melanocortin therapy is likely attributable to a direct action on podocytes (Qiao et al. 2016).

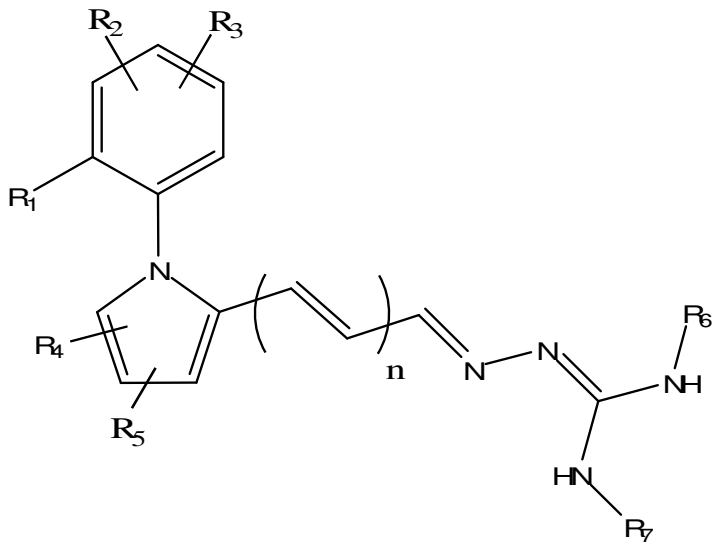
It is at present therefore not possible to predict which melanocortin agonists and which associated targets will present as useful candidates for treatment of proteinuric diseases such as kidney diseases.

Phenyl pyrrole aminoguanidine derivatives with activity on the melanocortin receptors are disclosed in WO 2007/141343. One example of such compound is the anti-inflammatory AP1189 (*(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium acetate) which was first shown to bind the MC1R (WO 2007/141343) and later was identified as a biased dual agonist at receptors MC1R and MC3R that does not provoke canonical cAMP generation (and hence no MC1R-induced melanogenesis) but instead appear to induce alternative pathways including ERK1/2-phosphorylation and Ca^{2+} mobilization (Montero-Melendez et al. 2015).

Summary

The present inventors have found that the phenyl pyrrole aminoguanidine derivative AP1189 (*(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium acetate) significantly reduces proteinuria in Passive Haymann Nephritis, a nephropathy model, as compared to vehicle, measured as a significant reduction of albumin excretion rate and FR_{Alb} (fraction albumin excretion); and also has a significantly higher GFR (glomerular filtration rate; creatinine clearance) and a significantly reduced FR_{Alb} compared to treatment with ACTH(1-24). This implies that AP1189 and related compounds are candidates for the improved treatment of proteinuric kidney diseases.

In one aspect, the present disclosure refers to a use of a composition comprising a compound of formula (Ia):



formula (Ia)

including tautomeric and stereoisomeric forms thereof in the manufacture of a medicament for treating primary nephrotic syndrome (primary glomerulonephrosis);

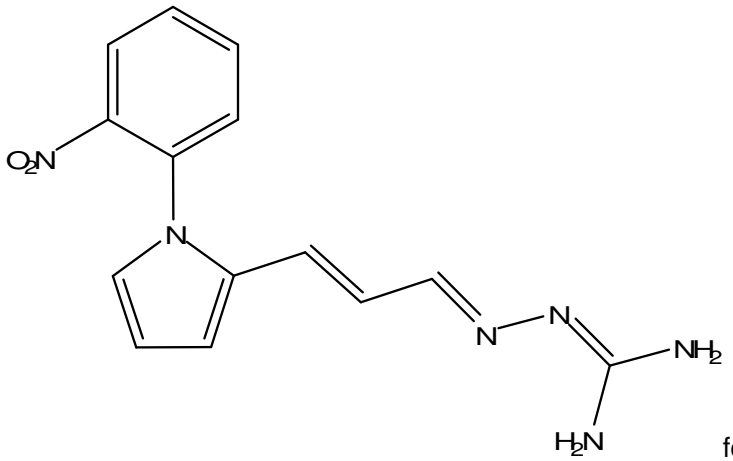
wherein n is 1; and

R_1 is CF_3, CCl_3, F, Cl, NO_2 or CN, and R_2, R_3, R_4, R_5, R_6, and R_7 are hydrogen; or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure refers to a use of a composition comprising (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate (AP1189) in the manufacture of a medicament for treating primary nephrotic syndrome, such as minimal change disease (MCD).

It is an example of the present disclosure to provide a composition comprising a compound of formula (I) or (Ia):

It is also an example of the present disclosure to provide a composition comprising a compound of formula (II):



formula (II)

including tautomeric and isomeric forms, such as enantiomeric forms, diastereomeric forms and racemic forms, thereof;

or a pharmaceutically acceptable derivative thereof, for use in the treatment of a kidney disease.

It is also an example of the present disclosure to provide a composition comprising a compound selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine; {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate; *(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine; and *(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate, or a pharmaceutically acceptable derivative thereof, for use in the treatment of a kidney disease.

In one example said kidney disease is a kidney disease that present with proteinuria.

In one example said kidney disease is a glomerular disease, such as a disease affecting the podocytes of the glomeruli.

In one example said kidney disease is nephrotic syndrome (glomerulonephrosis), such as primary nephrotic syndrome or secondary nephrotic syndrome.

Definitions

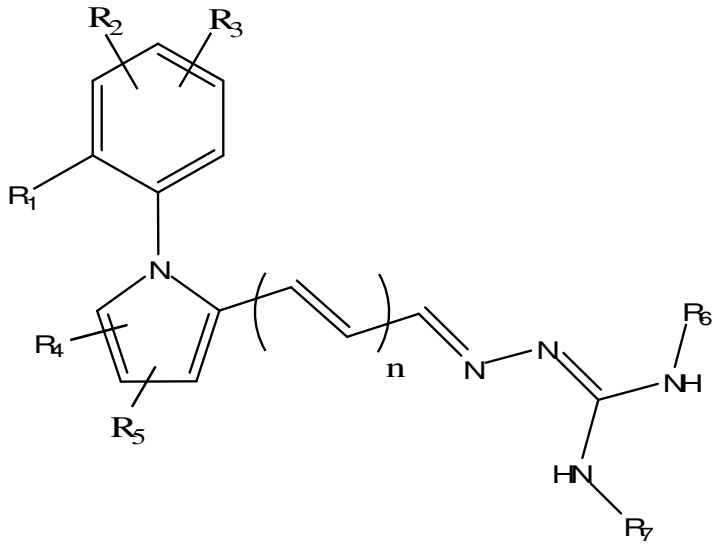
The term “pharmaceutically acceptable derivative” in the present context includes pharmaceutically acceptable salts, which indicate a salt which is not harmful to the patient. Such salts include pharmaceutically acceptable basic or acid addition salts as well as pharmaceutically acceptable metal salts, ammonium salts and alkylated ammonium salts. A pharmaceutically acceptable derivative further includes esters and prodrugs, or other precursors of a compound which may be biologically metabolized into the active compound, or crystal forms of a compound.

The term “acid addition salt” is intended to include “pharmaceutically acceptable acid addition salt” which indicates salts which are not harmful to the patient. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 66, 2, (1977) which is incorporated herein by reference.

The term "therapeutically effective amount" of a compound as used herein refers to an amount sufficient to cure, alleviate, prevent, reduce the risk of, or partially arrest the clinical manifestations of a given disease or disorder and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

Claims

1. Use of a composition comprising a compound of formula (Ia):



formula (Ia)

including tautomeric and stereoisomeric forms thereof in the manufacture of a medicament for treating primary nephrotic syndrome (primary glomerulonephrosis);
wherein n is 1; and
R_1 is CF_3, CCl_3, F, Cl, NO_2 or CN, and R_2, R_3, R_4, R_5, R_6, and R_7 are hydrogen;
or a pharmaceutically acceptable salt thereof.

2. The use according to claim 1, wherein said compound is a biased agonist of the MC1R and MC3R, that does not stimulate melanogenesis via the MC1R.

3. The use according to claim 1, wherein said primary nephrotic syndrome is membranous glomerulonephritis (MGN) (or membranous nephropathy (MN)).

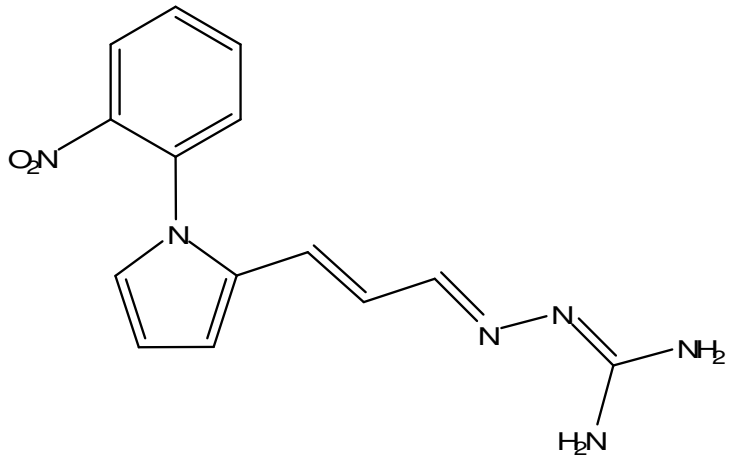
4. The use according to claim 1, wherein said primary nephrotic syndrome is focal segmental glomerulosclerosis (FSGS).

5. The use according to claim 1, wherein said primary nephrotic syndrome is membranoproliferative glomerulonephritis (MPGN) (mesangiocapillary glomerulonephritis); such as MPGN selected from Type 1 MPGN and Type 2 MPGN

6. The use according to claim 1, wherein said primary nephrotic syndrome is rapidly progressive glomerulonephritis (RPGN) (crescentic GN).

7. The use according to claim 1, wherein said primary nephrotic syndrome is minimal change disease (MCD).

8. The use according to any of the preceding claims, wherein the compound is of formula (II)



formula (II)

including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable salt thereof.

9. The use according to any of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof.

10. The use according to any of the preceding claims, wherein said pharmaceutically acceptable salt is a pharmaceutically acceptable salt of an inorganic acid or an organic acid.

11. The use according to claim 10, wherein said organic acid is selected from the group consisting of: formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, propionic acid, benzoic acid, cinnamic acid, citric acid, fumaric acid, glycolic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, oxalic acid, picric acid, pyruvic acid, salicylic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, tartaric acid, ascorbic acid, pamoic acid, bismethylene salicylic acid, ethanedisulfonic acid, gluconic acid, citraconic acid, aspartic acid, stearic acid, palmitic acid, EDTA, glycolic acid, p-aminobenzoic acid, glutamic acid, benzenesulfonic acid and p-toluenesulfonic acid; such as wherein said organic acid is acetic acid, succinic acid, tartaric acid or propionic acid; such as wherein said organic acid is acetic acid; and/or wherein said inorganic acid is selected from the group consisting of: hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulphuric acid and nitric acid.

12. The use according to any of the preceding claims, wherein said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate (AP1189).

13. The use according to any of the preceding claims, wherein said composition comprises, separately or together, one or more additional active pharmaceutical ingredients, such as one or more additional active pharmaceutical ingredients used for the treatment of kidney disease.

14. The use according to any of the preceding claims, wherein said compound is to be administered in an amount of 1 mg to 1000 mg per day, such as 1 to 5 mg, 5 to 10 mg, 10 to 15 mg, 15 to 20 mg, 20 to 30 mg, 30 to 60 mg, 60 to 80 mg, 80 to 100 mg, 100 to 130 mg, 130 to 160 mg, 160 to 200 mg, 200 to 240 mg, 240 to 280 mg, 280 to 320 mg, 320 to 360 mg, 360 to 400 mg, 400 to 440 mg, 440 to 500 mg, 500 to 560 mg, 560 to 620 mg, 620 to 680 mg, 680 to 740 mg, 740 to 800 mg, 800 to 860 mg, 860 to 920 mg, 920 to 980 mg, 980 to 1000 mg, for example 500 to 1000 mg per day.

15. Use of a composition comprising (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate (AP1189) in the manufacture of a

medicament for treating primary nephrotic syndrome, such as minimal change disease (MCD).