

blockers identified to date are venom peptides derived from various types of venomous organisms, such as snakes, arachnids (such as scorpions and spiders), sea anemones, etc.. Such Kv1.3 blockers include the peptides ShK, Oskl, margatoxin and kaliotoxin, reviewed by Chandy et al., Trends in Pharmacol. Sci. 25:280-9, 2004. See also Abdel-Mottaleb et al., Toxicon 51:1424-30, 2008, and Mouhat et al., Biochem. J. 385(Pt 1):95-104, 2005.

Various attempts to engineer toxin peptides for particular properties, including specificity or potency, have been described, e.g. in WO2006/002850, WO2006/042151, WO2008/088422, WO2006/116156, WO2010/105184 and WO2014/116937.

However, there remains a need for alternative Kv1.3 blockers. Blockers having improved specificity compared to known blockers may be particularly desirable, although improvements in other properties such as stability and potency may also be useful.

## **SUMMARY**

The disclosure relates to ion channel blockers from the scorpion *Parabuthus transvaalicus*, having the amino acid sequences:

QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR (PaT1); and

QMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR (PaT2);

and variants thereof.

Amongst other desirable properties, these molecules have been found to be extremely selective blockers for Kv1.3 over other voltage-gated potassium channels, and typically also have high potency at the Kv1.3 channel.

In one aspect, the present disclosure therefore provides an ion-channel blocker comprising a Kv1.3 inhibitor component, said Kv1.3 inhibitor component comprising: the sequence of PaT1:

QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR;

or a variant thereof which differs from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are at amino acid positions selected from positions 1-5, 7-11, 13-15, 17-23, 25, 28-31, 33 and 35-37; and wherein said Kv1.3 inhibitor component has Kv1.3 inhibitor activity and is selective for Kv1.3;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure refers to an ion channel blocker which is  
H-NMDMRC(1)SASVEC(2)KQKC(3)LKAIGSIFGKC(1)MNKKC(2)KC(3)YPR-OH  
5 (Cpd. 3) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine  
residues which participate together in a disulphide bond are indicated by the same  
numeral in parentheses.

In yet another aspect, the present disclosure refers to an ion channel blocker which is  
10 H-NMDMRC(1)SASVEC(2)AQKC(3)LKAIGSIFGKC(1)MNKKC(2)KC(3)YPR-NH2  
(Cpd. 30) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine  
residues which participate together in a disulphide bond are indicated by the same  
numeral in parentheses.

15 In one aspect, the present disclosure refers to an ion channel blocker which is  
H-NID[Nle]RC(1)SASVEC(2)KQKC(3)LKAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-OH  
(Cpd. 95) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine  
residues which participate together in a disulphide bond are indicated by the same  
numeral in parentheses.

20

In another aspect, the present disclosure refers to an ion channel blocker which is  
H-P[Nle]E[Nle]RC(1)SASVEC(2)KQKC(3)LAAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-  
OH (Cpd. 97) or a pharmaceutically acceptable salt thereof, wherein a pair of  
cysteine residues which participate together in a disulphide bond are indicated by the  
25 same numeral in parentheses.

In yet another aspect, the present disclosure refers to an ion channel blocker which is  
H-PIE[Nle]RC(1)SASVEC(2)KQKC(3)LAAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-OH  
(Cpd. 101) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine  
30 residues which participate together in a disulphide bond are indicated by the same  
numeral in parentheses.

In one aspect, the present disclosure refers to an ion channel blocker which is  
H-P[Nle]E[Nle]RC(1)SASVEC(2)AQKC(3)LAAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-  
35 OH (Cpd. 103) or a pharmaceutically acceptable salt thereof, wherein a pair of  
cysteine residues which participate together in a disulphide bond are indicated by the  
same numeral in parentheses.

Thus, the Kv1.3 inhibitor component of the ion channel blocker can contain up to 9 amino acid changes compared to the sequence of PaT1. Except where otherwise specified, each those 9 changes can independently be selected from a single amino acid insertion, deletion or substitution. In an example, the Kv1.3 inhibitor component of the ion channel blocker may contain 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid changes compared to the sequence of PaT1. In an example, the Kv1.3 inhibitor component of the ion channel blocker contains 6 amino acid changes compared to the sequence of PaT1.

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The amino acid residues of PaT1 are numbered from 1 to 33, in the conventional direction of N- to C-terminus. Throughout this specification, amino acid positions in variants of PaT1 are numbered according to the corresponding position in PaT1 when optimally aligned therewith. Thus, especially for inhibitors which contain one or more insertions or deletions compared to PaT1, the numbering of any given residue reflects the corresponding residue in PaT1 and does not necessarily reflect its linear position in the relevant sequence.

The residue present at a specific position may be indicated by the number of the relevant position alongside the single letter code or three letter code for the residue present. Thus, 1Q or Q1 (the two formats are interchangeable) indicates a glutamine (Q) residue at position 1, while 2Nle, 2[Nle], Nle2 or [Nle]2 indicates a norleucine residue at position 2.

25 An asterisk may be used to denote the position of a deletion relative to the sequence of PaT1. For example, "1\*" indicates a deletion of the residue at position 1 as compared to PaT1.

An insertion may be indicated by a string of consecutive residues at a single position, e.g. "1QA" indicates an insertion of an alanine (A) residue after the glutamine (Q) residue at position 1.

In some examples, it may be desirable that one or more of positions 28, 31, 34, 35, 36 or 37 are identical to the corresponding position in PaT1, i.e. the residue present in the relevant position(s) is identical to the residue present in PaT1 at the corresponding position. For example, one or more of positions 28, 31, 34 and 35 may be identical to the corresponding position in PaT1. In some examples, all of

- the residue at position 28 is selected from Nle, A and L;  
the residue at position 29 is V;  
the residue at position 30 is selected from G and D;  
the residue at position 31 is selected from D, Q, E and H;  
5 the residue at position 33 is selected from H, V, D, Q and R;  
the residue at position 35 is selected from T, F(4-NH<sub>2</sub>), F(4-F), F(4-NO<sub>2</sub>) and F(4-CH<sub>3</sub>);  
the residue at position 36 is selected from Q, S and G or is deleted;  
the residue at position 37 is selected from K, E, S and C or is deleted.
- 10 In some examples, the Kv1.3 inhibitor component may differ from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are made only at the following positions wherein, if different from PaT1:
- 15 the residue at position 1 is selected from N, P, I, V, H, Y and S or is deleted;  
the residue at position 2 is selected from Nle, I, V, L, T, Q and E or is deleted;  
the residue at position 3 is selected from E, S and N or is deleted;  
the residue at position 4 is selected from Nle, I, V, L, A, E and S or is deleted;  
the residue at position 5 is selected from K, Q, A and L or is deleted;  
20 the residue at position 7 is selected from K, R and Q;  
the residue at position 8 is selected from I, H, S, L, Y and G;  
the residue at position 9 is selected from A, Abu, P, F, V and L;  
the residue at position 10 is selected from R, K and P;  
the residue at position 11 is Q;  
25 the residue at position 13 is selected from L, A, E, Q, I, K, H and G;  
the residue at position 14 is selected from V, K, E, L and 2-amino-5-carboxypentanoyl;  
the residue at position 15 is selected from S and L;  
the residue at position 17 is selected from K, Y, R, Q and D or is deleted;  
30 the residue at position 18 is selected from D, A, Y, G, V, Q, hQ and L or is deleted ;  
the residue at position 19 is selected from R, Y and Q or is deleted;  
the residue at position 20 is selected from Y, E and R or is deleted;  
the residue at position 21 is selected from R, H and E;  
the residue at position 22 is selected from R, M, D, L and C;  
35 the residue at position 23 is selected from R, K, hK, P and G;  
the residue at position 28 is Nle;  
the residue at position 30 is selected from G and D;

- the residue at position 31 is selected from D, Q, E and H;  
the residue at position 33 is selected from H, V, D, Q and R;  
the residue at position 35 is selected from T, F(4-NH<sub>2</sub>), F(4-F), F(4-NO<sub>2</sub>) and F(4-CH<sub>3</sub>);
- 5 the residue at position 36 is selected from Q, S and G or is deleted;  
the residue at position 37 is selected from K, S and C or is deleted.
- In some examples, the Kv1.3 inhibitor component may differ from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are made
- 10 only at the following positions wherein, if different from PaT1:
- the residue at position 1 is selected from N, P, I, V, H, Y and S or is deleted;  
the residue at position 2 is selected from Nle, I, V, L, T, Q and E or is deleted;  
the residue at position 3 is selected from E, S and N or is deleted;
- 15 the residue at position 4 is selected from Nle, I, V, L, A, E and S or is deleted;  
the residue at position 5 is selected from K, Q, A and L or is deleted;  
the residue at position 7 is selected from K, R and Q;  
the residue at position 8 is selected from I, H and G;  
the residue at position 9 is selected from A, Abu and L;
- 20 the residue at position 10 is selected from R, K and P;  
the residue at position 11 is Q;  
the residue at position 13 is selected from L, A, E, Q, I, K, H and G;  
the residue at position 14 is selected from V, K, E, L and 2-amino-5-carboxypentanoyl;
- 25 the residue at position 15 is selected from S and L;  
the residue at position 17 is selected from K, Y, R, Q and D or is deleted;  
the residue at position 18 is selected from D, A, Y, G, V, Q, hQ and L or is deleted ;  
the residue at position 19 is selected from R, Y and Q or is deleted;  
the residue at position 20 is selected from Y, E and R or is deleted;
- 30 the residue at position 21 is selected from R, H and E;  
the residue at position 22 is selected from R, M, D, L and C;  
the residue at position 23 is selected from R, K, hK, P and G;  
the residue at position 28 is Nle;  
the residue at position 30 is selected from G and D;
- 35 the residue at position 31 is selected from D, Q, E and H;  
the residue at position 33 is selected from H, V, D, Q and R;

the residue at position 35 is selected from F(4-NH<sub>2</sub>), F(4-F), F(4-NO<sub>2</sub>) and F(4-CH<sub>3</sub>);  
the residue at position 36 is selected from Q, S and G or is deleted;  
the residue at position 37 is selected from S and C or is deleted.

5

In some examples, the Kv1.3 inhibitor component of the molecule comprises the sequence of PaT1:

QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR

- 10 or differs from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are made only at the following positions wherein, if different from PaT1:

the residue at position 1 is selected from N and P or is deleted;

- 15 the residue at position 2 is Nle, I, V and L;

the residue at position 3 is selected from E and S;

the residue at position 4 is Nle, I, V and L;

the residue at position 8 is I;

the residue at position 10 is R;

- 20 the residue at position 11 is Q;

the residue at position 13 is A;

the residue at position 14 is V;

the residue at position 18 is selected from D, Y and A;

the residue at position 19 is R;

- 25 the residue at position 20 is Y;

the residue at position 21 is R;

the residue at position 22 is selected from R and C;

the residue at position 23 is selected from R and G;

the residue at position 28 is Nle;

- 30 the residue at position 30 is G;

the residue at position 33 is H;

the residue at position 37 is C.

In some examples the disclosure provides an ion-channel blocker comprising a Kv1.3

- 35 inhibitor component, said Kv1.3 inhibitor component comprising:

the sequence of PaT1:

QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR;

or a sequence which has at least 75% identity with the sequence of PaT1, wherein any differences from the sequence of PaT1 are at amino acid positions selected from positions 1-5, 7-11, 13-15, 17-23, 25, 28-31, 33 and 35-37; and wherein said Kv1.3 inhibitor component has Kv1.3 inhibitor activity and is selective for Kv1.3;  
5 or a pharmaceutically acceptable salt thereof.

In some examples the Kv1.3 inhibitor component has at least 75% identity with the sequence of PaT1. In some examples the Kv1.3 inhibitor component has at least  
10 80% identity with the sequence of PaT1. In some examples the Kv1.3 inhibitor component has at least 85% identity with the sequence of PaT1. In some examples the Kv1.3 inhibitor component has at least 90% identity with the sequence of PaT1. In some examples the Kv1.3 inhibitor component has at least 95% identity with the sequence of PaT1. In some examples the Kv1.3 inhibitor component has at least  
15 97% identity with the sequence of PaT1.

The Kv1.3 inhibitor component may comprise one or more insertions or deletions as compared to the sequence of PaT1.

20 Typically, the Kv1.3 inhibitor component comprises a maximum of three insertions as compared to the sequence of PaT1, e.g. precisely 3 insertions, precisely 2 insertions, or precisely 1 insertion.

Typically, only a single amino acid is inserted at any given site, although insertions of  
25 multiple amino acids may be tolerated. For the avoidance of doubt, an insertion of two amino acids at the same site is considered as two insertions and hence as two of the permitted differences from the sequence of PaT1.

Typically, the Kv1.3 inhibitor component contains no more than 7 deletions compared  
30 to the sequence of PaT1, e.g. no more than 6, no more than 5, no more than 5, no more than 4, no more than 3, no more than 2 deletions, no more than one deletion, or no deletions at all.

In order to preserve the spacing of the cysteine residues, and hence the pattern of  
35 disulphide bonding, it may be desirable that any insertions and deletions are not located between the cysteine residue at position 6 (6C) and the cysteine residue at

position 34 (34C). Thus, any insertion or deletion may preferably be located N-terminal of 6C or C-terminal of 34C.

5 However, if the Kv1.3 inhibitor component contains one or more insertions or deletions between 6C and 34C, then it may be desirable to incorporate the same number of both insertions and deletions within that region. e.g. to restore the relative spacing of the cysteine residues.

10 In many examples the Kv1.3 inhibitor component has no insertions as compared to the sequence of PaT1.

15 If a deletion is present between 6C and 34C, it may be desirable that only one such deletion is present. It may, for example, be at position 17, 18, 19 or 20, especially if the molecule does not contain a corresponding insertion to maintain the spacing of the cysteine residues.

20 Without wishing to be bound by theory, it is believed that multiple deletions may be better tolerated in the N-terminal sequence (residues 1-5) and C-terminal sequence (residues 36-37). Multiple deletions may be tolerated in these regions. For deletions in the N-terminal sequence (positions 1-5), if a residue at position X is deleted, it may be desirable that all residues N-terminal of that residue are also deleted. Thus, for example, residues 1, 1 and 2, 1 to 3, 1 to 4 or 1 to 5 may be deleted. For deletions at the C-terminus (positions 36-37), if the residue at position 36 is deleted, it may be desirable that the residue at position 37 is also deleted. Thus, for example, residues 25 37, or 36 and 37, may be deleted.

30 For the avoidance of doubt, a deletion of two consecutive amino acids is considered as two amino acid deletions and hence as two of the permitted differences from the sequence of PaT1.

35 Glutamine (Q) residues can be unstable, either in vivo or in vitro, e.g. during storage in aqueous solution. This may be of particular relevance when the glutamine residue is located at the N-terminus of the molecule, as the side chain may be sterically capable of interacting with the free alpha amino group, resulting in dehydration to pyroglutamate. Thus it may be desirable that the residue at position 1 is not Q, especially if the ion channel blocker does not contain any additional sequence N-

terminal of the Kv1.3 inhibitor. For example, the residue at position 1 may be N or P, or may be deleted; i.e. the Kv1.3 inhibitor may comprise 1N, 1P or 1\*.

Additionally or alternatively, it may be desirable that one, two or all three of the residues at positions 2, 4 and 28 are not M, since methionine (M) residues are susceptible to oxidation. Preferably one, two or all three methionine residues are either individually substituted with a residue having a non-oxidisable side chain, or are deleted. Any suitable residue with a non-oxidisable residue may be used, with Nle, I, V and L being particularly suitable.

Suitable combinations of residues at some or all of positions 2, 4 and 28 include:

2\* + 4Nle, 4I, 4V or 4L;

2Nle + 4Nle, 4I, 4V or 4L;

2I + 4Nle, 4I, 4V or 4L;

2V + 4Nle, 4I, 4V or 4L;

2L + 4Nle, 4I, 4V or 4L.

Any of the above may be combined with 28Nle.

2Nle + 4Nle + 28Nle may be particularly preferred.

In some examples, the Kv1.3 inhibitor component contains the residues 22S + 23I or 22R + 23G.

In addition to any differences at positions 1, 2, 4 and 28, it may be desirable that the Kv1.3 inhibitor component contains only 4 further differences, only 3 further differences, only 2 further differences, or only 1 further difference from the sequence of PaT1.

The Kv1.3 inhibitor component may be identical to PaT1 or PaT2 at all positions apart from positions 1, 2, 4 and 28.

Additionally or alternatively, the Kv1.3 inhibitor component may comprise the residues 13A and/or 18A.

For example, it may comprise

The ion channel blocker may comprise a linker peptide located between the Kv1.3 inhibitor and the heterologous component.

- 5     The various components may be in any appropriate orientation. For example, the Kv1.3 inhibitor may be located N-terminal of the heterologous component, or the heterologous component may be located N-terminal of the Kv1.3 inhibitor, with the linker (where present) between them.
- 10    A peptide linker is typically between 3 and 30 amino acids in length, with a high proportion of small and hydrophilic amino acid residues (e.g. glycine and serine) to provide the required flexibility without compromising aqueous solubility of the molecule. For example, it may comprise at least 50% glycine and serine residues, at least 60% glycine and serine residues, at least 70% glycine and serine residues, at
- 15    least 80% glycine and serine residues, or at least 90% glycine and serine residues. It may also contain a protease cleavage site to enable separation of the Kv1.3 inhibitor and heterologous component.

- 20    The Kv1.3 inhibitor may also be inserted within a heterologous polypeptide, which may be regarded as a “scaffold” for the Kv1.3 inhibitor. In such cases, the ion channel blocker may be considered to comprise heterologous components N- and C-terminal of the Kv1.3 inhibitor, wherein the heterologous components are derived from the same molecule and interact with one another, e.g. to fold into a scaffold, having the Kv1.3 inhibitor displayed at its surface. Thus, the Kv1.3 inhibitor may be inserted within a surface loop of a
- 25    heterologous protein, e.g. into the CDR sequence of an antibody or a fragment thereof containing the antigen binding domain. It has been demonstrated that a Kv1.3 inhibitor retains activity when inserted into a CDR (e.g. CDR3L) of a humanised immunoglobulin designated “Syn”, directed against respiratory syncytial virus. (Wang et al., Proc. Natl. Acad. Sci. USA 113(41), 11501-11506, 2016.) The Syn antibody, or a fragment thereof
- 30    containing the antigen binding domain, may therefore be used as a scaffold. If the antibody scaffold contains an Fc domain, it may be desirable that this is functionally “Fc-null”, i.e. it is not capable of binding to the Fc receptor. Such mutations are described by Wang et al., *op cit.*

- 35    In some examples, the ion channel blocker may have a maximum length of 200 amino acids, e.g. of 150 amino acids, 125 amino acids, 100 amino acids, 75 amino

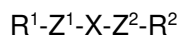
acids or 50 amino acids, e.g. 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38 or 37 amino acids, or even shorter where the Kv1.3 inhibitor component contains one or more deletions compared to the sequence of PaT1.

- 5 The ion channel blocker may further comprise up to 10 additional residues at the N-terminus, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional residues at the N-terminus. Additionally or alternatively, the ion channel blocker may further comprise up to 10 residues at the C-terminus, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional residues at the C-terminus, within the constraint that the molecule is not more than 50 amino acids in  
10 length.

For example, the additional sequence at the N-terminus may comprise or consist of the sequence GG or SG. Additionally or alternatively, the additional sequence at the C-terminus may comprise or consist of the sequence RRTA, HRRK, QSKA, AGPR,  
15 RSRT, RHKR, GGKR, PKTA, TDAR, HRQQ, RPRH, ARNA, TGRK, HERT, NTRT, QRNG, AHRN, PRSA, QRQS, QRRK, ARAK, AKRD, RDKT, HRRK, RAKR, QRTR, ATRH, ARRS, AKTR, NRQR, PRNT, e.g. RRTA or HRRK. All of these sequences have been shown to be compatible with Kv1.3 inhibitor activity and selectivity when added to the C-terminus of Odk2 analogues (see WO 12014/116937).

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Thus the disclosure also provides an ion channel blocker having the formula:



25

where

$R^1$  is hydrogen,  $C_{1-4}$  alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

$R^2$  is OH,  $NH_2$  or  $CH_2OH$ ,

30

X is a Kv1.3 inhibitor having the sequence of PaT1 or a variant thereof as described above, and

$Z^1$  and  $Z^2$  are independently sequences of up to 10 amino acid residues;

with the proviso that the ion channel blocker have a maximum length of 50 amino  
35 acids;

or a pharmaceutically acceptable salt thereof.

As set out above, Z<sup>1</sup> may comprise or consist of the sequence GG or SG.

Additionally or alternatively, Z<sup>2</sup> may comprise or consist of the sequence RRTA,  
5 HRRK, QSKA, AGPR, RSRT, RHKR, GGKR, PKTA, TDAR, HRQQ, RPRH, ARNA,  
TGRK, HERT, NTRT, QRNG, AHRN, PRSA, QRQS, QRRK, ARAK, AKRD, RDKT,  
HRRK, RAKR, QRTR, ATRH, ARRS, AKTR, NRQR, PRNT, e.g. RRTA or HRRK.

Additionally or alternatively, R<sup>2</sup> can be CH<sub>2</sub>OH and can be comprised in (4-amino-5-  
10 hydroxypentyl)guanidine or 4-amino-5-hydroxypentanamide.

The Kv1.3 inhibitor component of the molecule contains 6 cysteine (C) residues  
which together form three disulphide bonds, between residues 6C and 27C, residues  
12C and 32C, and residues 16C and 34C. It is believed that these bonds are  
15 important for the conformation and activity of the Kv1.3 inhibitor.

The disulphide bonds may be indicated graphically as follows by reference to PaT1:

QMDMR[C(1)]SASVE[C(2)]KQK[C(3)]LKAIGSIFGK[C(1)]MNKK[C(2)]K[C(3)]YPR  
20

where a pair of cysteine residues which participate together in a disulphide bond are  
indicated by the same numeral in parentheses. Similar notation can be applied to  
any of the other sequences in this application. Except where the context demands  
otherwise, it should be understood that an active inhibitor compound includes  
25 appropriate disulphide bonding.

It may be desirable that no other cysteine residues are introduced into the Kv1.3  
inhibitor component by substitution. Additionally or alternatively, it may be desirable  
that no cysteine residues are present in any N- or C-terminal additional sequence.  
30 Thus, in some examples, the molecule contains no other cysteine residues apart from  
those at positions 6, 12, 16, 27, 32 and 34 of PaT1.

However, in some examples, the inhibitor component comprises 8 cysteine residues,  
which together form four disulphide bonds, between residues 6C and 27C, residues 12C  
35 and 32C, residues 16C and 34C, and cysteine residues at positions corresponding to  
positions 22 and 37 of Pat1. Compound 87 is an example of such a molecule, and the  
disulphide bonding may be indicated graphically as follows:

P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRAK  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYP-[(4-amino-5-hydroxypentyl)guanidine]  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-[4-amino-5-hydroxypentanamide]  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRST  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRRY  
 P[Nle]E[Nle]RCSSSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSLSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSAPVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASPECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASQECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECLQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQPCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCEASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCFASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSYSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSAFVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR

In some examples, the ion channel blocker does not have the sequence:

QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR

or

- 5 QMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR.

In some examples, R<sup>1</sup> is H and R<sup>2</sup> is NH<sub>2</sub> or OH. In some examples, it may be desirable that R<sup>2</sup> is OH.

- 10 Ion channel blockers include the following:

|                                                         |          |
|---------------------------------------------------------|----------|
| H-QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH              | (Cpd. 1) |
| H-QMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR-OH              | (Cpd. 2) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH              | (Cpd. 3) |
| H-NMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR-OH              | (Cpd. 4) |
| H-MDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH               | (Cpd. 5) |
| H-DMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                | (Cpd. 6) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub> | (Cpd. 7) |
| H-NIDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH              | (Cpd. 8) |

OH

In an example, the ion channel blocker of the disclosure is:

H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH (Cpd. 97).

5 In some examples, the ion channel blocker is not:

H-QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH (Cpd. 1)

or

H-QMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR-OH (Cpd. 2).

10 In one aspect, the present disclosure further provides a nucleic acid encoding an ion channel blocker, a Kv1.3 inhibitor, or a peptide Z<sup>1</sup>-X-Z<sup>2</sup> as described.

In another aspect, the present disclosure also provides an expression vector comprising a nucleic acid as described.

15

In yet another aspect, the present disclosure further comprises a host cell comprising a nucleic acid or an expression vector of the disclosure, and capable of expressing an ion channel blocker, a Kv1.3 inhibitor, or a peptide Z<sup>1</sup>-X-Z<sup>2</sup> as described. The host cell may be capable of secreting the ion channel blocker, a Kv1.3 inhibitor, or a  
20 peptide Z<sup>1</sup>-X-Z<sup>2</sup> as described.

In one aspect, the present disclosure further provides a method of synthesising an ion channel blocker of the disclosure, the method comprising:

- 25 (a) synthesising the ion channel blocker by means of solid-phase or liquid-phase peptide synthesis methodology and recovering the peptide thus obtained;
- (b) expressing the ion channel blocker from a nucleic acid construct that encodes the ion channel blocker and recovering the expression product; or
- (c) expressing a precursor peptide from a nucleic acid construct that encodes the precursor peptide sequence, recovering the expression product, and modifying the  
30 precursor peptide to yield the ion channel blocker.

In another aspect, the present disclosure further provides a pharmaceutical composition comprising an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.

The present disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in a method of medical treatment. In one aspect, the present disclosure refers to an ion channel blocker or pharmaceutically acceptable salt thereof for use in therapy. In another aspect, the present disclosure refers to a method of inhibiting weight gain, promoting weight loss, and reducing excess body weight, wherein the method comprises an ion channel blocker or pharmaceutically acceptable salt as disclosed herein to be administered to a subject in need thereof. In yet another aspect, the present disclosure refers to the use of an ion channel blocker or pharmaceutically acceptable salt as disclosed herein in the manufacture of a medicament for inhibiting or reducing inflammation; or treating obesity, or in the treatment of obesity linked inflammation, obesity linked gallbladder disease or obesity induced sleep apnoea. In one aspect, the present disclosure refers to the use of an ion channel blocker or pharmaceutically acceptable salt as disclosed herein in the manufacture of a medicament for treating an inflammatory condition or disorder, preferably wherein the inflammatory condition or disorder is an autoimmune disorder, allergy or hypersensitivity, allograft rejection, graft versus host disease, hay fever, asthma, anaphylaxis, allergic rhinitis, urticaria, eczema, alopecia areata, dermatomyositis, inclusion body myositis, polymyositis, ankylosing spondylitis, vasculitis, arthritis (including rheumatoid arthritis, osteoarthritis, psoriatic arthritis), Sjogren's syndrome, systemic lupus erythematosus (SLE), uveitis, inflammatory fibrosis (e.g. scleroderma, lung fibrosis, cirrhosis), chronic obstructive pulmonary disease (COPD), hepatitis, chronic inflammatory demyelinating polyneuropathy, inflammatory bowel disease, colitis (e.g. Crohn's disease and ulcerative colitis), erythema, thyroiditis, psoriasis, atopic dermatitis, allergic contact dermatitis, scleroderma, glomerulonephritis, inflammatory bone resorption, multiple sclerosis, type 1 diabetes, transplant rejection or graft-versus-host disease; or a condition caused by or associated with impaired glucose control, preferably wherein the condition is metabolic syndrome, insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose or type 2 diabetes; or a smooth muscle proliferative disorder, preferably wherein said disorder is restenosis; or a neuroinflammatory or neurodegenerative disorder, preferably wherein said disorder is Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease or amyotrophic lateral sclerosis (ALS); or cancer, preferably wherein said cancer is breast cancer, prostate cancer or lymphoma, preferably wherein said lymphoma is non-Hodgkin lymphoma (NHL), preferably wherein said NHL is large B-cell lymphoma, follicular lymphoma, Burkitt lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, mycosis fungoides, anaplastic large

cell lymphoma, peripheral T-cell lymphoma, precursor T-lymphoblastic lymphoma or Sézary syndrome.

In one aspect, the present disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in a method of  
5 inhibiting or reducing inflammation, especially in the treatment of an inflammatory condition or disorder, including autoimmune disorders.

An inflammatory condition or disorder may be any condition or disorder in which reduction of inflammation is desirable, e.g. where inflammation contributes to symptoms or pathogenesis.

10 Such conditions include autoimmune diseases, allergy and hypersensitivity, allograft rejection and graft versus host disease.

Specific conditions include hay fever, asthma, anaphylaxis, allergic rhinitis, urticaria, eczema, alopecia areata, dermatomyositis, inclusion body myositis, polymyositis, ankylosing spondylitis, vasculitis, arthritis (including rheumatoid arthritis,  
15 osteoarthritis, psoriatic arthritis), Sjogren's syndrome, systemic lupus erythematosus (SLE, or simply "lupus"), and uveitis, inflammatory fibrosis (e.g. scleroderma, lung fibrosis, cirrhosis), chronic obstructive pulmonary disease (COPD), hepatitis, chronic inflammatory demyelinating polyneuropathy, inflammatory bowel disease, colitis (including Crohn's disease and ulcerative colitis), erythema, thyroiditis, psoriasis,  
20 atopic dermatitis, allergic contact dermatitis, scleroderma, glomerulonephritis, inflammatory bone resorption, multiple sclerosis, type 1 diabetes, transplant rejection and graft-versus-host disease.

The disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in a method of inhibiting weight gain,  
25 promoting weight loss, reducing excess body weight or treating obesity (e.g. by control of appetite, feeding, food intake, calorie intake, and/or energy expenditure), or in the treatment of obesity linked inflammation, obesity linked gallbladder disease or obesity induced sleep apnoea.

30 An effect on body weight may be therapeutic or cosmetic.

The disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in treatment of a condition caused by

or associated with impaired glucose control, such as metabolic syndrome, insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose or type 2 diabetes.

5 The disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in treatment of a smooth muscle proliferative disorder such as restenosis, e.g. in patients following vascular surgery (e.g. angioplasty).

10 The disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in the treatment of a neuroinflammatory or neurodegenerative disorder, such as Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease or amyotrophic lateral sclerosis (ALS) (e.g. following viral infection).

15 The disclosure further provides an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof for use in treatment of cancer, e.g. breast cancer, prostate cancer or lymphoma, such as non-Hodgkin lymphoma (NHL). NHL includes T-cell NHL and B-cell NHL.

20 Forms of B-cell NHL include diffuse large B-cell lymphoma, follicular lymphoma, Burkitt lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and mantle cell lymphoma. Forms of T-cell NHL include mycosis fungoides, anaplastic large cell lymphoma, peripheral T-cell lymphoma, precursor T-lymphoblastic lymphoma, and Sézary syndrome.

25 The disclosure further provides use of an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof in the preparation of a medicament for inhibiting or reducing inflammation, especially in the treatment of an inflammatory condition or disorder, including autoimmune disorders. Further details of such conditions are set out above.

30 The disclosure further provides use of an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in inhibiting weight gain, promoting weight loss, reducing excess body weight or treating obesity (e.g. by control of appetite, feeding, food intake, calorie intake, and/or

energy expenditure), or in the treatment of obesity linked inflammation, obesity linked gallbladder disease or obesity induced sleep apnoea.

5 The disclosure further provides use of an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treatment of a condition caused by or associated with impaired glucose control, such as metabolic syndrome, insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose or type 2 diabetes.

10 The disclosure further provides use of an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treatment of a smooth muscle proliferative disorder such as restenosis, e.g. in patients following vascular surgery (e.g. angioplasty).

15 The disclosure further provides use of an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treatment of a neuroinflammatory or neurodegenerative disorder, such as Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease or amyotrophic lateral sclerosis (ALS) (e.g. following viral infection).

20 The disclosure further provides use of an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treatment of cancer, e.g. breast cancer, prostate cancer or lymphoma, such as non-Hodgkin lymphoma (NHL).

25 The disclosure further provides a method of inhibiting or reducing inflammation (especially in the treatment of an inflammatory condition or disorder, including autoimmune disorders) comprising administering an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof to a subject in need thereof. Further details of such conditions are set out above.

30 The disclosure further provides a method of inhibiting weight gain, promoting weight loss, reducing excess body weight or treating obesity (e.g. by control of appetite, feeding, food intake, calorie intake, and/or energy expenditure), or treating obesity linked inflammation, obesity linked gallbladder disease or obesity induced sleep apnea, comprising administering an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof to a subject in need thereof.

The disclosure further provides a method of treating a condition caused by or associated with impaired glucose control, such as metabolic syndrome, insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose or type 2 diabetes, comprising administering an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof to a subject in need thereof.

The disclosure further provides a method of treating a smooth muscle proliferative disorder such as restenosis, e.g. in patients following vascular surgery (e.g. angioplasty), comprising administering an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof to a subject in need thereof.

The disclosure further provides a method of treating a neuroinflammatory or neurodegenerative disorder, such as Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease or amyotrophic lateral sclerosis (ALS) (e.g. following viral infection), comprising administering an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof to a subject in need thereof.

The disclosure further provides a method of treating cancer, e.g. breast cancer, prostate cancer or lymphoma, such as non-Hodgkin lymphoma, comprising administering an ion channel blocker of the disclosure or a pharmaceutically acceptable salt thereof to a subject in need thereof.

## **DETAILED DESCRIPTION OF THE INVENTION**

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

All patents, published patent applications and non-patent publications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

Each embodiment of the invention described herein may be taken alone or in combination with one or more other embodiments of the invention.

## CLAIMS

1. An ion-channel blocker comprising a Kv1.3 inhibitor component, said Kv1.3 inhibitor component comprising:  
5 the sequence of PaT1:  
QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR;  
or a variant thereof which differs from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are at amino acid positions selected from positions 1-5, 7-11, 13-15, 17-23, 25, 28-31, 33 and 35-37; and  
10 wherein said Kv1.3 inhibitor component has Kv1.3 inhibitor activity and is selective for Kv1.3; or a pharmaceutically acceptable salt thereof.
2. An ion channel blocker or pharmaceutically acceptable salt according to claim 1 wherein  
15 (a) one or more of positions 28, 31, 34, 35, 36 or 37 are identical to the corresponding position in PaT1, or  
(b) one or more of positions 28, 31, 34 and 35 are identical to the corresponding position in PaT1, or  
(c) all of positions 28, 31, 34 and 35 are identical to the corresponding positions in PaT1,  
20 or  
(d) all of positions 28, 31, 34, 35, 36 and 37 are identical to the corresponding positions in PaT1.
3. An ion channel blocker or pharmaceutically acceptable salt according to any one of  
25 the preceding claims wherein the Kv1.3 inhibitor component comprises the sequence of PaT1:  
QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
or differs from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are made only at the following positions wherein, if different from  
30 PaT1:  
the residue at position 1 is selected from N, P, I, V, H, Y and S or is deleted;  
the residue at position 2 is selected from Nle (norleucine), I, V, L, T, Q and E or is deleted;  
the residue at position 3 is selected from E, S and N or is deleted;  
35 the residue at position 4 is selected from Nle, I, V, L, A, E and S or is deleted;  
the residue at position 5 is selected from K, Q, A, L, E and D or is deleted;

the residue at position 7 is selected from K, R, Q, E, F and A;  
 the residue at position 8 is selected from I, H, S, L, Y and G;  
 the residue at position 9 is selected from A, Abu (aminobutyric acid), P, F, V and L;  
 the residue at position 10 is selected from R, K, P, A, Q and L;  
 5 the residue at position 11 is selected from Q and D;  
 the residue at position 13 is selected from L, A, E, Q, I, K, H, D, V and G;  
 the residue at position 14 is selected from V, K, E, L, D and 2-amino-5-carboxypentanoyl;  
 the residue at position 15 is selected from S, L and P;  
 10 the residue at position 17 is selected from K, Y, R, Q, D, V and E or is deleted;  
 the residue at position 18 is selected from D, A, Y, G, V, Q, hQ and L or is deleted ;  
 the residue at position 19 is selected from R, Y and Q or is deleted;  
 the residue at position 20 is selected from Y, E and R or is deleted;  
 the residue at position 21 is selected from R, H, E and D;  
 15 the residue at position 22 is selected from R, M, D, L and C;  
 the residue at position 23 is selected from R, K, hK (homo-lysine), P, G and H;  
 the residue at position 26 is homo-lysine;  
 the residue at position 28 is selected from Nle, A and L;  
 the residue at position 29 is V;  
 20 the residue at position 30 is selected from G and D;  
 the residue at position 31 is selected from D, Q, E and H;  
 the residue at position 33 is selected from H, V, D, Q and R;  
 the residue at position 35 is selected from T, F(4-NH<sub>2</sub>), F(4-F), F(4-NO<sub>2</sub>) and F(4-CH<sub>3</sub>);  
 25 the residue at position 36 is selected from Q, S and G or is deleted;  
 the residue at position 37 is selected from K, E, S and C or is deleted.

4. An ion channel blocker or pharmaceutically acceptable salt according to claim 3  
 wherein the Kv1.3 inhibitor component differs from PaT1 by up to 9 substitutions, insertions  
 30 or deletions, wherein any substitutions or deletions are made only at the following positions  
 wherein, if different from PaT1:

the residue at position 1 is selected from N, P, I, V, H, Y and S or is deleted;  
 the residue at position 2 is selected from Nle, I, V, L, T, Q and E or is deleted;  
 the residue at position 3 is selected from E, S and N or is deleted;  
 35 the residue at position 4 is selected from Nle, I, V, L, A, E and S or is deleted;  
 the residue at position 5 is selected from K, Q, A and L or is deleted;  
 the residue at position 7 is selected from K, R and Q;

the residue at position 8 is selected from I, H, S, L, Y and G;  
 the residue at position 9 is selected from A, Abu, P, F, V and L;  
 the residue at position 10 is selected from R, K and P;  
 the residue at position 11 is Q;  
 5 the residue at position 13 is selected from L, A, E, Q, I, K, H and G;  
 the residue at position 14 is selected from V, K, E, L and 2-amino-5-carboxypentanoyl;  
 the residue at position 15 is selected from S and L;  
 the residue at position 17 is selected from K, Y, R, Q and D or is deleted;  
 10 the residue at position 18 is selected from D, A, Y, G, V, Q, hQ and L or is deleted ;  
 the residue at position 19 is selected from R, Y and Q or is deleted;  
 the residue at position 20 is selected from Y, E and R or is deleted;  
 the residue at position 21 is selected from R, H and E;  
 the residue at position 22 is selected from R, M, D, L and C;  
 15 the residue at position 23 is selected from R, K, hK, P and G;  
 the residue at position 28 is Nle;  
 the residue at position 30 is selected from G and D;  
 the residue at position 31 is selected from D, Q, E and H;  
 the residue at position 33 is selected from H, V, D, Q and R;  
 20 the residue at position 35 is selected from T, F(4-NH<sub>2</sub>), F(4-F), F(4-NO<sub>2</sub>) and F(4-CH<sub>3</sub>);  
 the residue at position 36 is selected from Q, S and G or is deleted;  
 the residue at position 37 is selected from K, S and C or is deleted,  
 preferably wherein the Kv1.3 inhibitor component differs from PaT1 by up to 9 substitutions,  
 25 insertions or deletions, wherein any substitutions or deletions are made only at the following  
 positions wherein, if different from PaT1:  
 the residue at position 1 is selected from N, P, V, H, Y and S or is deleted;  
 the residue at position 2 is selected from Nle, I, V and L or is deleted;  
 the residue at position 3 is selected from E and S or is deleted;  
 30 the residue at position 4 is selected from Nle, I, V, L, E and S or is deleted;  
 the residue at position 7 is selected from K and R;  
 the residue at position 8 is selected from I and H;  
 the residue at position 9 is selected from Abu and L;  
 the residue at position 10 is selected from R and K;  
 35 the residue at position 11 is Q;  
 the residue at position 13 is selected from L, A, E, Q, V and G;

the residue at position 14 is selected from V, K, E, L and 2-amino-5-carboxypentanoyl;

the residue at position 15 is selected from S and L;

the residue at position 17 is selected from K, Y and R or is deleted;

5 the residue at position 18 is selected from D, A, Y, G, V, Q, hQ and L or is deleted ;

the residue at position 19 is selected from R and Y or is deleted;

the residue at position 20 is selected from Y, E and R or is deleted;

the residue at position 21 is selected from R, H and E;

the residue at position 22 is selected from R and C;

10 the residue at position 23 is selected from R, K, hK, P and G;

the residue at position 28 is Nle;

the residue at position 30 is G;

the residue at position 33 is selected from H, V and R;

the residue at position 35 is selected from F(4-NH<sub>2</sub>), F(4-F), F(4-NO<sub>2</sub>) and F(4-CH<sub>3</sub>);

15 the residue at position 36 is selected from Q, S and G or is deleted;

the residue at position 37 is selected from S and C or is deleted,

more preferably wherein the Kv1.3 inhibitor component differs from PaT1 by up to 9 substitutions, insertions or deletions, wherein any substitutions or deletions are made only at the following positions wherein, if different from PaT1:

20 the residue at position 1 is selected from N and P or is deleted;

the residue at position 2 is Nle, I, V and L;

the residue at position 3 is selected from E and S;

the residue at position 4 is Nle, I, V and L;

the residue at position 8 is I;

25 the residue at position 10 is R;

the residue at position 11 is Q;

the residue at position 13 is A;

the residue at position 14 is V;

the residue at position 18 is selected from D, Y and A;

30 the residue at position 19 is R;

the residue at position 20 is Y;

the residue at position 21 is R;

the residue at position 22 is selected from R and C;

the residue at position 23 is selected from R and G;

35 the residue at position 28 is Nle;

the residue at position 30 is G;

the residue at position 33 is H;

the residue at position 37 is C.

5. An ion channel blocker or pharmaceutically acceptable salt according to any one of the preceding claims wherein
- 5 (a) the Kv1.3 inhibitor component contains no more than 3 deletions, no more than two deletions, or no more than one deletion compared to the sequence of PaT1; and/or
- (b) none of positions 20-33 is deleted; and/or
- (c) if the Kv1.3 inhibitor component contains more than one deletion, one of those deletions is at position 1; and/or
- 10 (d) if the Kv1.3 inhibitor component contains more than two deletions, two of those deletions are at positions 1 and 2; and/or
- (e) the Kv1.3 inhibitor component comprises a maximum of three insertions as compared to the sequence of PaT1; and/or
- (f) wherein the residue at position 1 is not Q; and/or
- 15 (g) the Kv1.3 inhibitor component comprises 1N, 1P or 1\* (a deletion of the residue at position 1); and/or
- (h) one, two or all three of the residues at positions 2, 4 and 28 of the Kv1.3 inhibitor component are not methionine; and/or
- (i) the Kv1.3 inhibitor component comprises one of the following combinations of
- 20 residues:
- 2\* (a deletion of the residue at position 2) + 4Nle, 4I, 4V or 4L;
- 2Nle + 4Nle, 4I, 4V or 4L;
- 2I + 4Nle, 4I, 4V or 4L;
- 2V + 4Nle, 4I, 4V or 4L; or
- 25 2L + 4Nle, 4I, 4V or 4L; and/or
- (j) the Kv1.3 inhibitor comprises 28Nle; and/or
- (k) the Kv1.3 inhibitor component contains the residues 22S + 23I or 22R + 23G; and/or
- (l) the Kv1.3 inhibitor component contains the residues 13A and/or 18A; and/or
- (m) the Kv1.3 inhibitor component contains one of the following combination of residues:
- 30 2Nle + 13A;
- 2Nle + 18A;
- 2Nle + 13A + 18A;
- 2Nle + 4Nle + 13A + 28Nle;
- 2Nle + 4Nle + 18A + 28Nle;
- 35 2Nle + 4Nle + 13A + 18A + 28Nle;
- 2Nle + 4Nle + 28Nle;
- 2Nle + 3E + 4Nle + 28Nle;

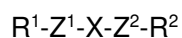
2Nle + 3E + 4Nle + 18A + 28Nle;  
1P + 2Nle + 4Nle + 28Nle;  
1P + 2Nle + 3E + 4Nle + 28Nle; or  
1P + 2Nle + 3E + 4Nle + 18A + 28Nle; and/or

5 (n) the Kv1.3 inhibitor component contains the residues 22C + 37C.

6. An ion channel blocker or pharmaceutically acceptable salt according to any one of the preceding claims which is a fusion protein comprising the Kv1.3 inhibitor component and one or more heterologous polypeptide sequences, preferably wherein the Kv1.3 inhibitor  
10 component is inserted within a heterologous scaffold polypeptide.

7. An ion channel blocker or pharmaceutically acceptable salt according to any one of the preceding claims wherein the ion channel blocker has a maximum length of 200 amino acids, 150 amino acids, 125 amino acids, 100 amino acids, 75 amino acids or 50 amino  
15 acids.

8. An ion channel blocker or pharmaceutically acceptable salt according to any of the preceding claims having the formula:



20 where

R<sup>1</sup> is hydrogen, C<sub>1-4</sub> alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R<sup>2</sup> is OH or NH<sub>2</sub>

X is a Kv1.3 inhibitor having the sequence of PaT1 or a variant thereof as described in any of the preceding claims, and

25 Z<sup>1</sup> and Z<sup>2</sup> are independently sequences of up to 10 amino acid residues;

with the proviso that the ion channel blocker has a maximum length of 50 amino acids.

9. An ion channel blocker or pharmaceutically acceptable salt according to claim 8 wherein

30 (a) Z<sup>1</sup> comprises or consists of the sequence GG or SG; and/or

(b) Z<sup>2</sup> comprises or consists of the sequence RRTA, HRRK, QSKA, AGPR, RSRT, RHKR, GGKR, PKTA, TDAR, HRQQ, RPRH, ARNA, TGRK, HERT, NTRT, QRNG, AHRN, PRSA, QRQS, QRRK, ARAK, AKRD, RDKT, HRRK, RAKR, QRTR, ATRH, ARRS, AKTR, NRQR or PRNT.

35

10. An ion channel blocker or pharmaceutically acceptable salt according to any one of the preceding claims wherein the Kv1.3 inhibitor component comprises one of the sequences:

QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
QMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR  
MDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
DMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NIDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDVRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCKDAIGSIFGKCMNKKCKCYPR  
NMEMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
N[Nie]DMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMD[Nie]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
NMDMRCSASVECKVKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQLCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCKKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLDAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIRSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIESIFGKCMNKKCKCYPR  
NMDMRCKASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSISVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASRECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVQCKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECLQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECAQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKEKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKLKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAHSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSKFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSRFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNGKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCHCYPR

NMDMRCSASVECKQKCLKAIGSIFGKCMNKKVCYPR  
 N[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
 N[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCRASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSASVECEQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSASVECQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSASVECKKKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]S[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSHSVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSASVECKQSCLKAIGSIFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSASVECKQKCKAIGSIFGKC[Nle]NKKCKCYPR  
 NMDMRCSASVECKQKCYKAIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCRKAIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLAAIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLYAIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLAIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKYIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKRIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKIGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKAYGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKAEGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKARGSIFGKCMNKKCKCYPR  
 NMDMRCSASVECKQKCLKAGSIFGKCMNKKCKCYPR  
 N[Nle]D[Nle]RCSASVECKQKCLKAIGSPFGKC[Nle]NKKCKCYPR  
 N[Nle]D[Nle]RCSASKECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 H[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 Y[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 V[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 S[Nle]D[Nle]RCSA[Abu]VECKQKCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFG[homo-Lys]CMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-NH<sub>2</sub>)]PR  
 S[Nle]D[Nle]RCSASVECGQKCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECVQKCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECK[2-Amino-5-

carboxypentanoyl]KCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYQ  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCRCYPR  
 S[Nle]DERCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLGAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLVAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECAQSCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECAQKCLAAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECAQLCLAAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]D[Nle]RCSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC  
 S[Nle]D[Nle]RCSASVECKEKCLQAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]D[Nle]RCSASVECKEKCL[homo-Gln]AIGSIFGKC[Nle]NKKCKCYPR  
 CSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC  
 S[Nle]D[Nle]RCSASVECKQKCLAAIGCIFGKC[Nle]NKKCKCYPC  
 P[Nle]D[Nle]RCSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC  
 S[Nle]D[Nle]RCSALVECKQKCLKAIGSIFGKCMNKKCKCYPR  
 S[Nle]D[Nle]RCSAVVECKQKCLKAIGSIFGKCMNKKCKC(3)YPR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-F)]PR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-NO<sub>2</sub>)]PR  
 S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-CH<sub>3</sub>)]PR  
 [Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 NID[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 PIE[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQKCLLAIGSIFGKC[Nle]NKKCKCYPR  
 PIDERCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 PIE[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]D[Nle]RCSASVECAQKCLAAIGSIFGKCMNKKCKCYPR  
 P[Nle]E[Nle]RCSASVECAQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 SKCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 LRCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR

CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPS  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYS  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYG  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCY  
 RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 LRCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 LRCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 LRCSASVECKQKCLAAIGSIFGKCMNKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKEKLAAIGSIFGKC[Nle]NKKCKCYPR  
 p[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYR  
 [Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRY  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRL  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRH  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRE  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRKS  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRFE  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRHR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRAK  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYP-[(4-amino-5-  
 hydroxypentyl)guanidine]  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-[4-amino-5-  
 hydroxypentanamide]  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRST  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRRY  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSLSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSAPVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASPECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASQECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECLQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQPCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCEASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR

P[Nle]E[Nle]RCFASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]E[Nle]RCSYSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]E[Nle]RCSAFVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR

11. An ion channel blocker or pharmaceutically acceptable salt according to any one of the preceding claims comprising or consisting of one of the sequences:

QMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
QMDMRCASVECKQKCLKAIGRGFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIGRGFGKCMNKKCKCYPR  
MDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
DMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NIDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDVRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCKDAIGSIFGKCMNKKCKCYPR  
GGNMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMEMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
SGNMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
N[Nle]DMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMD[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
NMDMRCASVECKVKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQLCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCKKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLDAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIRSIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIESIFGKCMNKKCKCYPR  
NMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPRRRTA  
NMDMRCASVECKQKCLKAIGSIFGKCMNKKCKCYPRHRRK  
NMDMRCKASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCISVECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASRECKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVQCKQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECLQKCLKAIGSIFGKCMNKKCKCYPR  
NMDMRCASVECAQKCLKAIGSIFGKCMNKKCKCYPR

NMDMRCSASVECKEKLKLAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKLKCLKLAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIHSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSKFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSRFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNGKCKCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCHCYPR  
NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCVCYPR  
N[Nie]D[Nie]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
N[Nie]D[Nie]RCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
P[Nie]D[Nie]RCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCRASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSASVECEQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSASVECCQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSASVECKKKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]S[Nie]RCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSHSVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSASVECKQSCLKAIGSIFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSASVECKQKCKAIGSIFGKC[Nie]NKKCKCYPR  
NMDMRCSASVECKQKCYKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCRKAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLAAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLYAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLAIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKYIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKRIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKIGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAYGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAEGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKARGSIFGKCMNKKCKCYPR  
NMDMRCSASVECKQKCLKAGSIFGKCMNKKCKCYPR  
N[Nie]D[Nie]RCSASVECKQKCLKAIGSPFGKC[Nie]NKKCKCYPR  
N[Nie]D[Nie]RCSASKECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
H[Nie]D[Nie]RCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
Y[Nie]D[Nie]RCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR  
S[Nie]D[Nie]RCSASVECKQKCLKAIGSIFGKC[Nie]NKKCKCYPR

V[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
S[Nle]D[Nle]RCSA[Abu]VECKQKCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFG[homo-Lys]CMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-NH<sub>2</sub>)]PR  
S[Nle]D[Nle]RCSASVECGQKCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECVQKCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECK[2-Amino-5-carboxypentanoyl]KCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYQ  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCRCYPR  
S[Nle]DERCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLGAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLVAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECAQSCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECAQKCLAAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECAQLCLAAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]D[Nle]RCSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC  
S[Nle]D[Nle]RCSASVECKEKCLQAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]D[Nle]RCSASVECKEKCL[homo-Gln]AIGSIFGKC[Nle]NKKCKCYPR  
CSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC  
S[Nle]D[Nle]RCSASVECKQKCLAAIGCIFGKC[Nle]NKKCKCYPC  
P[Nle]D[Nle]RCSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC  
S[Nle]D[Nle]RCSALVECKQKCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSAVVECKQKCLKAIGSIFGKCMNKKCKCYPR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-F)]PR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-NO<sub>2</sub>)]PR  
S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-CH<sub>3</sub>)]PR  
[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
NID[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
PIE[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]E[Nle]RCSASVECKQKCLLAIGSIFGKC[Nle]NKKCKCYPR  
PIDERCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
PIE[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
P[Nle]D[Nle]RCSASVECAQKCLAAIGSIFGKCMNKKCKCYPR

P[Nle]E[Nle]RCSASVECAQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 SKCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 LRCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPS  
 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYS  
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 CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCY  
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 LRCSASVECKQKCLAAIGSIFGKCMNKKCKCYPR  
 CSASVECKQKCLKAIGSIFGKCMNKKCKCYPR  
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 p[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYR  
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 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRY  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRL  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRH  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRE  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRKS  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRFE  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRHR  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRAK  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYP-[(4-amino-5-  
 hydroxypentyl)guanidine]  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-[4-amino-5-  
 hydroxypentanamide]  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRST  
 P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRRY  
 P[Nle]E[Nle]RCSSSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSLSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR

P[Nle]E[Nle]RCSAPVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASPECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASQECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECLQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSASVECKQPCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCEASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCFASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSYSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR  
 P[Nle]E[Nle]RCSAFVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR

12. An ion channel blocker or pharmaceutically acceptable salt according to any one of the preceding claims selected from:

|                                                             |           |
|-------------------------------------------------------------|-----------|
| H-QMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                  | (Cpd. 1)  |
| H-QMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR-OH                  | (Cpd. 2)  |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                  | (Cpd. 3)  |
| H-NMDMRCSASVECKQKCLKAIGRGFGKCMNKKCKCYPR-OH                  | (Cpd. 4)  |
| H-MDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                   | (Cpd. 5)  |
| H-DMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                    | (Cpd. 6)  |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 7)  |
| H-NIDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                  | (Cpd. 8)  |
| H-NMDVRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                  | (Cpd. 9)  |
| H-NMDMRCSASVECKQKCKDAIGSIFGKCMNKKCKCYPR-OH                  | (Cpd. 10) |
| H-GGNMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                | (Cpd. 11) |
| H-NMEMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                  | (Cpd. 12) |
| H-SGNMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                | (Cpd. 13) |
| H-N[Nle]DMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub> | (Cpd. 14) |
| H-NMD[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub> | (Cpd. 15) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 16) |
| H-NMDMRCSASVECKVKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 17) |
| H-NMDMRCSASVECKQLCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 18) |
| H-NMDMRCSASVECKQKCKKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 19) |
| H-NMDMRCSASVECKQKCLDAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 20) |
| H-NMDMRCSASVECKQKCLKAIRSIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 21) |
| H-NMDMRCSASVECKQKCLKAIESIFGKCMNKKCKCYPR-NH <sub>2</sub>     | (Cpd. 22) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPRRRTA-NH <sub>2</sub> | (Cpd. 23) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCKCYPRHRRK-NH <sub>2</sub> | (Cpd. 24) |

|                                                                  |           |
|------------------------------------------------------------------|-----------|
| H-NMDMRCKASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 25) |
| H-NMDMRCSISVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 26) |
| H-NMDMRCSASRECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 27) |
| H-NMDMRCSASVQCKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 28) |
| H-NMDMRCSASVECLQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 29) |
| H-NMDMRCSASVECAQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 30) |
| H-NMDMRCSASVECKEKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 31) |
| H-NMDMRCSASVECKLKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 32) |
| H-NMDMRCSASVECKQKCLKAHISIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 33) |
| H-NMDMRCSASVECKQKCLKAIGSKFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 34) |
| H-NMDMRCSASVECKQKCLKAIGSRFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 35) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNGKCKCYPR-NH <sub>2</sub>          | (Cpd. 36) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKCHCYPR-NH <sub>2</sub>          | (Cpd. 37) |
| H-NMDMRCSASVECKQKCLKAIGSIFGKCMNKKVCYPR-NH <sub>2</sub>           | (Cpd. 38) |
| H-N[Ni]D[Ni]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>    | (Cpd. 39) |
| H-N[Ni]D[Ni]RCSASVECKQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 40) |
| H-P[Ni]D[Ni]RCSASVECKQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 41) |
| H-N[Ni]D[Ni]RCRASVECKQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 42) |
| H-N[Ni]D[Ni]RCSASVECEQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 43) |
| H-N[Ni]D[Ni]RCSASVEEQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub>  | (Cpd. 44) |
| H-N[Ni]D[Ni]RCSASVECKKKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 45) |
| H-N[Ni]S[Ni]RCSASVECKQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 46) |
| H-N[Ni]D[Ni]RCSHSVECKQKCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 47) |
| H-N[Ni]D[Ni]RCSASVECKQSCLKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub> | (Cpd. 48) |
| H-N[Ni]D[Ni]RCSASVECKQKCKAIGSIFGKC[Ni]NKKCKCYPR-NH <sub>2</sub>  | (Cpd. 49) |
| H-NMDMRCSASVECKQKCYKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 50) |
| H-NMDMRCSASVECKQKCRKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 51) |
| H-NMDMRCSASVECKQKCLAAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 52) |
| H-NMDMRCSASVECKQKCLYAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 53) |
| H-NMDMRCSASVECKQKCLAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>           | (Cpd. 54) |
| H-NMDMRCSASVECKQKCLKYIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 55) |
| H-NMDMRCSASVECKQKCLKRIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 56) |
| H-NMDMRCSASVECKQKCLKIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>           | (Cpd. 57) |
| H-NMDMRCSASVECKQKCLKAYGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 58) |
| H-NMDMRCSASVECKQKCLKAEGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 59) |
| H-NMDMRCSASVECKQKCLKARGSIFGKCMNKKCKCYPR-NH <sub>2</sub>          | (Cpd. 60) |

|                                                                                            |           |
|--------------------------------------------------------------------------------------------|-----------|
| H-NMDMRCSASVECKQKCLKAGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                                     | (Cpd. 61) |
| H-N[Nle]D[Nle]RCSASVECKQKCLKAIGSPFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 62) |
| H-N[Nle]D[Nle]RCSASKECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 63) |
| H-H[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 64) |
| H-Y[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 65) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 66) |
| H-V[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 67) |
| H-S[Nle]D[Nle]RCSA[Abu]VECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 68) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFG[homo-Lys]CMNKKCKCYPR-NH <sub>2</sub>                   | (Cpd. 69) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-NH <sub>2</sub> )]PR-NH <sub>2</sub>      | (Cpd. 70) |
| H-S[Nle]D[Nle]RCSASVECGQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 71) |
| H-S[Nle]D[Nle]RCSASVECVQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 72) |
| H-S[Nle]D[Nle]RCSASVECK[2-Amino-5-carboxypentanoyl]KCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub> | (Cpd. 73) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKCYQ-NH <sub>2</sub>                             | (Cpd. 74) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCRCYPR-NH <sub>2</sub>                            | (Cpd. 75) |
| H-S[Nle]DERCSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                                | (Cpd. 76) |
| H-S[Nle]D[Nle]RCSASVECKQKCLGAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 77) |
| H-S[Nle]D[Nle]RCSASVECKQKCLVAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 78) |
| H-S[Nle]D[Nle]RCSASVECAQSCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 79) |
| H-S[Nle]D[Nle]RCSASVECAQKCLAAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 80) |
| H-S[Nle]D[Nle]RCSASVECAQLCLAAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 81) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-OH                                     | (Cpd. 82) |
| H-P[Nle]D[Nle]RCSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC-NH <sub>2</sub>                        | (Cpd. 83) |
| H-S[Nle]D[Nle]RCSASVECKEKCLQAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                        | (Cpd. 84) |
| H-P[Nle]D[Nle]RCSASVECKEKCL[homo-Gln]AIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>               | (Cpd. 85) |
| H-CSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC-NH <sub>2</sub>                                     | (Cpd. 86) |
| H-S[Nle]D[Nle]RCSASVECKQKCLAAIGCIFGKC[Nle]NKKCKCYPC-NH <sub>2</sub>                        | (Cpd. 87) |
| H-P[Nle]D[Nle]RCSASVECKQKCLKAIGCIFGKC[Nle]NKKCKCYPC-OH                                     | (Cpd. 88) |
| H-S[Nle]D[Nle]RCSALVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 89) |
| H-S[Nle]D[Nle]RCSAVVECKQKCLKAIGSIFGKCMNKKCKCYPR-NH <sub>2</sub>                            | (Cpd. 90) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-F)]PR-NH <sub>2</sub>                     | (Cpd. 91) |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-NO <sub>2</sub> )]PR-NH <sub>2</sub>      | (Cpd. 92) |

|                                                                                       |            |
|---------------------------------------------------------------------------------------|------------|
| NH <sub>2</sub>                                                                       |            |
| H-S[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKCMNKKCKC[F(4-CH <sub>3</sub> )]PR-NH <sub>2</sub> | (Cpd. 93)  |
| H-[Nle]D[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-OH                                 | (Cpd. 94)  |
| H-NID[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-OH                                    | (Cpd. 95)  |
| H-PIE[Nle]RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-OH                                    | (Cpd. 96)  |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                | (Cpd. 97)  |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                   | (Cpd. 98)  |
| H-P[Nle]E[Nle]RCSASVECKQKCLLAIGSIFGKC[Nle]NKKCKCYPR-OH                                | (Cpd. 99)  |
| H-PIDRCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                         | (Cpd. 100) |
| H-PIE[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                    | (Cpd. 101) |
| H-P[Nle]D[Nle]RCSASVECAQKCLAAIGSIFGKCMNKKCKCYPR-OH                                    | (Cpd. 102) |
| H-P[Nle]E[Nle]RCSASVECAQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                | (Cpd. 103) |
| H-CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                                | (Cpd. 104) |
| Ac-CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                               | (Cpd. 105) |
| H-RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                               | (Cpd. 106) |
| Ac-SKCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                             | (Cpd. 107) |
| Ac-LRCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-NH <sub>2</sub>                             | (Cpd. 108) |
| Ac-CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPS-NH <sub>2</sub>                               | (Cpd. 109) |
| Ac-CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYS-NH <sub>2</sub>                                | (Cpd. 110) |
| Ac-CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYG-NH <sub>2</sub>                                | (Cpd. 111) |
| Ac-CSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCY-NH <sub>2</sub>                                 | (Cpd. 112) |
| Ac-RCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-OH                                           | (Cpd. 113) |
| H-LRCSASVECKQKCLKAIGSIFGKC[Nle]NKKCKCYPR-OH                                           | (Cpd. 114) |
| Ac-LRCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                          | (Cpd. 115) |
| Ac-LRCSASVECKQKCLAAIGSIFGKCMNKKCKCYPR-OH                                              | (Cpd. 116) |
| H-CSASVECKQKCLKAIGSIFGKCMNKKCKCYPR-OH                                                 | (Cpd. 117) |
| H-P[Nle]E[Nle]RCSASVECKEKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                | (Cpd. 118) |
| H-p[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                | (Cpd. 119) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYR-OH                                 | (Cpd. 120) |
| H-[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                 | (Cpd. 121) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRR-OH                               | (Cpd. 122) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRY-OH                               | (Cpd. 123) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRL-OH                               | (Cpd. 124) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRH-OH                               | (Cpd. 125) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRE-OH                               | (Cpd. 126) |

|                                                                                         |            |
|-----------------------------------------------------------------------------------------|------------|
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRKS-OH                                | (Cpd. 127) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRFE-OH                                | (Cpd. 128) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRHR-OH                                | (Cpd. 129) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRAK-OH                                | (Cpd. 130) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYP-[(4-amino-5-hydroxypentyl)guanidine] | (Cpd. 131) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-[4-amino-5-hydroxypentanamide]      | (Cpd. 132) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRST-OH                                | (Cpd. 133) |
| H-P[Nle]E[Nle]RCSASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPRRY-OH                                | (Cpd. 134) |
| H-P[Nle]E[Nle]RCSSSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 135) |
| H-P[Nle]E[Nle]RCSLSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 136) |
| H-P[Nle]E[Nle]RCSAPVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 137) |
| H-P[Nle]E[Nle]RCSASPECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 138) |
| H-P[Nle]E[Nle]RCSASQECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 139) |
| H-P[Nle]E[Nle]RCSASVECLQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 140) |
| H-P[Nle]E[Nle]RCSASVECKQPCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 141) |
| H-P[Nle]E[Nle]RCEASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 142) |
| H-P[Nle]E[Nle]RCFASVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 143) |
| H-P[Nle]E[Nle]RCSYSVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 144) |
| H-P[Nle]E[Nle]RCSAFVECKQKCLAAIGSIFGKC[Nle]NKKCKCYPR-OH                                  | (Cpd. 145) |

13. An ion channel blocker which is

H-NMDMRC(1)SASVEC(2)KQKC(3)LKAIGSIFGKC(1)MNKKC(2)KC(3)YPR-OH (Cpd. 3)

or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine residues which

5 participate together in a disulphide bond are indicated by the same numeral in parentheses.

14. An ion channel blocker which is

H-NMDMRC(1)SASVEC(2)AQKC(3)LKAIGSIFGKC(1)MNKKC(2)KC(3)YPR-NH<sub>2</sub> (Cpd. 30)

or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine residues which

10 participate together in a disulphide bond are indicated by the same numeral in parentheses.

15. An ion channel blocker which is

H-NID[Nle]RC(1)SASVEC(2)KQKC(3)LKAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-OH

(Cpd. 95) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine residues

15 which participate together in a disulphide bond are indicated by the same numeral in parentheses.

16. An ion channel blocker which is  
H-P[Nle]E[Nle]RC(1)SASVEC(2)KQKC(3)LAAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-OH  
(Cpd. 97) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine residues  
5 which participate together in a disulphide bond are indicated by the same numeral in  
parentheses.
17. An ion channel blocker which is  
H-PIE[Nle]RC(1)SASVEC(2)KQKC(3)LAAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-OH  
10 (Cpd. 101) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine residues  
which participate together in a disulphide bond are indicated by the same numeral in  
parentheses.
18. An ion channel blocker which is  
15 H-P[Nle]E[Nle]RC(1)SASVEC(2)AQKC(3)LAAIGSIFGKC(1)[Nle]NKKC(2)KC(3)YPR-OH  
(Cpd. 103) or a pharmaceutically acceptable salt thereof, wherein a pair of cysteine residues  
which participate together in a disulphide bond are indicated by the same numeral in  
parentheses.
- 20 19. A nucleic acid encoding an ion channel blocker, a Kv1.3 inhibitor component, or a  
peptide Z<sup>1</sup>-X-Z<sup>2</sup> as defined in any of the preceding claims.
20. An expression vector comprising a nucleic acid according to claim 19.
- 25 21. A host cell comprising a nucleic acid according to claim 19 or an expression vector  
according to claim 20 and capable of expressing an ion channel blocker, a Kv1.3 inhibitor  
component, or a peptide Z<sup>1</sup>-X-Z<sup>2</sup> as defined in any of claims 1 to 18.
22. A method of synthesising an ion channel blocker according to any of claims 1 to 18,  
30 the method comprising:
- (a) synthesising the ion channel blocker by means of solid-phase or liquid-phase peptide  
synthesis methodology and recovering the peptide thus obtained;
  - (b) expressing the ion channel blocker from a nucleic acid construct that encodes the ion  
channel blocker and recovering the expression product; or

- (c) expressing a precursor peptide from a nucleic acid construct that encodes the precursor peptide sequence, recovering the expression product, and modifying the precursor peptide to yield the ion channel blocker.
- 5     23.     A pharmaceutical composition comprising an ion channel blocker or pharmaceutically acceptable salt according to any one of claims 1 to 18, in admixture with a pharmaceutically acceptable carrier.
24.     An ion channel blocker or pharmaceutically acceptable salt according to any one of  
10     claims 1 to 18 for use in therapy.
25.     A method of inhibiting weight gain, promoting weight loss, and reducing excess body weight, wherein the method comprises an ion channel blocker or pharmaceutically acceptable salt according to any one of claims 1 to 18 to be administered to a subject in  
15     need thereof.
26.     Use of an ion channel blocker or pharmaceutically acceptable salt according to any one of claims 1 to 18 in the manufacture of a medicament for
- (a)     inhibiting or reducing inflammation; or
- 20     (b)     treating obesity, or in the treatment of obesity linked inflammation, obesity linked gallbladder disease or obesity induced sleep apnoea.
27.     Use of an ion channel blocker or pharmaceutically acceptable salt according to any one of claims 1 to 18 in the manufacture of a medicament for treating
- 25     (a)     an inflammatory condition or disorder, preferably wherein the inflammatory condition or disorder is an autoimmune disorder, allergy or hypersensitivity, allograft rejection, graft versus host disease, hay fever, asthma, anaphylaxis, allergic rhinitis, urticaria, eczema, alopecia areata, dermatomyositis, inclusion body myositis, polymyositis, ankylosing spondylitis, vasculitis, arthritis (including rheumatoid arthritis, osteoarthritis, psoriatic arthritis), Sjogren's syndrome, systemic lupus erythematosus (SLE), uveitis, inflammatory fibrosis (e.g. scleroderma, lung fibrosis, cirrhosis), chronic obstructive pulmonary disease (COPD), hepatitis, chronic inflammatory demyelinating polyneuropathy, inflammatory bowel disease, colitis (e.g. Crohn's disease and ulcerative colitis), erythema, thyroiditis, psoriasis, atopic dermatitis, allergic contact dermatitis, scleroderma, glomerulonephritis, inflammatory  
30     bone resorption, multiple sclerosis, type 1 diabetes, transplant rejection or graft-versus-host disease; or  
35     disease; or

- (b) a condition caused by or associated with impaired glucose control, preferably wherein the condition is metabolic syndrome, insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose or type 2 diabetes; or
- (c) a smooth muscle proliferative disorder, preferably wherein said disorder is  
5 restenosis; or
- (d) a neuroinflammatory or neurodegenerative disorder, preferably wherein said disorder is Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease or amyotrophic lateral sclerosis (ALS); or
- (e) cancer, preferably wherein said cancer is breast cancer, prostate cancer or  
10 lymphoma, preferably wherein said lymphoma is non-Hodgkin lymphoma (NHL), preferably wherein said NHL is large B-cell lymphoma, follicular lymphoma, Burkitt lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, mycosis fungoides, anaplastic large cell lymphoma, peripheral T-cell lymphoma, precursor T-lymphoblastic lymphoma or Sézary syndrome.

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