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

wherein:

X is halogen, or trifluoromethyl;

Y is $-N(R^2)_2$;

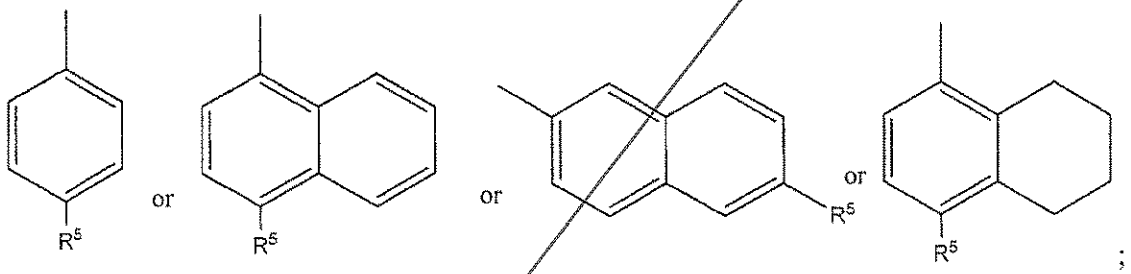
R^1 is hydrogen;

each R^2 is $-R^7$;

R^3 and R^4 are each, independently, hydrogen, or a group represented by formula A, with the proviso that at least one of R^3 and R^4 is a group represented by the formula A;

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

A^1 is



;

each R^L is, independently, $-R^7$;

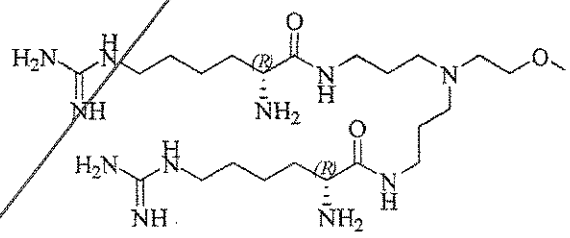
each o is, independently, an integer from 0 to 10;

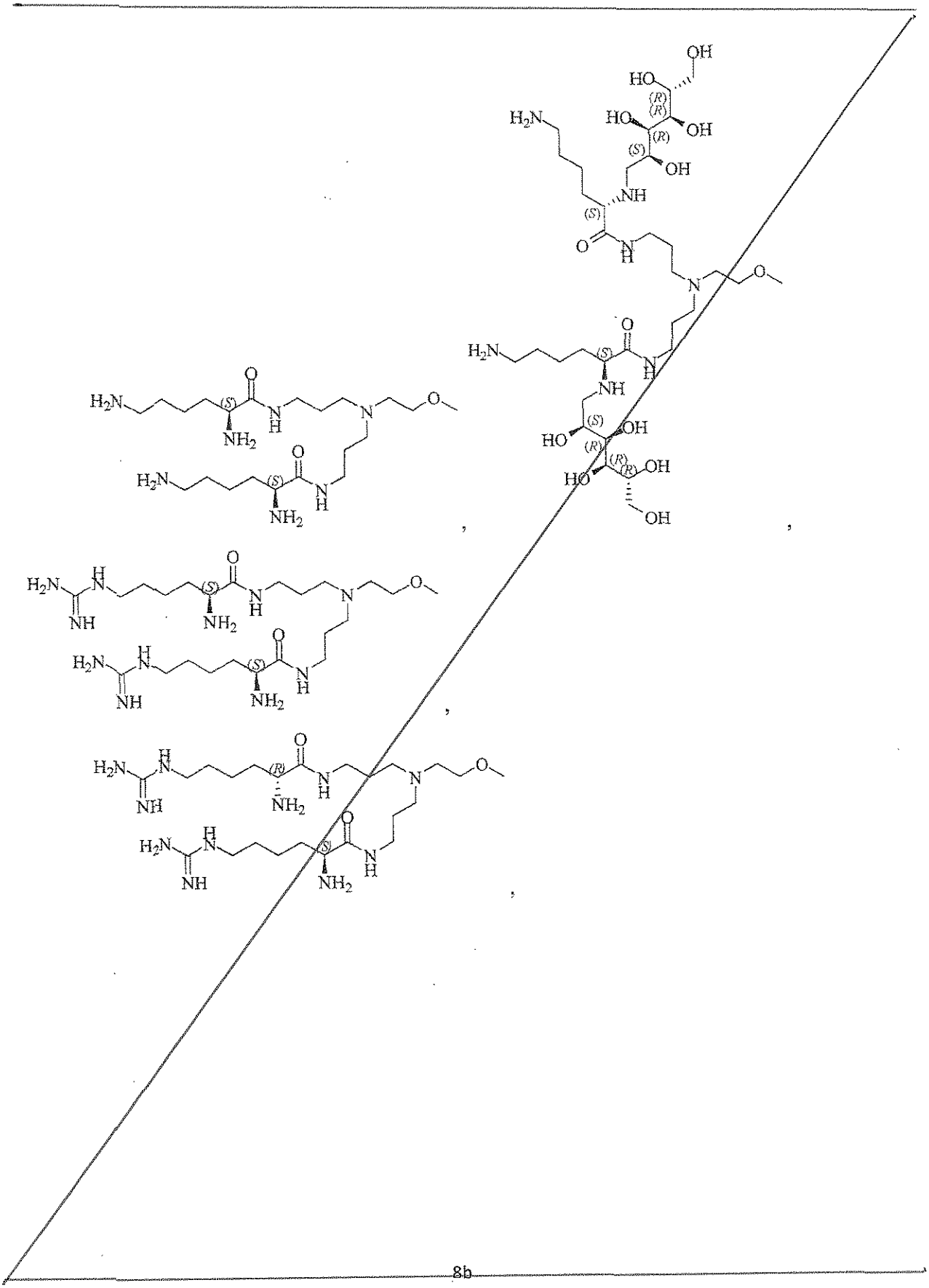
each p is, independently, an integer from 0 to 10;

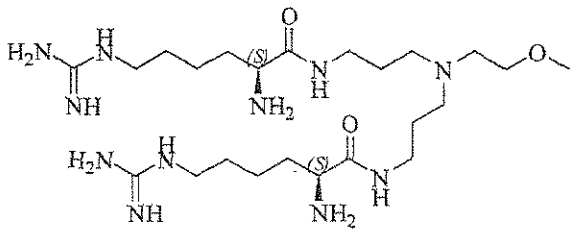
with the proviso that the sum of o and p in each contiguous chain is from 1 to 10;

each x is, independently, a single bond;

each R^5 is, independently, represented by one of the following formulas:







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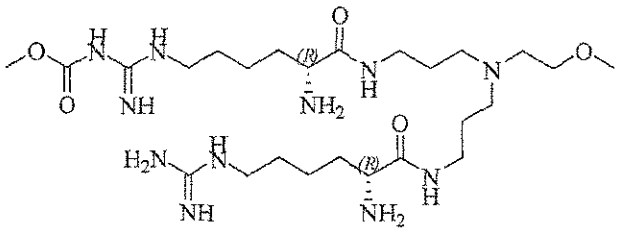

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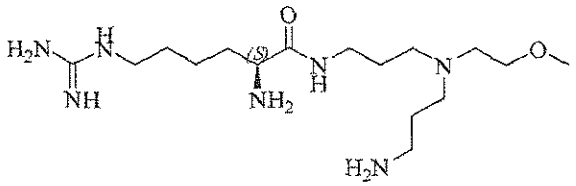

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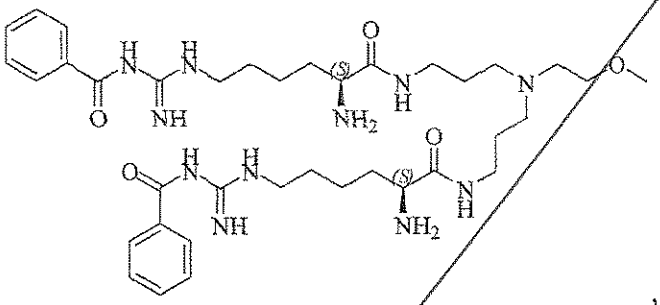

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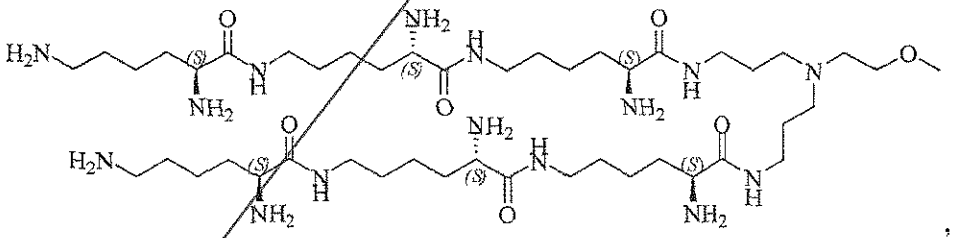

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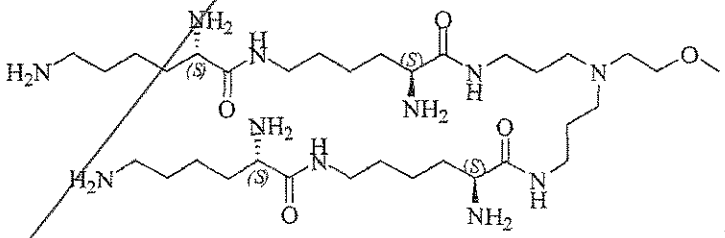

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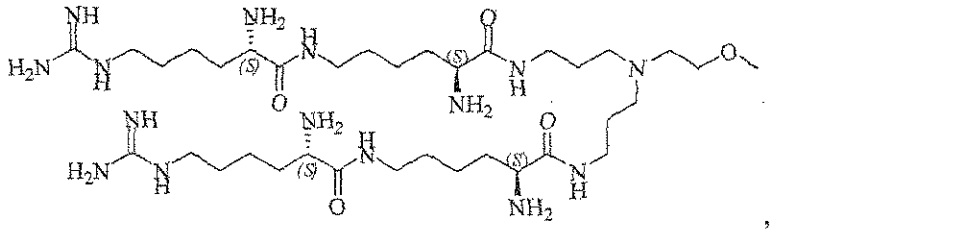

