METHOD FOR TREATING AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

FIELD

[0001] The present disclosure in some aspects relates generally to methods for treating autosomal dominant polycystic kidney disease (ADPKD).

BACKGROUND

[0002] Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease and the fourth leading cause of end-stage kidney disease in adults worldwide. Approximately 78 percent of families with ADPKD have an abnormality on chromosome 16 (PKD1 locus). Most of the remaining families (14 percent) have a different defect that involves a gene on chromosome 4 (the PKD2 locus). Mutation of PKD1 or PKD2 results in the progressive development of hypertension, kidney cysts, flank pain, proteinuria, kidney function impairment and ultimately kidney failure. Among most patients, kidney function remains intact until the fourth decade of life. Once the glomerular filtration rate (GFR) starts to decline, the average reduction is 4.4 to 5.9 mL/min per year.

[0003] ADPKD is characterized by glomerular hyperfiltration and progressive growth of renal cysts, resulting in renal enlargement and, eventually, renal failure. It has been shown that the occurrence of glomerular hyperfiltration in ADPKD is associated with a significantly faster decline in renal function and higher rate of kidney enlargement over time (Helal I, Reed B, McFann K, et al, Glomerular hyperfiltration and renal progression in children with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 2011; 6: 2439-2443; the content of which is incorporated herein by reference in its entirety). When the genes encoding polycystin 1 (PKD1) and polycystin 2 (PKD2) are disrupted, tubular epithelial cells in vasopressin-sensitive distal nephrons and collecting ducts fail to concentrate urine, and a urine-concentrating defect is thought to be the cause of the increased vasopressin level in PKD. The increased vasopressin acts on V2-receptors increases the glomerular pressure by means of the activation of tubuloglomerular feedback and afferent vasodilation (Torres VE. Vasopressin in chronic kidney disease, an elephant in the room? Kidney International. 2009; 76 (9): 925-928; the content of

which is incorporated herein by reference in its entirety). The increased vasopressin also promotes kidney-cyst cell proliferation and chloride-driven fluid secretion.

[0004] Currently the only approved medication for ADPKD is the selective vasopressin V2 receptor antagonist (tolvaptan), which suppresses vasopressin production, release, or action by means of hydration, and reduce cyst burden, decrease glomerular hyperfiltration, and protect kidney function (Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017; 377:1930-42; the content of which is incorporated herein by reference in its entirety).

[0005] However, there are several limitations for using tolvaptan in ADPKD. First of all, tolvaptan has limited effect on correcting intraglomerular pressure by blocking vasopressin induced tubuloglomerular feedback and it is not curative but only slows down disease progression. Secondly, the adverse effects of tolvaptan are mostly related to increased aquaresis: thirst, polyuria, nocturia and polydipsia, as a result of the excretion of electrolyte-free water, which have significant impact on the quality of life and patients' compliance. Furthermore, although rare, significant elevations of liver enzyme levels have been described in ADPKD patients on tolvaptan. Since the progression of ADPKD is relatively slow during the early course, there remain needs for effective ADPKD treatments with a minimum adverse event.

[0006] In addition to tolvaptan, some PPAR gamma inhibitors, such as Pioglitazone, have been tested for regulating PKD model. However, the data from *in vivo* study was controversial. Two PPAR gamma agonists, pioglitazone and rosiglitazone, attenuated cyst growth in the PCK rats, a slowly progressing model of PKD (Blazer-Yost BL, Haydon J, Eggleston-Gulyas T et al. Pioglitazone attenuates cystic burden in the PCK rodent model of polycystic kidney disease. PPAR Res 2010; 2010: 274376; Flaig SM, Gattone VH, Blazer-Yost BL. Inhibition of cyst growth in PCK and Wpk rat models of polycystic kidney disease with low doses of peroxisome proliferator-activated receptor gamma agonists. J Transl Int Med 2016; 4: 118–126; the contents of which is incorporated herein by reference in their entirety). However, pioglitazone did not improve renal survival and cystic parameter in Tamoxifen-inducible kidney-specific Pkd1 deletion mice (Kanhai AA, Bange H, Verburg L, et al. Renal cyst growth is attenuated by a combination treatment of tolvaptan and pioglitazone, while pioglitazone treatment alone is not effective. Nature 2020; 10: 1672). Further, a low-dose pioglitazone was tested in a Phase 1b

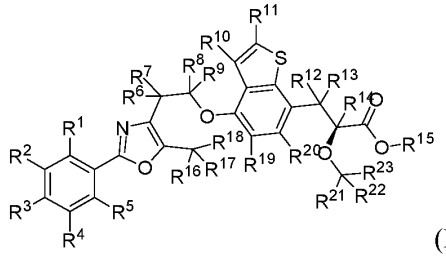
clinical trial with a cross-over design in ADPKD patients, and no significant decrease in the change of TKV was observed in the comparison to placebo.

[0007] Apart from PPAR gamma agonist, mTOR inhibitors also showed effect in animal PKD models on cyst reduction and prolonged renal survival, but until now, none of these agents showed clinical benefit to preserve renal function in ADPKD patients (see Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease N Engl J Med 2010; 363:820-829; the content of which is incorporated herein by reference in its entirety). Furthermore, unlike tolvaptan, neither pioglitazone nor mTOR inhibitors has hemodynamic effect to correct intraglomerular pressure, which may suggest that in addition to the proved effect in animal model on cyst growth and renal outcome, correction on glomerular hyperfiltration may play a heavy weight in ADPKD management.

[0008] Therefore, there remains a need for efficacious treatment for ADPKD and improving renal survival, without severe adverse effects.

SUMMARY

[0009] In one aspect, provided herein is a method of treating autosomal dominant polycystic kidney disease (ADPKD) in an individual, comprising administering to the individual a compound of Formula (I):

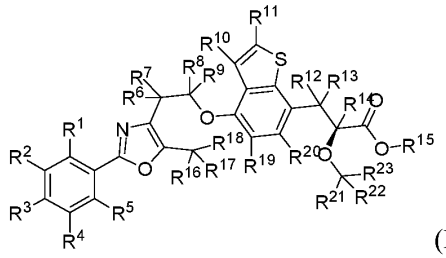


(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D.

[0010] In one aspect, provided herein is a method of improving renal survival in an individual having ADPKD, comprising administering to the individual a compound of Formula (I):

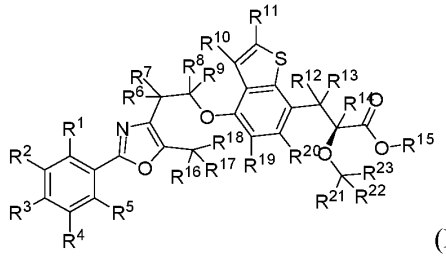


(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D.

[0011] In one aspect, provided herein is a method of slowing the decline of estimated glomerular filtration rate (eGFR) in an individual having ADPKD, comprising administering to the individual a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D.

[0012] In some embodiments of the foregoing, wherein at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty one, twenty two or twenty three of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} is D.

[0013] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing epithelial thinning or tubular attenuation in the individual. In some embodiments, the amount of the compound or the pharmaceutically

acceptable salt thereof administered is effective in reducing tubular dilatation in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing tubular casts in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing blood urea level of the individual by at least about 5%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing down the growth of cystic areas. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2% compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

[0014] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic areas in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing down the increase of cystic index. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic index in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic grade in the individual.

[0015] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of glomerular atrophy or sclerosis in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of tubular inflammation in the individual.

[0016] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing kidney volume. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing the ratio of kidney volume to kidney weight (KV/KW). In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index.

[0017] In some embodiments, the individual is a mammal. In some embodiments, the individual is a human. In some embodiments, the individual has a mutation in PKD1 or PKD2. In some embodiments, the individual has a mutation in PKD1. In some embodiments, the individual has a mutation in PKD2.

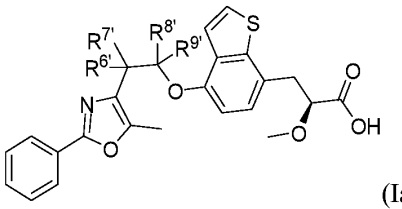
[0018] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 50 μg, about 75 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 225 μg, about 250 μg, about 275 μg, about 300 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg.

[0019] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered when the individual is fasted. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered for 14 days. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered for at least 14 days.

[0020] In some embodiments, no more than one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty one, twenty two or twenty three of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} is D. In some embodiments, at least one, two, three or four of R^6, R^7, R^8 and R^9 is D. In some embodiments, no more than one, two, three or four of R^6, R^7, R^8 and R^9 is D. In some embodiments, one or two of R^6 or R^7 is D. In some embodiments, one or two of R^8 or R^9 is D. In some embodiments, all of R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, all of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D. In some embodiments, no more than one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D. In some embodiments, all of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, all of R^1, R^2, R^3, R^4 and R^5 are D, and all of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, at least one, two, three, four, five, six, seven, eight or nine of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is D. In some embodiments, no more than one, two, three, four, five, six, seven, eight or nine of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is D. In some embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D and at least one, two, three, or four of R^6, R^7, R^8 and R^9 is D. In some embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D and at least one or two of R^8 and R^9 is D. In some embodiments, at least one or two of R^1 and R^5 is D and at least one or two of R^8 and R^9 is D. In some embodiments, all of R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, at least one, two or three of R^{12}, R^{13} and R^{14} is D. In some embodiments, no more than one, two or three of R^{12}, R^{13} and R^{14} is D. In some embodiments, at least one or two of R^{12} and R^{13} is D and R^{14} is D. In some embodiments, all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, at least one, two or three of R^{16}, R^{17} and R^{18} is D. In some embodiments, no more than one, two or three of R^{16}, R^{17} and R^{18} is D. In some embodiments, all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In some embodiments, at least one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} is D. In some embodiments, no more than one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} is D. In some embodiments, at least one or two of R^8 and R^9 is D and at least one, two or three of R^{16}, R^{17} and R^{18} is D. In some embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4, and R^5 is D and at least one, two or three of R^{16}, R^{17} and R^{18} is D. In some embodiments, all of, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

[0021] In some embodiments, the compound of Formula (I) is a compound of Formula (Ia):

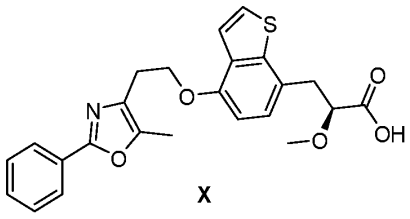


(Ia)

wherein, $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ independently from each other are H or D, wherein at least one, two, three or four of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ is D.

[0022] In some embodiments, no more than one, two, three or four of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ is D. In some embodiments, at least one or two of $R^{8'}$ and $R^{9'}$ is D. In some embodiments, at least one or two of $R^{6'}$ and $R^{7'}$ is D. In some embodiments, both of $R^{6'}$ and $R^{7'}$ are H when at least one or two of $R^{8'}$ and $R^{9'}$ is D. In some embodiments, both of $R^{6'}$ and $R^{7'}$ are H when both of $R^{8'}$ and $R^{9'}$ is D. In some embodiments, both of $R^{8'}$ and $R^{9'}$ are H when at least one or two $R^{6'}$ and $R^{7'}$ of is D.

