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(54) Benævnelse: **Farmaceutisk sammensætning omfattende thrombolytisk peptid-tetrahydroisoquinolin-konjugat**

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WO-A1-2014/036821
US-A1- 2016 083 423
QIQI FENG ET AL: "DHDMIQK(KAP): a novel nano-delivery system of dihydroxyl-tetrahydro-isoquinoline-3-carboxylic acid and KPAK towards the thrombus", JOURNAL OF MATERIALS CHEMISTRY. B, vol. 4, no. 36, 1 January 2016 (2016-01-01), GB, pages 5991 - 6003, XP055311968, ISSN: 2050-750X, DOI: 10.1039/C6TB00874G
FENG ET AL.: "DHDMIQK(KAP): a novel nano-delivery system of dihydroxyl-tetrahydro-isoquinoline -3-carboxylic acid and KPAK towards the thrombus", JOURNAL OF MATERIALS CHEMISTRY B, vol. 4, 16 August 2016 (2016-08-16), pages 5991 - 6003, XP055311968, DOI: 10.1039/C6TB00874G

DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a pharmaceutical composition comprising a thrombolytic peptide-tetrahydroisoquinoline conjugate and a pharmaceutically acceptable carrier having a pH less than pH 6.5.

BRIEF DESCRIPTION OF THE DRAWINGS

[0002]

Fig. 1A shows the chemical structure of DC009.

Fig. 1B shows the chemical structure of DC009 with the detail of NH-Lys-Ala-Pro.

DETAILED DESCRIPTION OF THE INVENTION

[0003] Disclosed herein is a pharmaceutical composition comprising DC009, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. DC009 is also abbreviated as LT3001, with a chemical name of 3S-6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-isoquinoline-3-acyl-Lys(Pro-Ala-Lys) or L-Lysine, N6-(L-prolyl-L-alanyl-L-lysyl)-N2-[[(3S)-1,2,3,4-tetrahydro-6,7-dihydroxy-1,1-dimethyl-3-isoquinolinyl]carbonyl] (CAS RN: 1639303-73-3). The structure of DC009 is shown in FIG. 1A, the amide bond between the Lysine linking arm and the Pro-Ala-Lys peptide is shown in FIG.1B. DC009 is a binary conjugate that can be formed by coupling a thrombolytic peptide (Pro-Ala-Lys) and a tetrahydroisoquinoline compound having two C1-4 alkyl groups via a Lysine linking arm. The preparation of DC009 compound is disclosed in Example 63 of US Publication No. 2016-0083423. A pharmaceutical acceptable salt of DC009 includes any salt that are pharmaceutically acceptable; for example, a hydrochloride salt, i.e. L-lysine, N6-(L-prolyl-L-alanyl-L-lysyl)-N2-[[(3S)-1,2,3,4-tetrahydro-6,7-dihydroxy-1,1-dimethyl-3-isoquinolinyl]carbonyl]-hydrochloride (1:3) (CAS RN: 2419930-71-3).

[0004] The term "pharmaceutically acceptable" means biologically or pharmacologically

compatible for in vivo use in animals or humans. In some embodiments, "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0005] In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, in some embodiments, the pharmaceutical compositions of the present invention encompass any composition made by admixing 0.1 to 50%, of the active ingredient with a pharmaceutically acceptable carrier. In yet other embodiments, the pharmaceutical compositions of the present invention encompass any composition made by admixing 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% of the active ingredient with a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical compositions of the present invention encompass any composition made by admixing 0.2%-5%, of the active ingredient with a pharmaceutically acceptable carrier. In other embodiments, the pharmaceutical compositions of the present invention encompass any composition made by admixing 0.5 % to 5%, of the active ingredient with a pharmaceutically acceptable carrier.