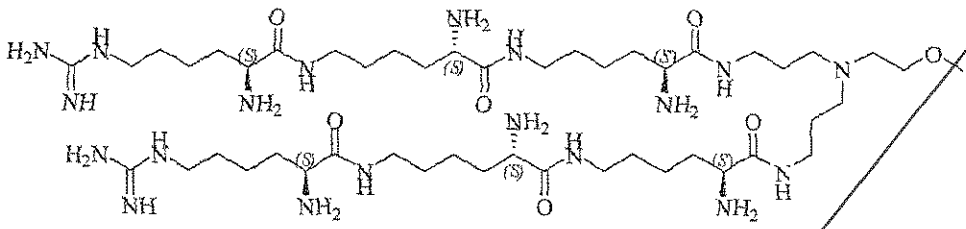

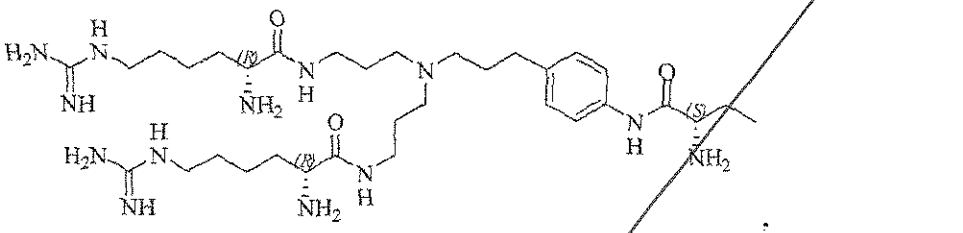

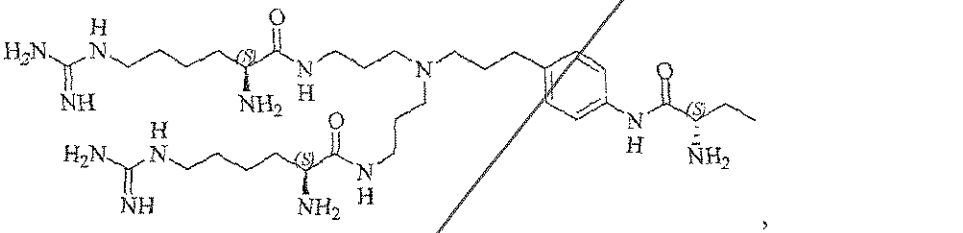

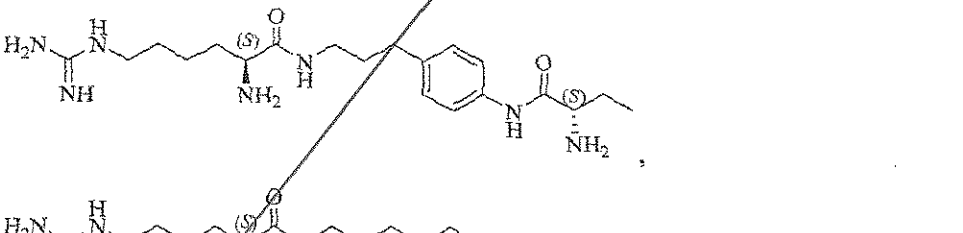

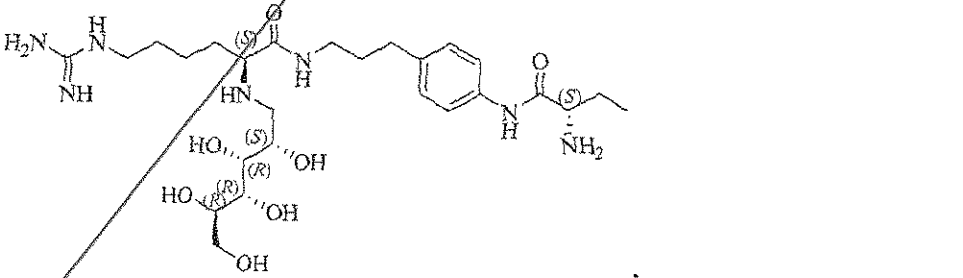

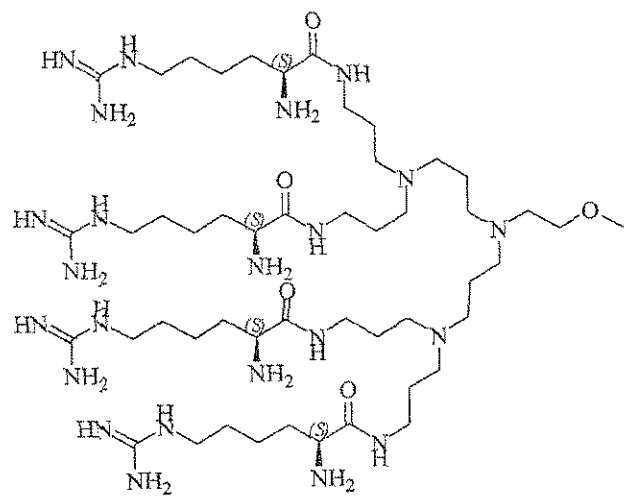

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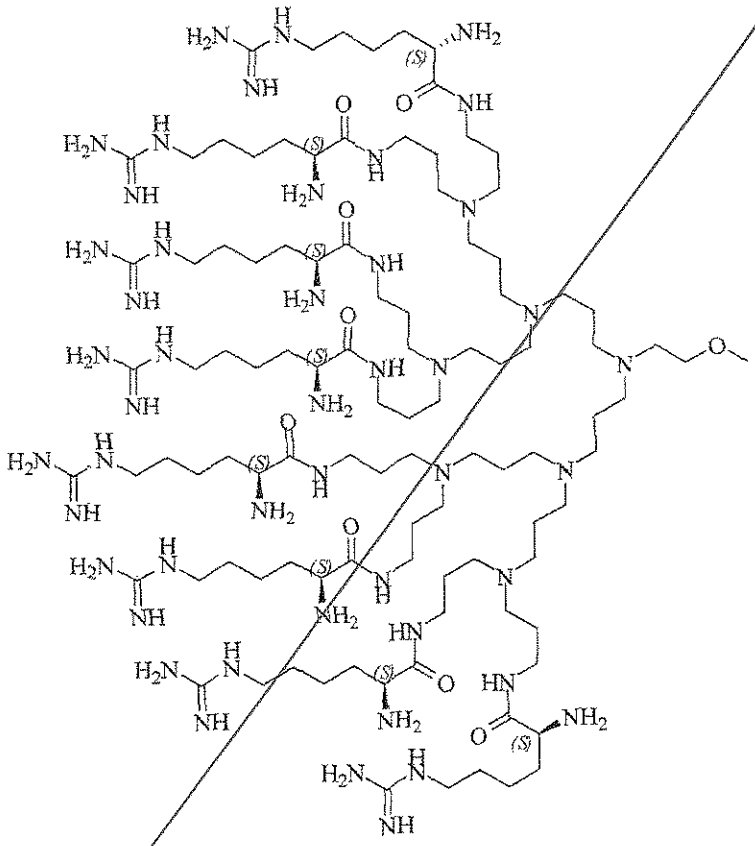

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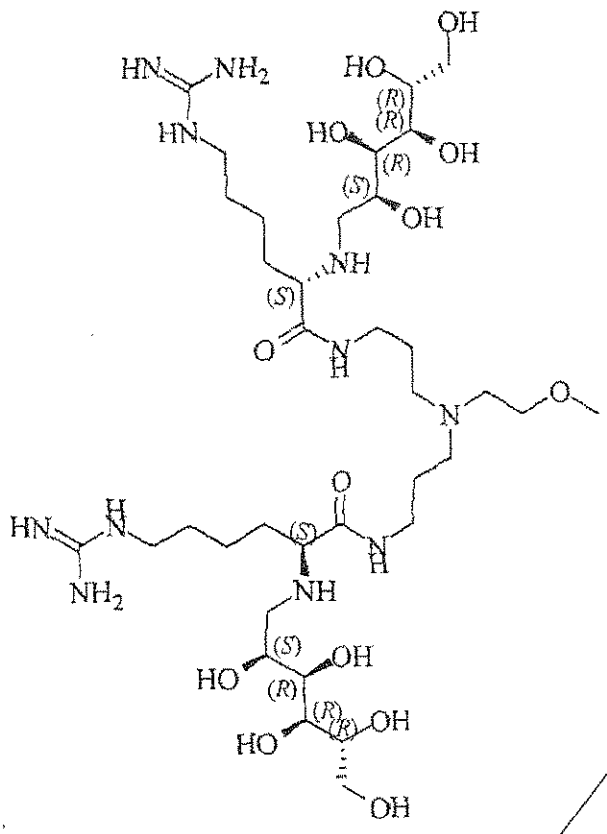

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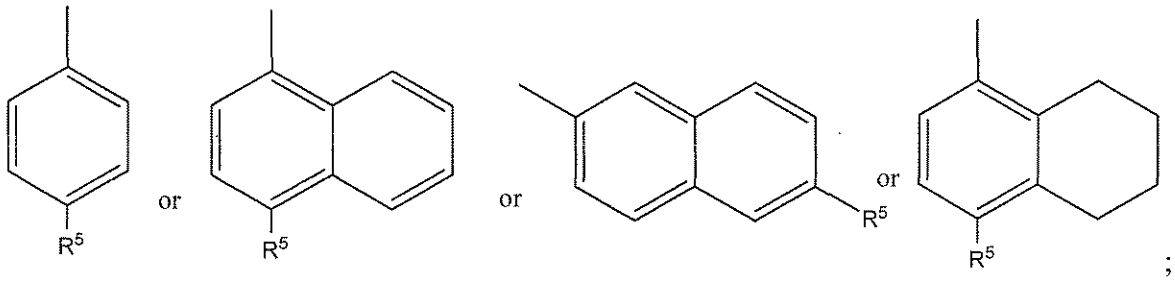

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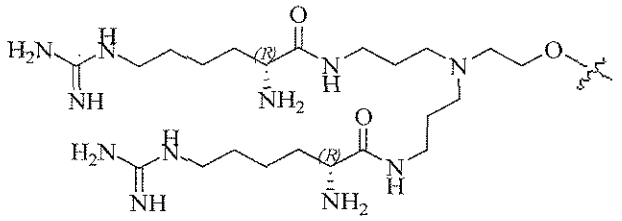

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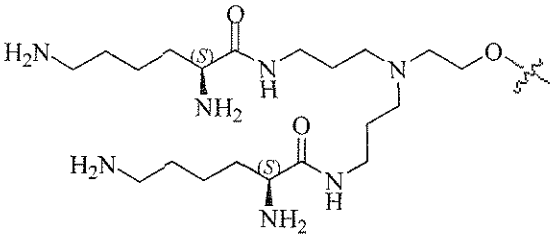

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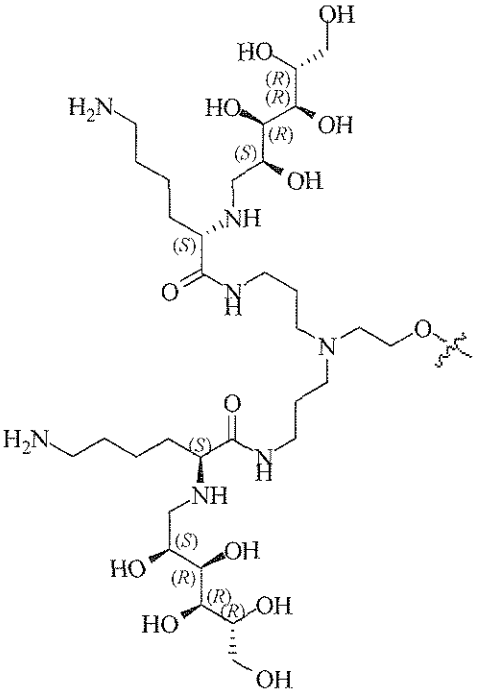

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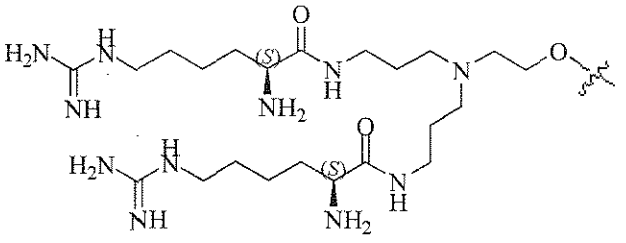

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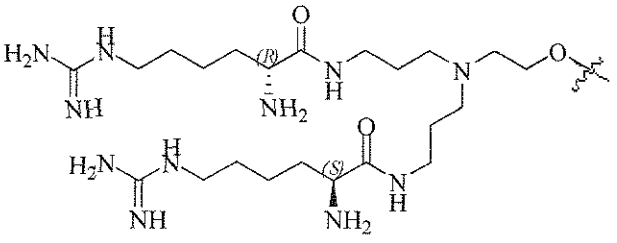

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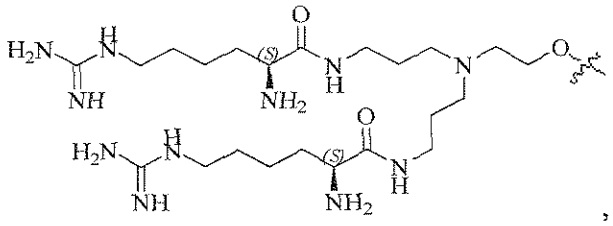

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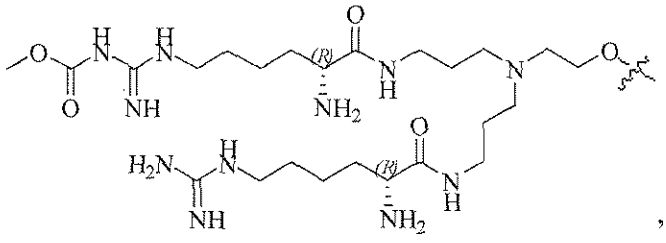

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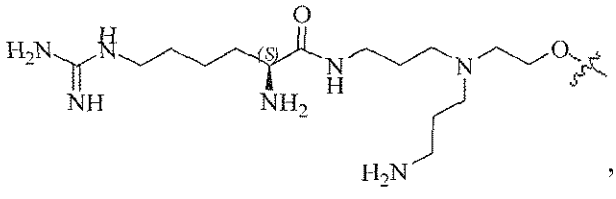

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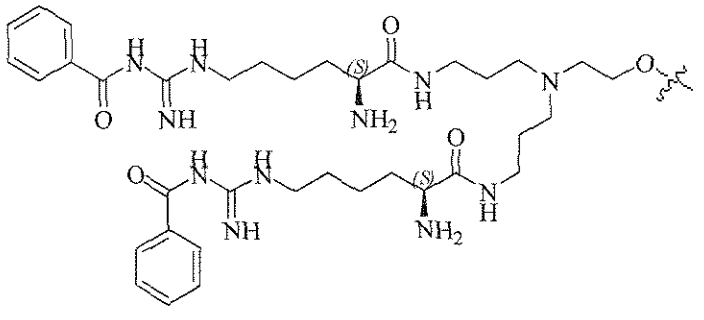

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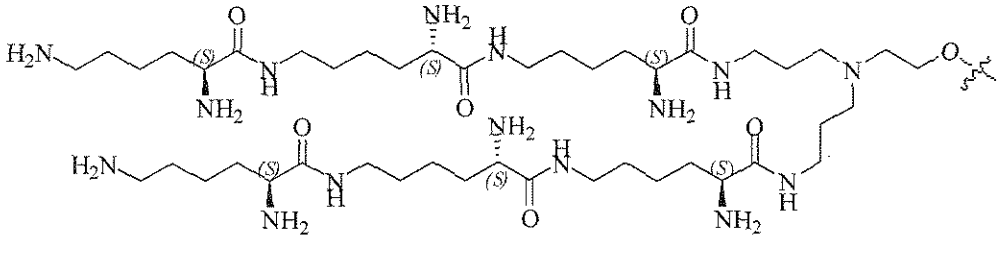

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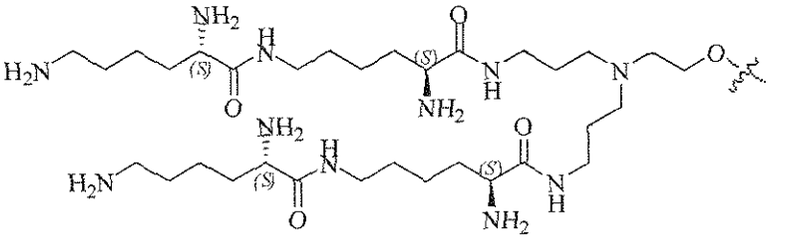

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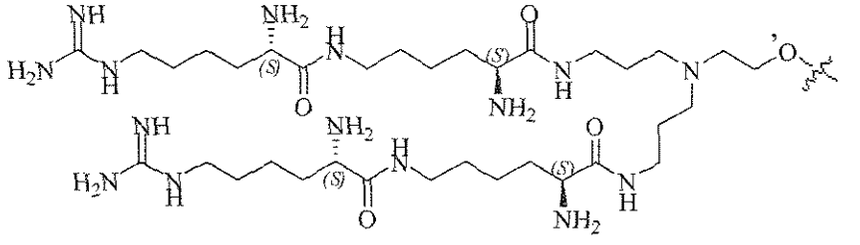

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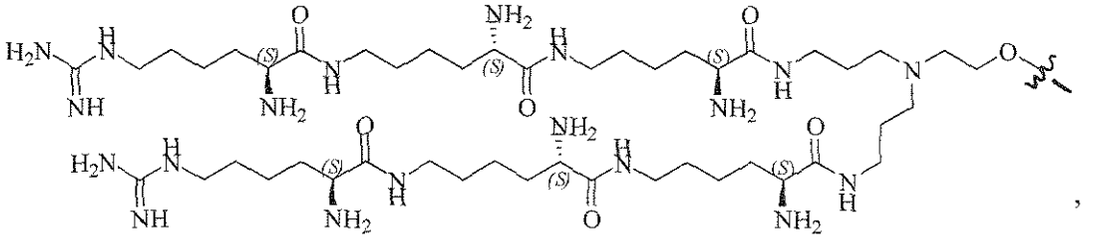

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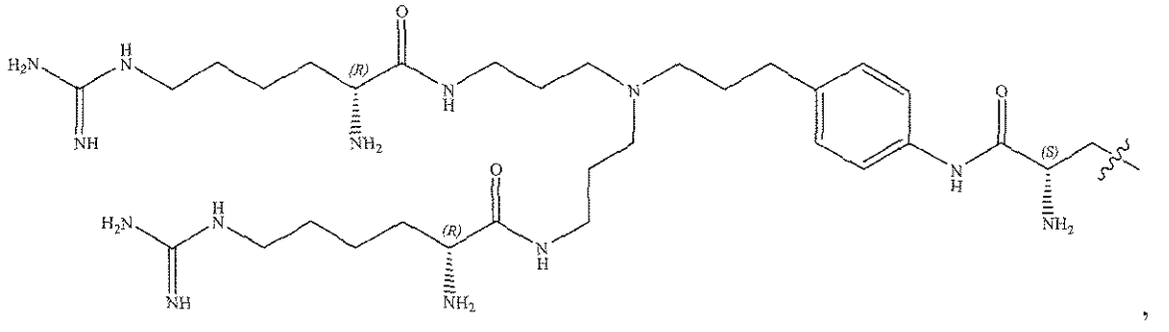

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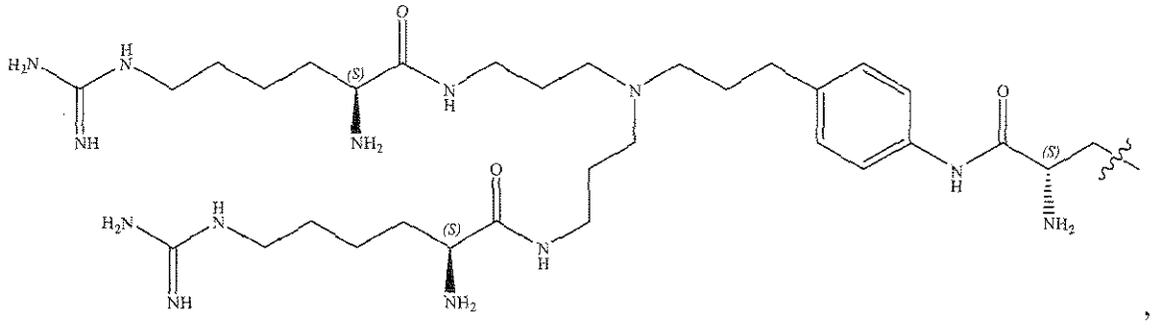

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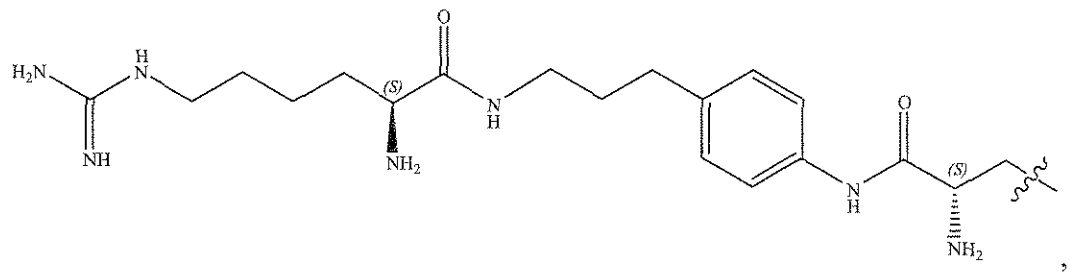

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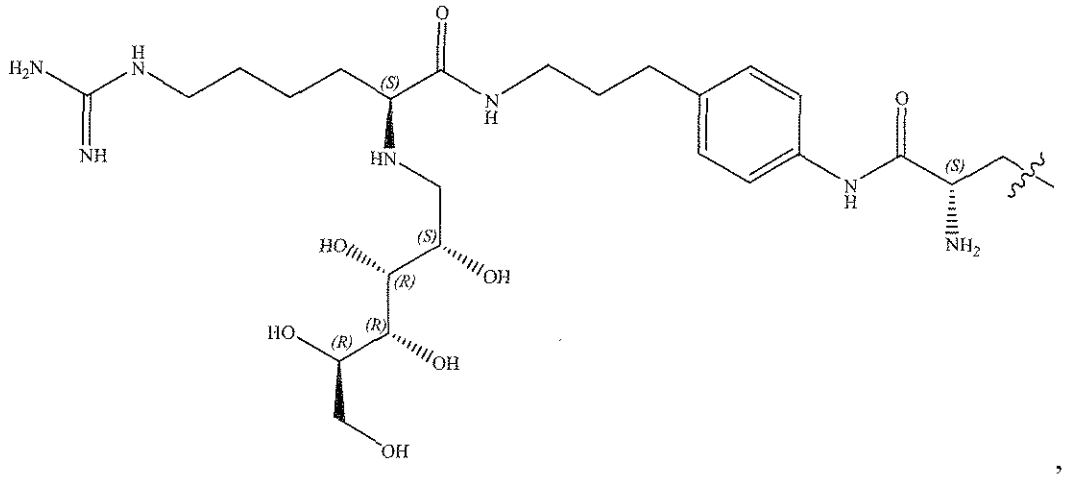

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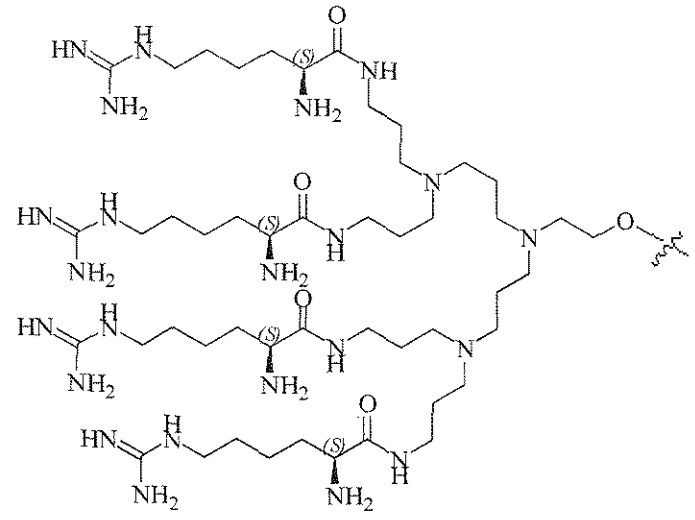

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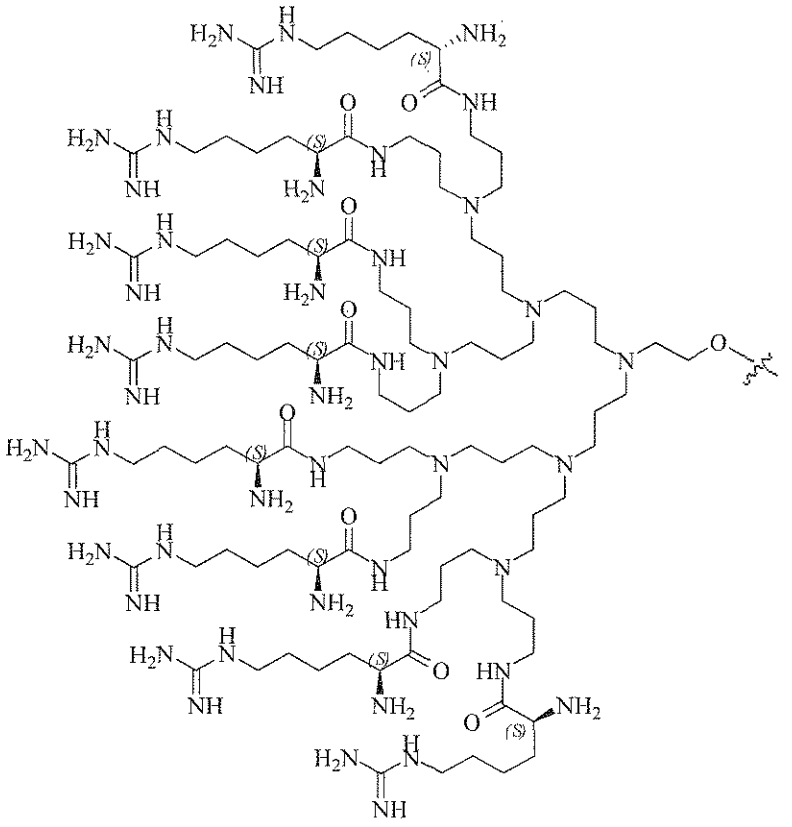

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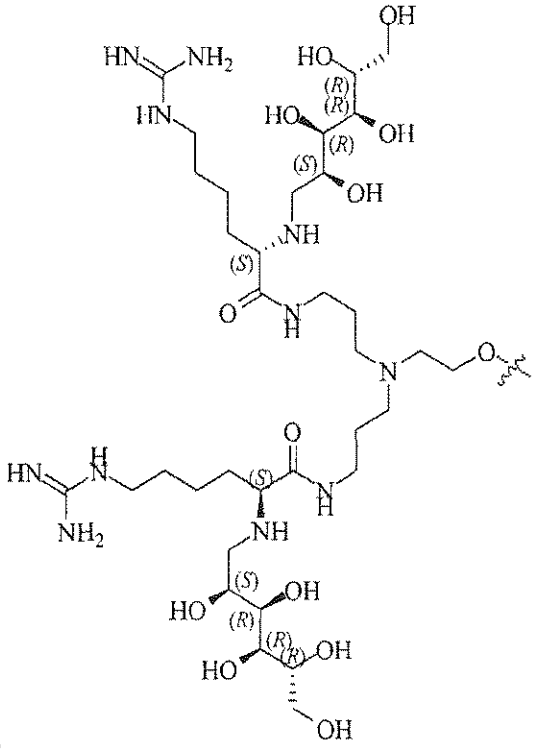


;

each R^7 is, independently, hydrogen.

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 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 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~~Disclosed is 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 also provides a method of blocking ENaC, comprising:

The present disclosure 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 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 embodiment of the present disclosure 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 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 to provide compositions which contain sodium channel blockers of formula (I) and osmolytes.

~~In one aspect, there is provided~~Disclosed is 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 may be accomplished with a method of treating a disease ameliorated by increased mucociliary clearance and mucosal hydration comprising

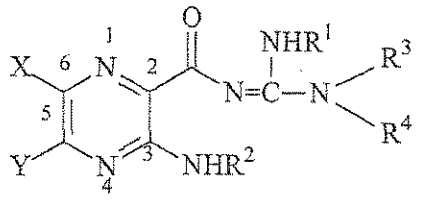
administering an effective amount of a compound of formula (I) as defined herein and an osmolyte to a subject to a subject in need of increased mucociliary clearance and mucosal hydration.

The objects of the disclosure 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.

~~What is claimed is:~~

1. A compound represented by formula (I):



(I)

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

wherein:

X is halogen, or trifluoromethyl;

Y is $-N(R^2)_2$;

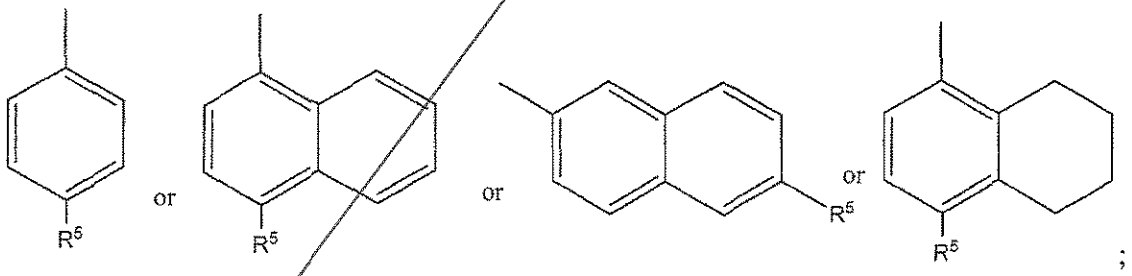
R^1 is hydrogen;

each R^2 is $-R^7$;

R^3 and R^4 are each, independently, hydrogen, or a group represented by formula A, with the proviso that at least one of R^3 and R^4 is a group represented by the formula A;

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

A^1 is



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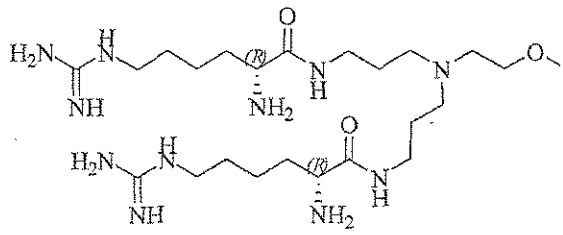

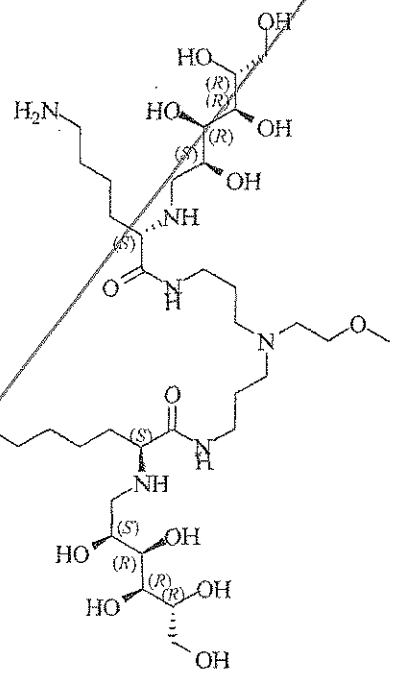

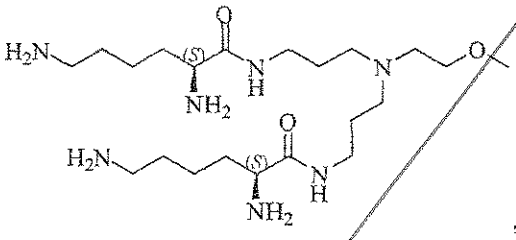

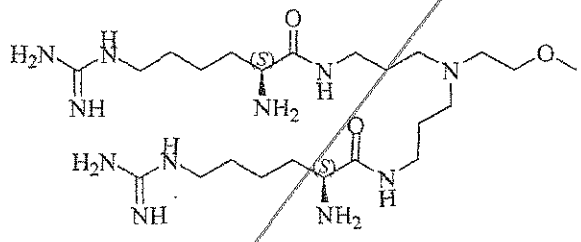

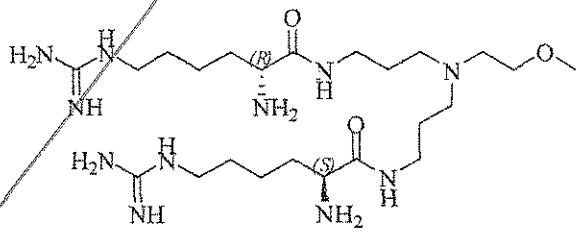

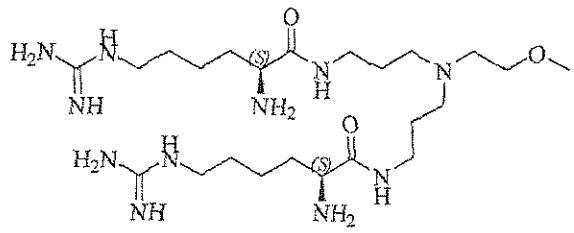

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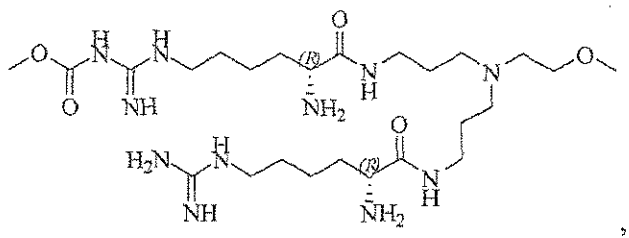

