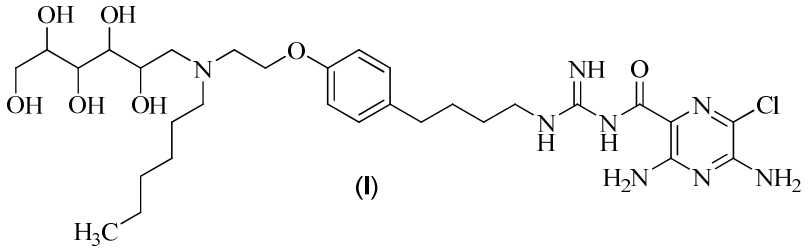
imbalance between mucin secretion and relative ASL depletion. Failure to secrete Cl- (and liquid) in the proximal small intestine, combined with increased Na^+ (and liquid) absorption in the terminal ileum leads to the distal intestinal obstruction syndrome (DIOS). In older patients excessive Na^+ (and volume) absorption in the descending colon produces constipation and diverticulitis.

The published literature includes number of patent applications and granted patents to Parion Sciences Inc., directed toward pyrazinoylguanidine analogs as sodium channel blockers. Examples of such publications include PCT Publication Nos. WO2003/070182, WO2003/070184, WO2004/073629, WO2005/025496, WO2005/016879, WO2005/018644, WO2006/022935, WO2006/023573, WO2006/023617, WO2007/018640, WO2007/146869, WO2008/031028, WO2008/031048, and US Patent Nos. 6858614, 6858615, 6903105, 7064129, 7186833, 7189719, 7192958, 7192959, 7192960, 7241766, 7247636, 7247637, 7317013, 7332496, 7368447, 7368450, 7368451, 7375102, 7388013, 7399766, 7410968, 7807834, 7842697, and 7868010.

There remains a need for novel sodium channel blocking compounds with enhanced potency and effectiveness on mucosal tissues. There also remains the need for novel sodium channel blocking compounds that provide therapeutic effect, but minimize or eliminate the onset or progression of hyperkalemia in recipients.

Summary

This disclosure provides the compound 3,5-diamino-6-chloro-N-(N-(4-(4-(2-(hexyl(2,3,4,5,6-pentahydroxyhexyl)amino)ethoxy)phenyl)butyl) carbamimidoyl)pyrazine-2-carboxamide, of the formula:

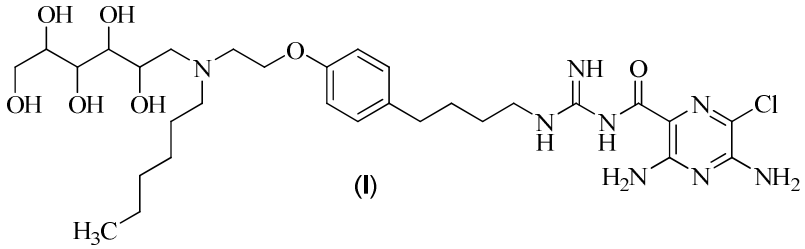


(I)

or a pharmaceutically acceptable salt form thereof. The disclosure also provides solvates and hydrates, individual stereoisomers, including optical isomers (enantiomers and diastereomers) and geometric isomers (cis-/trans-isomerism), mixtures of stereoisomers, and tautomers of 3,5-diamino-6-chloro-N-(N-(4-(4-(2-(hexyl(2,3,4,5,6-pentahydroxyhexyl)amino)ethoxy)phenyl)butyl) carbamimidoyl)pyrazine-2-carboxamide, or a pharmaceutically acceptable salt

thereof, as well as pharmaceutical compositions comprising the compound, or a pharmaceutically acceptable salt thereof, its use in methods of treatment, and methods for its preparation.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and an osmolyte.

In one aspect, the present disclosure refers to use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for promoting hydration of mucosal surfaces and/or improving mucociliary clearance in a human.

In one aspect, the present disclosure refers to a pharmaceutical composition as disclosed herein for use as a medicament.

In one aspect, the present disclosure refers to use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating reversible or irreversible airway obstruction, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, acute bronchitis, chronic bronchitis, post-viral cough, cystic fibrosis, emphysema, pneumonia, panbronchiolitis, transplant-associate bronchiolitis, or ventilator-associated tracheobronchitis or for preventing ventilator-associated pneumonia in a human in need thereof.

In one aspect, the present disclosure refers to use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, nasal dehydration, dry eye, Sjogren's disease, promoting ocular or corneal hydration, treating distal intestinal obstruction syndrome, otitis media, primary ciliary dyskinesia, esophagitis, constipation, or chronic diverticulitis in a human in need thereof.

In one aspect, the present disclosure refers to a kit comprising the pharmaceutical composition as disclosed herein, an aerosolization device selected from a nebulizer, a dry powder inhaler, and a metered dose inhaler, instructions for administering the pharmaceutical composition, and a container.

Brief Description of the Drawings

A more complete appreciation of the invention and many of the advantages thereof may be readily obtained by reference to the information herein in conjunction with the following figures:

FIG. 1 is a representative plot of the concentration-effect relationship of Compound (Ia) on short-circuit current by canine bronchial epithelial (CBE) cells.

FIG. 2 is a plot of the dose-response of Compound (Ia) on sheep mucociliary clearance (MCC) at 4h post-dose.

FIG. 3 is a plot of the effect of Compound (Ia) and hypertonic saline (HS) on sheep MCC at 4h post-dose.

FIG. 4 is a plot of the effect Compound (Ia) and HS on sheep MCC at 8h post-dose.

FIG. 5 is a plot of the effect of sodium channel blocking of Compound (Ia) on surface liquid retention 0-8 h in the *in vitro* CBE cell model.

FIG. 6 is a bar graph of the effect of Compound (Ia) on surface liquid retention at 24 hours in the *in vitro* CBE model.

FIG. 7 is a plot of the effect of ENaC blockers Compound Ia and Comparative Example I on sheep MCC at 8 hrs.

FIG. 8 is a plot of the effect of ENaC Blockers Compound Ia and Comparative Example 1 on sheep plasma potassium levels

FIG. 9 is a plot comparing the activity of Comparative Example 4 and Compound 1a on sheep MCC at 4h Post-dose.

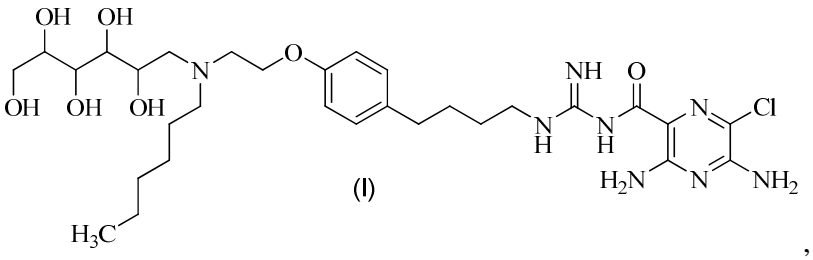
FIG. 10 is a plot comparing the effect on sheep Plasma K^+ levels of Comparative Example 4 and Compound 1a.

Detailed Description of the Invention

CLAIMS

That Which Is Claimed Is:

1. A pharmaceutical composition comprising a compound of Formula (I):

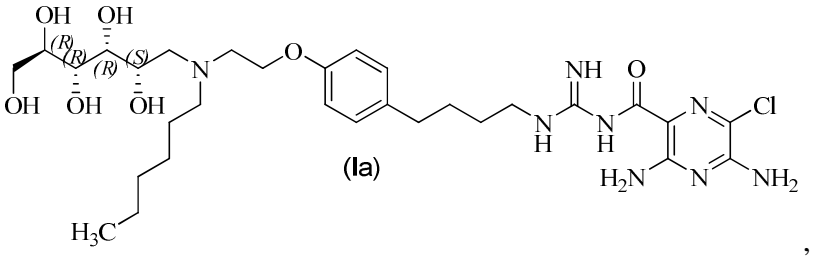


(I)

,

or a pharmaceutically acceptable salt thereof, and an osmolyte.

2. The pharmaceutical composition of claim 1, wherein the compound of Formula (I) is of Formula (Ia):



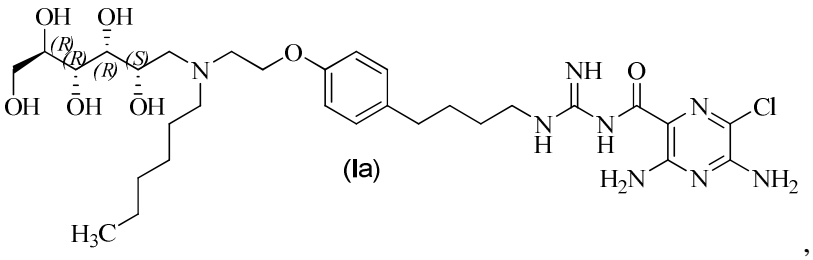
(Ia)

,

or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim 1 or 2, wherein the osmolyte is hypertonic saline.

4. A pharmaceutical composition according to claim 3 comprising a compound of Formula (Ia):

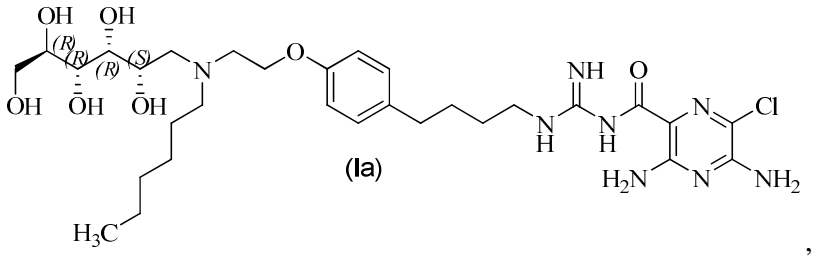


(Ia)

,

or a pharmaceutically acceptable salt thereof, and hypertonic saline.

5. The pharmaceutical composition of claim 4, comprising a compound of Formula (Ia):



(Ia)

,

and hypertonic saline.

6. The pharmaceutical composition of claim 3, 4, or 5, wherein the hypertonic saline has a concentration of 4%-5% w/v.

7. The pharmaceutical composition of claim 3, 4, or 5, wherein the hypertonic saline has a concentration of about 4%.

8. The pharmaceutical composition of any one of claims 1-7, further comprising a CFTR modulator.

9. The pharmaceutical composition of claim 8, wherein the CFTR modulator is N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide.

10. The pharmaceutical composition of claim 8, wherein the CFTR modulator is (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

11. The pharmaceutical composition of claim 8, wherein the CFTR modulator is N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide and (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

12. The pharmaceutical composition of any one of claims 1-11, wherein the composition is suitable for inhalation.

13. The pharmaceutical composition of any one of claims 1-11, wherein the composition is a solution for aerosolization and administration by nebulizer.

14. The pharmaceutical composition of any one of claims 1-11, wherein the composition is a solution for administration by metered dose inhaler.

15. The pharmaceutical composition of claim 1 or claim 2, wherein the composition is a dry powder suitable for administration by dry powder inhaler.

16. Use of a pharmaceutical composition according to any one of claims 1-15 in the manufacture of a medicament for promoting hydration of mucosal surfaces and/or improving mucociliary clearance in a human.

17. A pharmaceutical composition according to any one of claims 1-15 for use as a medicament.

18. Use of a pharmaceutical composition according to any one of claims 1-15 in the manufacture of a medicament for treating reversible or irreversible airway obstruction, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, acute bronchitis, chronic bronchitis, post-viral cough, cystic fibrosis, emphysema, pneumonia, panbronchiolitis, transplant-associate bronchiolitis, or ventilator-associated tracheobronchitis or for preventing ventilator-associated pneumonia in a human in need thereof.

19. Use of a pharmaceutical composition according to any one of claims 1-15 in the manufacture of a medicament for treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, nasal dehydration, dry eye, Sjogren's disease, promoting ocular or corneal hydration, treating distal intestinal obstruction syndrome, otitis media, primary ciliary dyskinesia, esophagitis, constipation, or chronic diverticulitis in a human in need thereof.

20. The use according to claim 18, wherein the medicament is for the treatment of cystic fibrosis.

21. The use according to claim 18, wherein the medicament is for the treatment of chronic obstructive pulmonary disease (COPD).

22. The use according to claim 19, wherein the medicament is for the treatment of primary ciliary dyskinesia.

23. The use according to claim 19, wherein the medicament is for the treatment of bronchiectasis.

24. The use according to any one of claims 16, or 18-23, wherein an effective amount of a pharmaceutical composition of any of claims 1-15 and a CFTR modulator are to be administered.

25. The use according to claim 24, wherein the CFTR modulator is N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide.

26. The use according to claim 24, wherein the CFTR modulator is (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

27. The use according to claim 24, wherein the CFTR modulator is N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide and (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

28. The use according to any of claims 24-27, wherein the pharmaceutical composition of any of claims 1-15 and the CFTR modulator are to be administered concomitantly or sequentially in any therapeutically appropriate combination.

29. A kit comprising the pharmaceutical composition of any one of claims 1-15, an aerosolization device selected from a nebulizer, a dry powder inhaler, and a metered dose inhaler, instructions for administering the pharmaceutical composition, and a container.

30. The kit of claim 29 further comprising a pharmaceutical composition comprising N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide, (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, or a combination of both.

31. The kit of claim 30, wherein the pharmaceutical compositions are in separate containers.

32. The kit of claim 31, wherein the container is a bottle, vial, blister pack, or a combination thereof, with at least one container suitable for use in an aerosolization device.