[0006] Pharmaceutically acceptable carriers, which are inactive ingredients, can be selected by those skilled in the art using conventional criteria. Pharmaceutically acceptable carriers include non-aqueous based solutions, suspensions, emulsions, microemulsions, micellar solutions, gels, and ointments. The pharmaceutically acceptable carriers may also contain ingredients that include saline and aqueous electrolyte solutions; ionic and nonionic osmotic agents such as sodium chloride, potassium chloride, glycerol, and dextrose; pH adjusters and buffers such as salts of hydroxide, phosphate, citrate, acetate, borate; and trolamine; antioxidants such as salts, acids and/or bases of bisulfite, sulfite, metabisulfite, thiosulfite, ascorbic acid, acetyl cysteine, cystein, glutathione, butylated hydroxyanisole, butylated hydroxytoluene, tocopherols, and ascorbyl palmitate; surfactants such as lecithin, phospholipids, including phosphatidylcholine, phosphatidylethanolamine and phosphatidyl inositiol; poloxamers and ploxamines, polysorbates such as polysorbate 80, polysorbate 60, and polysorbate 20, polyvinyls such as polyvinyl alcohol and povidone; cellulose derivatives such as methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose and hydroxypropyl methylcellulose and their salts; petroleum derivatives such as mineral oil and white petrolatum; fats such as lanolin, peanut oil, palm oil, soybean oil; mono-, di-, and triglycerides; polymers of acrylic acid such as carboxypolymethylene gel, and hydrophobically modified cross-linked acrylate copolymer; polysaccharides and glycosaminoglycans such as sodium hyaluronate. Such pharmaceutically acceptable carriers may be preserved against bacterial contamination using well-known preservatives, these include benzalkonium chloride, ethylene diamine tetra-acetic acid and its salts, benzethonium chloride, chlorhexidine, chlorobutanol, methylparaben, thimerosal, and phenylethyl alcohol, or may be formulated as a

non-preserved formulation for either single or multiple use.

[0007] In some embodiment, the pharmaceutical composition comprises DC009 and a pharmaceutically acceptable carrier, wherein the composition has a pH<7 or a pH < 6.5. In some embodiment, the composition has a pH about pH 1- pH 6. In some embodiment, the composition has a pH about pH 2- pH 5.5. In some embodiment, the composition has a pH about pH 3- pH 6. In some embodiment, the composition has a pH about pH 3.5- pH 5.5. In some embodiment, the composition has a pH about pH 3.5, pH 4, pH 4.5, pH 5 or pH 5.5. In some embodiments, the composition has a pH about 4.5.

[0008] As used in this application, "about" refers to ± 5% of the recited value.

[0009] In some embodiments, the pharmaceutical composition comprises DC009 and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient is a disaccharide or a sugar alcohol.

[0010] In some embodiments, the sugar alcohol is mannitol, sorbitol, ethylene glycol, glycerol, erythritol, threitol, arabitol, xylitol, ribitol, galactitol, fucitol, Iditol, inositol, volemitol, isomalt, maltitol or lactitol. In some embodiments, the sugar alcohol is arabitol, xylitol, ribitol, mannitol, sorbitol, galactitol, fucitol, iditol, or inositol. In some embodiments, the sugar alcohol is arabitol, xylitol, ribitol, mannitol, sorbitol, galactitol, fucitol, Iditol or inositol. A preferred sugar alcohol is mannitol or sorbitol.

[0011] In some embodiments, the disaccharide is sucrose, lactose, trehalose (β,β-trehalose, α,β-trehalose), lactulose, maltose, cellobiose, chitobiose, kojibiose, nigerose, sophorose, laminaribiose, gentiobiose, turanose, maltulose, palatinose, gentiobiulose, mannobiose, melibiose, melibiulose, rutinose, rutinulose or xylobiose. In some embodiments, the disaccharide is sucrose, lactulose, lactose, trehalose, cellobiose or chitobiose. A preferred disaccharide is sucrose, lactose, or trehalose.

