

COMPOUNDS AND USES THEREOF

FIELD OF INVENTION

The present invention relates to metal-organic frameworks (MOFs) that find utility in the treatment or prevention of hyperphosphatemia. The present invention also relates to pharmaceutical compositions comprising a MOF defined herein.

BACKGROUND

The listing or discussion of a prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

Hyperphosphatemia, characterized by elevated blood phosphate levels, is a common complication in patients with chronic kidney disease (CKD). To manage this condition, dietary phosphate restriction and dialysis are often supplemented with phosphate binders. Early phosphate binders, such as aluminum hydroxide ($\text{Al}(\text{OH})_3$), were effective in reducing phosphate levels but raised significant concerns regarding aluminum toxicity, including encephalopathy and bone disease. These safety issues led to the development of calcium-based binders, such as calcium carbonate (CaCO_3) and calcium acetate ($\text{Ca}(\text{Ac})_2$). However, these alternatives posed risks of hypercalcemia and vascular calcification, particularly detrimental to CKD patients.

To mitigate these risks, non-calcium and non-aluminum binders, including sevelamer hydrochloride and lanthanum carbonate ($\text{La}_2(\text{CO}_3)_3$), were developed. Sevelamer hydrochloride reduces phosphate levels without increasing calcium or aluminum levels, additionally offering cardiovascular health benefits. $\text{La}_2(\text{CO}_3)_3$ is also effective in binding phosphate, though there are ongoing concerns about its long-term toxicity. Recent innovations include iron-based phosphate binders like ferric citrate and sucroferric oxyhydroxide. These binders not only manage phosphate levels but also address iron deficiency anemia, which is common in CKD patients.

Table 1: Details including name, class and mode of action of previous phosphate binders.

Phosphate Binders	Class of material	Mode of action
Calcium Carbonate	Calcium-based Binder	Forms insoluble Calcium-phosphate complexes
Calcium acetate	Calcium-based Binder	Forms insoluble Calcium-phosphate complexes

Sevelamer Carbamate	polymeric amine	Binds phosphate ions through ionic and hydrogen bonding
Sevelamer Hydrochloride	polymeric amine	Binds phosphate ions through ionic and hydrogen bonding
Lanthanum carbonate	Lanthanum- based Binder	Forms insoluble Lanthanum-phosphate complexes
Iron Citrate	Iron-based Binder	Forms insoluble iron-phosphate complexes
Sucroferric oxyhydroxide	Iron-Based Binder	Forms insoluble iron-phosphate complexes
Tenapenor	sodium/hydrogen exchanger isoform 3 (NHE3) inhibitor	Reduces intestinal phosphate absorption predominantly through reduction of passive paracellular phosphate flux

The need for new phosphate binders arises from the limitations and challenges associated with existing treatments for hyperphosphatemia in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Current phosphate binders, including calcium-based, non-calcium-based, and iron-based binders, have significant drawbacks that impact patient compliance, efficacy, and overall health outcomes. Some of these concerns are explained below:

- **Safety concerns:** Calcium-based binders (e.g., calcium acetate, calcium carbonate) can lead to hypercalcemia and vascular calcification, exacerbating cardiovascular risk in CKD patients. Non-calcium-based binders (e.g., sevelamer) can cause gastrointestinal side effects, such as bloating and constipation, and may interfere with the absorption of other medications and nutrients. Iron-based binders (e.g., ferric citrate) might contribute to iron overload, constipation and discoloured faeces.
- **Cost and accessibility:** Non-calcium-based and iron-based binders tend to be more expensive, limiting their accessibility, especially in lower-income populations. This cost burden can reduce adherence to treatment regimens.
- **Efficacy and compliance:** The pill burden with current binders can be high, leading to poor patient compliance. Additionally, variability in patient response necessitates multiple adjustments in therapy, complicating treatment plans. Some binders require specific dietary restrictions or timing relative to meals, adding complexity to their use.

- *pH dependent performance*: The gastrointestinal tract exhibits significant pH variability, ranging from highly acidic in the stomach (pH 1-3) to more neutral or slightly alkaline in the intestines (pH 6-7.5). A phosphate binder that maintains its efficacy across this range ensures consistent phosphate binding throughout the entire digestive system. Few phosphate binders like sucroferric oxyhydroxide show varying phosphate binding at different pH in the gut.
- *Potential Drug Interactions*: Existing phosphate binders can interact with other medications, affecting their absorption and efficacy, complicating the management of CKD patients who often take multiple medications.

A new phosphate binder should aim to address some or all of these limitations by providing improved safety profiles, enhanced efficacy, lower costs, reduced pill burden, minimal drug interactions, and better overall patient compliance, or at least offer the public a useful alternative. Such advancements would significantly improve the quality of life and health outcomes for CKD and ESRD patients, making a compelling case for the development of innovative phosphate-binding therapies.

Thus, there remains a need for improved and/or alternative phosphate binders suitable for the treatment or prevention of hyperphosphatemia.

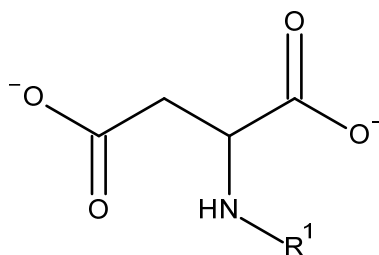
SUMMARY OF INVENTION

The present invention provides a metal-organic framework (MOF) that finds utility in the treatment or prevention of hyperphosphatemia,

wherein the MOF comprises a plurality of metal ions, each coordinated to a plurality of organic ligands, and

wherein the plurality of metal ions comprises Zr^{4+} ions, Fe^{3+} ions, or a combination of Zr^{4+} and Fe^{3+} ions, and

the plurality of organic ligands are selected from one or more members of the group consisting of a compound according to formula (I):



(I)

wherein,

R¹ is selected from the group consisting of H, -C(O)C₁₋₆alkyl, and -S(O)(O)-R², wherein said C₁₋₆alkyl is optionally substituted by 1, 2 or 3 halogens, and

R² is selected from the group consisting of C₁₋₆alkyl and C₅₋₁₀aryl, wherein said C₅₋₁₀aryl is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of C₁₋₆alkyl, halogen, NH₂, N(CH₃)₂, NO₂, and OH;

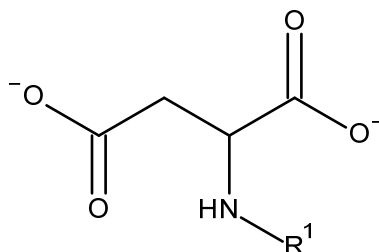
a C₂₋₆alkane substituted by two carboxylate groups and optionally substituted by one or two OH groups; a C₄₋₆alkene substituted by two carboxylate groups; a benzenedicarboxylate optionally substituted by one or two NH₂ groups; a benzenetricarboxylate; a 5-6 membered heteroaromatic ring comprising 1 or 2 atoms selected from the group consisting of N, S and O, wherein said heteroaromatic ring is substituted by two carboxylate groups; cyclohexane substituted by two carboxylate groups; and cystinate; or

a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, the MOF of the present invention comprises a plurality of metal ions, each coordinated to a plurality of organic ligands,

wherein the plurality of metal ions comprises Zr⁴⁺ ions, Fe³⁺ ions, or a combination of Zr⁴⁺ and Fe³⁺ ions, and

the plurality of organic ligands are selected from one or more compounds according to formula (I):



(I)

wherein,

R¹ is selected from the group consisting of -C(O)C₁₋₆alkyl and -S(O)(O)-R², wherein said C₁₋₆alkyl is optionally substituted by 1, 2 or 3 halogens; and

R² is selected from the group consisting of C₁₋₆alkyl and C₅₋₁₀aryl, wherein said C₅₋₁₀aryl is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of C₁₋₆alkyl, halogen, NH₂, N(CH₃)₂, NO₂, and OH.

The present invention also provides a pharmaceutical composition comprising a MOF of the present invention, and one or more pharmaceutically acceptable carriers or excipients. The MOF and pharmaceutical composition of the present invention find utility in the treatment or prevention of hyperphosphatemia.

Preferred but optional features are set out in the dependent claims. Additional aspects and embodiments of the MOFs, compositions, methods and uses of the present invention will be apparent from the following description, figures and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic description for MOF synthesis (1a) and their adsorption mechanism (1b).

FIG. 2 is a graph of the phosphate binding profiles of various MOFs at pH 7.5, 4.5 and 2.1.

FIG. 3 is a graph showing the phosphate binding capacity of Compound ID 1 (sevelamer carbonate), Compound ID 2 (50 mg of sucroferric oxyhydroxide), Compound ID 3 (160 mg of sucroferric oxyhydroxide), Compound ID 17 (50 mg of Zr-Asp MOF), Compound ID 23 (50 mg of Fe^(III)-Asp MOF), and Compound ID 25 (50 mg of Fe^(III)-*N*-acetyl Asp MOF).

FIG. 4 is a graph comparing the iron release of sucroferric oxyhydroxide (Compound ID 2) and MOFs Compound ID 23 and 25 on a simulated empty stomach.

FIG. 5 is a graph of the zirconium release of Compound ID 17-P (Zr-Asp MOF in a gastric solution with phosphate) and Compound ID 17-NP (Zr-Asp MOF in gastric solution without phosphate) on a simulated empty stomach.

FIG. 6 is a Field Emission Scanning Electron Microscopy (FESEM) image of Compound ID 17.

FIG. 7 is an FESEM image of Compound ID 23.

FIG. 8 is an FESEM image of Compound ID 25.

FIG. 9 is an FESEM image of Compound ID 20.

FIG. 10 is a Particle Size Distribution (PSD) plot showing the average particle size of Compound ID 17 is 13.7 μm .

FIG. 11 is a PSD plot showing the average particle size of Compound ID 23 is 37.9 μm .

FIG. 12 is a PSD plot showing the average particle size of Compound ID 25 is 88.2 μm .

FIG. 13 is a PSD plot showing the average particle size of Compound ID 20 is 28.1 μm .

FIG. 14 is a PSD plot showing the average particle size of Compound ID 13 is 14.0 μm . Note: The particle size distribution (PSD) for Compound ID 13 was analyzed using a sample that has not undergone sonication.

FIG. 15 is a Thermogravimetric (TG) residue profile and Differential Thermogravimetry (DTG) decomposition profile for Compound ID 17, The TG analysis was conducted in a nitrogen (N_2) atmosphere, with the temperature ramped from room temperature to 800°C at a heating rate of 15°C per minute.

FIG. 16 is a TG residue profile and DTG decomposition profile for compound ID 23, The Thermogravimetric Analysis (TGA) was conducted in a nitrogen (N_2) atmosphere, with the temperature ramped from room temperature to 800°C at a heating rate of 15°C per minute.

FIG. 17 is a TG residue profile and DTG decomposition profile for Compound ID 25. The TG analysis was conducted in a nitrogen (N_2) atmosphere, with the temperature ramped from room temperature to 800°C at a heating rate of 15°C per minute.

FIG. 18 is a TG residue profile and DTG decomposition profile for Compound ID 20, The Thermogravimetric Analysis (TGA) was conducted in a nitrogen (N_2) atmosphere, with the temperature ramped from room temperature to 800°C at a heating rate of 15°C per minute.

FIG. 19 is a TG residue profile and DTG decomposition profile for Compound ID 13, The Thermogravimetric Analysis (TGA) was conducted in a nitrogen (N_2) atmosphere, with the temperature ramped from room temperature to 800°C at a heating rate of 15°C per minute.

FIG. 20 is a plot of the BET Surface Area of Compound ID 17: Specific Surface Area of 103.48 m^2/g with a Linear Fit ($r = 0.9999$).

FIG. 21 is a plot of the BET Surface Area Analysis of Compound ID 23: Specific Surface Area of 230.169 m^2/g with a Linear Fit ($r = 0.9998$).

FIG. 22 is a plot of the BET Surface Area Analysis of Compound ID 25: Specific Surface Area of 95.991 m^2/g with a Linear Fit ($r = 0.9999$).

FIG. 23 is a plot of the BET Surface Area Analysis of Compound ID 20: Specific Surface Area

of 85.175 m²/g with a Linear Fit ($r = 0.9996$).

FIG. 24 is a plot of the BET Surface Area Analysis of Compound ID 13: Specific Surface Area of 264.186 m²/g with a Linear Fit ($r = 0.9999$).

FIG. 25 is a plot of the FTIR Spectrum of Compound ID 17: Characterization of Functional Groups with Prominent Peaks at 2972 cm⁻¹ (C-H stretching), 1600 cm⁻¹ (C=O stretching), and 1434 cm⁻¹ (C-O bending).

FIG. 26 is a plot of the FTIR Spectrum of Compound ID 23: Characterization of Functional Groups with Prominent Peaks at 3243 cm⁻¹ (C-H stretching), 1588 cm⁻¹ (C=O stretching), and 1403 cm⁻¹ (C-O bending).

FIG. 27 is an FTIR Spectrum of Compound ID 20: Characterization of Functional Groups with Prominent Peaks at 2965 cm⁻¹ (C-H stretching), 1588 cm⁻¹ (C=O stretching), and 1434 cm⁻¹ (C-O bending).

FIG. 28 is an FTIR Spectrum of Compound ID 25: Characterization of Functional Groups with Prominent Peaks at 3278 cm⁻¹ (C-H stretching), 1577 cm⁻¹ (C=O stretching), and 1428 cm⁻¹ (C-O bending).

FIG. 29 is an FTIR Spectrum of Compound ID 13: Characterization of Functional Groups with Prominent Peaks at 2966 cm⁻¹ (C-H stretching), 1538 cm⁻¹ (C=O stretching), and 1391 cm⁻¹ (C-O bending) 976.62 cm⁻¹ (C-H bending in alkenes) 797.47 cm⁻¹ (C-H bending in aromatic compounds).

DESCRIPTION

The term "metal-organic framework" or "MOF" refers to a one-, two-, or three-dimensional coordination polymer composed of metal ions and ligands that act as organic structural units (referred herein as organic ligands). A portion of the metal ions are coordinated to at least one bi-, tri-, or polydentate organic structural unit. The MOFs disclosed herein are constructed by combining metal ions or clusters with organic ligands, resulting in a three-dimensional porous structure (FIG.1, 1a). The metal ions (e.g. Zr⁴⁺ or Fe³⁺) act as nodes, while the organic ligands connect the nodes, forming a highly porous framework. MOFs are characterized by their large surface areas, well-defined repeating structures, and tuneable properties, which can be modified by selecting different metal ions and organic linkers. The pores within MOFs can be utilized to adsorb or bind various molecules, enabling their removal from a system (FIG. 1, 1b).

The present inventors have found that the MOFs defined herein are surprisingly effective at adsorbing phosphate. The MOFs are also biocompatible and capable of adsorbing phosphate

over a wide pH range, thus making them especially effective as oral adsorbents, in particular as oral phosphate binders for the treatment or prevention of hyperphosphatemia. For example, as described in the Examples section herein, the present inventors demonstrate in that the MOFs of the present invention can adsorb phosphate in solution at a pH of from about 2 to about 7.5, and show low levels of metal leaching in simulated gastric fluid. The present inventors also demonstrate that the MOFs of the invention have good biocompatibility, as demonstrated using *in vitro* toxicity experiments and *in vivo* inflammation experiments. In particular, the present inventors demonstrate that the MOFs referred to herein as Compound IDs 17 and 23 did not have a negative effect on the viability of human intestinal epithelium cells (Caco-2) *in vitro*, and that the MOFs referred to herein as Compound IDs 13, 17, 20, 23 and 25 did not have any notable effects on inflammatory marker levels in male pigs (*Sus scrofa*) administered a diet supplemented with the MOFs.

Thus, the MOFs defined herein find utility in the treatment or prevention of hyperphosphatemia. For example, the MOFs defined herein may find use in the treatment or prevention of hyperphosphatemia in a subject suffering from chronic kidney disease (CKD) or end-stage renal disease (ESRD). The MOFs may also find use in the treatment or prevention of hyperphosphatemia in a subject suffering from, or at risk of developing, cardiovascular disease, for example cardiovascular disease characterised by the presence of vascular calcification.

Accordingly, one aspect of the present invention relates to a use of a MOF as defined herein in the manufacture of a medicament for the treatment or prevention of hyperphosphatemia. As also disclosed herein, the MOFs defined herein may be used in the treatment or prevention of hyperphosphatemia, or may be used in a method of treating or preventing hyperphosphatemia, said method comprising the step of administering a dose of a MOF defined herein to a subject known to have, suspected of having, or at risk of developing hyperphosphatemia.

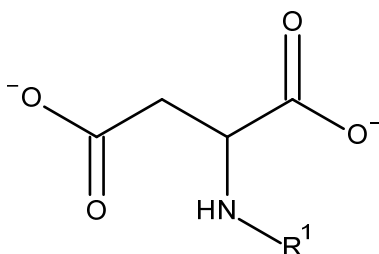
The MOFs of the present invention comprise a plurality of metal ions, each coordinated to a plurality of organic ligands,

wherein the plurality of metal ions comprises Zr^{4+} , Fe^{3+} , or a combination of Zr^{4+} and Fe^{3+} , and

the plurality of organic ligands are selected from the group consisting of a compound according to formula (I); a C_{2-6} alkane substituted by two carboxylate groups and optionally substituted by one or two OH groups; a C_{4-6} alkene substituted by two carboxylate groups; a benzenedicarboxylate optionally substituted by one or two NH_2 groups; a benzenetricarboxylate; a 5-6 membered heteroaromatic ring comprising 1 or 2 atoms selected

from the group consisting of N, S and O, wherein said heteroaromatic ring is substituted by two carboxylate groups; cyclohexane substituted by two carboxylate groups; and cystinate.

The compound of formula (I) is according to:



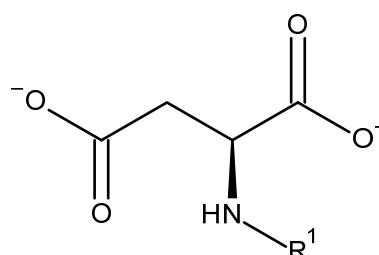
(I)

In the compound of formula (I), R^1 is selected the group consisting of H, $-C(O)C_{1-6}\text{alkyl}$, and $-S(O)(O)-R^2$, wherein said $C_{1-6}\text{alkyl}$ is optionally substituted by 1, 2 or 3 halogens. For example, R^1 may be $-C(O)C_{1-4}\text{alkyl}$, for example R^1 may be acetyl (i.e. $-C(O)CH_3$).

In the compound of formula (I), R^2 is selected from the group consisting of $C_{1-6}\text{alkyl}$ and $C_{5-10}\text{aryl}$, wherein said $C_{5-10}\text{aryl}$ is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of $C_{1-6}\text{alkyl}$, halogen, NH_2 , $N(CH_3)_2$, NO_2 , and OH.

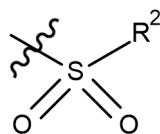
For the avoidance of doubt, when a compound structure is depicted or named herein, the compound structure or name is considered to encompass all stereoisomers of the compound, unless stated otherwise. For example, if the stereochemistry of the compound is not indicated in the compound structure or name, the compound structure or name encompass all stereoisomers of the compound.

In certain embodiments, the compound of formula (I) is according to formula (Ia):



(Ia)

Also, for the avoidance of doubt, the group referred to herein as “ $-S(O)(O)-R^2$ ” has the structural formula of:



wherein,  denotes the point of attachment of -S(O)(O)-R² to formula (I) or (Ia). Thus, when R¹ in formula (I) (or likewise, formula (Ia)) is -S(O)(O)-R², the compound of formula (I) (or formula (Ia)) is an *N*-sulfonyl derivative of aspartate. R² may be selected from the group consisting of C₁₋₆alkyl and C₅₋₁₀aryl, wherein said C₅₋₁₀aryl is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of C₁₋₆alkyl, halogen, NH₂, N(CH₃)₂, NO₂, and OH. For example, R² may be methyl, ethyl, phenyl or naphthalene, optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of C₁₋₆alkyl, Cl, F, NH₂, N(CH₃)₂, NO₂, and OH. For example, R² may be methyl, ethyl, trifluoromethyl, trifluoroethyl, phenyl, naphthalyl, 5-(dimethylamino)-1-naphthalyl, nitrophenyl, bromophenyl or chlorophenyl.

In certain exemplary embodiments, the compound of formula (I) is aspartate or *N*-acetyl aspartate (e.g. L-aspartate or *N*-acetyl-L-aspartic acid).