[0023] In some embodiments, the compound of Formula (I) is a compound selected from the group consisting of:



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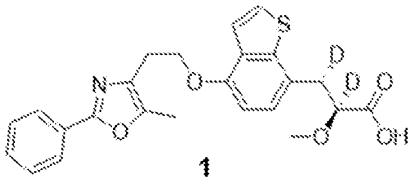

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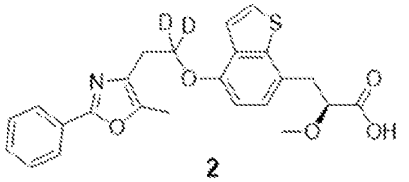

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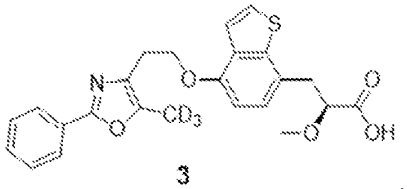

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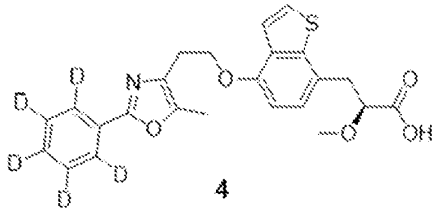

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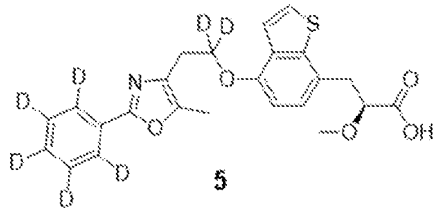

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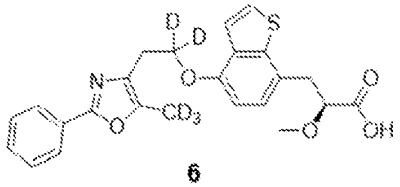

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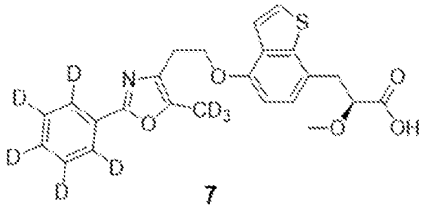

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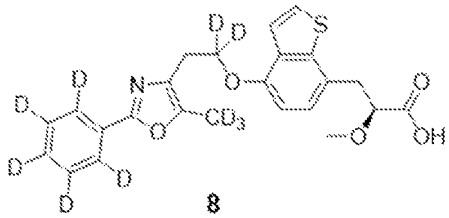

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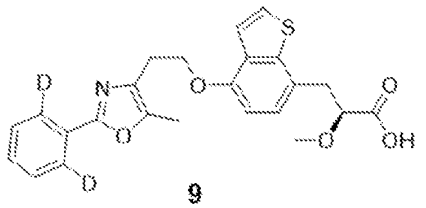

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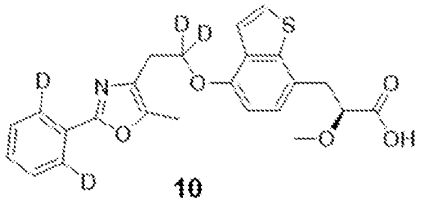

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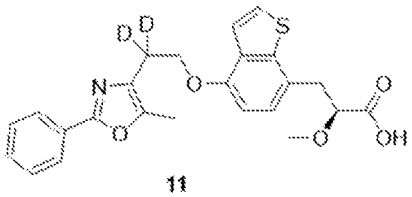

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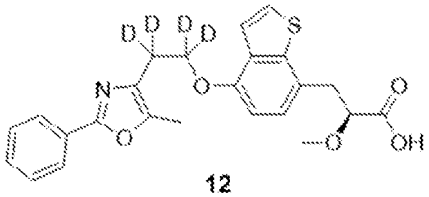

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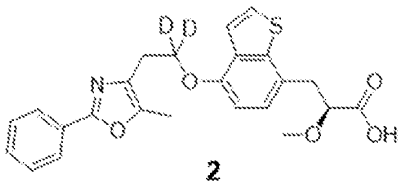
, or a pharmaceutically acceptable salt thereof.

[0024] In some embodiments, the compound of Formula (I) is



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, or a pharmaceutically acceptable salt thereof.

[0025] In some embodiments, deuterium enrichment in the compound of Formula (I) is no less than 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99%. In some embodiments, deuterium enrichment in the compound of Formula (I) is no more than 99.9%, 99%, 98%, 97%, 96%, 95%, or 90%.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] The drawings illustrate certain embodiments of the features and advantages of this disclosure. These embodiments are not intended to limit the scope of the appended claims in any manner.

[0027] FIG. 1 shows the progression of mouse body weights (mean ±SEM) in the compound 2 treatment groups (groups treated with Tolvaptan or Compound 2) and control groups (healthy control and Tamoxifen-induced control) from postnatal day (PND) 18 to 110.

[0028] FIG. 2 shows the distribution of the total body weight in control groups on the day of termination.

[0029] FIG. 3 shows the distribution of the total body weight in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0030] FIG. 4 shows the comparison of the total kidney weight in control groups on the day of termination.

[0031] FIG. 5 shows the comparison of the total kidney weight in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0032] FIG. 6 shows the comparison of the total kidney weight, corrected for body weight (2KW/BW*100%), in control groups on the day of termination.

[0033] FIG. 7 shows the comparison of the total kidney weight, corrected for body weight (2KW/BW*100%), in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0034] FIG. 8 shows the comparison of the urea level in control groups on the day of termination.

[0035] FIG. 9 shows the comparison of the urea level in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0036] FIG. 10 shows the survival rates of the control groups without treatments.

[0037] FIG. 11 shows the survival rates of the treatment groups (groups treated with Tolvaptan or Compound 2) with treatments.

[0038] FIG. 12 shows the comparison of the right kidney volume, corrected for body weight (KV/BW*100%), in control groups on PND41.

[0039] FIG. 13 shows the comparison of the right kidney volume, corrected for body weight (KV/BW*100%), in treatment groups (groups treated with Tolvaptan or Compound 2) on PND41.

[0040] FIG. 14 shows the comparison of the right kidney volume, corrected for body weight (KV/BW*100%), in control groups on PND76.

[0041] FIG. 15 shows the comparison of the right kidney volume, corrected for body weight (KV/BW*100%), in treatment groups (groups treated with Tolvaptan or Compound 2) on PND76.

[0042] FIG. 16 shows the comparison of the right kidney volume, corrected for body weight (KV/BW*100%), in control groups on PND97.

[0043] FIG. 17 shows the comparison of the right kidney volume, corrected for body weight (KV/BW*100%), in treatment groups (groups treated with Tolvaptan or Compound 2) on PND97.

[0044] FIG. 18 shows the comparison of the cystic index (CI) in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0045] FIG. 19 shows the distribution of the cystic grades in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0046] FIG. 20 shows the distribution of the tubular dilatation in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0047] FIG. 21 shows the distribution of the tubular casts in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0048] FIG. 22 shows the distribution of the tubular inflammation grades in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0049] FIG. 23 shows the distribution of the glomerular atrophy grades in treatment groups (groups treated with Tolvaptan or Compound 2) on the day of termination.

[0050] FIG. 24 shows the change of Mean eGFR in Compound 2 treatment and Control Clinical Trial Groups.

DETAILED DESCRIPTION

[0051] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

[0052] In one aspect, provided herein is a method of treating autosomal dominant polycystic kidney disease (ADPKD) and/or improving renal survival in an individual, comprising administering to the individual a compound of Formula (I) (e.g., compound 2) or a pharmaceutical acceptable salt thereof. The present invention is based, at least in part, on the surprising discovery that the methods described herein (i) show high efficacy in slowing the decline of estimated glomerular filtration rate (eGFR); (ii) improve renal survival; (iii) may be able to correct the glomerular hyperfiltration via a mechanism different from tolvaptan; and (iv) are effective and safe in treating ADPKD and improving renal survival. Therefore, the methods provided herein offer promising approaches for ADPKD treatment and long-term life quality management in individuals having ADPKD.

I. Definition

[0053] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0054] The term "about" indicates and encompasses an indicated value and a range above and below that value. In certain embodiments, the term "about" indicates the designated value ± 10%, ± 5%, or ± 1%. In certain embodiments, the term "about" indicates the designated value ± one standard deviation of that value.

[0055] The singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, *e.g.*, reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more compounds and equivalents thereof known to those skilled in the art.

[0056] The terms "patient," "subject," "individual," and the like are used interchangeably herein, and refer to any animal, in some embodiments a mammal, and in some embodiments, a human, having a complement system, including a human in need of therapy for, or susceptible to, a condition or its sequelae. The individual may include, for example, dogs, cats, pigs, cows, sheep, goats, horses, rats, rabbits, hamsters, guinea pigs, monkeys, mice, and humans. In some embodiments, the individual is a human.

[0057] As used herein, "treatment" or "treating" is an approach for obtaining a beneficial or desired result, such as a clinical result. For purposes of this disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one variation, beneficial or desired clinical results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease described herein. Preferably, treatment of a disease or condition with a compound of the disclosure, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is accompanied by no or fewer side effects than are associated with currently available therapies for the disease or condition and/or improves the quality of life of the individual.

[0058] The terms "effective amount" and "pharmaceutically effective amount" refer to a sufficient amount of an agent to provide the desired biological result. That result can be reduction (e.g., reducing at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100%) and/or alleviation of the signs, symptoms, or causes of a disease or disorder, or any other desired alteration of a biological system.

[0059] As used herein, by "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0060] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another and "diastereomers," which refers to stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0061] It is understood that aspects and embodiments described herein as "comprising" include "consisting of" and "consisting essentially of" embodiments.

[0062] Certain compounds disclosed herein contain one or more ionizable groups (groups from which a proton can be removed (*e.g.*, -COOH) or added (*e.g.*, amines) or which can be quaternized (*e.g.*, amines)). All possible ionic forms of such molecules and salts thereof are intended to be included individually in the disclosure herein. With regard to salts of the compounds described herein, one of ordinary skill in the art can select from among a wide variety of available counterions those that are appropriate. In specific applications, the selection of a given anion or cation for preparation of a salt may result in increased or decreased solubility of that salt.

II. Method of Treating ADPKD and Methods of Improving Renal Survival

[0063] Provided herein are methods of (i) treating autosomal dominant polycystic kidney disease (ADPKD); and/or (ii) improving renal survival; and/or (iii) slowing the decline of estimated glomerular filtration rate (eGFR); and/or (iv) improving kidney function; and/or (v) improving quality of life in an individual, comprising administering to the individual any of the compounds described herein (e.g., compound 2), or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

[0064] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index. In some embodiments, the individual is a human. In

some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food.

[0065] In one aspect, provided herein is a method of treating ADPKD in an individual, comprising administering to the individual any of the compounds described herein (e.g., a compound of Formula (I), a compound of Formula (Ia), compound X, or any one of compounds 1-12), or a pharmaceutically acceptable salt thereof. In some embodiments, the method treats ADPKD. In some embodiments, the method prevents the occurrence of ADPKD. Hence in some embodiments, provided herein is a method of preventing the occurrence of ADPKD in an individual, comprising administering to the individual any of the compounds described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the method slows down the progression ADPKD or any symptom associated with it, such as slows down the progression by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%. Hence in some embodiments, provided herein is a method of slowing down the progression ADPKD in an individual, comprising administering to the individual any of the compounds described herein (e.g., a compound of Formula (I), a compound of Formula (Ia), compound X, or any one of compounds 1-12), or a pharmaceutically acceptable salt thereof.

[0066] In one aspect, provided herein is a method of improving renal survival in an individual having ADPKD, comprising administering to the individual any of the compounds described herein (e.g., a compound of Formula (I), a compound of Formula (Ia), compound X, or any one of compounds 1-12), or a pharmaceutically acceptable salt thereof. In some embodiments, the method improves kidney function in the individual. In some embodiments, the method improves quality of life of the individual. Hence in some embodiments, provided herein is a method of improving kidney function and/or improving quality of life in an individual having ADPKD, comprising administering to the individual any of the compounds described herein (e.g., a

compound of Formula (I), a compound of Formula (Ia), compound X, or any one of compounds 1-12), or a pharmaceutically acceptable salt thereof.

