baricitinib, CCX140, CTP140, GKT137831, VPI-2690B, GS-4997, PF-04634817, and Allopurinol.

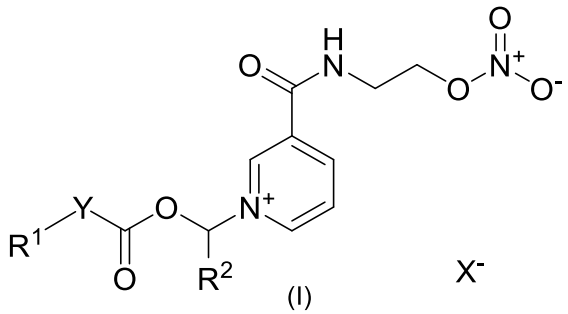
[0004] Nicorandil is a vasodilatory drug used to treat angina and acute heart failure. It is a nitrate and K+ATP channel agonist. In addition to treat angina, nicorandil may be useful to treat kidney diseases (Lee et al., J. Hypertension 2009, 27, 618-625; Iranirad et al., Cardiology Journal (online) 2017, DOI 10.5603/cj.a2017.0028; Ko et al., Yonsei Med J. 2013, 54(4), 957-964; Tamura et al., Am. J. Physiol Renal Physiol 2012, 303, 339-349; Nawa et al., Int. J. Cardiology 2015, 195, 228-234; Tanabe et al., Am. J. Physiol Renal Physiol 2012, 302, 151-160; and US20110257202).

SUMMARY

[0005] Described herein are pyridyl compounds and pharmaceutical compositions thereof. Also described herein are methods for treating diseases and conditions related to kidney using the compounds and pharmaceutical compositions.

[0006] Also described herein are uses of the pyridyl compounds and the pharmaceutical compositions in the treatment of kidney diseases or conditions. Further described are pharmaceutical compositions that include the pyridyl compounds. Specifically, described herein are conjugated nicorandil compounds capable of forming nicorandil in vivo and methods of use thereof to treat diseases and conditions related to kidney.

[0007] Thus, in some examples, the present disclosure provides methods for preventing, treating or ameliorating in a mammal a disease or condition that is related to the kidney or kidney function, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to Formula (I) having the structure:



(I)

or a pharmaceutical composition thereof;

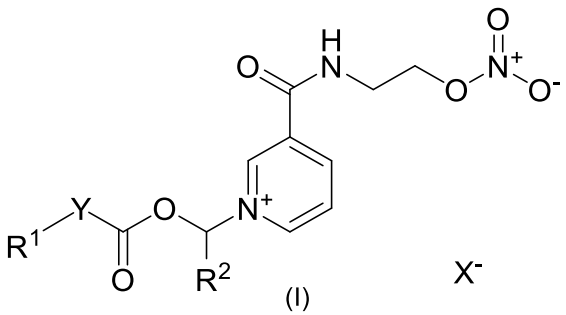
wherein X^- is a counter ion; Y is–$C(H)_2$-, -O-, or –$N(R^3)$-;

R^1 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_7-cycloalkyl, or substituted or unsubstituted 4-7 membered heterocycloalkyl;

R^2 is H or C_1-C_4 alkyl; and

R^3 is H or substituted or unsubstituted C_1-C_4 alkyl; or R^1 and R^3 are joined together to form a 4-7 membered substituted or unsubstituted heterocycloalkyl.

[0008] In some examples, the present disclosure provides use of a compound according to Formula (I) having the structure:



(I)

in a treatment of a disease or a condition related to kidney;

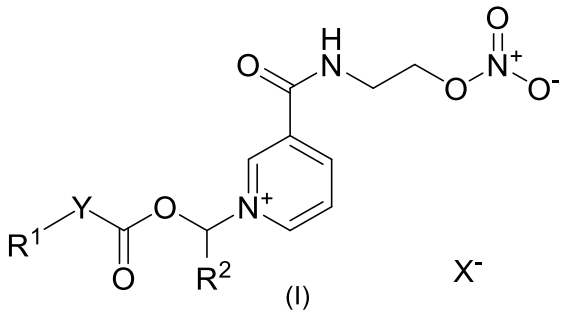
wherein X^- is a counter ion; Y is–$C(H)_2$-, -O-, or –$N(R^3)$-;

R^1 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_7-cycloalkyl, or substituted or unsubstituted 4-7 membered heterocycloalkyl;

R^2 is H or C_1-C_4 alkyl; and

R^3 is H or substituted or unsubstituted C_1-C_4 alkyl; or R^1 and R^3 are joined together to form a 4-7 membered substituted or unsubstituted heterocycloalkyl.

[0008a] In one aspect, the present disclosure provides use of a compound according to formula (I):



(I)

in the manufacture of a medicament for the treatment of a disease or a condition related to kidney;

wherein X^- is a counter ion; Y is–$C(H)_2$-, -O-, or –$N(R^3)$-;

R^1 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_7-cycloalkyl, or substituted or unsubstituted 4-7 membered heterocycloalkyl;

R^2 is H or C_1-C_4 alkyl; and

R^3 is H or substituted or unsubstituted C_1-C_4 alkyl; or R^1 and R^3 are joined together to form a 4-7 membered substituted or unsubstituted heterocycloalkyl.

[0009] In some examples, Y is–$C(H)_2$-. In some examples, Y is -O-. In some examples, Y is–$N(R^3)$-. In particular examples, Y is–N(H)-.

[0010] In some examples, R^2 is H, Me, Et, or i-Pr. In a particular example, R^2 is H.

[0011] In some examples, R^1 is ethyl substituted with cyclohexyl.

[0012] In some examples, R^1 is 2-cyclohexyl-ethyl.

[0013] In some examples, the disease or condition is Chronic Kidney Disease, Diabetic Nephropathy, IgA Nephropathy, Acute Kidney Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome.

[0014] In a particular example, the disease or condition is Contrast Induced Nephropathy.

[0015] In a particular example, the disease or condition is Tenofovir induced AKI.

[0016] In a particular example, the disease or condition is Aminoglycosides induced AKI.

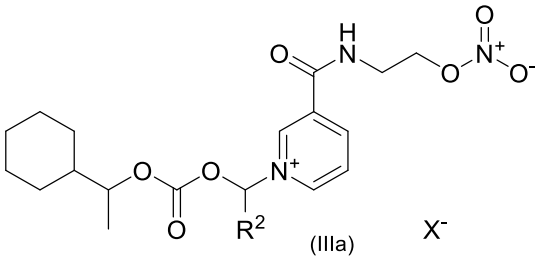
[0017] In a particular example, the disease or condition is AKI after surgery.

[0018] In a particular example, the disease or condition is AKI in patients with Dialysis.

[0019] In a particular example, the disease or condition is Diabetic Nephropathy.

[0020] In a more particular example, the disease or condition is chronic kidney disease or CKD.

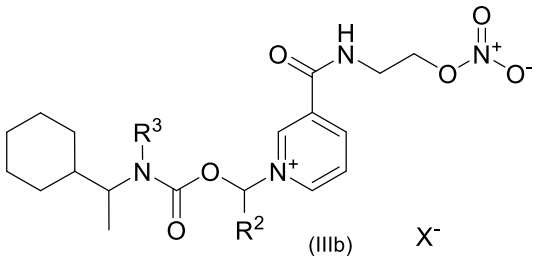
[0021] In some examples, the compound is:



(IIIa)

wherein X^-, and R^2 are as described for formula (I) herein.

[0022] In some examples, the compound is:



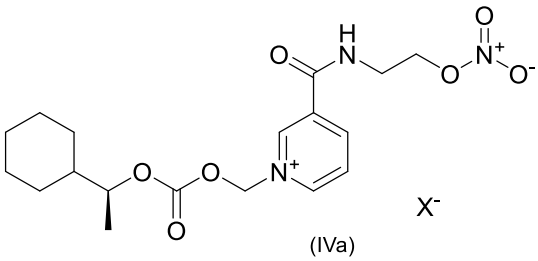
(IIIb)

wherein X^-, and R^2 are as described for formula (I) herein.

[0023] In some examples, with respect to formula (IIIa) or (IIIb), R^2 is H or Me. In some examples, R^3 is H, Me, Et, or i-Pr. In particular examples, each R^2 and R^3 is H.

[0024] In some examples, with respect to formula (IIIa) or (IIIb), the compound is an R- isomer. In some examples, with respect to formula (IIIa) or (IIIb), the compound is an S- isomer.

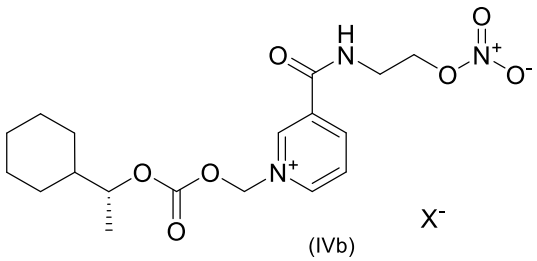
[0025] In some examples, the compound is:



(IVa)

wherein X^- is as described for formula (I) herein.

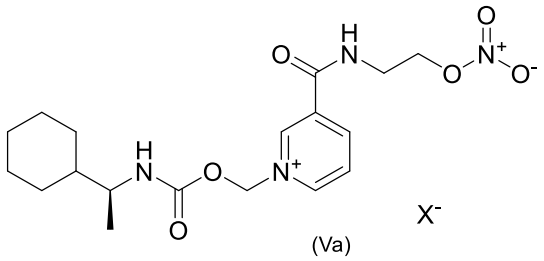
[0026] In some examples, the compound is:



(IVb)

wherein X^- is as described for formula (I) herein.

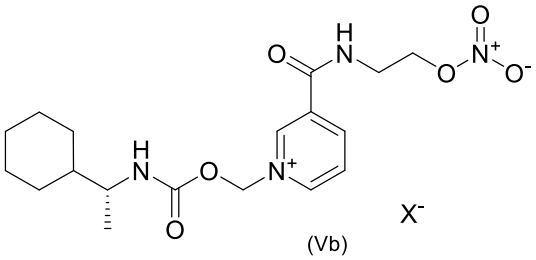
[0027] In some examples, the compound is:



(Va)

wherein X^- is as described for formula (I) herein.

[0028] In some examples, the compound is:



(Vb)

wherein X^- is as described for formula (I) herein.

[0029] In some examples, X^- is Cl^-. In another example, X^- is Br^-. In another example, X^- is I^-. In another example, X^- is F^-. In another example, X^- is $MeSO_2O^-$.

[0030] In some examples, the present disclosure provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition comprising the compound of formula (I) is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration. In some examples, the present disclosure provides methods for treating a disease or condition comprising administering to a patient in need a therapeutically effective amount of a compound of formula (I). In some examples the disease is selected from Chronic Kidney Disease (CKD), Diabetic Nephropathy, IgA Nephropathy, Acute Kidney Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI

post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome. In some examples, the present disclosure provides a method for treating a CKD disease or condition comprising administering to a patient in need a therapeutically effective amount of a compound of formula (I). In some examples, the disease is diabetic nephropathy. In some examples, the disease or condition is acute kidney failure (AKI).

[0031] In some examples the disease or condition is acute kidney failure and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome.

[0032] In some examples, the present disclosure provides a method for treating Chronic Kidney Disease, Diabetic Nephropathy, IgA Nephropathy, Acute Kidney Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome comprising administering to a patient in need a therapeutically effective amount of a compound of Formula (I).

[0033] It is understood that one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those set forth herein.

[0034] In some examples, the present disclosure provides pharmaceutical compositions, which include a therapeutically effective amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate. In certain examples, compositions provided herein further include a pharmaceutically acceptable diluent, excipient and/or binder.

[0035] Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically effective derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of diseases, disorders or conditions that are kidney related, are provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases, disorders or conditions disclosed herein.

[0036] In certain examples, provided herein is a pharmaceutical composition containing: i) a physiologically acceptable carrier, diluent, and/or excipient; and ii) one or more compounds provided herein.

[0037] In some examples, provided herein are methods for treating a patient of treating a disease,

disorder, or condition, which related to kidney, in a patient, which includes administering to the patient a therapeutically effective amount of at least one of any of the compounds herein, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate.

[0038] In some examples, compounds provided herein are administered to a human.

[0039] In some examples, compounds provided herein are orally administered.

[0040] In some examples, compounds provided herein are used for the formulation of a medicament for treating a disease, disorder, or condition, which is related to kidney. In some examples, compounds provided herein are used for the formulation of a medicament for kidney disease or condition.

[0041] Articles of manufacture including packaging material, a compound or composition or pharmaceutically acceptable derivative thereof provided herein, which is effective for treating the kidney disease or condition, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for treating the kidney disease or condition, are provided.

[0042] In some examples, provided herein is a method for treating the kidney disease or condition in a subject in need thereof by administering to the subject thereof a composition containing a therapeutically effective amount of at least one compound having the structure of formula (I). In some examples, the subject in need is suffering from Chronic Kidney Disease, Diabetic Nephropathy, IgA Nephropathy, Acute Kidney Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome.

[0043] In some examples, the subject in need is suffering from a kidney condition or disease, e.g., Chronic Kidney Disease, Diabetic Nephropathy, IgA Nephropathy, Acute Kidney Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome.

[0044] In some examples, provided herein is a method for treating the kidney disease or condition by administering to a subject in need thereof a composition containing a therapeutically effective amount of at least one compound having the structure of Formula (I)-(Vb). In some examples, kidney disease or condition is Chronic Kidney Disease, Diabetic Nephropathy, IgA Nephropathy, Acute Kidney

Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome.

[0045] In any of the aforementioned examples are some examples in which administration is enteral, parenteral, or both, and wherein (a) an effective amount of a provided compound is systemically administered to the mammal; (b) an effective amount of a provided compound is administered orally to the mammal; (c) an effective amount of a provided compound is intravenously administered to the mammal; (d) an effective amount of a provided compound is administered by inhalation; (e) an effective amount of a provided compound is administered by nasal administration; or (f) an effective amount of a provided compound is administered by injection to the mammal; (g) an effective amount of a provided compound is administered topically (dermal) to the mammal; (h) an effective amount of a provided compound is administered by ophthalmic administration; or (i) an effective amount of a provided compound is administered rectally to the mammal.

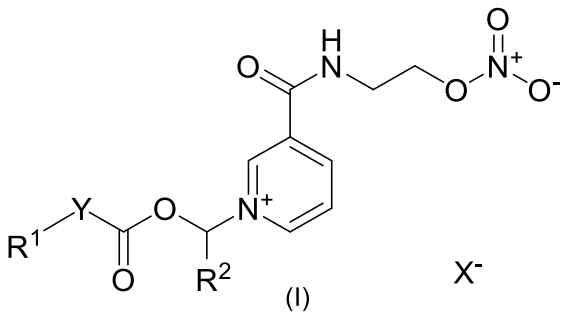
[0046] In any of the aforementioned examples are some examples comprising single administrations of an effective amount of a provided compound including some examples in which (i) a provided compound is administered once; (ii) a provided compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0047] In any of the aforementioned examples are some examples comprising multiple administrations of an effective amount of a provided compound, including some examples in which (i) a provided compound is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) a provided compound is administered to the mammal every 8 hours. In some examples, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[0048] Other objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments or examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present disclosure will become apparent to those skilled in the art from this detailed description. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

WHAT IS CLAIMED IS:

1. Use of a compound according to formula (I):



(I)

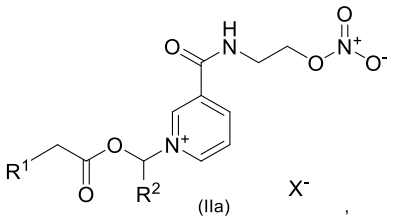
in the manufacture of a medicament for the treatment of a disease or a condition related to kidney; wherein X^- is a counter ion; Y is–$C(H)_2$-, -O-, or –$N(R^3)$-;

R^1 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_7-cycloalkyl, or substituted or unsubstituted 4-7 membered heterocycloalkyl;

R^2 is H or C_1-C_4 alkyl; and

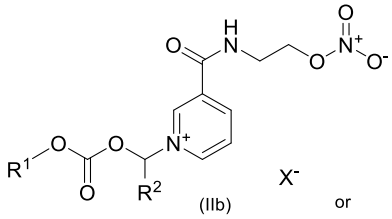
R^3 is H or substituted or unsubstituted C_1-C_4 alkyl; or R^1 and R^3 are joined together to form a 4-7 membered substituted or unsubstituted heterocycloalkyl.

2. The use of claim 1, wherein R^2 is H, Me, Et, or i-Pr.
3. The use of claim 1, wherein R^2 is H.
4. The use according to any one of claims 1-3, wherein Y is–$C(H)_2$-.
5. The use according to any one of claims 1-3, wherein Y is-O-.
6. The use according to any one of claims 1-3, wherein Y is–$N(R^3)$-.
7. The use according to any one of claims 1-6, wherein the compound is according to formula (IIa), (IIb), or (IIc):



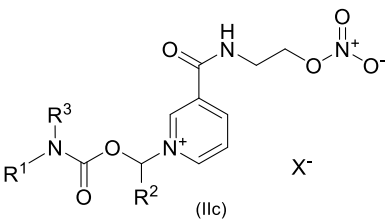
(IIa)

,



(IIb)

or



(IIc)

wherein

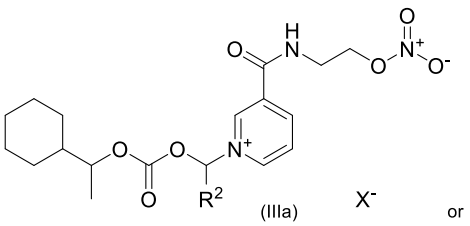
X^- is a counter ion; R^1 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_7-cycloalkyl, or substituted or unsubstituted 4-7 membered heterocycloalkyl;

R^2 is H or C_1-C_4 alkyl; and

R^3 is H or substituted or unsubstituted C_1-C_4 alkyl; or R^1 and R^3 are joined together to form a 4-7 membered substituted or unsubstituted heterocycloalkyl.

8. The use according to any one of claims 1-7, wherein R^1 is substituted or unsubstituted C_1-C_4 alkyl.

9. The use according to any one of claims 1-7, wherein R^1 is C_1-C_4 alkyl, unsubstituted or substituted with C_3-C_7 cycloalkyl.
10. The use according to any one of claims 1-7, wherein R^1 is Me, Et, i-Pr, n-Pr, n-Bu, i-Bu, sec-Bu, or t-Bu.
11. The use according to any one of claims 1-7, wherein R^1 is Me or Et substituted with cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
12. The use according to any one of claims 1-7, wherein R^1 is C_3-C_7-cycloalkyl unsubstituted or substituted with Me or Et.
13. The use according to any one of claims 1-7, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
14. The use according to any one of claims 1-14, wherein R^3 is H or substituted or unsubstituted C_1-C_4 alkyl.
15. The use according to any one of claims 1-14, wherein R^3 is H.
16. The use according to any one of claims 1-14, wherein R^3 is Me, Et, i-Pr, n-Pr, n-Bu, i-Bu, sec-Bu, or t-Bu.
17. The use according to any one of claims 1-14, wherein R^1 and R^3 are joined together to form a 4-7 membered substituted or unsubstituted heterocycloalkyl.
18. The use according to any one of claims 1-14, wherein R^1 and R^3 are joined together to form pyrrolidinyl, piperidinyl, or morpholinyl.
19. The use according to any one of claims 1-18, wherein the compound is according to formula (IIIa), or (IIIb):

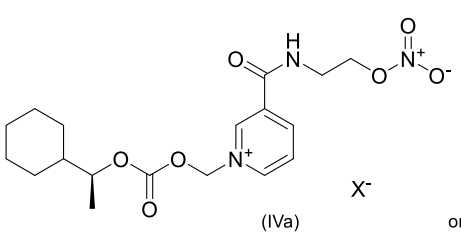


wherein

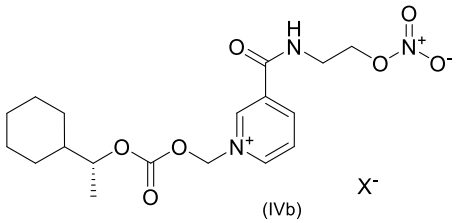
X^- is a counter ion; R^2 is H or C_1-C_4 alkyl; and

R^3 is H or substituted or unsubstituted C_1-C_4 alkyl.

20. The use according to claim 19, wherein R^3 is H, Me, Et, or i-Pr.
21. The use according to claim 19, wherein R^3 is H.
22. The use according to any one of claims 1-21, wherein R^2 is H or Me.
23. The use according to any one of claims 1-21, wherein the compound is according to formula (IIIb); and each R^2 and R^3 is H.
24. The use according to any one of claims 1-21, wherein the compound is according to formula (IVa), or (IVb):


(IVa)

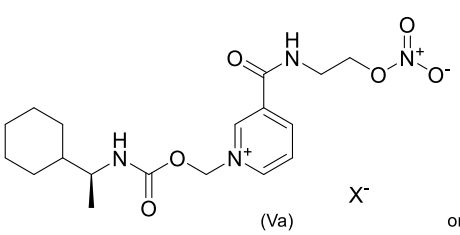
or


(IVb)

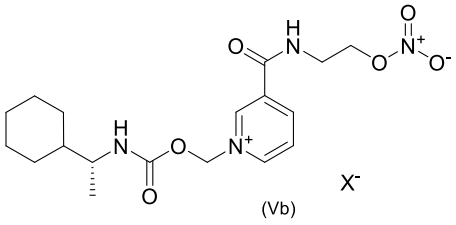
;

wherein X^- is a counter ion.

25. The use according to any one of claims 1-21, wherein the compound is according to formula (Va), or (Vb):


(Va)

or


(Vb)

wherein X^- is a counter ion.

26. The use according to any one of claims 1-25, wherein X^- is F^-, Cl^-, Br^-, I^-, or $MeSO_2O^-$.
27. The use according to any one of claims 1-25, wherein X^- is Cl^-, or I^-.
28. The use according to any one of claims 1-27, wherein the pharmaceutical composition comprises a pharmaceutically acceptable excipient.
29. The use of claim 28, wherein the pharmaceutical compostion is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration.
30. The use according to any one of claims 1-29, wherein the disease or condition is Chronic Kidney Disease, Diabetic Nephropathy, IgA Nephropathy, Acute Kidney Failure, Acute tubular necrosis, Transplant related Ischemia, Acute Kidney Disease and types of AKI such as Cisplatin induced AKI, Aminoglycosides induced AKI, Tenofovir induced AKI, Contrast Induced Nephropathy, AKI after surgery for partial nephrectomy, AKI post kidney transplant, AKI in patients with Dialysis, AKI after Cardiac surgery, AKI in patients inside ICU, AKI caused by Cirrhosis or Sepsis and AKI caused by hepatorenal syndrome.
31. The use according to any one of claims 1-29, wherein the disease or condition is Chronic Kidney Disease.
32. The use according to any one of claims 1-29, wherein the disease or condition is Acute Kidney Failure.
33. The use of any of claims 1-32, wherein the compound of formula (I) is to be administered orally.