[0012] In the present application, the weight ratio of DC009 versus the pharmaceutically acceptable excipient (DC009/excipient ratio) may be expressed as either, for example, 9:1 or 9. For example, a DC009/excipient ratio expressed as 0.5:1 is the same as a DC009/excipient ratio expressed as 0.5. A range of DC009/ excipient ratios may be expressed as 1:1 - 9:1 for example.

[0013] In some embodiments, the pharmaceutical composition comprises DC009 and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient is mannitol, sorbitol, sucrose, lactose or trehalose, and wherein the weight ratio of DC009 versus the pharmaceutically acceptable excipient is 1:1 - 1:9. If the ratio is lower than 1:1, the volume is too small to be lyophilized, and if the ratio is higher than 1:9, the osmolarity is too high for intravenous use.

[0014] In some embodiments, the ratio of DC009 versus the pharmaceutically acceptable

excipient is 1:9. In one embodiment, the pharmaceutical composition comprises about 1% DC009, and about 9% pharmaceutically acceptable excipient. For example, the pharmaceutically acceptable excipient is sucrose, lactose, sorbitol or trehalose.

[0015] In some embodiments, the pharmaceutical composition comprises DC009 and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient is mannitol, and the weight ratio of DC009 versus mannitol is 1:1- 1:7, preferably 1:1 -1:5. For example, the weight ratio of DC009 versus mannitol is about 1:1, 1:1.3, 1:3.8, or 1:5. In various embodiments, the weight ratio of DC009 versus mannitol is 1:5. In one embodiment, the pharmaceutical composition comprises about 1% DC009, and about 5% mannitol.

[0016] In various embodiments, the ratio of DC009 versus the pharmaceutically acceptable excipient is about 1:3.8. In one embodiment, the pharmaceutical composition comprising about 1% DC009, and about 3.8% mannitol. In one embodiment, the pharmaceutical composition comprising about 4% DC009, and about 14.8 % mannitol.

[0017] In various embodiments, the ratio of DC009 versus the pharmaceutically acceptable excipient is about 1:1.3. In some embodiments, the pharmaceutical composition comprises about 2% DC009, and about 2.6% mannitol.

[0018] In some embodiments, the pharmaceutical composition comprises about 1% DC009, and about 3.8% mannitol, and wherein the composition has a pH of about pH 3.5- pH 5.5, more preferably, the composition has a pH of about pH 4.5.

[0019] In some embodiments, the pharmaceutical composition comprises about 2% DC009, and about 2.6% mannitol, and wherein the composition has a pH of about pH 3.5- pH 5.5, more preferably, the composition has a pH about 4.5.

[0020] The following examples further illustrate the present invention.

EXAMPLES

Example 1. Preparation and purity determination for DC009

[0021] DC009 were prepared according to the US Publication Application No. 2016-0083423. The final product was washed repetitively by DCM, THF and ethyl ether several times to increase the purity of the final product. The concentration and purity of DC009 in a solution are determined by HPLC with the following conditions.

Column: alkyl reversed-phase bounded phase column

Mobile Phase (MP): MP A: 0.1% by volume TFA in DI water / MP B: 0.1% by volume TFA in

acetonitrile

Detection Wavelength: 214 & 280 nm

Column Temperature: 20 -25°C

Sample Temperature: 10-15°C

Injection Volumn: 10-20 µL

Gradient: MP A and MP B

[0022] In Examples 2-6, the stability of each formulation is shown as "Assay Recovery" or "Relative purity level". Samples at each time point was analyzed by HPLC as described above. For "Assay Recovery", the % number is calculated by dividing the DC009 concentration at the time point by the DC009 concentration at T= 0. For "Relative purity level", the % number is calculated by (Peak area % of DC009 at Tn/ Peak area % of DC009 at T0)*100%.

Example 2. Formulation stability in different pH solutions

[0023] Seven formulations listed in Table 1 contained 10mg/mL DC009 were prepared, DC009 were dissolved in each buffer and adjust to the indicated pH by NaOH and HCl.

Table 1. Formulation T-1 ~ T-7

Formulation ID	pH	Buffer
T-1	4	5 mM sodium acetate
T-2	5	5 mM sodium acetate
T-3	6	5 mM sodium citrate
T-4	7	50 mM sodium phosphate
T-5	7	DI water
T-6	7	0.9% NaCl
T-7	8	5 mM sodium phosphate

[0024] These formulations were stored at 40°C and 60°C to evaluate the assay recovery and total impurity. The appearance and stability at each storage condition were recorded at Table 2 and Table 3. No precipitate was observed in any of the samples.

Table 2. Appearance of formulation T-1 ~ T-7

Formulation ID	Appearance		
	Initial	40°C × 7d	60°C × 7d
T-1	clear and colorless liquid	Slight yellow, clear liquid	Yellow, clear liquid
T-2	clear and colorless liquid	Slight yellow, clear liquid	Yellow, clear liquid
T-3	clear and colorless liquid	Slight yellow, clear liquid	Yellow, clear liquid
T-4	Slight yellow, clear liquid	Light yellow, clear liquid	Yellow, clear liquid
T-5	Slight yellow, clear liquid	Light yellow, clear liquid	Yellow, clear liquid
T-6	Slight yellow, clear liquid	Light yellow, clear liquid	Yellow, clear liquid
T-7	Light orange, clear liquid	Orange, clear liquid	Dark orange, clear liquid

Table 3. Stability of formulation T-1 ~ T-7

DC009 Assay recovery (%)						
Sample	pH	T=0	40°C		60°C	
			1 day	4 days	1 day	4 days
T-1	4	100	97	98	96	95
T-2	5	100	100	100	97	95
T-3	6	100	99	98	97	91
T-4	7	100	94	88	88	73
T-5	7	100	95	93	94	82
T-6	7	100	96	92	93	82
T-7	8	100	87	63	73	45

[0025] In the accelerated stability study, the assay recovery of T-1 (pH 4) and T-2 (pH 5) were ≥ 98% at the 4th day at 40°C, and were 95% and 60°C. The assay recovery of T-1 and T-2 at the 7th day were 95% and 96 % at 40°C, and were both 90% at 60°C (data not shown). Whereas, the assay recovery of the formulations at pH 7-8 (T-4 to T-7) dropped below 90% after storage at 60°C for 4 days, which indicate that impurity % grew significantly. These data suggest that DC009 was stable at acidic conditions, and was very stable at pH between 4 and 5. 5 mM sodium acetate is sufficient to maintain a stable pH between pH 4 and pH 5 for a 10 mg/mL DC-009 solution.

Example 3. Formulation stability in different pH solutions

[0026] In another independent experiment, 9 formulations listed in Table 4 contained 10mg/mL DC009 were prepared, DC009 were dissolved in each buffer and adjust to the indicated pH by NaOH and HCl.

Table 4. Formulation P1~P6

Sample	pH	Buffer
P1	pH 7.0	5 mM sodium phosphate
P2	pH 6.5	5 mM sodium phosphate
P3	pH 6.0	5 mM sodium citrate
P4	pH 5.5	5 mM sodium citrate
P5	pH 5.0	5 mM sodium acetate
P6	pH 4.0	5 mM sodium acetate
P7	pH 3.5	5 mM sodium acetate
P8	pH 2.0	5 mM sodium acetate
P9	pH 1.0	5 mM sodium acetate

[0027] These formulations were stored at 60°C to evaluate the stability of the sample at different pH. The relative purity level of DC009 in total formulation are recorded at Table 5, the purity of DC009 is defined as 100% at T=0. Data suggest that DC009 was stable at all acidic conditions (pH<7) and maintained > 95% purity level for 10 days at 60°C. After one-month storage at 60°C (Day 38), DC009 was stable at pH 1 to pH 6 and maintained > 86% purity level. The best stability was shown at pH 2.0-5.5.

Table 5 Stability (relative purity level) of formulation P1-P7

Sample	pH	T=0	60°C		
			Day 5	Day 10	Day 38
P1	pH 7.0	100.00	95.36	93.18	70.88
P2	pH 6.5	100.00	97.94	97.01	88.28
P3	pH 6.0	100.00	99.44	99.17	92.16
P4	pH 5.5	100.00	99.67	99.59	97.74
P5	pH 5.0	100.00	99.54	99.28	97.61
P6	pH 4.0	100.00	99.53	99.18	99.23
P7	pH 3.5	100.00	99.74	99.73	99.73
P8	pH 2.0	100.00	99.98	99.88	97.78
P9	pH 1.0	100.00	99.70	99.39	86.18

*Relative purity level: (Peak area % of DC009 at Tn/ Peak area % of DC009 at T0)*100%

Example 4A. Formulation stability in different excipients

[0028] Six formulations listed in Table 6 contained 10mg/mL DC009 and different amounts of excipients (in mg/g) were prepared, each formulation was adjusted to pH 4.5 by NaOH and HCl. These formulations were stored at 40°C and 60°C to evaluate the assay recovery and total impurity. Stability data are summarized in Table 7.

Table 6. Formulation E1~E6

Component (mg/g)	**E1**	**E2**	**E3**	**E4**	**E5**	**E6**
DC-009	10	10	10	10	10	10
Sodium acetate, anhydrous	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM
EDTA2Na2H_2O	0.055	0.055	0.055	0.055	0.055	0.055
Glycine	22					
Lactose		90				
Mannitol			50			
Trehalose dihydrate				90		
Sucrose					90	

Table 7. Stability of formulation E1~E5

DC009 Assay recovery (%)							
Sample	**Main Excipient (ME)**	**40°C**			**60°C**		**DC009/ ME weight ratio**
		T=0	**2 Weeks**	**4 Weeks**	**1 Week**	**2 Weeks**	
E1	Glycine	100	93	82	65	51	1:2.2
E2	Lactose	100	99	100	95	90	1:9
E3	Mannitol	100	100	101	96	90	1:5
E4	Trehalose	100	100	102	96	92	1:9
E5	Sucrose	100	99	100	96	91	1:9
E6	-	100	98	97	92	80	-

[0029] In the accelerated stability study, the assay recovery of E2-E5 were ≥ 90% at 2 weeks at 60°C (Table 7). E1 glycine excipient significantly reduced the stability comparing with control E6, whereas mannitol, trehalose, sucrose, and lactose improved the stability comparing with control E6.

Example 4B. Formulation stability in different excipients

[0030] In a separate experiment, different excipients list on Table 8 were tested for the effect on stabilizing DC009. For formulation S1-S10, 10mg/mL DC009 were prepared in 5mM Sodium acetate buffer, the concentration of each excipient is 3.8% and the pH of the formulations were adjusted to pH 4.5. These formulations are store at 60°C for two weeks. The relative purity level of DC009 in total formulation were recorded at Table 8, the purity of DC009 were defined as 100% at T=0. The purity level of S1 and S3 were >80% at 2 weeks at 60°C. The results show that mannitol and sorbitol provided better stability than other excipients.

Table 8. Stability (relative purity level in %) of formulation S1~S10

Sample	Excipient	Day 0	Day 6	Day 10	Day 14
S1	Mannitol	100.00	90.33	89.01	88.92
S2	Maltose	100.00	84.43	81.58	69.91
S3	Sorbitol	100.00	88.71	85.57	81.47
S4	Arginine	100.00	81.96	68.01	56.00
S5	Glucose	100.00	82.91	61.12	46.77
S6	Raffinose	100.00	87.72	67.89	48.89
S7	Ethylene glycol	100.00	72.68	59.53	50.83
S8	Dextose	100.00	83.16	62.49	45.60
S9	Maltitol	100.00	88.77	83.75	74.74
S10	Histidine	100.00	88.76	78.86	69.85

Example 5. Stability in formulations containing mannitol

[0031] Four formulations listed in Table 9 containing 10mg/mL DC009 were prepared, each formulation was adjusted to pH 4.5 by NaOH and HCl. M1-M3 contained 50 mg/g D-mannitol, and M4 did not contain D-mannitol. These formulations were stored at 40°C and 60°C to evaluate the assay recovery. The stability results at each storage condition are recorded at Table 10.

