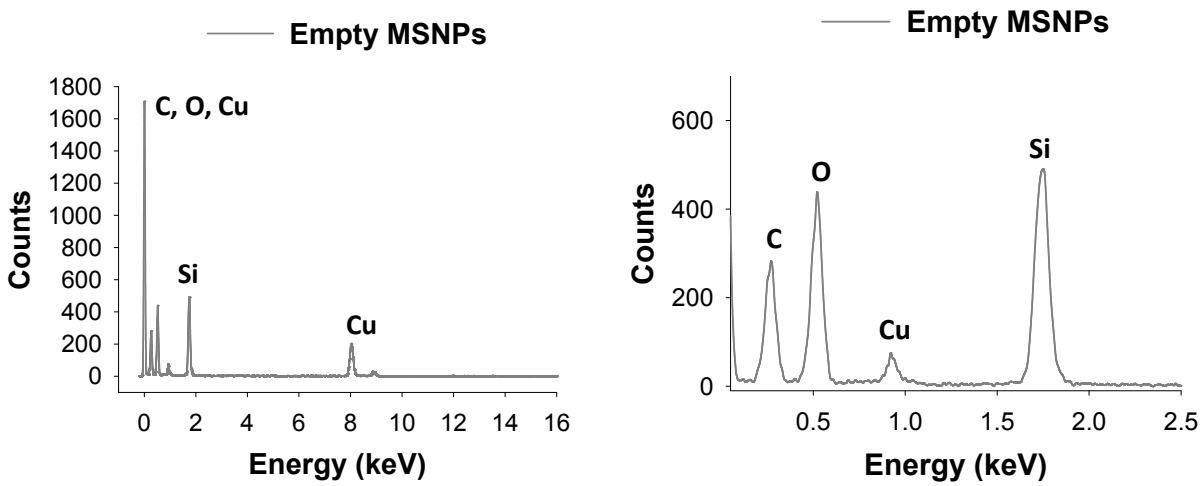


Figure S42. Energy Dispersive Spectroscopy (EDS) for Empty MSNPs, showing the presence of Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

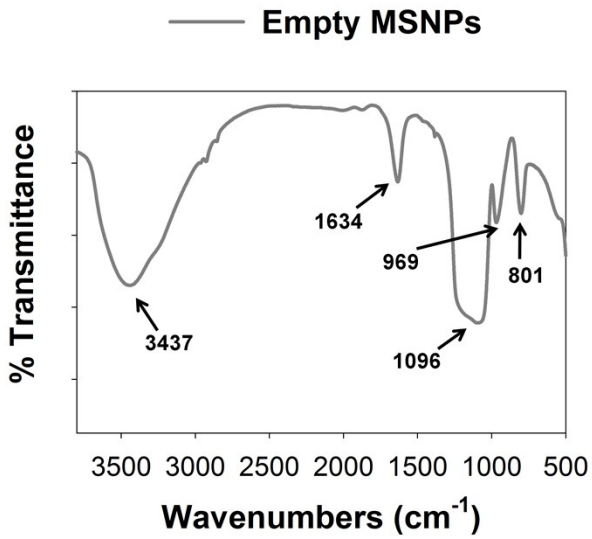


Figure S43. FTIR Spectra of the as synthesized Empty MSNPs. MSNPs are characterized by long and branched siloxane chains as a result of which the Si-O-Si absorption band around 1200-1000 cm^{-1} becomes broader and more complex. The broad band centered at 1096 cm^{-1} is characteristic of MSNPs. Prominent and common transmittance peaks are pointed out.

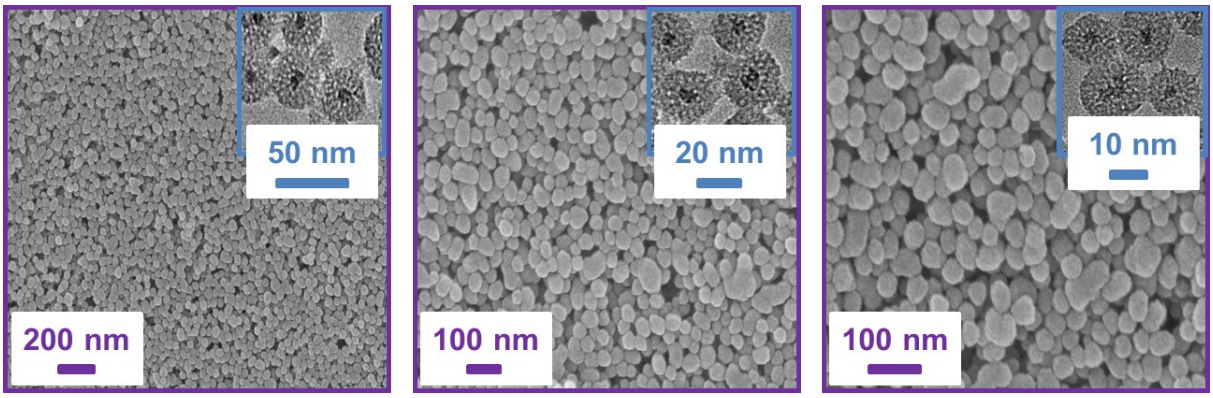


Figure S44. TEM (*inset*) and Scanning Electron Microscopy (SEM) images of TaO_x@MSNP-OH NPs. The left, center and right panels correspond to TaO_x@MSNP-OH NPs obtained from three different batches that quite clearly show the homogeneity in size and the efficiency in packing of TaO_x NC2 within the mesoporous silica shell.

