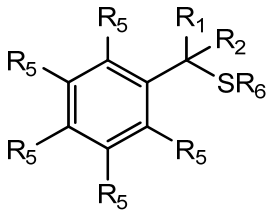
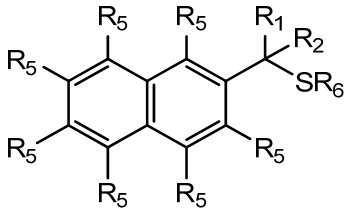
CLAIMS

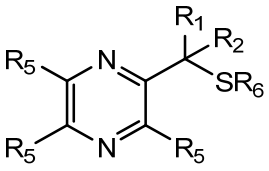
1. A compound represented by formula (Ia)-(Id):



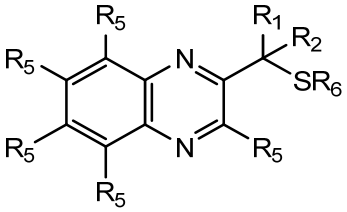
Ia



Ib



Ic



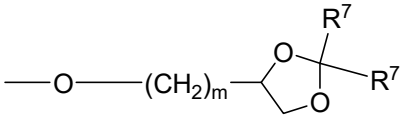
Id

wherein

R^1 and R^2 are each, independently, hydrogen, lower alkyl, halogen, trifluoromethyl, 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;

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;

each R^5 is, independently, hydrogen, halogen, trifluoromethyl, lower alkyl, unsubstituted or substituted phenyl, lower alkyl-thio, phenyl-lower alkyl-thio, lower alkyl-sulfonyl, or phenyl-lower alkyl-sulfonyl, OH, $-(CH_2)_m-OR^8$, $-O-(CH_2)_m-OR^8$, $-O-(CH_2)_m-NR^7R^{10}$, $-O-(CH_2)_m-NR^7R^7$, $-O-(CH_2)_m-NR^{10}R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$, $-O-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$, $-O-(CH_2)_m-C(=O)NR^7R^{10}$, $-(CH_2)_n-(Z)_g-R^7$, $-O-(CH_2)_m-(Z)_g-R^7$, $-(CH_2)_n-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2)_n-CO_2R^7$, $-O-(CH_2)_m-CO_2R^7$, $-OSO_3H$, -O-glucuronide, -O-glucose,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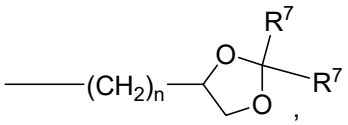
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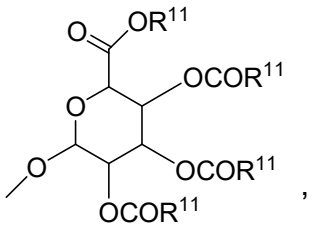

,

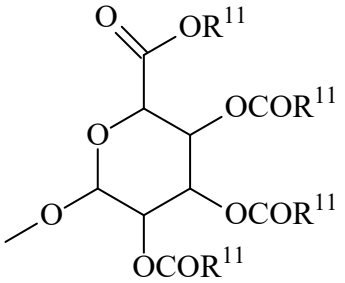
-Link–$(CH_2)_m$-CAP, -Link-$(CH_2)_n(CHOR^8)(CHOR^8)_n$-CAP, -Link-$(CH_2CH_2O)_m$-$CH_2$-CAP, -Link-$(CH_2CH_2O)_m$-$CH_2CH_2$-CAP, -Link-$(CH_2)_m$-$(Z)_g$-CAP, -Link–$(CH_2)_n(Z)_g$-$(CH_2)_m$-CAP, -Link-$(CH_2)_n$-$NR^{13}$-$CH_2(CHOR^8)(CHOR^8)_n$-CAP, -Link-$(CH_2)_n$-$(CHOR^8)_mCH_2$-$NR^{13}$-$(Z)_g$-CAP, -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,

with the proviso that at least one R^5 group contains at least one basic nitrogen;

each R^6 is, independently, hydrogen, -C(=O)-R^7, or an amino acyl of the natural configuration;

each R^7 is, independently, hydrogen, lower alkyl, phenyl, substituted phenyl, lower alkyl phenyl, -$CH_2(CHOR^8)_m$-CH_2OR^8; 2-furyl or 3- furyl;

each R^8 is, independently, hydrogen, lower alkyl, lower alkyl phenyl, -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^{7}R^{10})-, -(C=NR^{10})-, -(CH$_2$)$_n$-, -(CHNR^{13}R^{13})-, -(C=NR^{13})- , or -CO$_2$H;