[0067] In some embodiments, the renal survival and/or kidney function may be evaluated by estimated glomerular filtration rate (eGFR) or the decline rate of eGFR. In some embodiments, the method slows the decline of eGFR in the individual, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof or slows the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.. Hence in some embodiments, provided herein is a method of slowing the decline of estimated glomerular filtration rate (eGFR) in an individual (e.g., an individual with ADPKD), comprising administering to the individual any of the compounds described herein (e.g., a compound of Formula (I), a compound of Formula (Ia), compound X, or any one of compounds 1-12), or a pharmaceutically acceptable salt thereof.

[0068] In some embodiments, the renal survival and/or kidney function may be evaluated by blood urea nitrogen (BUN). In some embodiments, the method decreases BUN in the individual, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, or 70%, or about any of 1, 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 mg/dL. Hence in some embodiments, provided herein is a method of decreasing BUN level in an individual, comprising administering to the individual any of the compounds described herein (e.g., a compound of Formula (I), a compound of Formula (Ia), compound X, or any one of compounds 1-12), or a pharmaceutically acceptable salt thereof.

[0069] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing (e.g., by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%) epithelial thinning or tubular attenuation in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing (e.g., by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%) tubular dilatation in the individual. In some

embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing (e.g., by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%) tubular casts in the individual. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing blood urea level of the individual by at least about 5% (e.g., by at least about any of 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, or 70%).

[0070] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing down the growth of cystic areas, such as slowing down by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%.

[0071] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 100% compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

[0072] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing kidney volume, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, or 70%, or by at least about any of 5 g, 10 g, 15 g, 20 g, 35 g, 40 g, 55 g, 60 g, 65 g, 70 g, 75 g, 80 g, 85 g, 90 g, 95 g, or 100 g. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing the ratio of kidney volume to kidney weight (KV/KW), such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, or 70%.

[0073] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing tubular cast rate, such as by at least about any of

2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, or 70%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing proteinuria, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, or 70%.

[0074] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic areas in the individual, such as not inducing a reduction of cystic areas by more than about any of 12%, 10%, 8%, 7%, 6%, 5%, 4%, or 3%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in inducing at least about 0.1% reduction of cystic areas in the individual, such as at least about any of 1%, 2%, 3%, 4%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, or 20% reduction of the cystic areas. In some embodiments, the cystic areas may be calculated as the sum of areas of any tubules that have lumen diameter of more than about 9 microns and/or the sum of the areas (calculated in millimeters) of the cystic lesions, in which dilated tubules are included.

[0075] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing down the increase of cystic index, such as slowing down by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic index in the individual, such as not inducing a reduction of cystic index by more than about any of 12%, 10%, 8%, 7%, 6%, 5%, 4%, or 3%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in inducing at least about 0.1% reduction of cystic index in the individual, such as at least about any of 1%, 2%, 3%, 4%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, or 20% reduction of cystic index. In some embodiments, cystic index may be calculated by (cyst area/total area)*100%, wherein the cyst area is the sum of the areas (calculated in millimeters) of the cystic lesions found in all the section analyzed, in which dilated tubules are included, while dilated veins and pelvic cavity are excluded.

[0076] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic grade in the individual, such as not inducing a reduction of cystic grade by more than about any of 12%, 10%, 8%, 7%, 6%, 5%, 4%, or 3%. In some embodiments, the amount of the compound or the

pharmaceutically acceptable salt thereof administered is effective in inducing at least about 0.1% reduction of cystic grade in the individual, such as at least about any of 1%, 2%, 3%, 4%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, or 20% reduction of cystic grade. In some embodiments, cystic grade may be calculated by semi-quantitatively assessing cystic lesions on a scale of 0 to 5 with 0.5 interval based on the following grading system: 0: no cysts visible; 1: from 1 to a few, scattered, small cysts; 2: mild number of cysts; 3: moderate number of cysts; 4: numerous cysts present; 5: almost all the parenchyma replaced by cysts.

[0077] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of glomerular atrophy or sclerosis in the individual, such as not inducing a reduction of glomerular atrophy or sclerosis by more than about any of 12%, 10%, 8%, 7%, 6%, 5%, 4%, or 3%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in inducing at least about 0.1% reduction of glomerular atrophy or sclerosis in the individual, such as at least about any of 1%, 2%, 3%, 4%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, or 20% reduction of glomerular atrophy or sclerosis.

[0078] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of tubular inflammation in the individual, such as not inducing a reduction of tubular inflammation by more than about any of 12%, 10%, 8%, 7%, 6%, 5%, 4%, or 3%. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in inducing at least about 0.1% reduction of tubular inflammation in the individual, such as at least about any of 1%, 2%, 3%, 4%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, or 20% reduction of tubular inflammation.

[0079] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival (e.g., slowing the decline rate of eGFR to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.) while does not induce a more than about 15% (e.g., no more than about any of 12%, 10%, 8%, 7%, 6%, 5%, 4%, or 3%) reduction of cystic index.

[0080] In some embodiments, the individual is a mammal. In some embodiments, the individual is a human. In some embodiments, the individual has a mutation in PKD1 or PKD2. In some embodiments, the individual has a mutation in PKD1. In some embodiments, the individual has a mutation in PKD2.

Dose and Administration

[0081] In some embodiments, the compound or the pharmaceutically acceptable salt thereof can be administered daily. In some embodiments, a doctor determines the dosage which they consider most appropriate according to a preventive or curative treatment and according to the age, weight, condition, and other factors specific to the individual to be treated.

[0082] In some embodiments, the frequency and dosage may also vary according to factors specific for each individual depending on the specific therapy (e.g., therapeutic or prophylactic), the route of administration, as well as age, body, weight, response, and the past medical history of the individual. In some embodiments, the dose of the compound or pharmaceutical compositions thereof can be administered according to a suitable schedule, for example, any of about every day, about every two days, about every three days, about every four days, about every five days, about every six days, about once a week, about once every two weeks, about once every three weeks, and about once a month. In some embodiments, the compound or the pharmaceutically acceptable salt thereof can administered (e.g., orally) three times a day, twice a day, once a day, every two days, every three days, every four days, every five days, every six days, or every seven days. In some embodiments, the compound or the pharmaceutically acceptable salt thereof can administered (e.g., orally) three times a day, twice a day, or once a day.

[0083] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 50 μg, about 75 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 225 μg, about 250 μg, about 275 μg, about 300 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the

compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 75 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 100 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 125 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once or twice a day at a daily dose of about 150 μg.

[0084] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values.

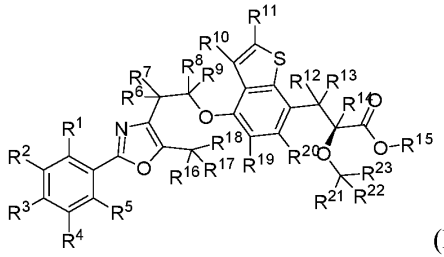
[0085] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg.

[0086] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered for a duration of at least 2 days, such as about any of about 2 days to about 30 days, about 3 days to about 28 days, about 7 days to about 28 days, or about 14 days. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered for a duration of 14 days.

[0087] In some variations, the compound or a pharmaceutically acceptable salt thereof can be administered *via* any accepted mode of administration for therapeutic agents including, but not limited to, oral, sublingual, subcutaneous, parenteral, intravenous, intranasal, topical, transdermal, intraperitoneal, intramuscular, intrapulmonary, vaginal, rectal, or intraocular administration. In some embodiments, the compound or composition is administered intravenously. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered when the individual is fasted.

Compounds

[0088] The methods provided herein comprises administering a compound or a pharmaceutically acceptable salt thereof to an individual, wherein the compound is a compound of formula (I), or its pharmaceutical acceptable salt,



(I)

wherein, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D, and at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty one, twenty two or twenty three of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} is D.

[0089] In certain embodiments, a range of between one and twenty three, between one and twenty two, between one and twenty one, between one and twenty, between one and nineteen, between one and eighteen, between one and seventeen, between one and sixteen, between one and fifteen, between one and fourteen, between one and thirteen, between one and twelve, between one and eleven, between one and ten, between one and nine, between one and eight, between one and seven, between one and six, between one and five, between one and four, between one and three, or between one and two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are D.

[0090] In certain embodiments, a range of between one and six of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are D. In certain embodiments, a range of between one and four of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are D. In certain embodiments, one or two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are D.

[0091] In certain embodiments, at least one, two, three or four of R^6, R^7, R^8 and R^9 is D. In certain embodiments, a range of between one and four, between one and three, or between one and two of R^6, R^7, R^8 and R^9 are D. In certain embodiments, four of R^6, R^7, R^8 and R^9 are D. In certain embodiments, two of R^6, R^7, R^8 and R^9 are D. In certain embodiments, one or two of R^6 or R^7 is D. In certain embodiments, one of R^6 or R^7 is D. In certain embodiments, R^6 or R^7 are both D. In certain embodiments, one or two of R^8 or R^9 is D. In certain embodiments, one of R^8 or R^9 is D. In certain embodiments, R^8 or R^9 are both D. In certain embodiments, all of R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In certain embodiments, all of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In certain embodiments, all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

[0092] In certain embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D. In certain embodiments, a range of between one and five, between one and four, between one and three, or between one and two of R^1, R^2, R^3, R^4 and R^5 are D. In certain embodiments, R^1, R^2, R^3, R^4 and R^5 are all D. In certain embodiments, all of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In certain embodiments, all of R^1, R^2, R^3, R^4 and R^5 are D, and all of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In certain embodiments, at least one, two, three, four, five, six, seven, eight or nine of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is D. In certain embodiments, a range of between one and nine, between one and eight, between one and seven, between one and six, between one and five, between one and four, between one and three, or between one and two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is D. In certain embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D and at least one, two, three, or four of R^6, R^7, R^8 and R^9 is D. In certain embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D and at least one or two of R^8 and R^9 is D. In certain embodiments, at least one or two of R^1 and R^5 is D and at least one or two of R^8 and R^9 is D. In certain embodiments, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are all D. In certain embodiments, all of R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

[0093] In certain embodiments, at least one, two or three of R^{12}, R^{13} and R^{14} is D. In certain embodiments, a range of between one and three, or between one and two of R^{12}, R^{13} and R^{14} are D. In certain embodiments, one of R^{12}, R^{13} and R^{14} is D. In certain embodiments, at least one or

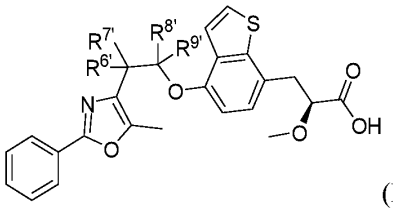
two of R^{12} and R^{13} is D and R^{14} is D. In certain embodiments, R^{12} and R^{14} are both D. In certain embodiments, R^{13} and R^{14} are both D. In certain embodiments, R^{12}, R^{13} and R^{14} are all D.

[0094] In certain embodiments, all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

[0095] In certain embodiments, at least one, two or three of R^{16}, R^{17} and R^{18} is D. In certain embodiments, a range of between one and three, or between one and two of R^{16}, R^{17} and R^{18} are D. In certain embodiments, one of R^{16}, R^{17} and R^{18} is D. In certain embodiments, all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H. In certain embodiments, at least one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} is D. In certain embodiments, a range of between one and twelve, between one and eleven, between one and ten, between one and nine, between one and eight, between one and seven, between one and six, between one and five, between one and four, between one and three, or between one and two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} are D.

[0096] In certain embodiments, at least one or two of R^8 and R^9 is D and at least one, two or three of R^{16}, R^{17} and R^{18} is D. In certain embodiments, at least one, two, three, four or five of R^1, R^2, R^3, R^4, and R^5 is D and at least one, two or three of R^{16}, R^{17} and R^{18} is D. In certain embodiments, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} are all D. In certain embodiments, all of R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

[0097] In another aspect, the present invention provides a compound of formula (Ia), or its pharmaceutical acceptable salt,



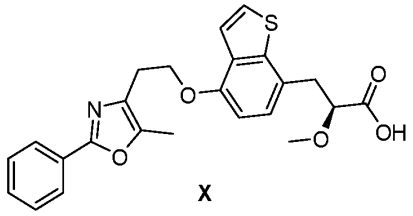
(Ia)

wherein, $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ independently from each other are H or D, wherein at least one, two, three or four of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ is D.