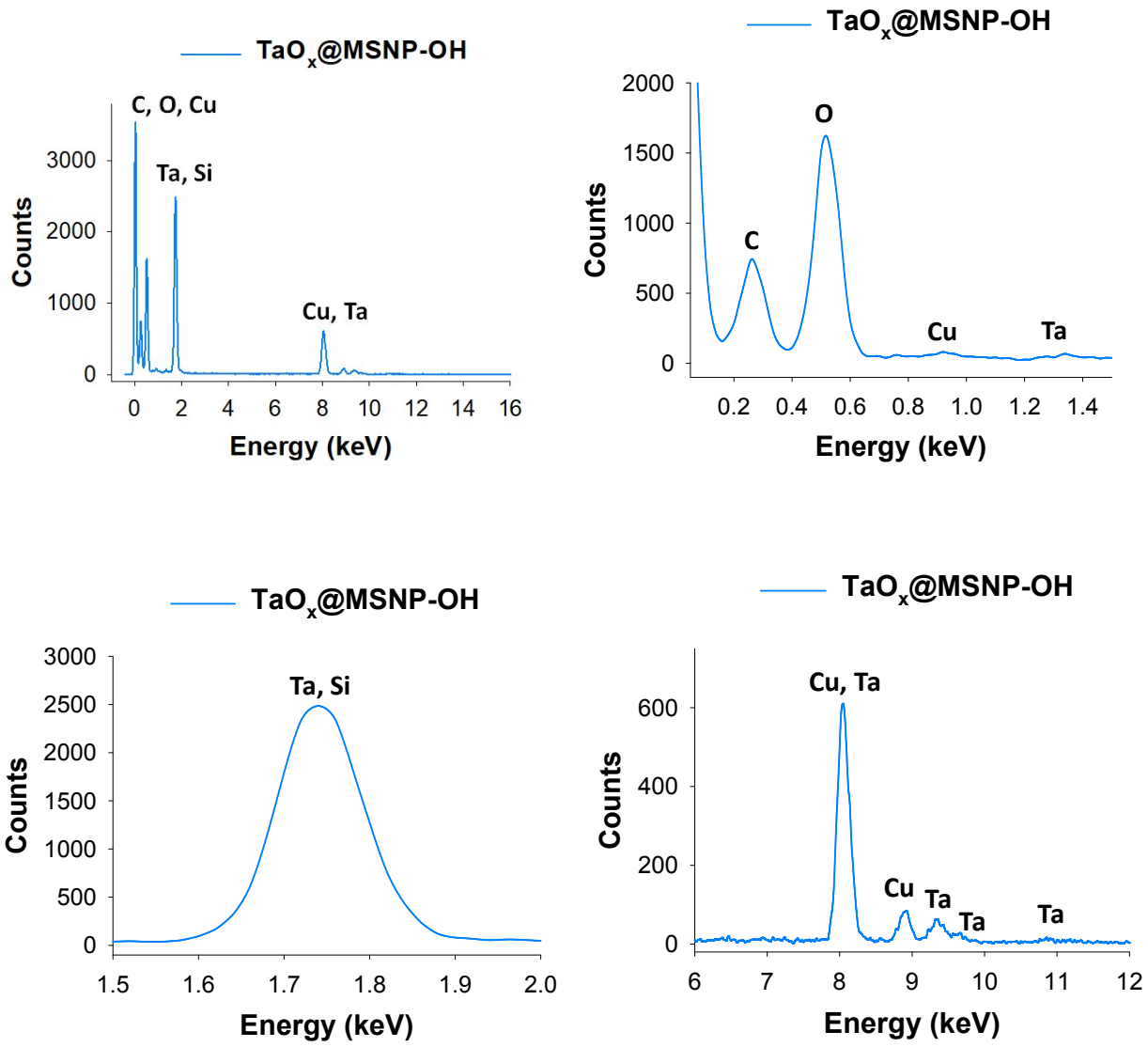


Figure S45. Energy Dispersive Spectroscopy (EDS) for TaO_x@MSNP-OH NPs, showing the presence of Ta and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