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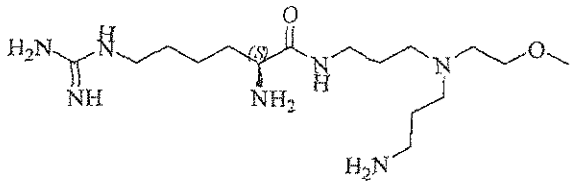

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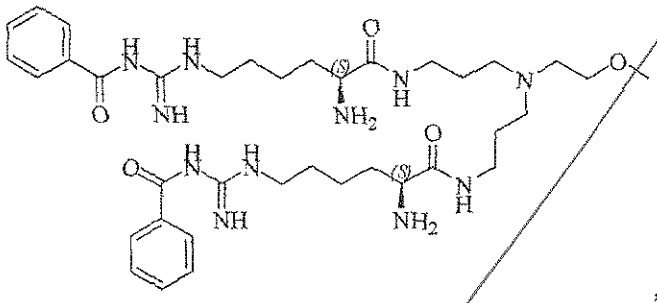

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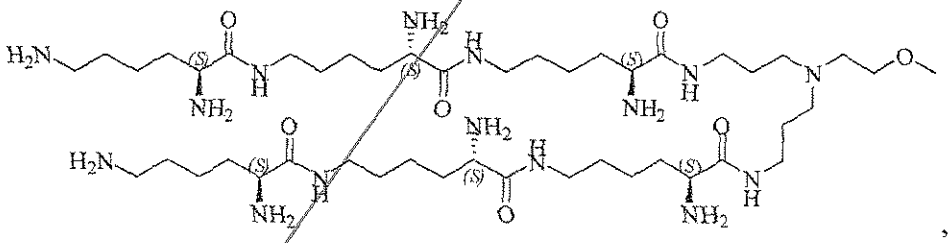

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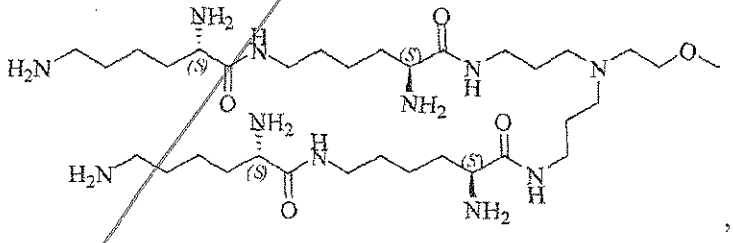

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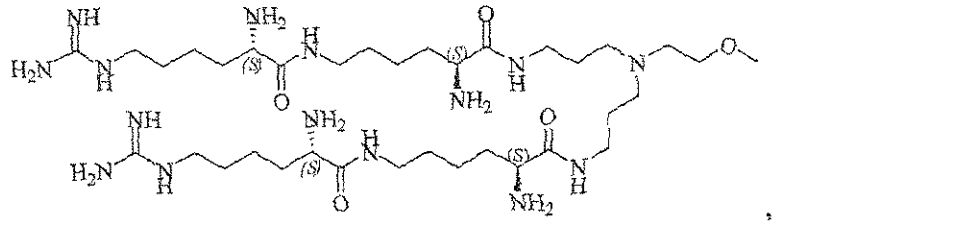

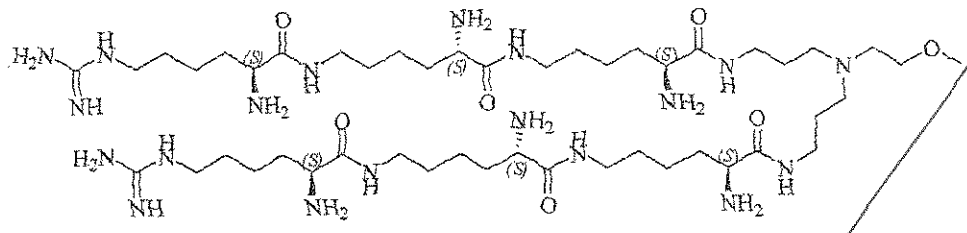

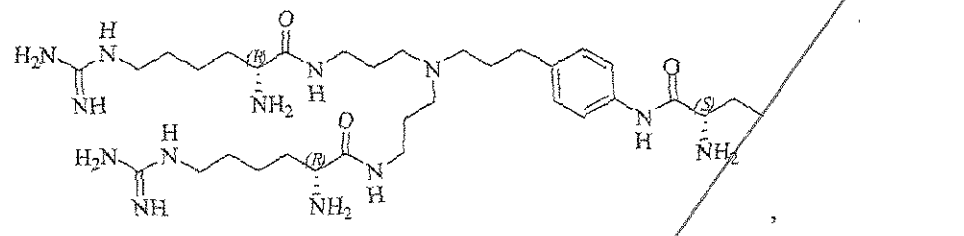

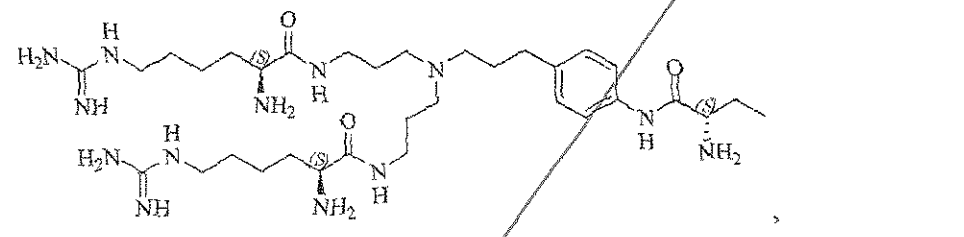

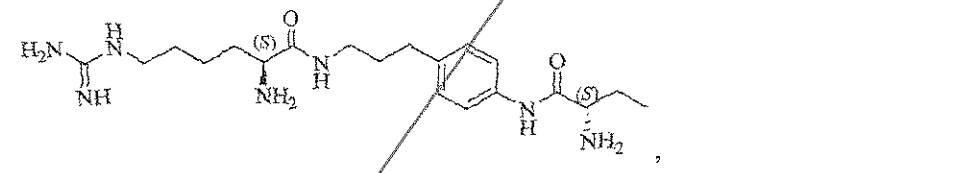

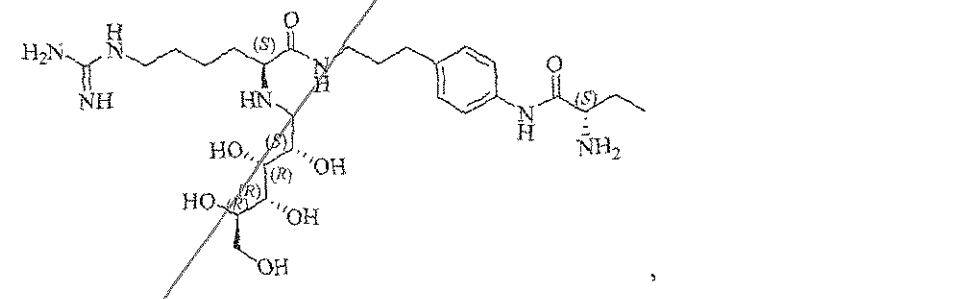

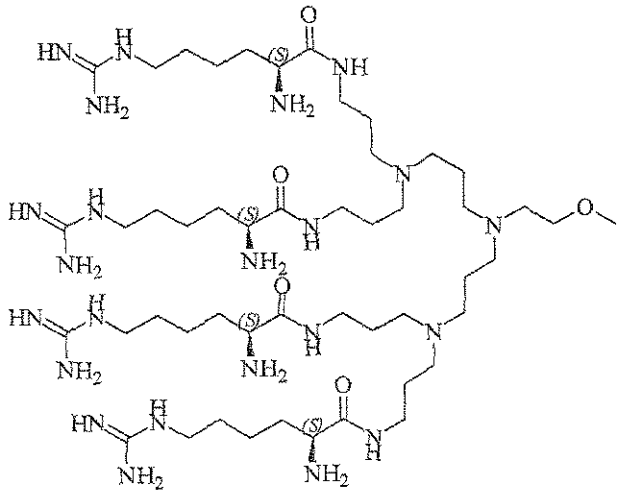

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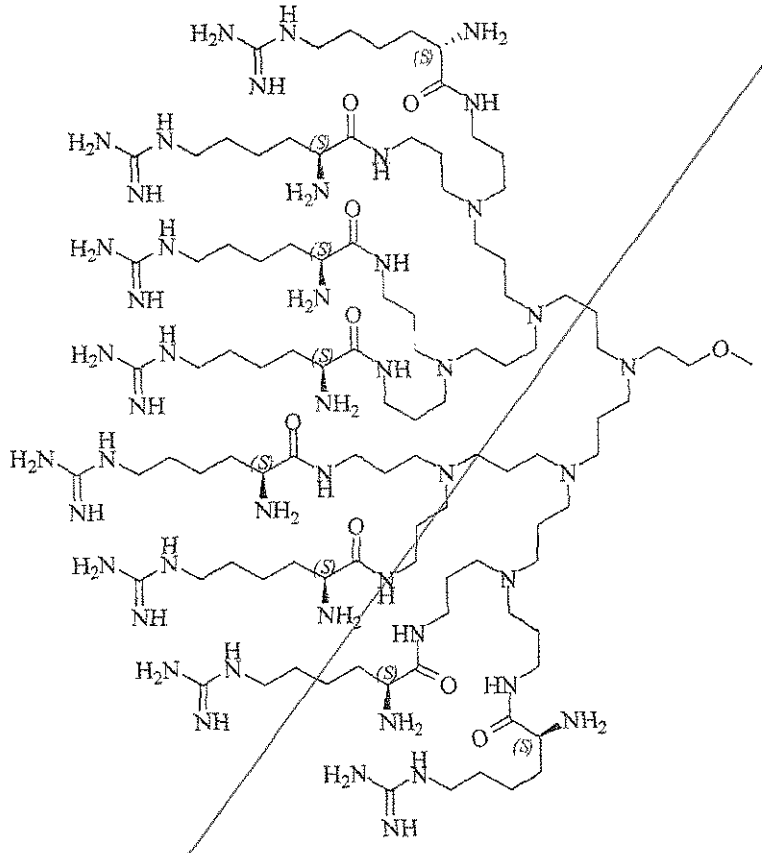

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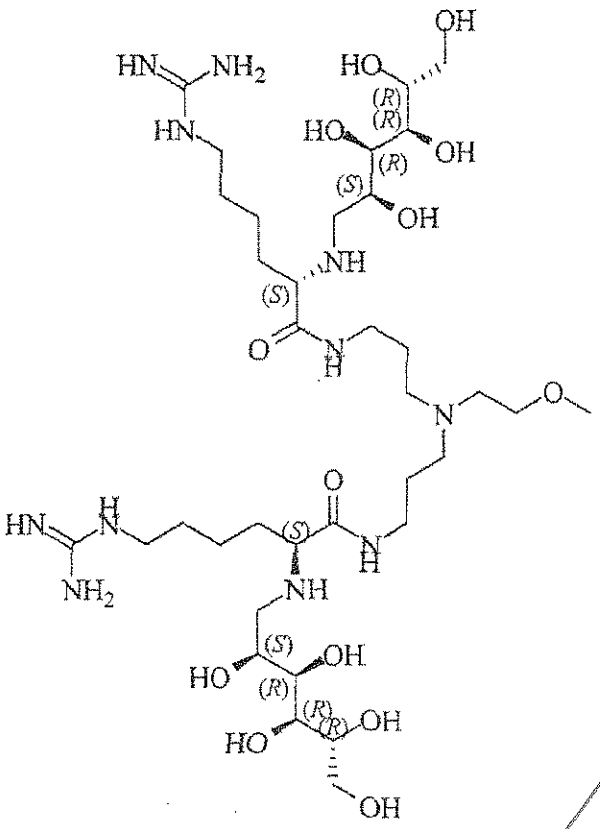
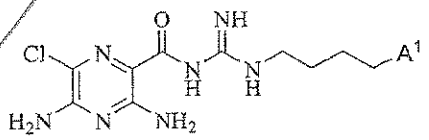


;

each R^7 is, independently, hydrogen.

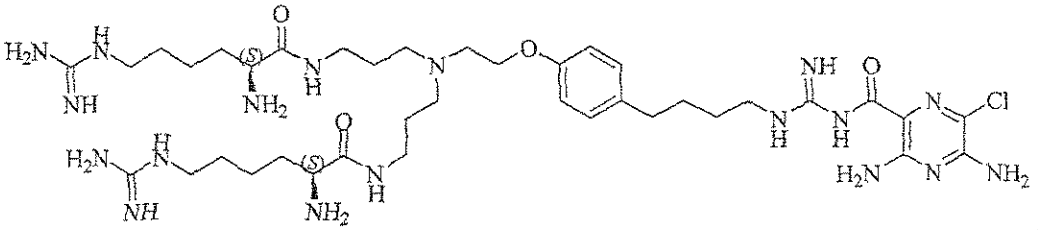
2. The compound according to claim 1, which is represented by formula II:

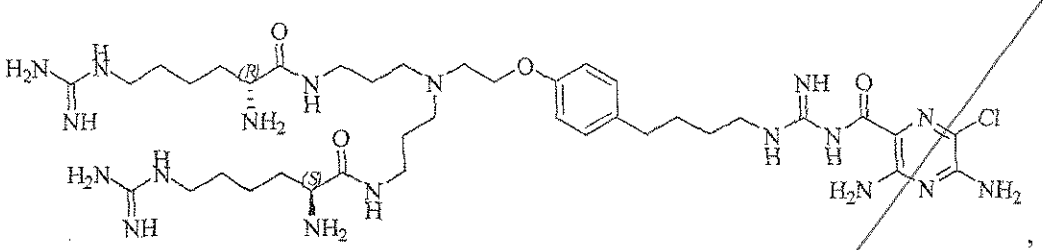


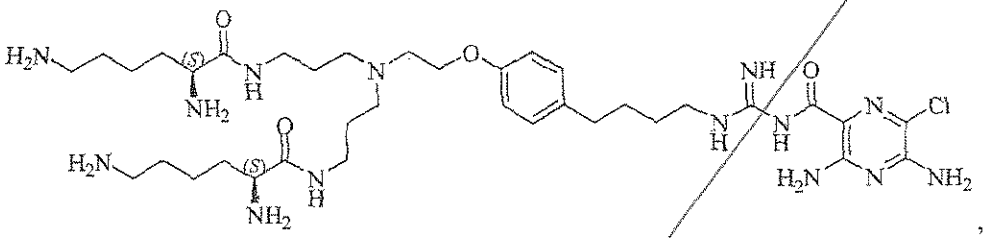
formula II

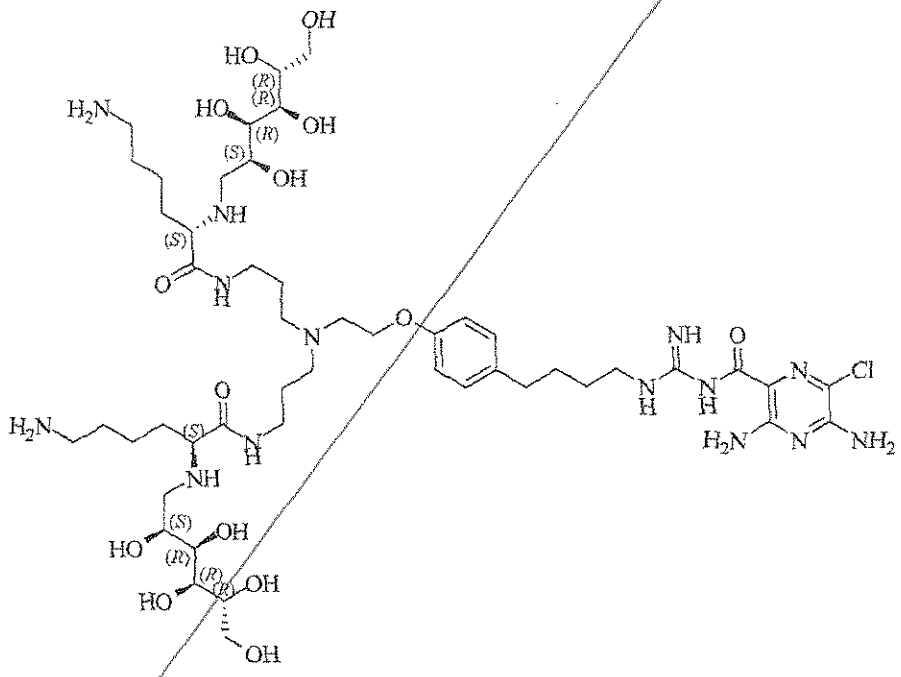
and racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and pharmaceutically acceptable salts, thereof.

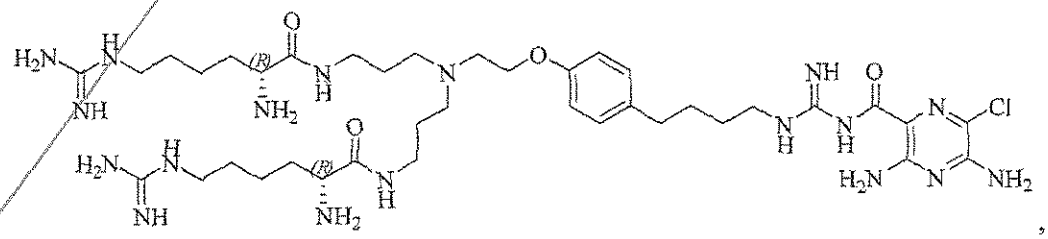
3. A compound represented by one of the following formulas:

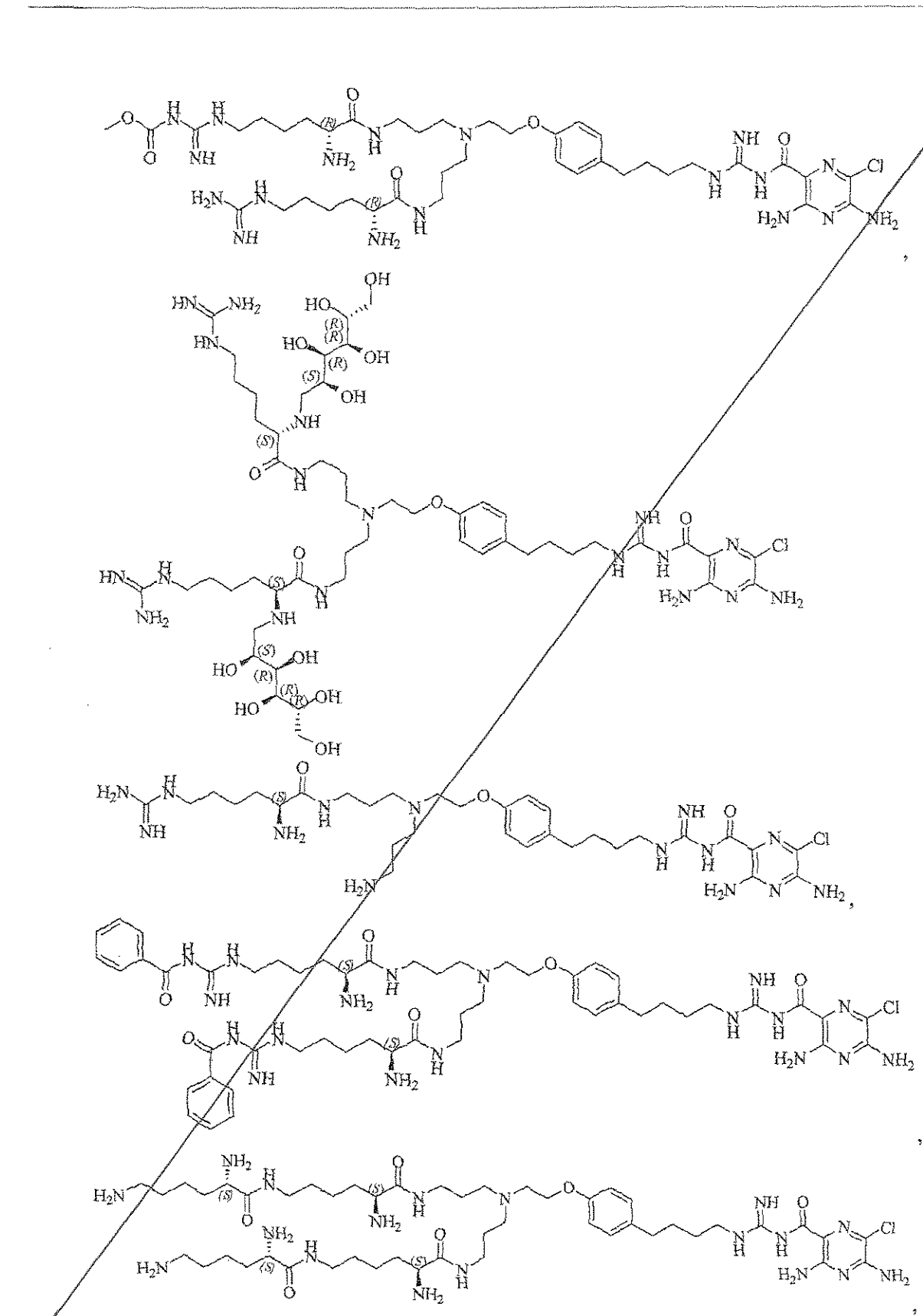


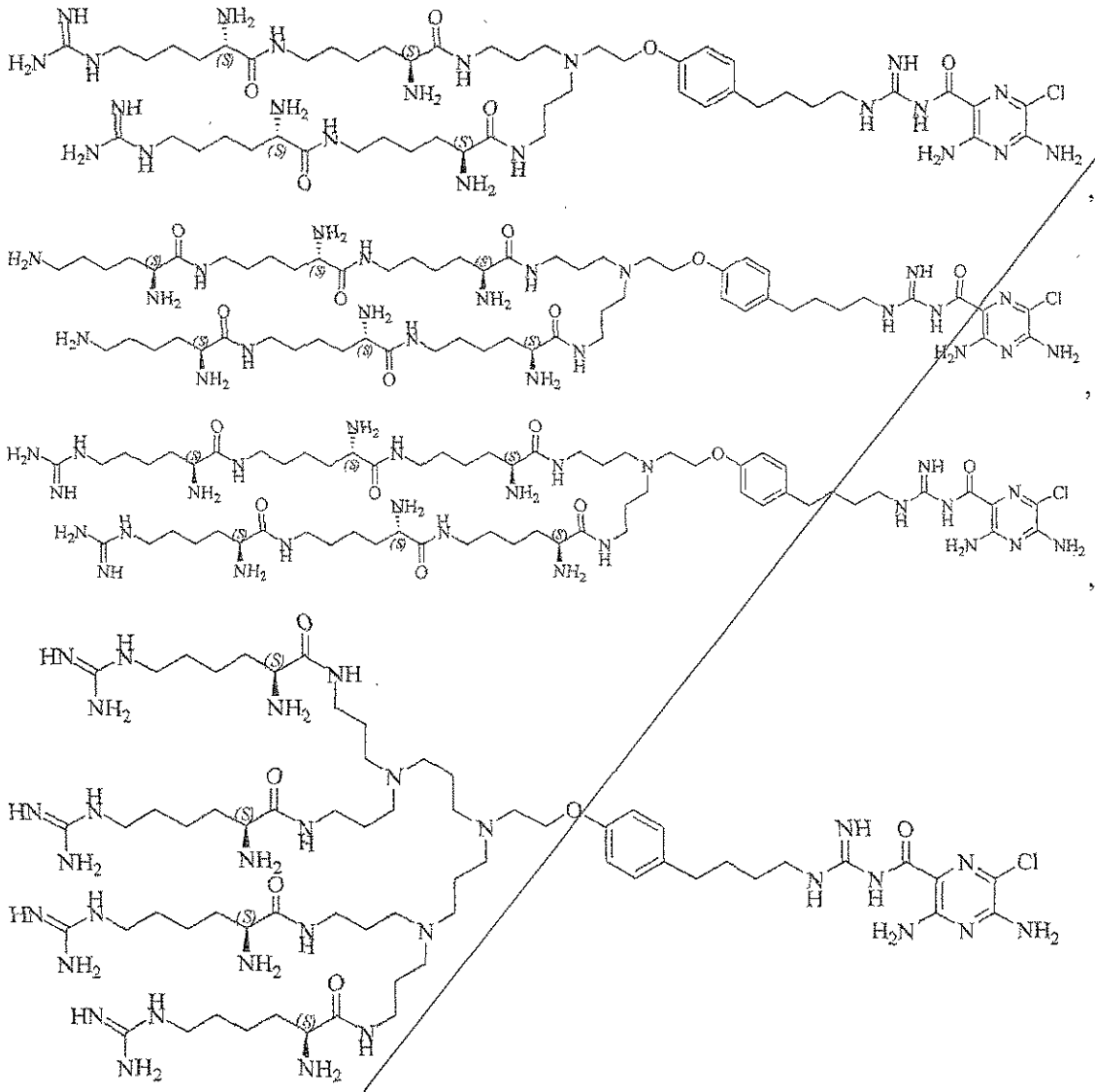


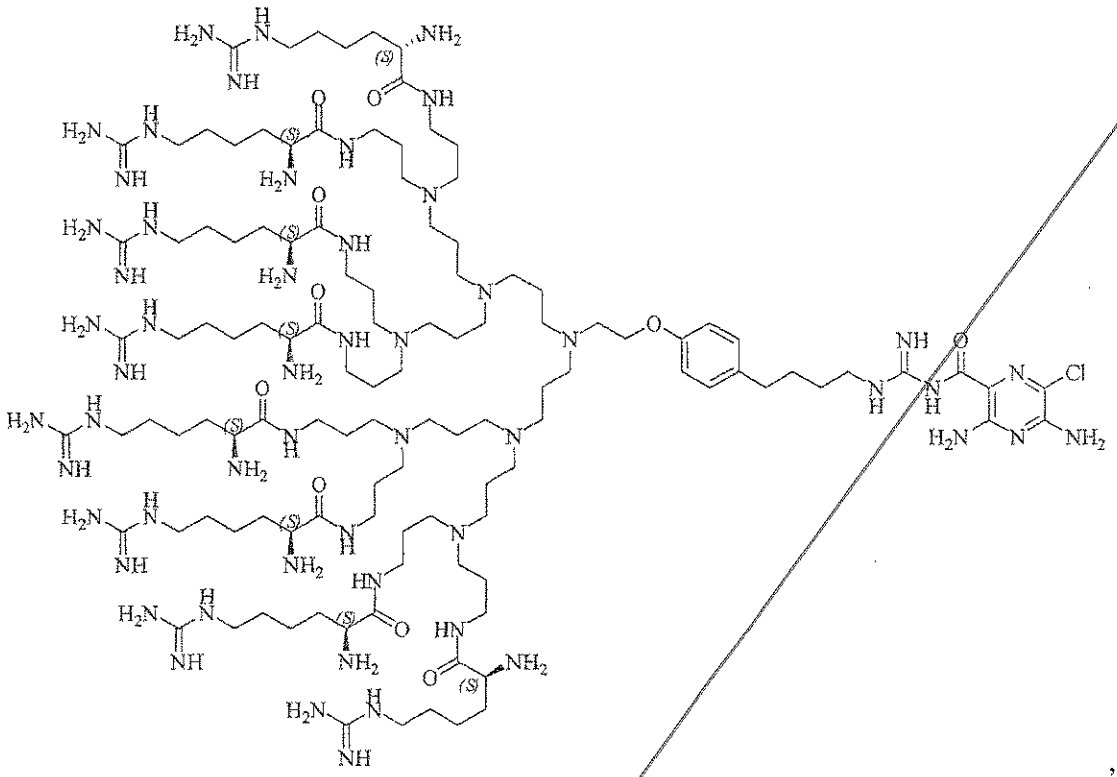












or a pharmaceutically active salt thereof.

4. 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.

5. The pharmaceutical composition according to claim 4, 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.

6. The composition according to claim 4, wherein said composition is a solution for administration by eye drops.

7. 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.

8. 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.

9. Use of an effective amount of the compound according to claim 1 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.

10. Use of an effective amount of the compound according to claim 1 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 .

11. The use according to claim 9, 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.

12. A composition, comprising:

(a) a compound or a pharmaceutically acceptable salt thereof according to claim 1 and (b) an osmolotically active compound.

13. The composition according to claim 4, 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.

14. Use of an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament.

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

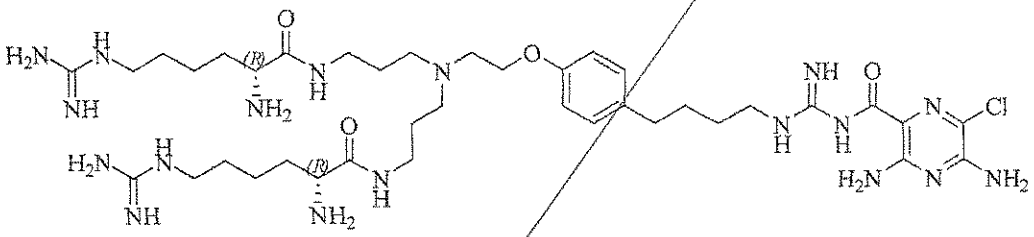
16. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, for use in treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration, treating chronic bronchitis, treating 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 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.

17. A composition comprising a compound according to claim 1, 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.

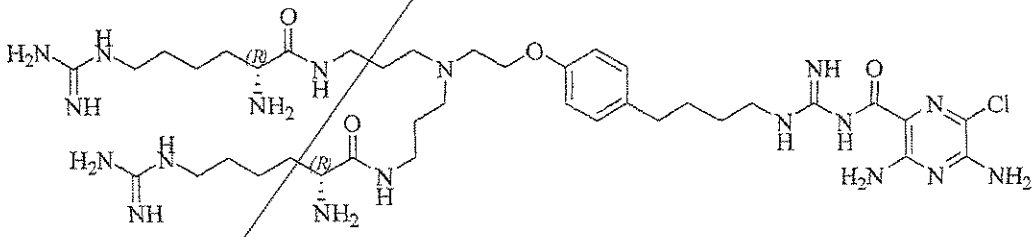
18. Use of an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing, mitigating, and/or treating deterministic health effects to the respiratory tract and/or other bodily organs caused by respirable aerosols containing radionuclides in a human in need thereof.

19. The use according to claim 7, wherein the compound is:



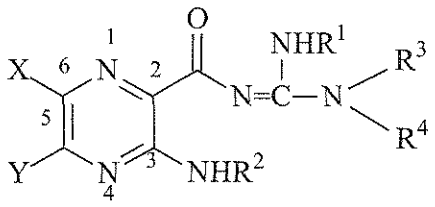
or a pharmaceutically acceptable salt thereof.

20. The hydrochloride salt of:



What is claimed is:

1. A compound represented by formula (I):



(I)

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

wherein:

X is halogen, or trifluoromethyl;

Y is $-N(R^2)_2$;

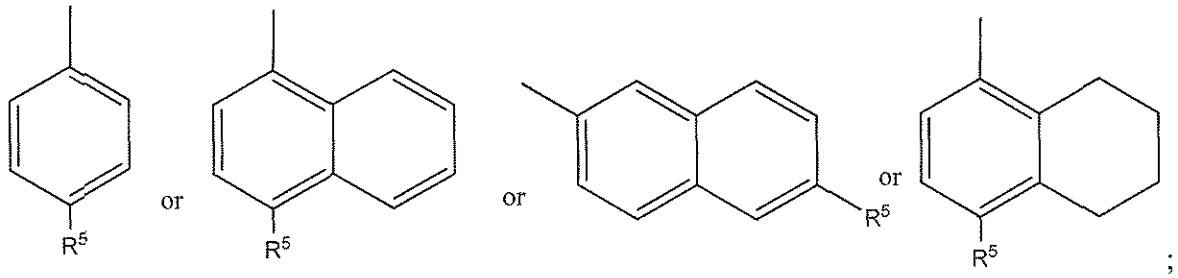
R^1 is hydrogen;

each R^2 is $-R^7$;

R^3 and R^4 are each, independently, hydrogen, or a group represented by formula A, with the proviso that at least one of R^3 and R^4 is a group represented by the formula A;

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

A^1 is



;

each R^L is, independently, $-R^7$;

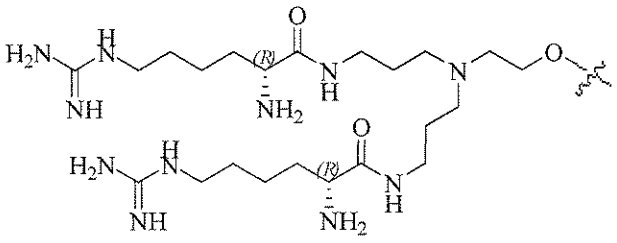
each o is, independently, an integer from 0 to 10;

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, a single bond;

each R^5 is, independently, represented by one of the following formulas:



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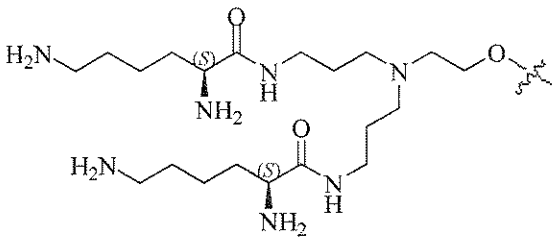

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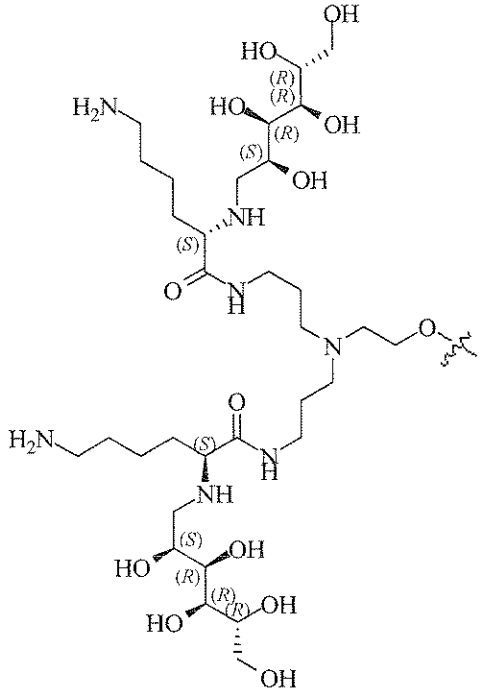

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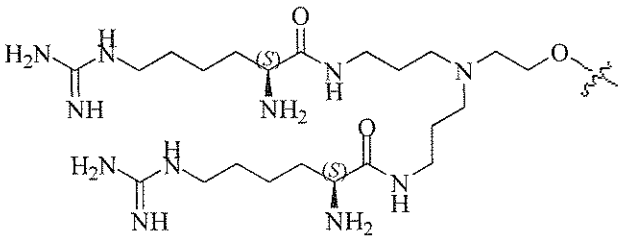

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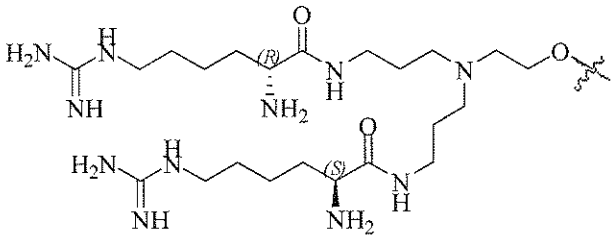

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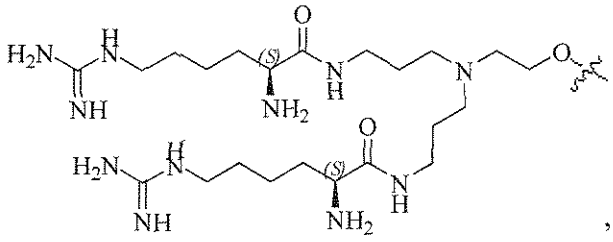

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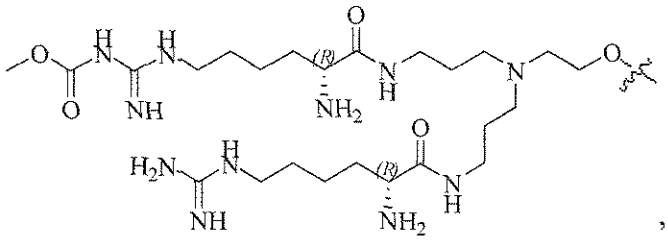

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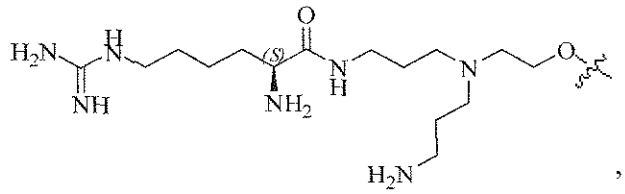

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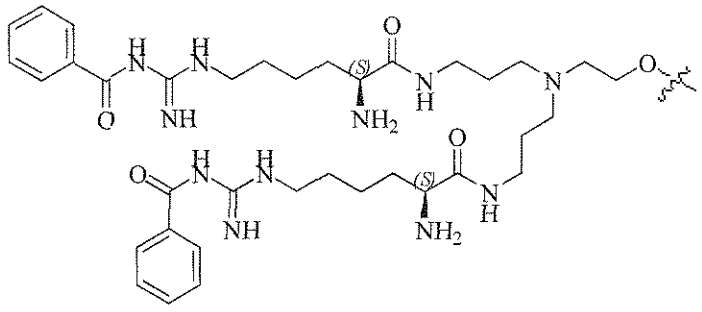

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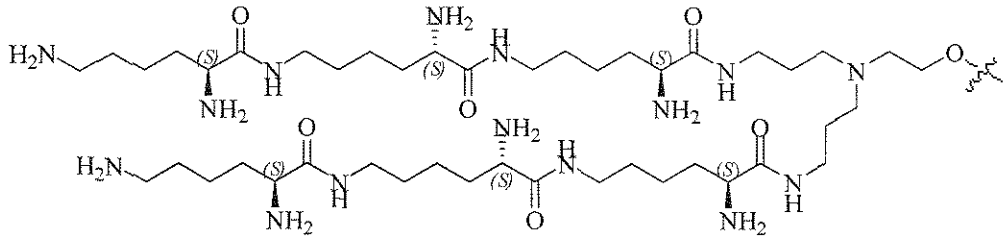

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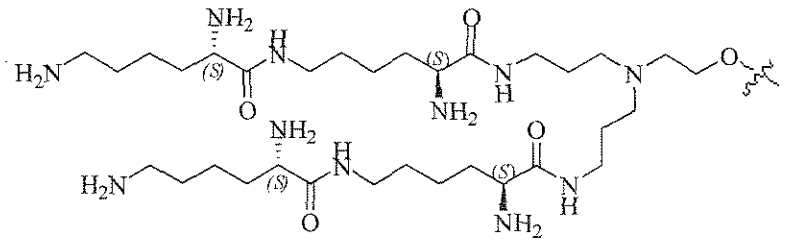

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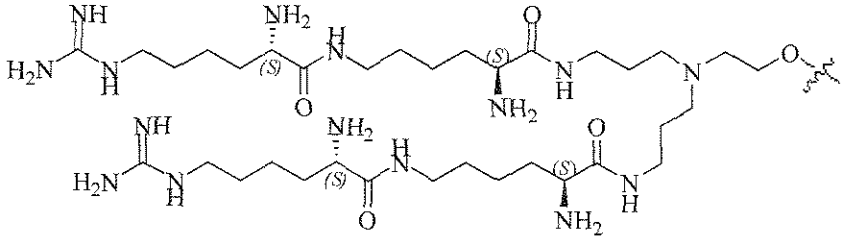

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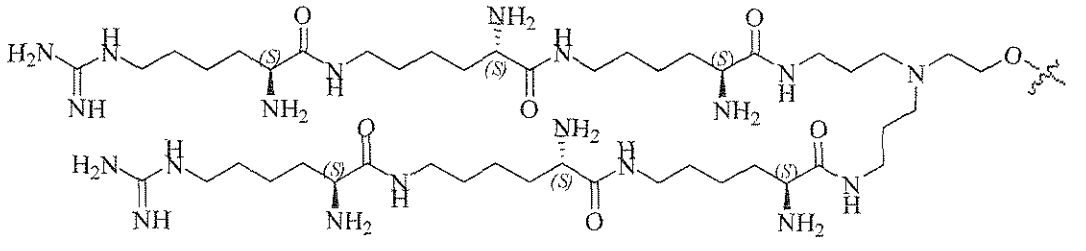

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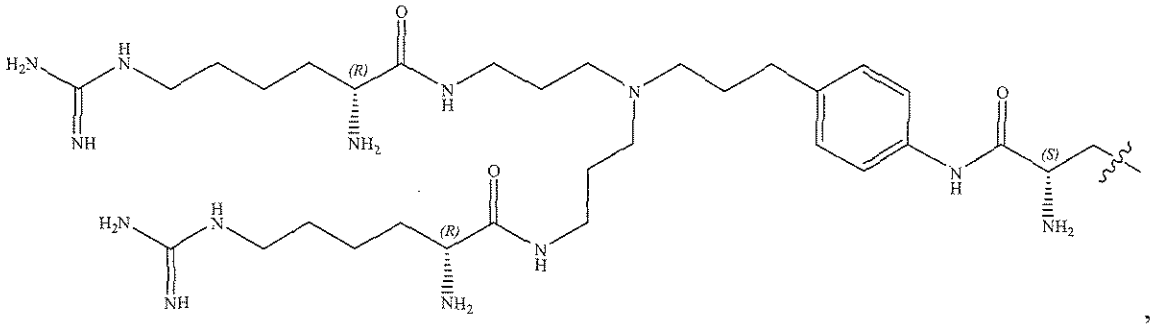

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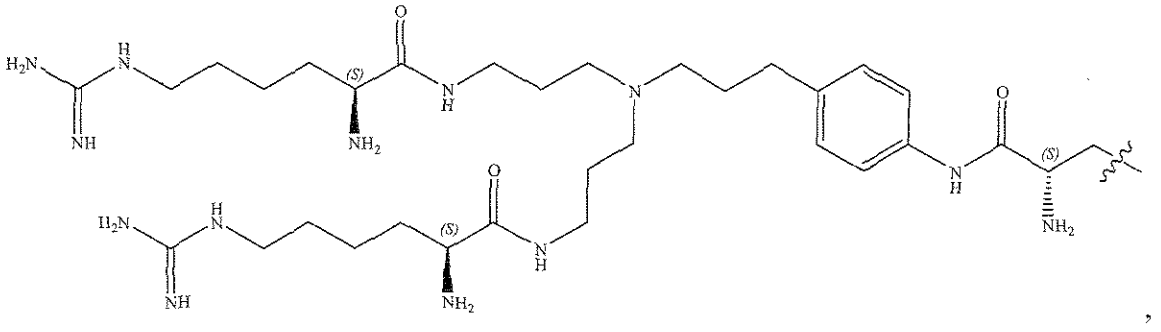

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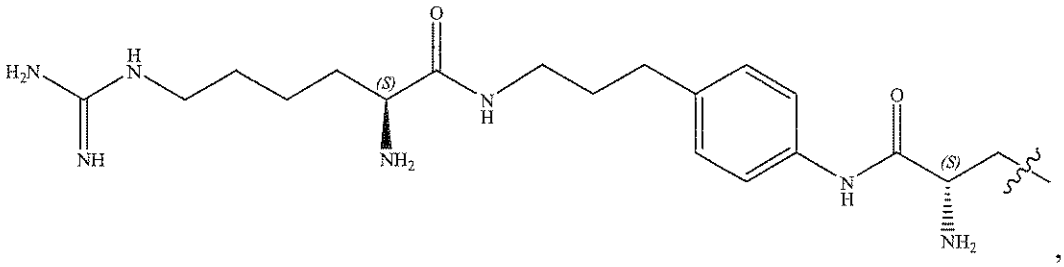

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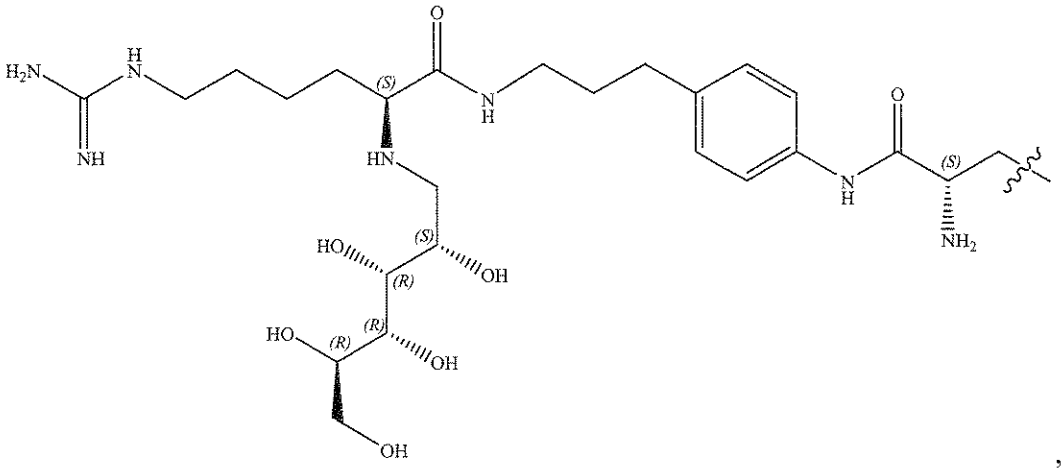

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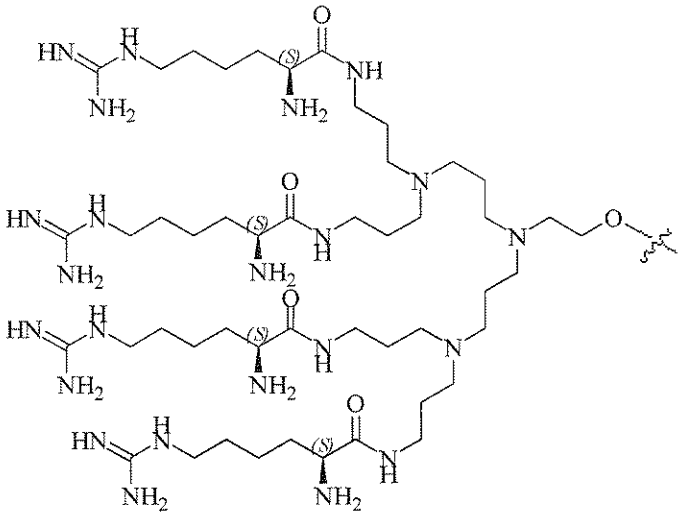

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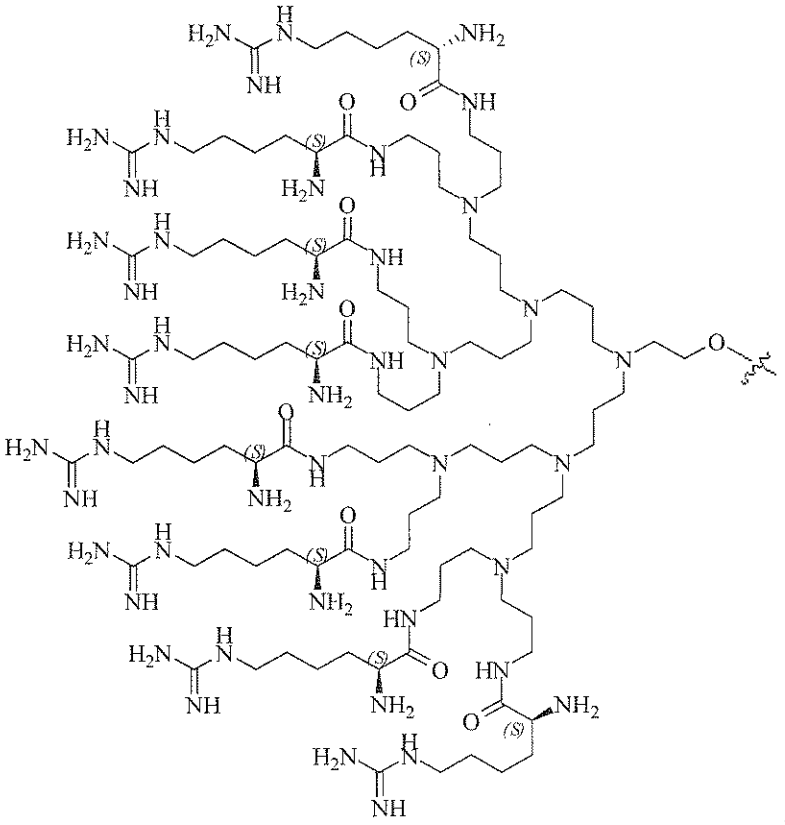

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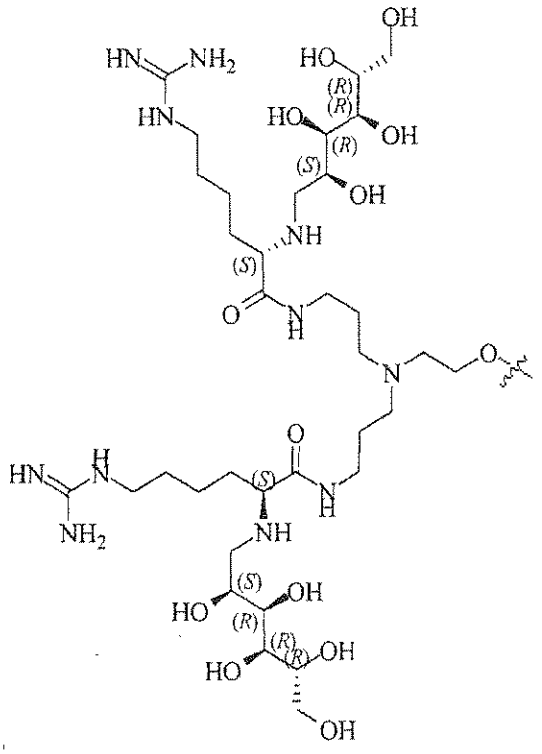

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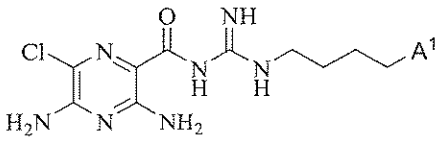
each R^7 is, independently, hydrogen.

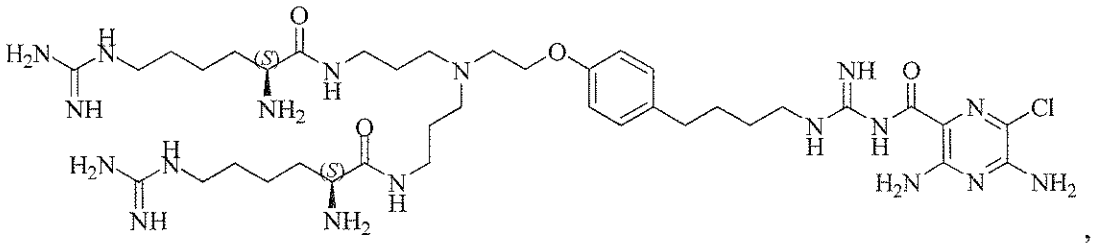
2. The compound according to claim 1, which is represented by formula II:



formula II

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

3. A compound represented by one of the following formulas:



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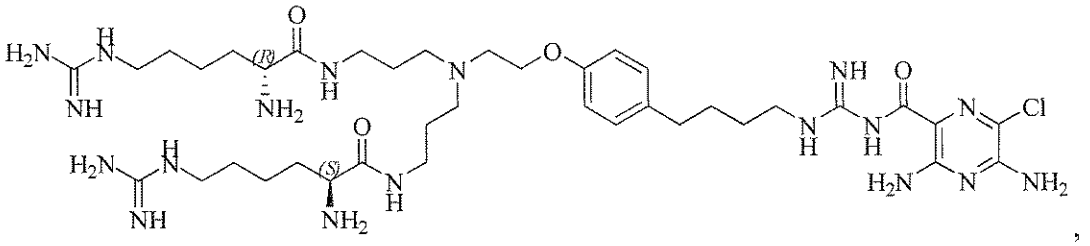

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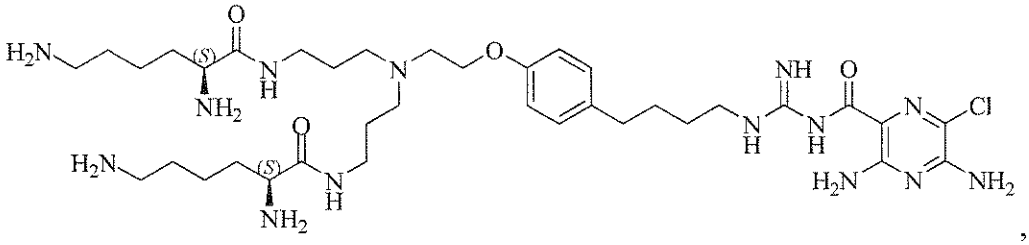

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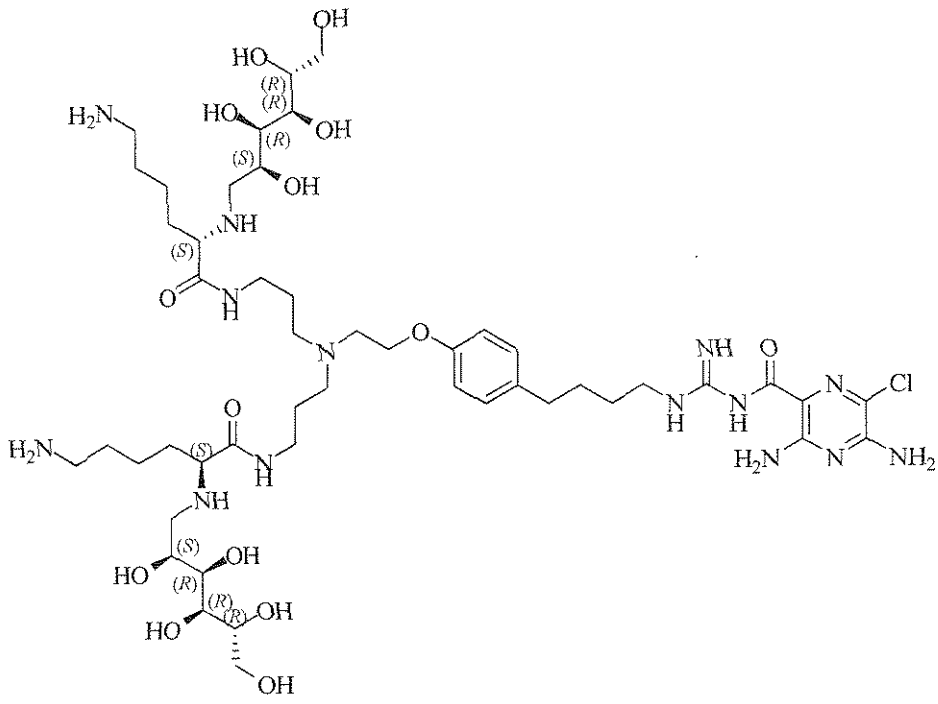

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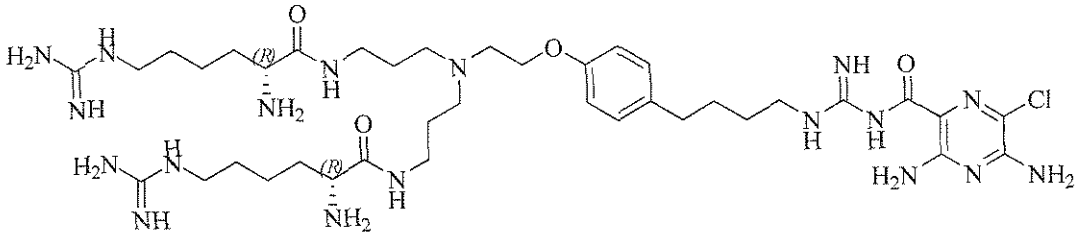

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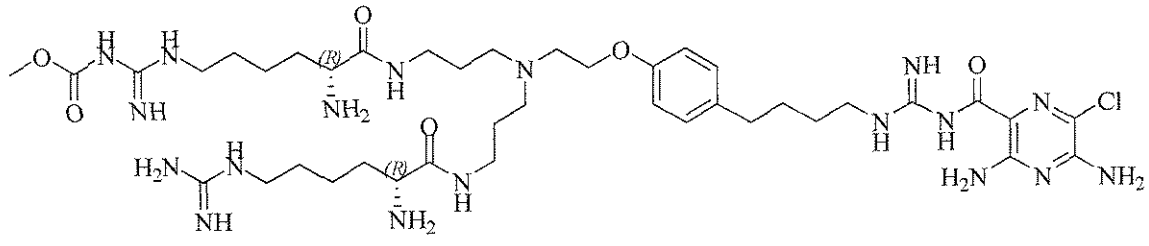