As used herein, the term “alkyl” means both linear and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, sec-butyl, pentyl and hexyl groups. Examples of linear alkyl groups include methyl, ethyl, n-propyl, isopropyl and n-butyl groups. Examples of branched alkyl groups include tert-butyl, sec-butyl, isobutyl, 1-ethylpropyl and 1-ethylbutyl groups.

As used herein, the term “C₅₋₁₀aryl” refers to a monocyclic or polycyclic aromatic hydrocarbon group containing 5 to 10 carbon atoms. Examples of C₅₋₁₀aryl groups include cyclopentadienyl, phenyl, and naphthyl. The C₅₋₁₀aryl may be unsubstituted or optionally substituted with one or more suitable substituents, such as alkyl, halogen, nitro, hydroxyl, or other suitable functional groups.

As used herein, the term “halogen” means fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are preferred, and fluorine and chlorine are particularly preferred.

For the avoidance of doubt, the term “Zr⁴⁺ ions” refers to zirconium ions in their oxidation state of +4. The term “Fe³⁺ ions” refers to iron ions in their oxidation state of +3. In certain preferred embodiments, the MOF of the present invention comprises a plurality of Zr⁴⁺ ions or Fe³⁺ ions.

In certain embodiments, the plurality of organic ligands of the MOF of the present invention are selected from one or more members of the group consisting of a compound according to formula (I), fumarate, terephthalate, succinate, malate, adipate, 2-aminoterephthalate; trimesate, pyridinedicarboxylate (e.g. 3,5-pyridinedicarboxylate), cyclohexanedicarboxylate

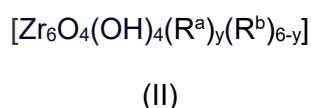
(e.g. 1,4-cyclohexyldicarboxylate), and cystinate (e.g. L-cystinate). In certain exemplary embodiments, the plurality of organic ligands of the MOF is a compound according to formula (I), fumarate, terephthalate, succinate, malate, adipate, 2-aminoterephthalate; trimesate, pyridinedicarboxylate (e.g. 3,5-pyridinedicarboxylate), cyclohexanedicarboxylate (e.g. 1,4-cyclohexyldicarboxylate), or cystinate (e.g. L-cystinate).

For example, in certain embodiments wherein the MOF comprises a plurality of Zr^{4+} ions, the plurality of organic ligands may be selected from one or more members of the group consisting of a compound according to formula (I), fumarate, terephthalate, succinate, malate, adipate, 2-aminoterephthalate, pyridinedicarboxylate (e.g. 3,5-pyridinedicarboxylate), cyclohexanedicarboxylate (e.g. 1,4-cyclohexyldicarboxylate), and cystinate (e.g. L-cystinate).

For example, in certain embodiments wherein the MOF comprises a plurality of Fe^{3+} ions, the plurality of organic ligands may be selected from one or more members of the group consisting of a compound according to formula (I), fumarate, terephthalate, succinate, 2-aminoterephthalate, trimesate, and cystinate (e.g. L-cystinate).

In certain preferred embodiments, the MOF of the present invention comprises a plurality of metal ions consisting of Zr^{4+} ions or Fe^{3+} ions, wherein the plurality of organic ligands are selected from one or more members of the group consisting of aspartate, *N*-acetyl aspartate, terephthalate, and fumarate.

In embodiments wherein the MOF comprises a plurality of Zr^{4+} ions and the organic ligands each comprise two carboxylate groups, the MOF may be represented by formula (II):



wherein,

R^a and R^b are each independently selected from the group consisting of a compound according to formula (I) as defined herein; a C_{2-6} alkane substituted by two carboxylate groups and optionally substituted by one or two OH groups; a C_{4-6} alkene substituted by two carboxylate groups; a benzenedicarboxylate optionally substituted by one or two NH_2 groups; a 5-6 membered heteroaromatic ring comprising 1 or 2 atoms selected from the group consisting of N, S and O, wherein said heteroaromatic ring is substituted by two carboxylate groups; cyclohexane substituted by two carboxylate groups; and cystinate (e.g. L-cystinate); and

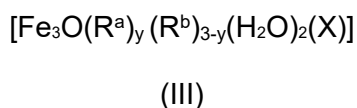
y is an integer from 0 to 6, for example, y may be 6.

In certain embodiments, in formula (II), R^a and R^b are each independently a compound according to formula (I), fumarate, terephthalate, 2-aminoterephthalate, adipate, succinate, or malate. In certain exemplary embodiments, the one or more organic ligands of the MOF is a compound according to formula (I), fumarate, terephthalate, succinate, malate, adipate, 2-aminoterephthalate, pyridinedicarboxylate, cyclohexanedicarboxylate, or cystinate. For example, in formula (II), R^a and R^b may each independently be aspartate, *N*-acetyl aspartate, fumarate, terephthalate, succinate, malate, adipate, 2-aminoterephthalate, pyridinedicarboxylate (e.g. 3,5-pyridinedicarboxylate), cyclohexanedicarboxylate (e.g. 1,4-cyclohexyldicarboxylate), or cystinate (e.g. L-cystinate).

In certain preferred embodiments, in formula (II), y is 6, R^a is compound according to formula (I), fumarate, terephthalate, 2-aminoterephthalate, adipate, succinate, or malate, and R^b is absent. For example, y is 6, R^a may be aspartate or *N*-acetyl aspartate, and R^b is absent.

In certain embodiments, the MOF is according to formula (II), wherein R^a is cystinate and R^b is terephthalate, and wherein y is an integer from 0 to 6, for example, y may be 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, or 6 (e.g. y is 3). In certain other embodiments, the MOF is according to formula (II), wherein R^a is fumarate and R^b is terephthalate, and wherein y is an integer from 0 to 6, for example, y may be 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, or 6 (e.g. y may be 3).

In embodiments wherein the MOF comprises a plurality of Fe^{3+} ions and the organic ligands each comprise two carboxylate groups, the MOF may be represented by formula (III):



wherein,

R^a and R^b are each independently selected from the group consisting of a compound according to formula (I), as defined herein; a C_{2-6} alkane substituted by two carboxylate groups and optionally substituted by one or two OH groups; a C_{4-6} alkene substituted by two carboxylate groups; a benzenedicarboxylate optionally substituted by one or two NH_2 groups; a 5-6 membered heteroaromatic ring comprising 1 or 2 atoms selected from the group consisting of N, S and O, wherein said heteroaromatic ring is substituted by two carboxylate groups; cyclohexane substituted by two carboxylate groups; and cystinate (e.g. L-cystinate);

X is a counterion selected from the group consisting of Cl^- , OH^- or NO_3^- ; and

y is an integer from 0 to 3, for example, y may be 1, 1.5, 2, 2.5, or 3, for example, 1, 1.5, or 2.

In certain embodiments, in formula (III), R^a and R^b are each independently a compound according to formula (I), fumarate, terephthalate, 2-aminoterephthalate, succinate, or cystinate

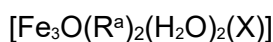
(e.g. L-cystinate). For example, in formula (III), R^a and R^b may each independently be aspartate, *N*-acetyl aspartate, fumarate, terephthalate, 2-aminoterephthalate, succinate, or cystinate (e.g. L-cystinate).

In certain embodiments, in formula (III), y is 3, R^a is a compound according to formula (I), fumarate, terephthalate, 2-aminoterephthalate, succinate, or cystinate (e.g. L-cystinate), and R^b is absent.

In certain other embodiments, the MOF of the present invention comprises a plurality of Fe^{3+} ions, and a combination of terephthalate and fumarate molecules. In such embodiments, the MOF is formed from Fe^{3+} ions and a mixture of fumarate and terephthalate, wherein the mixture of fumarate and terephthalate contains a molar ratio of fumarate to terephthalate of from about 2:1 to about 1:2 (e.g. 1:1, 1:2 or 2:1). The molar ratio of fumarate to terephthalate present in the MOF is expected to be similar or the same as the molar ratio of the two organic ligands in the mixture used in the preparation of the MOF. Thus, in such embodiments, the MOF may be represented by formula (III) wherein R^a is fumarate, R^b is terephthalate, and y is about 1, about 1.5, about 2, or about 2.5 (e.g. y may be about 1, about 1.5, or about 2).

In certain other embodiments, the MOF of the present invention comprises a plurality of Fe^{3+} ions, and a combination of cystinate (e.g. L-cystinate) and terephthalate. In such embodiments, the MOF is from a suitable iron(III) salt and a mixture of cystinate and terephthalate, wherein the mixture of cystinate and terephthalate contains a molar ratio of cystinate to terephthalate of from about 2:1 to about 1:2 (e.g. 1:1, 1:2 or 2:1). The molar ratio of cystinate to terephthalate present in the MOF is expected to be similar or the same as the molar ratio of the two organic ligands in the mixture used in the preparation of the MOF. Thus, in such embodiments, the MOF may be represented by formula (III) wherein R^a is cystinate, R^b is terephthalate, and y is about 1, about 1.5, about 2, or about 2.5 (e.g. y may be about 1, about 1.5, or about 2).

In embodiments wherein the MOF comprises a plurality of Fe^{3+} ions and the organic ligands each comprise three carboxylate groups, the MOF may be represented by formula (IV):



(IV)

wherein,

R^a is a benzenetricarboxylate, for example R^a may be trimesate; and

X is a counterion selected from the group consisting of Cl^- , OH^- or NO_3^- .

The present inventors demonstrate that when the MOF of the present invention comprises a plurality of Zr^{4+} or Fe^{3+} ions and a plurality of aspartate or *N*-acetyl aspartate molecules, the

MOF displays especially high phosphate binding capacity, which makes these MOFs highly attractive for use as an oral phosphate binder.

Thus, in certain preferred embodiments, the MOF comprises a plurality of Zr^{4+} ions and a plurality of aspartate or *N*-acetyl aspartate molecules. In such embodiments, the MOF may be represented by the structural formula $[Zr_6O_4(OH)_4(N\text{-acetyl aspartate})_6]$ or $[Zr_6O_4(OH)_4(\text{aspartate})_6]$, and these MOFs may also be generally referred to herein as Zr-aspartate MOF or Zr-*N*-acetyl aspartate MOF. In certain other preferred embodiments, the MOF comprises a plurality of Fe^{3+} ions and a plurality of aspartate or *N*-acetyl aspartate molecules. In such embodiments, the MOF may be represented by the structural formula $[Fe_3O(\text{aspartate})_3(H_2O)_2(X)]$ or $[Fe_3O(N\text{-acetyl aspartate})_3(H_2O)_2(X)]$, wherein X is a counterion selected from the group consisting of Cl^- , ^-OH or NO_3^- (e.g. X may be Cl^-), and such MOFs may also be generally referred to herein as $Fe^{(III)}$ -aspartate MOF or $Fe^{(III)}$ -*N*-acetyl aspartate MOF.

