sublingual and submandibular glands to secrete liquid despite continued Na^+ (ENaC) transport mediated liquid absorption from the oral cavity.

In rhinosinusitis, there is an imbalance, as in CB, between mucin secretion and relative ASL depletion. Finally, in the gastrointestinal tract, failure to secrete C1- (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 a 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. WO2007146867, WO2003/070182, WO2003/070184, WO2004/073629, WO2005/025496, WO2005/016879, WO2005/018644, WO2006/022935, WO2006/023573, WO2006/023617, WO2007/018640, WO2007146870, WO2007/146869, WO2008030217, WO2008/031028, WO2008/031048, WO2013/003386, WO2013/003444, and US Patent Nos. 6858614, 6858615, 6903105, 6,995,160, 7,026,325, 7,030,117, 7064129, 7186833, 7189719, 7192958, 7192959, 7192960, 7241766, 7247636, 7247637, 7317013, 7332496, 7368447, 7368450, 7368451, 7375102, 7,375,107, 7388013, 7399766, 7410968, 7807834, 7,820,678, 7842697, 7868010, 7,956,059, 7,981,898, 8,008,494, 8,022,210, 8,058,278, 8,124,607, 8,143,256, 8,163,758, 8,198,286, 8,211,895, 8,198,286, 8,227,474, and 8,324,218.

There remains a need for novel sodium channel blocking compounds with enhanced potency and effectiveness on mucosal tissues, especially ocular 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~~

It is an object of the present ~~invention~~ disclosure to provide compounds that are more potent and/or absorbed less rapidly from mucosal surfaces, such as ocular surfaces, and/or are less reversible as compared to known compounds.

~~It is another aspect of the present invention to p~~Provided herein are compounds that are more potent and/or absorbed less rapidly and/or exhibit less reversibility, as compared to compounds such as amilorde, benzamil, and phenamil. Therefore, the compounds will give a prolonged pharmacodynamic half-life on mucosal surfaces as compared to known compounds.

It is another object of the present disclosure~~invention~~ to provide compounds which (1) are absorbed less rapidly from mucosal surfaces, especially ocular surfaces, as compared to known compounds and (2) when absorbed from mucosal surfaces after administration to the these surfaces, are excreted mainly non-renally in order to minimize the chances of hyperkalemia.

It is another object of the present disclosure~~invention~~ to provide compounds which are (1) absorbed less rapidly from mucosal surfaces, especially ocular surfaces, as compared to known compounds and (2) are converted in vivo into metabolic derivatives thereof which have reduced efficacy in blocking sodium channels as compared to the administered parent compound in order to minimize the chances of hyperkalemia.

It is another object of the present disclosure~~invention~~ to provide compounds that are more potent and/or absorbed less rapidly and/or exhibit less reversibility, as compared to compounds such as amiloride, benzamil, and phenamil. Therefore, such compounds will give a prolonged pharmacodynamic half-life on mucosal surfaces as compared to previous compounds.

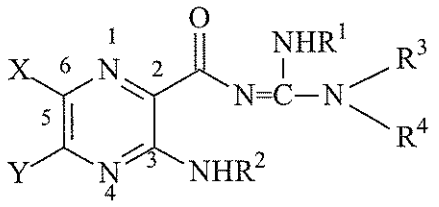
It is another object of the present disclosure~~invention~~ to provide compounds that are metabolically stable. Therefore, such compounds will give a prolonged pharmacodynamic half-life on mucosal surfaces as compared to previous compounds.

It is another object of the present disclosure~~invention~~ to provide methods of treatment that take advantage of the pharmacological properties of the compounds described above.

In particular, it is an object of the present disclosure~~invention~~ to provide methods of treatment which rely on rehydration of mucosal surfaces.

In particular, it is an object of the present disclosure~~invention~~ to provide methods of treating dry eye and related ocular diseases.

In one aspect, there is provided a compound represented by formula (I):



(I)

and racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and pharmaceutically acceptable salts, thereof,

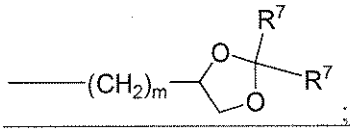
wherein:

X is hydrogen, halogen, trifluoromethyl, lower alkyl, unsubstituted or substituted phenyl, lower alkyl-thio, phenyl-lower alkyl-thio, lower alkyl-sulfonyl, or phenyl-lower alkyl-sulfonyl;

Y is hydrogen, hydroxyl, mercapto, lower alkoxy, lower alkyl-thio, halogen, lower alkyl, unsubstituted or substituted mononuclear aryl, or $-N(R^2)_2$;

R^1 is hydrogen or lower alkyl;

each R^2 is, independently, $-R^7$, $-(CH_2)_m-OR^8$, $-(CH_2)_m-NR^7R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$, $-(CH_2)_n-(Z)_q-R^7$, $-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2)_n-CO_2R^7$, or



;

R^3 and R^4 are each, independently, hydrogen, lower alkyl, hydroxyl-lower alkyl, phenyl, (phenyl)-lower alkyl, (halophenyl)-lower alkyl, ((lower-alkyl)phenyl)-lower-alkyl, ((lower-alkoxy)phenyl)-lower-alkyl, (naphthyl)-lower-alkyl, or (pyridyl)-lower-alkyl, or a group represented by formula A or formula B, with the proviso that at least one of R^3 and R^4 is a group represented by the formula A or formula B;

formula A: $-(C(R^L)_2)_o-x-(C(R^L)_2)_pA^1$

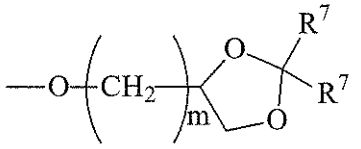
formula B: $-(C(R^L)_2)_o-x-(C(R^L)_2)_pA^2$

A^1 is a C_6-C_{15}-membered aromatic carbocycle substituted with at least one R^5 and the remaining substituents are R^6;

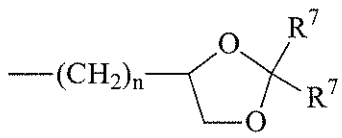
A^2 is a six to fifteen-membered aromatic heterocycle substituted with at least one R^5 and the remaining substituents are R^6 wherein said aromatic heterocycle comprises 1-4 heteroatoms selected from the group consisting of O, N, and S;

each R^L is, independently, $-R^7$, $-(CH_2)_n-OR^8$, $-O-(CH_2)_m-OR^8$, $-(CH_2)_n-NR^7R^{10}$, $-O-(CH_2)_m-NR^7R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$,

$-O-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$, $-O-(CH_2)_m-C(=O)NR^7R^{10}$, $-(CH_2)_n-(Z)_g-R^7$, $-O-(CH_2)_m-(Z)_g-R^7$, $-(CH_2)_n-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2)_n-CO_2R^7$, $-O-(CH_2)_m-CO_2R^7$, $-OSO_3H$, -O-glucuronide, -O-glucose,



, or



;

each o is, independently, an integer from 0 to 10;

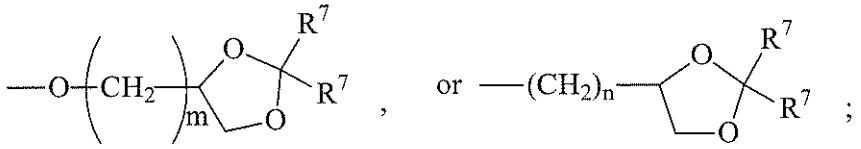
each p is, independently, an integer from 0 to 10;

with the proviso that the sum of o and p in each contiguous chain is from 1 to 10;

each x is, independently, O, NR^{10}, C(=O), CHOH, $C(=N-R^{10})$, $CHNR^7R^{10}$, or a single bond;

each R^5 is, independently, $-Link-(CH_2)_m-CAP$, $-Link-(CH_2)_n(CHOR^8)(CHOR^8)_n-CAP$, $-Link-(CH_2CH_2O)_m-CH_2-CAP$, $-Link-(CH_2CH_2O)_m-CH_2CH_2-CAP$, $-Link-(CH_2)_m-(Z)_g-CAP$, $-Link-(CH_2)_n(Z)_g-(CH_2)_m-CAP$, $-Link-(CH_2)_n-NR^{13}-CH_2(CHOR^8)(CHOR^8)_n-CAP$, $-Link-(CH_2)_n-(CHOR^8)_mCH_2-NR^{13}-(Z)_g-CAP$, $-Link-(CH_2)_nNR^{13}-(CH_2)_m(CHOR^8)_nCH_2NR^{13}-(Z)_g-CAP$, $-Link-(CH_2)_m-(Z)_g-(CH_2)_m-CAP$, $-Link-NH-C(=O)-NH-(CH_2)_m-CAP$, $-Link-(CH_2)_m-C(=O)NR^{13}-(CH_2)_m-CAP$, $-Link-(CH_2)_n-(Z)_g-(CH_2)_m-(Z)_g-CAP$, or $-Link-Z_g-(CH_2)_m-Het-(CH_2)_m-CAP$;