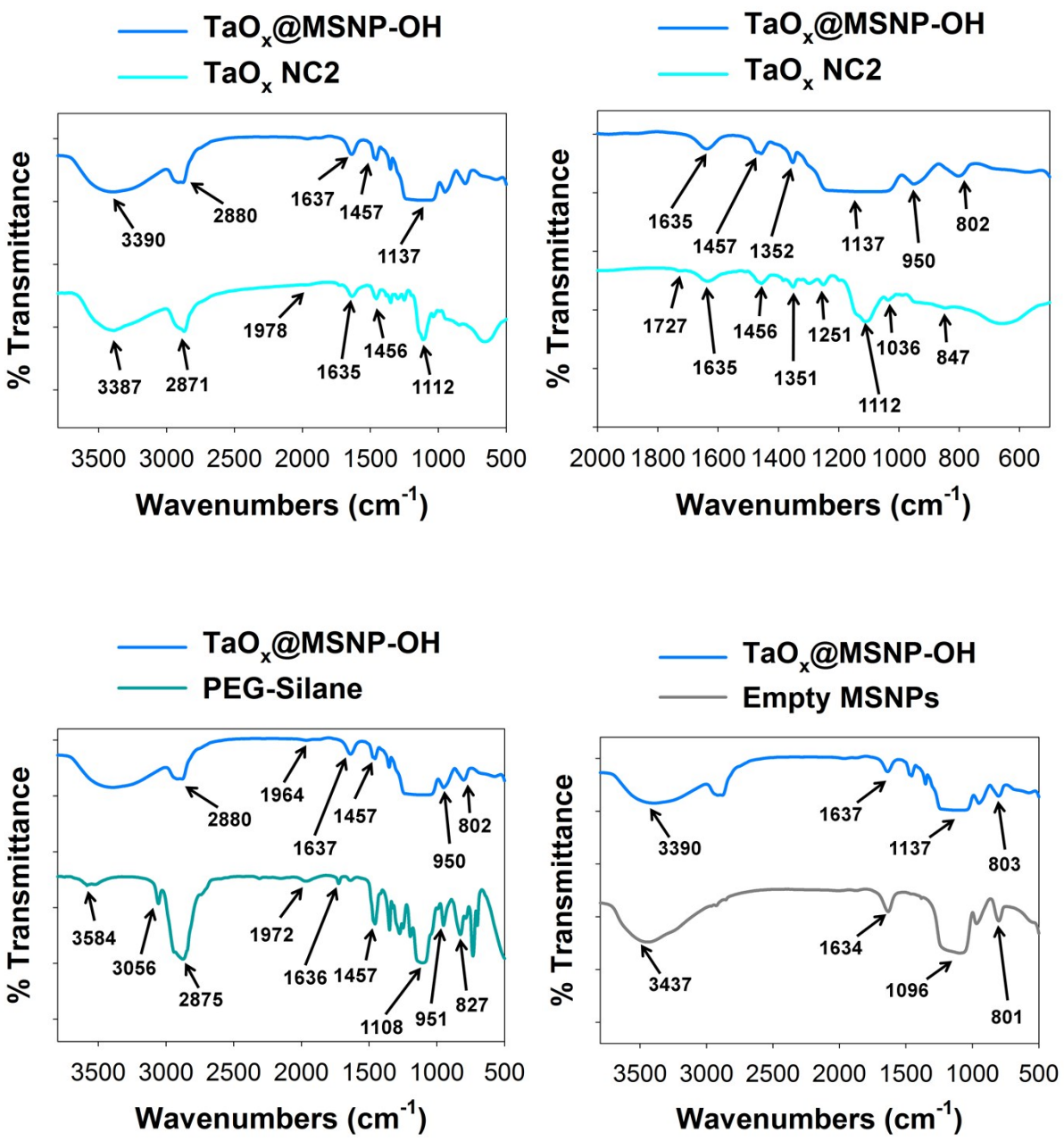


Figure S46. FTIR Spectra comparing the as synthesized TaO_x@MSNP-OH NPs and the starting material TaO_x NC2 (*top panel*). The consequent comparison with PEG-Silane and Empty MSNPs with the as synthesized TaO_x@MSNP-OH NPs is shown in the *bottom panel*. Prominent and common transmittance peaks are pointed out.

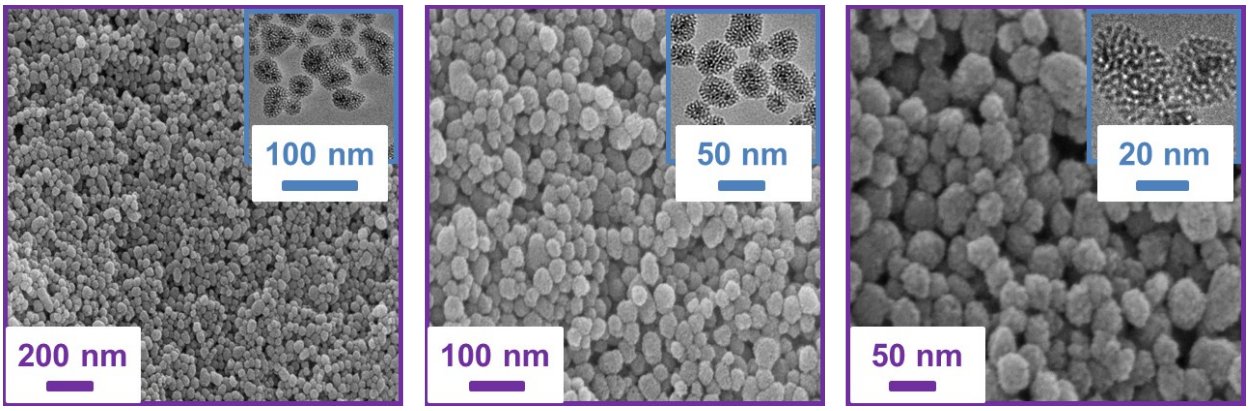


Figure S47. TEM (*inset*) and Scanning Electron Microscopy (SEM) images of TaO_x@MSNP-Phos NPs. The left, center and right panels correspond to TaO_x@MSNP-Phos NPs obtained from three different batches that quite clearly show the homogeneity in size and the efficiency in packing of TaO_x NC2 within the mesoporous silica shell.