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

each R^{13} is, independently, hydrogen, lower alkyl, phenyl, substituted phenyl or -CH$_2$(CHOR^{8})$_m$-CH$_2$OR^{8}, -SO$_2$CH$_3$, -CO$_2$R^{7}, -C(=O)NR^{7}R^{9}, -C(=O)R^{7}, -CH$_2$-(CHOH)$_n$-CH$_2$OH, –(CH$_2$)$_m$-NR^{7}R^{10}, –(CH$_2$)$_m$- NR^{7}R^{7}, –(CH$_2$)$_m$-NR^{11}R^{11}, –(CH$_2$)$_m$-(NR^{11}R^{11}R^{11})$^{+}$, –(CH$_2$)$_m$-(CHOR^{8})$_m$-(CH$_2$)$_m$NR^{11}R^{11}, –(CH$_2$)$_m$-(CHOR^{8})$_m$-(CH$_2$)$_m$NR^{7}R^{10}, -(CH$_2$)$_m$-NR^{10}R^{10}, –(CH$_2$)$_m$-(CHOR^{8})$_m$-(CH$_2$)$_m$-(NR^{11}R^{11}R^{11})$^{+}$, –(CH$_2$)$_m$-(CHOR^{8})$_m$-(CH$_2$)$_m$NR^{7}R^{7};

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

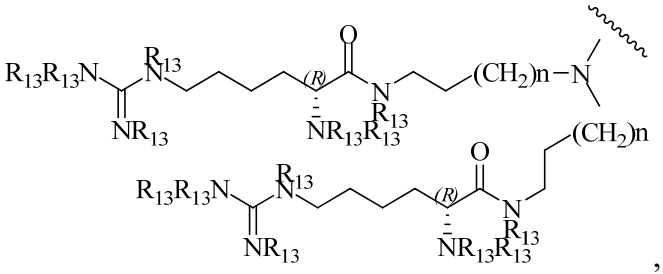
each m is, independently, an integer from 1 to 7;

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$_2$NH-, -NHSO$_2$-, -NR^{7}CO-, -CONR^{7}-, -N(R^{13})-, -SO$_2$NR^{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$_2$NR^{7}-, -SO$_2$NR^{10}-, or -Het-;

each CAP is, independently



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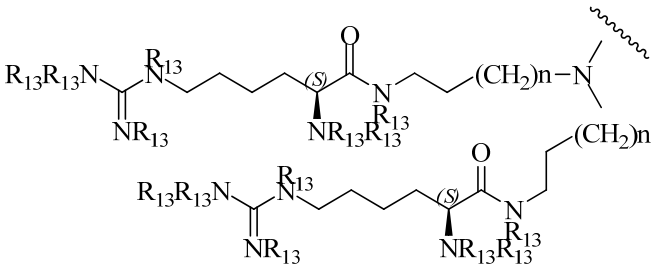

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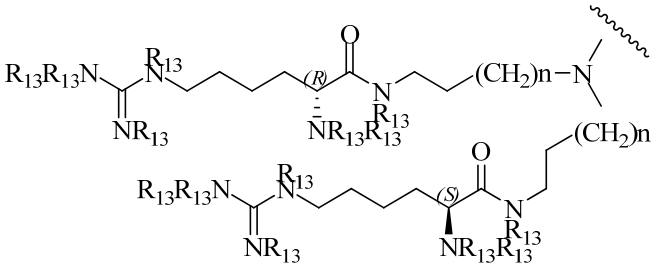

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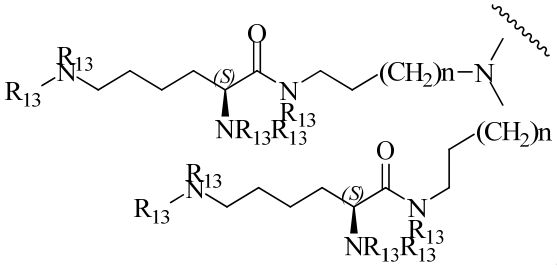

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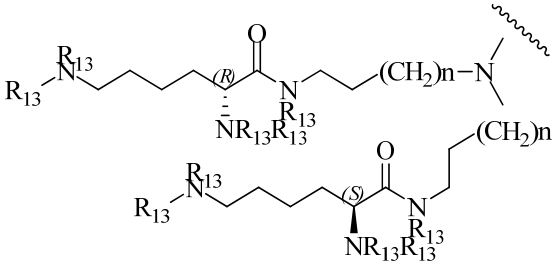

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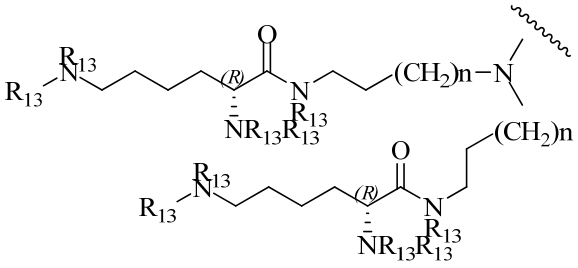

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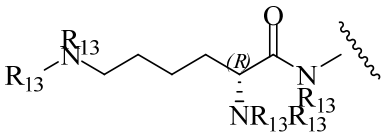

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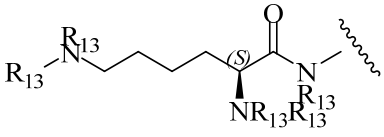

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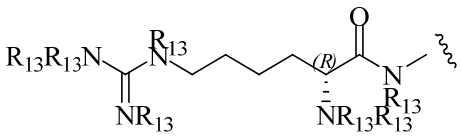

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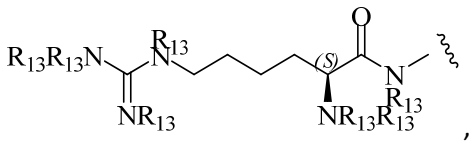

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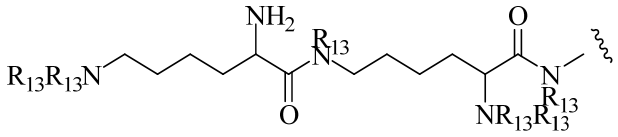

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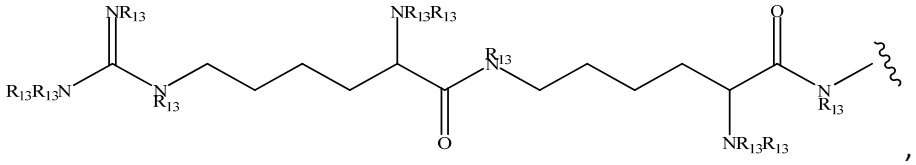

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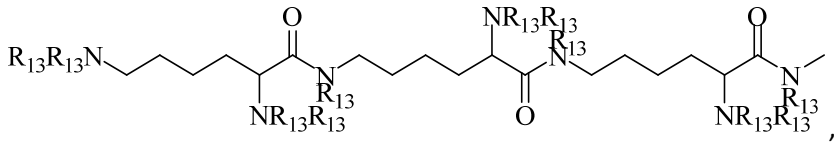

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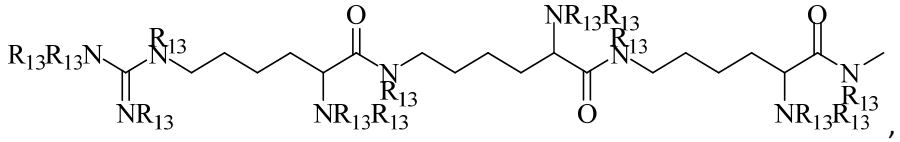

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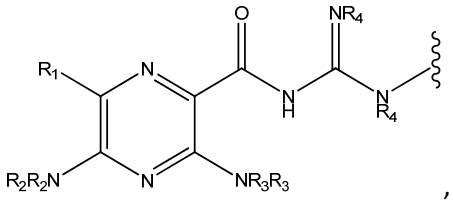

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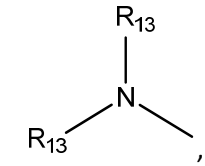

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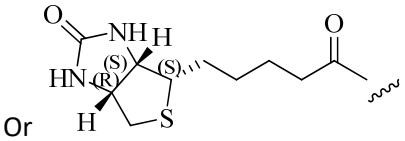


Or ;

with the proviso that when any -CHOR^8- or –CH$_2$OR^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;

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

2. A non-therapeutic use of the compound of claim 1 to liquefy mucus from mucosal surfaces, wherein the compound is to be administered to a mucosal surface of a subject.

3. A non-therapeutic use of the compound of claim 1 to promote any one or more of the following conditions: ocular hydration, corneal hydration, and mucus clearance in mucosal surfaces, or to induce sputum for diagnostic purposes.

4. The compound of claim 1 for use in therapy.

5. The compound of claim 1 for use in the treatment of any one or more of the following conditions: chronic bronchitis, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, sinusitis, vaginal dryness, dry eye, Sjogren's disease, distal intestinal obstruction syndrome, esophagitis, dry mouth, ventilator-induced pneumonia, asthma primary ciliary dyskinesia, otitis media, cystinosis, emphysema, pneumonia, constipation, chronic diverticulitis and rhinosinusitis.

6. The compound of claim 1 for use in the treatment of an eye disease characterized by the presence of ocular discharge.

7. The compound of claim 6, wherein the eye disease is one or more conditions selected from the group consisting of blepharitis, allergies, conjunctivitis, corneal ulcer, trachoma, congenital herpes simplex, corneal abrasions, ectropion, eyelid disorders, gonococcal conjunctivitis, herpetic keratitis, ophthalmitis, Sjogren's Syndrome, Stevens-Johnson Syndrome.

8. The compound of claim 1 and an osmolyte for use in the treatment of a disease ameliorated by increased mucociliary clearance and mucosal hydration.

9. Use of the compound of claim 1 in the manufacture of a medicament for the treatment of any one or more of the following conditions: chronic bronchitis, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, sinusitis, vaginal dryness, dry eye, Sjogren's disease, distal intestinal obstruction syndrome, esophagitis, dry mouth, ventilator-induced pneumonia, asthma, primary ciliary dyskinesia,

otitis media, cystinosis, emphysema, pneumonia, constipation, chronic diverticulitis and rhinosinusitis.

10. Use of the compound of claim 1 in the manufacture of a medicament for the treatment of an eye disease characterized by the presence of ocular discharge.

11. Use according to claim 10, wherein the eye disease is one or more conditions selected from the group consisting of blepharitis, allergies, conjunctivitis, corneal ulcer, trachoma, congenital herpes simplex, corneal abrasions, ectropion, eyelid disorders, gonococcal conjunctivitis, herpetic keratitis, ophthalmitis, Sjogren's Syndrome, Stevens-Johnson Syndrome.

12. Use of the compound of claim 1 and an osmolyte in the manufacture of a medicament for the treatment of a disease ameliorated by increased mucociliary clearance and mucosal hydration, wherein the disease is one or more conditions selected from the group consisting of chronic bronchitis, bronchiectasis, pulmonary fibrosis, cystic fibrosis, asthma, sinusitis, vaginal dryness, dry eye, Sjogren's disease, distal intestinal obstruction syndrome, esophagitis, dry mouth (xerostomia), asthma, primary ciliary dyskinesia, otitis media, chronic obstructive pulmonary disease, emphysema, pneumonia, diverticulitis, rhinosinusitis, and airborne infections.

13. The compound of claim 1 and an osmolyte for use according to claim 8, wherein the disease is one or more conditions selected from the group consisting of chronic bronchitis, bronchiectasis, pulmonary fibrosis, cystic fibrosis, asthma, sinusitis, vaginal dryness, dry eye, Sjogren's disease, distal intestinal obstruction syndrome, esophagitis, dry mouth (xerostomia), asthma, primary ciliary dyskinesia, otitis media, chronic obstructive pulmonary disease, emphysema, pneumonia, diverticulitis, rhinosinusitis, and airborne infections.

14. The compound of claim 1 and an osmolyte for use according to claim 8, or the use of claim 12, wherein the compound is to be administered preceding administration of the osmolyte.

15. The compound of claim 1 and an osmolyte for use according to claim 8, or the use of claim 12, wherein the compound is to be administered concurrent with administration of the osmolyte.

16. The compound of claim 1 and an osmolyte for use according to claim 8, or the use of claim 12, wherein the compound is to be administered following administration of the osmolyte.

17. The compound of claim 1 and an osmolyte for use according to claim 8, or the use of claim 12, wherein the osmolyte is hypertonic saline or mannitol.

18. The compound of claim 1 and an osmolyte for use according to claim 8, or the use of claim 12, wherein the osmolyte is sodium chloride which is delivered as a micronized particle of respirable size.

19. The compound of claim 1 and an osmolyte for use according to claim 8, or the use of claim 12, wherein the osmolyte and a compound of formula (Ia)-(Id) is to be administered by aerosolization using a device capable of delivering the formulation to the nasal passages or pulmonary airway wherein the aerosol is a respirable size.

20. A composition, comprising:
(a) the compound of claim 1 and (b) an osmotically active compound.

21. A non-therapeutic use of the compound of claim 1 and an osmolyte to induce sputum in a subject in need of increased mucociliary clearance and mucosal hydration.

22. The compound of claim 1 and an osmolyte for use in therapy.

23. The compound of claim 1 for use in the prophylactic, post-exposure prophylactic, preventive or therapeutic treatment against diseases or conditions caused by a pathogen, in a subject in need of increased mucociliary clearance and mucosal hydration.

24. The compound of claim 23, wherein the pathogen is anthrax or plague.

25. Use of the compound of claim 1 in the manufacture of a medicament for the prophylactic, post-exposure prophylactic, preventive or therapeutic treatment against diseases or conditions caused by a pathogen, in a subject in need of increased mucociliary clearance and mucosal hydration, wherein the pathogen is anthrax or plague.

26. The compound of claim 1, or a pharmaceutically acceptable salt thereof, for use in the prevention, mitigation, and/or treatment of deterministic health effects to the respiratory tract and/or other bodily organs caused by respirable aerosols containing radionuclides in a human in need thereof.

27. Use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention, mitigation, and/or treatment of deterministic health effects to the respiratory tract and/or other bodily organs caused by respirable aerosols containing radionuclides in a human in need thereof.

28. A pharmaceutical composition, comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

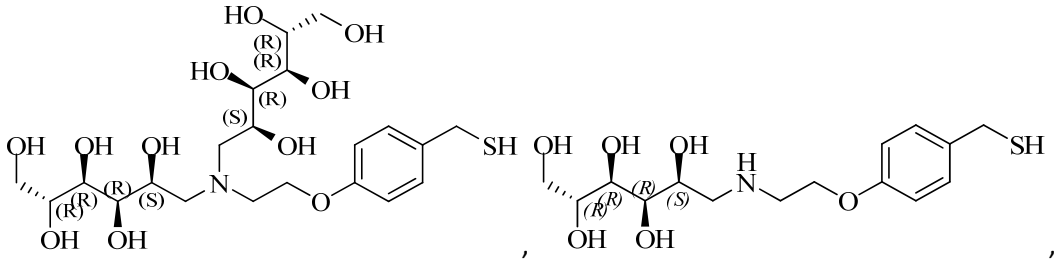
29. The compound of claim 1 and a second therapeutic agent for use in improving mucus penetration of therapeutic agents.

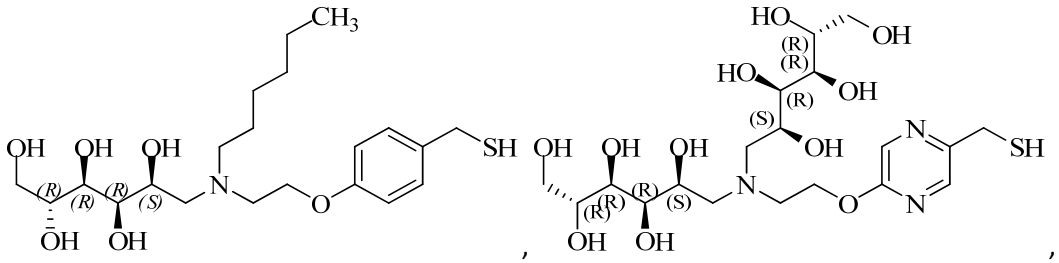
30. The compound of claim 1 and a second therapeutic agent for use according to claim 29, wherein the therapeutic agents is an osmolyte, a sodium channel blocker, a secretogogue, a bronchodilator, an anti-infective, an anti-inflammatory, or a gene carrier.

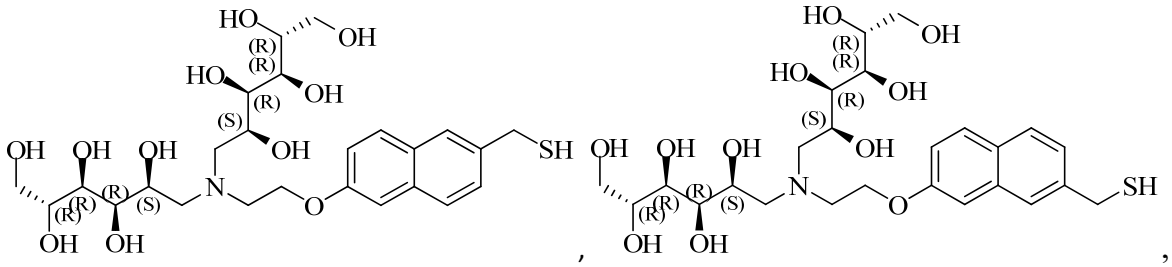
31. A non-therapeutic use of the compound of claim 1 to decrease mucosal oxygen free radicals.

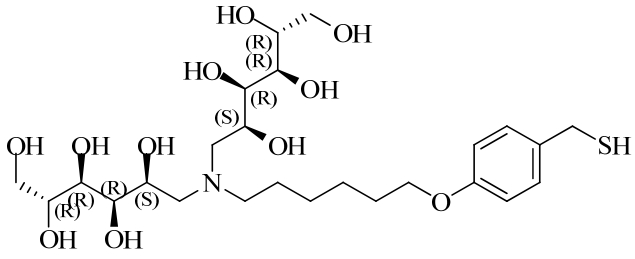
32. The compound of claim 1 for use in decreasing mucosal oxygen free radicals.

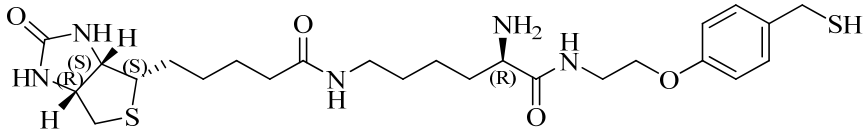
33. The compound of claim 1, which is represented by the formula:

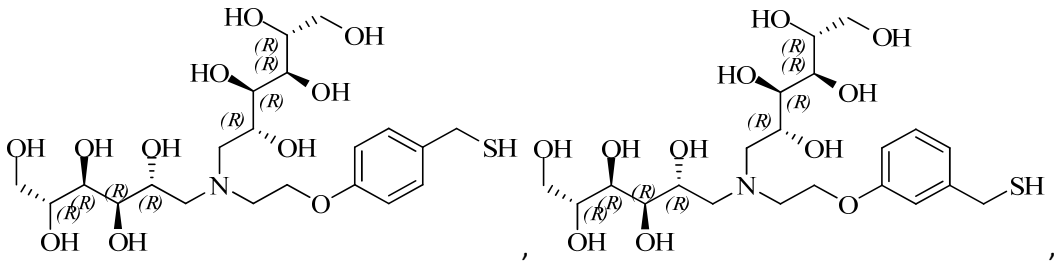


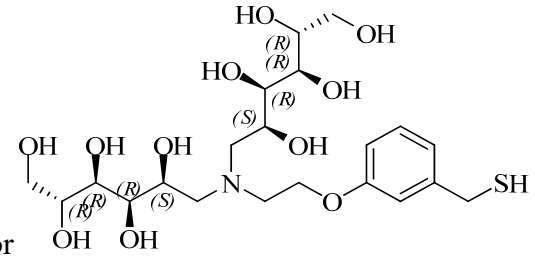










or 

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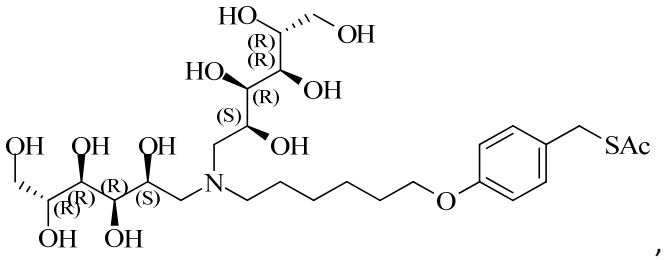
34. The compound of claim 1, which is an acid addition salt of an inorganic acid or an organic acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, furmaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalensulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, and lactic acid.

35. A prodrug compound represented by the formula:



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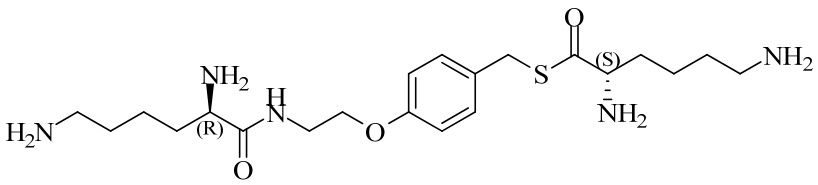

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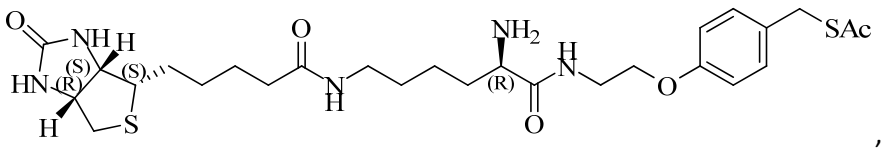

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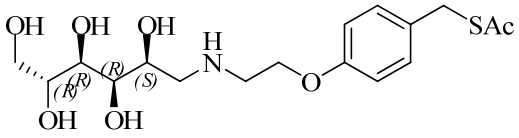
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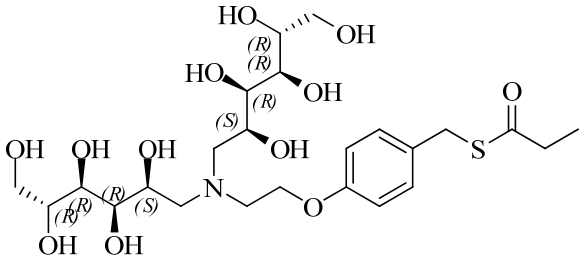
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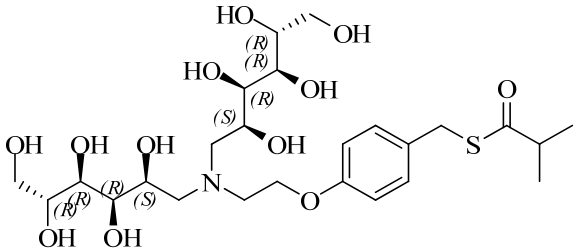
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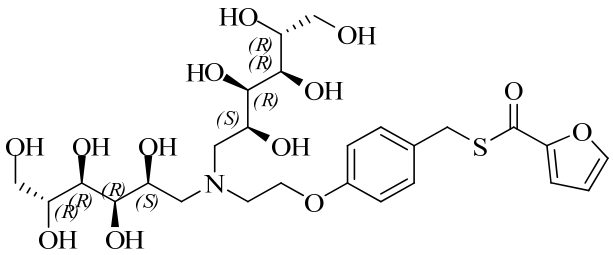
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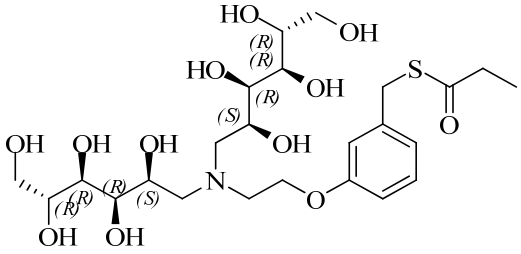
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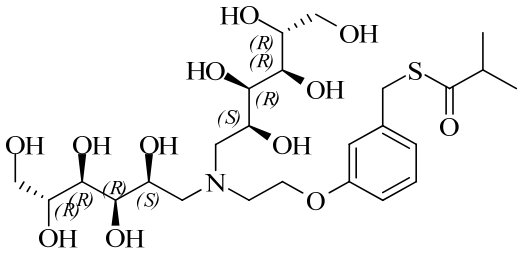
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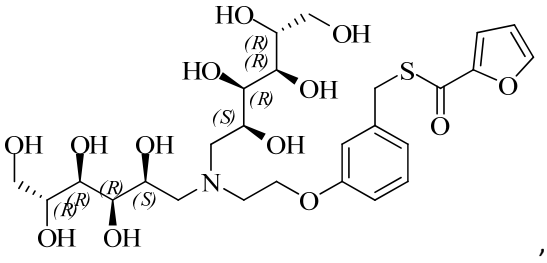
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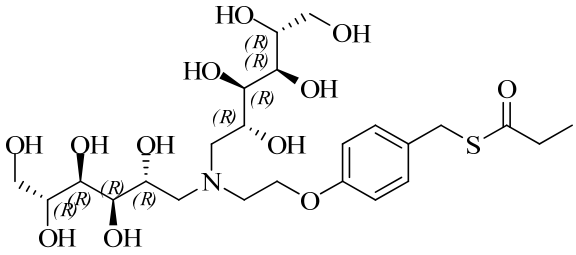

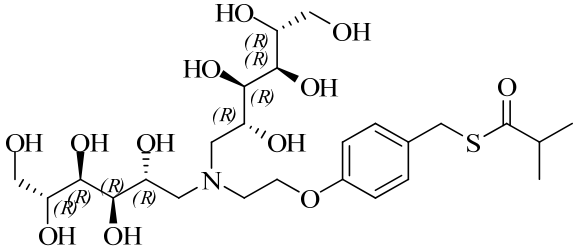

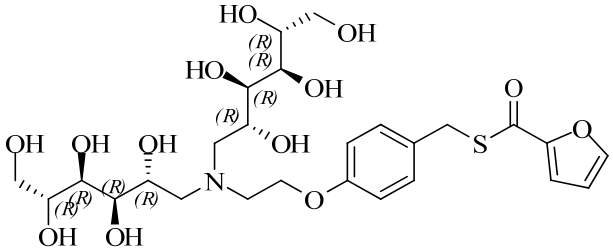
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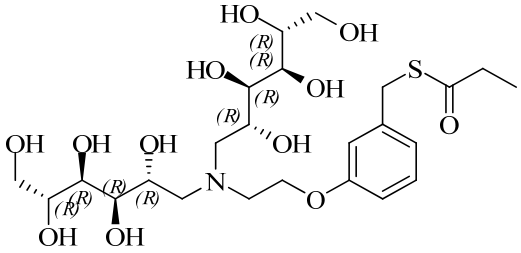
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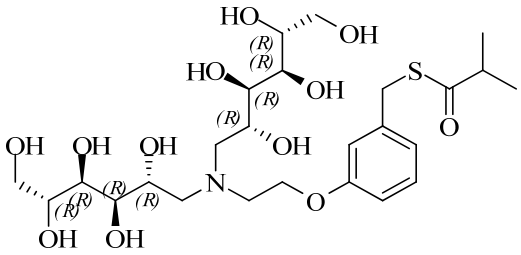
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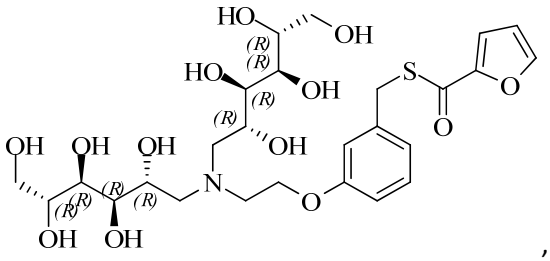
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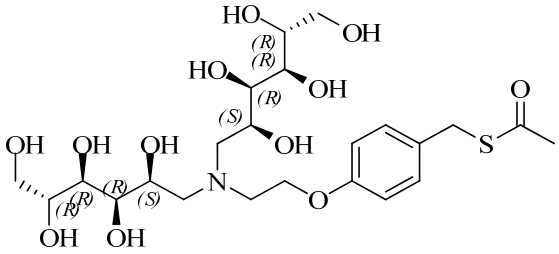
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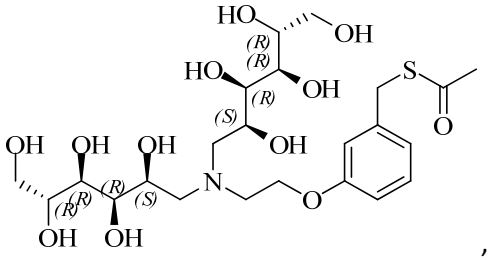
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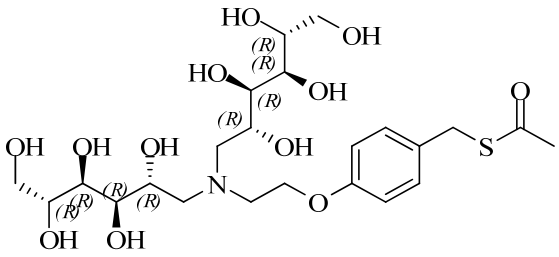

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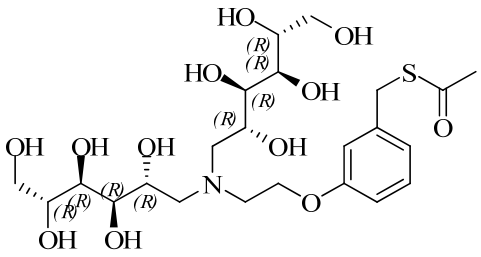

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