[0098] In certain embodiments, no more than one, two, three or four of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ is D. In certain embodiments, a range of between one and four, between one and three, or between

one and two of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ are D. In certain embodiments, at least one or two of $R^{8'}$ and $R^{9'}$ is D. In certain embodiments, $R^{8'}$ and $R^{9'}$ are both D. In certain embodiments, at least one or two of $R^{6'}$ and $R^{7'}$ is D. In certain embodiments, both of $R^{6'}$ and $R^{7'}$ are H when at least one or two of $R^{8'}$ and $R^{9'}$ is D. In certain embodiments, both of $R^{6'}$ and $R^{7'}$ are H when both of $R^{8'}$ and $R^{9'}$ is D. In certain embodiments, both of $R^{6'}$ and $R^{7'}$ are H and both of $R^{8'}$ and $R^{9'}$ are D. In certain embodiments, both of $R^{8'}$ and $R^{9'}$ are H when at least one or two $R^{6'}$ and $R^{7'}$ of is D. In certain embodiments, both of $R^{8'}$ and $R^{9'}$ are H and both $R^{6'}$ and $R^{7'}$ of are D.

[0099] In some embodiments, the compound is a compound selected from the group consisting of:



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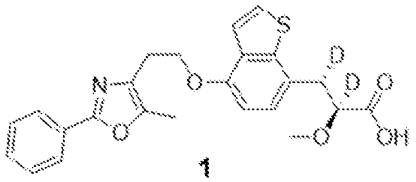

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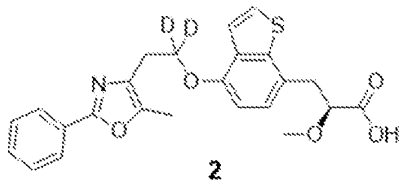

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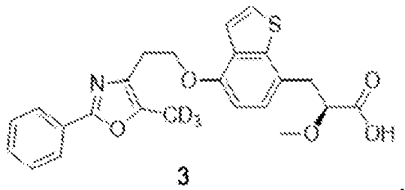

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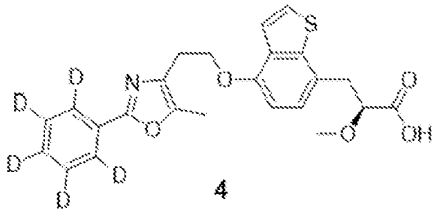

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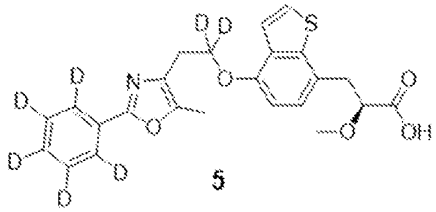

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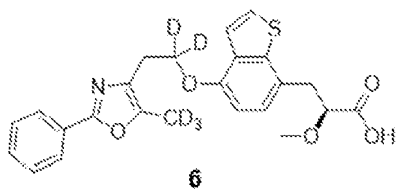

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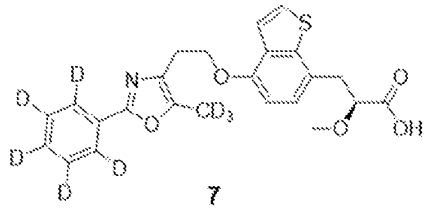

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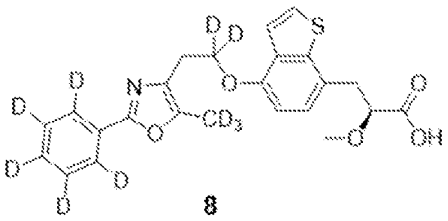

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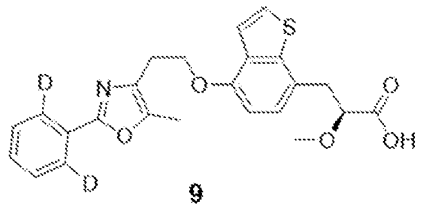

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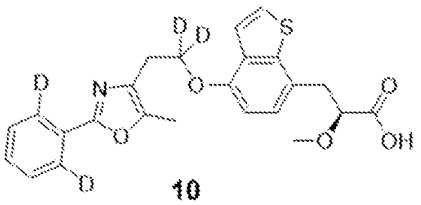

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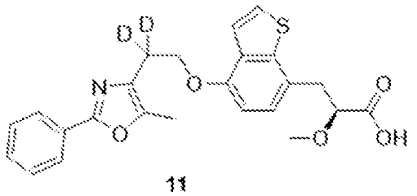

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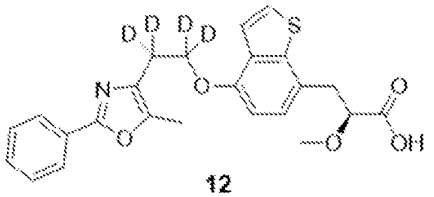
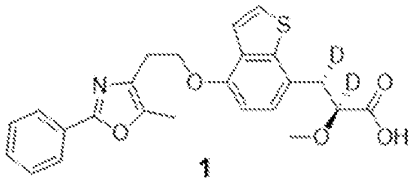


12

, or a pharmaceutically acceptable salt thereof.

[0100] In some embodiments, the compound is a compound selected from the group consisting of:



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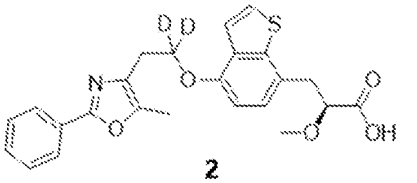

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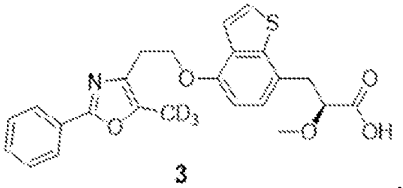

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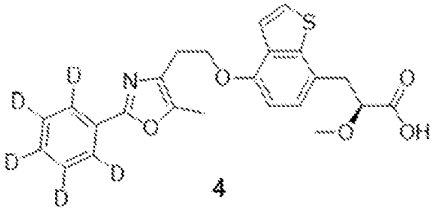

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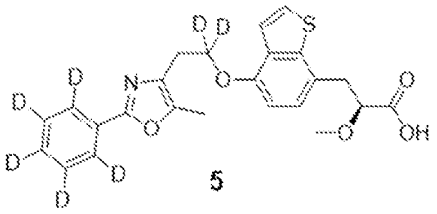

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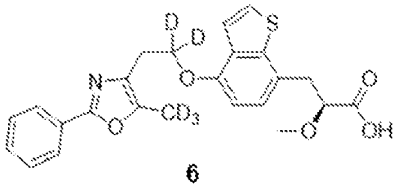

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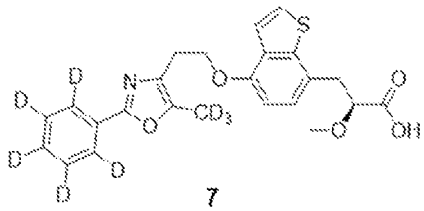

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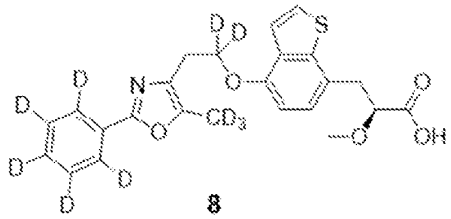

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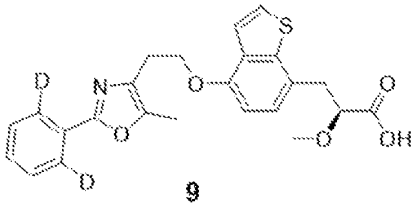

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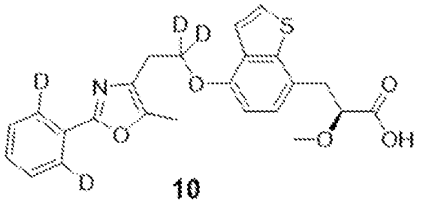

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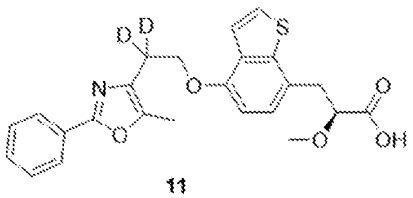

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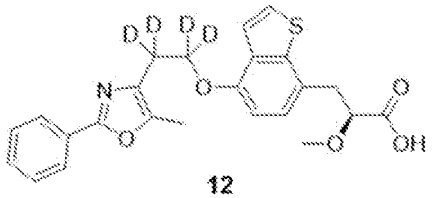

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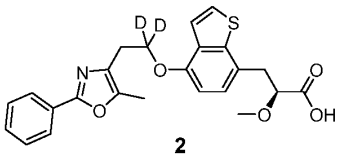
, or a pharmaceutically acceptable salt thereof.

[0101] In certain embodiments, the compound is



2

, or its pharmaceutical acceptable salt.

[0102] The term "is/are deuterium/D", when used to describe a given position in a molecule or a drawing of a molecular structure, means that the specified position is deuterium or that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium.

[0103] Deuterium (^{2}H or D) is a stable and non-radioactive isotope of hydrogen which has approximately twice the mass of protium (^{1}H), the most common isotope of hydrogen.

[0104] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also, unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[0105] In certain embodiments, deuterium enrichment of the compound provided herein is no less than about any of 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99%.

[0106] In certain embodiments, deuterium enrichment of the compound provided herein is no more than about any of 99.9%, 99%, 98%, 97%, 96%, 95%, or 90%.

[0107] In certain embodiments, deuterium enrichment of the compound provided herein is in a range, such as between 50% and 99.9%; between 50% and 99%; between 50% and 98%; between 50% and 97%; between 50% and 96%; between 50% and 95%; between 50% and 90%; between 60% and 99.9%; between 60% and 99%; between 60% and 98%; between 60% and 97%; between 60% and 96%; between 60% and 95%; between 60% and 90%; between 70% and 99.9%; between 70% and 99%; between 70% and 98%; between 70% and 97%; between 70% and 96%; between 70% and 95%; between 70% and 90%; between 80% and 99.9%; between 80% and 99%; between 80% and 98%; between 80% and 97%; between 80% and 96%; between 80% and 95%; between 80% and 90%; between 90% and 99.9%; between 90% and 99%; between 90% and 98%; between 90% and 97%; between 90% and 96%; between 90% and 95%; between 95% and 99.9%; between 95% and 99%; between 95% and 98%; between 95% and 97%; between 95% and 96%; between 96% and 99.9%; between 96% and 99%; between 96% and 98%; between 96% and 97%; between 97% and 99.9%; between 97% and 99%; between 97% and 98%; between 98% and 99.9%; between 98% and 99%; or between 99% and 99.9%.

[0108] In certain embodiments, deuterium enrichment of the compound provided herein is between 90% and 99.9%, preferably between 95% and 99.9%, preferably between 97% and 99%, preferably between 98% and 99%, particularly 98.5%. Overall deuterium enrichment of the compounds of the disclosure can be determined using mass spectroscopy, according to methods known in the art.

[0109] The term "deuterium enrichment" as used herein refers to the percentage of incorporation of deuterium at a given position in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy.

[0110] In some embodiments, the method provided herein comprises administering a pharmaceutically acceptable salt of the compound provided herein to an individual.

[0111] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group.