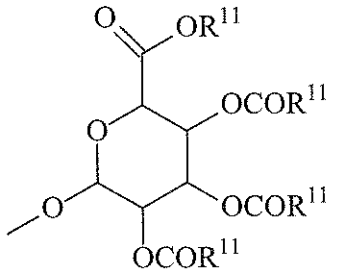
each R^6 is, independently, R^5, $-R^7$, $-OR^{11}$, $-N(R^7)_2$, $-(CH_2)_m-OR^8$, $-O-(CH_2)_m-OR^8$, $-(CH_2)_n-NR^7R^{10}$, $-O-(CH_2)_m-NR^7R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$, $-O-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$, $-O-(CH_2)_m-C(=O)NR^7R^{10}$, $-(CH_2)_n-(Z)_g-R^7$, $-O-(CH_2)_m-(Z)_g-R^7$, $-(CH_2)_n-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2)_n-CO_2R^7$, $-O-(CH_2)_m-CO_2R^7$, $-OSO_3H$, -O-glucuronide, -O-glucose,



wherein when two R^6 are $-OR^{11}$ and are located adjacent to each other on the aromatic carbocycle or aromatic heterocycle, the two OR^{11} may form a methylenedioxy group;

each R^7 is, independently, hydrogen, lower alkyl, phenyl, substituted phenyl or $-CH_2(CHOR^8)_m-CH_2OR^8$;

each R^8 is, independently, hydrogen, lower alkyl, $-C(=O)-R^{11}$, glucuronide, 2-tetrahydropyranyl, or



each R^9 is, independently, $-CO_2R^7$, $-CON(R^7)_2$, $-SO_2CH_3$, $-C(=O)R^7$, $-CO_2R^{13}$, $-CON(R^{13})_2$, $-SO_2CH_2R^{13}$, or $-C(=O)R^{13}$;

each R^{10} is, independently, -H, $-SO_2CH_3$, $-CO_2R^7$, $-C(=O)NR^7R^9$, $-C(=O)R^7$, or $-CH_2-(CHOH)_n-CH_2OH$;

each Z is, independently, -(CHOH)-, -C(=O)-, $-(CHNR^7R^{10})-$, $-(C=NR^{10})-$, $-NR^{10}-$, $-(CH_2)_n-$, $-(CHNR^{13}R^{13})-$, $-(C=NR^{13})-$, or $-NR^{13}-$;

each R^{11} is, independently, hydrogen, lower alkyl, phenyl lower alkyl or substituted phenyl lower alkyl;

each R^{12} is, independently, $-SO_2CH_3$, $-CO_2R^7$, $-C(=O)NR^7R^9$, $-C(=O)R^7$, $-CH_2(CHOH)_n-CH_2OH$, $-CO_2R^7$, $-C(=O)NR^7R^7$, or $-C(=O)R^7$;

each R^{13} is, independently, hydrogen, $-OR^7$, R^{10}, R^{11} or R^{12};

each g is, independently, an integer from 1 to 6;

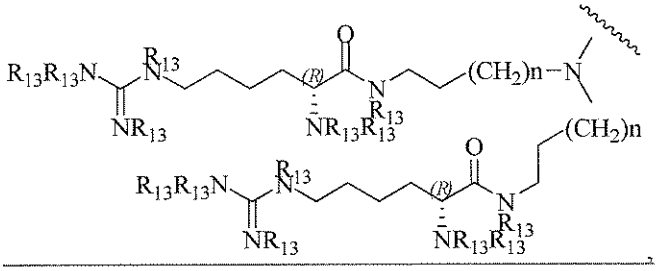
each m is, independently, an integer from 1 to 7;

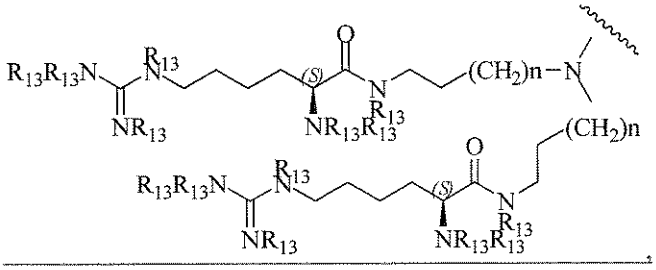
each n is, independently, an integer from 0 to 7;

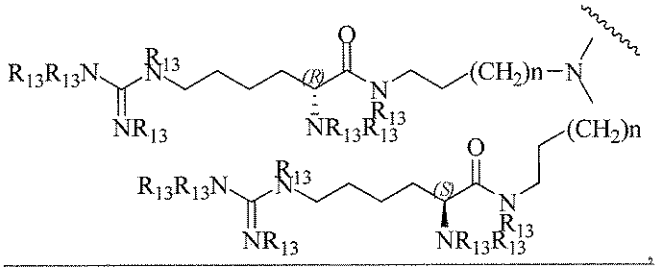
each –Het- is, independently, -N(R^7)-, -N(R^{10})-, -S-, -SO-, -SO_2-; -O-, -SO_2NH-, -$NHSO_2$-, -NR^7CO-, -$CONR^7$-, -N(R^{13})-, -SO_2NR^{13}-, -NR^{13}CO-, or -$CONR^{13}$-;

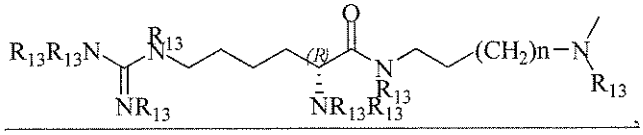
each Link is, independently, -O-, -$(CH_2)_n$-, -O$(CH_2)_m$-, -NR^{13}-C(=O)-NR^{13}-, -NR^{13}-C(=O)-$(CH_2)_m$-, -C(=O)NR^{13}-$(CH_2)_m$-, -$(CH_2)_n$-$(Z)_g$-$(CH_2)_n$-, -S-, -SO-, -SO_2-, -SO_2NR^7-, -SO_2NR^{10}-, or -Het-;

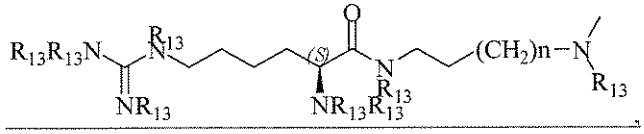
each CAP is

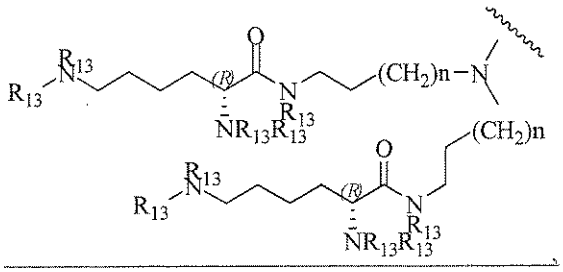


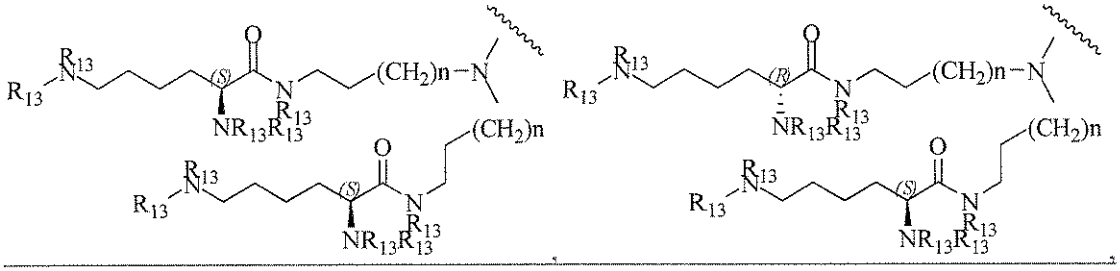


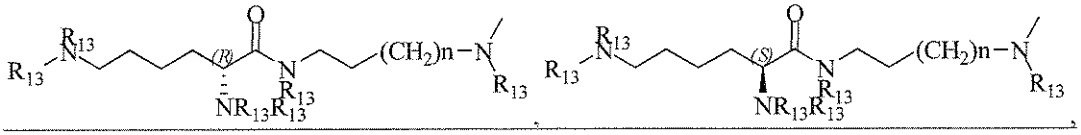


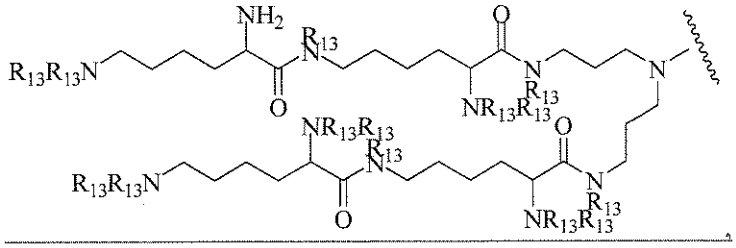


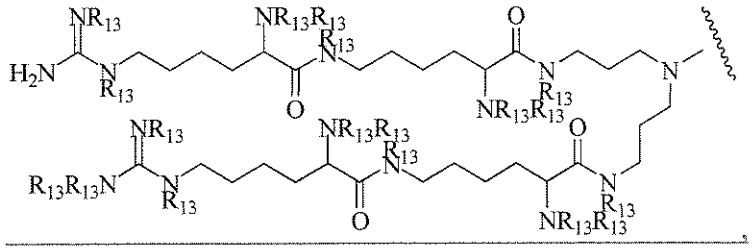


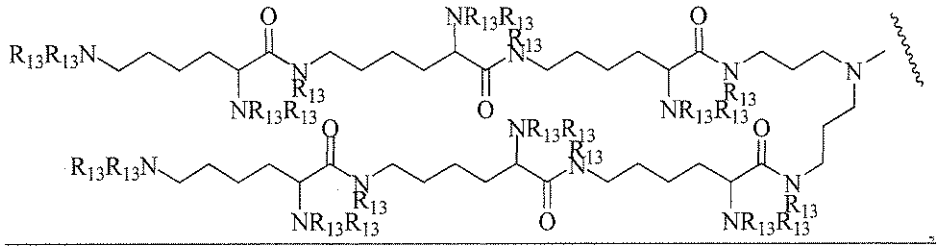


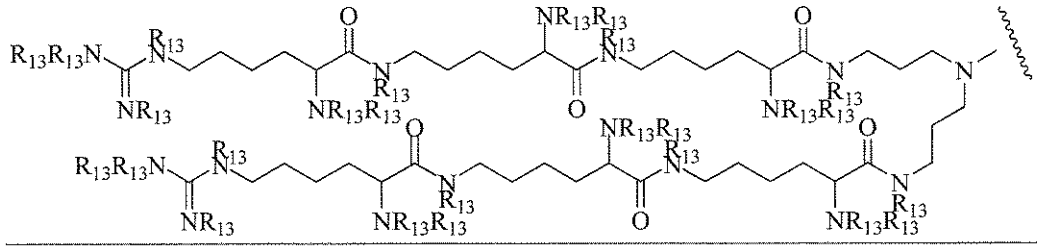


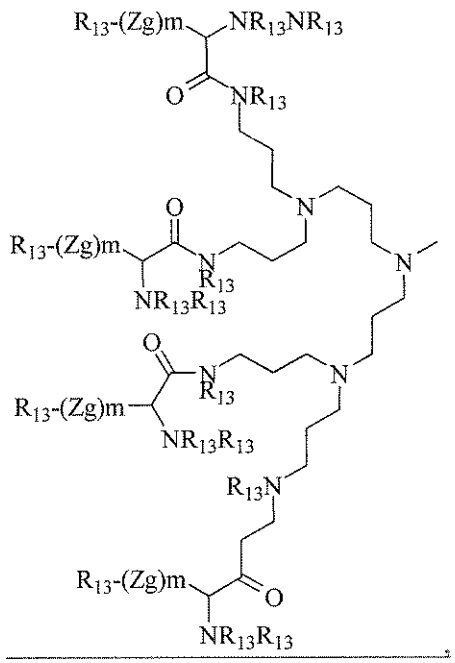


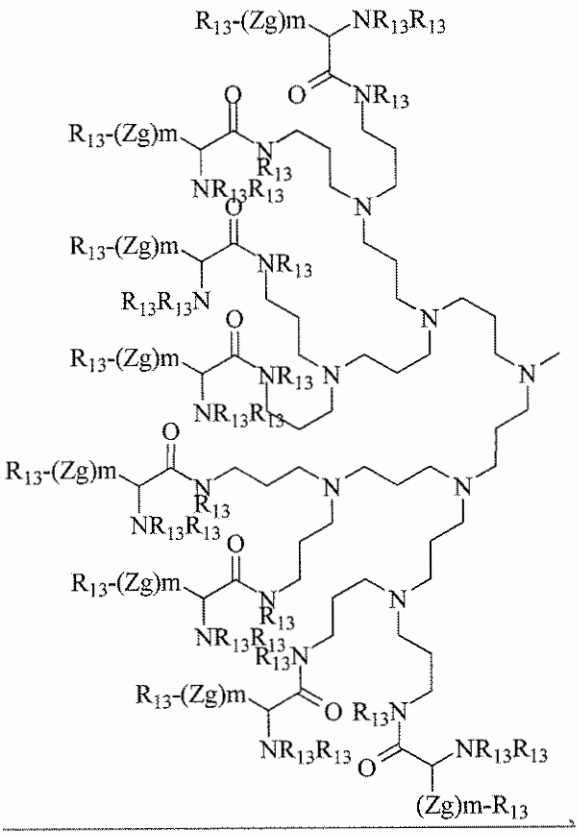


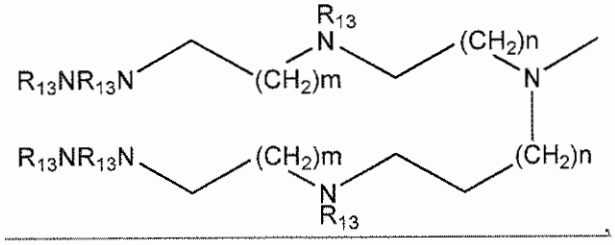


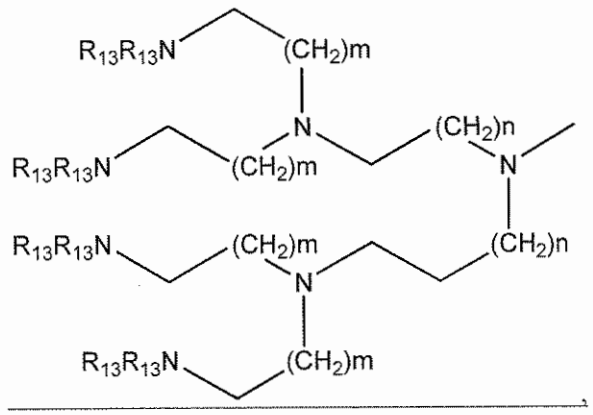


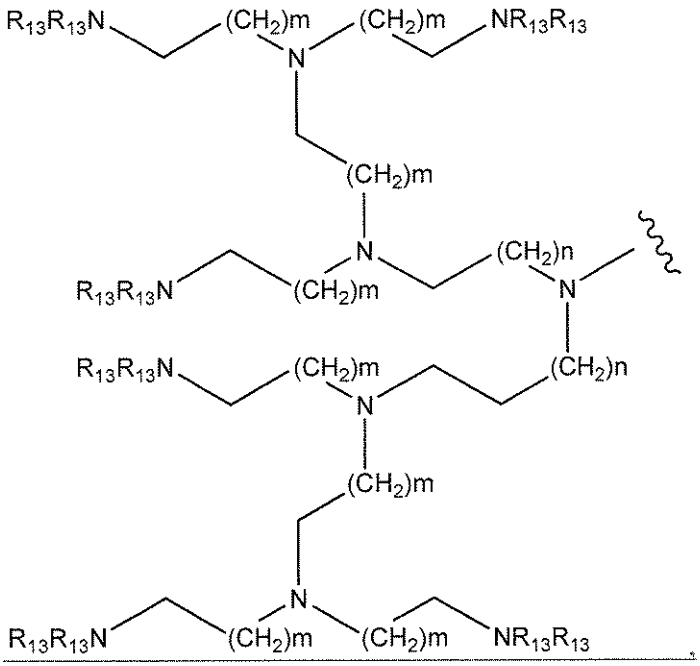


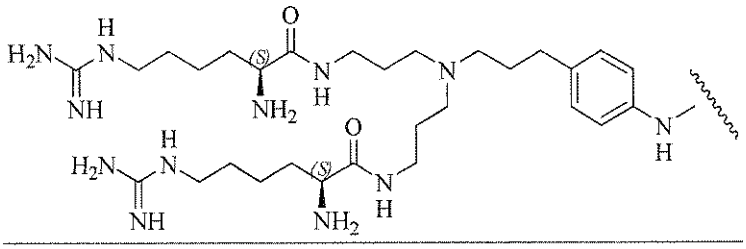




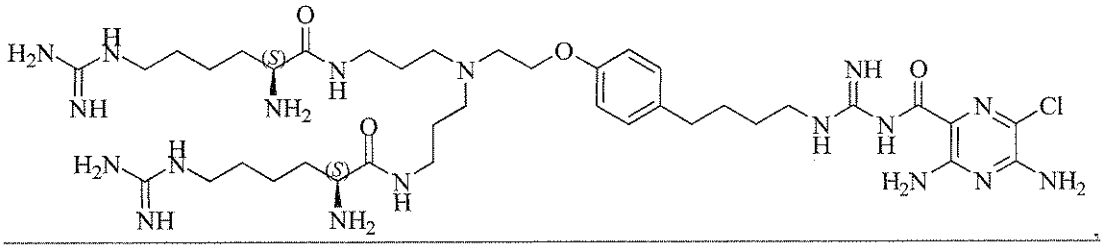


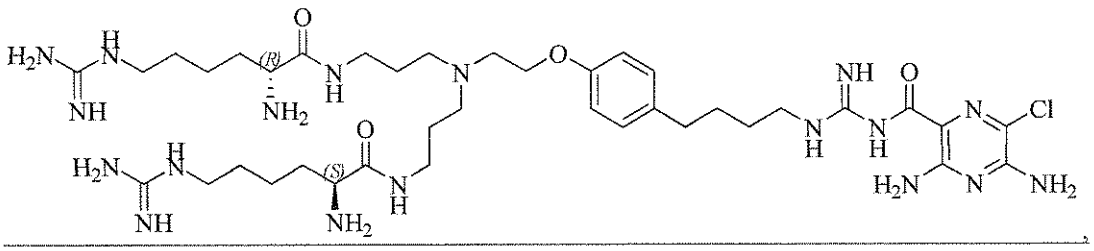


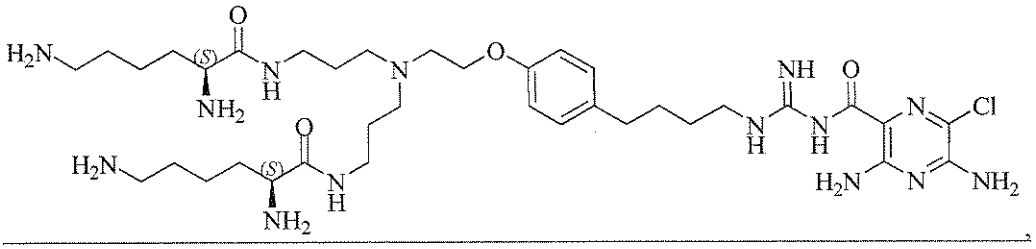


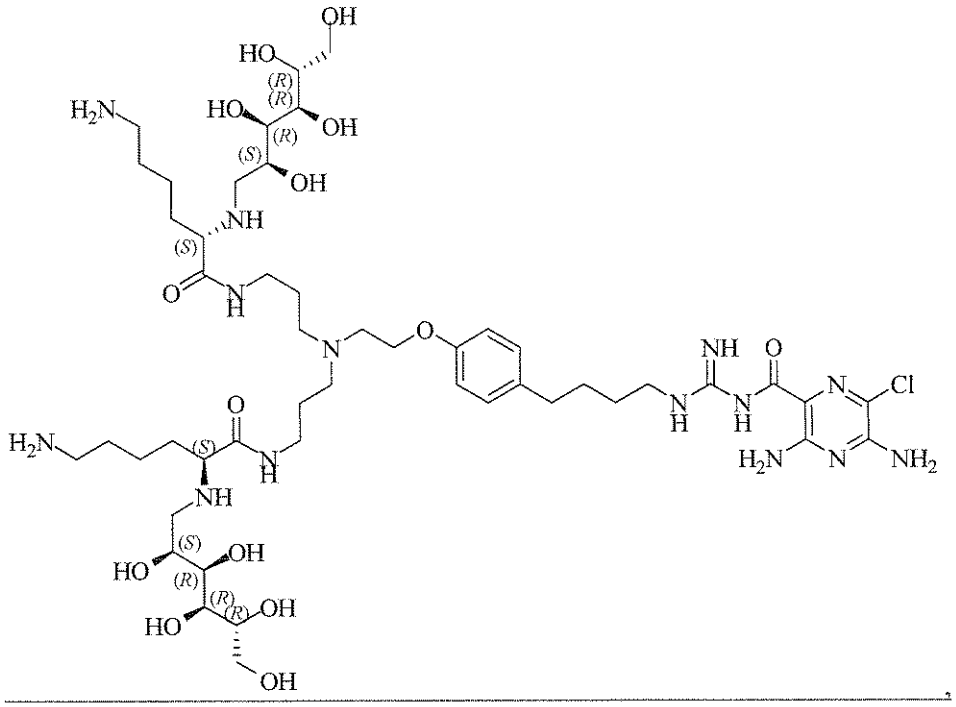


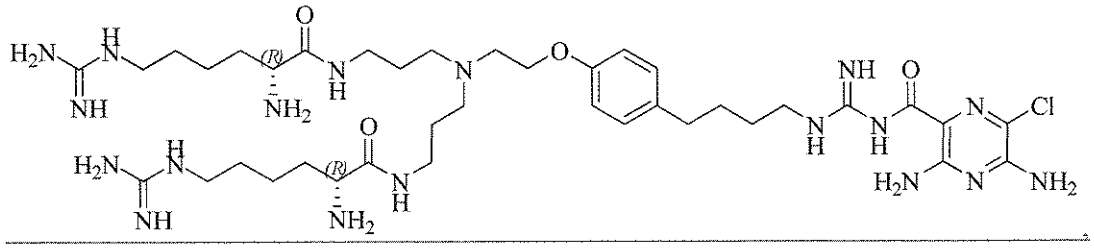
In one aspect, there is provided a compound represented by one of the following formulas:

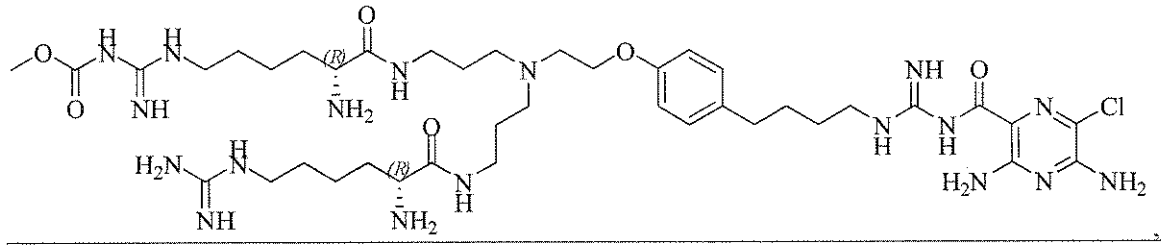


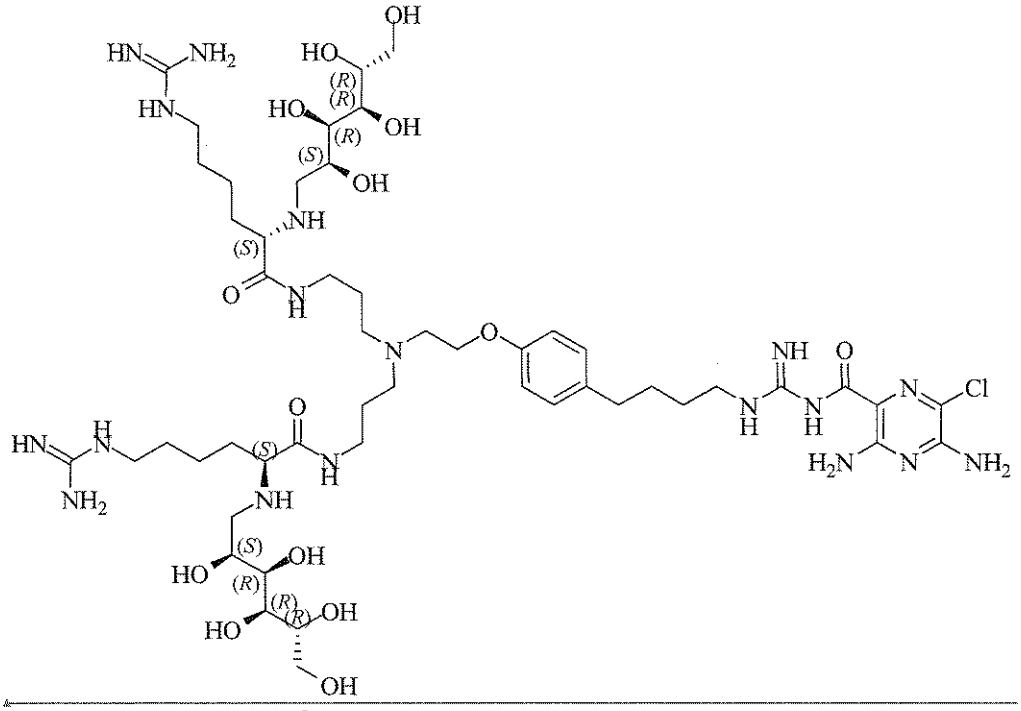


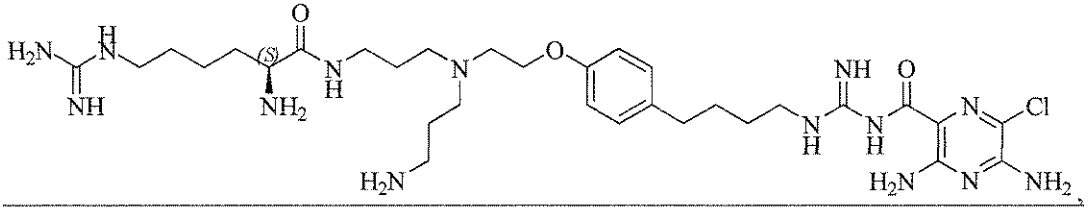


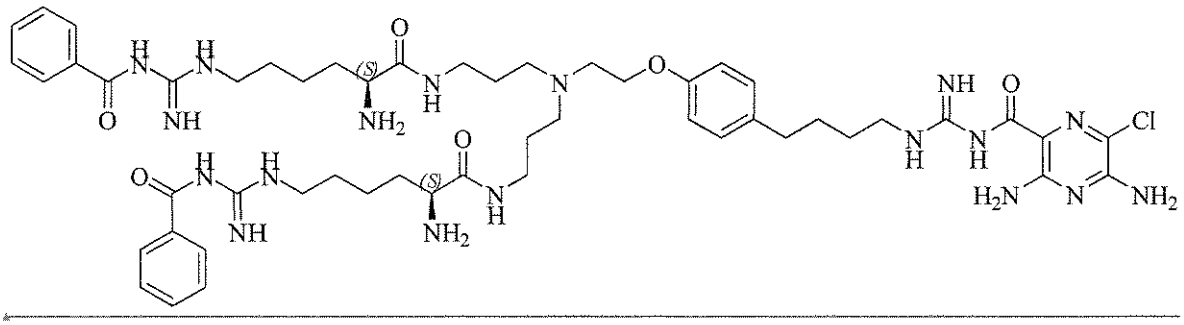


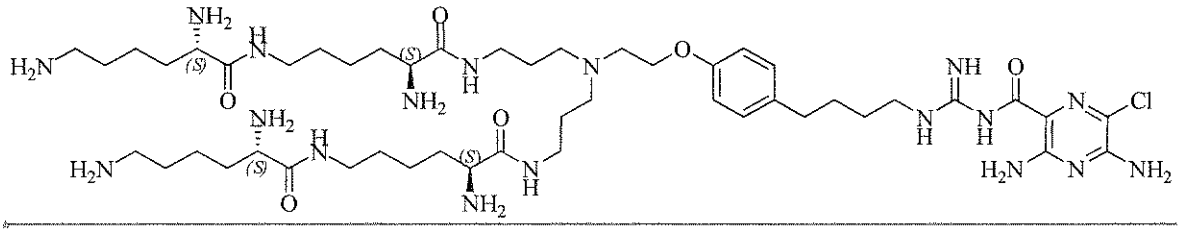


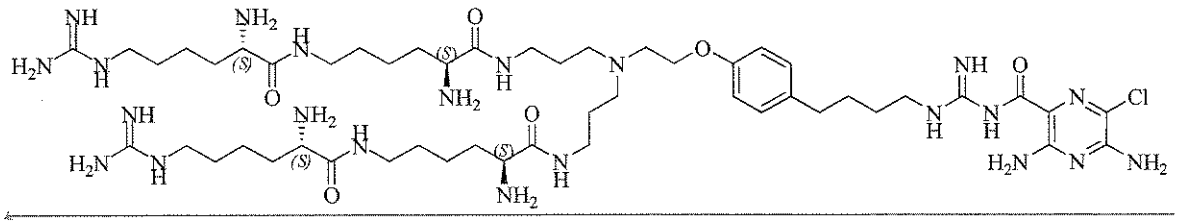


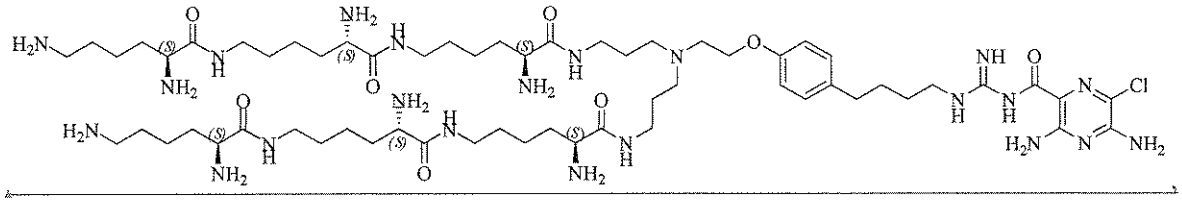


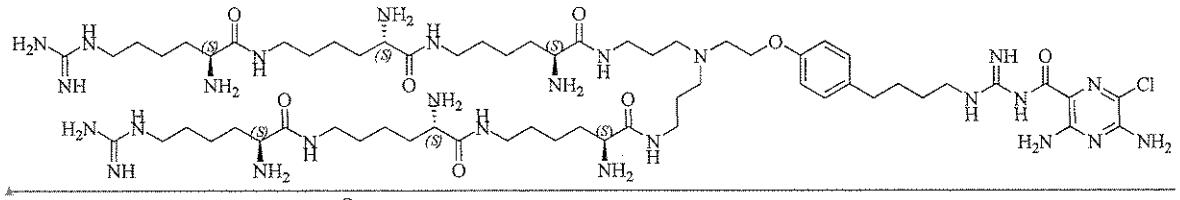


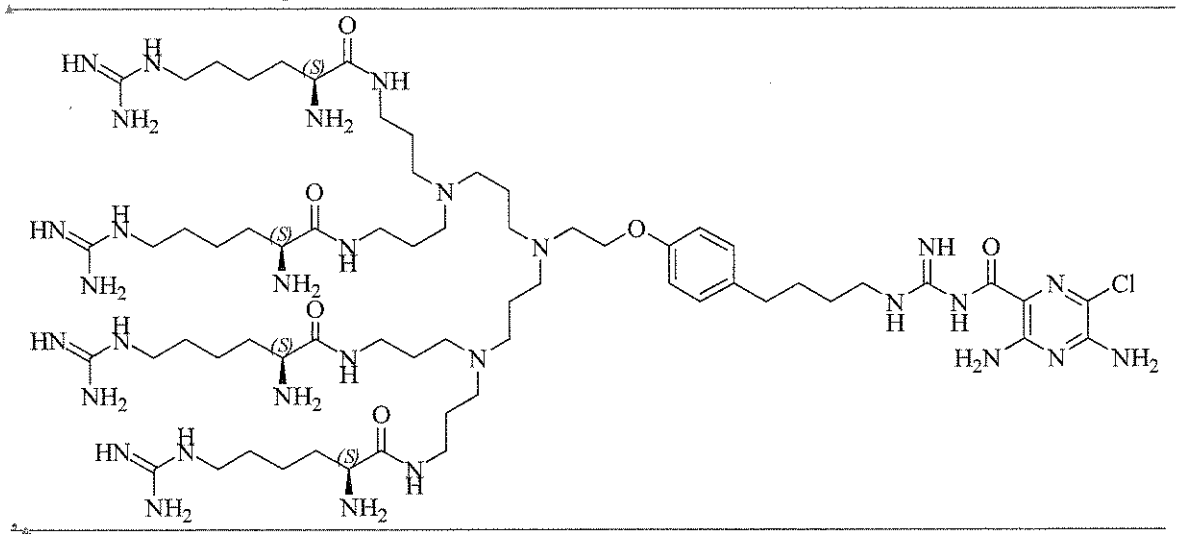


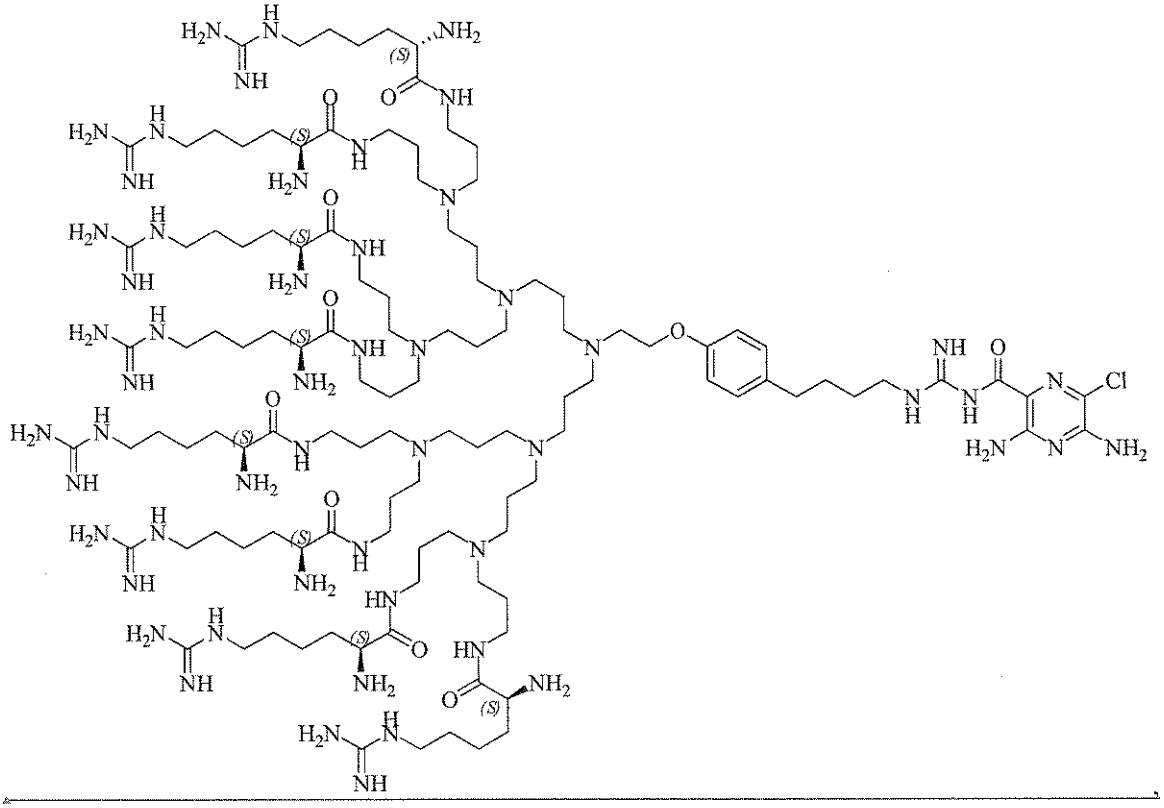






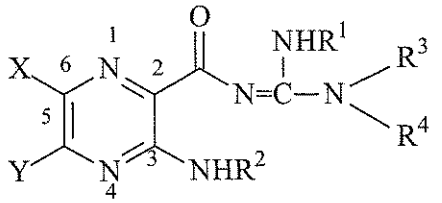






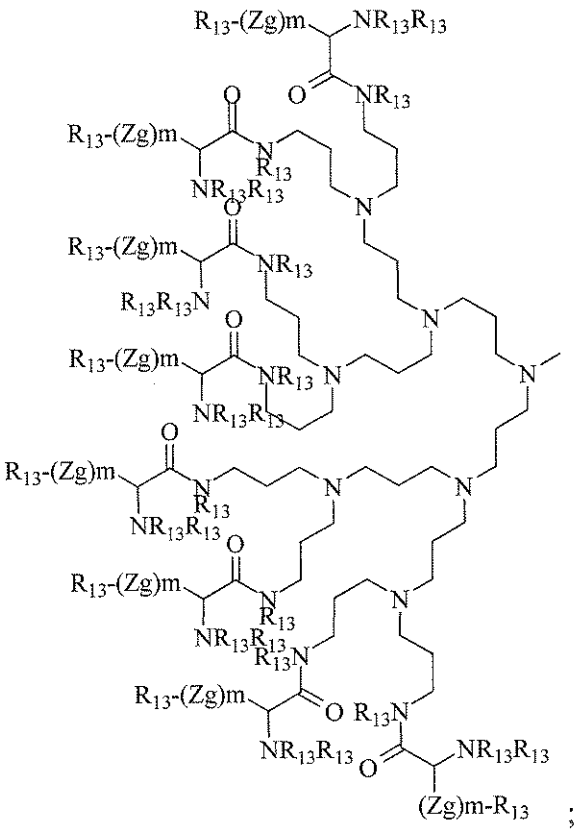
or a pharmaceutically active salt thereof.

The objects of the present disclosure~~invention~~ may be accomplished with a class of pyrazinoylguanidine represented by a compound of formula (I):



(I)

and includes racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and pharmaceutically acceptable salts, thereof, wherein:



with the proviso that when any -CHOR^8- or –CH_2OR^8 groups are located 1,2- or 1,3- with respect to each other, the R^8 groups may, optionally, be taken together to form a cyclic mono- or di-substituted 1,3-dioxane or 1,3-dioxolane.

In one aspect, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof for use as a medicament.

In one aspect, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), treating cystic fibrosis, treating sinusitis, treating vaginal dryness, promoting mucus clearance in mucosal surfaces, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth, treating nasal dehydration (including nasal dehydration brought on by administering dry

oxygen to the subject), treating ventilator-induced pneumonia, treating asthma, treating primary ciliary dyskinesia, treating otitis media, inducing sputum for diagnostic purposes, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, or treating rhinosinusitis in a human in need thereof.

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

The present also provides pharmaceutical compositions which comprise a compound described herein.

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

In one aspect, there is provided use of an effective amount of a compound as described 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.

The present disclosure~~invention~~ also provides a method of promoting hydration of mucosal surfaces, comprising:

administering an effective amount of a compound described herein to a mucosal surface of a subject.

The present disclosure~~invention~~ also provides a method of restoring mucosal defense, comprising:

topically administering an effective amount of compound described herein to a mucosal surface of a subject in need thereof.

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

The present disclosure~~invention~~ also provides a method of blocking ENaC, comprising:

contacting sodium channels with an effective amount of a compound represented by described herein.

The present disclosure~~invention~~ also provides a method of promoting mucus clearance in mucosal surfaces, comprising:

administering an effective amount of a compound represented described herein to a mucosal surface of a subject.

In one aspect, there is provided use of an effective amount of the compound as described herein in the manufacture of a medicament for treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), treating cystic fibrosis, treating sinusitis, treating vaginal dryness, promoting mucus clearance in mucosal surfaces, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth, treating nasal dehydration (including nasal dehydration brought on by administering dry oxygen to the subject), treating ventilator-induced pneumonia, treating asthma, treating primary ciliary dyskinesia, treating otitis media, inducing sputum for diagnostic purposes, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, or treating rhinosinusitis in a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating dry eye, comprising:

administering an effective amount of a compound described herein to the eye of the subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating Sjogren's disease-associated dry eye, comprising:

administering an effective amount of a compound described herein to the eye of the subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating eye inflammation caused by dry eye, comprising:

administering an effective amount of a compound described herein to the eye of the subject in need thereof.

The present disclosure~~invention~~ also provides a method of promoting ocular hydration, comprising:

administering an effective amount of a compound described herein to the eye of the subject.

The present disclosure~~invention~~ also provides a method of promoting corneal hydration, comprising:

administering an effective amount of a compound described herein to the eye of the subject.

The present disclosure~~invention~~ also provides a method of treating chronic bronchitis, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating cystic fibrosis, comprising:

administering an effective amount of compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating rhinosinusitis, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating nasal dehydration, comprising:

administering an effective amount of a compound described herein to the nasal passages of a subject in need thereof.

In a specific embodiment, the nasal dehydration is brought on by administering dry oxygen to the subject.

The present disclosure~~invention~~ also provides a method of treating sinusitis, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating pneumonia, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating ventilator-induced pneumonia, comprising:

administering an effective compound described herein to a subject by means of a ventilator.

The present disclosure~~invention~~ also provides a method of treating asthma, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating primary ciliary dyskinesia, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating otitis media, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of inducing sputum for diagnostic purposes, comprising:

administering an effective amount of compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating chronic obstructive pulmonary disease, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating emphysema, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating Sjögren's disease, comprising:

administering an effective amount of compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating vaginal dryness, comprising:

administering an effective amount of a compound described herein to the vaginal tract of a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating dry skin, comprising:

administering an effective amount of a compound described herein to the skin of a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating dry mouth (xerostomia), comprising:

administering an effective amount of compound described herein to the mouth of the subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating distal intestinal obstruction syndrome, comprising:

administering an effective amount of compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating esophagitis, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating bronchiectasis, comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

The present disclosure~~invention~~ also provides a method of treating constipation, comprising:

administering an effective amount of a compound described herein to a subject in need thereof. In one embodiment of this method, the compound is administered either orally or via a suppository or enema.

The present disclosure~~invention~~ also provides a method of treating chronic diverticulitis comprising:

administering an effective amount of a compound described herein to a subject in need thereof.

It is an object of the present disclosure~~invention~~ to provide treatments comprising the use of osmolytes together with sodium channel blockers of formula (I) that are more potent, more specific, and/or absorbed less rapidly from mucosal surfaces, and/or are less reversible as compared to compounds such as amiloride, benzamil, and phenamil.

It is another ~~aspect~~ embodiment of the present disclosure~~invention~~ to provide treatments using sodium channel blockers of formula (I) that are more potent and/or absorbed less rapidly and/or exhibit less reversibility, as compared to compounds such as amiloride, benzamil, and phenamil when administered with an osmotic enhancer. Therefore, such sodium channel blockers when used in conjunction with osmolytes will give a prolonged pharmacodynamic half-life on mucosal surfaces as compared to either compound used alone.

It is another object of the present disclosure~~invention~~ to provide treatments using sodium channel blockers of formula (I) and osmolytes together which are absorbed less rapidly from mucosal surfaces, especially airway surfaces, as compared to compounds such as amiloride, benzamil, and phenamil.

It is another object of the disclosure~~invention~~ to provide compositions which contain sodium channel blockers of formula (I) and osmolytes.

In one aspect, there is provided use of an effective amount of the compound as described herein in the manufacture of a medicament for treating a disease ameliorated by increased mucociliary clearance and mucosal hydration in a subject in need of increased mucociliary clearance and mucosal hydration, wherein the medicament is to be administered with an effective amount of an osmolyte.

The objects of the disclosure~~invention~~ may be accomplished with a method of treating a disease ameliorated by increased mucociliary clearance and mucosal hydration comprising administering an effective amount of a compound of formula (I) as defined herein and an osmolyte to a subject to a subject in need of increased mucociliary clearance and mucosal hydration.

The objects of the disclosure~~invention~~ may also be accomplished with a method of inducing sputum for diagnostic purposes, comprising administering an effective amount of a compound of formula (I) as defined herein and an osmolyte to a subject in need thereof.

The objects of the disclosure~~invention~~ may also be accomplished with a method of treating anthrax, comprising administering an effective amount of a compound of formula (I) as defined herein and an osmolyte to a subject in need thereof.

In one aspect, there is provided use of an effective amount of a compound as described 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.

The objects of the disclosure~~invention~~ may also be accomplished with a method of prophylactic, post-exposure prophylactic, preventive or therapeutic treatment against diseases or conditions

caused by pathogens, particularly pathogens which may be used in bioterrorism, comprising administering an effective amount of a compound of formula (I) to a subject in need thereof. In one aspect, there is provided a composition, comprising:

(a) a compound or a pharmaceutically acceptable salt thereof as described herein and (b) an osmolotically active compound.

The objects of the disclosure~~invention~~ may also be accomplished with a composition, comprising a compound of formula (I) as defined herein and an osmolyte as defined herein. In one aspect, there is provided a composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), treating cystic fibrosis, treating sinusitis, treating vaginal dryness, promoting mucus clearance in mucosal surfaces, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth, treating nasal dehydration (including nasal dehydration brought on by administering dry oxygen to the subject), treating ventilator-induced pneumonia, treating asthma, treating primary ciliary dyskinesia, treating otitis media, inducing sputum for diagnostic purposes, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, or treating rhinosinusitis.

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:

Figure 1: Tear volume assessments over 6 hours in ExLac rats with Amiloride. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

Figure 2: Tear volume assessments over 6 hours in ExLac rats with Compound **51**.

Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

Figure 3: Tear volume assessments over 6 hours in ExLac rats with Compound **75**. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

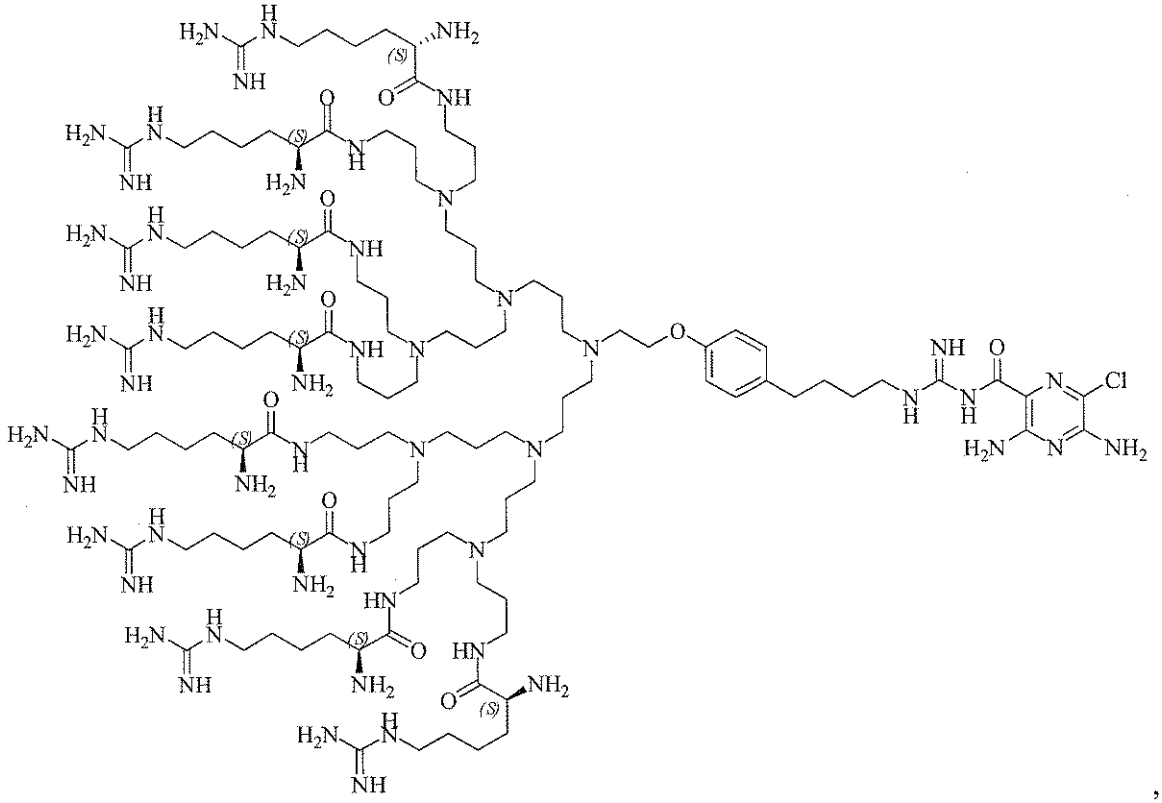
Figure 4: Tear volume assessments over 6 hours in ExLac rats with Compound P-**59**. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

Figure 5: Tear volume assessments over 6 hours in ExLac rats with Compound **46**. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

Figure 6: Tear volume assessments over 6 hours in ExLac rats with Compound **45**. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

Figure 7: Tear volume assessments over 6 hours in ExLac rats with Compound **145**. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.

Figure 8: Tear volume assessments over 6 hours in ExLac rats with Compound **82**. Tear volume from ExLac and Normal rats treated with a vehicle are shown for comparison. Error bars are standard error.



or a pharmaceutically active salt thereof.

7. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

8. The pharmaceutical composition according to claim 7, wherein the compound is (2R, 2'R)-N,N'-(3,3'-(2-(4-(4-(3-(3,5-diamino-6-chloropyrazine-2-carbonyl)guanidino)butyl)phenoxy)ethylazanediyl)bis(propane-3,1-diyl))bis(2-amino-6-guanidinohexanamide), or a pharmaceutically acceptable salt thereof.

9. The composition according to claim 7, wherein said composition is a solution for administration by eye drops.

10. ~~A method for blocking sodium channels in a human comprising administering to said human~~ Use of an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for blocking sodium channels in a human.

11. ~~A method for promoting hydration of mucosal surfaces or restoring mucosal defense in a human comprising administering to said human~~ Use of an effective amount of a compound according to claim 1, 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.

12. Use of an effective amount of the compound according to claim 1 in the manufacture of a medicament for ~~A method of~~ treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), treating cystic fibrosis, treating sinusitis, treating vaginal dryness, promoting mucus clearance in mucosal surfaces, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth, treating nasal dehydration (including nasal dehydration ~~is~~ brought on by administering dry oxygen to the subject), treating ventilator-induced pneumonia, treating asthma, treating primary ciliary dyskinesia, treating otitis media, inducing sputum for diagnostic purposes, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, or treating rhinosinusitis~~, comprising: administering an effective amount of the compound according to claim 1 to~~ in a subject in need thereof.

13. Use of an effective amount of the compound according to claim 1 in the manufacture of a medicament for ~~A method of~~ treating a disease ameliorated by increased mucociliary clearance and mucosal hydration ~~comprising administering to~~in a subject in need of increased mucociliary clearance and mucosal hydration, wherein the medicament is to be administered with an effective amount of an osmolyte ~~and the compound according to claim 1~~.

14. The use ~~method~~ according to claim 12, wherein the disease is one or more conditions selected from the group consisting of dry eye, chronic bronchitis, bronchiectasis, cystic fibrosis, sinusitis, vaginal dryness, Sjogren's disease, distal intestinal obstruction syndrome, dry skin, esophagitis, dry mouth (xerostomia), nasal dehydration, asthma, primary ciliary dyskinesia, otitis media, chronic obstructive pulmonary disease, emphysema, pneumonia, diverticulitis, rhinosinusitis, and airborne infections.

15. A composition, comprising:

(a) a compound or a pharmaceutically acceptable salt thereof according to claim 1 and

(b) an osmolotically active compound.

16. The composition according to claim 7, further comprising a pharmaceutically effective amount of a therapeutically active agent selected from anti-inflammatory agents, anticholinergic agents, β-agonists, P2Y2 receptor agonists, peroxisome proliferator-activated receptor agonists, kinase inhibitors, antiinfective agents and antihistamines.

17. ~~A method comprising administering to a human,~~ Use of an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament.

18. A compound according to claim 1, or a pharmaceutically acceptable salt thereof for use as a medicament.

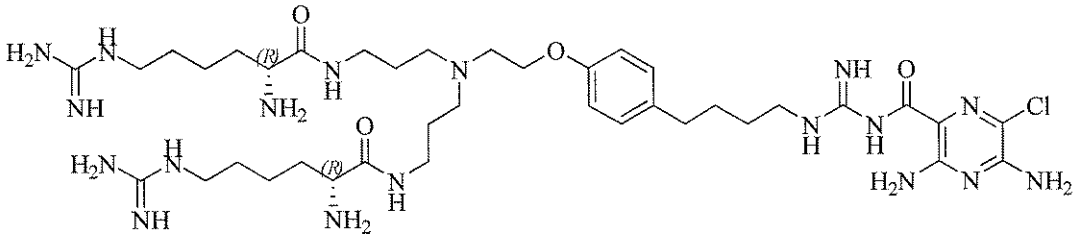
19. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, for use in treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), treating cystic fibrosis, treating sinusitis, treating vaginal dryness, promoting mucus clearance in mucosal surfaces, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth, treating nasal dehydration (including nasal dehydration ~~is~~ brought on by administering dry oxygen to the subject), treating ventilator-induced pneumonia, treating asthma, treating primary ciliary dyskinesia, treating otitis media, inducing sputum for diagnostic purposes, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, or treating rhinosinusitis in a human in need thereof.

20. A composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for ~~of~~ treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating bronchiectasis (including bronchiectasis due to conditions other than cystic fibrosis), treating cystic fibrosis, treating sinusitis, treating vaginal dryness, promoting mucus clearance in

mucosal surfaces, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth, treating nasal dehydration (including nasal dehydration ~~is~~ brought on by administering dry oxygen to the subject), treating ventilator-induced pneumonia, treating asthma, treating primary ciliary dyskinesia, treating otitis media, inducing sputum for diagnostic purposes, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, or treating rhinosinusitis.

21. Use of an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament ~~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~~, said method comprising administering to said human an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof~~.

22. The method according to claim 10, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

23. The hydrochloride salt of:

