Article

Metal-Organic Frameworks as efficient oral detoxifying agents

Sara Rojas, Tarek Baati, Leila Njim, Lisbeth Manchego, Fadoua Neffati, Nissem Abdejelil, Saad Saguem, Christian Serre, Mohamed Fadhel Najjar, Abdelfateh Zakhama, and Patricia Horcajada

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 10 Jul 2018

Metal-Organic Frameworks as efficient oral detoxifying agents

Sara Rojas,[a,‡] Tarek Baati,[a,b,‡] Leila Njim,[c] Lisbeth Manchego,[a] Fadoua Neffati,[d] Nissem Abdejelil,[a,e] Saad Saguem,[e] Christian Serre,[a,f] Mohamed Fadhel Najjar,[d] Abdelfateh Zakhama,[c] Patricia Horcajada[a,g,*]

[a] Institut Lavoisier, CNRS UMR 8180. UVSQ, Université Paris-Saclay. 45, Av. Des Etats Unis 78035 Versailles Cedex, France

[b] Laboratoire des Substances Naturelles, Institut National de Recherche et d'Analyse Physico-Chimique (INRAP), BiotechPole Sidi Thabet Ariana 2020, Tunisie

[c] Service d'Anatomie et de Cytologie Pathologiques, CHU Monastir, Tunisie

[d] Laboratoire de Biochimie et de Toxicologie, CHU de Monastir, Tunisie

[e] Laboratoire de Biophysique, Faculté de Médecine de Sousse, Université de Sousse, Tunisie

[f] Institut des Matériaux Poreux de Paris, FRE 2000 CNRS Ecole Normale Supérieure. Ecole Supérieure de Physique et de Chimie Industrielles de Paris, PSL Research University, 24 rue Lhomond, 75005 Paris, France

[g] Advanced Porous Materials Unit, IMDEA Energy Institute. Av. Ramón de la Sagra 3, 28935 Móstoles-Madrid, Spain

[‡] These authors contributed equally to this work.

Supporting Information Placeholder

ABSTRACT: Poisoning and accidental oral intoxication is a major health worldwide problem. Considering the insufficient efficacy of the currently available detoxification treatments, a pioneering oral detoxifying adsorbent agent based on a single biocompatible Metal-Organic Framework (MOF) is here proposed for the efficient decontamination of drugs commonly implicated in accidental or voluntary poisoning. Further, the *in vivo* toxicity and biodistribution of a MOF *via* oral administration have been investigated for the first time. Orally in more than 40 times administered upon a salicylate overdose, this MOF is able to reduce the salicylate gastrointestinal absorption and toxicity (avoiding histological damage), while proving an exceptional gastrointestinal stability (>9% degradation), poor intestinal permeation and safety.

INTRODUCTION. Poisoning and accidental intoxication *via* ingestion has become a growing health worldwide problem with both a significant cost and severe health problems, even death.[1,2] Unfortunately, for the vast majority of these poisonings, there are no specific pharmacological antidotes and currently available detoxification methods (*i.e.* gastric lavage, activated charcoal, and antidotes) are usually ineffective, and even involve severe adverse effects, limiting their use.[3–5] In general, activated charcoal is more effective than gastric emptying. Single doses of oral activated charcoal effectively avoid the gastrointestinal (GI) absorption of many drugs and toxins present in the stomach, preventing their uptake into blood and subsequent distribution to target organs.[6] However, some toxins present poor affinity to charcoal (*e.g.* alcohols, hydrocarbons, nicotinic acid, and some metals as iron or lithium),[7,8] reducing the efficacy of activated charcoal. Although the ability of various nanomaterials (*e.g.* liposomes, antibody fragments, microemulsions) to capture drugs and other toxins has been reviewed,[9,10] only an injectable γ-cyclodextrine (*Sugammadex*) has reached so far the clinical stage for the reversal neuromuscular blockade induced by specific anesthetics.[11] Consequently, there is a great interest in developing safe and effective detoxification treatments.

As selective adsorbents, Metal-Organic Frameworks (MOFs) appear as innovative and promising detoxifying agents. These crystalline hybrid materials, exhibiting an exceptional porosity and chemical and structural versatility, have already proven interesting performances on the selective adsorption and removal of hazardous molecules either in water or air.[12–17] Furthermore, certain MOFs have recently emerged in the biomedical field, disclosing interesting features such as important capacities of a large variety of active ingredients and a lack of *in vivo* toxicity.[18–21] Despite being extensively studied for biomedical applications, no biocompatible MOF has been reported so far as oral drug detoxifying agent. In this regard, only a composite constituted by an activated carbon containing a Ln-MOF has been proposed for the removal of a pesticide in rats by Oliveira *et al*.[22]

In this study, we pioneering target the oral detoxification of drugs using a single biocompatible MOF. Additionally, the *in vivo* toxicity and biodistribution of a MOF orally administered will be addressed for the first time. The cubic microporous Soc-MOF(Fe) or MIL-127 structure,[23,24] based on iron(III) octahedra trimers and 3,3´,5,5´-azobenzenetetracarboxylate anions ($TazBz^{4-}$), has been selected as efficient adsorbent. This solid exhibits *a priori* several advantages: *i)* a good biocompatibility, as based on the endogenous iron cation and as proven *in vitro* (inhibitory concentration 50; IC_{50} > 2.00 and 0.44 $mg \cdot mL^{-1}$ in HeLa and J774 cell lines, respectively),[25] *ii)* a high porosity (Brunaeur-Emmett-Teller surface area S_{BET} = 1400 $m^2\ g^{-1}$ and pore volume = 0.7 $cm^3 \cdot g^{-1}$), associated with an important adsorption capacity, *iii)* a high chemical stability under different pH values that might insure its stability along the GI tract, and *iv)* a gram-scale synthesis at the

macrometric scale,[26] with crystal dimensions larger than the maximum size absorbed by the intestinal mucosa (~20 μm),[27] preventing its intestinal crossing and potential related toxicity.

On the other hand, we use the salicylate derivative aspirin (acetylsalicylic acid or ASA) as model overdose pain medication. Although here used as model, pain medication leads the list of most common substances implicated in accidental or voluntary adult poison exposures (11.6%, Poison Statistics US National Data 2016), being the second cause of pediatric fatalities (17.5%, US Poison Control from 2012 through 2016).[1,28] For instance, more than 40,000 cases of human exposure to salicylates were reported in emergency departments in the United States in 2004,[29] 44% of these involving children under the age of 6 years. In particular, ASA was involved as a single agent in 45% of the cases. In addition, the detoxification of salicylates requires nowadays from repeated doses of activated charcoal to reduce the risk of desorption.[6] Thus, the ASA detoxification by using MOFs could avoid needing repeated doses.

Thus, we firstly evaluated the *in vitro* stability of MIL-127 and its ASA encapsulation capacity under simulated GI conditions. Secondly, the ASA detoxification efficiency and safety of MIL-127 were orally evaluated in an animal model. Finally, an *ex vivo* intestinal model was used to assess the MIL-127 and ASA bypass across the intestinal barrier.

RESULTS AND DISCUSSION. The structural, textural and compositional integrity of the MIL-127 was initially confirmed (see PXRD, FTIR and N_2 sorption analyses disclosed in Supporting Information-SI, Section 2) under simulated GI conditions, mimicking both gastric (HCl, pH = 1.2 at 37 ºC for 2 h) and intestinal conditions found in healthy vertebrates (Ringer medium based on a phosphate buffer saline solution pH = 6.0 at 37 ºC for 24 h).[30] Note that this digestion model simulates the composition, pH, residence time and temperature conditions in the different portions of the human digestive tract.[31]

Then, to select the most suitable dose of MIL-127 to be administered upon an ASA overdose, different ASA concentrations were put in contact with a fix amount of MIL-127 (ASA:MIL-127 ratio = 1.5:1 and 3:1) in gastric medium followed by intestinal conditions, mimicking the GI transit (SI, Section 3). The ASA removal and matrix chemical stability were monitored by quantifying the release of the MIL-127 constitutive organic linker (H_4TazBz) and ASA to the media by HPLC (see SI, Section 1). Note here that due to the important GI hydrolysis of ASA to salicylic acid (SA) (*i.e.* 2 and 20% under simulated gastric conditions for 2 h and intestinal conditions for 24 h, respectively; SI, Figure S5), both salicylate derivatives were considered for the quantification. Under GI conditions (Figure 1), MIL-127 can adsorb 25.2% of the total salicylates using a 3:1 ratio (corresponding to 8.6% + 16.6% in the gastric and intestinal conditions, respectively) and 39.4% with a ratio 1.5:1 (corresponding to 13.6% + 25.8% in the gastric and intestinal conditions, respectively). Therefore, as expected, the most suitable detoxifying dose of MIL-127 corresponds to the highest MOF ratio (*i.e.* ASA:MIL-127 = 1.5:1) able to remove ~40% of salicylates. However, the drug loading (grams of drug entrapped *per* gram of MIL-127) did not depend on the amount of MOF, reaching in both cases a maximum ASA capacity of around 0.14 $g \cdot g^{-1}$. It is also interesting to mention that after the medium exchange (from gastric to intestinal one), no release of salicylates was detected, supporting an excellent affinity of the drug by the MIL-127 matrix and suggesting a good stability of the adsorbent under GI conditions. The chemical (< 2% of degradation; Figure 1) and structural (SI, Figure S6) integrity of MIL-127 was further confirmed after its incubation in gastric (2 h) and intestinal (24 h) media supplemented with ASA, regardless the ASA:MIL-127 ratio. Finally, the MIL-127 adsorption capacity was compared with other adsorbent materials: a commonly used commercial activated charcoal (Norit®) and two archetypical Zr-terephthalate MOFs (UiO-66 and UiO-66-NH_2)[32,33] (SI, Table S2). Although the active charcoal works better as detoxifying agent under gastric media than MIL-127 (94 *vs*. 13% efficiency), it releases a significant amount of the adsorbed salicylates when passing to intestinal conditions (11%). In contrast, MIL-127 adsorbent, exhibiting a similar ASA removal after 26 h-GI conditions than active charcoal (*ca.* 34%), is able to retain its salicylate cargo along the GI tract. Further comparison with other benchmarked MOF structures, known by their chemical robustness and high adsorption capacity, shows that MIL-127 adsorbs more efficiently salicylates than UiO-66 and UiO-66-NH_2 (33% *vs*. 6 and 9%, respectively).

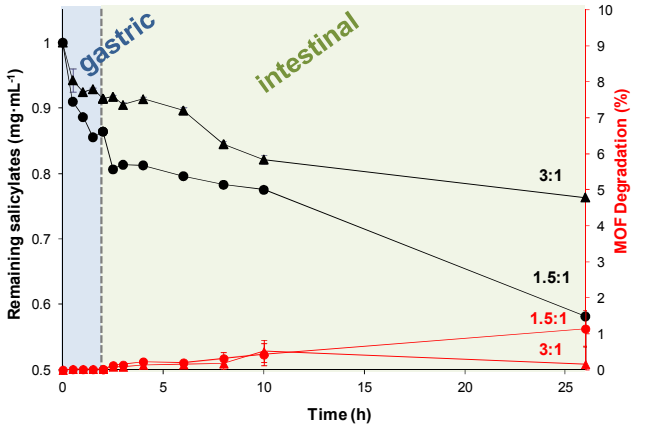


Figure 1. Evolution of salicylates removal (left, black) and MIL-127 matrix degradation (right, red) under simulated GI conditions (blue and green background represents respectively gastric and intestinal media). Different ASA:MIL-127 ratios have been studied: 3:1 (triangles) and 1.5:1 (circles). Note that concentration of salicylates has been normalized for an easier comparison.

The oral detoxification ability of MIL-127 was then *in vivo* evaluated using the best ASA:MIL-127 ratio (*i.e.* 1.5:1). Considering both the safety and lethal 50 oral (LD_{50}) doses of ASA in rats (*ca.* 3 $mg \cdot Kg^{-1}$ and 900 – 1200 $mg \cdot Kg^{-1}$, respectively),[34,35] we have orally administered more than 10 times the safety oral dose of ASA (350 $mg \cdot Kg^{-1}$), which might be enough to determine the detoxification efficiency of MIL-127 in a drug overdose without causing euthanasia and/or distress of the animal. After 1 h of the ASA overdose, 1 $g \cdot Kg^{-1}$ of the MIL-127 adsorbent was orally administered (SI, Section 4). Remarkably, after 24 h, the plasma and urine concentration of salicylates, determined by HPLC (SI, Section 4), was reduced three times in presence of the MIL-127 (Table 1), reaching similar results as previously published for the adsorption of ASA by activated carbon.[36] Similarly, salicylates concentration in different portions of the small intestine, which are associated with higher villi and microvilli absorptive surface area,[37] were around 30 times lower after the administration of the MIL-127 when compared with the ASA control group (Table 1, and SI Figure S9). These findings unequivocally prove the lower GI absorption of salicylates and thus, the efficiency of the MIL-127 on the detoxification of ASA overdosed rats.

Table 1. Salicylates concentration in plasma, urine and small intestine.

	ASA	ASA@MIL-127
Plasma ($mg \cdot mL^{-1}$)	0.21±0.11	0.07±0.04
Urine ($mg \cdot mL^{-1}$)	15.8±7.4	6.4±2.2
Duodenum ($mg \cdot mL^{-1}$)	0.144±0.006	0.02±0.01
Jejunum ($mg \cdot mL^{-1}$)	0.46±0.01	0.016±0.007
Ileum ($mg \cdot mL^{-1}$)	0.5±0.1	0.019±0.007

We further *ex vivo* evaluated the intestinal barrier bypass of ASA by means of the Ussing diffusion chambers. Briefly, two compartments (donor and receptor), separated by an intestinal biopsy (*i.e.* jejunum), are filled with simulated intestinal media (*i.e.* Ringer), incubating the ASA in presence or not of the MIL-127 in the donor compartment and monitoring the transport by quantifying the salicylates in the receptor chamber (SI, Section 6). Remarkably, the presence of 1 or 2 mg·mL^{-1} of MIL-127 drastically reduced (more than 40 times) the intestinal absorption of salicylates (Figure 2). The above *in vivo* and *ex vivo* results highlighted for the first time the unique properties of MOFs in terms of efficient oral drug detoxifying agents in living beings.

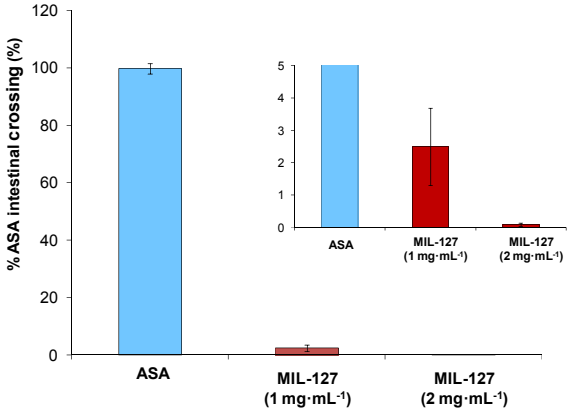


Figure 2. Salicylates *ex vivo* intestinal bypass in presence of 1 or 2 mg·mL^{-1} of MIL-127.

To address the benefit-risk balance of the MIL-127 in ASA overdose treatment, different parameters (animal behavior, body and organs weight, biomarkers, etc.) were evaluated. First, no behavioral changes or significant differences in body or organs weight were noted in all groups (SI, Figure S10). The macroscopic aspect of the organs was totally normal, without hypertrophy, cell necrosis or color change.

Microscopic examination of stomach, jejunum and liver showed a protective effect of MIL-127 against ASA overdose. Stomach histological sections of control groups revealed a normal architecture consisting of mucosa (M) which is separated from submucosa (SM) by a thin muscularis mucosa (MM) (SI, Section 5, Fig S11). The mucosa consists of superficial foveolar epithelium (F) and deeper gastric glands (Gg). Each foveolar serves as a conduit for gastric secretions to be released into the lumen (L). Microscopic examinations of stomach of the ASA group shows an evident toxicity, highlighted by the formation of mucosal erosions with cellular desquamation and necrosis of the foveolar epithelium mucosal epithelium (yellow arrows) as reported for ASA histological damage.[38] In addition, the ASA alters the stomach mucus coating and the tissues become damaged from exposure to acid, inducing the formation of ulcers. Hence, MIL-127 seems to limit this effect as confirming by the normal stomach mucosal architecture, free from any pathological changes observed in the ASA@MIL-127 and MIL-127 groups both are similar to the control. This funding confirmed the gastroprotective effect of MIL-127 particles, which are shown to be located in the stomach lumen and in the mucosa on the surface of the foveolar epithelium (SI, Fig. S11, black arrows). Likewise, jejunum histological sections showed an important amount of MIL-127 particles around the intestinal microvilli, which might prevent the salicylates intestinal absorption (Fig. 3(b,d), black arrows). Similarly to stomach, ASA overdoses (ASA group) produced important toxicity with focal erosions in the intestinal mucosa, showing extensive damage and abnormalities in the tissue structure (see SI for further details, Section 5).[38] In particular, we can observe destruction and transformation of villi into edema accompanied by loss and disorganization of enterocytes surface and brush border with a partial edema of the lamina propria and a microvilli enlargement associated with lightened contents. Notably, these deleterious effects are not present in the MIL-127 treated group. Further, the ASA@MIL-127 group showed reasonably well-preserved jejunum epithelia without any histological lesion. Although the normal villi were lost in the form of villus fusion and swelling and fusion of villus (Fig.3, ASA@MIL-127 red arrows), any destruction of the enterocytes surface and brush border was observed, supporting again the protective effect of the MIL-127 adsorbent. These results are of particular importance since they rule out the gastric and intestinal toxicity of MIL-127 that remains adhered on the microvilli, working as ASA detoxifying and gastric and intestinal mucosa protective agent.

Liver examination of MIL-127 and glucose control group revealed a normal parenchyma architecture without any apparent change in the hepatocytes structure (SI, Figure S12). In contrast, neutrophils infiltrations were observed in the liver upon ASA overdose (Figure S12(c), yellow arrows), suggesting an acute inflammation due to the accumulation of ASA.[39,40] The treatment with MIL-127 reduced the hepatotoxic effect of ASA, as shown by the decrease of neutrophils infiltrations in liver of ASA@MIL-127 group. In addition, hepatocellular toxicity was assessed by the activity of typical biomarkers of hepatic cytolysis (alanine and aspartate aminotransferases-ALT and AST, respectively).[41] ALT and AST activities significantly increase in the ASA, MIL-127 and ASA@MIL-127 groups (SI, Figure S17). If ASA high-doses are considered as hepatotoxic,[39,40] iron accumulation upon intestinal absorption (see biodistribution below) can also lead to transient higher transaminase activity, as previously reported for intravenously administered Fe-MOFs.[42] Also, it is known that ASA induces a significant increase in the intestinal amylase and lipase,[43] observing similar values, higher than the control group, for both the ASA and ASA@MIL-127 groups. Although intestinal absorption of ASA is reduced in presence of MIL-127, the ASA hepatotoxicity is not fully avoided.

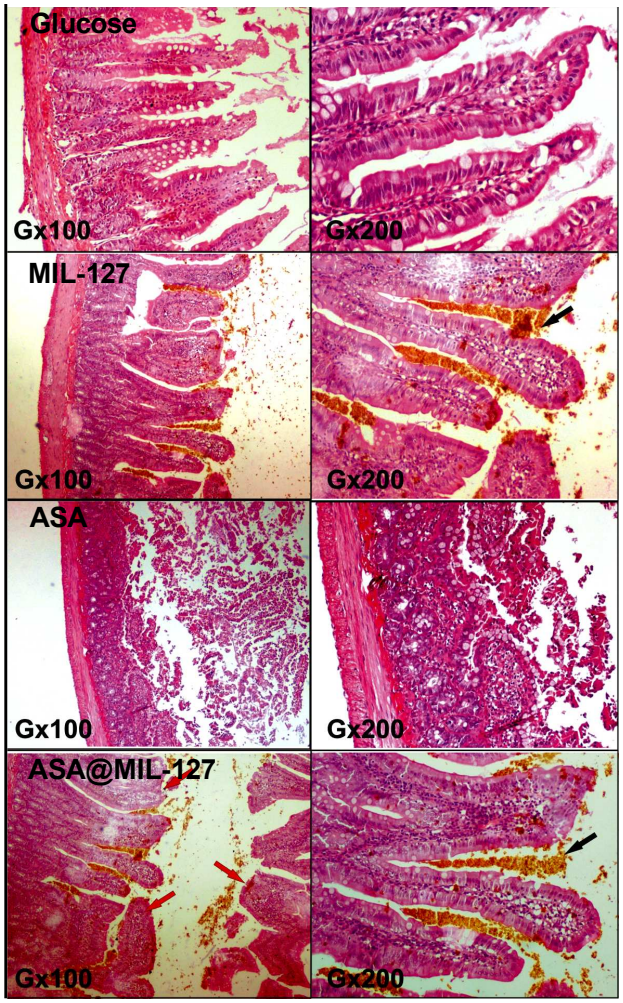


Figure 3. Histological sections of rat jejunum after 24 h of 10% glucose (negative control), MIL-127, ASA (positive control), and ASA@MIL-127 administration.

Once proved the safety and efficiency of MIL-127 as oral ASA detoxifying agent, we investigated the *in vivo* fate of the adsorbent, as a critical point for its future application. First, the integrity of the MIL-127 adsorbent was evaluated along the GI tract by recovering the content within all the GI portions. Despite the quite aggressive GI conditions (*e.g.* pH, presence of competing highly complexant groups such as phosphates, enzymes, intestinal motility), MIL-127 possesses a remarkably high stability, retaining its crystalline structure all along the GI tract, as confirmed by PXRD (SI, Figures 4 and S13). Further chemical analyses of the GI contents by HPLC demonstrated that only 8.7% of the material was degraded. Moreover, MIL-127 exhibited more than 10 times lower degradation in presence of ASA when compared with the single administrated MIL-127 (SI, Table S3), suggesting the MIL-127 stabilization by a potential "template" effect of the encapsulated salicylates. In addition, considering the ASA blood concentration (Table 1), we can estimate the salicylate molecules adsorbed *per* metal node cluster, corresponding to 1.05. The possible coordination of around one salicylate to the iron trimer makes the metal sites less accessible to water molecules and therefore, might stabilize the MIL-127 solid. In addition, the presence of intact MIL-127 particles was visually confirmed in the entire GI track (from stomach to colon) as well as in feces, observing crystalline (see PXRD patterns in SI, Figure 4) and well-faceted cubic particles by field-emission-gun scanning electron microscopy (FEG-SEM in SI, Figure S14).[26] Furthermore, the iron levels were determined by inductively coupled plasma atomic emission spectroscopy (ICP-OES) in feces, observing a 5-times higher iron concentration than the negative control group (1.3 ± 0.3 *vs.* 6.9 ± 3.5 $mg \cdot g^{-1}$), which is in concordance with the fecal excretion of the MIL-127 particles.

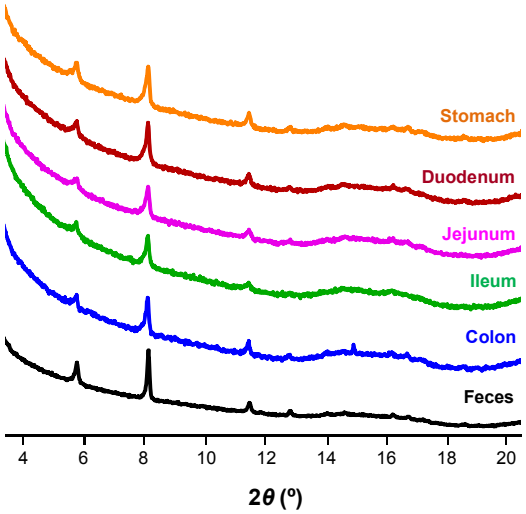


Figure 4. PXRD patterns of MIL-127 material after passing through the entire GI tract. MIL-127 remains stable along the GI track. Data were collected using the high-throughput Bruker D8 Advance diffractometer.

The 24 h biodistribution of MIL-127 was also investigated by quantifying the iron (by atomic absorption spectroscopy (AAS), SI, Figure S15-16) in plasma, stomach, duodenum, jejunum, ileum, heart, liver, spleen, and kidneys. Except for duodenum and jejunum, iron levels were found to be normal, with no significant difference when compared with the negative control group, ruling out an important GI absorption of the MIL-127 and/or its constitutive iron cation. However, statistical analysis of the Fe content confirmed significant differences ($p < 0.05$) in duodenum and jejunum. Considering that iron absorption mainly occurs in the duodenum and upper jejunum,[44] this result suggests a partial degradation of MIL-127 (8.7% at the ileum level, see above) and then, a slight iron absorption within this small intestine region.

Finally, we evaluated *ex vivo* (*i.e.* Ussing chambers) the intestinal barrier bypass of MIL-127 and its constitutive organic ligand H_4TazBz, as well as their potential toxicity over the intestine (SI, Section 6). 1 $mg \cdot mL^{-1}$ of MIL-127 or the corresponding amount of the H_4TazBz ligand were incubated in the donor compartment of the Ussing permeation chamber using as biological barrier jejunum and ileum biopsies, since they are associated with a high absorption capacity. It is worth mentioning that very low ligand concentrations are able to cross the intestine (0.1 and 2 $\mu g \cdot mL^{-1}$, corresponding to *ca.* 0.01 ad 0.30% of the initial dose; SI, Figure S18). Furthermore, the diffusion flux (F) and the apparent permeability of the membrane ($Papp$) for MIL-127 and H_4TazBz ligand were calculated (Table 2),[45,46] observing very low values, regardless the intestine section. Interestingly, MIL-127 exhibits an even lower permeation flux than the free ligand (*ca.* 0.05 *vs.* 1.1 $\mu g \cdot cm^{-2} \cdot h^{-1}$ in both intestinal sections), probably due to the progressive leaching of the linker from the MIL-127 to the medium. In addition, the large particle size of MIL-127 (*ca.* 28 µm) is in agreement with a lower intestinal transport *via* enterocytes, as previously demonstrated for other particles.[47] Furthermore, the H_4TazBz ligand exhibits a very low permeation when compared with other known small uncharged solutes like caffeine (0.001 $cm \cdot h^{-1}$ *vs.* 7.2 $cm \cdot h^{-1}$).[48] Both the high chemical stability of MIL-127 and the low ligand permeation rule out an important intestinal absorption of the MIL-127, preventing any severe toxicity associated with its accumulation within the body.

Table 2. Diffusion flux (*F*) and permeability coefficient parameter of the membrane (*P*)

	Jejunum		Ileum	
	H_4TazBz	MIL-127	H_4TazBz	MIL-127
F **(μg·cm^{-2}·h^{-1})**	1.05	0.05	1.12	0.04
Papp **(cm·h^{-1})**	0.0014	0.0013	0.0010	0.0011

Furthermore, the viability of the intestinal membrane was checked by measuring the transepithelial resistance (TEER), which is accepted as good model for determining the membrane integrity after the transport of chemicals.[49] For this purpose, upon the intestinal bypass of the MIL-127 and H_4TazBz, the conductivity of this polarized membrane was studied *via* the modulation of the ion channels (SI, Figure S19). The response of the membrane to the addition of forskolin or biotin, which modifies the voltage-dependent K^+ of a healthy membrane, supports the lack of toxicity of both, MOF and H_4TazBz ligand.

CONCLUSIONS. In conclusion, MIL-127, combining an exceptional GI stability and an important drug adsorbent capacity, is a promising safe and efficient oral detoxification treatment. Upon a salicylate overdose, MIL-127 is able to drastically reduced more than 40 times its intestinal absorption (decreasing a third the ASA concentration in blood), avoiding associated histological damages. In addition, except for a minor GI degradation (< 9%) and subsequent slight iron absorption in duodenum and jejunum, the integrity of MIL-127 was preserved along the GI tract, being excreted by feces without any sign of severe toxicity. Further biodistribution studies demonstrated a lack of intestinal absorption of MIL-127, due to its large particle size, high structural and chemical stability and poor intestinal permeation of both MIL-127 and its constitutive ligand. These results open fascinating perspectives for the safe and efficient treatment of poisoning and accidental intoxications using biocompatible MOFs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information provides full details of the synthetic procedures, biological simulated media, stability studies (PXRD, FTIR, N_2 sorption measurements), HPLC determinations, *in vitro* tests, *in vivo* biodistribution and *ex vivo* intestinal permeation studies.

AUTHOR INFORMATION

Corresponding Author

*patricia.horcajada@imdea.org

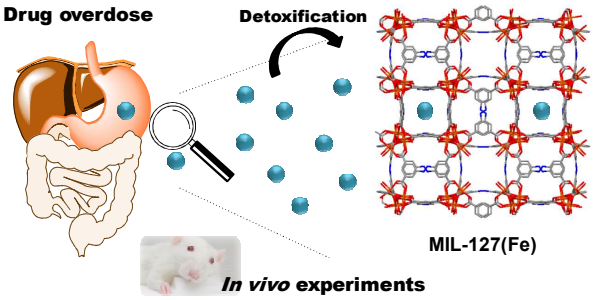
ACKNOWLEDGMENT

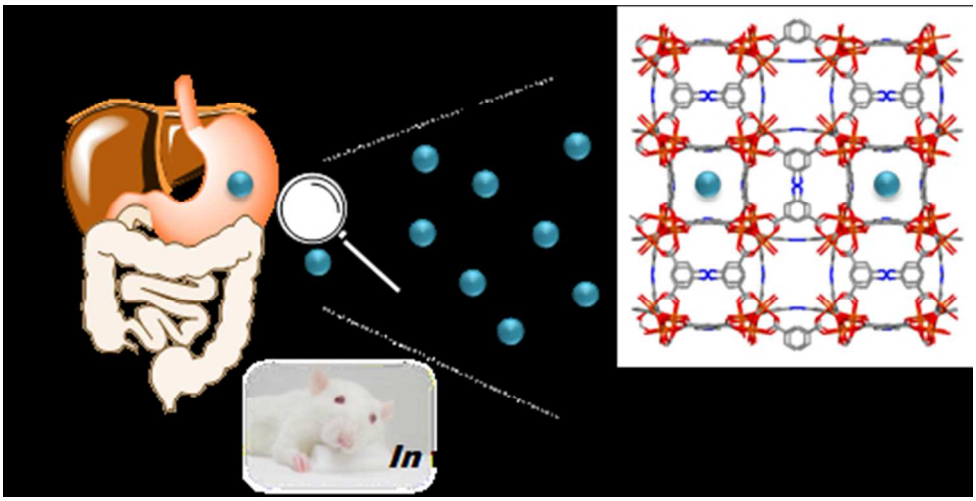
This works was supported by UniverSud Paris (ref: 2010–25) and CNRS/DGRST ref: 24432) projects. SR and PH acknowledge the Marie Sklodowska-Curie Programme (MSCA-IF-EF-ST-2015-705529). PH acknowledges the Spanish Ramón y Cajal Programme (grant agreement no. 2014-16823) and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement no. 291803. Authors would like to acknowledge Laura García for the ICP-OES characterizations, Carine Livage for the FEG-SEM observations and Carmen Sanchez for the cover art design.

REFERENCES

(1) http://www.poison.org/poison-statistics-national.
(2) Eddleston, M. Patterns and Problems of Deliberate Self-Poisoning in the Developing World. *QJM* **2000**, *93*, 715–731.
(3) Graham, L. M.; Nguyen, T. M.; Lee, S. B. Nanodetoxification: Emerging Role of Nanomaterials in Drug Intoxication Treatment. *Nanomedicine (Lond)* **2011**, *6*, 921–928.
(4) Bae, H.; Lee, K. Medico□legal Consideration of Gastric Lavage in Acutely Intoxicated Patients. *Emerg. Med. J.* **2007**, *24*, 233.
(5) Watson, W. A.; Cremer, K. F.; Chapman, J. A. Gastrointestinal Obstruction Associated With Multiple-Dose Activated Charcoal. *J. Emerg. Med.* **1986**, *4*, 401–407.
(6) Neuvonen, P. J.; Olkkola, K. T. Oral Activated Charcoal in the Treatment of Intoxications. *Med. Toxicol. Adverse Drug Exp.* **1988**, *3*, 33–58.
(7) Willey II, J. F.; Osterhoudt, K. C. Poisonings. In *Pediatric Emergency Medicine Secrets*; Saunders, E., Ed.; Philadelphia, 2015; pp 312–332.
(8) Roivas, L.; Neuvonen, P. J. Reversible Adsorption of Nicotinic Acid onto Charcoal In Vitro. *J. Pharm. Sci.* **1992**, *81*, 917–919.
(9) Leroux, J. Injectable Nanocarriers for Biodetoxification. *Nat. Nanotechnol.* **2007**, *2*, 679–684.
(10) Howell, B. A.; Chauhan, A. Current and Emerging Detoxification Therapies for Critical Care. *Materials (Basel).* **2010**, *3*, 2483–2505.
(11) Bom, A.; Bradley, M.; Cameron, K.; Clark, J. K.; Egmond, J. Van; Feilden, H.; Maclean, E. J.; Muir, A. W.; Palin, R.; Rees, D. C.; Zhang, M. A Novel Concept of Reversing Neuromuscular Block: Chemical Encapsulation of Rocuronium Bromide by a Cyclodextrin-Based Synthetic Host. *Angew. Chem. Int. Ed.* **2002**, *41* (2), 265–271.
(12) Dias, E. M.; Petit, C. Towards the Use of Metal-Organic Frameworks for Water Reuse: A Review of the Recent Advances in the Field of Organic Pollutants Removal and Degradation and the next Steps in the Field. *J. Mater. Chem. A* **2015**, *3*, 22484–22506.
(13) Wang, B.; Lv, X. L.; Feng, D.; Xie, L. H.; Zhang, J.; Li, M.; Xie, Y.; Li, J. R.; Zhou, H. C. Highly Stable Zr(IV)-Based Metal-Organic Frameworks for the Detection and Removal of Antibiotics and Organic Explosives in Water. *J. Am. Chem. Soc.* **2016**, *138* (19), 6204–6216.
(14) Zeng, T.; Zhang, X.; Wang, S.; Niu, H.; Cai, Y. Spatial Confinement of a Co3O4 Catalyst in Hollow Metal–Organic Frameworks as a Nanoreactor for Improved Degradation of Organic Pollutants. *Environ. Sci. Technol.* **2015**, *49*, 2350–2357.
(15) Wang, J. H.; Li, M.; Li, D. An Exceptionally Stable and Water-Resistant Metal-Organic Framework with Hydrophobic Nanospaces for Extracting Aromatic Pollutants from Water. *Chem. - A Eur. J.* **2014**, *20*, 12004–12008.
(16) Zhang, Q.; Yu, J.; Cai, J.; Song, R.; Cui, Y.; Yang, Y.; Chen, B.; Qian, G. A Porous Metal–organic Framework with –COOH Groups for Highly Efficient Pollutant Removal. *Chem. Commun.* **2014**, *50*, 14455–14458.
(17) Shi, P.-F.; Zhao, B.; Xiong, G.; Hou, Y.-L.; Cheng, P. Fast Capture and Separation of, and Luminescent Probe for, Pollutant Chromate Using a Multi-Functional Cationic Heterometal-Organic Framework. *Chem. Commun.* **2012**, *48*, 8231–8233.
(18) Simon-Yarza, T.; Giménez-Marqués, M.; Mrimi, R.; Mielcarek, A.; Gref, R.; Horcajada, P.; Serre, C.; Couvreur, P. A Smart Metal-Organic -Framework Nanomaterials for Lung Targeting. *Angew. Chem. Int. Ed.* **2017**, *56*, 15565–15569.
(19) Simon-Yarza, T.; Baati, T.; Neffati, F.; Njim, L.; Couvreur, P.; Serre, C.; Gref, R.; Najjar, M. F.; Zakhama, A.; Horcajada, P. In Vivo Behavior of MIL-100 Nanoparticles at Early Times after Intravenous Administration. *Int. J. Pharm.* **2016**, *511* (2), 1042–1047.
(20) Wu, M. X.; Yang, Y. W. Metal–Organic Framework (MOF)-Based Drug/Cargo Delivery and Cancer Therapy. *Adv. Mater.* **2017**, *29*, 1606134.
(21) Hidalgo, T.; Giménez-Marqués, M.; Bellido, E.; Avila, J.; Asensio, M. C.; Salles, F.; Lozano, M. V.; Guillevic, M.; Simón-Vázquez, R.; González-Fernández, A.; Serre, C.; Alonso, M. J.; Horcajada, P. Chitosan-Coated Mesoporous MIL-100(Fe) Nanoparticles as Improved Bio-Compatible Oral Nanocarriers. *Sci. Rep.* **2017**, *7* (March), 43099.
(22) de Oliveira, C. A. F.; da Silva, F. F.; Jimenez, G. C.; da S. Neto, J. F.; de Souza, D. M. B.; de Souza, I. A.; Junior, S. A. MOF@activated Carbon: A New Material for Adsorption of

Aldicarb in Biological Systems. *Chem. Commun.* **2013**, *49*, 6486–6488.
(23) Dhakshinamoorthy, A.; Alvaro, M.; Chevreau, H.; Horcajada, P.; Devic, T.; Serre, C.; Garcia, H. Iron(III) Metal–organic Frameworks as Solid Lewis Acids for the Isomerization of α-Pinene Oxide. *Catal. Sci. Technol.* **2012**, *2*, 324–330.
(24) Liu, Y.; Eubank, J. F.; Cairns, A. J.; Eckert, J.; Kravtsov, V. C.; Luebke, R.; Eddaoudi, M. Assembly of Metal-Organic Frameworks (MOFs) Based on Indium-Trimer Building Blocks: A Porous MOF with Soc Topology and High Hydrogen Storage. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 3278–3283.
(25) Tamames-Tabar, C.; Cunha, D.; Imbuluzqueta, E.; Ragon, F.; Serre, C.; Blanco-Prieto, M. J.; Horcajada, P. Cytotoxicity of Nanoscaled Metal–organic Frameworks. *J. Mater. Chem. B* **2014**, *2*, 262–271.
(26) Chevreau, H.; Permyakova, A.; Nouar, F.; Fabry, P.; Livage, C.; Ragon, F.; Garcia-Marquez, A.; Devic, T.; Steunou, N.; Serre, C.; Horcajada, P. Synthesis of the Biocompatible and Highly Stable MIL-127(Fe): From Large Scale Synthesis to Particle Size Control. *CrystEngComm* **2016**, *18*, 4094–4101.
(27) Patel, J.; Patel, A. Toxicity of Nanomaterials on the Liver, Kidney, and Spleen. In *Biointeractions of Nanomaterials*; 2015; pp 286–306.
(28) https://www.statista.com/statistics/654778/pediatric-poisoning-deaths-major-substances-united-states/.
(29) Mund, M. E.; Gyo, C.; Brüggmann, D.; Quarcoo, D.; Groneberg, D. A. Acetylsalicylic Acid as a Potential Pediatric Health Hazard: Legislative Aspects Concerning Accidental Intoxications in the European Union. *J. Occup. Med. Toxicol.* **2016**, *11*, 1–5.
(30) Smyth, D. H. *Biomembranes*, 1st ed.; Springer: Sheffield, 1974.
(31) Versantvoort, C. H. M.; Oomen, A. G.; Van De Kamp, E.; Rompelberg, C. J. M.; Sips, A. J. A. M. Applicability of an in Vitro Digestion Model in Assessing the Bioaccessibility of Mycotoxins from Food. *Food Chem. Toxicol.* **2005**, *43*, 31–40.
(32) Cavka, J. H.; Jakobsen, S.; Olsbye, U.; Guillou, N.; Lamberti, C.; Bordiga, S.; Lillerud, K. P. A New Zirconium Inorganic Building Brick Forming Metal Organic Frameworks with Exceptional Stability. *J. Am. Chem. Soc.* **2008**, *130*, 13850–13851.
(33) Kandiah, M.; Nilsen, M. H.; Usseglio, S.; Jakobsen, S.; Olsbye, U.; Tilset, M.; Larabi, C.; Quadrelli, E. A.; Bonino, F.; Lillerud, K. P.; Lyon, D. Synthesis and Stability of Tagged UiO-66 Zr-MOFs. *Chem. Mater.* **2010**, No. 10, 6632–6640.
(34) Boyd, E. M. The Acute Oral Toxicity of Acetylsalicylic Acid. *Toxicol. Aplpied Pharmacol.* **1959**, *1*, 229–239.
(35) Nair, A.; Jacob, S. A Simple Practice Guide for Dose Conversion between Animals and Human. *J. Basic Clin. Pharm.* **2016**, *7*, 27–31.
(36) Decker, W. J.; Corby, D. G.; Ibanez, J. D. Aspirin Adsorption with Activated Charcoal. *Lancet.* **1968**, *7545*, 754–755.
(37) Pang, K. S. Modeling of Intestinal Drug Absorption: Roles of Transporters and Metabolic Enzymes (for the Gillette Review Series). *Drug Metab. Dispos.* **2003**, *31* (12), 1507–1519.
(38) Wang, Z.; Hasegawa, J.; Wang, X.; Matsuda, A.; Tokuda, T.; Miura, N.; Watanabe, T. Protective Effects of Ginger against Aspirin-Induced Gastric Ulcers in Rats. *Yonago Acta Med.* **2011**, *54*, 11–19.
(39) Laster, J.; Satoskar, R. Aspirin-Induced Acute Liver Injury. *ACG Case Reports J.* **2014**, *2* (1), 48–49.
(40) Zimmerman, H. J. Effects of Aspirin and Acetaminophen on the Liver. *Arch. Intern. Med.* **1981**, *141*, 333–342.
(41) Silva, A. H.; Locatelli, C.; Filippin-monteiro, F. B.; Zanetti-ramos, B. G.; Conte, A.; Creczynski-pasa, T. B. Solid Lipid Nanoparticles Induced Hematological Changes and Inflammatory Response in Mice. *Nanotoxicology* **2014**, *8* (March), 212–219.
(42) Baati, T.; Njim, L.; Neffati, F.; Kerkeni, A.; Bouttemi, M.; Gref, R.; Najjar, M. F.; Zakhama, A.; Couvreur, P.; Serre, C.; Horcajada, P. In Depth Analysis of the in Vivo Toxicity of Nanoparticles of Porous Iron(III) Metal-Organic Frameworks. *Chem. Sci.* **2013**, *4*, 1597–1607.
(43) Nasif, W. A.; Lotfy, M.; Mahmoud, M. R. Protective Effect of Gum Acacia against the Aspirin Induced Intestinal and Pancreatic Alterations. *Eur. Rev. Med. Pharmacol. Sci.* **2011**, *15*, 285–292.
(44) Steele, T. M.; Frazer, D. M.; Anderson, G. J. Systemic Regulation of Intestinal Iron Absorption. *IUBMB Life* **2005**, *57*, 499–503.
(45) Pretorius, E.; Bouic, P. J. D. Permeation of Four Oral Drugs through Human Intestinal Mucosa. *AAPS PharmSciTech* **2009**, *10*, 270–275.
(46) Mustapha, R. Ben; Lafforgue, C.; Fenina, N.; Marty, J. P. Influence of Drug Concentration on the Diffusion Parameters of Caffeine. *Indian J. Pharmacol.* **2011**, *43*, 157–162.
(47) He, C.; Yin, L.; Tang, C.; Yin, C. Size-Dependent Absorption Mechanism of Polymeric Nanoparticles for Oral Delivery of Protein Drugs. *Biomaterials* **2012**, *33*, 8569–8578.
(48) Levitt, D. G. Quantitation of Small Intestinal Permeability during Normal Human Drug Absorption. *BMC Pharmacol. Toxicol.* **2013**, *14*, 1–17.
(49) Srinivasan, B.; Kolli, A. R.; Esch, M. B.; Abaci, H. E.; Shuler, M. L.; Hickman, J. J. TEER Measurement Techniques for In Vitro Barrier Model Systems. *J. Lab. Autom.* **2015**, *20*, 107–126.


Drug overdose
Detoxification
MIL-127(Fe)
In vivo experiments



Poisoning and accidental intoxication via ingestion is a major worldwide public health problem that causes both a significant cost and severe health problems, even death. In this study, we pioneering target the oral detoxification of drugs using a single biocompatible MOF.

81x41mm (150 x 150 DPI)