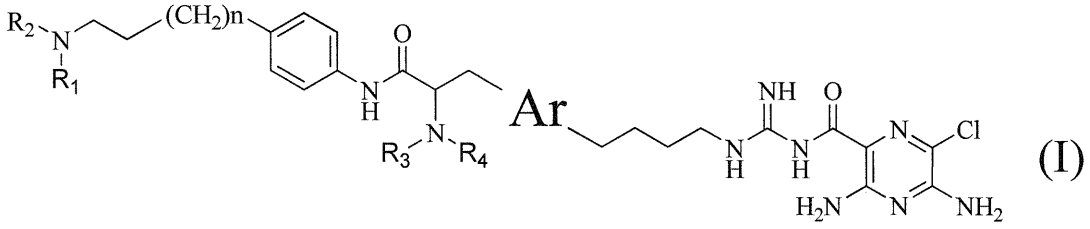
rhinosinusitis, there is an imbalance between mucin secretion and relative ASL depletion. Failure to secrete Cl- (and liquid) in the proximal small intestine, combined with increased Na^+ (and liquid) absorption in the terminal ileum leads to the distal intestinal obstruction syndrome (DIOS). In older 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

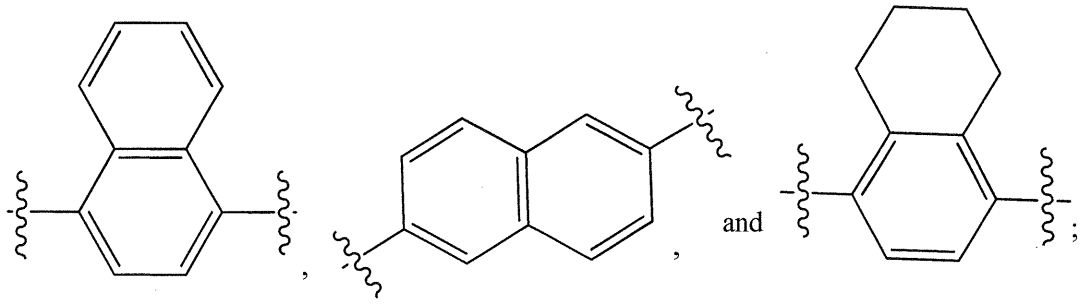
In one aspect, there is provided a compound of the formula **I**:



(I)

wherein:

Ar is selected from the group of:



n is an integer selected from 0, 1, 2, 3, 4, 5, or 6;

R^1 is selected from hydrogen, C_1-C_8 alkyl, and a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

R^2 is hydrogen or a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

R^3 and R^4 are each, independently, hydrogen or C_1-C_3 alkyl;

or a pharmaceutically acceptable salt thereof.

This 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 compounds of the formula (I), or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions comprising the compounds, or a pharmaceutically acceptable salts thereof, their use in methods of treatment, and methods for their preparation.

In one aspect, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In one aspect, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and an osmolyte.

In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in a method for promoting hydration of mucosal surfaces or restoring mucosal defense in a human.

In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating chronic obstructive pulmonary disease (COPD) in a human in need thereof.

In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating cystic fibrosis in a human in need thereof.

In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating bronchiectasis in a human in need thereof.
In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating primary ciliary dyskinesia in a human in need thereof.
In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof for use as a medicament.
In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a composition as defined herein, for use in treating a disease associated with reversible or irreversible airway obstruction, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), acute bronchitis, chronic bronchitis, post-viral cough, cystic fibrosis, emphysema, pneumonia, panbronchiolitis, transplant-associate bronchiolitis, and ventilator-associated tracheobronchitis, or preventing ventilator-associated pneumonia in a human in need thereof.
In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a composition as defined herein, for use in treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, nasal dehydration, including nasal dehydration brought on by administering dry oxygen, dry eye, Sjogren's disease, distal intestinal obstruction syndrome, otitis media, primary ciliary dyskinesia, distal intestinal obstruction syndrome, esophagitis, constipation, or chronic diverticulitis, or promoting ocular or corneal hydration, in a human in need thereof.
In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a composition as defined herein, for use in a method for preventing, mitigating, and/or treating deterministic health effects to the respiratory tract and/or other bodily organs caused by respirable aerosols containing radionuclides in a human in need thereof.
This disclosure also provides the compound 3,5-diamino-N-(N-(4-(4-((S)-2-amino-3-(4-(3-(bis((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)propyl)phenylamino)-3-oxopropyl) naphthalen-1-yl)butyl)carbamimidoyl)-6-chloropyrazine-2-carboxamide, or a pharmaceutically acceptable salt thereof, as well as optical isomers (enantiomers and diastereomers) and geometric isomers (cis-/trans-isomerism), mixtures of stereoisomers, and tautomers 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.

BRIEF DESCRIPTION OF THE DRAWINGS

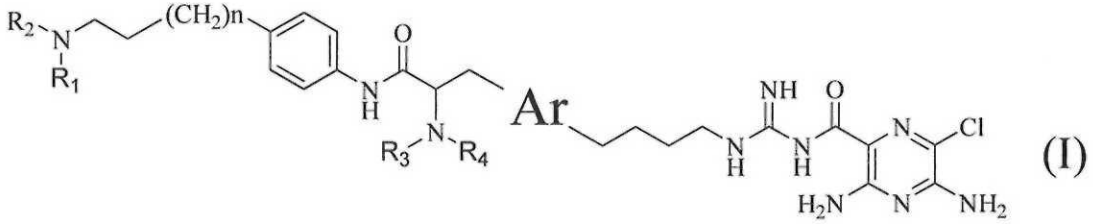
A more complete appreciation of the invention and many of the advantages thereof may be readily obtained by reference to the information herein in conjunction with the following figures:

FIG. 1 is a plot of the effect of Compound 33 on Sheep MCC at 4 hours post-dose.

CLAIMS

That Which Is Claimed Is:

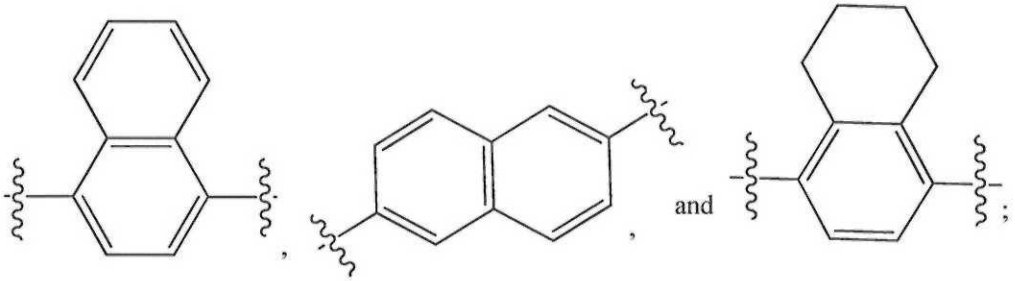
1. A compound of the formula:



(I)

wherein:

Ar is selected from:



n is an integer selected from 0, 1, 2, 3, 4, 5, or 6;

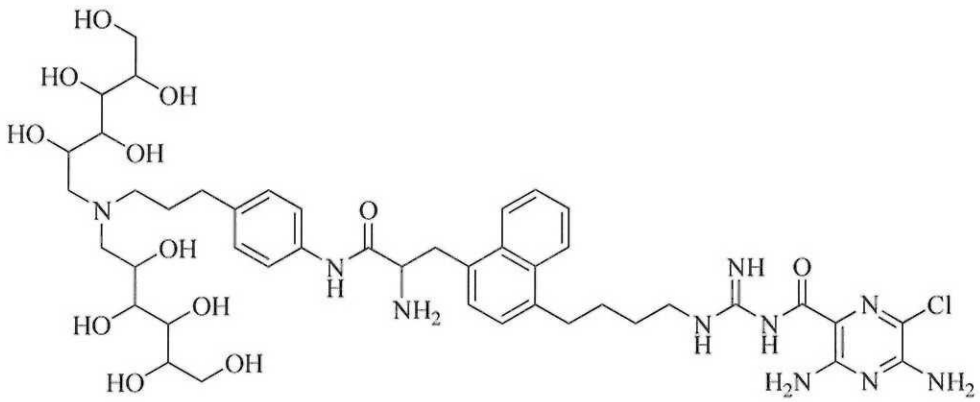
R^1 is selected from hydrogen, C_1-C_8 alkyl, and a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

R^2 is hydrogen or a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

R^3 and R^4 are each, independently, hydrogen or C_1-C_3 alkyl;

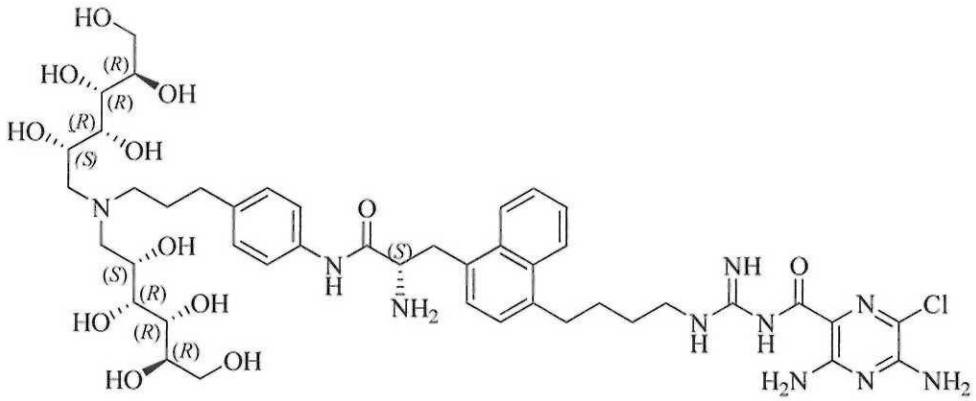
or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 having the formula:



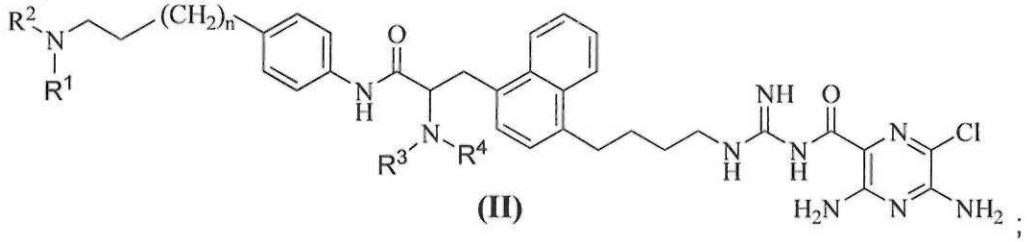
or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 which is:



or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 1 of Formula (II):



(II)

;

wherein:

n is an integer selected from 1, 2, 3, 4, 5, or 6;

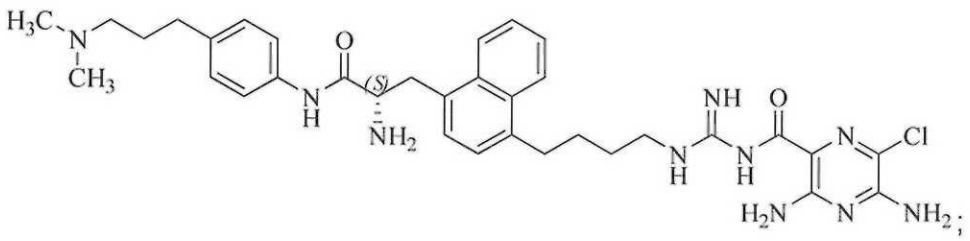
R^1 is selected from hydrogen, C_1-C_8 alkyl, and a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

R^2 is hydrogen or a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

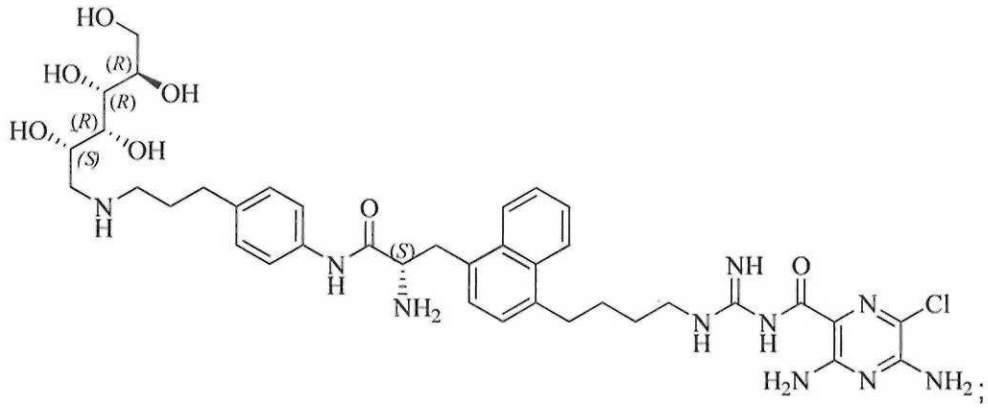
R^3 and R^4 are each, independently, hydrogen or C_1-C_3 alkyl;

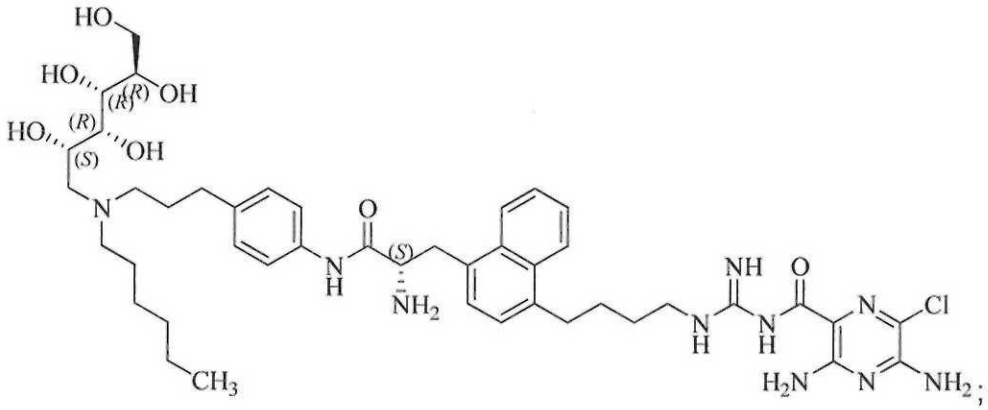
or a pharmaceutically acceptable salt thereof.

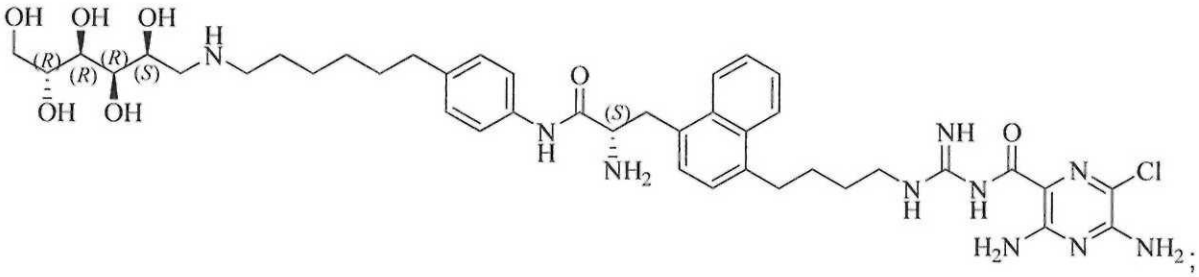
5. A compound of Claim 4 selected from the group of:

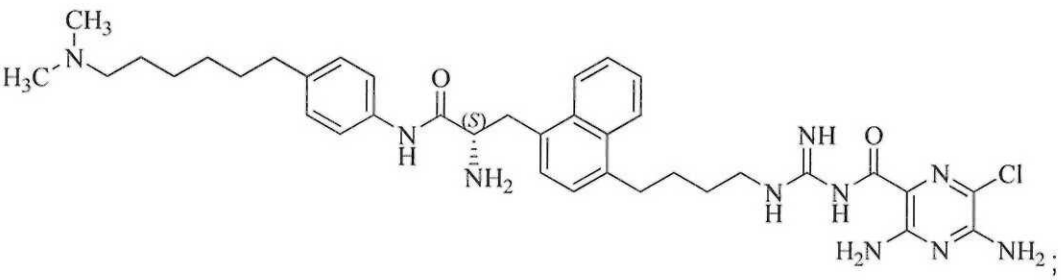


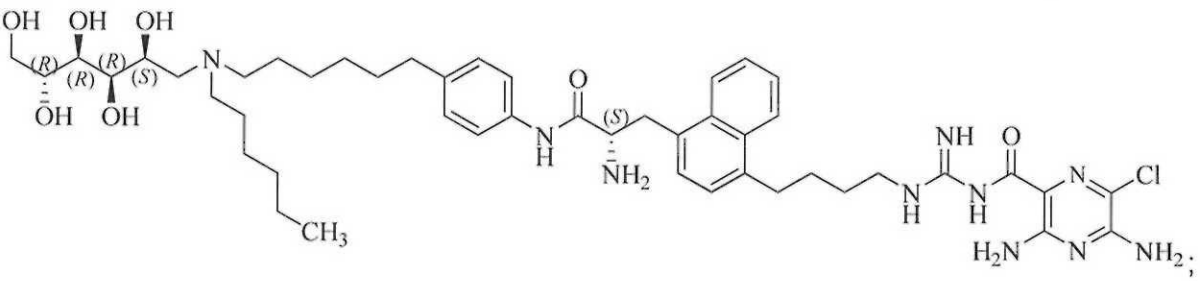
;

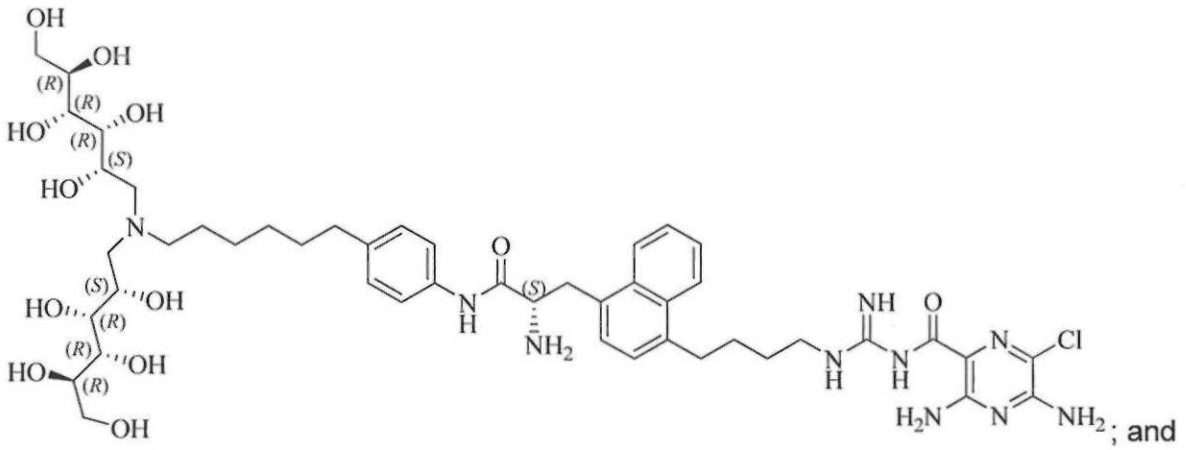




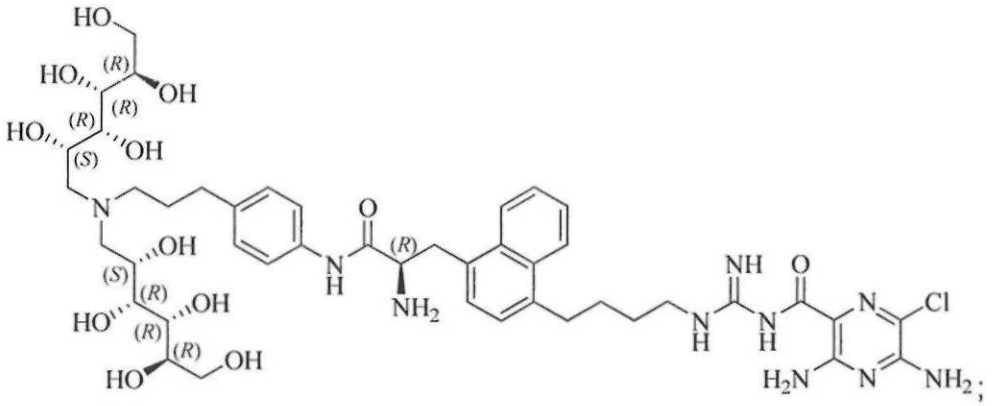








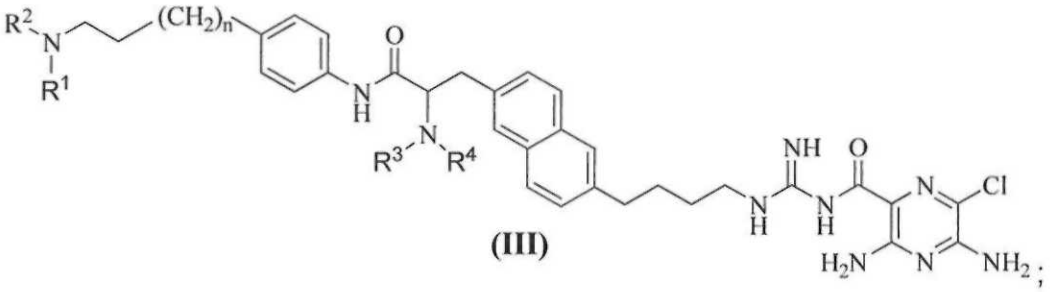
; and



;

or a pharmaceutically acceptable salt thereof.

6. A compound of Claim 1 of Formula (III):



(III)

;

wherein:

n is an integer selected from 1, 2, 3, 4, 5, or 6;

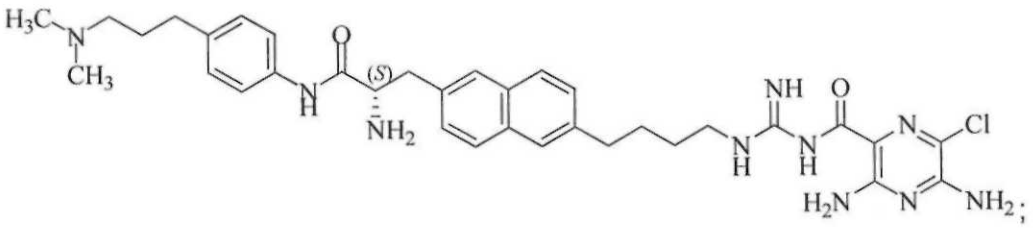
R^1 is selected from hydrogen, C_1-C_8 alkyl, and a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

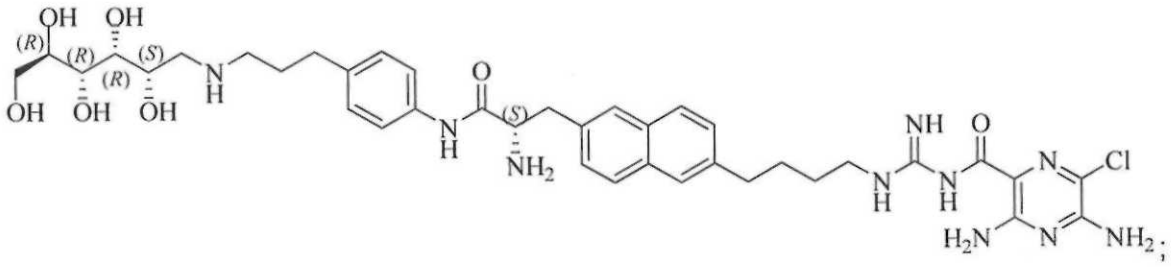
R^2 is hydrogen or a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

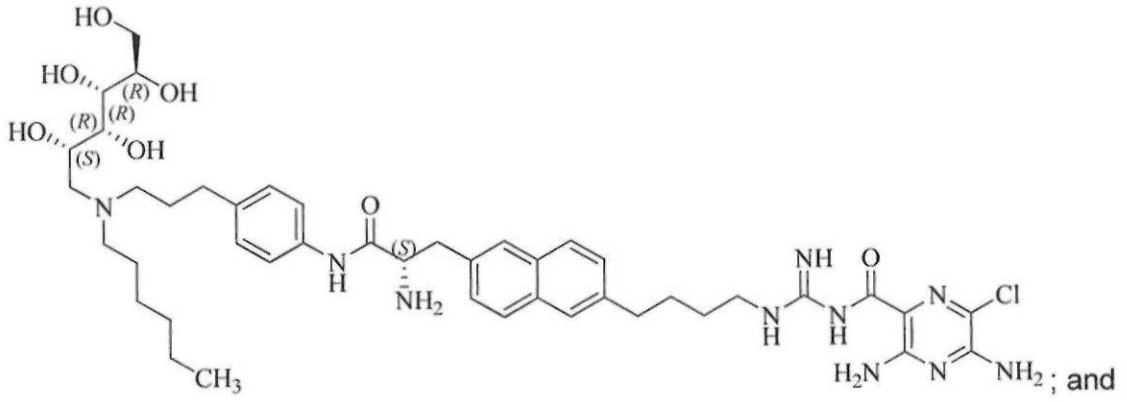
R^3 and R^4 are each, independently, hydrogen or C_1-C_3 alkyl;

or a pharmaceutically acceptable salt thereof.

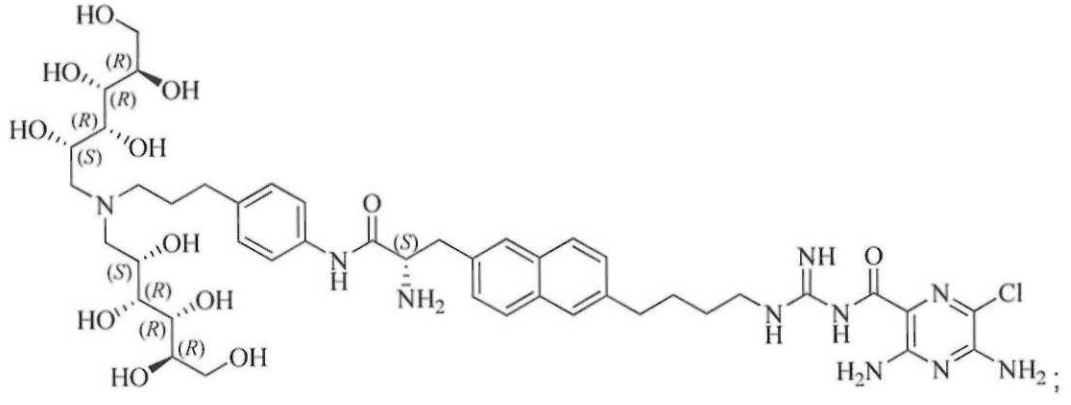
7. A compound of Claim 6 selected from:





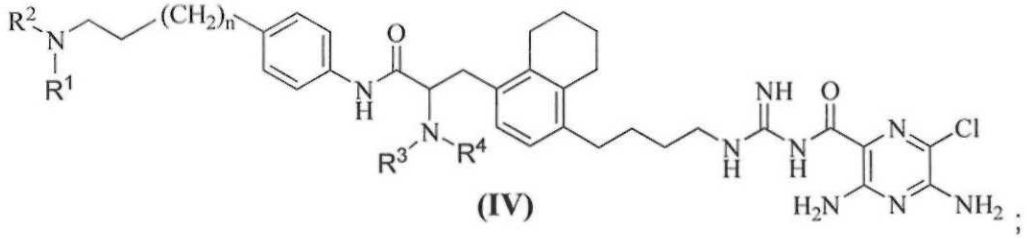


; and



or a pharmaceutically acceptable salt thereof.

8. A compound of Claim 1 of Formula (IV):



(IV)

wherein:

n is an integer selected from 1, 2, 3, 4, 5, or 6;

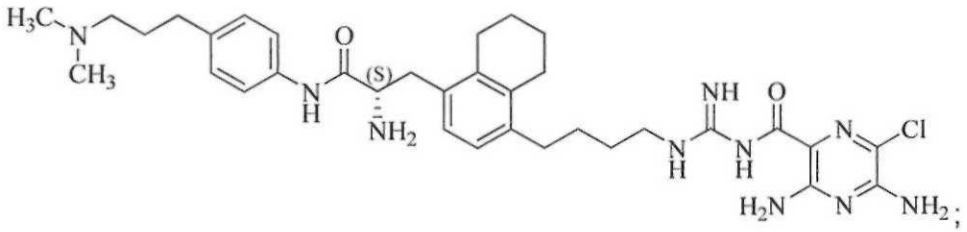
R^1 is selected from hydrogen, C_1-C_8 alkyl, and a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

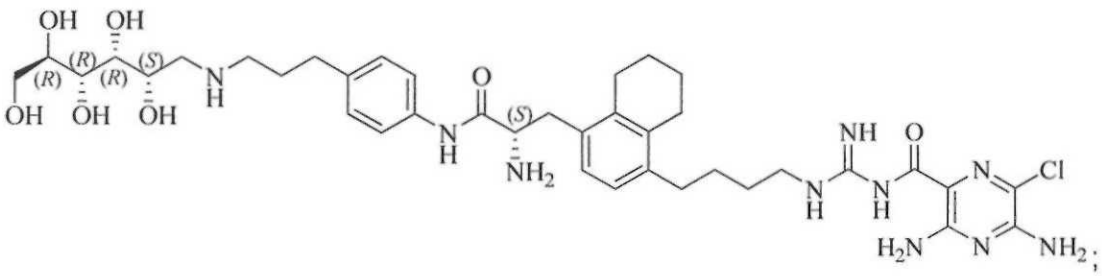
R^2 is hydrogen or a polyhydroxylated alkyl group having from 3 to 8 carbon atoms;

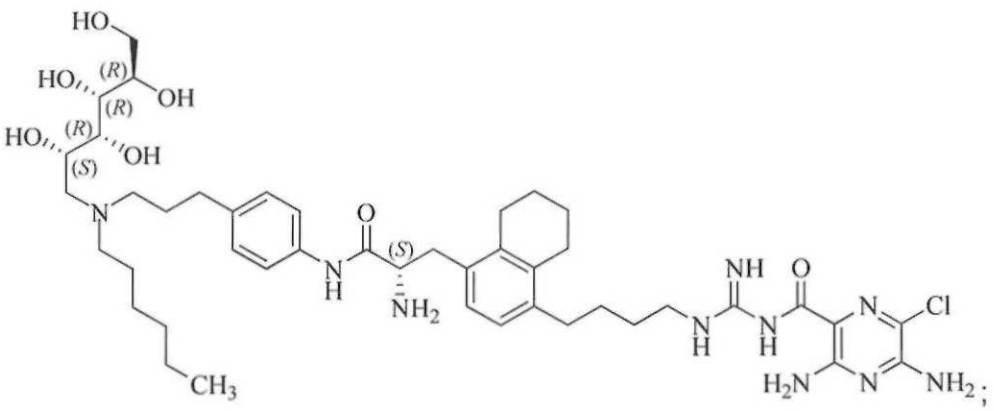
R^3 and R^4 are each, independently, hydrogen or C_1-C_3 alkyl;

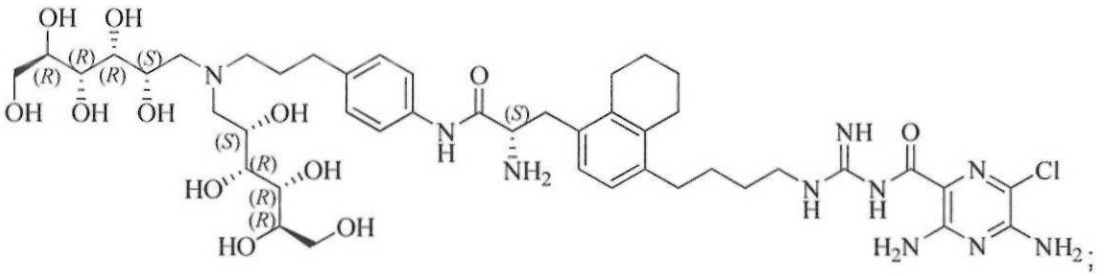
or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 8 selected from:









or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claims 1, 2, 3, 4, 5, 6, 7, 8, or 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

11. The pharmaceutical composition of Claim 10 wherein the compound is 3,5-diamino-N-(N-(4-(4-((S)-2-amino-3-(4-(3-(bis((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)amino)propyl) phenylamino)-3-oxopropyl)naphthalen-1-yl)butyl)carbamimidoyl)-6-chloropyrazine-2-carboxamide, or a pharmaceutically acceptable salt thereof.

12. The composition according to either of Claims 10 or 11, wherein said composition is suitable for inhalation or is a solution for aerosolization and administration by nebulizer or suitable for administration by metered dose inhaler or a dry powder suitable for administration by dry powder inhaler.

13. The composition according to either of Claims 10, 11, or 12 further comprising a pharmaceutically effective amount of a therapeutically active agent selected from CFTR modulators, anti-inflammatory agents, anticholinergic agents, β-agonists, P2Y2 receptor agonists, peroxisome proliferator-activated receptor agonists, kinase inhibitors, antiinfective agents and antihistamines.

14. A compound according to any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in a method for promoting hydration of mucosal surfaces or restoring mucosal defense in a human .

15. A compound according to any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in a method for treating chronic obstructive pulmonary disease (COPD) in a human in need thereof.

16. A compound according to any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in a method for treating cystic fibrosis in a human in need thereof.

17. A compound according to any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in a method for treating bronchiectasis in a human in need thereof.

18. A compound according to any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in a method for treating primary ciliary dyskinesia in a human in need thereof.

19. A compound according to any of claims 1-9, or a pharmaceutically acceptable salt thereof for use as a medicament.

20. A compound according to any of claims 1-9, or a pharmaceutically acceptable salt thereof, or a composition according to any of claims 10 to 13, 23, and 24, for use in treating a disease associated with reversible or irreversible airway obstruction, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), acute bronchitis, chronic bronchitis, post-viral cough, cystic fibrosis, emphysema, pneumonia, panbronchiolitis, transplant-associate bronchiolitis, and ventilator-associated tracheobronchitis, or preventing ventilator-associated pneumonia in a human in need thereof.

21. A compound according to any of claims 1-9, or a pharmaceutically acceptable salt thereof, or a composition according to any of claims 10 to 13, 23, and 24, for use in treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, nasal dehydration, including nasal dehydration brought on by administering dry oxygen, dry eye, Sjogren's disease, distal intestinal obstruction syndrome, otitis media, primary ciliary dyskinesia, distal intestinal obstruction syndrome, esophagitis, constipation, or chronic diverticulitis, or promoting ocular or corneal hydration, in a human in need thereof.

22. A compound according to any of claims 1-9, or a pharmaceutically acceptable salt thereof, or a composition according to any of claims 10 to 13, 23, and 24, for use in a method for preventing, mitigating, and/or treating deterministic health effects to the respiratory tract and/or other bodily organs caused by respirable aerosols containing radionuclides in a human in need thereof.

23. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, or a pharmaceutically acceptable salt thereof, and an osmolyte.

24. The pharmaceutical composition of Claim 23 wherein the osmolyte is hypertonic saline or mannitol.