Electronic Supplementary Material (ESI) for Journal of Materials Chemistry B

SUPPLEMENTARY INFORMATION

1. Reactants

The organic linkers 1,3,5-benzeneticarboxylic acid (BTC), fumaric acid (Fum), 2-nitroterephtalic acid (BDC_NO_2), 2-aminoterephtalic acid (BDC_NH_2) were purchased at Sigma-Aldrich (France). The metallic precursors iron (III) chloride hexahydrate ($FeCl3 \cdot 6H_2O$), iron (III) perchlorate hydrate ($Fe(ClO_4)_3 \cdot 6H_2O$) and zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$) were acquired at Sigma-Aldrich (France) whereas zirconium oxychloride ($ZrOCl_2 \cdot 8H_2O$) was acquired at Alfa Aesar (France). The solvents for organic syntheses hydrogen chloride (HCl), absolute ethanol (EtOH abs), ethanol 96.2 (EtOH 96.2), sulphuric acid (H_2SO_4), chloroform ($CHCl_3$), dichloromethane (DCM) and N,N-dimethylformamide (DMF) were purchased at Carlo Erba (Italy), and sodium hydroxide (NaOH) was obtained at Alfa Aesar (France). Furazan ((R)-(-)-4-(3-aminopyrrolidino)-7-nitrobenzofuran) and the MTT reactant (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) were acquired at Sigma-Aldrich (France). Cell culture reagents were acquired at Gibco® (France). N-octanol was purchased at Merck (Germany). For confocal studies, TOPRO-3 (Invitrogen™) was acquired at Life Technologies (France).

5-nitroisophthalic acid (BDC-NO_2): Sigma Aldrich; sodium hydroxide (NaOH): Alfa Aesar; aluminium: Sigma Aldrich; glucose: Sigma Aldrich; hydrogen chloride (HCl): Carlo Erba; H_2SO_4 95%: Carlo Erba; sodium nitrite ($NaNO_2$); toluene: Acros; chloroform ($CHCl_3$): Carlo Erba; N,N-dimethylformamide (DMF): Carlo Erba; ethanol (EtOH): VWR; methanol (MeOH): Carlo Erba; Acetone: Carlo Erba; iron (III) perchlorate hexahydrate ($Fe(ClO_4)_3 \cdot 6H_2O$): Sigma Aldrich; iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$): Alfa Aesar; zirconyl (IV) chloride ($ZrOCl_2$): Alfa Aesar; zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$): Sigma Aldrich; fumaric acid: Sigma Aldrich; 1,4-terephtalic acid (BDC): Sigma Aldrich; 1,3,5-benzenetricarboxylic acid (BTC): BASF; 2-methyl-terephthalonitrile: Sigma Aldrich; 1,2,4,5-tetramethylbenzene: Sigma Aldrich; 2-amino-terephtalic acid (BDC-NH_2): Alfa Aesar; 2-nitroterephtalic acid (BDC-NO_2): Alfa Aesar; 2-methylimidazole: Alfa Aesar.

2. Synthesis of the organic linkers

The non-commercialised organic linkers 3,3',5,5'-azobenzene tetracarboxylic acid (Tazb; S2.1 SI[1]), dimethylterephthalic acid (BDC_$2CH_3$; S 2.4[2]), 2,3,5,6-tetramethylterephtalic acid (BDC_$4CH_3$; S 2.10[3, 4]) and 2,5-diperfluoroterephthalic acid (BDC_$2CF_3$; S 211[5]) were synthesised following the published methods.

3. Material synthesis

3.1) MIL-127_nano or ($Fe_3O(OH)(H_2O)_3[(C_{16}N_2O_8H_6]_3.n\ H_2O$) 537 mg of 3,3',5,5'-azobenzenetetracarboxylic acid[1] and 15 mL of DMF were added into a 50 mL round bottom flask and set into reflux in order to dissolve all the components. 810 mg of $FeCl_3 \cdot 6H_2O$ were added to the prior mixture. After 1 h of reflux, the nanoparticles (NPs) were collected by centrifugation (10,500 rpm/15 min) and then washed with EtOH 96.2% in order to eliminate remaining DMF. The activation was performed by suspending the NPs in DMF at 50 °C during 1 h, continued by four washes with EtOH.

