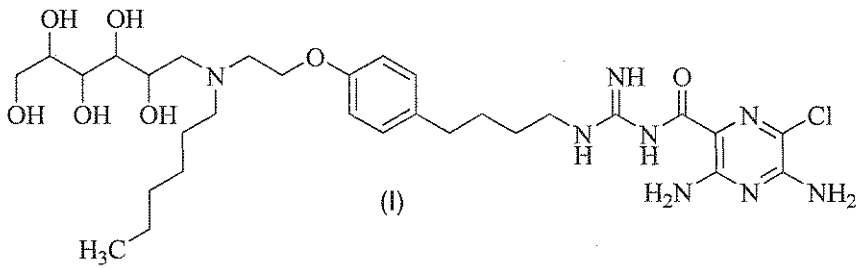
imbalance between mucin secretion and relative ASL depletion. Failure to secrete Cl- (and liquid) in the proximal small intestine, combined with increased Na^+ (and liquid) absorption in the terminal ileum leads to the distal intestinal obstruction syndrome (DIOS). In older patients excessive Na^+ (and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

This disclosure~~invention~~ 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:



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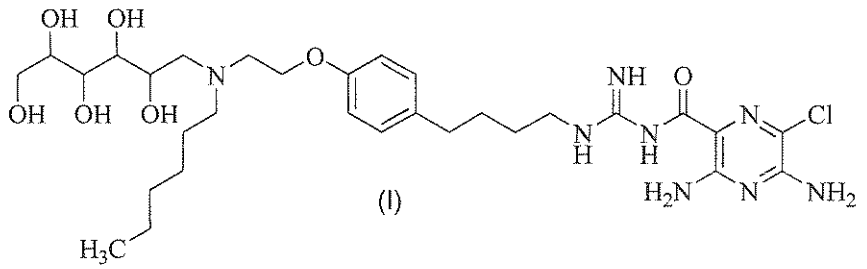
or a pharmaceutically acceptable salt form thereof. The disclosure~~invention~~ also provides solvates and hydrates, individual stereoisomers, including optical isomers (enantiomers and diastereomers) and geometric isomers (cis-/trans-isomerism), mixtures of stereoisomers, and tautomers of 3,5-diamino-6-chloro-N-(N-(4-(4-(2-(hexyl(2,3,4,5,6-pentahydroxyhexyl)amino)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, there is provided a compound of the formula:



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or a pharmaceutically acceptable salt thereof.

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 the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a pulmonary disease in a human in need thereof.

In one aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for blocking sodium channels in a human.

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

In one aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease selected from the group of 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 the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) in a human in need thereof.

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

In one aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, or nasal dehydration, including nasal dehydration brought on by administering dry oxygen, dry eye or Sjogren's disease, promoting ocular or corneal hydration, treating distal intestinal obstruction syndrome, treating otitis media, primary ciliary diskinesia, distal intestinal obstruction syndrome, esophagitis, constipation, or chronic diverticulitis 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 for use in treating a pulmonary disease.

In one aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof 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, for use in treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, or nasal dehydration, including nasal dehydration brought on by administering dry oxygen, dry eye or Sjogren's disease, promoting ocular or corneal hydration, treating distal intestinal obstruction syndrome, treating otitis media, primary ciliary diskinesia, distal intestinal obstruction syndrome, esophagitis, constipation, or chronic diverticulitis in a human in need thereof.

In one aspect, there is provided a composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for 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 one aspect, there is provided a composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for treating dry mouth (xerostomia), dry skin, vaginal dryness, sinusitis, rhinosinusitis, or nasal dehydration, including nasal dehydration brought on by administering dry oxygen, dry eye or Sjogren's disease, promoting ocular or corneal hydration, treating distal intestinal obstruction syndrome, treating otitis media, primary ciliary diskinesia, distal intestinal obstruction syndrome, esophagitis, constipation, or chronic diverticulitis.

In one aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament 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.

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