Table 9. Formulation M1~M4

Component (mg)	M1	M2	M3	M4
DC-009	10	10	10	10
Sodium acetate, anhydrous		5 mM	5 mM	5 mM
EDTA2Na2H_2O			0.055	0.055
D-mannitol	50	50	50	

Table 10. Stability of formulation M1~M4

DC009 Assay recovery (%)					
Sample	**40°C**			**60°C**	
	T=0	**2 Weeks**	**4 Weeks**	**1 Week**	**2 Weeks**
M1	100	98	99	95	94
M2	100	98	99	95	92
M3	100	100	101	96	90
M4	100	98	97	92	80

[0032] In the accelerated stability study, the assay recovery of M1-M3 were ≥ 90 at 2 weeks at 60°C. Data suggest that adding mannitol improved the formulation stability comparing with the M4 formulation without mannitol.

Example 6. Formulation stability study lipolyzed formulation

[0033] Two formulations listed in Table 11 were prepared. Each formulation was lyophilized in a lyophilizer and was stored at 25°C and 40°C to evaluate the assay recovery. The stability results at each storage condition are summarized in Table 12.

Table 11. Lyophilized formulation

Component	**F-1**	**F-1H**
DC009	1	2
Mannitol	3.8	2.6
DI Water	QS to 100	QS to 100
1N NaOH/HCl to pH 4.5	+	+
DC009/mannitol ratio	1:3.8	1:1.3

Table 12. Stability of lyophilized formulations

DC009 Assay recovery (%)							
Sample	**T=0**	**1 month**		**2 months**		**3 months**	
	25°C	**25°C**	**40°C**	**25°C**	**40°C**	**25°C**	**40°C**
F1	100	103	101	101	102	102	102
F1-H	100	99	98	100	99	99	95

[0034] Two stable solution intravenous lyophilized formulations (F-1 and F-1H) were developed for DC009 at 10 mg/mL and 20 mg/mL, respectively. Based on the stability tests conducted, F-1 and F-1H were physically and chemically stable at 25°C and 40°C for 3 months. The lyophilized formulations can be reconstituted with normal saline before intravenous injection.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

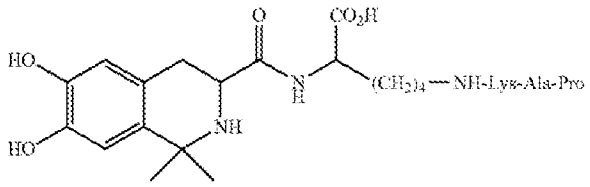
- US20160083423A [0003] [0021]

Non-patent literature cited in the description

- CHEMICAL ABSTRACTS, 1639303-73-3 [0003]
- CHEMICAL ABSTRACTS, RN: 2419930-71-3 [0003]

Krav:

1. Farmaceutisk sammensætning omfattende en forbindelse med følgende formel eller et farmaceutisk acceptabelt salt deraf:



og en farmaceutisk acceptabel bærer, hvori sammensætningen har en pH < 6,5.

2. Farmaceutisk sammensætning ifølge krav 1, hvori sammensætningen har en pH på ca. pH 1 - pH 6.

3. Farmaceutisk sammensætning ifølge krav 1, hvori sammensætningen har en pH på ca. pH 2 - pH 6.

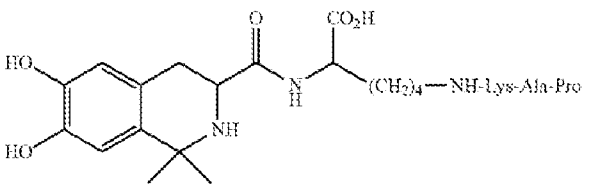
4. Farmaceutisk sammensætning ifølge krav 1, hvori sammensætningen har en pH på ca. pH 2 - pH 5,5.

5. Farmaceutisk sammensætning ifølge krav 1, hvori sammensætningen har en pH på ca. pH 3,5 - pH 5,5.

6. Farmaceutisk sammensætning ifølge krav 5, hvori sammensætningen har en pH på ca. pH 4,5.

7. Farmaceutisk sammensætning ifølge krav 1, hvori det farmaceutisk acceptable salt er hydrochloridsalt.

8. Farmaceutisk sammensætning omfattende en forbindelse med følgende formel eller et farmaceutisk acceptabelt salt deraf:



,

og en farmaceutisk acceptabel excipiens, hvori sammensætningen har en pH på < 6,5, hvori det farmaceutisk acceptable excipiens er mannitol, sorbitol, saccharose, lactose eller trehalose.

9. Farmaceutisk sammensætning ifølge krav 8, hvori det farmaceutisk acceptable excipiens er mannitol.

10. Farmaceutisk sammensætning ifølge krav 8, hvori vægtforholdet mellem forbindelsen og det farmaceutisk acceptable excipiens er ca. 1:1 til 1:9.

11. Farmaceutisk sammensætning ifølge krav 10, hvori vægtforholdet mellem forbindelsen og det farmaceutisk acceptable excipiens er ca. 1:1 til 1:5.

12. Farmaceutisk sammensætning ifølge krav 11, hvori det farmaceutisk acceptable excipiens er mannitol.

13. Farmaceutisk sammensætning ifølge krav 12, hvori sammensætningen har en pH på ca. pH 3,5 - pH 5,5.

14. Farmaceutisk sammensætning ifølge krav 13, hvori sammensætningen er en lyofiliseret formulering.

15. Farmaceutisk sammensætning ifølge krav 8, hvori det farmaceutisk acceptable salt er hydrochloridsalt.

DRAWINGS

Drawing

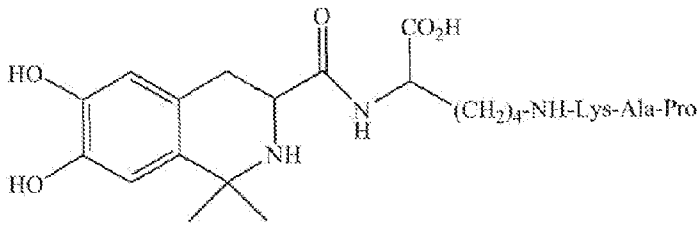


Fig. 1A

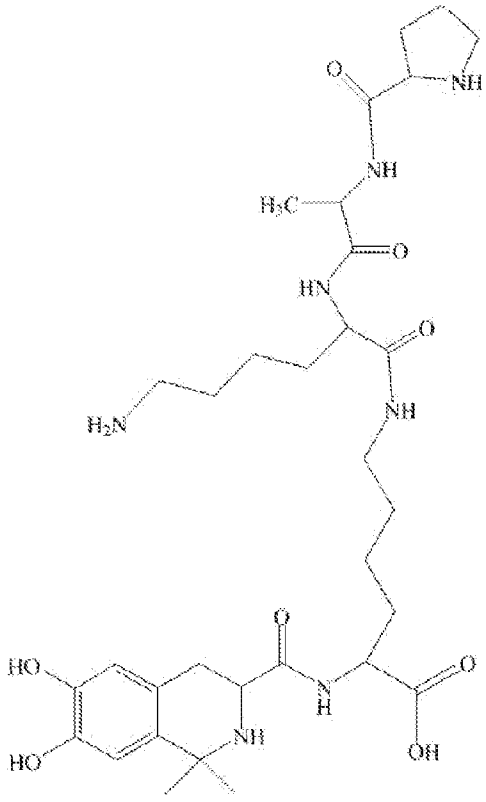


Fig. 1B