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(54) Title: COMPOUNDS AND METHODS FOR THE TREATMENT OF POLYCYSTIC KIDNEY DISEASE (PKD)

(57) Abstract: Described herein are methods for treating PKD in a subject suffering from PKD, the method comprising administering a therapeutically effective amount of at least one compound of the general formula (I), (I) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein R1-R5 are defined herein.

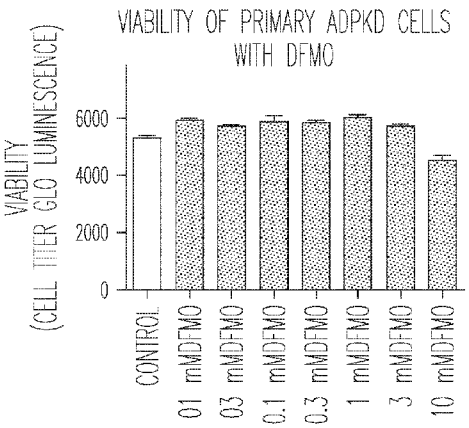
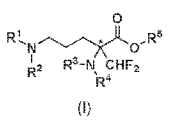


Fig. 1



(I)

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COMPOUNDS AND METHODS FOR THE TREATMENT OF POLYCYSTIC KIDNEY DISEASE (PKD)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial No. 62/784,133, filed December 21, 2018, which is incorporated by reference as if fully set forth herein.

BACKGROUND

[0002] Polycystic Kidney Disease (PKD) is a common hereditary disease affecting 600,000 Americans (15 million worldwide) of all racial and ethnic backgrounds, and accounts for about 10% of all end-stage renal disease (ESRD). Guler, S., et al. (2015). Diagnosis and Treatment Modalities of Symptomatic Polycystic Kidney Disease. Polycystic Kidney Disease. X. Li. Brisbane (AU). PMID 27512786. About 85% of Autosomal Dominant PKD (ADPKD) arises from mutations in the PKD-1 gene (Chromosome 16p13.3) encoding the Polycystin-1 (PC1) protein and another 15% of ADPKD arises in the PKD-2 gene (Chromosome 4q21) encoding the Polycystin-2 (PC2) protein. Patients with PKD-1 mutations have greatly increased numbers of cysts in the kidney with increased total kidney volume (TKV) and decreasing Glomerular Filtration Rates (GFRs) as they age. Helal, I. (2015). Treatment and Management of Autosomal Dominant Polycystic Kidney Disease. Polycystic Kidney Disease. X. Li. Brisbane (AU). PMID 27512783. While growth rates of overall kidney size in PKD patients as measured by ultrasound and/or Magnetic Resonance Imaging (MRI) vary widely, the supra-normal numbers of cysts, progressive growth of these cysts and significantly enlarged kidney size are common characteristics of the disease. Many PKD clinical trials are currently ongoing to explore therapies for PKD that change blood pressure, growth factor receptors, diet, pain, renal failure, cAMP levels, mTOR activities, somatostatin activities, insulin sensitivity, vitamin deficiencies, glucose control and others.

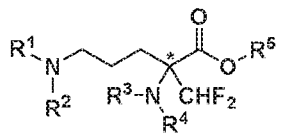
[0003] According to Wei et al., "the change from a tubular to cystic architecture in ADPKD occurs when a single cell in the wall of the tubule suffers a mutation in the PKD gene and the cell undergoes a phenotypic change that includes abnormal proliferation. The net effect of the consequent alteration leads to spherical expansion of one region of the tubule into the surrounding

interstitium, that is, cyst formation." Wei, F., et al., (2008). "Neutrophil gelatinase- associated lipocalin suppresses cyst growth by Pkd1 null cells in vitro and in vivo." Kidney Int. 74(10): 1310-1318. Access. No's.: 18974761 PMC3793389.

[0004] This idea that the cysts result from proliferation of the tubular epithelial cells is reinforced by the in vivo observation that cyst-lining cells in humans or in animals with PKD exhibit an increased mitotic index. Nadasdy, T., et al., (1995). "Proliferative activity of cyst epithelium in human renal cystic diseases." J. Am. Soc. Nephrol. 5(7): 1462-1468. Access. No's.: 7703384; and Lanoix, J., et al., (1996). "Dysregulation of cellular proliferation and apoptosis mediates human autosomal dominant polycystic kidney disease (ADPKD)." Oncogene 13(6): 1153-1160. Access. No's.: 8808689. Wei et al. (2008) also show that renal tubular epithelial cells in a mixture of collagen type 1 and Matrigel from PKD1-/- mice formed far greater numbers of cystic structures compared to their wild-type counterparts, and that this increase was due to an increased rate of proliferation and resistance to apoptosis following serum starvation. The growth in size and numbers of these cysts causes compression or obstruction of nephrons and blood vessels to reduce kidney function over time. This cyst growth leads to kidney failure and ESRD, which then requires dialysis and/or kidney transplants to replace lost function. While growth rates of overall kidney size in PKD patients as measured by ultrasound and MRI vary widely, the presence of cysts, supra-normal growth of cysts and/or enlarged kidney sizes are characteristic of the disease.

SUMMARY

[0005] The disclosure provides, among other things, methods for treating PKD in a subject suffering from PKD, the method comprising administering a therapeutically effective amount of at least one compound of the general formula (I):



(I)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof,

wherein:

R^1, R^2, R^3, and R^4 are each, independently, H, alkyl or acyl; and

R^5 is H or alkyl; or

one of R^1 and R^2 and one of R^3 and R^4, together with the nitrogen atoms to which they are attached, form a heterocyclic ring; or

R^5 and one of R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic ring; or

R^5 and one of R^3 and R^4, together with the nitrogen atom to which they are attached, form a heterocyclic ring.

DESCRIPTION OF THE DRAWINGS

[0006] The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed herein.

[0007] FIG. 1 is a plot of cell viability as a function of difluoromethyl ornithine (DFMO) concentration, showing the viability of primary ADPKD cells in 2D culture as measured by ATP release using Cell TiterGlo kit.

[0008] FIG. 2 is a plot of numbers of cysts as a function of DFMO concentration, showing that the numbers of cysts decrease in a dose-dependent manner with DFMO treatments.

[0009] FIG. 3 is a photomicrograph showing that ADPKD-cyst size increases with time of vehicle treatment in 3D culture.

[0010] FIG. 4 is a photomicrograph showing that ADPKD-cyst size decreases with time of 10 mM DFMO treatment in 3D culture.

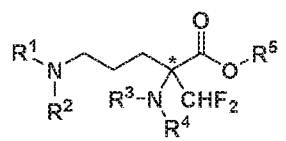
[0011] FIG. 5 is a photomicrograph showing tubulogenesis of vehicle treated NHK at Day 3.

[0012] FIG. 6 is a photomicrograph showing tubulogenesis of 10 mM DFMO treated NHK at Day 3.

DESCRIPTION

[0013] Reference will now be made in detail to certain examples of the disclosed subject matter. While the disclosed subject matter will be described in conjunction with the enumerated claims, it will be understood that the exemplified subject matter is not intended to limit the claims to the disclosed subject matter.

[0014] Embodiments of this disclosure are directed to methods for treating PKD in a subject suffering from PKD, the method comprising administering a therapeutically effective amount of at least one compound of the general formula (I):



(I)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof,

wherein:

R^1, R^2, R^3, and R^4 are each, independently, H, alkyl or acyl; and

R^5 is H or alkyl; or

one of R^1 and R^2 and one of R^3 and R^4, together with the nitrogen atoms to which they are attached, form a heterocyclic ring; or

R^5 and one of R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic ring; or

R^5 and one of R^3 and R^4, together with the nitrogen atom to which they are attached, form a heterocyclic ring.

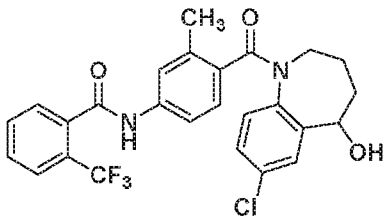
[0015] The compounds of the formula (I) can be compounds where R^1-R^5 are each hydrogen or prodrugs thereof that form compounds where R^1-R^5 are each hydrogen in vivo. The compound where R^1-R^5 are each hydrogen is known as difluoromethylornithine (DFMO) or eflornithine.

[0016] The compounds of the formula (I) can be compounds wherein R^5 can be a $(C_1$-$C_{40})$-alkyl group, such as a $(C_4$-$C_{40})$-alkyl group. In addition, the $(C_1$-$C_{40})$-alkyl group and $(C_4$-$C_{40})$-alkyl group can comprise one or more unsaturations in the chain, it being understood that when the $(C_1$-$C_{40})$-alkyl group comprises unsaturation, the $(C_1$-$C_{40})$-alkyl group cannot be C_1-alkyl. For example, the group $-OR^5$ can be derived from stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl, palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, or behenyl alcohol.

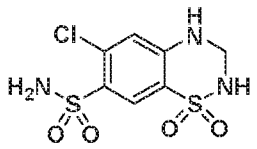
[0017] The compounds of the formula (I) can also be compounds wherein at least one of R^1-R^4 can be acyl, such as acyl-$(C_1$-$C_{40})$-alkyl and acyl-$(C_4$-$C_{40})$-alkyl. For example, at least one of R^1 and R^2 can be acyl-$(C_1$-$C_{40})$-alkyl and acyl-$(C_4$-$C_{40})$-alkyl; at least one of R^3 and R^4 can be acyl-$(C_1$-$C_{40})$-alkyl and acyl-$(C_4$-$C_{40})$-alkyl; or at least one of R^3 and R^4 can be acyl-$(C_1$-$C_{40})$-alkyl and acyl-$(C_4$-$C_{40})$-alkyl in addition to R^5 being a $(C_1$-$C_{40})$-alkyl group or a $(C_4$-$C_{40})$-alkyl group.

[0018] Also contemplated herein are methods for treating PKD by administering a compound of formula (I), such as DFMO, in combination with at least one other compound, or salts thereof, belonging to the vasopressin antagonist class (e.g., tolvaptan, lixivaptan, conivaptan, relcovaptan, nelivaptan, mozavaptan, and satavaptan), mTOR inhibotors (e.g., sirolimus, temsirolimus, everolimus, ridaforolimus, dactolisib, and sapanisertib), somatostatin analogs (e.g., lantreotide, octreotide, and pasireotride), glucosylceramide synthase

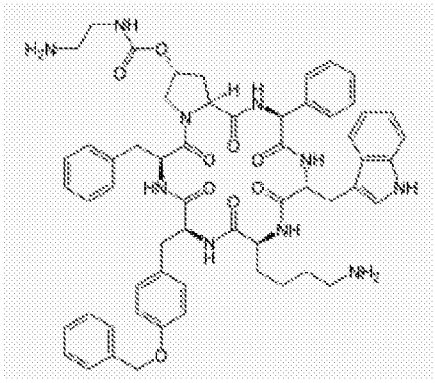
inhibitors (e.g., miglustat and eliglustat), metformin, AMPK activators, NSAIDs, aspirin, inhibitors of polyamine pathway, and any compound useful for the treatment of PKD. The structures of tolvaptan, hydrochlorothiazide, and pasireotide are as follows:



Tolvaptan



Hydrochlorothiazide



Pasireotide

or salts or prodrugs thereof.

[0019] Thus, for example, the compound of formula (I), such as DFMO, can be administered in combination with tolvaptan, hydrochlorothiazide or pasireotide or in combination with tolvaptan and hydrochlorothiazide.

[0020] The compound of formula (I), such as DFMO alone or in combination with one or more of the aforementioned compounds, can be administerd to treat diabetic kidney disease and renal diseases that lead to kidney failure.

[0021] Those of ordinary skill in the art will recognize that the compounds described herein can contain chiral centers, such as the carbon atom with the asterisk in the compounds of formula (I). All diastereomers of the compounds described herein are contemplated herein, as well as racemates. Prodrugs of the compounds described are also contemplated herein.

[0022] Various examples contemplate pharmaceutical compositions comprising one or more compounds of the various embodiments described herein and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof. A “pharmaceutical composition” refers to a

chemical or biological composition suitable for administration to a subject (e.g., mammal). Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, cutaneous, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can by means of capsule, drops, foams, gel, gum, injection, liquid, patch, pill, porous pouch, powder, tablet, or other suitable means of administration.

[0023] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" comprises a carrier, sometimes a liquid, in which an active therapeutic agent is formulated. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Examples of suitable formulations can be found, for example, in Remington, The Science And Practice of Pharmacy, 20th Edition, (Gennaro, A. R., Chief Editor), Philadelphia College of Pharmacy and Science, 2000, which is incorporated by reference in its entirety.

[0024] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one example, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual, or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions contemplated herein. Supplementary active compounds can also be incorporated into the compositions.

[0025] Pharmaceutical compositions may be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium

containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0026] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the compounds described herein can be formulated in a time release formulation, for example in a composition that includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0027] Oral forms of administration are also contemplated herein. Pharmaceutical compositions can be orally administered as a capsule (hard or soft), tablet (film coated, enteric coated or uncoated), powder or granules (coated or uncoated) or liquid (solution or suspension). Formulations can be conveniently prepared by any of the methods well-known in the art. Pharmaceutical compositions can include one or more suitable production aids or excipients including fillers, binders, disintegrants, lubricants, diluents, flow agents, buffering agents, moistening agents, preservatives, colorants, sweeteners, flavors, and pharmaceutically compatible carriers.

[0028] For each of the recited examples, the compounds can be administered by a variety of dosage forms as known in the art. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, chewable tablets, quick dissolve tablets, effervescent tablets, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, tablets, multi-layer tablets, bi-layer tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, beads, powders, gum, granules, particles, microparticles, dispersible granules, cachets,

douches, suppositories, creams, topicals, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, ingestibles, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0029] Other compounds which can be included by admixture are, for example, medically inert ingredients (e.g., solid and liquid diluent), such as lactose, dextrosesaccharose, cellulose, starch or calcium phosphate for tablets or capsules, olive oil or ethyl oleate for soft capsules and water or vegetable oil for suspensions or emulsions; lubricating agents such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate, binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinylpyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuff; sweeteners; wetting agents such as lecithin, polysorbates or laurylsulphates; and other therapeutically acceptable accessory ingredients, such as humectants, preservatives, buffers and antioxidants, which are known additives for such formulations.

[0030] Liquid dispersions for oral administration can be syrups, emulsions, solutions, or suspensions. The syrups can contain as a carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. The suspensions and the emulsions can contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

[0031] The amount of active compound can vary according to factors such as the disease state, age, gender, weight, patient history, risk factors, predisposition to disease, administration route, pre-existing treatment regime (e.g., possible interactions with other medications), and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of therapeutic situation.

[0032] "Dosage unit form," as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms can be

dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. In therapeutic use for treatment of conditions in mammals (e.g., humans) for which the compounds described herein or an appropriate pharmaceutical composition thereof are effective, the compounds can be administered in an effective amount. The dosages as suitable for the purposes of this disclosure can be a composition, a pharmaceutical composition or any other compositions described herein.

[0033] For each of the recited examples, the dosage is typically administered once, twice, or thrice a day, although more frequent dosing intervals are possible. The dosage may be administered every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, and/or every 7 days (once a week). In one example, the dosage may be administered daily for up to and including 30 days, preferably between 7-10 days. In another example, the dosage may be administered twice a day for 10 days. If the patient requires treatment for a chronic disease or condition, the dosage may be administered for as long as signs and/or symptoms persist. The patient may require "maintenance treatment" where the patient is receiving dosages every day for months, years, or the remainder of their lives. In addition, compositions contemplated herein can effect prophylaxis of recurring symptoms. For example, the dosage may be administered once or twice a day to prevent the onset of symptoms in patients at risk, especially for asymptomatic patients.

[0034] The compositions described herein can be administered in any of the following routes: buccal, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. The preferred routes of administration are buccal and oral. The administration can be local, where the composition is administered directly, close to, in the locality, near, at, about, or in the vicinity of, the site(s) of disease, e.g., inflammation, or systemic, wherein the composition is given to the patient and passes through the body widely, thereby reaching the site(s) of disease. Local administration can be administration to the cell, tissue, organ, and/or organ system, which encompasses and/or is affected by the disease, and/or where the disease signs and/or symptoms are active or are likely to occur. Administration can be topical

with a local effect, composition is applied directly where its action is desired. Administration can be enteral wherein the desired effect is systemic (non-local), composition is given via the digestive tract. Administration can be parenteral, where the desired effect is systemic, composition is given by other routes than the digestive tract.

[0035] Pharmaceutical compositions comprising a therapeutically effective amount of one or more compounds described herein are contemplated. Also contemplated is the use of the compounds described herein as a medicament for treating a patient in need of relief from a disease or a condition, such as PKD. Other embodiments are directed to a method for treating a patient (e.g., a human patient) in need of relief from PKD, the method comprising the step of administering to the patient a therapeutically effective amount of a compound described herein or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

[0036] The term "therapeutically effective amount" as used herein, refers to that amount of one or more compounds described herein that elicits a biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In some examples, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the condition being treated and the severity of the condition; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient: the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician. It is also appreciated that the therapeutically effective amount can be selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein.

[0037] Values expressed in a range format should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range were explicitly recited. For example, a range of "about 0.1% to about 5%" or "about 0.1% to 5%" should be interpreted to include not just about 0.1% to about 5%, but also the individual values (*e.g.*, 1%, 2%, 3%, and 4%) and the sub-ranges (*e.g.*, 0.1% to 0.5%, 1.1% to 2.2%, 3.3% to 4.4%) within the indicated range. The statement "about X to Y" has the same meaning as "about X to about Y," unless indicated otherwise. Likewise, the statement "about X, Y, or about Z" has the same meaning as "about X, about Y, or about Z," unless indicated otherwise.

[0038] In this document, the terms "a," "an," or "the" are used to include one or more than one unless the context clearly dictates otherwise. The term "or" is used to refer to a nonexclusive "or" unless otherwise indicated. In addition, it is to be understood that the phraseology or terminology employed herein, and not otherwise defined, is for the purpose of description only and not of limitation. Any use of section headings is intended to aid reading of the document and is not to be interpreted as limiting. Further, information that is relevant to a section heading may occur within or outside of that particular section. Furthermore, all publications, patents, and patent documents referred to in this document are incorporated by reference herein in their entirety, as though individually incorporated by reference.

[0039] In the methods described herein, the steps can be carried out in any order without departing from the principles of this disclosure, except when a temporal or operational sequence is explicitly recited. Furthermore, specified steps can be carried out concurrently unless explicit claim language recites that they be carried out separately. For example, a claimed step of doing X and a claimed step of doing Y can be conducted simultaneously within a single operation, and the resulting process will fall within the literal scope of the claimed process.

[0040] The term "about" as used herein can allow for a degree of variability in a value or range, for example, within 10%, within 5%, or within 1% of a stated value or of a stated limit of a range.

[0041] The term "substituted" as used herein refers to a group (e.g., alkyl, aryl, and heteroaryl) or molecule in which one or more hydrogen atoms contained thereon are replaced by one or more substituents. The term

"substituent" as used herein refers to a group that can be or is substituted onto a molecule or onto a group. Examples of substituents include, but are not limited to, a halogen (e.g., F, Cl, Br, and I); an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxylamines, nitriles, nitro groups, N-oxides, hydrazides, azides, and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR, $OC(O)N(R)_2$, CN, NO, NO_2, ONO_2, azido, CF_3, OCF_3, R, O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, SO_2R, $SO_2N(R)_2$, SO_3R, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}N(R)C(O)R$, $(CH_2)_{0-2}N(R)N(R)_2$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R, wherein R can be, for example, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl.

[0042] The term "alkyl" as used herein refers to substituted or unsubstituted, saturated or unsaturated monovalent and divalent straight chain and branched alkyl and cycloalkyl and cycloalkylene groups having from 1 to 40 carbon atoms (C_1-C_{40}), 1 to about 20 carbon atoms (C_1-C_{20}), 4 to 40 carbons (C_4-C_{40}), 6 to 22 carbons (C_6-C_{22}), 12 to 40 carbons (C_{12}-C_{40}), 1 to 12 carbons (C_1-C_{12}), 1 to 8 carbon atoms (C_1-C_8), or, in some examples, from 1 to 6 carbon atoms (C_1-C_6). Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Examples of straight chain divalent alkylene groups include those with from 1 to 8 carbon atoms such as ethyl ($-CH_2CH_2-$), n-propyl ($-CH_2CH_2CH_2-$), n-butyl ($-CH_2CH_2CH_2CH_2-$), n-pentyl ($-CH_2CH_2CH_2CH_2CH_2-$), n-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_2-$), n-heptyl ($-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$), and n-octyl ($-CH_2CH_2CH_2CH_2CH_2CH_2$ CH_2CH_2-) groups. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed herein, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and

halogen groups. When the alkyl group comprises one or more unsaturations in the chain, the alkyl group becomes an alkenyl or an alkynyl group.

[0043] The term "cycloalkyl" as used herein refers to substituted or unsubstituted cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some examples, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other examples the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. In some examples, cycloalkyl groups can have 3 to 6 carbon atoms (C_3-C_6). Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like.

[0044] The term "acyl" as used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of a substituted or unsubstituted alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-40, 6-10, 1-5 or 2-5 additional carbon atoms bonded to the carbonyl group. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

[0045] The term "aryl" as used herein refers to substituted or unsubstituted cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some examples, aryl groups contain about 6 to about 14 carbons (C_6-C_{14}) or from 6 to 10 carbon atoms (C_6-C_{10}) in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined herein. Representative substituted aryl groups can be mono-substituted or substituted more than once,

such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed herein.

[0046] The term "aralkyl" and "arylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein. Representative aralkyl groups include benzyl and phenylethyl groups.

[0047] The term "heterocyclyl" as used herein refers to substituted or unsubstituted aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Thus, a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some examples, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. In some examples, heterocyclyl groups include heterocyclyl groups that include 3 to 8 carbon atoms (C_3-C_8), 3 to 6 carbon atoms (C_3-C_6), 3 to 5 carbon atoms (C_3-C_5), 3 to 4 carbon atoms (C_3-C_4) or 6 to 8 carbon atoms (C_6-C_8). A heterocyclyl group designated as a C_2-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms equals the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an example of a heterocyclyl group. The phrase "heterocyclyl group" includes fused ring species including those that include fused aromatic and non-aromatic groups. Representative heterocyclyl groups include, but are not limited to piperidynyl, piperazinyl, morpholinyl, furanyl, pyrrolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, triazinyl, thiophenyl, tetrahydrofuranyl, pyrrolyl, oxazolyl, imidazolyl, triazyolyl, tetrazolyl, benzoxazolinyl, and benzimidazolinyl groups.

[0048] The term "alkoxy" as used herein refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined herein. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include one to about 12-20 or about 12-40 carbon atoms bonded to the oxygen atom, and can further include double or

triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structure are substituted therewith.

[0049] The term "alkenyloxy" as used herein refers to an oxygen atom connected to an alkenyl group.

[0050] The term "amine" as used herein refers to primary, secondary, and tertiary amines having, e.g., the formula $N(group)_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to alkylamines, arylamines, arylalkylamines; dialkylamines, diarylamines, diaralkylamines, heterocyclylamines and the like; and ammonium ions.

[0051] The term "alkylamino" as used herein refers to $N(group)_3$ group, wherein one of the groups is an alkyl group.

[0052] The term "alkenylamino" as used herein refers to $N(group)_3$ group, wherein one of the groups is an alkenyl group.

[0053] The terms "halo," "halogen," or "halide" group, as used herein, by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0054] As used herein, the term "salts" and "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. Pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

[0055] Pharmaceutically acceptable salts can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. In some instances, such salts can be prepared by reacting

the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, the disclosure of which is hereby incorporated by reference.

[0056] The term "solvate" means a compound, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0057] The term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound described herein. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a compound including biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Specific prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger's Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and Design and Application of Prodrugs (H. Bundgaard ed., 1985, Harwood Academic Publishers GmbH).

[0058] The terms and expressions that have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the embodiments of the present disclosure. Thus, it should be understood that although the present disclosure has been specifically disclosed by specific embodiments and optional features, modification and variation of the concepts herein disclosed can be resorted to by those of ordinary skill in the art, and that such modifications and variations are considered to be within the scope of embodiments of the present disclosure

[0059] The invention is now described with reference to the following Examples. The following working examples therefore, are provided for the purpose of illustration only and specifically point out certain embodiments of the

present invention, and are not to be construed as limiting in any way the remainder of the disclosure. Therefore, the examples should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Examples

[0060] The present invention can be better understood by reference to the following examples which are offered by way of illustration. The present invention is not limited to the examples given herein.

[0061] Studies were performed on DFMO, the metabolic product of DFMO-prodrugs, in primary cell cultures of 2 dimensional (2D) cellular toxicity assays, 3 dimensional (3D) cyst formation assays and 3D tubulogenesis assays. DFMO was less than 10% toxic (90% viable) to human renal mixed epithelial cells in 2D cultures from Autosomal Dominant Polycystic Kidney Disease (ADPKD) donors up to 10 mM DFMO concentration as measured using a Cell Titer Glo kit (FIG. 1). In the 3D cyst cultures, a population of mixed cells from a surgically resected cyst from a donor ADPKD kidney is combined with human kidney fibroblasts to grow cysts in a proprietary media (Discovery BioMed, Inc) that contains conditioned media from kidney fibroblasts and a Biogel matrix (DiscoveryBioMed). Using light microscopy to count cysts, the number of cysts formed in 3D cultures decreased in a dose-dependent fashion to 50% of controls at 10 mM DFMO (FIG. 2).

[0062] Photomicrographs of cysts formed from ADPKD donor cells in 3D cultures show a time dependent change in cyst size. In the vehicle treated cultures (FIG. 3), the black bar on Day 0 is about the diameter of a single cyst (and is repeated in each day's photo), which is then tracked over time for 4 days and shows a steady increase in cyst size over time. In contrast, 10 mM DFMO treated cultures show a slight increase on Day 1 followed by a steady decrease in cyst size by Day 4 when the cyst is smaller than on Day 0 (FIG. 4) (black bar is approximate diameter of the cyst on Day 0 in each photo). This result is directly supportive of our hypothesis that DFMO (and ultimately DFMO-prodrugs) will reduce polyamine production to reduce cyst number and to reduce cyst size, which may then reduce total kidney volume in a non-damaging way because ADPKD cells were not killed by DFMO in 2D cultures.

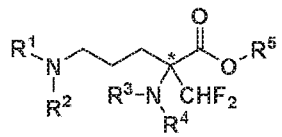
[0063] As a further proof of the potential utility of DFMO/DFMO-prodrugs in ADPKD patients, we also performed a tubulogenesis assay with normal human kidney cells in 3D cultures. Vehicle treated normal human kidney

(NHK) cells form tubules by Day 3 in 3D cultures (FIG. 5) as do 10 mM DFMO-treated NHK cells, which also form tubules under the same conditions (FIG. 6). From a visual perspective, the tubule numbers, maturation and elongation parameters over time appear similar between the vehicle and the DFMO-treated cultures.

CLAIMS

What is claimed is:

1. A method for treating PKD in a subject suffering from PKD, the method comprising administering a therapeutically effective amount of at least one compound of the general formula (I):



(I)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof,

wherein:

R^1, R^2, R^3, and R^4 are each, independently, H, alkyl or acyl; and

R^5 is H or alkyl; or

one of R^1 and R^2 and one of R^3 and R^4, together with the nitrogen atoms to which they are attached, form a heterocyclic ring; or

R^5 and one of R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic ring; or

R^5 and one of R^3 and R^4, together with the nitrogen atom to which they are attached, form a heterocyclic ring.

2. The method of claim 1, wherein R^1-R^5 are each hydrogen.

3. The method of claim 1, wherein R^5 is a $(C_4$-$C_{40})$-alkyl group.

4. The method of claim 3, wherein the $(C_4$-$C_{40})$-alkyl group can comprise one or more unsaturations in the chain.

5. The method of claim 1, wherein the group -OR^5 can be derived from stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl, palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, or behenyl alcohol.

6. The method of claim 1, wherein at least one of R^1-R^4 is acyl.

7. The method of claim 1, wherein at least one of R^1-R^4 is acyl-$(C_1$-$C_{40})$-alkyl or acyl-$(C_4$-$C_{40})$-alkyl.

8. The method of claim 7, wherein at least one of R^1 and R^2 is acyl-(C_1-C_{40})-alkyl or acyl-(C_4-C_{40})-alkyl.

9. The method of claim 1 or 8, wherein at least one of R^3 and R^4 is acyl-(C_1-C_{40})-alkyl or acyl-(C_4-C_{40})-alkyl.

10. The method of claims 6-9, wherein R^5 is a (C_1-C_{40})-alkyl group or a (C_4-C_{40})-alkyl group.

11. The method of claim 1, wherein the compound of formula (I) forms a compound wherein R^1-R^5 are each hydrogen in vivo.

12. The method of claim 1, comprising administering a compound of formula (I) in combination with at least one other compound useful for the treatment of PKD.

13. The method of claim 12, wherein the at least one other compound useful for the treatment of PKD is a vasopressin antagonist, an mTOR inhibitor, a somatostatin analog, a glucosylceramide synthase inhibitor, metformin, an AMPK activator, an NSAID, aspirin, and an inhibitor of the polyamine pathway.

14. The method of claim 13, wherein the vasopressin antagonist is at least one of tolvaptan and lixivaptan.

15. The method of claim 12, wherein the at least one other compound useful for the treatment of PKD is tolvaptan, hydrochlorothiazide or pasireotide.

16. The method of claim 12, wherein the compound of formula (I) is administered in combination with tolvaptan and hydrochlorothiazide.

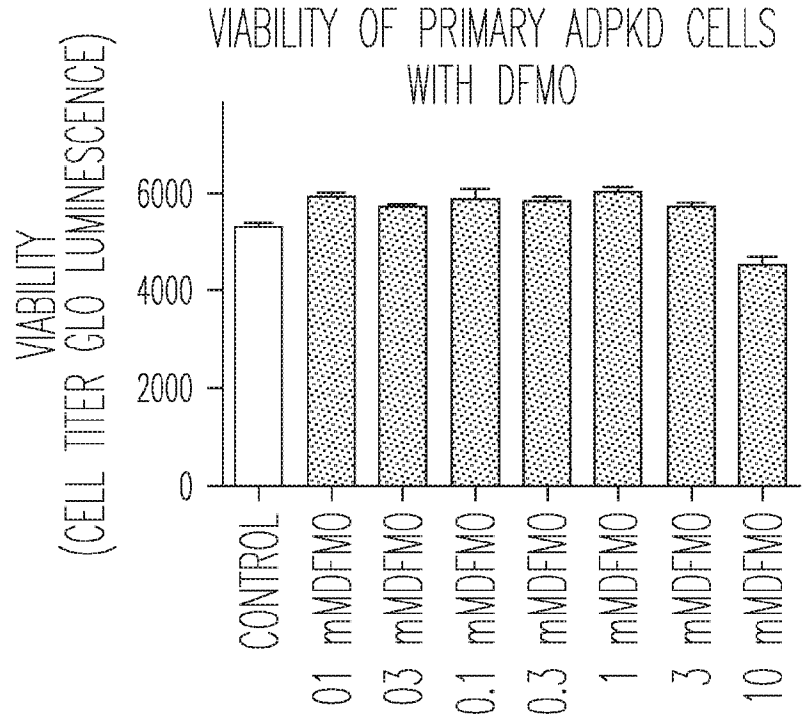

VIABILITY OF PRIMARY ADPKD CELLS
WITH DFMO
VIABILITY
(CELL TITER GLO LUMINESCENCE)
6000
4000
2000
0
CONTROL
01 mMDFMO
03 mMDFMO
0.1 mMDFMO
0.3 mMDFMO
1 mMDFMO
3 mMDFMO
10 mMDFMO

Fig. 1

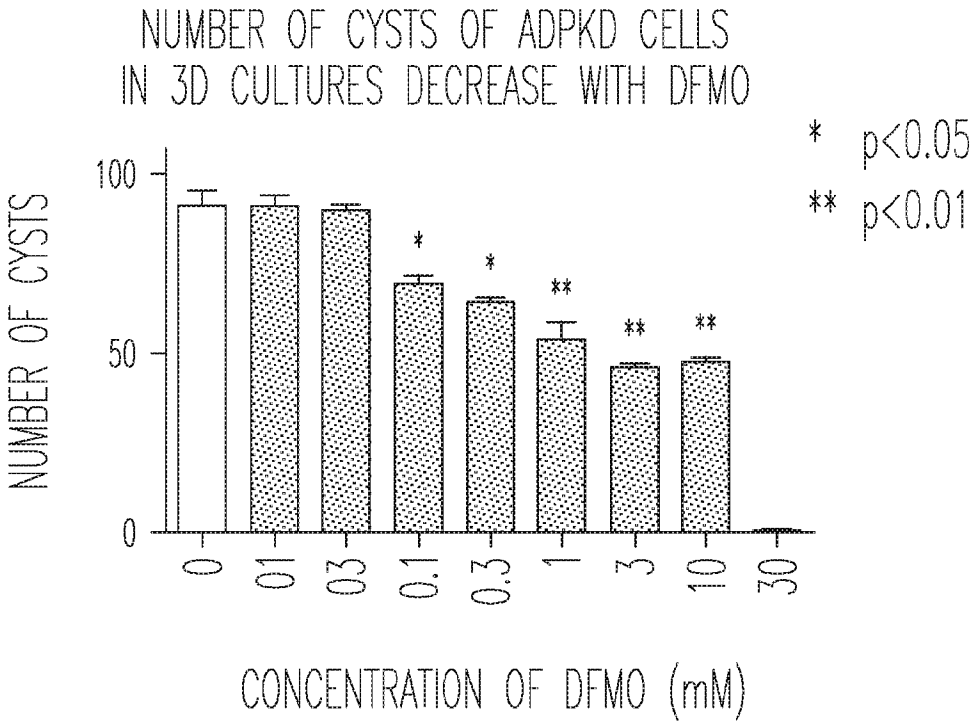

NUMBER OF CYSTS OF ADPKD CELLS
IN 3D CULTURES DECREASE WITH DFMO
* p<0.05
** p<0.01
NUMBER OF CYSTS
100
50
0
*
*
**
**
**
0
01
03
0.1
0.3
1
3
10
30
CONCENTRATION OF DFMO (mM)

Fig. 2

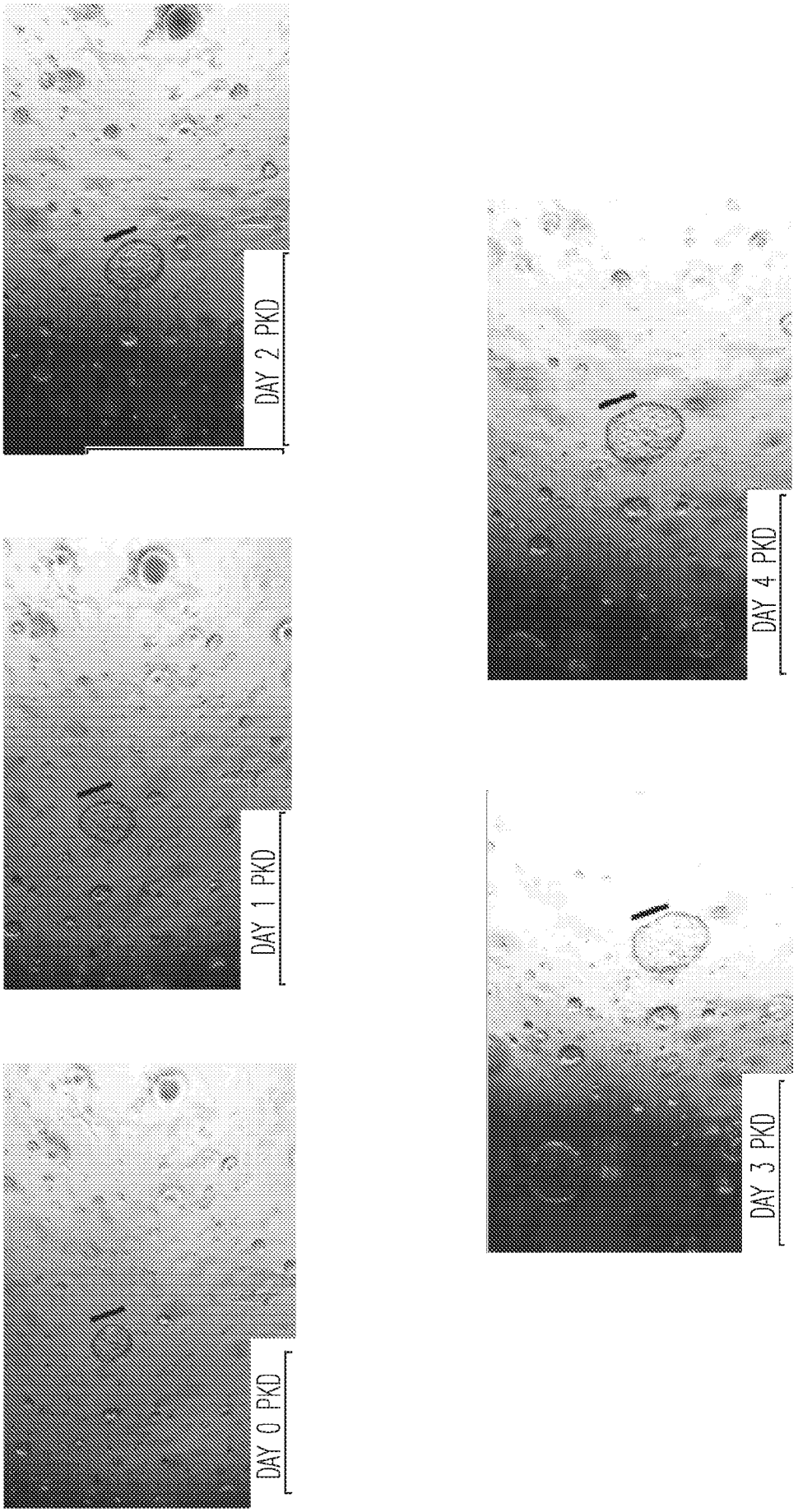


Fig. 3

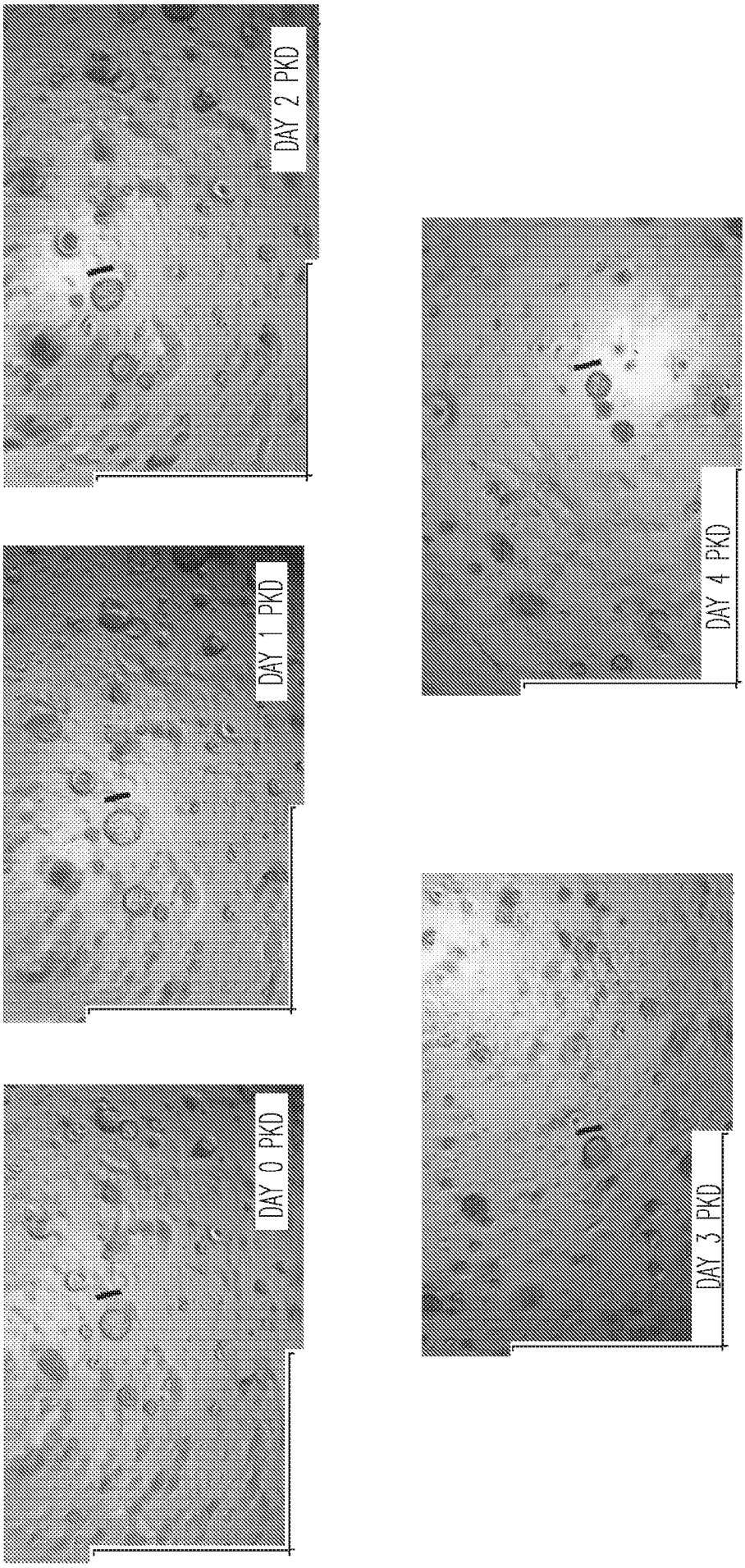


Fig. 4

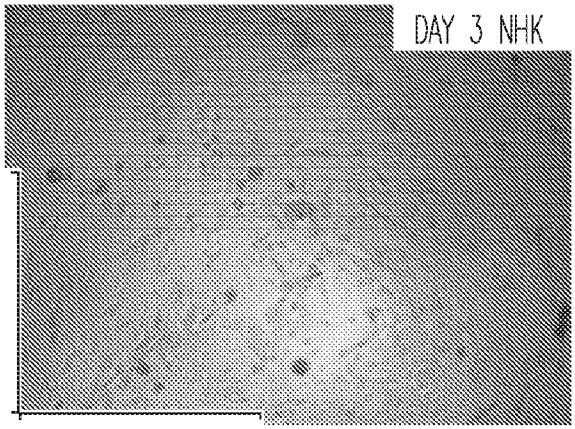


Fig. 5

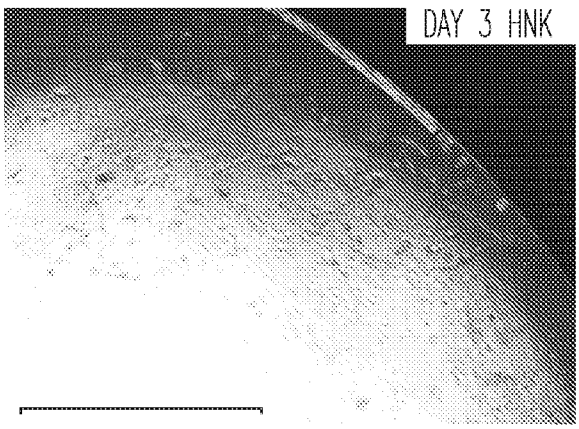


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/066502

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/197(2006.01)i, A61K 31/55(2006.01)i, A61K 31/549(2006.01)i, A61P 13/12(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/197; A61K 31/15; A61K 31/60; A61K 45/02; C07C 229/26; A61K 31/55; A61K 31/549; A61P 13/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), STN(Registry, Caplus) & keywords: polycystic kidney disease(PKD), difluoromethylornithine(DFMO)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010-0120727 A1 (XU, F.) 13 May 2010 claims 38, 41, 48; paragraphs [0027], [0032]-[0033]	1-9,11-16
X	US 4499072 A (SUNKARA, S. P. et al.) 12 February 1985 claims 1-3, 15	1-2
X	PEDERSEN, S. B. et al., "Inhibition of renal ornithine decarboxylase activity prevents kidney hypertrophy in experimental diabetes", Am. J. Physiol., 1993 Feb, Vol 264, pages C453-C456 page C453	1-2
X	HUMPHREYS, M. H. et al., "Renal ornithine decarboxylase activity, polyamines, and compensatory renal hypertrophy in the rat", American Journal of Physiology-Renal Physiology, 1988, Vol. 255, No. 2, pages F270-F277 page F270	1-2
X	THOMSON, S. C. et al., "Ornithine decarboxylase, kidney size, and the tubular hypothesis of glomerular hyperfiltration in experimental diabetes", J. Clin. Invest., 2001 Jan, Vol. 107, No. 2, pages 217-224 abstract	1-2

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2020 (17.04.2020)	**17 April 2020 (17.04.2020)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
HEO, Joo Hyung
Telephone No. +82-42-481-8150

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/066502

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 10
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2019/066502

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0120727 A1	13/05/2010	WO 2010-056919 A2 WO 2010-056919 A3	20/05/2010 30/09/2010
US 4499072 A	12/02/1985	None	