3.2) MIL-100 nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_3C_6H_3]_2\ n \cdot H_2O$)

The synthesis of MIL-100 NPs has been performed according to the published procedure[6]. 845 mg of 1,3,5-BTC (BTC) together with 2,425 mg of $FeCl_3 \cdot 6H_2O$ and 20 mL of distilled water were added into a Teflon lined autoclave. After 10 min of gentle magnetic stirring, the mixture was sealed and heated at 130 °C for 4 min in a microwave oven (at 400 W; Mars-5, CEM) with a heating temperature of 2 min. The NPs were recovered by centrifugation (10,500 rpm/15 min). The activation was performed by suspending the NPs in 20 mL of EtOH 96.2%, repeating this washing procedure 7 times till disappearance of the free acid.

3.3) MIL-100 micro or ($Fe_3O(H_2O)_2OH[C_6H_3(CO_2)_3]_2\ n \cdot H_2O$)

The synthesis of micrometric MIL-100 has been performed according to the published procedure [7]. 210 mg of 1,3,5-BTC together with 270 mg of $FeCl_3 \cdot 6H_2O$ and 5 mL of distilled water held at 130 °C in a Teflon-lined autoclave for 3 days. The light-orange solid product was recovered by filtration and washed with deionised water. A treatment in hot deionised water (80 °C) for 3 h was applied to decrease the amount of residual trimesic acid (typically, 1 g of MIL-100(Fe) in 350 mL of water).

3.4) MIL-101_2CH$_3$_nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_2(CH_3)_2]_3\ n \cdot H_2O$)

194 mg of 2,5-dimethylterephtalic acid[2] together with 354 mg of $Fe(ClO_4)_3 \cdot 6H_2O$ and 5 mL of DMF were added into a Parr bomb and heated at 100 ºC for 15 h. The orange NPs were recovered by centrifugation (10,500 rpm/15 min). The activation was performed suspending the NPs 5 times in 20 mL of EtOH 96.2% for 10 min.

3.5) MIL-101_NH$_2$_nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_3NH_2]_3\ n \cdot H_2O$)

The synthesis of MIL-101_NH_2 NPs has been performed according to the published procedure[8]. 90.5 mg of 2-aminoterephtalic acid (BDC-NH_2) together with 135 mg of $FeCl_3 \cdot 6H_2O$, 25 mL of EtOH 96.2% and 0.25 mL of HCl 1 M were placed into a Teflon-liner and heating till

reaching a temperature of 60 °C during 40 min and maintaining the temperature plateau for 5 min under microwave irradiation at 400 W. The obtained brown precipitated was recovered by centrifugation at 10,500 rpm for 10 min. The activation was performed by suspending the NPs in 20 mL of EtOH 96.2%, repeating this process 4 times.

3.6) MIL-88A_nano or $(Fe_3O(OH)(H_2O)_2[(CO_2)_2C_2H_2]_3\ n{\cdot}H_2O)$

290 mg of fumaric acid (FUM) together with 675 mg of $FeCl_3{\cdot}6H_2O$ and 25 mL of distilled water were added to a Teflon tube. After 10 minutes of gentle magnetic stirring, the Teflon tube was inserted inside the microwave and heated at 80 ºC for 10 min (600 W), as previously reported[9] Then, the obtained precipitated was recovered by centrifugation at 10,500 rpm for 10 min .The activation was performed in EtOH 96.2 by adding 20 mL of the solvent during 4 times.

3.7) MIL-88B_nano or $(Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_4]_3\ n{\cdot}H_2O)$

The synthesis of MIL-101_NH_2 NPs has been performed according to the published procedure[10, 11]. 332 mg of terephthalic acid (BDC) together with 344 mg of iron (III) acetate and 10 mL of MeOH) were added into a Parr bomb, heated in an oven at 100 °C for 2 h and then, a fast cool down. Then, the orange solid was recovered by filtration. The activation was made by washing the NPs with 20 mL of EtOH 96.2% for 10 min, repeating this protocol 3 times.