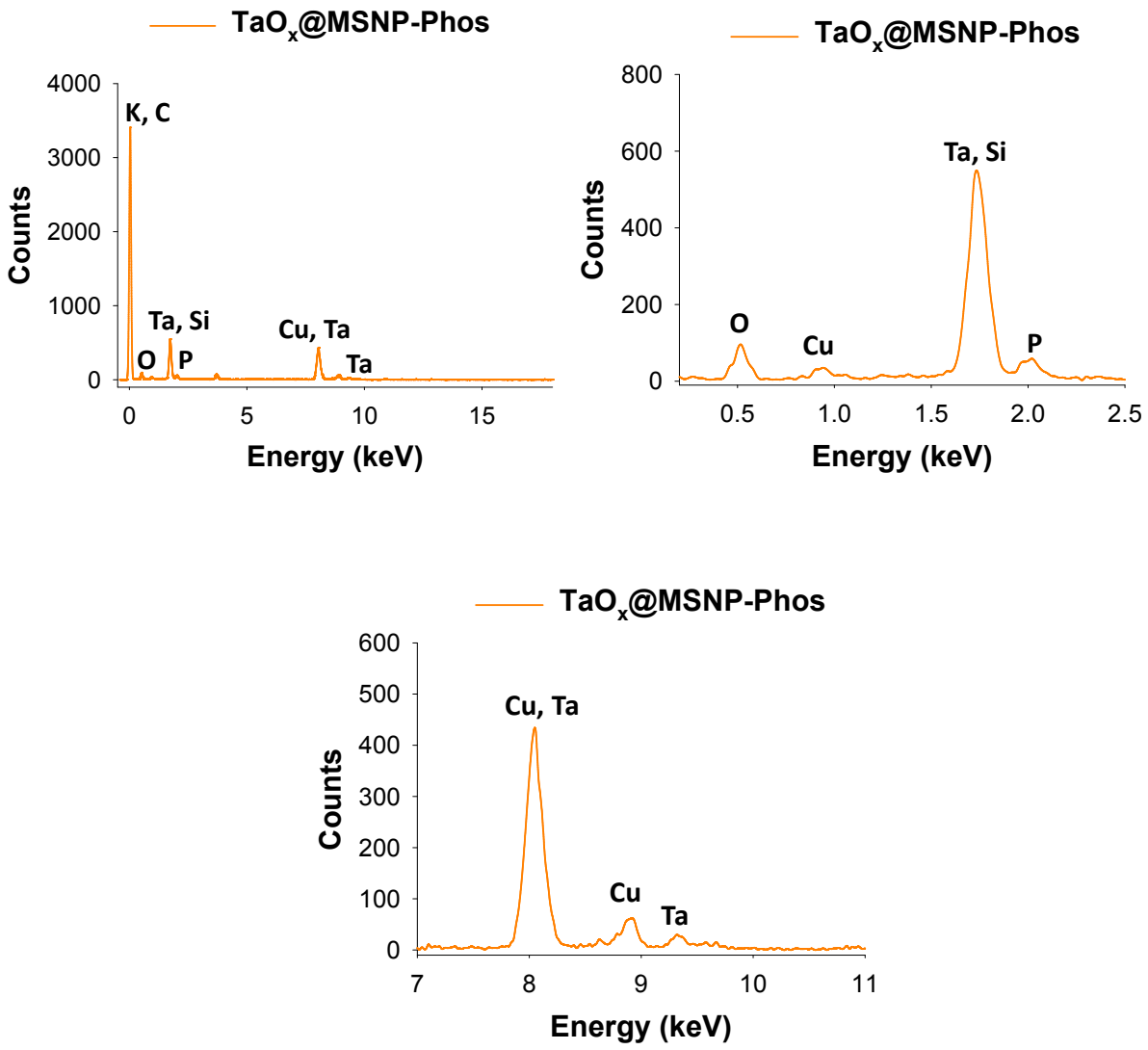


Figure S48. Energy Dispersive Spectroscopy (EDS) for TaO_x@MSNP-Phos NPs, showing the presence of Ta, P and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