[0112] As used herein, the term "pharmaceutically acceptable salt", unless otherwise indicated, includes salts that retain the biological effectiveness of the free acids and bases of the specified compound and that are not biologically or otherwise undesirable. Contemplated pharmaceutically acceptable salt forms include, but are not limited to, mono, bis, tris, tetrakis, and so on. Pharmaceutically acceptable salts are non-toxic in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0113] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate,

cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

[0114] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, t-butylamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 19thed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995; "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth, Wiley-VCH, Weinheim, Germany, 2002. Such salts can be prepared using the appropriate corresponding bases.

[0115] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound can be dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution containing the appropriate acid and then isolated by evaporating the solution. Thus, if the particular compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0116] Similarly, if the particular compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as L-glycine, L-lysine, and L-arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as

hydroxyethylpyrrolidine, piperidine, morpholine or piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0117] It is also to be understood that the compounds of present disclosure can exist in unsolvated forms, solvated forms (e.g., hydrated forms), and solid forms (e.g., crystal or polymorphic forms), and the present disclosure is intended to encompass all such forms.

[0118] As used herein, the term "solvate" or "solvated form" refers to solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water, the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

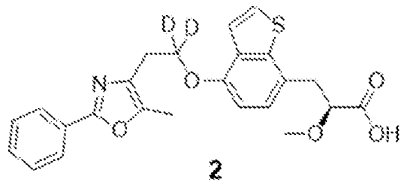
[0119] As used herein, the terms "crystal form", "crystalline form", "polymorphic forms" and "polymorphs" can be used interchangeably, and mean crystal structures in which a compound (or a salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

[0120] Those of skill in the art will appreciate that compounds of the present disclosure may exist in different tautomeric forms, and all such forms are embraced within the scope of the present disclosure. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. The presence and concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. By way of examples, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol, amide-imidic acid, lactam-lactim, imine-enamine isomerizations and annular forms where a proton can occupy two or more positions of a heterocyclic system. Valence tautomers include interconversions by

reorganization of some of the bonding electrons. Tautomers can be in equilibrium or sterically locked into one form by appropriate substitution. Compounds of the present disclosure identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

[0121] Synthesis of the compounds provided herein, including pharmaceutically acceptable salts thereof, are provided in WO2023016440 A1, the content of which is incorporated herein by reference in its entirety. The compounds provided herein may also be prepared using any known organic synthesis techniques and can be synthesized according to any possible synthetic routes.

[0122] In some embodiments, provided herein is a method of treating autosomal dominant polycystic kidney disease (ADPKD) in an individual, comprising administering to the individual compound 2:



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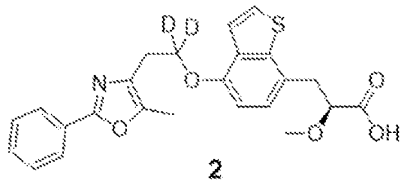
or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index. In some embodiments, the individual is a human. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered

(e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food.

[0123] In some embodiments, provided herein is a method of improving renal survival in an individual, comprising administering to the individual compound 2:



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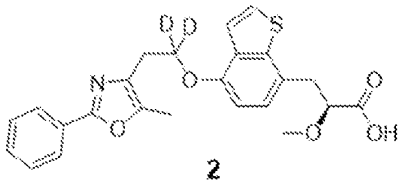
or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index. In some embodiments, the individual is a human. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150

μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food.

[0124] In some embodiments, provided herein is a method of slowing the decline of eGFR in an individual, comprising administering to the individual compound 2:



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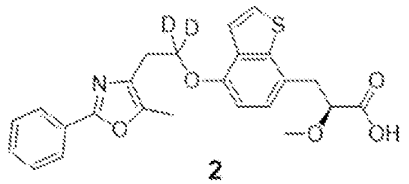
[0125] or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%, compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

[0126] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index. In some embodiments, the individual is a human. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the

compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food.

[0127] In some embodiments, provided herein is a method of improving kidney function in an individual, comprising administering to the individual compound 2:



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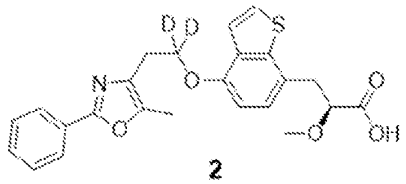
[0128] or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%, compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

[0129] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index. In some embodiments, the individual is a human. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a

day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food.

[0130] In some embodiments, provided herein is a method of improving quality of life in an individual, comprising administering to the individual compound 2:



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or a pharmaceutically acceptable salt thereof.

[0131] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%, such as by at least about any of 2%, 5%, 7.5%, 10%, 12%, 14%, 16%, 18%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%, compared to the individual not administered with the compound or the pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2.5 mL/min/1.73m^2 per year, such as no more than about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year, about 1 mL/min/1.73m^2 to about 1.5 mL/min/1.73m^2 per year, or about 1.5 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

[0132] In some embodiments, the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index. In some embodiments, the individual is a human. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered (e.g., orally) twice a

day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered orally. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered with food. In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered without food.

Composition

[0133] In some embodiments, the method provided herein comprising administering to the individual a pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof provided herein. In some embodiments, the pharmaceutical composition further comprises one or more additional medicinal agents, pharmaceutical agents, adjuvants, carriers, excipients, and the like. Suitable medicinal and pharmaceutical agents include those described herein. In some embodiments, the pharmaceutical composition includes a pharmaceutically acceptable excipient or adjuvant and at least one compound as described herein. Examples of pharmaceutically acceptable excipients include, but are not limited to, mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium croscarmellose, glucose, gelatin, sucrose, and magnesium carbonate.

[0134] Pharmaceutically acceptable compositions include solid, semi-solid, liquid and aerosol dosage forms, such as tablet, capsule, powder, liquid, suspension, suppository, and aerosol forms. The pharmaceutical composition may be administered in sustained or controlled release dosage forms (*e.g.*, controlled/sustained release pill, depot injection, osmotic pump, or transdermal (including electrotransport patch forms) for prolonged timed, and/or pulsed administration at a predetermined rate. In some embodiments, the pharmaceutical composition may be administered in unit dosage forms suitable for single administration of a precise dose.

[0135] In some embodiments, the pharmaceutical composition may take the form of a pill or tablet and thus the pharmaceutical composition may comprise, along with the compound or pharmaceutically acceptable salt thereof, one or more of a diluent (*e.g.*, lactose, sucrose, dicalcium phosphate), a lubricant (*e.g.*, magnesium stearate), and/or a binder (*e.g.*, starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives). Other solid dosage forms

include a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils or triglycerides) encapsulated in a gelatin capsule.

[0136] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing or suspending etc. a compound or a pharmaceutical salt thereof, and optional pharmaceutical additives in a carrier (*e.g.*, water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution or suspension. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, as emulsions, or in solid forms suitable for dissolution or suspension in liquid prior to injection. The percentage of the compound contained in such parenteral compositions depends, for example, on the physical nature of the compound, the activity of the compound and the needs of the subject (*e.g.*, human).

[0137] Pharmaceutical compositions of the compound or pharmaceutical salt thereof may also be administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the pharmaceutical composition may have diameters of less than 50 microns, or in some embodiments, less than 10 microns.

Kit

[0138] Also provided herein are kits for carrying out the methods described herein, which comprises one or more compounds described herein, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmacological composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein or a pharmaceutically acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for use in the treatment of ADKPD.

[0139] In some embodiments, the kit comprises suitable packaging. The kit may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. One or more components of a kit may be sterile and/or may be contained within sterile packaging.

[0140] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein (*e.g.*, a therapeutically effective amount) and/or a second pharmaceutically active compound useful for a disease detailed herein (*e.g.*, ADPKD) to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0141] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods described herein. The instructions included with the kit generally include information as to the components and their administration to an individual.

[0142] Also provided herein are compositions for use in any of the methods (e.g., method of treating ADPKD) described here. Also provided herein are use of any one of the compound described herein for the manufacture of medicament for treating ADPKD.

EXAMPLES

Example 1. Efficacy Study of Compound 2 in P18 Tamoxifen-Induced Polycystic Kidney Disease Mouse Model.

[0143] The study objective was to determine the efficacy of Compound 2 in a P18 Tamoxifen-induced polycystic kidney disease model (Ksp-TamCre x Pkd1Lox). Animals were dosed daily with either compound 2 or controls, and eventually humanely sacrificed. The parameters that were determined during and at the end of this study were body weight and kidney weight, blood urea levels, right kidney volume by ultrasound, and histopathological assessment including cyst ratio.

Animal Group and Dose

[0144] Animals were subdivided in different experimental groups; one for each compound formulation. Additionally, the following control groups were included: a healthy control group

dosed with Tamoxifen vehicle and with the compound vehicle via oral gavage, a negative control group dosed with Tamoxifen and the compound vehicle via oral gavage, and a reference control group dosed with Tamoxifen and Tolvaptan (the active component of Otsuka Tolvaptan) in the food. Compound 2 was dosed at 0.1 mg/kg mouse or 0.5 mg/kg mouse respectively. Tamoxifen was introduced orally to induce polycystic kidney disease in selected groups at postnatal day (PND) 18, 19 and 20. The compound 2 and various control formulations were administered starting from PND42 until maximally PND110, as shown in Table B-1.

Table B-1: Summary of experimental groups with corresponding dosage regimen.

Group N°	Tamoxifen		Compound		N mice
	Administration (PND)	Dose (mg/kg)	Administration (PND)	Dose (mg/kg)	
A	18+19+20	0	42 - 110	0 (Vehicle – healthy control)	10
B		150	42 - 110	0 (Vehicle – negative control)	22
C		150	42 - 110	Tolvaptan 0.1% (reference control)	22
D		150	42 - 110	0.1 mg/kg (compound 2)	22
E		150	42 - 110	0.5 mg/kg (compound 2)	22

[0145] Solutions suitable for oral administration were prepared fresh every 6 days. The prepared test items were stored at 4°C. The daily dosage was:

- 0.1% Tolvaptan dosed in the food,
- 0.1 mg compound 2 per kg mouse (0.01 mg/mL; 10 mL/kg),
- 0.5 mg compound 2 per kg mouse (0.05 mg/mL; 10 mL/kg).

[0146] The vehicle which was used for preparation of the Tamoxifen dilutions was corn oil. The vehicle for the compound 2 formulation was 0.5% sodium arboxymethylcellulose. This was prepared before the start of dosing as this solution could be stably stored at room temperature.

[0147] The formulation of compound 2 was kept at 4°C (protected from light) for 6 days without any issues regarding compound stability. The compound 2 has not shown toxicity or other adverse effects at the formulated concentrations.

Accommodation And Environmental Control

[0148] Animals were transferred to the rodent unit where they were housed individually in ventilated cages (IVC) from Innovive with a filter top, sterilized corncob bedding (irradiated,

dust-free supplied by Innovive, USA) and a shelter-like device (if feasible; PLEXX, The Netherlands) to stimulate natural patterns of behavior. Animals were maintained at 21 ± 2 °C and a relative humidity between 40 to 70%, on a 12/12 light/dark cycle with air renewed 8-20 times per hour. The documentation regarding air renewal and dark/light cycle were managed and archived by the responsible head of the animal management.

[0149] Quality control data of bedding, diet and water were evaluated at regular intervals. Documentation was retained in the Departmental Archives. No interactions were expected between the test item and the usual constituents and contaminants of bedding, food, and water, which were analyzed routinely.

Diet And Water Supply

[0150] During the in-life period, the animals had free access to standard pelleted food (Diet No. V1534-703, supplied by SNIFF, Germany). The animals had free access to water from Aquavive drinking bottles (Innovive), which were refreshed when necessary.

[0151] Tolvaptan diet was prepared by mixing Tolvaptan powder in standard pelleted food (diet No. V1534- 703, SNIFF, Germany) at 1g Tolvaptan/kg food. This mix was made into new food pellets by SNIFF, packed in sealed bags and ready for direct use.

Experimental Procedures And Parameters

[0152] Tamoxifen was administered orally on PND18, PND19, and PND20. One administration of 0.05 mL (to an animal of 5 g) solution was given without interval and anesthesia. From PND42, compound dosage was given on a daily base via oral gavage until PND110.

[0153] The animals were observed daily during the in-life period for any behavioral and physical abnormalities. When clinical observations were detected, animals were monitored and checked more frequently. In general, animals showing signs of weakness and/or weight loss were supplemented with a SC injection of saline. Four animals were observed with diarrhea on PND21. One animal of the Tamoxifen-induced control group, two animals of the compound 2 0.1 mg/kg group, and one animal of the compound 2 0.5 mg/kg group.

[0154] Body weight was determined daily from PND18 to PND20, and weekly from PND20 to PND110.

[0155] Starting from PND75, weekly blood sampling via the submandibular vein was performed for urea analysis. Plasma was used for urea level determination via the Urea Nitrogen

(BUN) colorimetric detection kit (REF: EIABUN; Invitrogen, Thermo Fisher Scientific). 2.5 μL plasma was added to a 96-well microplate, together with two test reagents and sterile water. Furthermore, a standard dilution was added to the 96-well microplate to analyze the data. Samples were tested in duplicate. Results were obtained via a 96-well microplate reader (Tecan, Infinite M200) with optical absorption at 450 nm.

[0156] Kidney volume was determined at three time points during the study: at PND41, PND76, and PND97. Mice were anesthetized via isoflurane anesthesia. As the right kidney volume was determined, the right side of the abdomen was shaved, and all remaining hairs were removed with hair removal creme. The mouse was kept under anesthesia while being placed on a heating path under the 3D motor with echo probe connected to the Vevo3100 ultrasound. The right kidney was imaged from the ventral aspect of the abdomen creating the transverse sagittal plane. The right kidney was centralized, and a complete 3D scan was taken whereafter the mouse was removed from isoflurane anesthesia and placed on a heating path until completely awake.

Terminal Procedures And Parameters

[0157] On the day of sacrifice, the animals were terminated 24 hours after the last dosing. Animals were sacrificed humanely by exsanguination using a 1 mL syringe and needle from the heart under deep isoflurane anesthesia (ISL-04-15). Termination was reassured by cervical dislocation. Subsequently, kidneys were isolated and processed after opening of the abdominal cavity. Animals that had to be euthanized due to illness would be autopsied and examined in detail for gross anatomical abnormalities (gross pathology). However, no animals needed to be euthanized prematurely due to illness and no gross anatomical abnormalities were detected at sacrifice.

[0158] As much blood as possible was collected via a heart puncture on the day of sacrifice. This blood sample was used for assessment of pharmacokinetics (PK) of the compounds. The collected blood was processed individually per animal for plasma collection. Plasma was stored at -80°C in controlled freezers until shipment to a designated lab.

[0159] Plasma was prepared by storing terminal blood samples on ice in EDTA-K2 plasma tubes (Sarstedt). Within 30 minutes, blood samples were centrifuged for 15 minutes at 2,000 g. The remaining supernatant was plasma and was stored in a 1.5 mL Eppendorf at -80°C.

[0160] Both kidneys were weighed before processing. One kidney was placed in 10% formalin (app. 4% formaldehyde in solution) for 48 hours, whereafter the kidney was cut in transverse

direction and the formalin was replaced by 70% ethanol. One half was sent to pathology and one half was preserved as a spare specimen. The other kidney was cut in transverse direction and weighed separately. One half was frozen separately by placing them in cryopreservation tubes in liquid nitrogen and then stored at -80 °C. The other half was cut to ≤0.5 cm in any dimension, followed by immersion in RNA later (Thermofisher, AM7021) and stored in a 2mL tube at 4°C overnight to allow the solution penetrate the tissue.

[0161] The fixated kidney was cut in transverse direction and processed for paraffin embedding and further pathological assessment after hematoxylin-eosin staining. This was done by a certified pathologist. For each kidney one section was evaluated. The cystic areas (any tubules that have lumen diameter >9 microns, which is the normal tubular diameter) was identified by a color thresholding method using an image analysis system (HALO-Indica Labs-Albuquerque, NM, USA). The cystic areas of a kidney was calculated as the sum of the areas (calculated in millimeters) of the cystic lesions found in all the section analyzed, in which dilated tubules are included, while dilated veins and pelvic cavity are excluded by manual tissue classifier option: (cyst area/total area)x100%.

Results And Discussion

Body weight

[0162] FIG. 1 showed the progression of body weight of the mice from PND 18-110. In all groups, there was a progression in growth over the course of the study, related to the normal physiological growth curve of mice in this age range. The healthy control group showed a steeper increase in body weight towards PND42 compared to the Tamoxifen-induced groups. Therefore, it seemed that dosing of Tamoxifen put a burden on the animals, resulting in a temporarily slower body weight increase compared to the healthy control group.

[0163] Body weight on the day of termination was presented in FIG. 2 and FIG. 3. There were no significant differences in body weight between the healthy control group and the Tamoxifen-induced control group (Unpaired t test), nor between the Tamoxifen-induced control group and the Tamoxifen- induced treatment groups (Kruskal-Wallis test with Uncorrected Dunn's post hoc testing).

Kidney weight and kidney weight corrected for bodyweight

[0164] FIG. 4 and FIG. 5 present total kidney weight on the day of termination. Total kidney weight was significantly lower in the healthy control group compared to the Tamoxifen-induced control group ($p<0.0001$, Mann-Whitney test). The Tamoxifen-induced treatment group of compound 2 at a dose of 0.1mg/kg tended to lower kidney weight compared to the Tamoxifen-induced control group .

[0165] FIG. 6 and FIG. 7 showed the total kidney weight corrected for body weight (2KW/BW*100%). Total kidney weight corrected for body weight was significantly lower in the healthy control group compared to the Tamoxifen-induced control group ($p<0.0001$, Mann-Whitney test). The Tamoxifen-induced treatment group of compound 2 at a dose of 0.1mg/kg tended to reduce the kidney weigh corrected for body weight when compared to the Tamoxifen-induced control group.

Urea level

[0166] Urea levels on the day of termination were presented in FIG. 8 and FIG. 9. Urea levels were significantly lower in the healthy control group compared to the Tamoxifen-induced control group ($p<0.0001$, Unpaired t test). The urea levels from the compound 2 at a dose of 0.1 mg/kg group were significantly lower compared to the Tamoxifen-induced control group ($p=0.0299$, Kruskal-Wallis test with Uncorrected Dunn's post hoc testing).

Survival rate

[0167] As a part of the approved experimental protocol, mice were tested for blood urea levels every week starting from PND75. The animals that exhibited a urea level of 20 mmol/L or higher (as a measure of renal function decline and an indicator of the onset of end-stage renal disease) were sacrificed prior to the termination of the experiment. Per protocol, the experiment was to be terminated at the latest on PND115, or when 50% of the animals in the corresponding vehicle control group reached the blood urea threshold of 20 mmol/L. This study was terminated at (on average) PND110, as the mice were between PND109 and PND111 at termination.

[0168] The study was terminated on PND110, but all mice that had not reached the urea threshold of 20 mmol/l at PND110 were considered to survive until after PND110, which was indicated as survival until PND111. All mice of the healthy control group survived until PND111. In the Tamoxifen-induced control group 7 out of 22 mice survived until PND111. In the Tolvaptan group 7 out of 22 mice survived until PND111. In the compound 2 at a dose of 0.1

mg/kg group, 11 out of 22 mice survived until PND111. In the compound 2 at a dose of 0.5 mg/kg group, 8 out of 22 mice survived until PND111.

[0169] FIG. 10 and FIG. 11 demonstrated the survival rates between groups, expressed in survival days after treatment. The survival rate was significantly lower in the Tamoxifen-induced control group compared to the healthy control group (Log-Rank (Mantel-Cox) test, p=0.0010). The Tamoxifen-induced treatment group of compound 2 at a dose of 0.1 mg/kg showed higher survival rate compared to Tamoxifen-induced control group (Log-Rank (Mantel-Cox) test), and the compound 2 at a dose of 0.1 mg/kg group showed a trend of improved renal survival rate in comparison to the Tamoxifen-induced control group.

Right kidney volumes corrected for bodyweight

[0170] Right kidney volume was determined on PND41, PND76, PND97, and corrected for body weight (KV/BW). These data are presented in FIG. 12 - FIG. 17.

[0171] On PND41, the healthy control group showed a significantly lower KV/BW compared to the Tamoxifen induced control group ($p<0.0001$, Unpaired t test). The Tamoxifen-induced treatment groups did not significantly change KV/BW compared to the Tamoxifen-induced control group (Kruskal-Wallis test with Uncorrected Dunn's post hoc testing).

[0172] On PND76 and PND97, the healthy control group showed a significantly lower KV/BW compared to the Tamoxifen induced control group ($p<0.0001$, Mann-Whitney test). The Tamoxifen-induced treatment groups tended to lower KV/BW compared to the Tamoxifen-induced control group (Kruskal-Wallis test with Uncorrected Dunn's post hoc testing), and the compound 2 at a dose of 0.1mg/kg group showed improved kidney volume/body weight in some extent, especially at PND76.

Histopathological Results And Discussion

[0173] 98 HE-stained slides of mouse kidneys were submitted for histopathologic evaluation. The slides were evaluated microscopically by a board-certified veterinary pathologist.

[0174] Cystic lesions were quantitatively assessed on the submitted slides, which were digitally scanned using a Nanozoomer. For each kidney one section was evaluated. The cystic areas (any tubules that had lumen diameter >9 microns, which is the normal tubular diameter) were identified by a colour thresholding method using an image analysis system (HALO-Indica Labs-Albuquerque, NM, USA). The cystic areas of a kidney were calculated as the sum of the areas (calculated in square millimetres) of the cystic lesions found in all the sections analysed, in

which dilated tubules are included, while dilated veins and pelvic cavity are excluded by manual tissue classifier option. The cystic index (CI) was defined as the area percentage of lumen over the total surface area and was calculated as follow: (cyst area/total area) x100%.

[0175] Cystic lesions were also semi-quantitatively assessed on a scale of 0 to 5 with 0.5 interval based on the following grading system: 0: no cysts visible; 1: from 1 to a few, scattered, small cysts; 2: mild number of cysts; 3: moderate number of cysts; 4: numerous cysts present; 5: almost all the parenchyma replaced by cysts.

[0176] Non-cystic/other lesions in the kidney were evaluated based on severity (Grade 0: no lesion; 1: minimal; 2: mild; 3: moderate; 4: severe) and using the following criteria:

[0177] Proliferation of immature mesenchyme around cystic structures, histologically visible as concentric layers of large, immature fibroblasts.

[0178] Tubular changes: A) attenuation/dilatation; B) necrosis and loss of tubules; C) regeneration of the tubular epithelial cells; D) presence of hyaline, proteinaceous or other types of casts; E) presence of inflammatory cells.

[0179] Glomerular changes: A) atrophic/sclerotic glomeruli (small glomeruli with peripheral nuclei and unapparent capillaries); B) Increased cellularity; C) Mesangial matrix deposition; D) presence of inflammatory cells.

[0180] Table B-2 provided an overview of group averages of main histological lesions of the Tamoxifen-induced groups.

Table B-2: Cystic and main non-cystic lesions: overview average values per group

Group	Glomerular Atrophy	Tubular attenuation	Cysts	
			Cystic grade	Cystic Index
Tamoxifen-induced control	2.61	2.73	3.84	42.45%
Tolvaptan 0.1%	2.34	2.66	3.93	43.92%
Compound 2 0.1mg/kg	2.14	2.30	3.59	41.76%
Compound 2 0.5mg/kg	2.45	2.45	3.68	41.63%

[0181] Cystic index (cystic area/total surface area *100) was presented in FIG. 18. There was a significantly higher cystic index in the Tamoxifen-induced control group compared to the healthy control group ($p<0.0001$, Mann-Whitney test). This difference confirmed

histopathological cyst development by Tamoxifen induction in this Ksp-TamCre x Pkd1Lox mouse model. There was no significant difference in cystic index between the Tamoxifen-induced control group and the Tamoxifen-induced treatment groups (one-way ANOVA with Uncorrected Fisher's LSD post hoc testing).

[0182] Cystic grade was presented in FIG. 19. There was a significantly higher cystic grade in the Tamoxifen- induced control group compared to the healthy control group ($p<0.0001$, Mann-Whitney test). No significant difference was observed between the Tamoxifen-induced treatment groups and the Tamoxifen-induced control group (Kruskall-Wallis test with Uncorrected Dunn's post hoc testing).

[0183] Epithelial thinning without cyst formation (tubular attenuation) was seen as an early stage of cyst formation, followed by tubular dilatation. Tubular dilatation grade was presented in FIG. 20. Tubular dilatation was significantly lower in the compound 2 at a dose of 0.1 mg/kg group compared to the Tamoxifen-induced control group ($p=0.0445$, Kruskall-Wallis test with Uncorrected Dunn's post hoc testing).

[0184] Proteinuria and casts reflected glomerular dysfunction. The presence of casts was presented in FIG. 21. It was expected that the higher the cyst rate, the higher the proteinuria would be. There was a significant lower tubular cast rate in the Tolvaptan group and the compound 2 at a dose of 0.1mg/kg group compared to the Tamoxifen-induced control group ($p=0.0475$ and $p=0.0039$, respectively, Kruskall-Wallis test with Uncorrected Dunn's post hoc testing).

[0185] Tubular inflammation was presented in FIG. 22. The Tamoxifen-induced treatment groups of compound 2 tended to lower the tubular inflammation grade compared to the Tamoxifen-induced control group (one-way ANOVA with Uncorrected Fisher's LSD post hoc testing).

[0186] Glomerular atrophy/sclerosis was a phenomenon of glomerular damage and was presented in FIG. 23. Due to compression (and associated vascular restrictions) and glomerular dysfunction, atrophy was initiated (most prone in the cortical periphery). There was no significant difference in glomerular atrophy/sclerosis grade between the Tamoxifen-induced treatment groups and the Tamoxifen- induced control group (Kruskall-Wallis test with Uncorrected Dunn's post hoc testing).

[0187] In general, the main histological lesions observed in the diseased kidney were that of a cystic kidney, characterized by tubular cysts. The smallest cystic index was observed in the compound 2 at a dose of 0.5 mg/kg group. The mildest pathology was observed in the compound 2 at a dose of 0.1 mg/kg group. There was no significant difference in cystic index, cystic grade, glomerular atrophy, and tubular inflammation if we compared the Tamoxifen-induced control group to the Tamoxifen-induced treatment groups, although the compound 2 at a dose of 0.1 mg/kg group consistently showed numerically better than the Tamoxifen-induced control group. Tubular dilatation and tubular casts were significantly lower in the compound 2 at a dose of 0.1 mg/kg group compared to the Tamoxifen-induced control group. Tubular casts were also significantly lower in the Tolvaptan group compared to the Tamoxifen-induced control group.

Summary

[0188] The kidney-specific inactivation of the Pkd1 gene resulted in a significant presentation of cystic kidney disease, characterized by tubular cysts. Tamoxifen-induced control animals exhibited extensive cyst formation within the nephron epithelia. Analysis of cystic index and cystic grade showed no significantly differences between the Tamoxifen-induced control group and the Tamoxifen-induced treatment groups. Tubular casts and tubular dilatation were significantly lower in the compound 2 at a dose of 0.1 mg/kg group compared to the Tamoxifen-induced control group. Tubular casts were also significantly lower in the Tolvaptan group compared to the Tamoxifen-induced control group.

[0189] Results showed that the Tamoxifen-induced treatment groups tended to reduce the total kidney weight and 2KW/BW ratio compared to the Tamoxifen-induced control group.

[0190] Right kidney volume was determined by ultrasound measurements and corrected for body weight (KV/BW) on PND41, PND76, and PND97. Tamoxifen- induced treatment groups tended to improve KV/BW ratio on PND76, and PND97 compared to the Tamoxifen-induced control group, and the compound 2 at a dose of 0.1mg/kg group showed improved kidney volume/body weight in some extent, especially at PND76.

[0191] In all groups, there was a similar progression in growth over the course of the study, related to the normal physiological growth curve of mice in this age range. There was no significant difference in body weight at termination when comparing the Tamoxifen-induced control group to the Tamoxifen- induced treatment groups.

[0192] The urea level of the compound 2 0.1 mg/kg group was significantly lower compared to the Tamoxifen- induced control group.

[0193] In summary, analysis of common anatomy and pathology parameters (cystic index and 2KW/BW ratio) showed no significant difference when comparing the Tamoxifen-induced control group to the Tamoxifen-induced treatment groups, although a trend of improvement can be seen in the compound 2 at a dose of 0.1 mg/kg group. Blood urea levels, tubular dilatation, and tubular casts were also significantly lower in the compound 2 at a dose of 0.1 mg/kg group compared to the Tamoxifen-induced treatment group. This indicated that compound 2 0.1 mg/kg elicited a positive therapeutic effect in a P18 Tamoxifen-induced mouse model of polycystic kidney disease (Ksp-TamCre x Pkd1Lox).

Example 2. Compound 2 In-Human Clinical Study

[0194] This study was a single-center, first in human (FIH), double-blind, randomized, placebo-controlled, Single Ascending Dose (SAD) and multiple Ascending Dose (MAD) study to evaluate the safety, tolerability, PK and PD of compound 2 following oral administration to healthy volunteers.

[0195] Exposure to compound 2 increased in a dose proportional manner across the dose escalation study, following both single doses (50 μg, 150 μg, 300 μg or 600 μg) and multiple doses (50 μg, 150 μg or 300 μg QD for 14 days). Peak plasma concentrations were reached at approximately 2 hours after oral administration under fasted conditions, and at approximately 2.2 hours after administration with food. Except for a slight delay in T_{max} and a slightly lower in C_{max} otherwise food had no clinically relevant effect on the bioavailability of compound 2. The apparent terminal half-life of compound 2 was in the range of 8 to 11 hours in healthy subjects. There was no accumulation of compound 2 after multiple dosing. Two metabolites M1(AP303C3) and M2(AP303C4), were confirmed as the major circulating metabolites, and both are pharmacologically inactive. Renal excretion of parent drug compound 2 was negligible.

[0196] The pharmacodynamic effects of compound 2 were assessed in the MAD part of this study in healthy subjects. The reduction of mean eGFR from baseline was evidenced after 14 days treatment in healthy subjects. The mean baseline (screening data) eGFR was 89.5, 91.5 and 93.7 mL/min/1.73m2 in 50 μg, 150 μg and 300 μg QD groups, the mean absolute changes and

the mean percentage reduction in eGFR between baseline and Day 13 (one day before the last dose) was 2.2 (2.5%); 6.2 (6.8%) and 10.3 mL/min/1.73m^2 (11.0%) in 50 µg, 150 µg and 300 µg QD cohorts respectively, as shown in FIG. 24 and Table B-3. The reduced eGFR in all dose groups was fully returned towards baseline level at the 14-day off-treatment follow-up visit, which suggested a clear glomerular hemodynamic effect.

Table B-3. Summary of Mean eGFR in Compound 2 Test and Control Clinical Trial Groups

	50 mcg QD	**150 mcg QD**	**300 mcg QD**
Mean Baseline eGFR (mL/min/1.73m2)	89.5	91.5	93.7
Mean eGFR at Day 13	87.3	85.3	83.4
Mean eGFR Change from Baseline	-2.2 (2.5%)	-6.2 (6.8%)	-10.3 (11.0%)
Mean eGFR at Day 28 (F/U)	93.3	93.3	96.4

NOTE: Up to date, only one human study of compound 2 has been completed in which single doses of up to 600 µg and multiple doses of up to 300 µg were administered daily for 14 days in healthy subjects. Compound 2 has been safe and well tolerated in this study, with adverse events (AEs) being comparable with the placebo group and generally mild in severity.

Example 3. Method of treating ADPKD in human

[0197] A multi-center, double-blind, placebo-controlled, randomized-withdrawal, parallel-group study is conducted to evaluate the safety, tolerability, the effect of Compound 2 on estimated GFR changes in patients with ADPKD at high risk of progression. The objectives of this study include: (1) evaluating the effect of Compound 2 treatment in reducing the change in estimated glomerular filtration rate (eGFR) from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in patients with ADPKD; (2) assessing the safety and tolerability of Compound 2 treatment in patients with ADPKD; (3) evaluating the effect of Compound 2 treatment on eGFR slope change as compared with placebo in patients with ADPKD; and (4) evaluating the effect of Compound 2 treatment on the change of height-adjusted total kidney volume (htTKV) as compared with placebo in patients with ADPKD.

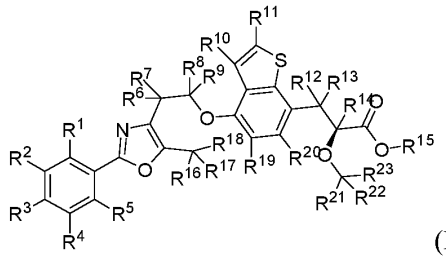
[0198] The study population includes male and female patients with ADPKD at high risk for progression, which is defined based on age and eGFR. The total duration of the study is approximately 32 weeks, which include up to 4 weeks for screening, 24-week randomized treatment period, and 4-week follow-up period.

[0199] During the study, two doses of Compound 2 between 75~150 μg as well as matching placebo are administered once a day orally with a light breakfast to all patients during the treatment period.

[0200] The efficacy, safety, drug tolerability, and PK parameters of Compound 2 after the oral administration are recorded and monitored in the subjects.

CLAIMS

1. A method of treating autosomal dominant polycystic kidney disease (ADPKD) in an individual, comprising administering to the individual a compound of Formula (I):

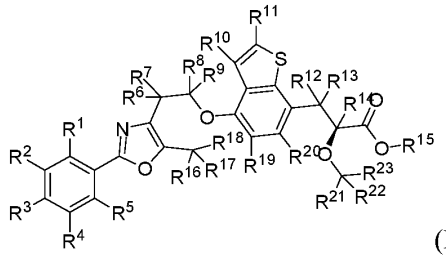


(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D.

2. A method of improving renal survival in an individual having ADPKD, comprising administering to the individual a compound of Formula (I):

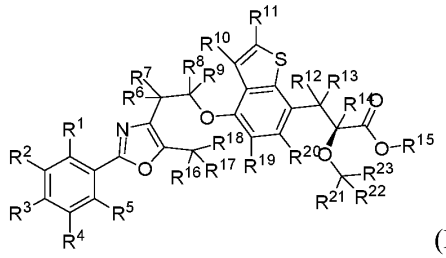


(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D.

3. A method of slowing the decline of estimated glomerular filtration rate (eGFR) in an individual having ADPKD, comprising administering to the individual a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently from each other are H or D.

4. The method of any one of claims 1-3, wherein at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty one, twenty two or twenty three of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} is D.

5. The method of any one of claims 1-4, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing epithelial thinning or tubular attenuation in the individual.

6. The method of any one of claims 1-5, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing tubular dilatation in the individual.

7. The method of any one of claims 1-6, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing tubular casts in the individual.

8. The method of any one of claims 1-7, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing blood urea level of the individual by at least about 5%.

9. The method of any one of claims 1-8, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing down the growth of cystic areas.

10. The method of any one of claims 1-9, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline of eGFR in the individual by at least about 2%.