3.8) MIL-88B_CH_3_nano or $(Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_3(CH_3)]_3\ n{\cdot}H_2O)$

The synthesis of MIL-88B_CH_3_nano has been performed according to the published procedure[4]. 180 mg of 2-methylterephtalic acid[12] together with 354 mg of $Fe(ClO_4)_3{\cdot}6H_2O$ and 5 mL of MeOH were placed in a Teflon-lined autoclave (23 mL) for 3 days at 100 °C. Then, the brown solid was recovered by centrifugation (10,500 rpm/15 min). The activation was performed by suspending the in 20 mL of EtOH twice (16 h).

3.9) MIL-88B_2CH_3_nano or $(Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_2(CH_3)_2]_3\ n{\cdot}H_2O)$

The synthesis of MIL-88B_2CH_3_nano has been performed according to the published procedure[4]. 194 mg of 2,5-dimethylterephthalic acid[2] together with 354 mg of $Fe(ClO_4)_3{\cdot}6H_2O$ and 5 mL of MeOH were placed in a Teflon-lined autoclave (23 mL) for 3 days at 100 °C. Then, the brown solid was recovered by centrifugation (10,000 rpm/15 min). The activation of this material has 2 steps: a first wash with 5 mL of DMF twice (1 h) and then washed with 20 mL of absolute EtOH.

3.10) MIL-88B_4CH$_3$_nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6(CH_3)_4]_3$ $n\cdot H_2O$)

MIL-88B_4CH$_3$_nano was prepared as previously reported[8]. 116 mg of 2,3,5,6-tetramethylterephtalic acid[3] together with 270 mg of $FeCl_3\cdot 6H_2O$ and 10 mL of DMF with 0.4 mL of NaOH 2M were added into a Parr bomb. The mixture was placed in a in a Teflon-lined autoclave (23 mL) at 100 °C for 2 h. After cooling the Paar bomb under water, the solid was recovered by centrifugation at 10,500 rpm for 10 min. The activation of this material was made by washing with 3 times with 20 mL of EtOH for 10 min.

3.11) MIL-88B_2CF$_3$_nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_2(CF_3)_2]_3.nH_2O$)

The synthesis of MIL-88B_2CF$_3$ has been performed according to the published procedure[4]. 775 mg of 2,5-trifluoromethylterephtalic acid[5] together with 675 mg of $FeCl_3\cdot 6H_2O$ and 25 mL of absolute EtOH were added into a Teflon tube and then heated at 100 ºC for 30 min and maintaining the temperature plateau at 100 ºC during 5 min using a microwave oven (400 W). The sample was recovered by centrifugation at 10,500 rpm for 10 min and activated in cold acetone (1 g MIL-88B-2CF$_3$ in 25 mL of cold acetone) under stirring during 4 h.

3.12) MIL-88B_NH$_2$_nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_3(NH_2)]_3$ $n\cdot H_2O$)

534 mg of BDC-NH$_2$ together with 405 mg of $FeCl_3\cdot 6H_2O$ and 25 mL of EtOH were added into a Teflon tube and then inserted inside the microwave and heated at 100 ºC for 40 min and maintaining at the temperature plateau of 100 ºC during 5 min (800 W). The sample was recovered by centrifugation at 10,500 rpm for 10 min and activated in 3 steps: 20 mL of DMF, then 20 mL of MeOH twice and finally 20 mL of EtOH 96.2%.

3.13) MIL-88B_NO$_2$_nano or ($Fe_3O(OH)(H_2O)_2[(CO_2)_2C_6H_3(NO_2)]_3.n\ H_2O$)

1,055 mg of 2-nitroterephtalic acid (BDC-NO$_2$) together with 1,350 mg of $FeCl_3\cdot 6H_2O$ and 25 mL of distilled water were added into a Teflon tube then inserted inside the microwave and heated at 100 ºC for 90 min maintaining then the sample at a temperature plateau of 100 ºC during 5 min (400 W). The sample was recovered by centrifugation at 10,500 rpm for 10 min and the activation was performed by suspending the solid in 20 mL of EtOH 96.2% heating at 100 °C for 30 min and maintaining at 100ºC temperature plateau during 5 min in the microwave (400 W). This protocol was repeated twice.

3.14) UiO-66_nano or ($Zr_6O_4(OH)_4(H_2O)_2[(CO_2)_2C_6H_4]_6.nH_2O$)

A solution of 0.83 g of 1,4-BDC, 1.6 g of $ZrOCl_2\cdot 8H_2O$, 25 mL of DMF and 0.8 mL of HCl 37% were placed into a Teflon-liner steel autoclave at 150 °C during 2 h in a 100 mL round bottom flask under continuous magnetic stirring. The activation of UiO-66 had three steps, a first with 5 mL of DMF, a second with 20 mL of MeOH, both overnight and under continuous

magnetic stirring and finally a last step washing with 20 mL of EtOH 96.2%. After each step, the particles were centrifuged at 10,500 rpm during 20 min.

3.15) ZIF-8_nano or $[Zn(C_4H_6N_2)_2 n\ H_2O]$

ZIF-8 nanoparticles were synthesised_ according to the published procedure[13]. A solution of zinc nitrate hexahydrate 2,933 g of $Zn(NO_3)_2 \cdot 6H_2O$ in 200 mL of MeOH was rapidly poured into a solution of 6,489 g 2-methylimidazole in 200 mL of MeOH under vigorous stirring at room temperature. The mixture slowly turns turbid and after 1 h the nanocrystals were separated from the milky dispersion by centrifugation at 10,500 rpm for 15 min. The activation was performed readily redispersing the material in absolute EtOH and recovering by centrifugation. Three washing cycles of the redispersion in absolute EtOH/centrifugation were carried out to activate the material.

4. Material characterisation

4.1) X-Ray Powder Diffraction (XRPD)

XRPD patterns were collected in a SIEMENS D5000 diffractometer (Siemens, Germany) (θ-2θ) using Cu Kα1 radiation (λ=1.54056 angstroms) from 5 to 13 º (2θ) using a step size of 0.04 º and 4 s per step in continuous mode (Fig. S1).

Note that XRPD patterns of some of the nanometric flexible structures differ from their micrometric analogues due to the different pore opening (pore content) as a consequence of their flexible structure[4].

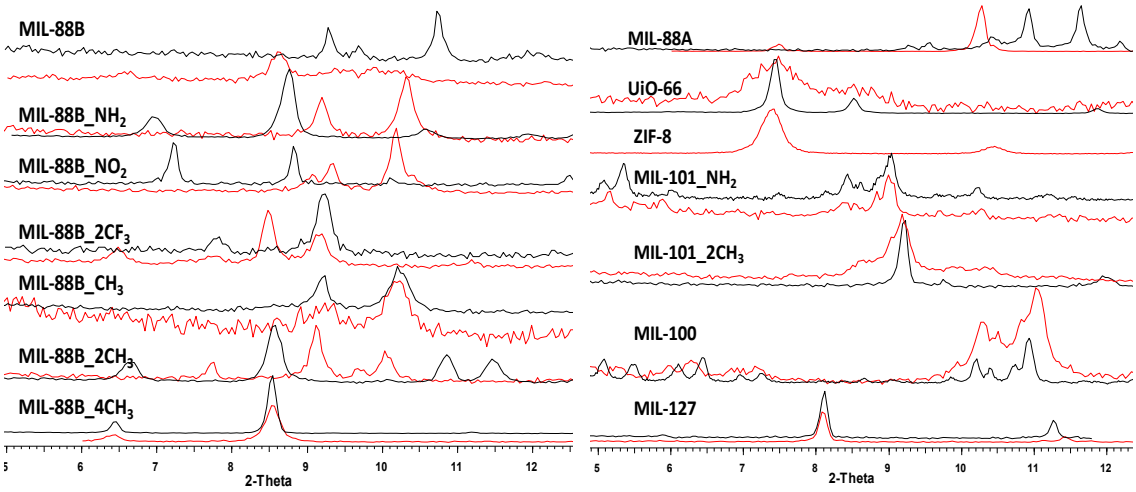

Fig. S1 XRPD patterns of the MOF micro (black) and nanoparticles (red) after their activation.