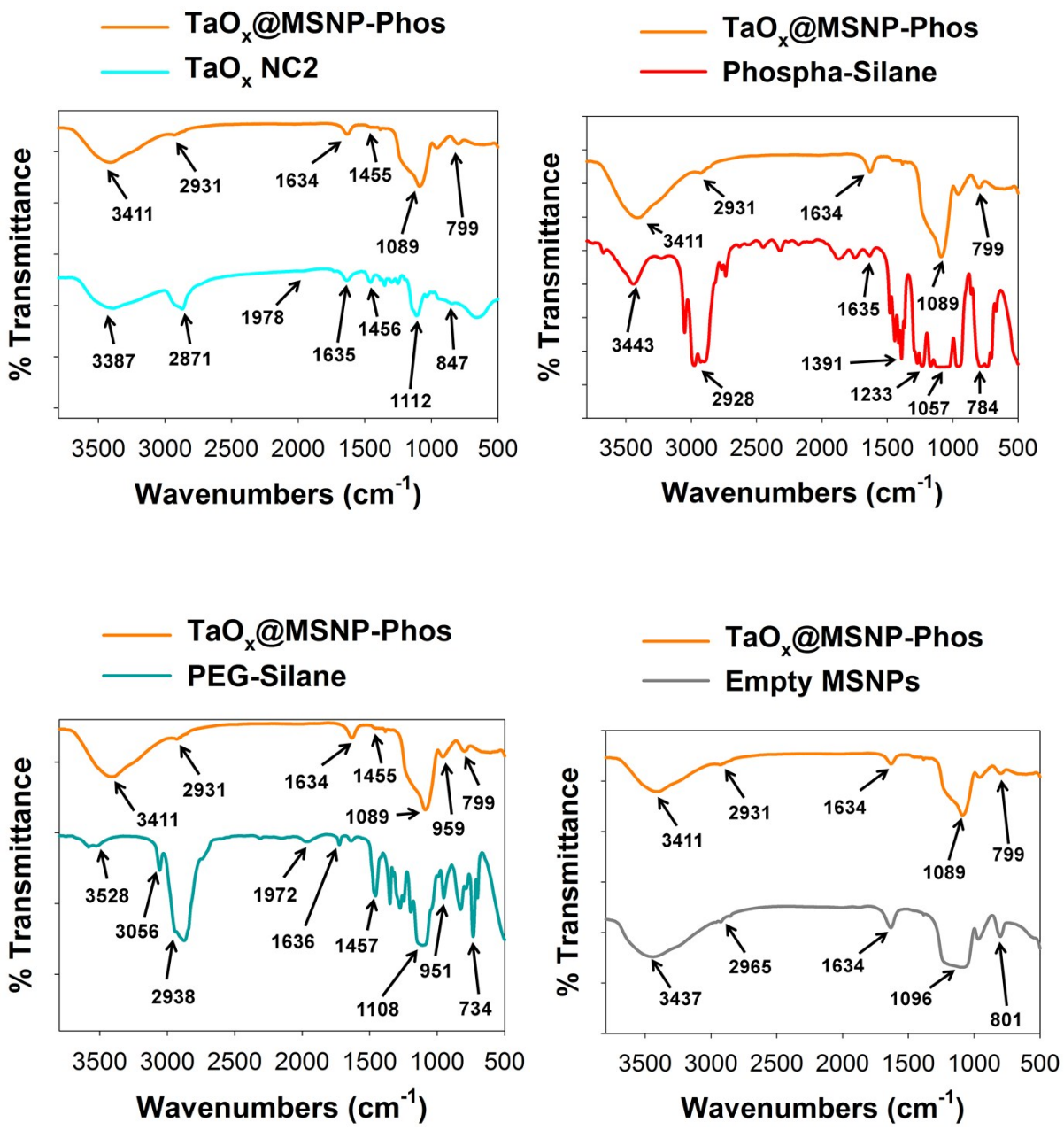


Figure S49. FTIR Spectra comparing the as synthesized TaO_x@MSNP-Phos NPs and the starting material TaO_x NC2 and Phospha-Silane (*top panel*). The consequent comparison with PEG-Silane and Empty MSNPs with the as synthesized TaO_x@MSNP-Phos NPs is shown in the *bottom panel*. Prominent and common transmittance peaks are pointed out.

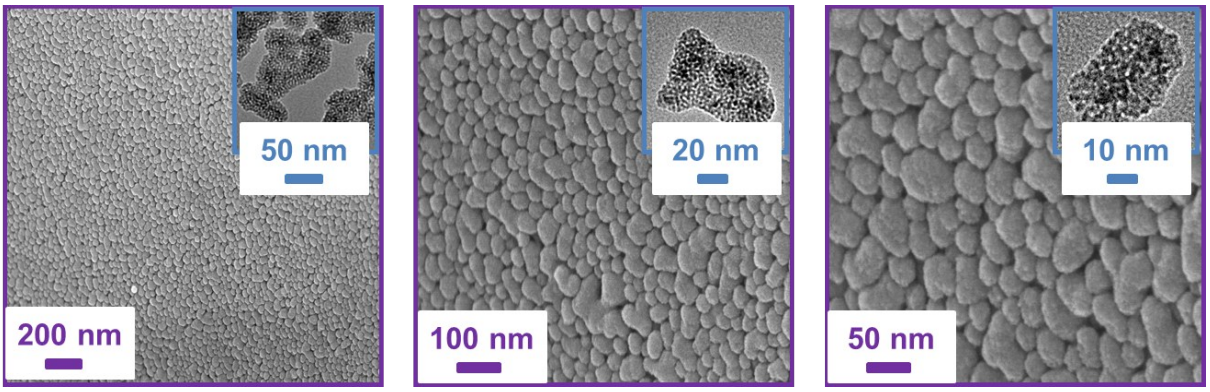


Figure S50. TEM (*inset*) and Scanning Electron Microscopy (SEM) images of FITC-TaO_x@MSNPs. The left, center and right panels correspond to FITC-TaO_x@MSNPs obtained from three different batches that quite clearly show the homogeneity in size and the efficiency in packing of FITC-TaO_x NC4 within the mesoporous silica shell.

