

5 U.S. Hypertensive nephropathy prevalence accounts for nearly 25% of kidney failures in the U.S. The current standard of care for kidney diseases includes angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). There remains a need for an alternative treatment for CKD.

Chen et al. (*Proceedings of the National Academy of Sciences* (PNAS), October 31,  
10 2006, vol. 103, NO:44, pp. 16580-16585) is an article entitled "Urocortin 2 modulates glucose utilization and insulin sensitivity in skeletal muscle." Further, in *Peptides* 27: 1806-1813 (2006), the authors disclose CRHR2 agonists including UCN2 analogs for the treatment of CRHR2 modulated disorders such as muscular atrophy. However, there is still a further need for novel therapeutic human UCN2 analogs that are agonists of CRHR2.

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### **Summary**

In one aspect of the present disclosure, there is provided a compound of the Formula:



20 wherein  $X_1$  denotes that the I residue is modified by either acetylation or methylation at the N-terminus;

wherein  $X_2$  is L or T;

wherein  $X_3$  is L or I;

wherein  $X_4$  is Q or E; and

25 wherein a modified K residue ("K\*") at position 29 is modified through conjugation to the epsilon-amino group of the K-side chain with a group of the formula  $-X_5-X_6$ , wherein

$X_5$  is selected from the group consisting of:

one to four more amino acids;

one to four ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) moieties; and

30 combinations of one to four amino acids and one to four ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) moieties;

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X<sub>6</sub> is a C<sub>14</sub>-C<sub>24</sub> fatty acid (SEQ ID NO:16);  
or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound comprising:  
the amino acid sequence

10 IVX<sub>2</sub>SLDVPIGLLQILX<sub>3</sub>EQEKQEKEKQQATX<sub>7</sub>NAX<sub>4</sub>ILAX<sub>8</sub>V-NH<sub>2</sub> (SEQ ID NO:67)

wherein X<sub>2</sub> is L or T;

wherein X<sub>3</sub> is L or I;

wherein X<sub>4</sub> is Q, R, or E;

wherein X<sub>7</sub> is T or E; and

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wherein X<sub>8</sub> is Q, H or R,

wherein a modified K residue (“K<sup>\*</sup>”) is substituted for the amino acid residue at  
position 10 or at any amino acid residue between position 14 and position 30

inclusive, wherein K<sup>\*</sup> is modified by having the epsilon amino group of the K-side  
chain bound to a group of the formula —X<sub>5</sub>—X<sub>6</sub>, wherein

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X<sub>5</sub> is selected from the group consisting of:

between one to four amino acid residues;

between one to four ([2-(2-Amino-ethoxy)-ethoxy]-acetyl moieties; and

combinations of one to four amino acid residues and one to four ([2-(2-

Amino-ethoxy)-ethoxy]-acetyl moieties;

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X<sub>6</sub> is a C<sub>14</sub>-C<sub>24</sub> fatty acid;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a pharmaceutical  
composition comprising a compound or salt disclosed herein and one or more  
pharmaceutically acceptable carriers, diluents, and excipients.

In another aspect of the present disclosure, there is provided a use of a compound or salt disclosed herein in the manufacture of a medicament for treating type II diabetes in a patient.

10 In a further aspect of the present disclosure, there is provided a use a compound or salt disclosed herein in the manufacture of a medicament for treating chronic kidney disease in a patient.

In another aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in therapy.

15 In a further aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in the treatment of type II diabetes.

In another aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in the treatment of chronic kidney disease.

In another aspect of the present disclosure, there is provided a compound of the Formula:

20  $X_1$  I V  $X_2$  S L D V P I G L L Q I L  $X_3$  E Q E K Q E K E K Q Q A K T N A  $X_4$  I L A Q V-NH<sub>2</sub>

wherein  $X_1$  denotes that the I residue is modified by either acetylation or methylation at the N-terminus;

wherein  $X_2$  is L or T;

25 wherein  $X_3$  is L or I;

wherein  $X_4$  is Q or E (SEQ ID NO:18).

In a further aspect of the present disclosure, there is provided a use of a compound or salt according to any one of SEQ. ID NOS. 1, 2, 3, 5, 6, and 7 in the manufacture of a medicament treating type II diabetes in a cat.

30 In another aspect of the present disclosure, there is provided a use of a compound or salt according to any one of SEQ. ID NOS. 1, 2, 3, 5, 6, and 7 in the manufacture of a medicament for treating chronic kidney disease in a cat.

**Description**

The present invention provides novel compounds that are CRHR2 agonists. The present invention also provides novel therapeutic CRHR2 agonists in the form of human UCN2 analogs which may be suitable for once weekly administration or other types of administration such as bi-monthly or monthly. The present invention also provides a novel compound that is a CRHR2 agonist for use in therapy, and in particular for use to treat T2D or CKD, or combinations thereof.

Accordingly, the present invention provides compounds which are urocortin molecules that have the amino acid sequence of Formula III:

15  $X_1IVX_2SLDVPIGLLQILX_3EQEKQEKEKQQATX_7NAX_4ILAX_8V-NH_2$  (Formula III),  
wherein

$X_1$  denotes that the I residue is unmodified or is modified at the N-terminus by either acetylation or methylation,

$X_2$  is L or T,

20  $X_3$  is L or I,

$X_4$  is Q, R, or E,

$X_7$  is T or E,

$X_8$  is Q, H or R (SEQ ID NO:67), and

Formula III further comprises a modified K residue (“K<sup>\*</sup>”) substituted at position 10 or at any  
25 one position between position 14 and position 30 inclusive,

5           29.    Use of a compound or salt according to any one of claims 1 to 28 in the manufacture of a medicament for treating type II diabetes in a patient.

          30.    Use a compound or salt according to any one of claims 1 to 28 in the manufacture of a medicament for treating chronic kidney disease in a patient.

10           31.    The use according to claim 30 wherein the chronic kidney disease is caused by diabetic nephropathy.

          32.    The use according to claim 30 wherein the chronic kidney disease is caused by  
15   hypertensive nephropathy.

          33.    The use according to any one of claims 30 to 32, wherein the compound or salt is to be administered subcutaneously to the patient in need of such treatment.

20           34.    A compound or salt according to any one of claims 1 to 28 for use in therapy.

          35.    A compound or salt according to any one of claims 1 to 28 for use in the treatment of type II diabetes.

25           36.    A compound or salt according to any one of claims 1 to 28 for use in the treatment of chronic kidney disease.

          37.    A compound of the Formula:

30            $X_1 I V X_2 S L D V P I G L L Q I L X_3 E Q E K Q E K E K Q Q A K T N A X_4 I L A Q V -$   
               $NH_2$

5        wherein  $X_1$  denotes that the I residue is modified by either acetylation or methylation at the N-terminus;

         wherein  $X_2$  is L or T;

         wherein  $X_3$  is L or I;

         wherein  $X_4$  is Q or E (SEQ ID NO:18).

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         38.    Use of a compound or salt according to any one of SEQ. ID NOS. 1, 2, 3, 5, 6, and 7 in the manufacture of a medicament treating type II diabetes in a cat.

         39.    Use of a compound or salt according to any one of SEQ. ID NOS. 1, 2, 3, 5, 6,  
15    and 7 in the manufacture of a medicament for treating chronic kidney disease in a cat.

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