11. The method of any one of claims 1-10, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of no more than about 2 mL/min/1.73m^2 per year.

12. The method of any one of claims 1-11, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing the decline rate of eGFR in the individual to a value of about 1 mL/min/1.73m^2 to about 2 mL/min/1.73m^2 per year.

13. The method of any one of claims 1-12, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic areas in the individual.

14. The method of any one of claims 1-13, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in slowing down the increase of cystic index.

15. The method of any one of claims 1-14, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic index in the individual.

16. The method of any one of claims 1-15, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of cystic grade in the individual.

17. The method of any one of claims 1-16, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of glomerular atrophy or sclerosis in the individual.

18. The method of any one of claims 1-17, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered does not induce a more than about 15% reduction of tubular inflammation in the individual.

19. The method of any one of claims 1-18, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing kidney volume.

20. The method of any one of claims 1-19, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in reducing the ratio of kidney volume to kidney weight (KV/KW).

21. The method of any one of claims 1-20, wherein the amount of the compound or the pharmaceutically acceptable salt thereof administered is effective in improving renal survival while does not induce a more than about 15% reduction of cystic index.

22. The method of any one of claims 1-21, wherein the individual is a mammal.

23. The method of any one of claims 1-22, wherein the individual is a human.

24. The method of any one of claims 1-23, wherein the compound or the pharmaceutically acceptable salt thereof is administered once or twice a day at a daily dose of about 50 μg, about 75 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 225 μg, about 250 μg, about 275 μg, about 300 μg, or a range between any two of the preceding values.

25. The method of any one of claims 1-24, wherein the compound or the pharmaceutically acceptable salt thereof is administered once or twice a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values.

26. The method of any one of claims 1-25, wherein the compound or the pharmaceutically acceptable salt thereof is administered once a day at a daily dose of about 75 μg, about 100 μg, about 125 μg, about 150 μg, or a range between any two of the preceding values.

27. The method of any one of claims 1-26, wherein the compound or the pharmaceutically acceptable salt thereof is administered twice a day at a dose of about 50 μg to about 75 μg, resulting a daily dose of about 100 μg to about 150 μg.

28. The method of any one of claims 1-27, wherein the compound or the pharmaceutically acceptable salt thereof is administered orally.

29. The method of any one of claims 1-28, wherein the compound or the pharmaceutically acceptable salt thereof is administered with food.

30. The method of any one of claims 1-29, wherein the compound or the pharmaceutically acceptable salt thereof is administered without food.

31. The method of any one of claims 1-30, wherein the compound or the pharmaceutically acceptable salt thereof is administered when the individual is fasted.

32. method of any one of claims 1-31, wherein the compound or the pharmaceutically acceptable salt thereof is administered for 14 days.

33. The method of any one of claims 1-32, wherein the individual has a mutation in PKD1 or PKD2.

34. The method of any one of claims 1-33, wherein the individual has a mutation in PKD1.

35. The method of any one of claims 1-34, wherein the individual has a mutation in PKD2.

36. , The method of any one of claims 1-35, wherein no more than one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty one, twenty two or twenty three of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} is D.

37. The method of any one of claims 1-36, wherein at least one, two, three or four of R^6, R^7, R^8 and R^9 is D.

38. The method of any one of claims 1-37, wherein no more than one, two, three or four of R^6, R^7, R^8 and R^9 is D.

39. The method of any one of claims 1-38, wherein one or two of R^6 or R^7 is D.

40. The method of any one of claims 1-39, wherein one or two of R^8 or R^9 is D.

41. The method of any one of claims 1-40, wherein all of R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

42. The method of any one of claims 1-41, wherein all of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

43. The method of any one of claims 1-42, wherein all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

44. The method of any one of claims 1-43, wherein at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D.

45. The method of any one of claims 1-44, wherein no more than one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D.

46. The method of any one of claims 1-45, wherein all of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

47. The method of any one of claims 1-46, wherein all of R^1, R^2, R^3, R^4 and R^5 are D, and all of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

48. The method of any one of claims 1-47, wherein at least one, two, three, four, five, six, seven, eight or nine of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is D.

49. The method of any one of claims 1-48, wherein no more than one, two, three, four, five, six, seven, eight or nine of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is D.

50. The method of any one of claims 1-49, wherein at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D and at least one, two, three, or four of R^6, R^7, R^8 and R^9 is D.

51. The method of any one of claims 1-50, wherein at least one, two, three, four or five of R^1, R^2, R^3, R^4 and R^5 is D and at least one or two of R^8 and R^9 is D.

52. The method of any one of claims 1-51, wherein at least one or two of R^1 and R^5 is D and at least one or two of R^8 and R^9 is D.

53. The method of any one of claims 1-52, wherein all of R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

54. The method of any one of claims 1-53, wherein at least one, two or three of R^{12}, R^{13} and R^{14} is D.

55. The method of any one of claims 1-54, wherein no more than one, two or three of R^{12}, R^{13} and R^{14} is D.

56. The method of any one of claims 1-55, wherein at least one or two of R^{12} and R^{13} is D and R^{14} is D.

57. The method of any one of claims 1-56, wherein all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

58. The method of any one of claims 1-57, wherein at least one, two or three of R^{16}, R^{17} and R^{18} is D.

59. The method of any one of claims 1-58, wherein no more than one, two or three of R^{16}, R^{17} and R^{18} is D.

60. The method of any one of claims 1-59, wherein all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

61. The method of any one of claims 1-60, wherein at least one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} is D.

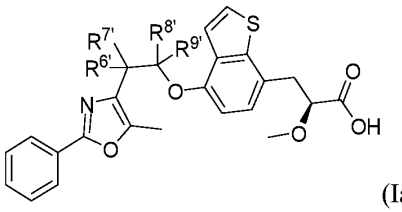
62. The method of any one of claims 1-61, wherein no more than one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{16}, R^{17} and R^{18} is D.

63. The method of any one of claims 1-62, wherein at least one or two of R^8 and R^9 is D and at least one, two or three of R^{16}, R^{17} and R^{18} is D.

64. The method of any one of claims 1-63, wherein at least one, two, three, four or five of R^1, R^2, R^3, R^4, and R^5 is D and at least one, two or three of R^{16}, R^{17} and R^{18} is D.

65. The method of any one of claims 1-64, wherein all of, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are H.

66. The method of any one of claims 1-34, wherein the compound of Formula (I) is a compound of Formula (Ia):



(Ia)

wherein, $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ independently from each other are H or D, wherein at least one, two, three or four of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ is D.

67. The method of claim 66, wherein no more than one, two, three or four of $R^{6'}$, $R^{7'}$, $R^{8'}$ and $R^{9'}$ is D.

68. The method of claim 66 or claim 67, wherein at least one or two of $R^{8'}$ and $R^{9'}$ is D.

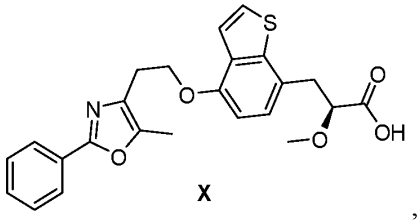
69. The method of any one of claims 66-68, wherein at least one or two of $R^{6'}$ and $R^{7'}$ is D.

70. The method of any one of claims 66-69, wherein both of $R^{6'}$ and $R^{7'}$ are H when at least one or two of $R^{8'}$ and $R^{9'}$ is D.

71. The method of any one of claims 66-70, wherein both of $R^{6'}$ and $R^{7'}$ are H when both of $R^{8'}$ and $R^{9'}$ is D.

72. The method of any one of claims 66-71, wherein both of $R^{8'}$ and $R^{9'}$ are H when at least one or two $R^{6'}$ and $R^{7'}$ of is D.

73. The method of any one of claims 1-34, wherein the compound of Formula (I) is a compound selected from the group consisting of:



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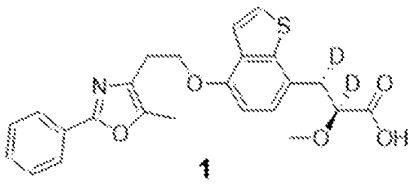

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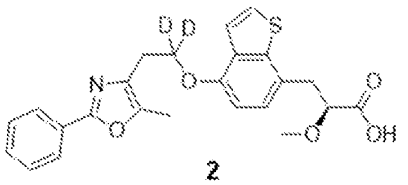

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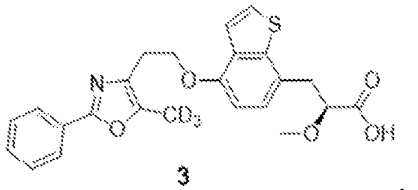

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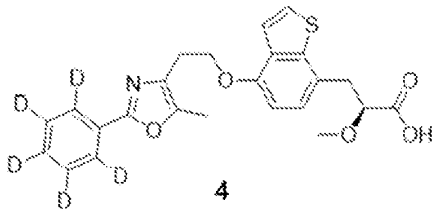

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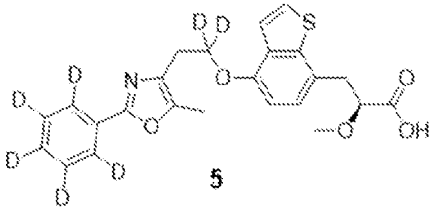

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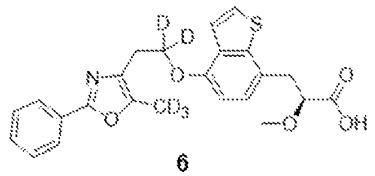

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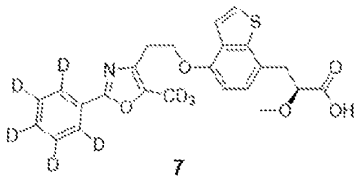

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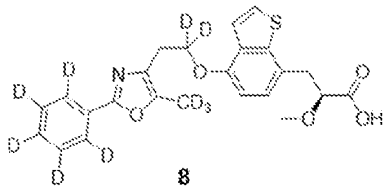

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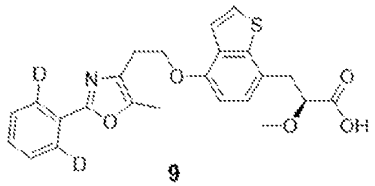

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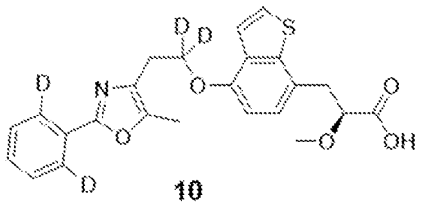

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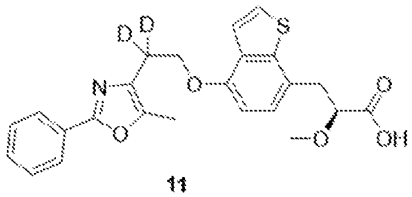

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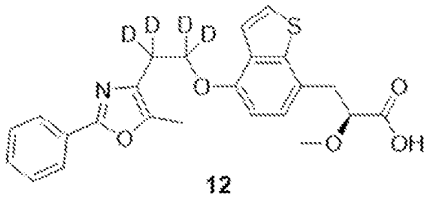
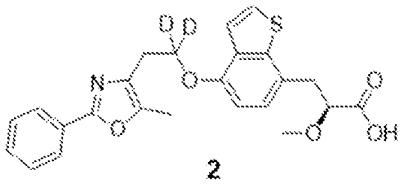


12 , or a pharmaceutically acceptable salt thereof.

74. The method of claim 73, wherein the compound of Formula (I) is



2 , or a pharmaceutically acceptable salt thereof.

75. The method of any one of claims 1-70, wherein deuterium enrichment in the compound of Formula (I) is no less than 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99%.

76. The method of any one of claims 1-71, wherein deuterium enrichment in the compound of Formula (I) is no more than 99.9%, 99%, 98%, 97%, 96%, 95%, or 90%.