METHODS OF TREATING ACUTE KIDNEY INJURY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/404,390, filed on October 5, 2016. The entire teachings of the aforementioned application are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is directed to methods of treating a human patient with acute kidney injury.

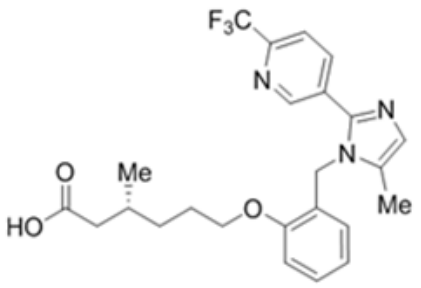
BACKGROUND OF THE INVENTION

Acute kidney injury (AKI), previously known as acute renal failure (ARF), is a clinical syndrome characterized by rapid deterioration of renal function that occurs within days. The principal feature of AKI is an abrupt decline in glomerular filtration rate (GFR), resulting in the retention of nitrogenous wastes (urea, creatinine). In the general world population, 170–200 cases of severe AKI per million population occur annually. To date, there is no specific treatment for established AKI. Several drugs have been found to prophylactically ameliorate toxic and ischemic experimental AKI, as manifested by lower serum creatinine levels, reduced histological damage and faster recovery of renal function in different animal models. These include anti-oxidants, calcium channel blockers, diuretics, vasoactive substances, growth factors, anti-inflammatory agents and more. However, these drugs have been studied in clinical trials and showed no benefit, and their use in clinical AKI has not been approved. Treatment once AKI has developed is even more difficult.

The compounds disclosed herein are exemplary modulators of peroxisome proliferator-activated receptor delta (PPARδ). PPARδ is a nuclear receptor that is capable of regulating mitochondria biosynthesis. Modulating the activity of PPARδ has been shown to be useful for the treatment of diseases.

SUMMARY

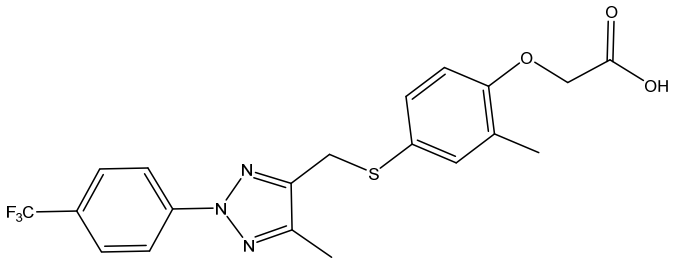
It has now been found that a compound, (*R*)-3-methyl-6-(2-((5-methyl-2-(6-(trifluoromethyl)pyridin-3-yl)-1*H*-imidazol-1-yl)methyl)phenoxy)hexanoic acid, represented by the following structural formula:



(hereinafter "Compound A")

reduced kidney injury in a rat model of acute kidney disease (see Example 2). Specifically, Compound A significantly reduced plasma creatinine levels, improves kidney function and reduces the early kidney injury biomarker NGAL, when administerd intravenously four hours after ischemic reperfusion injury was induced to the kidneys of laboratory rats.

It has also been found that Compound B, represented by the following structural formula:

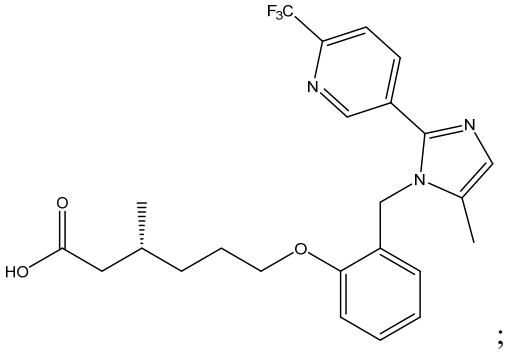


(hereinafter "Compound B")

reduced kidney injury in a rat model of acute kidney disease (see Example 3). Specifically, Compound B sigificantly reduced plasma creatinine levels and improves kidney function when administered orally four hours after ischemic reperfusion injury was induced to the kidneys of laboratory rats.

Based on these discoveries, methods of treating acute kidney injury are disclosed herein.

In one aspect of the present disclosure, there is provided a use of a compound represented by the following structural formula:



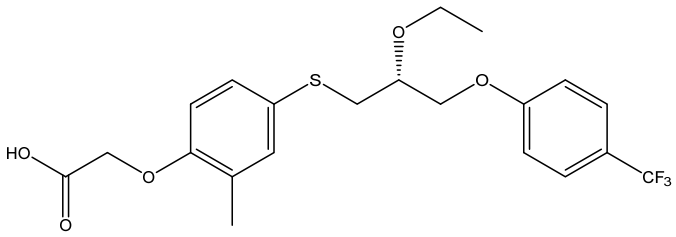
;

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the intravenous treatment of a human patient with acute kidney injury.

One example of the present disclosure is a method of treating a human patient with acute kidney injury. The method comprises intravenously administering to the patient an effective amount of Compound A or a pharmaceutically acceptable salt thereof.

Another example of the present disclosure is a method of treating a human patient with acute kidney injury. The method comprises administering to the patient an effective amount of Compound B or a pharmaceutically acceptable salt thereof. In one example, Compound B is administered orally; in another example, it is administered intravenously.

Yet another example of the present disclosure is a method of treating a human patient with acute kidney injury. The method comprises administering to the patient an effective amount of Compound C:



(hereinafter "Compound C");

or a pharmaceutically acceptable salt thereof. In one example, Compound C is administered orally; in another example, it is administered intravenously.

Another example of the present disclosure is Compound A or a pharmaceutically acceptable salt thereof, for use in intravenously treating a human patient with acute kidney injury.

Yet another example of the present disclosure is Compound B, or a pharmaceutically acceptable salt thereof, for use in treating a human patient with acute kidney injury. In one example, Compound B is for oral administration; in another example, Compound B is for intravenous administration.

Yet another example of the present disclosure is Compound C, or a pharmaceutically acceptable salt thereof, for use in treating a human patient with acute kidney injury. In one example, Compound C is for oral administration; in another example, Compound C is for intravenous administration.

Yet another example of the present disclosure is the use of Compound A or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for intravenously treating a human patient with acute kidney injury.

Yet another example of the present disclosure is the use of Compound B, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a human patient with acute kidney injury. In one example, Compound B is for oral administration; in another example, Compound B is for intravenous administration.

Still another example of the present disclosure is the use of Compound C, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a human patient with acute kidney injury. In one example, Compound C is for oral administration; in another example, Compound B is for intravenous administration.

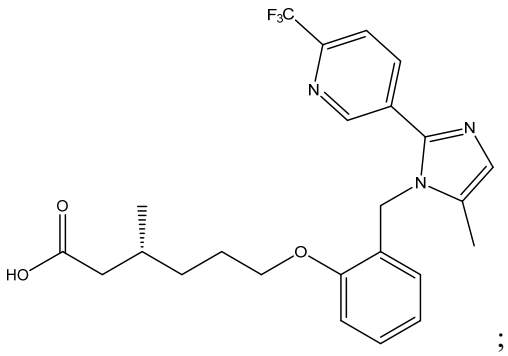
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 a, b and c are bar graphs showing the therapeutic effect of Compound A administered intravenously in a rat model of acute kidney injury. The bar graph 1a shows the plasma creatinine levels in mg/dL in rats 24 hours after kidney injury. The bars from left to

CLAIMS

What is claimed is:

1. Use of a compound represented by the following structural formula:



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or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the intravenous treatment of a human patient with acute kidney injury.

2. The use of claim 1, wherein an effective amount of the meglumine salt of the compound is to be intravenously administered to the patient.

3. The use of claim 1 or 2, wherein the patient is a surgical patient and the compound or a pharmaceutically acceptable salt thereof is administered to the patient after surgery.

4. The use of any one of claims 1-3, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof is from 0.1 mg to about 50 g per day.

5. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from acute interstitial nephritis.

6. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from glomerular renal disease.

7. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from acute vasculitic renal disease.

8. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from ischemia.

9. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from toxic injury.

10. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from prerenal azotemia.

11. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from acute postrenal destructive nephropathy.

12. The use of any one of claims 1–4, wherein the patient is to be treated for acute kidney injury from diabetes, underlying renal insufficiency, nephritic syndrome, atherosclerotic disease, sepsis, hypotension, hypoxia, myoglobinuria-hematuria, or liver disease.

13. The use of any one of claims 1–4, wherein the patient to be treated for acute kidney injury is elderly, pregnant, a surgical patient, or has been exposed to a nephrotoxic agent.

14. The use of claim 13, wherein the patient has been exposed to a nephrotoxic agent and the nephrotoxic agent is a drug or chemical capable of causing acute kidney injury.

15. The use of claim 14, wherein the drug or chemical is one or more of the compounds selected from the group consisting of cisplatin; gentamicin; cephaloridine; cyclosporine; amphotericin; carbon tetrachloride; trichloroethylene; and dichloroacetylene.