

C(O)-O-R⁶, -C(O)-N(R⁶)(R⁷), -CN, -O-R⁶, cycloalkyl, aryl, heteroaryl and heterocyclyl;

with the proviso that the heteroaryl or heterocyclyl moiety includes at least one ring nitrogen atom;

- 5 X¹, X², X³, X⁴, X⁵, X⁶, X⁷ and X⁸ are independently C(R⁴) or N, in which each R⁴ is independently hydrogen, alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, halo, -NO₂, haloalkyl, haloalkoxy, -CN, -O-R⁶, -S-R⁶, -N(R⁶)(R⁷), -S(=O)-R⁶, -S(=O)₂R⁶, -S(=O)₂-N(R⁶)(R⁷), -S(=O)₂-O-R⁶, -N(R⁶)-C(O)-R⁷, -N(R⁶)-C(O)-O-R⁷, -N(R⁶)-C(O)-N(R⁶)(R⁷), -C(O)-R⁶, -C(O)-O-R⁶, -C(O)-N(R⁶)(R⁷), or -N(R⁶)-S(=O)₂-R⁷, wherein
- 10 the alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl is further optionally substituted with one or more substituents selected from halo, oxo, -NO₂, -CF₃, -O-CF₃, -N(R⁶)(R⁷), -C(O)-R⁶, -C(O)-O-R⁷, -C(O)-N(R⁶)(R⁷), -CN, -O-R⁶; or
- X⁵ and X⁶ or X⁶ and X⁷ are joined to provide optionally substituted fused aryl or optionally substituted fused heteroaryl; and
- 15 with the proviso that at least one of X², X³, and X⁴ is C(R⁴);
- at least two of X⁵, X⁶, X⁷, and X⁸ are C(R⁴); and
- at least one of X², X³, X⁴, X⁵, X⁶, X⁷ and X⁸ is N.

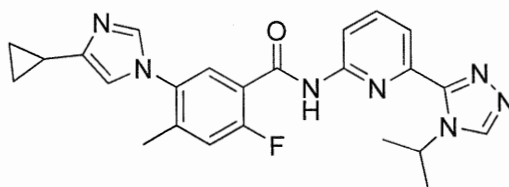
The above disclosures notwithstanding, there is a need for compounds that are potent and exhibit improved pharmacokinetic and/or pharmacodynamic profiles for the treatment of

20 diseases related to ASK1 activation.

Surprisingly, applicants have discovered a novel compound within the scope of U.S. patent publication US2011/0009410A exhibiting good potency, improved pharmacokinetic and/or pharmacodynamic profiles, on aggregate, compared to compounds disclosed therein.

SUMMARY OF THE INVENTION

- 25 ~~The present invention relates to~~ In one aspect, there is provided a compound of the formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

In one embodiment, the ~~invention~~disclosure relates to the use of a compound of formula (I) in the treatment of a disease in a patient in need of treatment with an ASK1 inhibitor.

In one aspect, there is provided a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the ~~invention~~disclosure relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

In another embodiment, the ~~invention~~disclosure is a method of treating diabetic nephropathy, or complications of diabetes, comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

In another embodiment, the ~~invention~~disclosure relates to a method of treating kidney disease, or diabetic kidney disease comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

In another embodiment, the ~~invention~~disclosure relates to a method of treating kidney fibrosis, lung fibrosis, or idiopathic pulmonary fibrosis (IPF) comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

In another embodiment, the ~~invention~~disclosure relates to a method of treating diabetic kidney disease, diabetic nephropathy, kidney fibrosis, liver fibrosis, or lung fibrosis comprising administering a therapeutically effective amount of a compound or salt of formula (I), to a patient in need thereof.

In another embodiment, the ~~invention~~disclosure relates to intermediates useful for the synthesis of the compound of formula (I).

In another embodiment, the ~~invention~~disclosure relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of chronic kidney disease.

In another embodiment, the ~~invention~~disclosure relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of diabetic kidney disease.

In another embodiment, the ~~invention~~disclosure relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of chronic kidney disease.

In yet another embodiment, the ~~invention~~disclosure relates to the compound of formula (I) for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

5 Figures

Figure 1 is a bar graph showing the levels of Collagen IV in the kidney cortex of rats subjected to seven days of unilateral ureteral obstruction and treated with either vehicle, or compound of formula (I) at 1, 3, 10, or 30 mg/kg b.i.d. per day.

10 Figure 2 shows representative images of kidney cortex sections stained with alpha-smooth muscle actin (a marker of activated myofibroblasts) from rats subjected to seven days of unilateral ureteral obstruction and treated with either vehicle, or compound of formula (I) at 1, 3, 10, or 30 mg/kg b.i.d. per day.

15 Definitions and General Parameters

As used herein, the following words and phrases are intended to have the meanings set forth below, except to the extent that the context in which they are used indicates otherwise. Where no indication or definition is given, the ordinary meaning of the word or phrase as found in a relevant dictionary or in common usage known to one of skill in the art is implied.

20 The term “chronic kidney disease” as used herein refers to progressive loss of kidney function over time typically months or even years. Chronic kidney disease (CKD) is diagnosed by a competent care giver using appropriate information, tests or markers known to one of skill in the art. Chronic kidney disease includes by implication kidney disease.

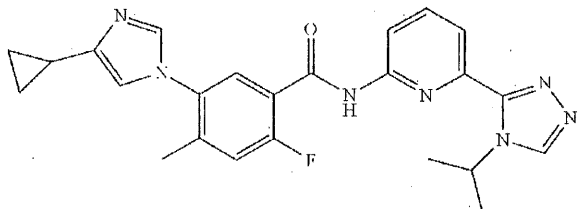
The term “diabetic kidney disease” as used herein refers to kidney disease caused by
25 diabetes, exacerbated by diabetes, or co-presenting with diabetes. It is a form of chronic kidney disease occurring in approximately 30% of patients with diabetes. It is defined as diabetes with the presence of albuminuria and/or impaired renal function (i.e. decreased glomerular filtration rate (See. de B, I, *et al.* Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011 Jun 22; **305**(24):2532-2539).

30 The term “pharmaceutically acceptable salt” refers to salts of pharmaceutical compounds e.g. compound of formula (I) that retain the biological effectiveness and properties of the underlying compound, and which are not biologically or otherwise undesirable. There are acid

What is claimed is:

1. A compound of formula (I)

(I)

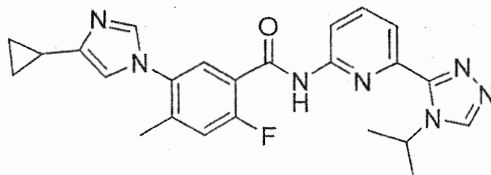


or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

What is claimed is:

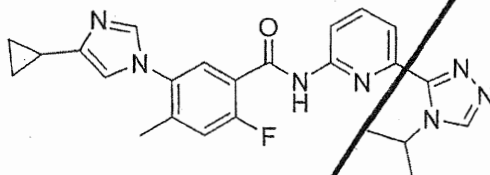
1. A compound of formula (I)



(I)

Namely, 5-(4-cyclopropyl-1H-imidazol-1-yl)-N-(6-(4-isopropyl-4H-1,2,4-triazol-3-yl)pyridin-2-yl)-2-fluoro-4-methylbenzamide, or a pharmaceutically acceptable salt thereof.

2. The compound of formula (I)

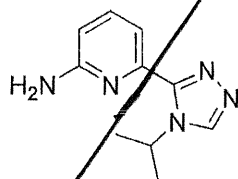


(I)

namely, 5-((4-cyclopropyl-1H-imidazol-1-yl)-2-fluoro-N-(6-(4-isopropyl-4H-1,2,4-triazole-3-yl)pyridine-2-yl)-4-methylbenzamide.

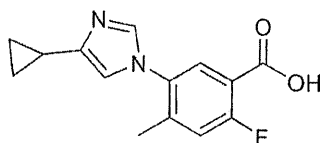
3. A pharmaceutical composition comprising a therapeutically effective amount of the compound or salt according to Claim 1 and a pharmaceutically acceptable carrier.
4. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to Claim 2 and a pharmaceutically acceptable carrier.
5. A method of treating chronic kidney disease comprising administering a therapeutically effective amount of a compound according to Claim 2, or pharmaceutically acceptable salt thereof, to a patient in need thereof.
6. A method of treating diabetic nephropathy comprising administering a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof, to a patient in need thereof,

7. A method of treating kidney fibrosis, liver fibrosis, or lung fibrosis comprising administering a therapeutically effective amount of a compound or salt according to Claim 1, to a patient in need thereof.
8. A method of treating diabetic kidney disease, comprising administering a therapeutically effective amount of a compound or salt according to Claim 1, to a patient in need thereof.
9. Use of a compound or salt according to Claim 1 in the manufacture of a medicament for the treatment of chronic kidney disease.
10. Use of a compound or salt according to Claim 1 in therapy.
11. An intermediate of formula:



namely, 2-amino, 5-(4-isopropyl-4H-1,2,4-triazol-3-yl) pyridine, or a salt or protected form thereof.

12. An intermediate of formula:



namely, 5-(4-cyclopropyl-1H-imidazol-1-yl)-2-fluoro-4-methylbenzoic acid, a salt or protected form thereof.