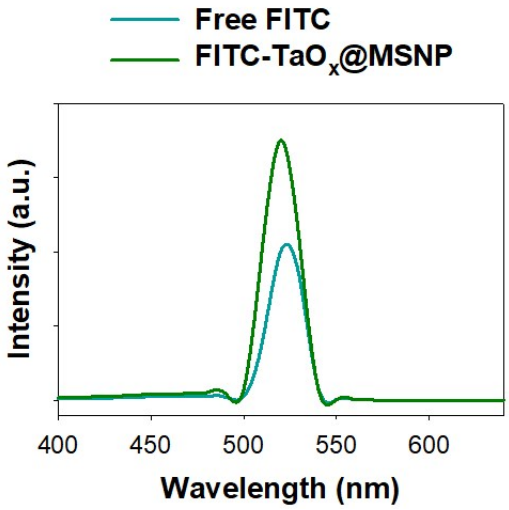
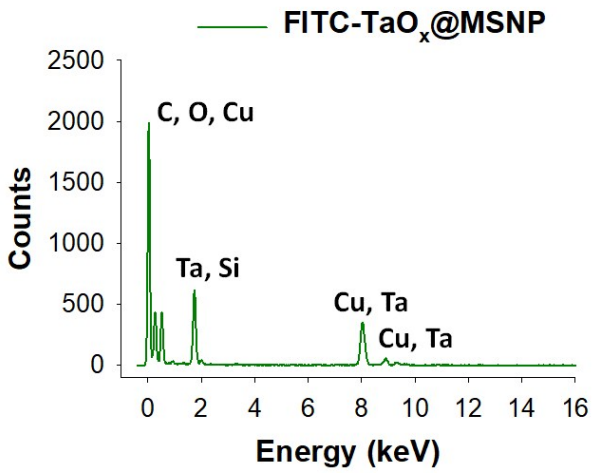
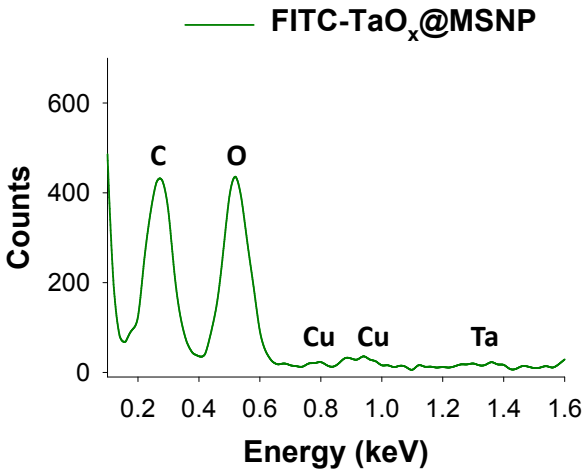
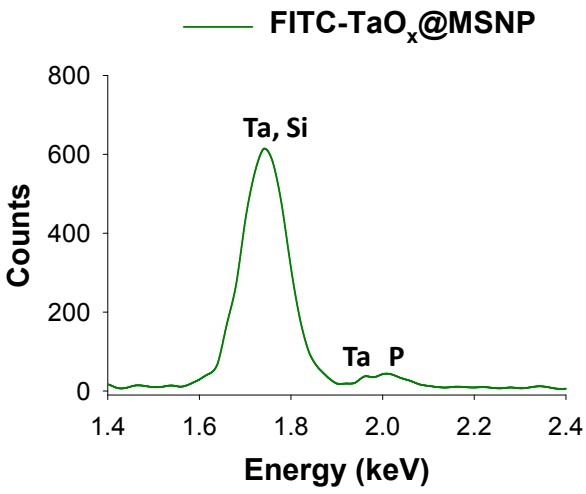


Figure S51. Fluorescence spectral comparison for free FITC and FITC-TaO_x@MSNP in PBS.


FITC-TaO$_x$@MSNP
Counts
Energy (keV)
C, O, Cu
Ta, Si
Cu, Ta
Cu, Ta


FITC-TaO$_x$@MSNP
Counts
Energy (keV)
C
O
Cu
Cu
Ta


FITC-TaO$_x$@MSNP
Counts
Energy (keV)
Ta, Si
Ta
P

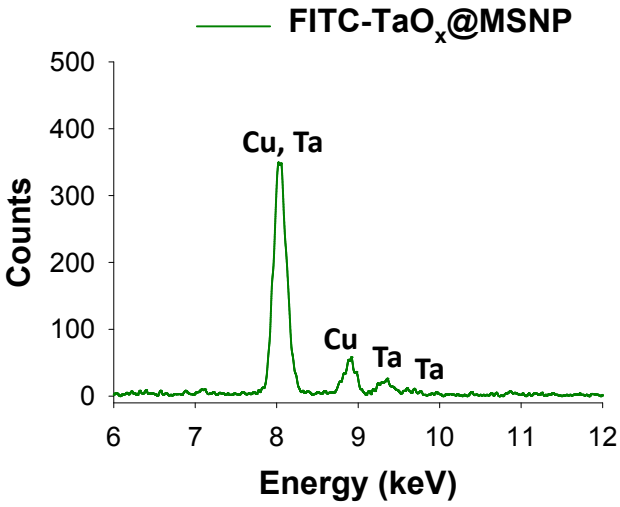

FITC-TaO$_x$@MSNP
Counts
Energy (keV)
Cu, Ta
Cu
Ta
Ta

Figure S52. Energy Dispersive Spectroscopy (EDS) for FITC-TaO_x@MSNPs, showing the presence of Ta, P and Si in the NCs. The peaks for carbon (C) and copper (Cu) in the EDS spectra are attributed to the grid mesh used as a sample holder for TEM imaging.

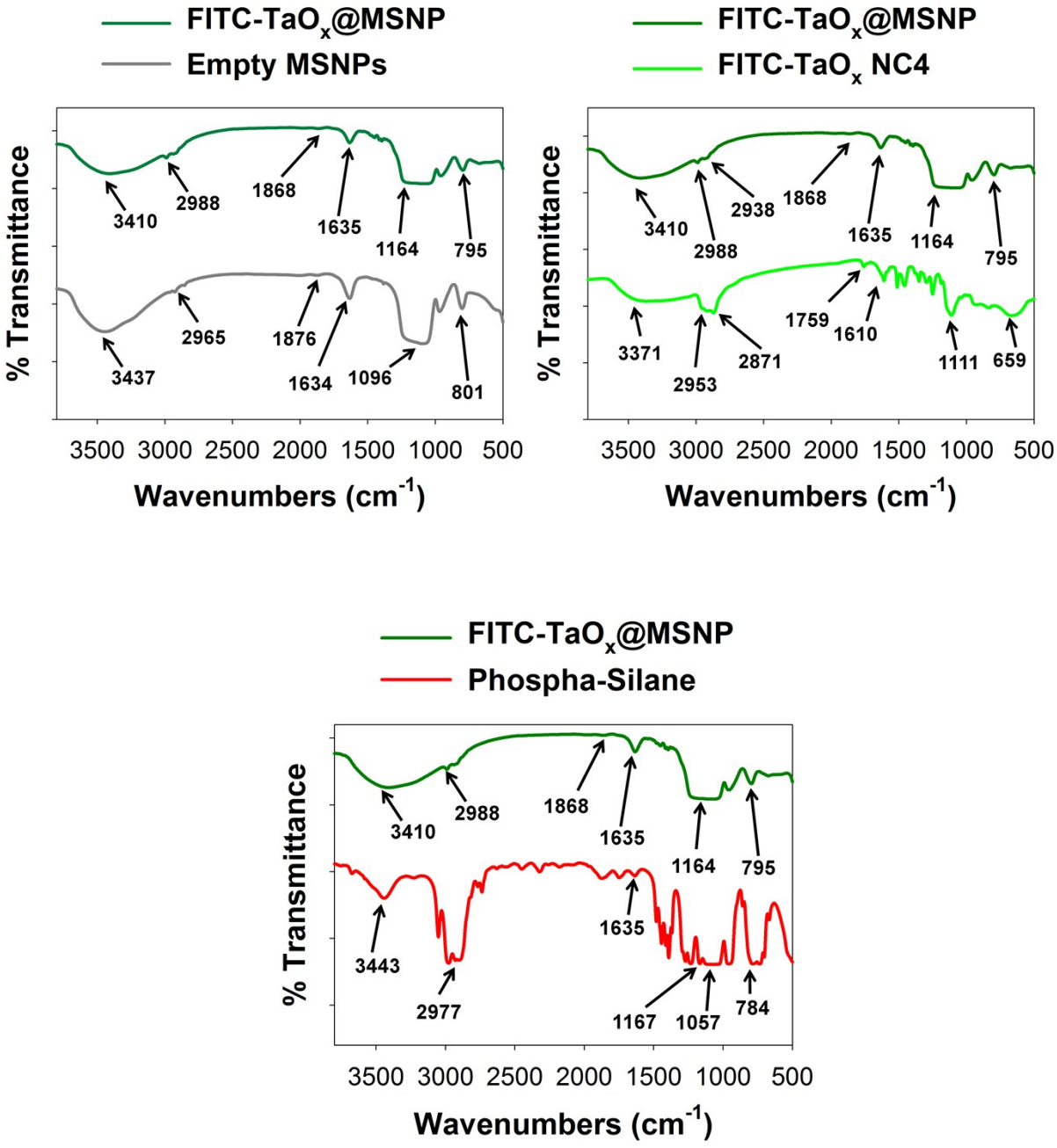


Figure S53. FTIR Spectra comparing the as synthesized FITC-TaO_x@MSNPs and the starting material FITC-TaO_x NC4 (*top panel*) and Phospha-Silane (*bottom panel*). Prominent and common transmittance peaks are pointed out.

11. Estimation of Ta content and Ta dissolution from TaO_x NPs.

11.1. *Ta content estimation using ICP-OES*:

To estimate the Ta content in various TaO_x NPs, a strategy identical to the one for NCs was adopted. All measurements were carried out in triplicates and the mean concentration have been reported. For specific details refer to Section 3.1.

11.2. In vitro Ta dissolution:

To analyze the dissolution of various TaO_x NPs in lysosomal media, an *in vitro* dissolution study was carried out. A similar strategy as with the NCs was adopted. For specific details, refer to Section 3.2. For both NP types, minimal Ta dissolution was observed during the first week. During the second week, dissolution ranged between 0.5 - 1%; for the third week, dissolution within 1.0 - 1.5% was observed while for the fourth week, a total of 2.5 – 3.0% Ta dissolution was recorded (**Figure S54**).

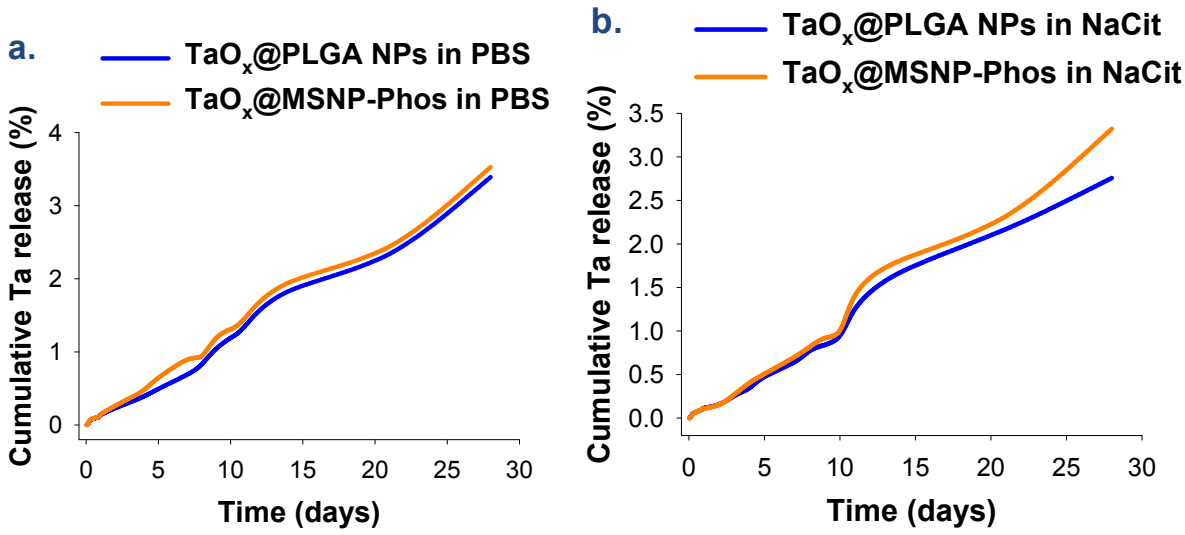


Figure S54. Ta dissolution from TaO_x@PLGA NPs and TaO_x@MSNP-Phos in (**a.**) PBS (pH 7.4) and (**b.**) sodium citrate (NaCit, pH 5.5) over 4 weeks using ICP-OES (n = 3, S.D. < 0.5).

12. Cellular Studies.

12.1. Cellular Viability using RAW 264.7 and HEK 293 Cells

To test the cytocompatibility of various TaO_x NP formulations, MTT assay using RAW 264.7 macrophage cells and HEK 293 cells was performed. For specific details, refer to Section 4.1.

13. *In vivo* micro-CT Experiments with TaO_x NPs.

13.1. General Information

We used micro-CT for quantifying the efficacy of TaO_x NPs when used as a high Z-value radiopaque contrast agent in an *in vivo* model.

In Vivo TaO_x NP X-Ray attenuation evaluation using micro-CT Image Acquisition and Analysis was performed on BALB/c Mice (Charles River Laboratories, Inc.; sex, male; age, ~ 3 months; body weight, ~ 25g) (n = 3) by injecting a localized bolus of TaO_x NPs, using the same micro-CT scan parameters previously detailed for *in vivo* biodistribution of TaO_x NCs, at a single scan time point: Immediate Post-Injection.

While under Isoflurane inhalant anesthesia, a 50 µL bolus of 50 mM TaO_x@PLGA NPs and a 50 µL bolus of 50 mM TaO_x@MSNP-OH were administered bilaterally (I.M.) between the Superficial Gluteal Muscle and Biceps Femoris Muscle (n = 1), a 50 µL bolus of 50 mM and a 50 µL bolus of 25 mM TaO_x@MSNP-OH were administered bilaterally (I.M.) between the Gastrocnemius Muscle and Caudal Tibial Muscle (n = 1), and a 50 µL bolus of 50 mM and a 50 µL bolus of 25 mM TaO_x@PLGA NPs were administered bilaterally (I.M.) between the Gastrocnemius Muscle and Caudal Tibial Muscle (n = 1). Following micro-CT image acquisition, animals were euthanized and carcasses discarded. No blood or tissues were collected.

Micro-CT Image Rendering, Segmentation, and Analysis was performed using Caliper AnalyzeDirect©, v12.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA.