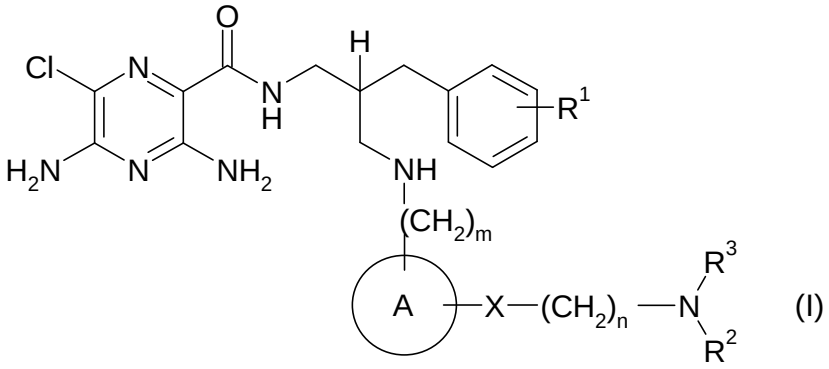
Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is selected from hydrogen or C_{1-4} alkyl;

m is 1 or 2;

A is selected from phenyl or heterocyclyl;

X is selected from –C(=O)–, –C(=O)–NR^4– or –O–C(=O)–NR^5–;

n is 2 or 3;

R^2 is selected from hydrogen or C_{1-8} alkyl;

R^3 is C_{5-6} alkyl–OH, wherein the said C_{5-6} alkyl group is further substituted by an additional 3 or 4 –OH groups; and

R^4 and R^5 are independently selected from hydrogen or C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-4} alkyl and R^4 and R^5 are both hydrogen.

3. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein A is phenyl.

4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein X is –C(=O)–NR^4–.

5. A compound according to any one of the preceding claims, wherein:

R^1 is C_{1-4} alkyl;

m is 1;

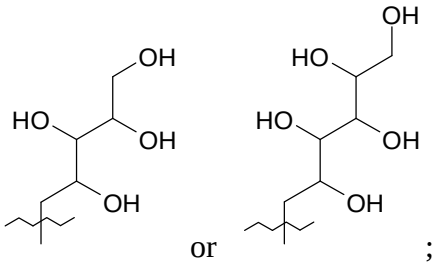
A is phenyl;

X is –C(=O)–NH–;

n is 2;

R^2 is C_{1-8} alkyl;

and R^3 is selected from the following:



;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^2 is n-hexyl.

7. A compound according to claim 1 selected from:

3,5-diamino-6-chloro-N-((R)-2-(2-methylbenzyl)-3-(((1-(3-(((2S,3R,4R)-2,3,4,5-tetrahydroxypentyl)amino)propanoyl)piperidin-4-yl)methyl)amino)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((4-((2-(hexyl((2S,3R,4R)-2,3,4,5-tetrahydroxypentyl)amino)ethyl)carbamoyl)benzyl)amino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((1-(2-(hexyl((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)ethylcarbamoyl)piperidin-4-yl)methylamino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((1-(3-(hexyl((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)propanoyl)piperidin-4-yl)methylamino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((1-(3-(hexyl((2S,3R,4R)-2,3,4,5-tetrahydroxypentyl)amino)propanoyl)piperidin-4-yl)methylamino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((1-(4-(hexyl((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)butanoyl)piperidin-4-yl)methylamino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-2-(2-methylbenzyl)-3-((1-(3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylamino)propanoyl)piperidin-4-yl)methylamino)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((1-(3-(hexyl((2R,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)propanoyl)piperidin-4-yl)methylamino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((4-((2-(hexyl((2R,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)ethyl)carbamoyl)benzyl)amino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((4-((2-(hexyl((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)ethyl)carbamoyl)benzyl)amino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

4-(((R)-3-(3,5-diamino-6-chloropyrazine-2-carboxamido)-2-(2-methylbenzyl)propylamino)methyl)phenyl 2-(hexyl((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)ethylcarbamate;

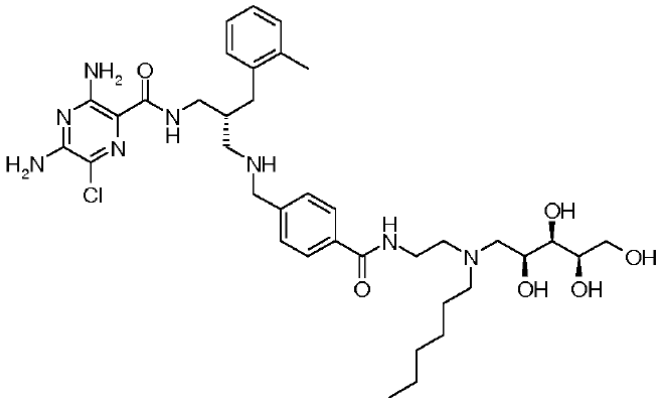
3,5-diamino-6-chloro-N-((R)-3-((4-((2-(hexyl((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)ethyl)carbamoyl)phenethyl)amino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

3,5-diamino-6-chloro-N-((R)-3-((4-((2-(hexyl((2S,3R,4R)-2,3,4,5-tetrahydroxypentyl)amino)ethyl)carbamoyl)phenethyl)amino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1, which is:

3,5-diamino-6-chloro-N-((R)-3-((4-((2-(hexyl((2S,3R,4R)-2,3,4,5-tetrahydroxypentyl)amino)ethyl)carbamoyl)benzyl)amino)-2-(2-methylbenzyl)propyl)pyrazine-2-carboxamide, and which has the formula (Ia):



, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, and a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, for use in therapy.

11. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, for the treatment of an ENaC mediated disease state.

11. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in the treatment of an ENaC mediated disease state.

12. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in the treatment of an ENaC mediated disease state.

13. A compound, or a pharmaceutically acceptable salt thereof according to claim 11 or 12, wherein the ENaC mediated disease state includes chronic obstructive pulmonary disease (COPD), cystic fibrosis, asthma, chronic bronchitis and bronchiectasis.

14. A compound, or a pharmaceutically acceptable salt thereof according to claim 11 or 12, wherein the ENaC mediated disease state is chronic obstructive pulmonary disease (COPD) or cystic fibrosis.

15. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, and one or more agents selected from the list comprising:

- a beta-adrenoceptor agonist;
- a muscarinic receptor antagonist;
- a joint muscarinic receptor antagonist and beta-adrenoceptor agonist;
- a toll-like receptor agonist (such as a TLR7 or TLR9 agonist);
- an adenosine antagonist;
- a glucocorticoid receptor agonist (steroidal or non-steroidal);
- a p38 antagonist;
- an IKK2 antagonist;
- a PDE4 antagonist;
- a modulator of chemokine receptor function (such as a CCR1, CCR2B, CCR5, CXCR2 or CXCR3 receptor antagonist);
- a CRTh2 antagonist; or
- an osmolyte, such as hypertonic saline.