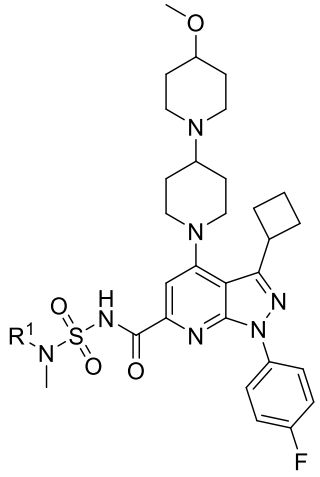
SUMMARY

[0009] The present disclosure relates to compounds that may be useful in the prophylaxis and/or treatment of polycystic kidney disease (PKD), more particularly autosomal dominant polycystic kidney disease (ADPKD). The present disclosure also provides methods for the production of the compound of the disclosure, pharmaceutical compositions comprising the compound of the disclosure, methods for the prophylaxis and/or treatment of polycystic kidney disease (PKD) by administering the compound of the disclosure.

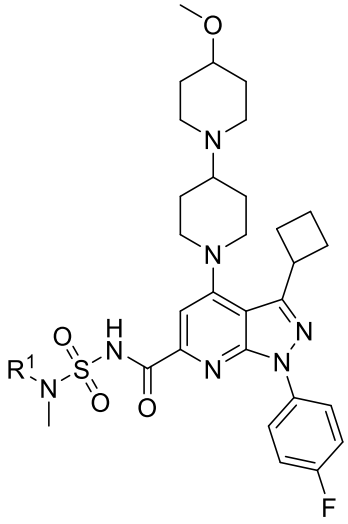
[0010] Accordingly, a compound of the disclosure according to Formula (I) is provided for use in the prophylaxis and/or treatment of polycystic kidney disease:



I

wherein R^1 is H or $–CH_3$;

[0010a] In one aspect of the present disclosure, a compound according to Formula (I) is provided for use in the prophylaxis and/or treatment of polycystic kidney disease:



wherein R^1 is H or $–CH_3$;

or a pharmaceutically acceptable salt, or a solvate or the pharmaceutically acceptable salt of a solvate thereof.

[0011] In one example, the compound of the disclosure is provided for use in the prophylaxis and/or treatment of polycystic kidney disease (PKD), and more particularly autosomal dominant polycystic kidney disease (ADPKD).

[0011a] In another aspect of the present disclosure, there is provided a compound or a pharmaceutically acceptable salt thereof as defined herein, or a pharmaceutical composition as defined herein, for use in the prophylaxis and/or treatment of autosomal dominant polycystic kidney disease.

[0012] Surprisingly, whereas the compounds of the disclosure have CFTR modulatory activity in CF patients, in particular protein folding and trafficking activity (WO 2017/060874), it has been unexpectedly observed that they inhibit in wild type CFTR (non-CF diseased), and therefore may prevent and/or reduce cysts formation and/or growth, in particular in PKD, and/or ovarian cysts.

[0013] The present disclosure provides pharmaceutical compositions for use in the prophylaxis and/or treatment of PKD, comprising a compound of the disclosure, and a pharmaceutical carrier, excipient or diluent. In a particular example, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the disclosure. In a more particular example, the further therapeutically active ingredient is an agent for the treatment of PKD.

[0013a] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt as defined herein, and a pharmaceutically acceptable carrier.

[0014] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0015] The present disclosure provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly PKD,

which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0016] The present disclosure also provides pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular example, the pharmaceutical composition is for use in the prophylaxis and/or treatment of PKD.

[0017] The present disclosure provides methods for synthesizing the compounds of the disclosure, with representative synthetic protocols and pathways disclosed later on herein.

[0018] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows the distribution of cyst sizes (cyst area, µm²) in the 3D human cyst growth assay after 8 days of test compound Cpd 1 and Cpd 2 at 10µM vs vehicle (DMSO) in box plot diagrams, wherein the box from bottom to top represents the 25% percentile value, the median value and the 75% percentile value of the data points, the bottom whisker represents the 10% percentile and the top whisker represents the 90% percentile.

Figure 2 shows the concentration dependent decrease in cyst numbers vs vehicle (DMSO) in the 3D human cyst growth assay after 8 days of test compound Cpd 1 filled circles) and Cpd 2 (filled triangle) at (3nM, 10nM, 30nM, 100nM, 300nM, 1 μ M, 3 μ M, and 10 μ M). The standard deviation is represented with bars for better visibility.

Figure 3 shows the distribution of cyst sizes (cyst area, µm²) vs vehicle (DMSO) in the 3D human cyst growth assay after 8 days of Cpd 1 at 3nM, 10nM, 30nM, 100nM, 300nM, 1µM, 3µM, and 10µM in box plot diagrams, wherein the box from bottom to top represents the 25% percentile value, the median value and the 75% percentile value of the data points, the bottom whisker represents the 10% percentile and the top whisker represents the 90% percentile.

Figure 4 shows the distribution of cyst sizes (cyst area, µm²) vs vehicle (DMSO) in the 3D human cyst growth assay after 8 days of Cpd 2 at 3nM, 10nM, 30nM, 100nM, 300nM, 1µM, 3µM, and 10µM in box plot diagrams, wherein the box from bottom to top represents the 25% percentile value, the median value and the 75% percentile value of the data points, the bottom whisker represents the 10% percentile and the top whisker represents the 90% percentile.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0019] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0020] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when