4.2) Infrared Spectroscopy (FTIR)

A small amount of solids was analysed by a Thermo Nicolet spectrometer (Thermo, USA). The spectra were recorded from 4,000-400 cm^{-1} at room temperature (Fig. S2).

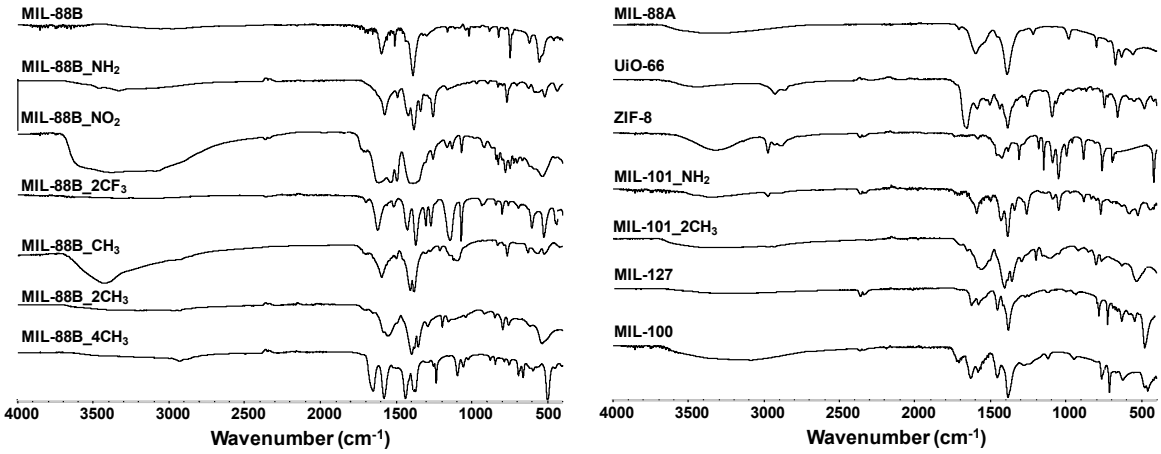

Fig. S2 Infrared spectroscopy spectra of the materials after their activation.

4.3) Thermogravimetric analysis (TGA)

Approximately 5-10 mg of each sample was used for TGA measurements. Samples were analysed under an oxygen flow (20 $mL \cdot min^{-1}$) using a Perkin Elmer Diamond TGA/DTA STA 6000 running from room temperature to 600 °C with a scan rate of 2 $°C \cdot min^{-1}$. (Tab. S1).

Tab. S1 Theoretical and experimental (estimated by TGA) composition of the MOF NPs.

MOF Sample	$\%M_xO_x$	
	Theoretical (anhydrous form)	**Experimental** (anhydrous form)
MIL-127_nano	32.8	29.8
MIL-100(Fe)_nano	39.0	40.8
MIL-101_2CH_3_nano	31.1	26.3
MIL-101_NH_2_nano	32.5	32.2
MIL-88A_nano	44.2	49.0
MIL-88B_nano	34.6	39.0
MIL-88B_CH_3_nano	32.6	30.9
MIL-88B_2CH_3_nano	31.1	25.3
MIL-88B_4CH_3_nano	27.9	26.6
MIL-88B_2CF_3_nano	21.9	20.5
MIL-88B_NH_2_nano	32.5	38.0
MIL-88B_NO_2_nano	26.1	22.0
UiO-66_nano	44.4	46.5
ZIF-8_nano	35.8	36.0

*M_xO_y corresponding to Fe_2O_3, ZnO and ZrO_2 according to the XRPD.

4.4) Nitrogen sorption porosimetry

N_2 isotherms were obtained at 77 K using a Belsorp Mini (Bel, Japan). Prior to the analysis, approximately 40-60 mg of activated rigid samples were evacuated for 12-24 h at 200 °C under vacuum (Tab. S2).

Tab. S2. BET surface area and pore volume of rigid materials.

MOF sample	S_{BET} ($m^2.g^{-1}$)	V_p ($cm^3.g^{-1}$)
MIL-127_nano	650	0.41
MIL-100(Fe) _nano	1900	0.98
MIL-101_2CH_3_nano	1780	1.22
MIL-101_NH_2_nano	1840	0.85
UiO-66_nano	1010	0.40
ZIF-8_nano	1700	0.66

4.5) pH variations

Despite the buffering capacity of the cell culture media, the polycarboxylate anions present on the external surface together with the release of the linker upon degradation are expected to induce changes in the pH media and therefore, possibly affect the cell-specific metabolic toxic effects. Thus, the pH of the media was followed during the MTT assay. Except for the BDC linker that exhibited a pH variation up to 1 unit (pH=6), the rest of the linkers led to a lower change in pH (~7). Despite the pH variation, the cytotoxicity of BDC was not severe (IC_{50}=0.43 $mg \cdot mL^{-1}$) when compared to other linkers (IC_{50} (BDC_NH_2)=0.02; (BTC) >1.00 $mg \cdot mL^{-1}$; see Tab. 1). Additionally, both cell lines can grow at those pH values, in agreement with the lack of influence of the pH, within the considered range, over the toxicity of MOF NPs.[14] Finally, no significant cytotoxicity differences have been observed whatever the linker, suggesting that the pH is not a main factor of the cytotoxicity for the HeLa and J774 cells.

4.6) Zeta potential

Zeta potential measurements were made to all the MOFs used in this study in DMEM cell culture medium + 10% FBS using a Zetasizer Nano-ZS® analyser (Malvern Instruments, UK).

Tab. S3. Results from the zeta potential measurements done in PBS and in DMEM cell culture medium + 10% FBS.

Zeta potential (mV)	PBS	DMEM
MIL-100	-18.3 ± 0.6	-8.1 ± 0.2
MIL-127	-38.5 ± 2.0	-8.9 ± 0.2
MIL-101_2CH$_3$	-24.2 ± 2.1	-14.7 ± 0.7
MIL-101-NH$_2$	-27.4 ± 1.5	-8.1 ± 0.4
MIL-88A	-25.0 ± 4.3	-10.7 ± 0.7
MIL-88B	-23.5 ± 1.8	-9.8 ± 0.4
MIL-88B_CH$_3$	-22.8 ± 2.2	-9.5 ± 0.2
MIL-88B_2CH$_3$	-26.0 ± 0.4	-10.2 ± 0.4
MIL-88B_4CH$_3$	-41.3 ± 0.6	-11.0 ± 0.5
MIL-88B_2CF$_3$	-53.7 ± 7.3	-10.8 ± 0.6
MIL-88B_NH$_2$	-25.7 ± 1.6	-8.0 ± 0.2
MIL-88B_NO$_2$	-28.4 ± 0.7	-7.7 ± 0.7
UiO-66	-26.3 ± 1.5	-11.5 ± 0.5
ZIF-8	-11.0 ± 0.6	-8.7 ± 1.2

4.7) Degradation tests

Degradation tests of all the studied MOF NPs were carried out during 24 h in DMEM cell culture medium + 10% FBS. The selected time of the study was 24 h, which was the time used for the cytotoxicity evaluation *via* the MTT assay. Here, 2 mL of DMEM cell culture medium +

10% FBS at 37 ºC was added to 1 mg of MOF NPs (C=500 $\mu g \cdot mL^{-1}$). The samples were maintained at 37 ºC during 24 h and after that time, they were centrifuged in an Eppendorf minispin centrifuge (Eppendorf, Germany) during 10 min at 6000 g. Then, the supernatants were collected for elemental analysis, in which the % of C and N was measured.

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