Furthermore, the present inventors have found that Zr-aspartate MOF (Compound ID 17) and $Fe^{(III)}$ -*N*-acetyl aspartate MOF (Compound ID 25) are particularly attractive as oral phosphate binders because they display high phosphate binding that is independent of pH, which allow phosphate binding throughout the gastrointestinal (GI) tract. Thus, in certain preferred embodiments, the MOF of the present invention comprises a plurality Zr^{4+} ions and a plurality aspartate molecules (e.g. the MOF may be $[Zr_6O_4(OH)_4(N\text{-acetyl aspartate})_6]$), or a plurality of Fe^{3+} ions and a plurality *N*-acetyl aspartate molecules (e.g. the MOF may be $[Fe_3O(N\text{-acetyl aspartate})_3(H_2O)_2(X)]$, wherein X is a counterion selected from the group consisting of Cl^- and ^-OH (e.g. X may be Cl^-)).

In certain exemplary embodiments, the MOF of the present invention is selected from the group consisting of:

- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of fumarate molecules (for example, the MOF may be referred to as a Zr-fumarate MOF (Compound ID 4));
- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of trimesate molecules (for example, the MOF may be referred to as a $Fe^{(III)}$ -trimesate MOF (Compound ID 5));
- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of aminoterephthalate molecules (for example, the MOF may be referred to as a $Fe^{(III)}$ -aminoterephthalate MOF (Compound ID 6));

- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of fumarate molecules (for example, the MOF may be referred to as a $\text{Fe}^{(\text{III})}$ -fumarate MOF (Compound ID 7));
- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of fumarate molecules, a plurality of terephthalate molecules, or a combination of fumarate molecules and terephthalate molecules (for example, the MOF may be referred to as a $\text{Fe}^{(\text{III})}$ -fumarate/terephthalate MOF (Compound ID 8, 13, 13a, 14, and 14a));
- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of terephthalate molecules (for example, the MOF may be referred to as a $\text{Fe}^{(\text{III})}$ -terephthalate MOF (Compound ID 9));
- a MOF comprising a plurality Fe^{3+} ions and Zr^{4+} ions, each coordinated with a plurality of fumarate molecules (for example, the MOF may be referred to as a $\text{Zr}/\text{Fe}^{(\text{III})}$ -fumarate MOF (Compound ID 10));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of terephthalate MOF (for example, the MOF may be referred to as a Zr-terephthalate MOF (Compound ID 11 and 11a));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of aminoterephthalate molecules (for example, the MOF may be referred to as a Zr-aminoterephthalate MOF (Compound ID 12 and 12a));
- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of cystinate molecules, a plurality of terephthalate molecules, or a combination of cystinate molecules and terephthalate molecules (for example, the MOF may be referred to as a $\text{Fe}^{(\text{III})}$ -cystinate/terephthalate MOF (Compound ID 15));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of terephthalate molecules (for example, the MOF may be referred to as a Zr-adipate MOF (Compound ID 16 and 19));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of aspartate molecules (for example, the MOF may be referred to as a Zr-aspartate MOF (Compound ID 17));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of succinate molecules (for example, the MOF may be referred to as a Zr-succinate MOF (Compound ID 18));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of aspartate molecules (for example, the MOF may be referred to as a Zr-*N*-acetyl aspartate MOF (Compound ID 20));

- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of succinate molecules (for example, the MOF may be referred to as an iron^(III)-succinate MOF (Compound ID 21));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of pyridinedicarboxylate molecules (for example, the MOF may be referred to as a Zr-pyridinedicarboxylate MOF (Compound ID 22));
- a MOF comprising a plurality Fe^{3+} ions, each coordinated with a plurality of aspartate molecules (for example, the MOF may be referred to as an iron^(III)-aspartate MOF (Compound ID 23));
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of cyclohexanedicarboxylate molecules (for example, the MOF may be referred to as a Zr- cyclohexanedicarboxylate MOF (Compound ID 24));
- a MOF comprising a plurality of Fe^{3+} ions, each coordinated with a plurality of aspartate molecules (for example, the MOF may be referred to as an iron^(III)-N-acetyl aspartate MOF (Compound ID 25)); and
- a MOF comprising a plurality Zr^{4+} ions, each coordinated with a plurality of malate molecules (for example, the MOF may be referred to as a Zr-malate MOF (Compound ID 26)).

The MOFs of the present invention may be prepared using methods known to those skilled in the art of organic chemistry. Exemplary procedures for the preparation of MOFs disclosed herein are described in the Examples section.

The MOF of the present invention may be in the form of a salt and/or solvate. Suitable salts for use in the present invention are those wherein a counterion is pharmaceutically acceptable. However, the use of salts having non-pharmaceutically acceptable counter-ions are within the scope of the present invention, for example, for use as intermediates in the preparation of the MOF of the present invention and their pharmaceutically acceptable salts and solvates. Suitable examples of MOF in the form of a pharmaceutically acceptable solvate include hydrates. Typically, when the MOF is in the form of a salt, the MOF comprises a counter ions selected from the group consisting of Cl^- , ^-OH and NO_3^- .

The word “comprising” as used herein may be interpreted as requiring the features mentioned, but not limiting the presence of other features. Alternatively, the word “comprising” may also relate to the situation where only the components/features listed are intended to be present (e.g. the word “comprising” may be replaced by the phrases “consists of” or “consists essentially of”). It is explicitly contemplated that both the broader and narrower interpretations can be applied to all aspects and embodiments of the present invention. In other words, the

word “comprising” and synonyms thereof may be replaced by the phrase “consisting of” or the phrase “consists essentially of” or synonyms thereof and *vice versa*.

The phrase “consists essentially of” and its pseudonyms may be interpreted herein to refer to a material where minor impurities may be present. For example, the material may be greater than or equal to 90% pure, such as greater than 95% pure, such as greater than 97% pure, such as greater than 99% pure, such as greater than 99.9% pure, such as greater than 99.99% pure, such as greater than 99.999% pure, such as 100% pure.

As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a composition” includes mixtures of two or more such compositions, and the like.

The term “about” as used herein can allow for a degree of variability in a value or range, for example, within 10%, within 5%, within 1%, within 0.5%, within 0.1%, within 0.05%, within 0.01%, within 0.005%, or within 0.001% of a stated value or of a stated limit of a range, and includes the exact stated value or range.

Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

In embodiments wherein the plurality of organic ligands of the MOF are selected from the group consisting of aspartate, *N*-acetyl aspartate, and a combination of fumarate and terephthalate, the MOF may have an average particle size of from about 10 μm to about 100 μm (e.g. from about 30 μm to about 90 μm). As used herein, the term “average particle size” refers to the mean particle size of a material based on the volume-based particle size distribution, often measured by the laser diffraction or dynamic light scattering particle size distribution measurements. Particle size can also be determined using Scanning Electron Microscopy (SEM). Further details of a method for determining the average particle size of the MOF of the present invention using dynamic light scattering are included in the Example section herein.

In embodiments the plurality of organic ligands of the MOF are selected from the group consisting of aspartate, *N*-acetyl aspartate, and a combination of fumarate and terephthalate,

the MOF may have a BET surface area of from about 70 m²/g to about 300 m²/g (e.g. from about 80 m²/g to about 300 m²/g). Such MOFs may also have a total pore volume of from 0.2 cm³/g to about 0.6 cm³/g and/or a mode average pore width of from about 0.7 nm to about 60 nm.

The BET surface areas of the MOFs described herein refer to the surface area of the material as determined from nitrogen adsorption data using the BET method (see J. Am. Chem. Soc. 1938, 60, 309-331, which is incorporated herein by reference).

The total pore volumes of the MOFs described herein refer to the total volume of the pores in a MOF, as determined by the single point calculation method described herein. Methods for determining the total pore volume of a MOF are known in the art. For example, the total pore volumes disclosed herein may be determined from a single point of an N₂ adsorption isotherm at 77.3 K with a saturation pressure of $p/p_0 > 0.99$, using the Gurvich rule (Rouquerol, J., Rouquerol, F., Llewellyn, P., Maurin, G. and Sing, K., 2013. Adsorption by powders and porous solids: principles, methodology and applications. Academic press).

The pore width of the MOFs described herein disclosed herein were determined from N₂ adsorption isotherms at 77.3 K and CO₂ adsorption isotherms at 273.15 K, using a 2D nonlocal density functional theory (2D-NLDFT) model to generate a pore size distribution plot (Ravikovitch, P. I., & Neimark, A. V. (2002). "Density functional theory model of adsorption on amorphous and microporous silica materials." Langmuir, 18(17), 1550-1560). The mode average pore widths of the MOFs may be determined from a pore size distribution plot (surface area vs. pore size) generated using the 2D-NLDFT model (Ravikovitch, P. I., & Neimark, A. V. (2002). "Density functional theory model of adsorption on amorphous and microporous silica materials." Langmuir, 18(17), 1550-1560).

Utility and Compositions:

The MOF of the present invention may be administered to a subject, for example administered orally to a subject. The subject may be one suffering from hyperphosphatemia, at risk of developing hyperphosphatemia, or at risk of suffering from a disease or condition associated with or caused by hyperphosphatemia.

In certain embodiments, the MOF of the present invention may be administered to a subject suffering from hyperphosphatemia or at risk of developing hyperphosphatemia, who is also suffering from chronic kidney disease (CKD) or end-stage renal disease (ESRD).

In certain other embodiments, the MOF of the present invention may be administered to a subject suffering from hyperphosphatemia or at risk of developing hyperphosphatemia, who is also suffering from or at risk of developing a cardiovascular disease. Hyperphosphatemia can be associated with vascular calcification, which itself is highly associated with

cardiovascular disease mortality (see, for example, Adv Chronic Kidney Dis. 2011; 18(2): 113–119). Thus, the subject may be suffering from, or at risk of developing, a cardiovascular disease characterised by the presence of vascular calcification.

The MOF of the present invention may be administered to a subject in combination with one or more further oral adsorbents selected from the group consisting of a phosphate binding agent, an activated carbon adsorbent, and a potassium binding agent. For example, the MOF of the present invention may be administered to a subject in combination with one or more further phosphate binding agents selected from the group consisting of calcium carbonate, calcium acetate, sevelamer carbamate, sevelamer hydrochloride, lathanum carbonate, iron citrate, sucroferic oxyhydroxide, and tenapanor.

The one or more further oral adsorbents may be used simultaneously, sequentially or separately with/from the administration of the MOF of the present invention. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. An ordinarily skilled physician can readily determine and administer the effective amount of one or more therapeutic interventions required to have the desired therapeutic effect. Preferred unit dosage compositions for use according to the invention are those containing an effective dose, or an appropriate fraction thereof, of the MOF of the present invention. The release of the MOF from certain composition may also be sustained, for example, if the composition contains suitable controlled-release excipients.

The MOF of the present invention may be used in the form of a composition comprising the MOF together with at least one binder, carrier or excipient. Preferably, the composition of the invention is a pharmaceutical composition. For example, the composition may be a pharmaceutical composition comprising the MOF of the present invention and at least one pharmaceutically acceptable binder, carrier or excipient. Preferably, the composition of the invention is a pharmaceutical composition suitable for oral administration. In certain embodiments, the composition of the present invention further comprises one or more further oral adsorbents selected from the group consisting of a phosphate binding agent, an activated carbon adsorbent, and a potassium binding agent. For example, the composition of the present invention may further comprise one or more further phosphate binding agents selected from the group consisting of calcium carbonate, calcium acetate, sevelamer carbamate, sevelamer hydrochloride, lathanum carbonate, iron citrate, sucroferic oxyhydroxide, and tenapanor.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a

predetermined amount of the MOF of the present invention; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The MOF of the present invention may also be presented as a bolus, electuary or paste. Suitable pharmaceutically acceptable binders, carriers or excipients for including in the pharmaceutical formulation of the present invention may be selected with due regard to the intended route of administration and standard pharmaceutical practice. Suitable pharmaceutical formulations may be found in, for example, Remington The Science and Practice of Pharmacy, 19th ed., Mack Printing Company, Easton, Pennsylvania (1995). Otherwise, the preparation of suitable formulations may be achieved routinely by the skilled person using routine techniques and/or in accordance with standard and/or accepted pharmaceutical practice.

As will be appreciated from the disclosure herein, the MOF of the present invention and pharmaceutical composition of the present invention may find utility as a medicament. The ability of the MOF of the present invention to adsorb phosphate makes them promising phosphate binding agents for the treatment of hyperphosphatemia. The medicament comprising the MOF of the present invention may be administered to a subject orally.

The MOF of the present invention may be administered daily (including several times daily), every second or third day, weekly, every second, third or fourth week or even as a high single dose depending on the subject and disease to be treated.

As used herein the terms "subject" or "patient" are well-recognized in the art, and, are used interchangeably herein to refer to a mammal, including dog, cat, rat, mouse, monkey, cow, horse, goat, sheep, pig, camel, and, most preferably, a human. The terms "subject" or "patient" do not denote a particular age or sex. Thus, adult and newborn subjects, whether male or female, are intended to be covered.

The amount of the MOF of the present invention or pharmaceutical composition of the present invention required to achieve a therapeutic effect will vary with the characteristics of the subject under treatment, for example the species, age, weight, sex, medical conditions, the particular disease (e.g. renal disease or liver disease) and its severity, and other relevant medical and physical factors. An ordinarily skilled physician can readily determine and administer an effective amount of the MOF of the present invention or pharmaceutical composition required for treatment or prevention of hyperphosphatemia.

The contents of the articles, patents, and patent applications, and all other documents and electronically available information mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically

and individually indicated to be incorporated by reference. The applicant reserves the right physically to incorporate into this application any and all materials and information from any such articles, patents, patent applications, or other physical and electronic documents.

Further aspects and embodiments of the invention will now be discussed by reference to the following non-limiting examples.

EXAMPLES

Abbreviations herein:

Zr: Zirconium

Fe: Iron

Fu: Fumaric acid

BDC: terephthalic acid

BTC: Trimesic acid

NH₂-BDC: 2-Aminoterephthalic acid

Asp: L-Aspartic acid

Cyclohexyl di-COOH: 1,4-cyclohexyl dicarboxylic acid

Succ: Succinic acid

N-acetyl Asp: N-Acetyl -L-aspartic acid

Pyridyl di-COOH: 3,5-Pyridinedicarboxylic acid

Materials and methods:

Chemicals were procured from Sigma Aldrich, and used as received unless otherwise specified. The material used in the fabrication of the MOF of the present invention are set out in Table 2.

Table 2: Chemicals used.

Chemical	Supplier
Zirconium (IV) Chloride	Sigma Aldrich
Iron (III) Chloride Hexahydrate	Sigma Aldrich; F2877
Iron (III) Nitrate	Sigma Aldrich; Product No-1003594361
L-Aspartic acid	Sigma Aldrich; Product No-A9256
Fumaric acid	Sigma Aldrich Product No-102565341
Terephthalic acid	Sigma Aldrich Product No- 1003290402

Trimesic acid	Sigma Aldrich Product No-482749
2-Aminoterephthalic acid	Sigma Aldrich Product No 1003298089
Adipic acid	Sigma Aldrich Product No-102318251
1,4-cyclohexyl dicarboxylic acid	Sigma Aldrich Product No-1003047426
Succinic acid	Sigma Aldrich Product No-1003656493
<i>N</i> -Acetyl-L-aspartic acid	Sigma Aldrich Product No-102709538
3,5-Pyridinedicarboxylic acid	Sigma Aldrich Product No-102676391
N, N-Dimethylformamide	Sigma Aldrich Product No-1003610969

Table 3 summarizes the methods used to prepare the MOFs tested for their ability to adsorb phosphate.

Table 3: List of MOF synthesized from Sample ID 4 to Sample ID 26, along with the reactants and reaction conditions for the synthesis.

Compound ID	Reactant 1	Reactant 2	Reactant 3	Ratio of Reactants	Solvent	Reaction conditions
4	Zirconium oxychloride	Fumaric acid		1:2	AcOH/ water	Protocol A
5	Iron (III) Nitrate	Trimesic acid		1:4	Water	Protocol B
6	Iron (III) Nitrate	Amino terephthalic acid		1:4	DMF	Protocol B
7	Iron (III) Chloride	Fumaric acid		1:1	AcOH/ water	Protocol A
8	Iron (III) Chloride	Terephthalic acid	Fumaric acid	1:0.5:0.5	DMF	Protocol C
9	Iron (III) Chloride	Terephthalic acid		1:1	DMF	Protocol C
10	Iron (III) Chloride	Zirconium chloride	Fumaric acid	1:1:0.5	DMF	Protocol C
11	Zirconium oxychloride	Terephthalic acid		2:1	DMF	Protocol C
11a	Zirconium oxychloride	Terephthalic acid		1:1	DMF	Protocol C
12	Zirconium oxychloride	Amino terephthalic acid		1:1	DMF	Protocol C
12a	Zirconium oxychloride	Amino terephthalic acid		2:1	DMF	Protocol C
13	Iron (III) Chloride	Terephthalic acid	Fumaric acid	1:0.25:0.75	DMF	Protocol C
13a	Iron (III) Chloride	Terephthalic acid	Fumaric acid	1:0.75:0.25	DMF	Protocol C
14	Zirconium oxychloride	Terephthalic acid	Fumaric acid	1:0.25:0.75	DMF	Protocol C
14a	Zirconium oxychloride	Terephthalic acid	Fumaric acid	1:0.75:0.25	DMF	Protocol C
15	Iron (III) Chloride	Terephthalic acid	L-Cystine	1:0.5:0.5	DMF	Protocol C

16	Zirconium oxychloride	Adipic acid		1:2	AcOH/ water	Protocol D
17	Zirconium (IV) Chloride	Aspartic acid		1:2.33	Water	Protocol E
18	Zirconium oxychloride	Succinic acid		1:4	DMF	Protocol F
19	Zirconium oxychloride	Adipic acid		1:4	DMF	Protocol F
20	Zirconium (IV) Chloride	N-acetyl aspartic acid		1:2	Water	Protocol E
21	Iron (III) Chloride	Succinic acid		1:1.5	Water	Protocol F
22	Zirconium (IV) Chloride	Pyridine dicarboxylic acid		1:2	Water	Protocol E
23	Iron (III) Chloride	Aspartic acid	NaOH	1:1:3	water	Protocol G
24	Zirconium oxychloride	Cyclohexyl dicarboxylic acid		1:2	DMF	Protocol H
25	Iron (III) Chloride	N-acetyl aspartic acid	NaOH	1:1:3	water	Protocol G

Protocol A:

Take Reactant 1 in a screw-capped vial and add a 1:1 mixture of AcOH (acetic acid) and water in a 10:1 ratio (AcOH/water to Reactant 1). Add Reactant 2 to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a sealed glass reactor, and heat the reaction mixture at 120 °C for 2 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours.

Protocol B:

Take Reactant 1 in a screw-capped vial and add water/DMF in a 10:1 ratio. Add Reactant 2 to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a sealed glass reactor, and heat the reaction mixture at 120 °C for 2 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours.

Protocol C:

Take Reactant 1 in a screw-capped vial and add DMF in a 10:1 ratio. Add Reactant 2 (and optionally Reactant 3) to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a sealed glass reactor, and heat the reaction mixture at 135°C for 2 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours

Protocol D:

Take Reactant 1 in a screw-capped vial and add a 1:1 mixture of AcOH (acetic acid) and water in a 10:1 ratio (AcOH/water to Reactant 1). Add Reactant 2 to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a steel bomb, place the steel bomb in the oven, and heat at 80 °C for 2 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours.

Protocol E:

Take Reactant 1 in a screw-capped vial and add water in a 10:1 ratio. Add Reactant 2 to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a sealed glass reactor, and heat the reaction mixture at 120 °C for 2.5 -12 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours.

Protocol F:

Take Reactant 1 in a screw-capped vial and add DMF in a 10:1 ratio. Add Reactant 2 to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a sealed glass reactor, and heat the reaction mixture at 120 °C for 7 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours.

Protocol G:

Take 7.89 g of aspartic acid and add it to 300 mL of DI water in a 2L glass bottle at 75 °C. Dissolve sodium hydroxide in 420 mL of DI water and iron^(III) chloride hexahydrate 16 g in 300 mL of DI water. Add the sodium hydroxide solution and iron^(III) chloride solution dropwise at a rate of 10 mL/min. Stir the solution at 100 rpm and heat it at 75 °C for 7 hours. Stop the heating and stirring, and allow the solid to settle for 18 hours. Remove the excess solution by decantation. Transfer the solid material into 250 mL centrifuge bottles. Add 50 mL of DI water into each centrifuge bottle and centrifuge the solution. Repeat the process with DI water two more times until the pH reaches around 5-6. Take the residual solid and lyophilize until completely dried to yield 6.2 g of brown solid.

Protocol H:

Take Reactant 1 in a screw-capped vial and add water/DMF in a 10:1 ratio. Add Reactant 2 to the mixture and sonicate for 10 minutes until all reactants dissolve completely. Transfer the clear solution to a Teflon-coated steel reactor, and heat the reaction mixture at 120 °C for 18 hours. After cooling the reaction mixture to room temperature, centrifuge to separate the solid product, discarding the supernatant. Disperse the obtained solid in water and centrifuge again, repeating this process twice more with water and twice more with ethanol to ensure thorough washing. Finally, dry the solid in an oven at 100 °C for 6 hours.

Characterization methods:

The Zeta potential of the MOFs was measured using Electrophoretic Light Scattering (ELS) in the Malvern Panalytical Zetasizer Pro/Red. In brief, 8-10 mg of a MOF sample was added to 10 mL of deionized water to provide a sample containing from 0.001% to 0.1% w/v MOF. Each MOF was tested in triplicate.

The metal content the MOFs was determined by Inductively Coupled Plasma Mass spectrometry (ICP-MS) following treatment of the MOF with H₂SO₄/HNO₃.

FESEM images of Compound IDs 17, 23, 25 and 20 were performed using a Sigma 300 SEM instrument. A dispersion of the MOFs was deposited and dried on a silica substrate supported by carbon adhesive tape, and examination was carried out at an acceleration voltage of 2-5 kV.

The average particle size of Compound IDs 17, 23, 25 and 20 in liquid suspensions were determined using dynamic light scattering with a Brookhaven Omni particle sizer. In brief, 50 mg of a MOF was dispersed into water, and then placed in a cell where a laser beam scatters off the particles, and the detector analyzes the scattered light intensity fluctuations.

Compound IDs 17, 23, 25 and 20 were also analyzed by thermogravimetric analysis (TGA) was performed using a NETZSCH TG 209 F3 instrument (Germany) over a temperature range of 25 °C to 800 °C under a nitrogen atmosphere. 50-70 mg of a MOF was loaded into the reactor chamber. The mass loss of the sample was recorded continuously as the temperature increased at a controlled rate of 15 °C per minute.

Compound IDs 17, 23, 25 and 20 were also analyzed by Fourier-Transform Infrared spectroscopy (FT-IR). In brief, FT-IR spectra were obtained using a PerkinElmer Spectrum 3 instrument, scanning over the range of 4000 to 600 cm⁻¹. Samples were prepared by the potassium bromide (KBr) pellet method, in which approximately 5-10 mg of the sample was mixed with 150-200 mg of KBr and compressed into a pellet under a pressure of 15 tons. The spectra were collected at a resolution of 4 cm⁻¹, with an average of 16 scans to enhance the signal-to-noise ratio. Baseline correction and normalization were applied to ensure accurate peak identification.

The BET surface areas of Compound IDs 13, 17, 20, 23, and 25 were determined. In brief, the BET surface area was determined using the BET equation on the linear zone of a BET plot generated using a Quantachrome, Autosorb iQ Station 2. Nitrogen adsorption was assessed at liquid nitrogen temperature (77 K) (see Determination of the specific surface area of solids by gas adsorption - BET method. 2022, ISO 9277:2022(en)). The total pore volume and mode average pore width of Compound IDs 13, 17, 20, 23, and 25 were determined from pore size distribution plots (surface area vs. pore size) generated for each MOF from N₂

adsorption isotherms at 77 K on silica with cylindrical pores, using the 2D nonlocal density functional theory (2D-NLDFT) (Ravikovitch, P. I., & Neimark, A. V. (2002). "Density functional theory model of adsorption on amorphous and microporous silica materials." *Langmuir*, 18(17), 1550-1560).

Example 1 - Optimization of phosphate adsorption/binding conditions:

To evaluate the phosphate binding capacity of MOFs under gut-mimicked conditions, a synthetic electrolyte solution containing 40 mg/dL of monosodium phosphate (NaH_2PO_4) with Phosphate content of 24 mg/L was prepared. 50 mg of MOF was added to three separate 50 mL samples of this solution. The pH of the samples was adjusted to 7.5, 4.5, and 2.1, respectively, and the solutions were placed on a shaker set to 150 rpm and maintained at a temperature of 37 °C for 4 h (refer to Table 4). Phosphate content in the solution was measured at regular intervals, specifically at 2 h and 4 h, using the Vitros 3500 instrument. The results indicated that phosphate adsorption was higher at lower pH levels (4.5 and 2.1) compared to the neutral pH condition. Additionally, we screened zirconium and iron-based MOFs with various combinations of organic linkers such as succinic acid, adipic acid, acetyl, aspartic acid, pyridyl, and cyclohexyl moieties at all three pH conditions. It was found that zirconium and iron-based MOFs exhibited significantly higher phosphate binding capacity compared to sucroferric oxyhydroxide. This suggests that these MOFs could be highly effective in removing excess phosphates from the gut, providing a promising new approach for managing hyperphosphatemia in CKD patients. Further exploration and in-depth studies under varied conditions are warranted. The binding capacity was calculated using the equation below (1):

$$\text{Binding capacity (mg of phosphate adsorbed by per gram of MOF)} = \frac{[(\text{Pre phosphate concentration (mmol/L)} - \text{Post phosphate concentration (mmol/L)}) \times \text{mwt of phosphate (PO}_4\text{)} \times \text{Volume of the fluid (L)}]}{\text{Amount of MOF (gm)}} \quad (1)$$

Table 4: Summary of adsorption profile of various phosphate binders at various pH conditions (Input phosphate: 236 mg/g).

Compound ID	Compound Description	Phosphate adsorbed mg per gram of MOF		
		pH = 7.5	pH = 4.5	pH = 2.1
1	Selevemar carbonate	-	65	-
2	Sucroferric oxyhydroxide 50 mg	43.9	72.85	69.8
3	Sucroferric oxyhydroxide 160 mg	117.9	156.6	190.1

4	Zr-Fu MOF	156.7	118.6	119.6
5	Fe ^(III) -BTC MOF	190.7	70.2	78.2
6	Fe ^(III) -NH ₂ -BDC MOF	84.5	112.5	124.3
7	Fe ^(III) -Fu MOF	237.0	165.6	69.4
8	Fe ^(III) -Fu BDC MOF	217.1	155.5	171.4
9	Fe ^(III) -BDC MOF	177.4	68.7	57.1
10	Fe ^(III) /Zr-Fu MOF	186.7	108.2	116.0
11	Zr-BDC MOF	85.0	103.9	137.8
12	Zr-NH ₂ -BDC MOF	77.7	77.0	106.3
13	Fe ^(III) -Fu/BDC MOF	236.9	226.3	192.6
14	Zr-Fu/BDC MOF	136.2	118.2	163.0
15	Fe ^(III) -Cys/BDC MOF	117.7	108.3	127.5
16	Zr-Adipic acid MOF	108.4	102.5	184.3
17	Zr-Asp MOF	209.1	206.7	224.1
18	Zr-Succ MOF	133.6	52.0	223.5
19	Zr-adipic acid MOF	3.0	205.7	212.2
20	Zr- <i>N</i> -acetyl Asp MOF	140.1	175.1	219.2
21	Fe ^(III) -succ MOF	160.1	64.7	242.1
22	Zr-Pyridyl diCOOH MOF	104.0	180.7	81.7
23	Fe ^(III) -Asp MOF	108.0	192.8	224.7
24	Zr-Cyclohexyl diCOOH MOF	201.6	132.7	216.3
25	Fe ^(III) - <i>N</i> -acetyl Asp MOF	219.0	219.0	213.0

In the invention (CN109970989B), MOF is used as an insoluble polymer substrate and improved binding of the phosphate is achieved by derivatizing the MOF with quaternary ammonium group. Presence of the positive ammonium group imparts positive charge, increasing positive zeta potential and help to bind phosphate strongly by electrostatic attraction.

Due to their strong cationic nature, cationic MOFs may non-selectively bind to other negatively charged ions in the gastrointestinal tract, such as chloride (Cl⁻). This could reduce their phosphate-binding efficiency and potentially lead to electrolyte imbalances in the body, which is particularly dangerous for patients with CKD who already suffer from electrolyte regulation issues.

Cationic surfaces can sometimes also act as immune stimulants, triggering local inflammation or immune responses in the gastrointestinal tract. The positively charged surface may interact

with cell membranes or proteins in the gut, leading to irritation, inflammation, or unwanted immune reactions. Due to potential toxicity and immune system interactions, long-term use of cationic MOFs could present significant risks, including inflammation, organ damage, or systemic toxicity from the release of metal ions or degradation of the MOF structure. This poses concerns, especially for patients with chronic conditions like CKD who may require long-term phosphate management.

If the cationic MOF degrades in the acidic stomach environment or in the neutral-to-alkaline environment of the small intestine, it could release quaternary ammonium chloride or other degradation products that might be harmful. Quaternary ammonium salts are known to have adverse effects if absorbed in large amounts.

The acidic environment of the stomach (pH ~1.5-3) could cause early degradation of the MOF structure, reducing its effectiveness as a phosphate binder. If the MOF degrades too quickly, it will not reach the small intestine (where most phosphate absorption occurs) in an intact form, leading to poor phosphate-binding performance.

The release of chloride ions from quaternary ammonium chloride (2, 3-epoxypropyltrialkyl ammonium chloride, 2-hydroxypropyl trimethyl ammonium chloride, 1, 2-epoxypropyldimethyldodecyl ammonium chloride or 3-chloro-2-hydroxypropyl dodecyl dimethyl ammonium chloride) might lead to hyperchloremia (elevated chloride levels in the blood), which can contribute to acid-base imbalances or acidosis in sensitive patients.

In order to overcome above limitations, in the present invention the MOF's are prepared using metals like iron (Fe), zirconium (Zr) and ligands like aspartic acid and *N*-substituted aspartic acid derivatives. Such MOFs have pore widths (e.g. 6-50 nm) that enable them to bind phosphate and hence a cationic charge is not required. However, high positive zeta potential created under acidic condition (simulated gut) due to protonation of the basic group in ligand also helps to bind the phosphate by strong electrostatic attraction. Hence, phosphate binding due to dual driving force (pore size and positive zeta potential) enables the MOF in current invention to have pH independent performance. Compound ID 23 which has free amine in ligand but small pores of size of 6 nm has pH dependent phosphate binding. At lower pH, high positive zeta potential (+30 mV) due to protonation of amine group facilitate higher binding compared to binding at higher pH (-27 mV). At high pH, binding of phosphate is facilitated by presence of pore size of suitable width (6 nm) although repulsion due to negative charge may result in lower absorption leading to pH dependent absorption. Compound ID 17, which also has free amine group has high positive zeta potential at pH 2 (+40 meV) and low negative zeta potential at high pH (-32 mV). However, presence of wider pore (29 nm) facilitate better higher binding at high pH making it pH independent phosphate binding. The same explanation

stays for pH independent binding behavior of Compound ID 25. Compound ID 12 has small pore width (1.1 nm) and less basic group (aromatic amine). Hence in acidic condition, it cannot develop high positive zeta potential (+5.5 mV) and resulting in low phosphate binding at any pH (see Table 5).

Table 5: Zeta Potential and BET analysis of MOFs.

	Compound ID 12	Compound ID 17	Compound ID 25	Compound ID 23
	Zr-NH₂-BDC MOF	Zr-Asp MOF	Fe-N-acetyl Asp MOF	Fe-Asp MOF
Pore volume (cm ³ /g)	0.281	0.519	0.707	0.59
BET Surface area (m ² /g)	305	103	95.99	230
Pore width (Mode) (nm)	1.144	29.13	50.7	6.079
Zeta (pH = 2) (mV)	5.5	40.197	28.3	30
Zeta (pH = 8) (mV)	-21	-32	-30	-27

Example 2 - Metal leaching on simulated empty stomach in the presence and absence of phosphate:

Leaching of metal (Fe and Zr) under simulated empty stomach (fasted situation) in presence and absence of phosphate was measured using procedure described below.

General Test Protocol:

Absence of phosphate: 200 mg of MOF or 250 mg of sucroferric oxyhydroxide (Compound ID 2) was added to 10 ml of simulated gastric (pH = 1.2) and mixture was incubated at 37 °C for 1 hour. The mixture was centrifuged and the fluid was decanted. The fluid was filtered through 0.2 µm filter and sample was analysed by ICP-MS and percentage of iron leaked compared to the iron in the MOF was calculated.

Presence of phosphate: 200 mg of MOF or 250 mg of sucroferric oxyhydroxide (Compound ID 2) was added to 10 ml of phosphate buffer with 0.36 mmol of phosphate (P) (pH = 1.2) and mixture was incubated at 37 °C for 1 hour. The mixture was centrifuged and fluid was decanted. The fluid was filtered through 0.2 µm filter and sample was analysed by ICP-MS and

percentage of Iron leaked compared to the iron in the MOF was calculated.

Preparation of simulated gastric juice: add 2 g of NaCl in 100 mL of water followed by adding 80 mL of 1 M HCl to make up the volume to 1000 mL. 10 mL of this fluid was used for the above experiment.

Results:

Compound ID 23 and Compound ID 25 showed 24% and 34.5% (w/w) iron leaching relative to the total mass of iron in the MOF vs 47.7% (w/w) of iron leached by sucroferric oxyhydroxide relative to the total mass of iron in the sucroferric oxyhydroxide, under similar conditions.

Fig 4: The graph shows the comparison of iron release between sucroferric oxyhydroxide (Compound ID 2) and MOFs Compound ID 23 and 25 on a simulated empty stomach

Fig 5: The graph shows the zirconium release of Compound ID 17-P (Zr-Asp MOF in a gastric solution with phosphate) and Compound ID 17-NP (Zr-Asp MOF in gastric solution without phosphate) on a simulated empty stomach.

The metal content of Compound IDs 17, 23 and 25 were determined by ICP-MS as follows (the % (w/w) of the metal is relative to the total MOF mass):

- Compound ID 17: 24.8% zirconium (w/w);
- Compound ID 23: 28.9% iron (w/w);
- Compound ID 25: 32.2% iron (w/w).

Example 3 – Cytotoxicity of the MOFs:

The biocompatibility of Compound IDs 2, 17, 23, and 25 was tested *in vitro* using Caco-2 cells.

Protocol used:

To prepare a 20 mg/mL test compound stock solution, 2 mg of a test compound was added into 100 μ L of DMSO and sonicated for 10 minutes. For a 10 mg/mL test compound stock solution, 30 μ L of the 20 mg/mL test compound stock solution was added into 30 μ L of DMSO and sonicated for 10 minutes. To create a 5 mg/mL test compound stock solution, 30 μ L of the 10 mg/mL test compound stock solution was added into 30 μ L of DMSO and sonicated for 10 minutes. For a 2.5 mg/mL test compound stock solution, 30 μ L of the 5 mg/mL test compound stock solution was added into 30 μ L of DMSO and sonicated for 10 minutes. Finally, to prepare a 1.0 mg/mL test compound stock solution, 10 μ L of the 2.5 mg/mL test compound stock solution was added into 25 μ L of DMSO and sonicated for 10 minutes. A negative control sample (NC_DMSO) was prepared by adding 10 μ L DMSO into 1 mL Dulbecco's

Modified Eagle Medium (DMEM), followed by sonication for 10 minutes.

DMEM, high glucose, pyruvate (DMEM) containing 1% Non-Essential Amino Acids (NEAA) and 1% Penicillin/Streptomycin (PS) was used as working medium and working solution was prepared by adding 10 µL a test compound stock solution into 1 mL DMEM followed by sonication for 10 minutes to prepare a working solution containing 0.2 mg/mL, 0.1 mg/mL, 0.05 mg/mL, 0.025 mg/mL, or 0.01 mg/mL of the compound being tested.

Caco-2 cells were incubated at 37±1°C, 5% CO₂ and saturated humidity. After reaching 80-90% confluency, the cells were gently detached with trypsin-EDTA solution. Cells were seeded in 100 µL on the 96-well insert system at the density of 3 ×10⁵ cells/mL and cultured in DMEM, high glucose, pyruvate (DMEM) containing 10% fetal bovine serum at 37 °C with 5% CO₂ for 4 h.

When the cell plate reach 70-80% confluence per well, the medium in each well was discarded and each well washed twice with Dulbecco's Phosphate Buffered Saline (DPBS). 100 µL of the working solution or negative control was added to each well, followed by incubating the 96-well insert system at 37 ° C with 5% CO₂ for 48 h.

Cytotoxicity Assay (CytoTox-Glo™ Cytotoxicity Assay – Promega): 60 µL of a AAF-Glo substrate working solution was added to wells containing the working solution (100 µL) and 100 µL of cell suspension (Caco-2 cells). This was mixed well and incubated at room temperature for 15 minutes. 120 µL of liquid from each well was transferred to a well of a white microplate and the Relative Light Unit (RLU) of dead cells was measured.

The remaining liquid was returned to the cell plate. 60 µL of cell lysis solution was added to each well, mixed, and incubated at room temperature for 15 minutes. The plates were agitated and 170 µL of the cell lysate from each well transferred to a white microplate to measure the RLU of total cells.

The relative survival rate of the cells was determined using equations (2) and (3).

$$RLU\ of\ survival\ cells = RLU\ of\ total\ cells - RLU\ of\ dead\ cells \quad (2)$$

$$Relative\ cell\ survival\ rate\ (\%) = RLU\ of\ viable\ cells\ in\ test\ article\ group / RLU\ of\ viable\ cells\ in\ vehicle\ control\ group \times 100 \quad (3)$$

Results:

The survival rates of Caco-2 cells treated with Compound ID 17, 23, or 25 are shown in Table 6 below.

Table 6: Results for RLU and Relative cell survival rate with succroferic oxyhydroxide (Compound ID 2), Zr-Asp MOF (Compound ID 17), and Fe-Asp MOF Compound ID 23).

Analyte	Test Conc. (mg/mL)	RLU of survival cells		Relative cell survival rate (%) (% of VC)	
		Mean (n=3)	RSD of Area Ratio	Mean (n=3)	RSD of Area Ratio
Compound ID 17	0.001	13757767	0.02	99.92	0.02
	0.025	13225000	0.03	96.05	0.03
	0.05	12998833	0.02	94.41	0.02
	0.1	12946300	0.02	94.03	0.02
	0.2	12777800	0.02	92.80	0.02
Compound ID 23	0.001	14911333	0.02	108.30	0.02
	0.025	14939500	0.03	108.50	0.03
	0.05	14929533	0.03	108.43	0.03
	0.1	14628333	0.02	106.24	0.02
	0.2	13802133	0.02	100.24	0.02
Compound ID 2	0.001	15395000	0.03	111.81	0.03
	0.025	15117333	0.02	109.79	0.02
	0.05	15228867	0.05	110.60	0.05
	0.1	14463700	0.04	105.05	0.04
	0.2	14538833	0.02	105.59	0.02
NC_DMSO	NA	13768833	0.03	100.00	0.03

Compared with the blank control group (NC_DMSO), the cell activity of Compound ID 17, Compound ID 23 and succroferic oxyhydroxide was not significantly decreased after incubation with Caco-2 cells at concentrations of 0.001, 0.025, 0.05, 0.1, and 0.2 mg/mL, indicating that Compound ID 17, Compound ID 23 and succroferic oxyhydroxide had no cytotoxicity to Caco-2 cells within the above concentration range.

Example 4 - Animal Study:

The study was conducted on a 5/6 nephrectomized male pig (*Sus scrofa*). The pig was removed from dialysis and maintained on a normal diet. A baseline study was carried out for the first 14 days, during which empty capsules (2 capsules per feed, twice a day) were administered to acclimatize the animal. Blood samples were drawn at regular intervals for analysis.

After the initial 14 days, the pig was given a phosphate binder (Compound ID 17 or 23) at a dosage of 1.5 g per day along with feed (each capsule containing 375 mg of Compound ID 17 or 23; 2 capsules per feed, twice a day) for another 14 days. Blood samples continued to be collected regularly for analysis.

The primary objective of the study was to monitor the pig's inflammatory response by measuring serum C-reactive protein (CRP), white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and platelet count as potential indicators of the compound's effect on systemic inflammation. Blood samples were taken at regular intervals to assess these inflammatory markers by immunoassay (Table 7).

Table 7: Inflammatory marker results during the base line and MOF administration periods.

Inflammatory marker	Base line*	Compound ID 17	Compound ID 23
WBC min-max ($10^9/L$)	10.5 - 13.2	10.7 - 12.9	9.67 - 11.2
CRP min- max(mg/L)	0.4 - 0.7	0.4 - 0.6	0.3 - 0.5
ESR min- max (mm/hr)	3.0 - 4.0	3.0 - 8.0	3 - 13
Platelet Count min- max ($10^9/L$)	296 - 370	305 - 398	283 - 407

*no supplementation of pig feed.

As shown in Table 7, the inflammatory markers WBC, CRP, ESR and platelet count remained within the normal range for the pigs following administration of a MOF. This result indicates that the MOFs tested caused no significant inflammatory response or adverse immune reaction in the pigs.

Example 5 - Characterization of MOFs:

FESEM images of Compound IDs 17, 23, 25, 20 and 13 are shown in FIGs 6-9, the particle size distributions for Compound IDs 17, 23, 25, 20 and 13 are shown in FIGs 10-14, the TG residue profile and DTG decomposition profiles for Compound IDs 17, 23, 25, 20 and 13 are shown in FIGs 15-19, the BET surface area analyses for Compound IDs 17, 23, 25, 20 and 13 are shown in FIGs 20-24, and the FT-IR spectra for Compound IDs 17, 23, 25, 20 and 13 are shown in FIGs 25-29.

The surface area, pore volume and pore size of Compound IDs 13, 17, 20, 23, and 25 were characterized (Table 8).

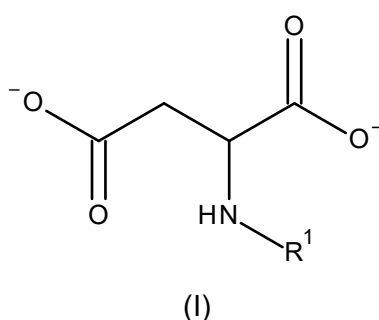
Table 8: Total pore volume, pore width, and BET surface area for the MOFs (Compound ID: 17, 23, 20, 25 and 13).

	Pore volume	Pore width (mode)	BET surface area
Compound ID 17	0.519 cm ³ /g	29.316 nm	103.481 m ² /g
Compound ID 23	0.590 cm ³ /g	6.079 nm	230.169 m ² /g
Compound ID 20	0.408 cm ³ /g	29.396 nm	85.175 m ² /g
Compound ID 25	0.707 cm ³ /g	50.727 nm	95.991 m ² /g
Compound ID 13	0.278 cm ³ /g	0.823 nm	264.186 m ² /g

As shown from the data present in Table 8, Compound ID 17 has a moderate surface area (103.5 m²/g) with mesopores (29.3 nm); Compound ID 20 has a high surface area (230.2 m²/g) with smaller mesopores (6.1 nm); Compound ID 25 has largest pore volume (0.707 cm³/g) with large mesopores (50.7 nm), and Compound 13 has the highest surface area (264.2 m²/g) with micropores (0.823 nm).

CLAIMS

1. Use of a metal-organic framework (MOF) in the manufacture of a medicament for the treatment or prevention of hyperphosphatemia,
wherein the MOF comprises a plurality of metal ions, each coordinated to a plurality of organic ligands, and
wherein the plurality of metal ions comprises Zr^{4+} ions, Fe^{3+} ions, or a combination of Zr^{4+} and Fe^{3+} ions, and
the plurality of organic ligands are selected from one or more members of the group consisting of a compound according to formula (I):



wherein,

R^1 is selected from the group consisting of H, $-\text{C}(\text{O})\text{C}_{1-6}\text{alkyl}$, and $-\text{S}(\text{O})(\text{O})-\text{R}^2$, wherein said $\text{C}_{1-6}\text{alkyl}$ is optionally substituted by 1, 2 or 3 halogens, and

R^2 is selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{5-10}\text{aryl}$, wherein said $\text{C}_{5-10}\text{aryl}$ is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, halogen, NH_2 , $\text{N}(\text{CH}_3)_2$, NO_2 , and OH ;

a $\text{C}_{2-6}\text{alkane}$ substituted by two carboxylate groups and optionally substituted by one or two OH groups; a $\text{C}_{4-6}\text{alkene}$ substituted by two carboxylate groups; a benzenedicarboxylate optionally substituted by one or two NH_2 groups; a benzenetricarboxylate; a 5-6 membered heteroaromatic ring comprising 1 or 2 atoms selected from the group consisting of N, S and O, wherein said heteroaromatic ring is substituted by two carboxylate groups; cyclohexane substituted by two carboxylate groups; and cystinate;

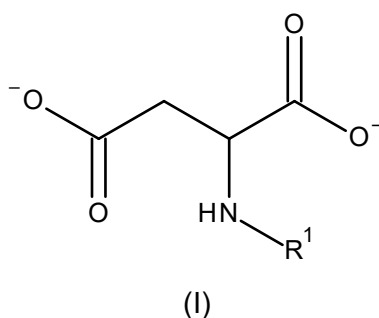
or a pharmaceutically acceptable salt or solvate thereof.

2. The use according to claim 1, wherein R^1 is selected from the group consisting of H and $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$.
3. The use according to claim 1 or 2, wherein the plurality of organic ligands are selected from one or more members of the group consisting of a compound according to formula

(l), fumarate, terephthalate, succinate, malate, adipate, 2-aminoterephthalate; trimesate, pyridinedicarboxylate, cyclohexanedicarboxylate, and cystinate.

4. The use according to any one of claims 1 to 3, wherein the plurality of organic ligands are selected from one or more members of the group consisting of aspartate, *N*-acetyl aspartate, terephthalate, and fumarate.
5. The use according to any one of claims 1 to 4, wherein the plurality of metal ions consists of Zr^{4+} , and the plurality of organic ligands are selected from one or more members of the group consisting of aspartate and *N*-acetyl aspartate.
6. The use according to claim 5, wherein the MOF has a molecular formula according to $[\text{Zr}_6\text{O}_4(\text{OH})_4(\text{aspartate})_6]$.
7. The use according to claim 5, wherein the MOF has a molecular formula according to $[\text{Zr}_6\text{O}_4(\text{OH})_4(\text{N-acetyl aspartate})_6]$.
8. The use according to claim 1, wherein the plurality of metal ions consists of Fe^{3+} ions, and the plurality of organic ligands are selected from one or more members of the group consisting of aspartate and *N*-acetyl aspartate.
9. The use according to claim 8, wherein the MOF has a structural formula according to $[\text{Fe}_3\text{O}(\text{N-acetyl aspartate})_3(\text{H}_2\text{O})_2(\text{X})]$, wherein X is a counterion selected from the group consisting of Cl^- , ^-OH , and NO_3^- (e.g. X may be Cl^-).
10. The use according to claim 8, wherein the MOF has a structural formula according to $[\text{Fe}_3\text{O}(\text{aspartate})_3(\text{H}_2\text{O})_2(\text{X})]$, wherein X is a counterion selected from the group consisting of Cl^- , ^-OH , and NO_3^- (e.g. X may be Cl^-).
11. The use according to claim 1, wherein the plurality of metal ions consists of Fe^{3+} ions, and the plurality of organic ligands are a combination of fumarate and terephthalate, optionally wherein the MOF is formed from Fe^{3+} ions and a mixture of fumarate and terephthalate, wherein the mixture of fumarate and terephthalate contains a molar ratio of fumarate to terephthalate of from about 2:1 to about 1:2.
12. The use according to any one of the preceding claims, wherein the medicament is to be administered orally.

13. The use according to any one of the preceding claims, wherein the medicament is to be administered in combination with one or more further oral adsorbents selected from the group consisting of a phosphate binding agent, an activated carbon adsorbent, and a potassium binding agent, for example wherein the medicament is to be administered in combination with one or more further phosphate binding agents selected from the group consisting of calcium carbonate, calcium acetate, sevelamer carbamate, sevelamer hydrochloride, lathanum carbonate, iron citrate, sucroferric oxyhydroxide, and tenapanor.
14. The use according to any one of the preceding claims, wherein the medicament is to be administered to a subject suffering from chronic kidney disease (CKD) or end-stage renal disease (ESRD), or a subject suffering from or at risk of developing a cardiovascular disease.
15. A metal-organic framework (MOF) comprising a plurality of metal ions, each coordinated to a plurality of organic ligands,
 wherein the plurality of metal ions comprises Zr^{4+} ions, Fe^{3+} ions, or a combination of Zr^{4+} and Fe^{3+} ions, and
 the plurality of organic ligands are selected from one or more compounds according to formula (I):



wherein,

R^1 is selected from the group consisting of $-\text{C}(\text{O})\text{C}_{1-6}\text{alkyl}$ and $-\text{S}(\text{O})(\text{O})-\text{R}^2$, wherein said $\text{C}_{1-6}\text{alkyl}$ is optionally substituted by 1, 2 or 3 halogens; and

R^2 is selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{5-10}\text{aryl}$, wherein said $\text{C}_{5-10}\text{aryl}$ is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, halogen, NH_2 , $\text{N}(\text{CH}_3)_2$, NO_2 , and OH .

16. The MOF of claim 15, wherein R^1 is $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$.

17. The MOF of claim 15, wherein the compound of formula (I) is *N*-acetyl aspartate.
18. The MOF of claim 17, wherein the MOF has a structural formula according to $[\text{Zr}_6\text{O}_4(\text{OH})_4(\textit{N}\text{-acetyl aspartate})_6]$.
19. The MOF of claim 17, wherein the MOF has a structural formula according to $[\text{Fe}_3\text{O}(\textit{N}\text{-acetyl aspartate})_3(\text{H}_2\text{O})_2(\text{X})]$, wherein X is a counterion selected from the group consisting of Cl^- , ^-OH , and NO_3^- (e.g. X may be Cl^-).
20. A pharmaceutical composition comprising the MOF of any one of claims 15 to 19, and one or more pharmaceutically acceptable carriers or excipients.