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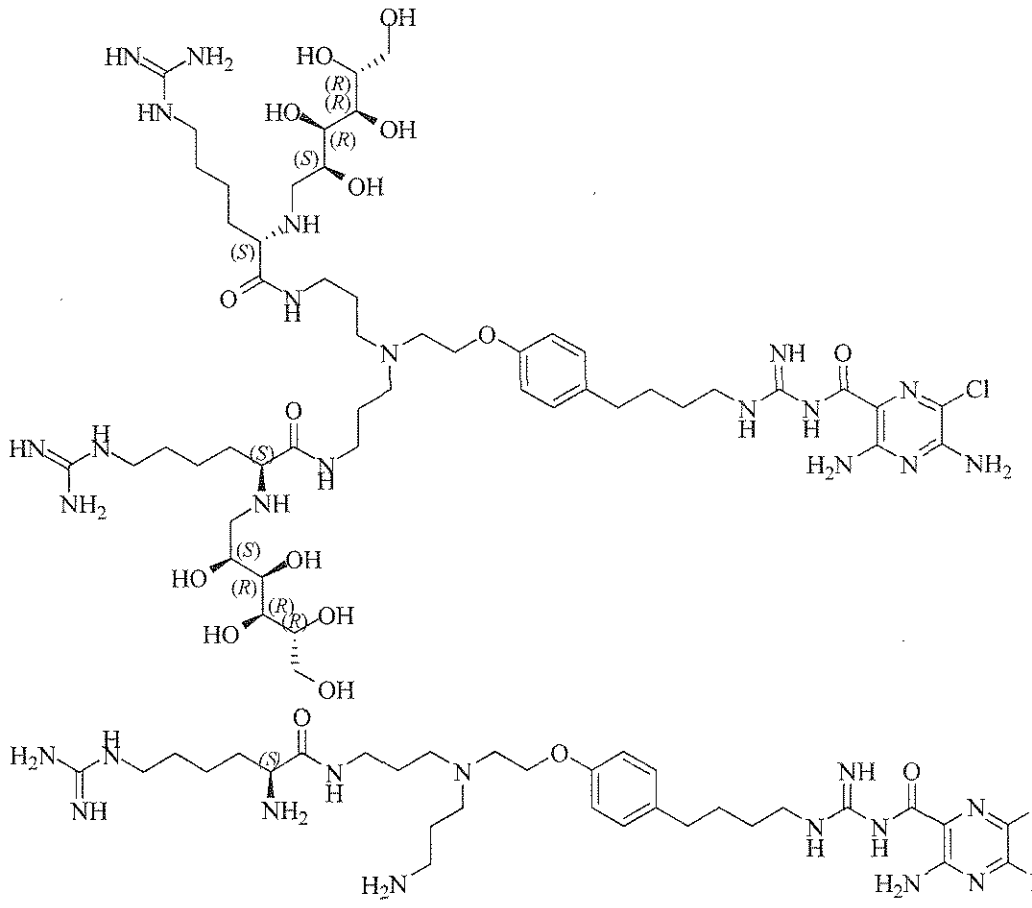

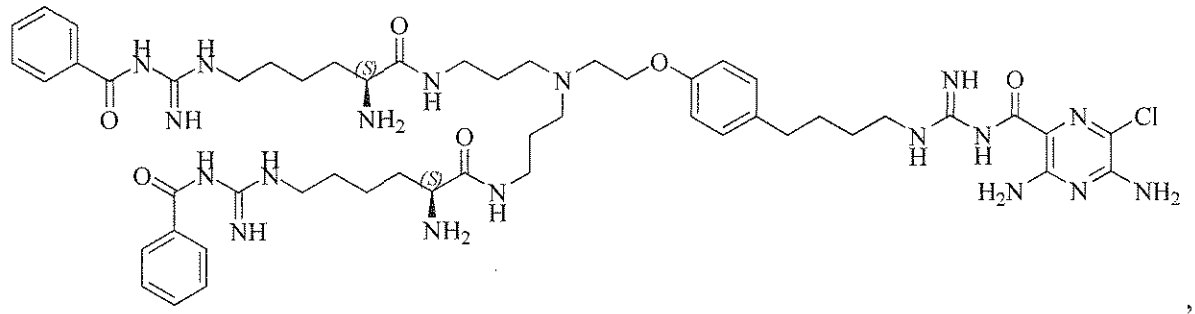

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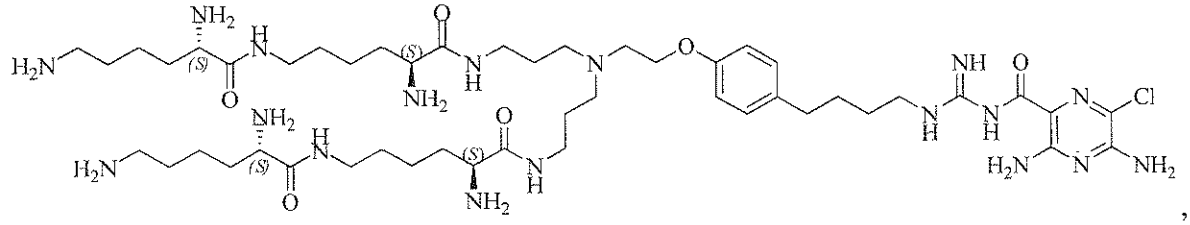

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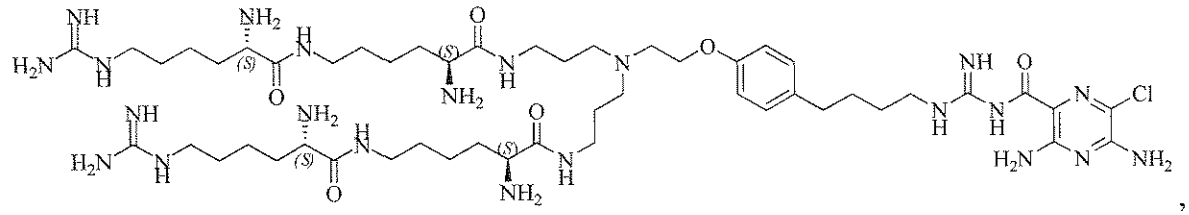

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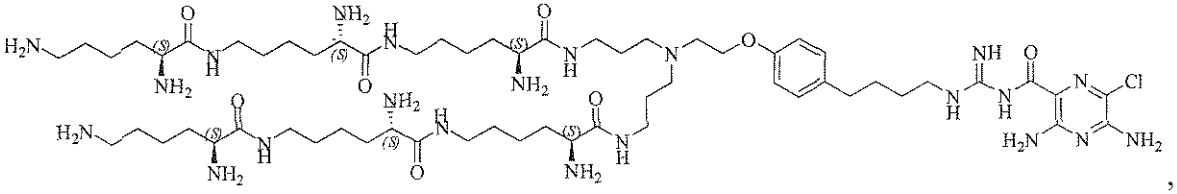

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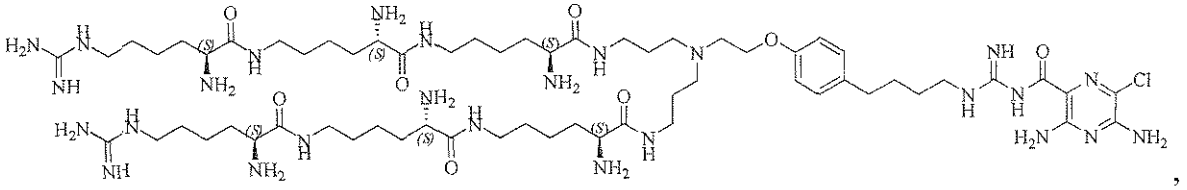

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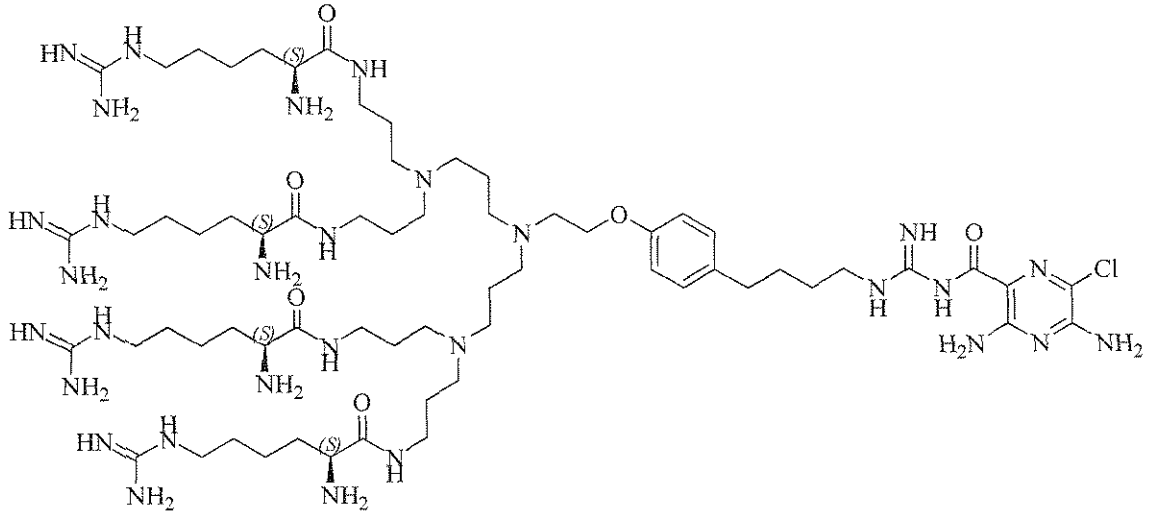
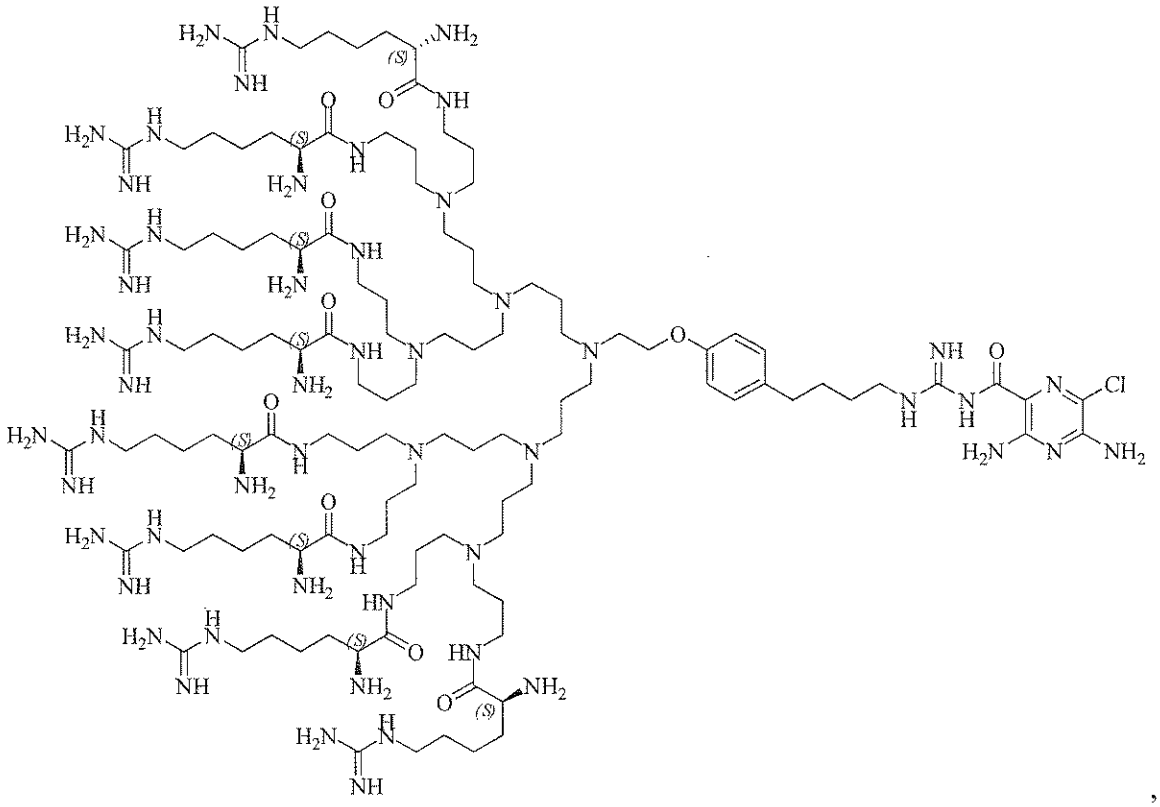




or a pharmaceutically active salt thereof.

4. 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.

5. The pharmaceutical composition according to claim 4, 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.

6. The composition according to claim 4, wherein said composition is a solution for administration by eye drops.

7. 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.

8. Use of an effective amount of the compound according to claim 1 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.

9. The use according to claim 8, 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.

10. A composition, comprising:
(a) a compound or a pharmaceutically acceptable salt thereof according to claim 1 and
(b) an osmolotically active compound.

11. The composition according to claim 4, 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.

12. Use of an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament.

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

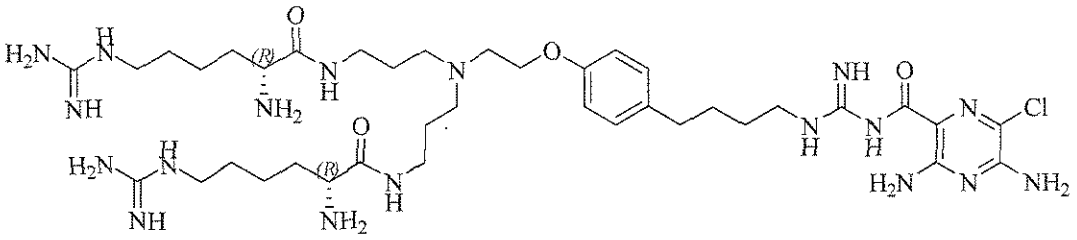
14. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, for use in treating dry eye, treating Sjogren's disease-associated dry eye, treating eye inflammation caused by dry eye , promoting ocular hydration, promoting corneal hydration,

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 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.

15. A composition comprising a compound according to claim 1, 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.

16. 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 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.

17. The use according to claim 7, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

18. The hydrochloride salt of:

