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(54) Titre : NOUVEAU PEPTIDE ET COMPOSITION PHARMACEUTIQUE POUR LE TRAITEMENT DE MALADIES OCULAIRES COMPRENANT LEDIT NOUVEAU PEPTIDE EN TANT QUE PRINCIPE ACTIF
(54) Title: NOVEL PEPTIDE AND PHARMACEUTICAL COMPOSITION FOR TREATING AN EYE DISEASE COMPRISING THE SAME AS AN ACTIVE PHARMACEUTICAL INGREDIENT

FIG 1

No. Lot Number	Peptide Name	Sequence	M.W.	Purity (%)	Amount (mg)	Solubility (5mg/ml)
1	K161389	YDE-001	OGQEGLAGPK (D : Hydroxyproline)	969.1	>99.7%	5.0mg 10.0mg Water
2	K161390	YDE-002	OGQNGLAGPK (D : Hydroxyproline)	954.0	>99.7%	5.0mg 10.0mg Water
3	K161391	YDE-003	OGQQGLAGPK (D : Hydroxyproline)	968.1	>99.7%	5.0mg 10.0mg Water
4	K161392	YDE-004	OGQHGLAGPK (D : Hydroxyproline)	977.1	>99.7%	5.0mg 10.0mg Water
5	K161393	YDE-005	OGQKGLAGPK (D : Hydroxyproline)	968.1	>99.8%	5.0mg 10.0mg Water
6	K161394	YDE-006	OGQGLAGPK (D : Hydroxyproline)	967.0	>99.8%	5.0mg 10.0mg Water
7	K161395	YDE-007	OGQTGLAGPK (D : Hydroxyproline)	941.0	>98.0%	5.0mg 10.0mg Water
8	K161396	YDE-008	OGQAGLAGPK (D : Hydroxyproline)	911.0	>98.8%	5.0mg 10.0mg Water
9	K161397	YDE-009	OGQVGLAGPK (D : Hydroxyproline)	999.1	>98.1%	5.0mg 10.0mg Water
10	K161398	YDE-010	OGQKGLAGPK (D : Hydroxyproline)	951.1	>99.9%	5.0mg 10.0mg Water
11	K161399	YDE-011	OGQGLAGPK (D : Hydroxyproline)	951.1	>98.3%	5.0mg 10.0mg Water
12	K161400	YDE-012	OGQFGLAGPK (D : Hydroxyproline)	987.1	>98.8%	5.0mg 10.0mg Water
13	K161401	YDE-013	OGQVGLAGPK (D : Hydroxyproline)	1003.1	>98.7%	5.0mg 10.0mg Water
14	K161402	YDE-014	OGQWGLAGPK (D : Hydroxyproline)	1026.2	>97.5%	5.0mg 10.0mg Water
15	K161403	YDE-015	OGQDVLAGPK (D : Hydroxyproline)	997.1	>99.1%	5.0mg 10.0mg Water
16	K161404	YDE-016	OGQDLAGPK (D : Hydroxyproline)	1011.1	>99.4%	5.0mg 10.0mg Water
17	K161405	YDE-017	OGQDLAGPK (D : Hydroxyproline)	1011.1	>98.0%	5.0mg 10.0mg Water
18	K161406	YDE-018	OGQDLAGPK (D : Hydroxyproline)	999.1	>99.6%	5.0mg 10.0mg Water
19	K161407	YDE-019	OGQFLAGPK (D : Hydroxyproline)	1045.2	>99.6%	5.0mg 10.0mg Water
20	K161408	YDE-020	OGQDYLAGPK (D : Hydroxyproline)	1061.2	>99.2%	5.0mg 10.0mg Water
21	K161409	YDE-021	OGQDVLAGPK (D : Hydroxyproline)	1064.2	>98.1%	5.0mg 10.0mg Water
22	K161410	YDE-022	OGQHLAGPK (D : Hydroxyproline)	1025.1	>98.8%	5.0mg 10.0mg Water
23	K161411	YDE-023	OGQDGLAGPK (D : Hydroxyproline)	983.1	>98.1%	5.0mg 10.0mg Water
24	K161412	YDE-024	OGQDTLAGPK (D : Hydroxyproline)	990.1	>98.9%	5.0mg 10.0mg Water
25	K161413	YDE-025	OGQD-Sar-LAGPK (Sar : me-Gly) (D : Hydroxyproline)	989.1	>95%	5.0mg 10.0mg Water
26	K161414	YDE-026	OGQPSGLAGPK (D : homo-Ser) (D : Hydroxyproline)	941.1	>95%	5.0mg 10.0mg Water
27	K161415	YDE-027	OGQDGLAGPK (D : D(OMe)) (D : Hydroxyproline)	969.1	>95%	5.0mg 10.0mg Water
28	K161416	YDE-028	OGQNSGLAGPK (D : N(OMe)) (D : Hydroxyproline)	968.1	>95%	5.0mg 10.0mg Water

(57) **Abrégé/Abstract:**
The present invention relates to a novel peptide and a pharmaceutical composition for treatment of eye diseases comprising the novel peptide as an active ingredient. When the novel peptide of the present invention is applied to an eye, the amount of tear secretion is increased and a damaged cornea is healed such that the novel peptide may be effectively used as a therapeutic agent for eye diseases.



ABSTRACT

The present invention relates to a novel peptide and a pharmaceutical composition for treating an eye disease, which comprises the same as an active pharmaceutical
5 ingredient. When the novel peptide of the present invention is administered to the eyes, it increases the amount of tear secretion and recovers the damaged cornea. Thus, it can be advantageously used as a therapeutic agent for treating an eye disease.

SPECIFICATION

[Title of the Invention]

5 NOVEL PEPTIDE AND PHARMACEUTICAL COMPOSITION FOR
TREATING AN EYE DISEASE COMPRISING THE SAME AS AN ACTIVE
PHARMACEUTICAL INGREDIENT

Technical Field

10 The present invention relates to novel peptides and pharmaceutical compositions
for treating eye diseases that comprises the same as an active pharmaceutical ingredient.

Background Art

Dry eye syndrome or keratoconjunctivitis sicca may be defined, in a broad sense,
15 as damage to the ocular surface due to tear secretion disorders (Joossen C *et al.*, *Exp.*
Eye Res., 146:172-8, 2016). Dry eye syndrome is known to cause tear secretion
disorders and damage and discomfort to the eyeball due to a combination of various
factors. Although the onset of dry eye syndrome is closely related to age, the incidence
thereof is increasing in younger age groups due to a long-term exposure to a dry
20 environment as the use of contact lenses, computers, and smart devices (Stern ME *et*
al., *Int. Rev. Immunol.*, 32: 19-41, 2013).

Specifically, dry eye syndrome reduces the mucus secretion of the corneal and
conjunctival epithelia and that of the mucus-secreting goblet cells, resulting in a sharp
decrease in the lubrication of the eyeball. In addition, dry eye syndrome causes damage
25 to the corneal surface, thereby increasing the penetration of a fluorescein dye into the
cornea. These symptoms of dry eye syndrome can be evaluated as changes in the tear
secretion through the Schirmer test, which uses cobalt chloride paper. Further, the
damage to the cornea that may accompany dry eye syndrome can be easily evaluated

using a general fluorescent dye and a slit-lamp fluorophotometer.

In the meantime, most of the treatments for dry eye syndrome are confined to symptom therapies, the treatment efficiency of which is often very low. Currently, artificial tears are the first choice for the treatment of dry eye syndrome. Since artificial tears as a representative symptom therapy merely supplement the insufficient tears; moreover, they suffer from the disadvantage that they need to be administered to the eyes frequently (Kim CS *et al.*, *Nutrients* 8. pii: E750, 2016). Sodium hyaluronate and eye drops derived from autologous serum have been developed and used in patients suffering from dry eye syndrome. In addition, such synthetic compounds as rebamipide (OPC-127959) and diquafosol sodium, which promote the secretion of tears and mucus, have been developed and used. Long-term use of these drugs, however, may give rise to various side effects such as ocular hyperemia and corneal calcification (Bernauer W *et al.*, *Br. J. Ophthalmol.*, 90:285-8, 2006). Therefore, there has been a demand for the development of a safe and effective therapeutic agent for treating dry eye syndrome.

15

[Disclosure of the Invention]

Problem to be Solved by the Invention

Therefore, the present inventors have endeavored to develop safe and effective therapeutic agents for treating an eye disease and, as a result, completed the present invention by way of synthesizing new peptides, administering them to the eyes of rats with dry eye syndrome, and confirming the eye protection effect through the Schirmer test and the fluorescent dye deposition test.

20

Means for Solving the Problem

In order to achieve the object of the present invention, one aspect of the present invention provides a compound represented by Formula 1.

25

Further, another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys.

In addition, still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys.

Further, still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa.

5 In addition, still another aspect of the present invention provides a peptide having an amino acid sequence represented by PD-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys.

Further, still another aspect of the present invention provides a peptide having any one amino acid sequence selected from the group consisting of Ala-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Ala-Lys, HyP-Gly-Gln-
10 Leu-Gly-Leu-Ala, HyP-Gly-Gln-Glu-Gly-Leu-Gly, HyP-Gly-Gln-Leu-Gly-Leu, D-HyP(2R, 4S)-Gly-D-Gln-D-Leu-Gly-D-Leu, HyP-Gly-Gln-Leu-Gly, HyP-Gly-Gln-D-Leu-Gly, and D-HyP(2R, 4S)-Gly-Gln-Leu-Gly.

In addition, still another aspect of the present invention provides a compound represented by Formula 8.

15 Further, still another aspect of the present invention provides a compound represented by Formula 10.

In addition, still another aspect of the present invention provides a pharmaceutical composition for treating an eye disease, which comprises the compound or the peptide as an active pharmaceutical ingredient.

20 Further, still another aspect of the present invention provides a method for treating an eye disease, which comprises administering the compound or the peptide to a subject.

Effects of the Invention

When a novel peptide of the present invention is administered to the eye, it
25 increases the amount of tear secretion and recovers promotes recovery of the damaged cornea. Hence, they can be advantageously used as therapeutic agents for treating eye diseases.

Brief Description of the Drawings

Fig. 1 is a diagram showing the sequence and characteristics of the peptides prepared according to an embodiment of the present invention.

Fig. 2 is a diagram showing a process for synthesizing the peptides prepared
5 according to an embodiment of the present invention.

Fig. 3 is a diagram showing a purification procedure of the peptides prepared according to an embodiment of the present invention.

Fig. 4 is a diagram confirming the purity of YDE-001 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 5 is a diagram confirming the purity of YDE-002 prepared according to an embodiment of the present invention through HPLC.

Fig. 6 is a diagram confirming the purity of YDE-003 prepared according to an embodiment of the present invention through HPLC.

15 Fig. 7 is a diagram confirming the purity of YDE-004 prepared according to an embodiment of the present invention through HPLC.

Fig. 8 is a diagram confirming the purity of YDE-005 prepared according to an embodiment of the present invention through HPLC.

Fig. 9 is a diagram confirming the purity of YDE-006 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 10 is a diagram confirming the purity of YDE-007 prepared according to an embodiment of the present invention through HPLC.

Fig. 11 is a diagram confirming the purity of YDE-008 prepared according to an embodiment of the present invention through HPLC.

25 Fig. 12 is a diagram confirming the purity of YDE-009 prepared according to an embodiment of the present invention through HPLC.

Fig. 13 is a diagram confirming the purity of YDE-010 prepared according to an embodiment of the present invention through HPLC.

Fig. 14 is a diagram confirming the purity of YDE-011 prepared according to an

embodiment of the present invention through HPLC.

Fig. 15 is a diagram confirming the purity of YDE-012 prepared according to an embodiment of the present invention through HPLC.

Fig. 16 is a diagram confirming the purity of YDE-013 prepared according to an
5 embodiment of the present invention through HPLC.

Fig. 17 is a diagram confirming the purity of YDE-014 prepared according to an embodiment of the present invention through HPLC.

Fig. 18 is a diagram confirming the purity of YDE-015 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 19 is a diagram confirming the purity of YDE-016 prepared according to an embodiment of the present invention through HPLC.

Fig. 20 is a diagram confirming the purity of YDE-017 prepared according to an embodiment of the present invention through HPLC.

15 Fig. 21 is a diagram confirming the purity of YDE-018 prepared according to an embodiment of the present invention through HPLC.

Fig. 22 is a diagram confirming the purity of YDE-019 prepared according to an embodiment of the present invention through HPLC.

Fig. 23 is a diagram confirming the purity of YDE-020 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 24 is a diagram confirming the purity of YDE-021 prepared according to an embodiment of the present invention through HPLC.

Fig. 25 is a diagram confirming the purity of YDE-022 prepared according to an embodiment of the present invention through HPLC.

25 Fig. 26 is a diagram confirming the purity of YDE-023 prepared according to an embodiment of the present invention through HPLC.

Fig. 27 is a diagram confirming the purity of YDE-024 prepared according to an embodiment of the present invention through HPLC.

Fig. 28 is a diagram confirming the purity of YDE-025 prepared according to an

embodiment of the present invention through HPLC.

Fig. 29 is a diagram confirming the purity of YDE-026 prepared according to an embodiment of the present invention through HPLC.

Fig. 30 is a diagram confirming the purity of YDE-027 prepared according to an
5 embodiment of the present invention through HPLC.

Fig. 31 is a diagram confirming the purity of YDE-028 prepared according to an embodiment of the present invention through HPLC.

Fig. 32 is a diagram confirming the purity of YDE-029 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 33 is a diagram confirming the purity of YDE-030 prepared according to an embodiment of the present invention through HPLC.

Fig. 34 is a diagram confirming the purity of YDE-031 prepared according to an embodiment of the present invention through HPLC.

15 Fig. 35 is a diagram confirming the purity of YDE-032 prepared according to an embodiment of the present invention through HPLC.

Fig. 36 is a diagram confirming the purity of YDE-033 prepared according to an embodiment of the present invention through HPLC.

Fig. 37 is a diagram confirming the purity of YDE-034 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 38 is a diagram confirming the purity of YDE-035 prepared according to an embodiment of the present invention through HPLC.

Fig. 39 is a diagram confirming the purity of YDE-036 prepared according to an embodiment of the present invention through HPLC.

25 Fig. 40 is a diagram confirming the purity of YDE-037 prepared according to an embodiment of the present invention through HPLC.

Fig. 41 is a diagram confirming the purity of YDE-038 prepared according to an embodiment of the present invention through HPLC.

Fig. 42 is a diagram confirming the purity of YDE-039 prepared according to an

embodiment of the present invention through HPLC.

Fig. 43 is a diagram confirming the purity of YDE-040 prepared according to an embodiment of the present invention through HPLC.

5 Fig. 44 is a diagram confirming the purity of YDE-041 prepared according to an embodiment of the present invention through HPLC.

Fig. 45 is a diagram confirming the purity of YDE-042 prepared according to an embodiment of the present invention through HPLC.

Fig. 46 is a diagram confirming the purity of YDE-043 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 47 is a diagram confirming the purity of YDE-044 prepared according to an embodiment of the present invention through HPLC.

Fig. 48 is a diagram confirming the purity of YDE-045 prepared according to an embodiment of the present invention through HPLC.

15 Fig. 49 is a diagram confirming the purity of YDE-047 prepared according to an embodiment of the present invention through HPLC.

Fig. 50 is a diagram confirming the purity of YDE-048 prepared according to an embodiment of the present invention through HPLC.

Fig. 51 is a diagram confirming the purity of YDE-049 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 52 is a diagram confirming the purity of YDE-050 prepared according to an embodiment of the present invention through HPLC.

Fig. 53 is a diagram confirming the purity of YDE-051 prepared according to an embodiment of the present invention through HPLC.

25 Fig. 54 is a diagram confirming the purity of YDE-052 prepared according to an embodiment of the present invention through HPLC.

Fig. 55 is a diagram confirming the purity of YDE-053 prepared according to an embodiment of the present invention through HPLC.

Fig. 56 is a diagram confirming the purity of YDE-054 prepared according to an

embodiment of the present invention through HPLC.

Fig. 57 is a diagram confirming the purity of YDE-055 prepared according to an embodiment of the present invention through HPLC.

Fig. 58 is a diagram confirming the purity of YDE-056 prepared according to an
5 embodiment of the present invention through HPLC.

Fig. 59 is a diagram confirming the purity of YDE-057 prepared according to an embodiment of the present invention through HPLC.

Fig. 60 is a diagram confirming the purity of YDE-058 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 61 is a diagram confirming the purity of YDE-059 prepared according to an embodiment of the present invention through HPLC.

Fig. 62 is a diagram confirming the purity of YDE-060 prepared according to an embodiment of the present invention through HPLC.

Fig. 63 is a diagram confirming the purity of YDE-064 prepared according to an
15 embodiment of the present invention through HPLC.

Fig. 64 is a diagram confirming the purity of YDE-066 prepared according to an embodiment of the present invention through HPLC.

Fig. 65 is a diagram confirming the purity of YDE-072 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 66 is a diagram confirming the purity of YDE-073 prepared according to an embodiment of the present invention through HPLC.

Fig. 67 is a diagram confirming the purity of YDE-074 prepared according to an embodiment of the present invention through HPLC.

Fig. 68 is a diagram confirming the purity of YDE-075 prepared according to an
25 embodiment of the present invention through HPLC.

Fig. 69 is a diagram confirming the molecular weight of YDE-001 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 70 is a diagram confirming the molecular weight of YDE-002 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 71 is a diagram confirming the molecular weight of YDE-003 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 72 is a diagram confirming the molecular weight of YDE-004 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 73 is a diagram confirming the molecular weight of YDE-005 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 74 is a diagram confirming the molecular weight of YDE-006 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 75 is a diagram confirming the molecular weight of YDE-007 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 76 is a diagram confirming the molecular weight of YDE-008 prepared according to an embodiment of the present invention through Ion-Mass.

15 Fig. 77 is a diagram confirming the molecular weight of YDE-009 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 78 is a diagram confirming the molecular weight of YDE-010 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 79 is a diagram confirming the molecular weight of YDE-011 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 80 is a diagram confirming the molecular weight of YDE-012 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 81 is a diagram confirming the molecular weight of YDE-013 prepared according to an embodiment of the present invention through Ion-Mass.

25 Fig. 82 is a diagram confirming the molecular weight of YDE-014 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 83 is a diagram confirming the molecular weight of YDE-015 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 84 is a diagram confirming the molecular weight of YDE-016 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 85 is a diagram confirming the molecular weight of YDE-017 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 86 is a diagram confirming the molecular weight of YDE-018 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 87 is a diagram confirming the molecular weight of YDE-019 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 88 is a diagram confirming the molecular weight of YDE-020 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 89 is a diagram confirming the molecular weight of YDE-021 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 90 is a diagram confirming the molecular weight of YDE-022 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 91 is a diagram confirming the molecular weight of YDE-023 prepared
15 according to an embodiment of the present invention through Ion-Mass.

Fig. 92 is a diagram confirming the molecular weight of YDE-024 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 93 is a diagram confirming the molecular weight of YDE-025 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 94 is a diagram confirming the molecular weight of YDE-026 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 95 is a diagram confirming the molecular weight of YDE-027 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 96 is a diagram confirming the molecular weight of YDE-028 prepared
25 according to an embodiment of the present invention through Ion-Mass.

Fig. 97 is a diagram confirming the molecular weight of YDE-029 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 98 is a diagram confirming the molecular weight of YDE-030 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 99 is a diagram confirming the molecular weight of YDE-031 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 100 is a diagram confirming the molecular weight of YDE-032 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 101 is a diagram confirming the molecular weight of YDE-033 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 102 is a diagram confirming the molecular weight of YDE-034 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 103 is a diagram confirming the molecular weight of YDE-035 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 104 is a diagram confirming the molecular weight of YDE-036 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 105 is a diagram confirming the molecular weight of YDE-037 prepared
15 according to an embodiment of the present invention through Ion-Mass.

Fig. 106 is a diagram confirming the molecular weight of YDE-038 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 107 is a diagram confirming the molecular weight of YDE-039 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 108 is a diagram confirming the molecular weight of YDE-040 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 109 is a diagram confirming the molecular weight of YDE-041 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 110 is a diagram confirming the molecular weight of YDE-042 prepared
25 according to an embodiment of the present invention through Ion-Mass.

Fig. 111 is a diagram confirming the molecular weight of YDE-043 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 112 is a diagram confirming the molecular weight of YDE-044 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 113 is a diagram confirming the molecular weight of YDE-045 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 114 is a diagram confirming the molecular weight of YDE-047 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 115 is a diagram confirming the molecular weight of YDE-048 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 116 is a diagram confirming the molecular weight of YDE-049 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 117 is a diagram confirming the molecular weight of YDE-050 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 118 is a diagram confirming the molecular weight of YDE-051 prepared according to an embodiment of the present invention through Ion-Mass.

15 Fig. 119 is a diagram confirming the molecular weight of YDE-052 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 120 is a diagram confirming the molecular weight of YDE-053 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 121 is a diagram confirming the molecular weight of YDE-054 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 122 is a diagram confirming the molecular weight of YDE-055 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 123 is a diagram confirming the molecular weight of YDE-056 prepared according to an embodiment of the present invention through Ion-Mass.

25 Fig. 124 is a diagram confirming the molecular weight of YDE-057 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 125 is a diagram confirming the molecular weight of YDE-058 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 126 is a diagram confirming the molecular weight of YDE-059 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 127 is a diagram confirming the molecular weight of YDE-060 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 128 is a diagram confirming the molecular weight of YDE-064 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 129 is a diagram confirming the molecular weight of YDE-066 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 130 is a diagram confirming the molecular weight of YDE-072 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 131 is a diagram confirming the molecular weight of YDE-073 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 132 is a diagram confirming the molecular weight of YDE-074 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 133 is a diagram confirming the molecular weight of YDE-075 prepared
15 according to an embodiment of the present invention through Ion-Mass.

Fig. 134 is a photograph showing a procedure of extraorbital lacrimal gland excision.

Fig. 135 is a diagram showing a change in the body weight of a rat model whose eyes have been administered with YDE-001 to YDE-028.

20 Fig. 136 is a diagram showing a change in the body weight of a rat model whose eyes have been administered with YDE-029 to YDE-043.

Fig. 137 is a photograph showing a procedure of administering an agent to the eyes of a rat model.

Fig. 138 is a photograph showing a procedure of measuring the amount of tear
25 secretion of a rat model using cobalt chloride paper.

Fig. 139 is a photograph showing the results of measuring the amount of tear secretion of a rat model whose eyes have been administered with YDE-001 to YDE-028 using cobalt chloride paper.

Fig. 140 is a diagram showing the changes in the amount of tear secretion of a rat model whose eyes have been administered with YDE-001 to YDE-028.

Fig. 141 is a photograph showing the results of measuring the amount of tear secretion of a rat model whose eyes have been administered with YDE-029 to YDE-043 using cobalt chloride paper.

Fig. 142 is a diagram showing the changes in the amount of tear secretion of a rat model whose eyes have been administered with YDE-029 to YDE-043.

Fig. 143 is a photograph showing a procedure of administering a fluorescent substance to the eyes of a rat model for confirming damage to the cornea thereof.

Fig. 144 is a photograph showing the results of measuring damage to the cornea of a rat model whose eyes have been administered with YDE-001 to YDE-028 using a fluorescent substance.

Fig. 145 is a diagram showing the permeability of a fluorescence dye to confirm the recovery of corneal damage of a rat model whose eyes have been administered with YDE-001 to YDE-028.

Fig. 146 is a photograph showing the results of measuring damage to the cornea of a rat model whose eyes have been administered with YDE-029 to YDE-043 using a fluorescent substance.

Fig. 147 is a diagram showing the permeability of a fluorescence dye to confirm the recovery of corneal damage of a rat model whose eyes have been administered with YDE-029 to YDE-043.

FIG. 148 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 1.

FIG. 149 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 2.

FIG. 150 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 3.

FIG. 151 is a diagram showing the cell growth rate after 48 hours from the

treatment of hEGF on human corneal epithelial cells of plate No. 4.

FIG. 152 is a diagram showing the cell growth rate after 72 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 1.

FIG. 153 is a diagram showing the cell growth rate after 72 hours from the
5 treatment of hEGF on human corneal epithelial cells of plate No. 2.

FIG. 154 is a diagram showing the cell growth rate after 72 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 3.

FIG. 155 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 4.

10 FIG. 156 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YY-101 on human corneal epithelial cells.

FIG. 157 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YY-102 on human corneal epithelial cells.

15 FIG. 158 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-011 on human corneal epithelial cells.

FIG. 159 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-038 on human corneal epithelial cells.

FIG. 160 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-042 on human corneal epithelial cells.

20 FIG. 161 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-043 on human corneal epithelial cells.

FIG. 162 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-044 on human corneal epithelial cells.

25 FIG. 163 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-045 on human corneal epithelial cells.

FIG. 164 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-049 on human corneal epithelial cells.

FIG. 165 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72

hours from the treatment of YDE-054 on human corneal epithelial cells.

FIG. 166 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-057 on human corneal epithelial cells.

FIG. 167 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-058 on human corneal epithelial cells.

FIG. 168 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-059 on human corneal epithelial cells.

FIG. 169 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-060 on human corneal epithelial cells.

FIG. 170 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-072 on human corneal epithelial cells.

FIG. 171 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-073 on human corneal epithelial cells.

FIG. 172 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-074 on human corneal epithelial cells.

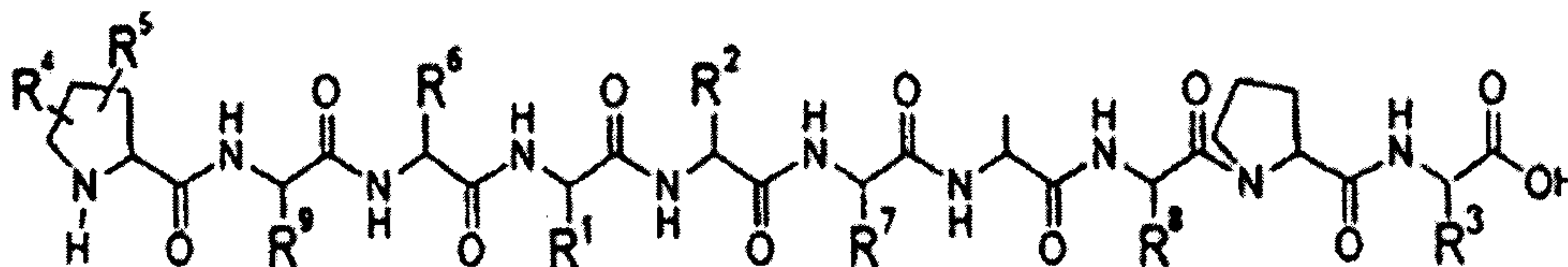
FIG. 173 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-075 on human corneal epithelial cells.

Detailed Description of the Invention

Hereinafter, the present invention will be described in detail.

An aspect of the present invention provides a compound represented by Formula 1.

[Formula 1]



In the above formula,

R¹ to R³ are each independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₁₀ alkoxy, substituted or unsubstituted C₁₋₁₀ haloalkyl, substituted or unsubstituted C₂₋₁₀ alkenyl, substituted or unsubstituted C₂₋₁₀ alkynyl, substituted or unsubstituted C₁₋₁₀ alkylene, substituted or unsubstituted C₁₋₁₀ alkenylene, substituted or unsubstituted C₁₋₁₀ alkynylene, substituted or unsubstituted C₅₋₁₂ aryl, substituted or unsubstituted C₇₋₁₂ arylalkyl, substituted or unsubstituted C₅₋₁₄ arylalkynyl, substituted or unsubstituted C₈₋₁₆ arylalkenyl, substituted or unsubstituted C₃₋₁₀ heteroalkyl, substituted or unsubstituted C₃₋₁₀ cycloalkyl, substituted or unsubstituted C₃₋₁₀ heterocycloalkyl, or substituted or unsubstituted C₅₋₁₂ heteroaryl, the heteroalkyl, heterocycloalkyl, or heteroaryl containing at least one of N, O, and S,

the substitution refers to a substitution with one or more non-hydrogen substituents, each non-hydrogen substituent being selected from the group consisting of -X₁, -R_a, -O⁻, =O, -OR_a, -SR_a, -S⁻, -N(R_a)₂, -N⁺(R_a)₃, =NR_a, -C(X₁)₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N-OH, =N₂, -N₃, -NHC(=O)R_a, -C(=O)R_a, -C(=O)NR_aR_a, -S(=O)₂O⁻, -S(=O)₂OH, -S(=O)₂R_a, -OS(=O)₂OR_a, -S(=O)₂NR_a, -S(=O)R_a, -OP(=O)(OR_a)₂, -C(=O)R_a, alkylene-C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, alkylene-C(=O)OR_a, -C(=O)O⁻, alkylene-C(=O)O⁻, -C(=S)OR_a, -C(=O)SR_a, -C(=S)SR_a, -C(=O)NR_aR_a, alkylene-C(=O)NR_aR_a, -C(=S)NR_aR_a, and -C(-NR_a)NR_aR_a, each X₁ is independently selected from F, Cl, Br, or I, each R_a is independently selected from hydrogen, C₁₋₆ alkyl, C₅₋₁₂ aryl, C₇₋₁₂ arylalkyl, or heterocycle,

R⁴ and R⁵ are each independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, -X₂, -R_b, -O⁻, =O, -CH₂OR_b, or -OR_b, X₂ is F, Cl, Br, or I, and R_b is H, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₅₋₁₂ aryl, substituted or unsubstituted C₇₋₁₂ arylalkyl, or substituted or unsubstituted heterocycle,

R⁶ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl, the substituent being -C(=O)NH₂,

R⁷ is hydrogen or C₁₋₆ alkyl, and

R⁸ and R⁹ are each independently hydrogen or unsubstituted C₁₋₆ alkyl.

In the definition of R_b , the substitution refers to a substitution with the non-hydrogen substituent.

According to the convention used in the art,  in the formulae herein is used to denote a bond, where a moiety or a substituent is attached to the nucleus or the backbone structure.

“Alkyl” is a hydrocarbon having primary, secondary, tertiary, and/or cyclic carbon atoms. For example, an alkyl group may have 1 to 20 carbon atoms (i.e., C_1 - C_{20} alkyl), 1 to 10 carbon atoms (i.e., C_1 - C_{10} alkyl), or 1 to 6 carbon atoms (i.e., C_1 - C_6 alkyl). Examples of a suitable alkyl group include methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$), and octyl ($-(CH_2)_7CH_3$), but it is not limited thereto.

“Alkoxy” refers to a group having the formula $-O$ -alkyl, wherein the alkyl group as defined above is attached to the parent compound via an oxygen atom. The alkyl moiety of the alkoxy group may have 1 to 20 carbon atoms (i.e., C_1 - C_{20} alkoxy), 1 to 12 carbon atoms (i.e., C_1 - C_{12} alkoxy), or 1 to 6 carbon atoms (i.e., C_1 - C_6 alkoxy). Examples of a suitable alkoxy group include methoxy ($-O-CH_3$ or $-OMe$), ethoxy ($-O-CH_2CH_3$), and propoxy ($-O-CH_2CH_2CH_3$), but it is not limited thereto.

OCH₂CH₃ or -OEt), and t-butoxy (-OC(CH₃)₃ or -O-tBu), but it is not limited thereto.

“Haloalkyl” is an alkyl group in which at least one of the hydrogen atoms of the alkyl group as defined above is substituted by a halogen atom. The alkyl moiety of the haloalkyl group may have 1 to 20 carbon atoms (i.e., C₁-C₂₀ haloalkyl), 1 to 12 carbon
 5 atoms (i.e., C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (i.e., C₁-C₆ haloalkyl). Examples of a suitable haloalkyl group include -CF₃, -CHF₂, -CFH₂, and -CH₂CF₃, but it is not limited thereto.

“Alkenyl” is a hydrocarbon having primary, secondary, tertiary, and/or cyclic carbon atoms, and having at least one unsaturated region, i.e., a carbon-carbon sp²
 10 double bond. For example, an alkenyl group may have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkenyl), 2 to 12 carbon atoms (i.e., C₂-C₁₂ alkenyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkenyl). Examples of a suitable alkenyl group include vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂), but it is not limited thereto.

15 “Alkynyl” is a hydrocarbon having primary, secondary, tertiary, and/or cyclic carbon atoms, and having at least two unsaturated regions, i.e., one carbon-carbon sp triple bond. For example, an alkynyl group may have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkynyl), 2 to 12 carbon atoms (i.e., C₂-C₁₂ alkynyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkynyl). Examples of a suitable alkenyl group include acetylenic (-C≡CH) and
 20 propargyl (-CH₂C≡CH), but it is not limited thereto.

“Alkylene” refers to a saturated hydrocarbon group that may be branched, straight, or cyclic and has two valencies derived by a removal of two hydrogen atoms from the same carbon atom or two different carbon atoms of a parent alkane. For example, an alkylene group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon
 25 atoms. Examples of a typical alkylene radical include methylene (-CH₂-), 1,1-ethylene (-CH(CH₃)-), 1,2-ethylene (-CH₂CH₂-), 1,1-propylene (-CH(CH₂CH₃)-), 1,2-propylene (-CH₂CH(CH₃)-), 1,3-propylene (-CH₂CH₂CH₂-), and 1,4-butylene (-CH₂CH₂CH₂CH₂-), but it is not limited thereto.

“Alkenylene” refers to an unsaturated hydrocarbon group that may be branched, straight, and/or cyclic and has two valencies derived by a removal of two hydrogen atoms from the same carbon atom or two different carbon atoms of a parent alkene. For example, an alkenylene group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Examples of a typical alkenylene group include 1,2-ethylene (-CH=CH-), but it is not limited thereto.

“Alkynylene” refers to an unsaturated hydrocarbon group that is branched, straight, and/or cyclic and has two valencies derived by a removal of two hydrogen atoms from the same carbon atom or two different carbon atoms of a parent alkyne. For example, an alkynylene group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Examples of a typical alkynylene radical include acetylenylene (-C≡C-), propargylene (-CH₂C≡C-), and 4-pentynylene (-CH₂CH₂CH₂C≡C-), but it is not limited thereto.

“Aryl” refers to an aromatic hydrocarbon group derived by a removal of one hydrogen atom from the six carbon atoms of a parent aromatic ring system. For example, an aryl group may have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Examples of a typical aryl group include a radical derived from benzene (e.g., phenyl), substituted benzene, substituted or unsubstituted naphthalene, substituted or unsubstituted anthracene, substituted or unsubstituted biphenyl, and the like, but it is not limited thereto.

“Arylalkyl” refers to an acyclic alkyl group in which one hydrogen atom bonded to a carbon atom, typically a terminal or other sp³ carbon atom, is substituted by an aryl group. Examples of a typical arylalkyl group include benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethane-1-yl, naphthobenzyl, 2-naphthophenylethane-1-yl, and the like (each of which is substituted or unsubstituted), but it is not limited thereto. An arylalkyl group may have 7 to 20 carbon atoms. For example, the alkyl moiety thereof may have 1 to 6 carbon atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

“Arylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom although an sp^2 carbon atom is also available, is substituted with an aryl radical. The aryl moiety of the arylalkenyl may be, for example, any aryl group described herein, and the alkenyl moiety of the arylalkenyl may comprise, for example, any of the alkenyl groups described herein. An arylalkenyl group may have 8 to 20 carbon atoms. For example, the alkenyl moiety thereof may have 2 to 6 carbon atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

“Cycloalkyl” refers to a saturated monocycle or polycycle that comprises only carbon atoms in the ring. A cycloalkyl group may have 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. A monocyclic cycloalkyl has 3 to 6 ring atoms, more typically 5 or 6 ring atoms. A bicyclic cycloalkyl may have 7 to 12 ring atoms arranged in a bicyclo[4,5], [5,5], [5,6], or [6,6] system or 9 to 10 ring atoms arranged in a bicyclo[5,6] or [6,6] system or in a spiro-bonded ring. Non-limiting examples of a monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl (each of which may be substituted or unsubstituted).

“Arylalkynyl” refers to an acyclic alkynyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or other sp^3 carbon atom, although an sp carbon atom may also be used, is substituted by an aryl group. The aryl moiety of the arylalkynyl may be, for example, any aryl group described herein, and the alkynyl moiety of the arylalkynyl may comprise, for example, any of the alkynyl groups described herein. An arylalkynyl group may have 8 to 20 carbon atoms. For example, the alkynyl moiety thereof may have 2 to 6 carbon atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

The term “substituted” with respect to alkyl, alkylene, aryl, arylalkyl, heterocyclyl, and the like, for example, “substituted alkyl,” “substituted alkylene,” “substituted aryl,” “substituted arylalkyl,” “substituted heterocyclyl,” and “substituted carbocyclyl (e.g.,

substituted cycloalkyl),” means that at least one hydrogen atom of the alkyl, alkylene, aryl, arylalkyl, heterocyclyl, or carbocyclyl (e.g., cycloalkyl) is each independently substituted by a non-hydrogen substituent. Examples of the typical substituent include -X, -R, -O⁻, =O, -OR, -SR, -S⁻, -NR₂, -N⁺R₃, =NR, -C(X)₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N-OH, =N₂, -N₃, -NHC(=O)R, -C(=O)R, -C(=O)NRR, -S(=O)₂O⁻, -S(=O)₂OH, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂NR, -S(=O)R, -OP(=O)(OR)₂, -C(=O)R, alkylene-C(=O)R, -C(S)R, -C(=O)OR, alkylene-C(=O)OR, -C(=O)O⁻, alkylene-C(=O)O⁻, -C(=S)OR, -C(=O)SR, -C(=S)SR, -C(=O)NRR, alkylene-C(=O)NRR, -C(=S)NRR, and -C(-NR)NRR, wherein X is each independently halogen such as F, Cl, Br, or I, and R is independently H, alkyl, aryl, arylalkyl, or heterocycle, but it is not limited thereto. The alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

Those skilled in the art will understand that when a moiety such as “alkyl,” “aryl,” “heterocyclyl,” and the like is substituted with at least one substituent, they may optionally be referred to as a moiety of “alkylene,” “arylene,” “heterocyclylene,” or the like (that is, at least one hydrogen atom of the parent “alkyl,” “aryl,” or “heterocyclyl” moiety is substituted by the substituent as described herein). If the moiety of “alkyl,” “aryl,” “heterocyclyl,” or the like is described herein as “substituted” or depicted in the drawings as substituted (or optionally substituted, for example, the number of substituents is 0 or a positive number), the term “alkyl,” “aryl,” “heterocyclyl,” or the like should be understood to be interchangeable with “alkylene,” “arylene,” “heterocyclylene,” or the like.

Those skilled in the art will recognize that the substituents and other moieties of the compound of Formula 1 should be selected so as to provide a compound that is sufficiently stable as a pharmaceutically useful compound that can be formulated into an acceptably stable pharmaceutical composition. The compound of Formula 1 having such stability is to be understood to fall within the scope of the present invention.

“Heteroalkyl” refers to an alkyl group in which at least one carbon atom is

substituted by a heteroatom such as O, N, or S. For example, if a carbon atom of the alkyl group attached to a parent molecule is substituted by a heteroatom (e.g., O, N, or S), the resulting heteroalkyl group may be an alkoxy group (e.g., -OCH₃), an amine group (e.g., -NHCH₃, -N(CH₃)₂, or the like), or a thioalkyl group (e.g., -SCH₃), respectively. If a non-terminal carbon atom of the alkyl group that is not attached to a parent molecule is substituted by a heteroatom (e.g., O, N, or S), the resulting heteroalkyl group may be an alkyl ether (e.g., -CH₂CH₂-O-CH₃ or the like), an alkylamine (e.g., -CH₂NHCH₃, -CH₂N(CH₃)₂, or the like), or a thioalkyl ether (e.g., -CH₂-S-CH₃), respectively. If the terminal carbon atom of the alkyl group is substituted by a heteroatom (for example, O, N, or S), the resulting heteroalkyl group may be a hydroxyalkyl group (e.g., -CH₂CH₂-OH), an aminoalkyl group (e.g., -CH₂NH₂), or an alkylthiol group (e.g., -CH₂CH₂-SH), respectively. For example, a heteroalkyl group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C₁-C₆ heteroalkyl group refers to a heteroalkyl group having 1 to 6 carbon atoms.

The term "heterocycle" or "heterocyclyl" used herein includes those described in the documents such as Paquette, Leo A., Principles of Modern Heterocyclic Chemistry (W. A. Benjamin, New York, 1968), specifically Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs (John Wiley & Sons, New York, from 1950 to the present), specifically Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566, but it is not limited thereto. In a specific embodiment of the present invention, "heterocycle" includes "carbocycle" as defined herein in which at least one (e.g., 1, 2, 3, or 4) carbon atom is substituted by a heteroatom (e.g., O, N, or S). The term "heterocycle" or "heterocyclyl" includes saturated, partially unsaturated, and aromatic rings (i.e., a heteroaromatic ring). Substituted heterocycle, for example, includes a heterocyclic ring substituted with any of the substituents disclosed herein, inclusive of a carbonyl group.

Examples of heterocycles include pyridyl, dihydropyridyl, tetrahydropyridyl(piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur-oxidized

tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidinyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, 5 octahydroisoquinolinyl, azocynyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxatiny, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phtheridinyl, 4aH-carbazolyl, 10 carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperazinyl, indoliny, isoindoliny, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, isothinoyl, and bis-tetrahydrofuranyl (each of which may 15 be substituted or unsubstituted), but it is not limited thereto.

As an example, a carbon-bonded heterocycle may be bonded at the 2, 3, 4, 5, or 6-position of pyrazine, at the 3, 4, 5, or 6-position of pyridazine, at the 2, 4, 5, or 6-position of pyrimidine, at the 2, 3, 5, or 6-position of pyrazine, at the 2, 3, 4, or 5-position of furan, tetrahydrofuran, thiofuran, thiophene, pyrrole, or tetrahydropyrrole, 20 at the 2, 4, or 5-position of oxazole, imidazole, or thiazole, at the 3, 4, or 5-position of isoxazole, pyrazole, or isothiazole, at the 2 or 3-position of aziridine, at the 2, 3, or 4-position of azetidine, at the 2, 3, 4, 5, 6, 7, or 8-position of quinoline, or at the 1, 3, 4, 5, 6, 7, or 8-position of isoquinoline, but it is not limited thereto. More typically, examples of a carbon-bonded heterocycle include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5- 25 pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl (each of which may be substituted or unsubstituted).

As an example, a nitrogen-bonded heterocycle may be bonded at the 1-position of aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, or 1H-indazole, at the 2-position of isoindole or isoindoline, at the 4-position of morpholine, and at the 9-position of carbazole or β -carboline (each of which may be substituted or unsubstituted), but it is not limited thereto. More typically, examples of a nitrogen-bonded heterocycle include 1-aziridinyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl (each of which may be substituted or unsubstituted).

“Heterocyclalkyl” refers to an acyclic alkyl radical in which one hydrogen atom bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is substituted by a heterocyclalkyl radical (i.e., a heterocyclalkyl-alkylene moiety). Examples of a typical heterocyclalkyl group include heterocyclalkyl-CH₂-, 2-(heterocyclalkyl)ethan-1-yl, and the like, but it is not limited thereto. The “heterocyclalkyl” moiety thereof used herein includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocyclalkyl group described above. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocyclalkyl group may be attached to the alkyl moiety of the heterocyclalkyl through a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclalkyl group may have 2 to 20 carbon atoms. For example, the alkyl moiety of the heterocyclalkyl group may have 1 to 6 carbon atoms, and the heterocyclalkyl moiety thereof may have 1 to 14 carbon atoms. Examples of the heterocyclalkyl include a 5-membered heterocycle containing sulfur, oxygen, and/or nitrogen such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, and the like; and a 6-membered heterocycle containing sulfur, oxygen, and/or nitrogen such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridazylmethyl, pyrimidinylmethyl, pyrazinylmethyl, and the like (each of which may be substituted or unsubstituted), but it is not limited thereto.

“Heterocyclalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom (although an sp^2 carbon atom may also be used), is substituted by a heterocycl radical (i.e., a heterocycl-alkenylene moiety). The heterocycl moiety of the heterocyclalkenyl group includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocycl group described herein. The alkenyl moiety of the heterocyclalkenyl group includes any alkenyl group described herein. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocycl group may be attached to the alkenyl moiety of the heterocyclalkenyl via a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclalkenyl group may have 3 to 20 carbon atoms. For example, the alkenyl moiety of the heterocyclalkenyl group may have 2 to 6 carbon atoms, and the heterocycl moiety thereof may have 1 to 14 carbon atoms.

“Heterocyclalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom (although an sp carbon atom may also be used), is substituted by a heterocycl radical (i.e., a heterocycl-alkynylene moiety). The heterocycl moiety of the heterocyclalkynyl group includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocycl group described herein. The alkynyl moiety of the heterocyclalkynyl group includes any alkynyl group described herein. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocycl group may be attached to the alkynyl moiety of the heterocyclalkynyl via a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclalkynyl group may have 3 to 20 carbon atoms. For example, the alkynyl moiety of the heterocyclalkynyl group may have 2 to 6 carbon atoms, and the heterocycl moiety thereof may have 1 to 14 carbon atoms.

“Heteroaryl” refers to an aromatic heterocycl containing at least one heteroatom in the ring. Non-limiting examples of a suitable heteroatom that may be contained in

the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of a heteroaryl ring include all of those enumerated in the definition of “heterocyclcyl” herein, inclusive of pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, furinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, and the like (each of which may be substituted or unsubstituted).

“Carbocycle” or “carbocyclcyl” refers to a saturated, partially unsaturated, or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. A monocyclic carbocycle has 3 to 6 ring atoms, more typically 5 or 6 ring atoms. A bicyclic carbocycle has 7 to 12 ring atoms arranged in a bicyclo[4,5], [5,5], [5,6], or [6,6] system or 9 to 10 ring atoms arranged in a bicyclo[5,6] or [6,6] system. Examples of a monocyclic or bicyclic carbocycle include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, and naphthyl (each of which may be substituted or unsubstituted).

“Acyl” refers to -C(=O)-alkyl, -C(=O)-carbocycle (which is substituted or unsubstituted), and -C(=O)-heterocycle (which is substituted or unsubstituted), wherein the alkyl, carbocycle, or heterocycle moiety is as defined herein. Non-limiting examples of “acyl” include -C(=O)CH₃, -C(=O)CH₂CH₃, -C(=O)CH(CH₃)₂, -C(=O)C(CH₃)₃, -C(=O)-phenyl (which is substituted or unsubstituted), -C(=O)-cyclopropyl (which is substituted or unsubstituted), -C(=O)-cyclobutyl (which is substituted or unsubstituted), -C(=O)-cyclopentyl (which is substituted or unsubstituted), -C(=O)-cyclohexyl (which is substituted or unsubstituted), and -C(=O)-pyridyl (which is substituted or unsubstituted).

“Arylheteroalkyl” refers to a heteroalkyl as defined herein, wherein a hydrogen atom (which may be attached to either a carbon atom or a heteroatom) is substituted by an aryl group as defined herein. If the resulting group is chemically stable, the aryl

group may be attached to a carbon atom of the heteroalkyl group or the heteroatom of the heteroalkyl group. For example, an arylheteroalkyl group may have a formula of -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, or the like. In addition, any
 5 alkylene moiety in the above formulae may be further substituted with any of the substituents defined or exemplified herein.

“Heteroarylalkyl” refers to an alkyl group as defined herein, wherein a hydrogen atom is substituted by a heteroaryl group as defined herein. Non-limiting examples of heteroarylalkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -
 10 CH₂-isoindolyl, -CH₂-furinyl, -CH₂-furanyl, -CH₂-thienyl, -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl, -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-furinyl, -CH(CH₃)-
 15 furanyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranyl, -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl, -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl, -CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-pyrazyl, and the like.

20 “Silyloxy” refers to the group -O-SiR₃, wherein R comprises alkyl, aryl (which is substituted or unsubstituted), heteroaryl (which is substituted or unsubstituted), or a combination thereof. Non-limiting examples of silyloxy include -O-Si(CH₃)₃, -O-Si(CH₃)₂tBu, -O-Si(tBu)₂CH₃, -O-Si(tBu)₃, -O-Si(CH₃)₂Ph, -O-Si(Ph)₂CH₃, and -O-Si(Ph)₃.

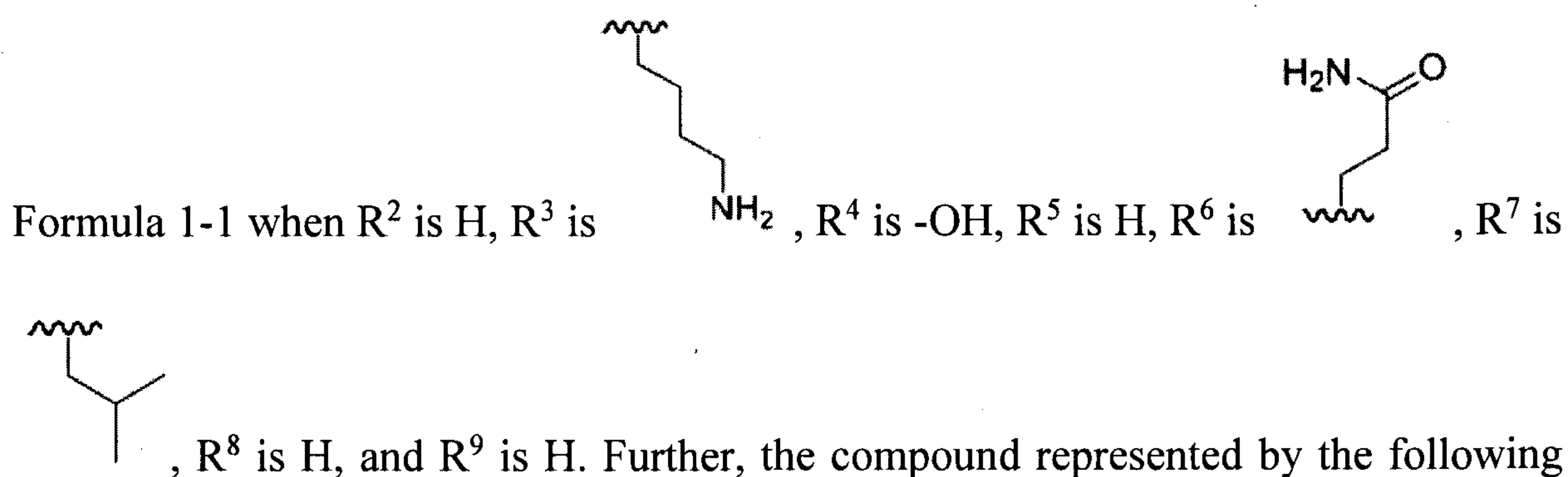
25 The term “optionally substituted” refers to a particular moiety (e.g., an optionally substituted aryl group) of the compound of Formula 1 that has one, two, or more substituents.

The term “ester thereof” refers to any ester of a compound wherein any -COOH

functional group of the molecule is substituted to a -COOR functional group or any -OH functional group of the molecule is substituted to a -C(=O)OR. Here, the R moiety of the ester may be any carbon-containing group that forms a stable ester moiety, which includes, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, and substituted derivatives thereof. Examples of the ester may also include an ester such as those described above of a “tautomeric enol” as described below.

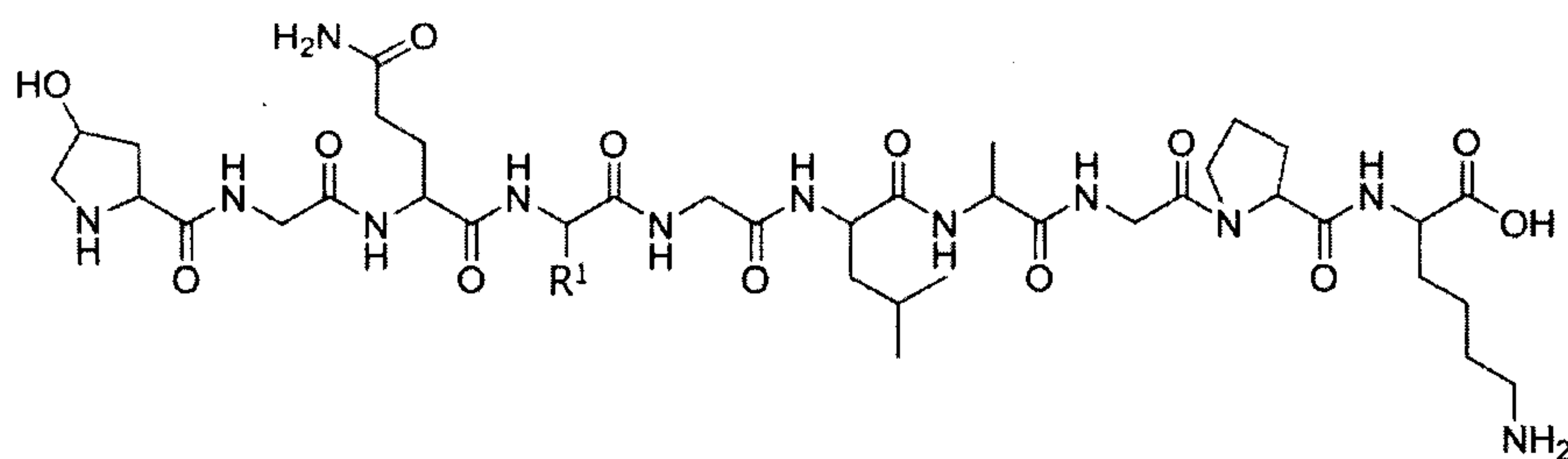
In the present invention, the compound represented by the above Formula 1 may be an optical isomer type L or D.

10 The compound represented by the above Formula 1 may be represented by



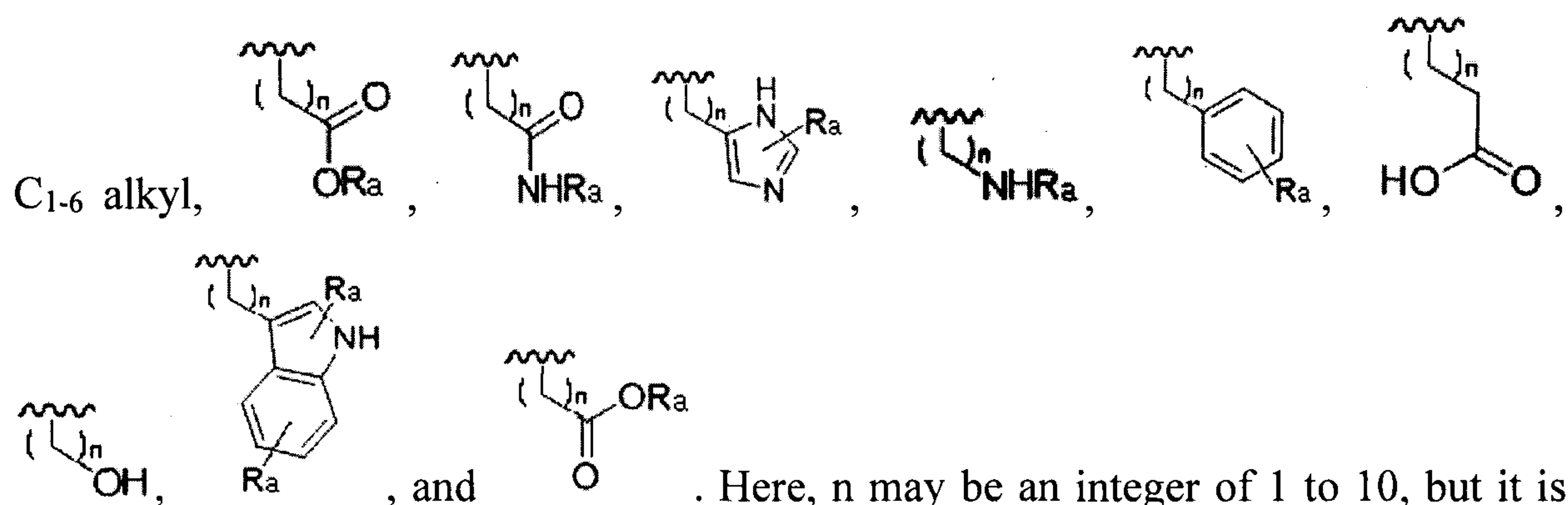
Formula 1-1 may be an optical isomer type L or D.

[Formula 1-1]



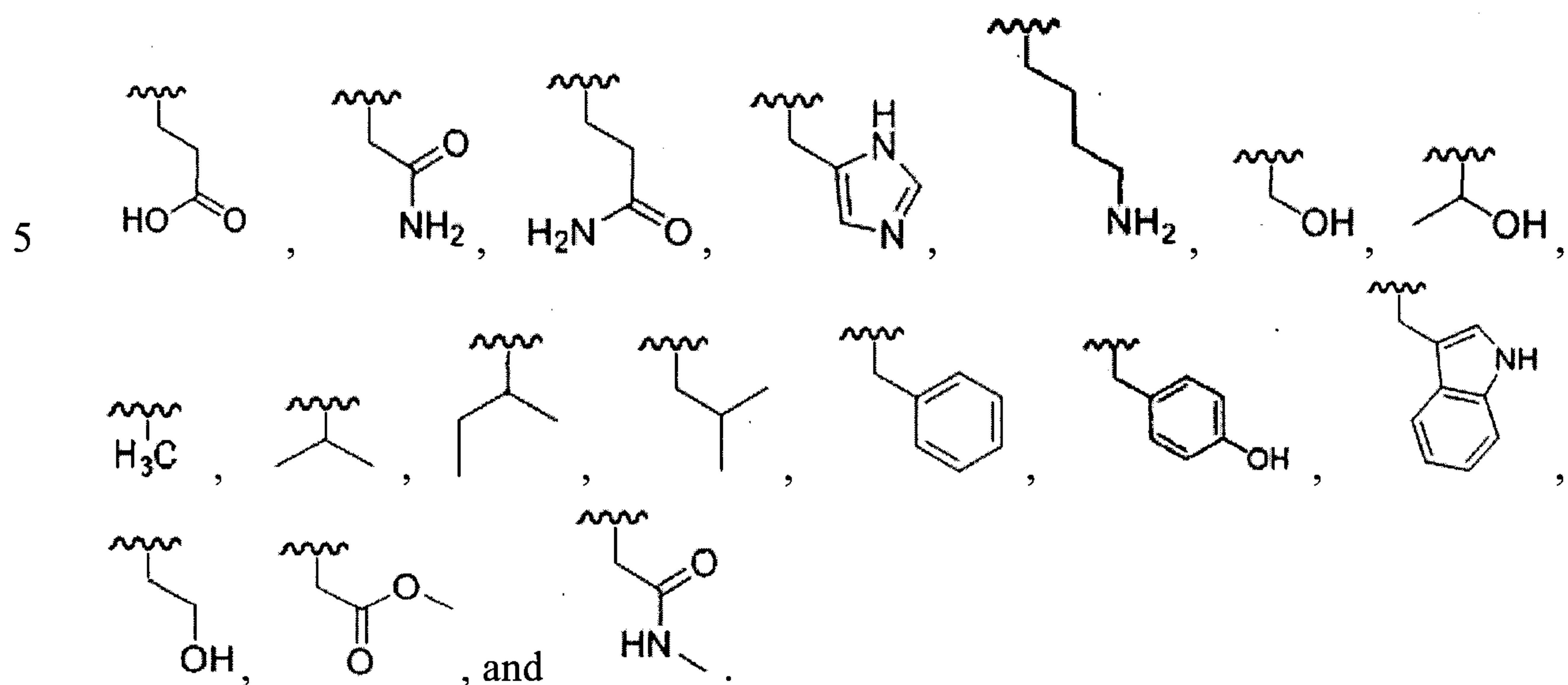
15

R¹ may be one selected from the group consisting of substituted or unsubstituted



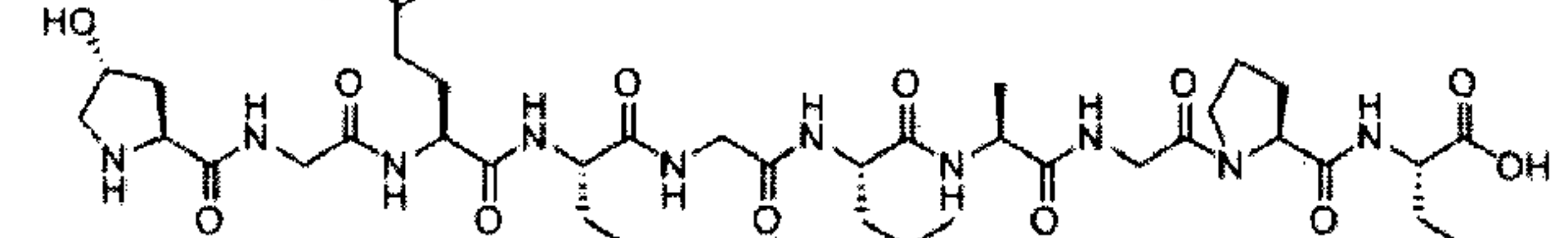
not limited thereto. R_a may be hydrogen or C₁₋₆ alkyl.

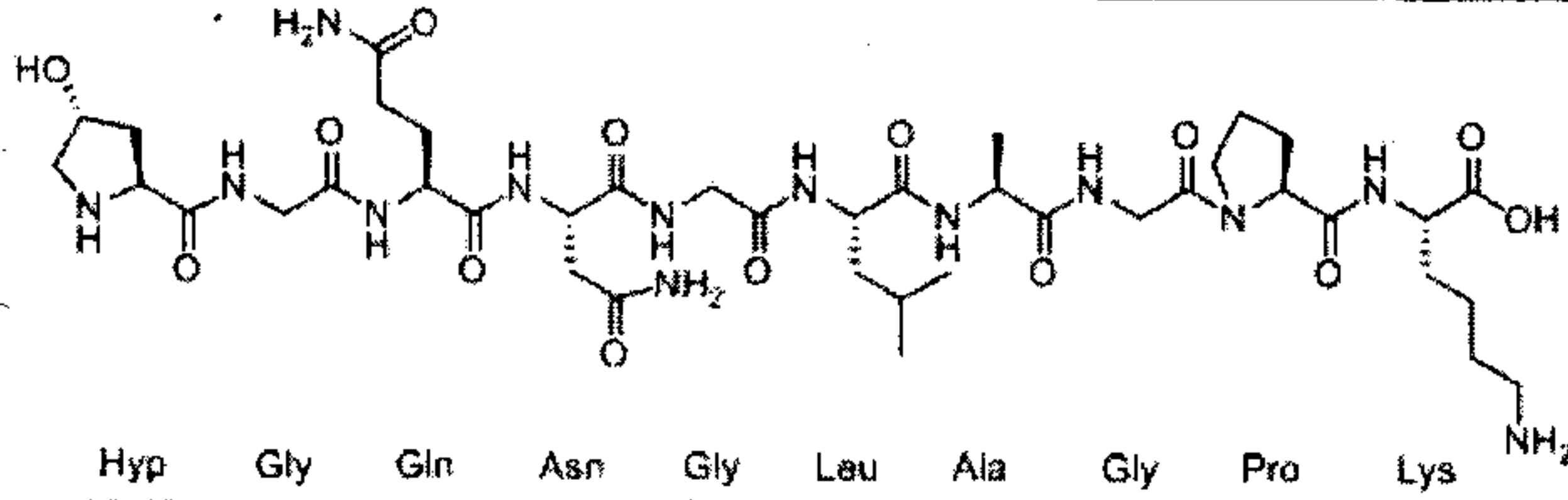
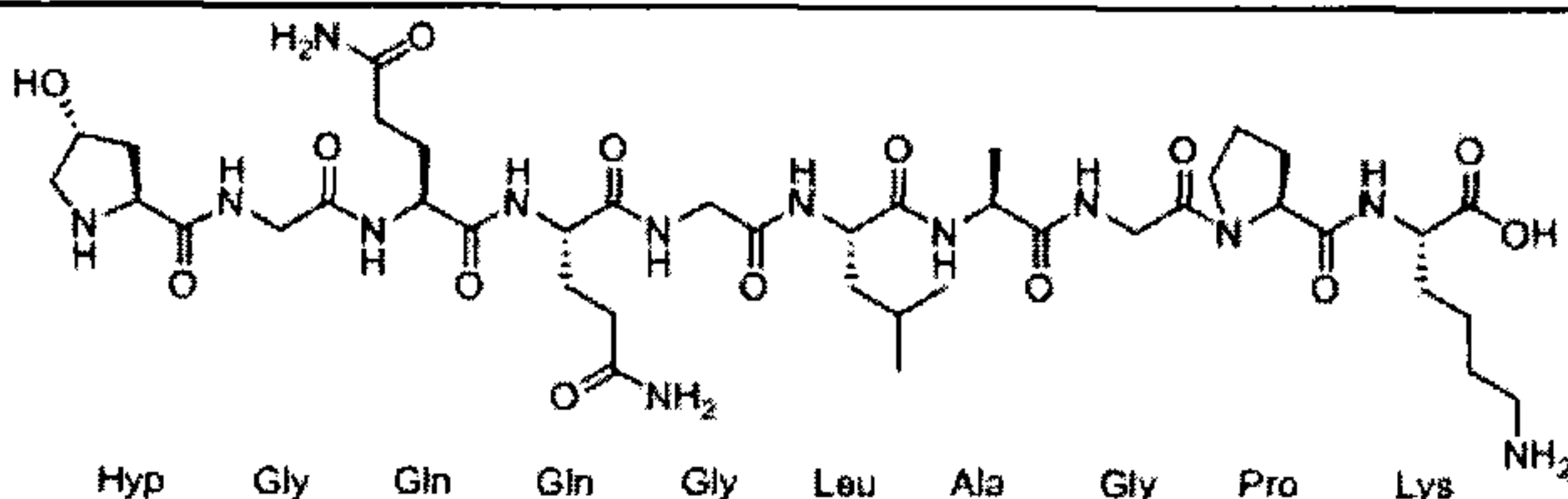
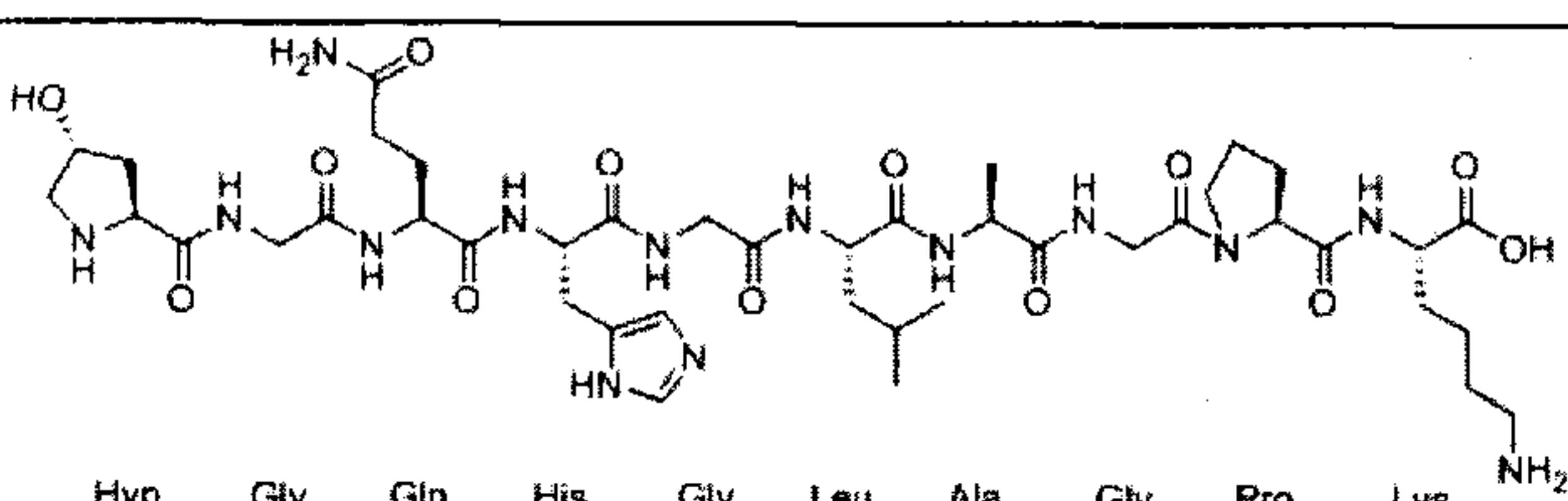
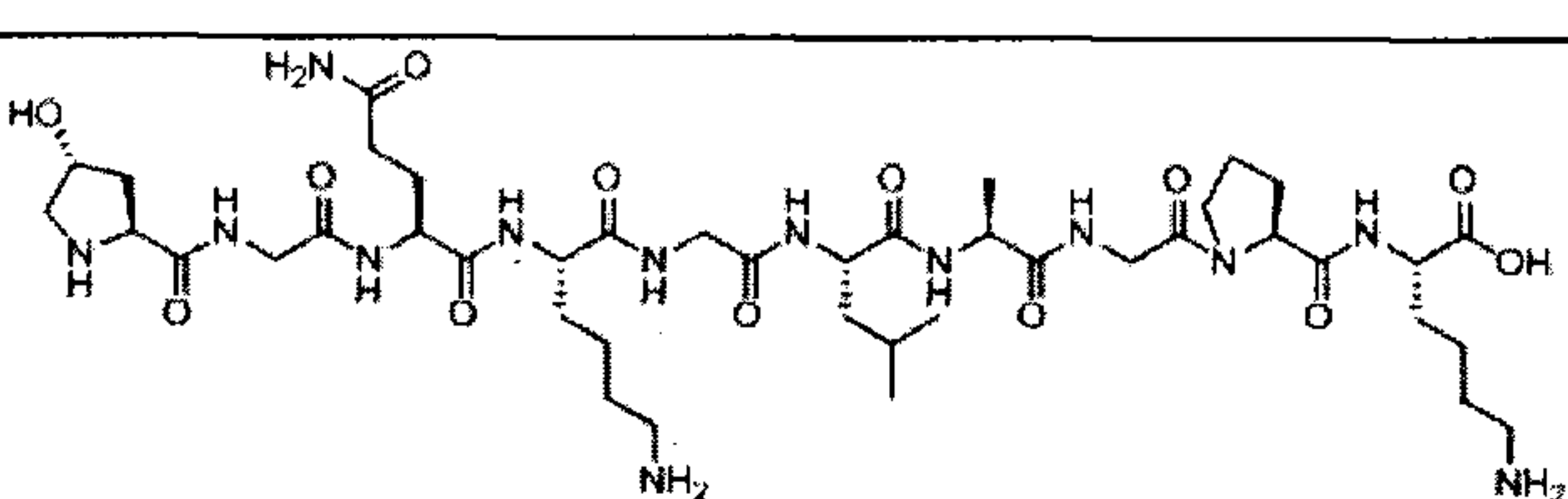
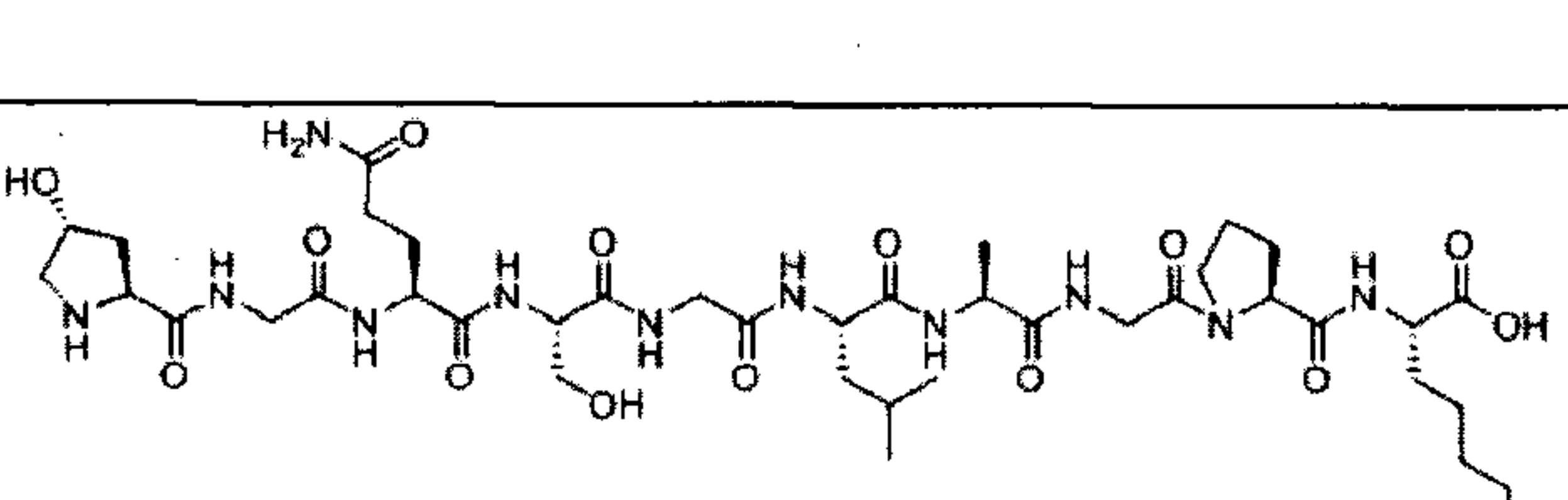
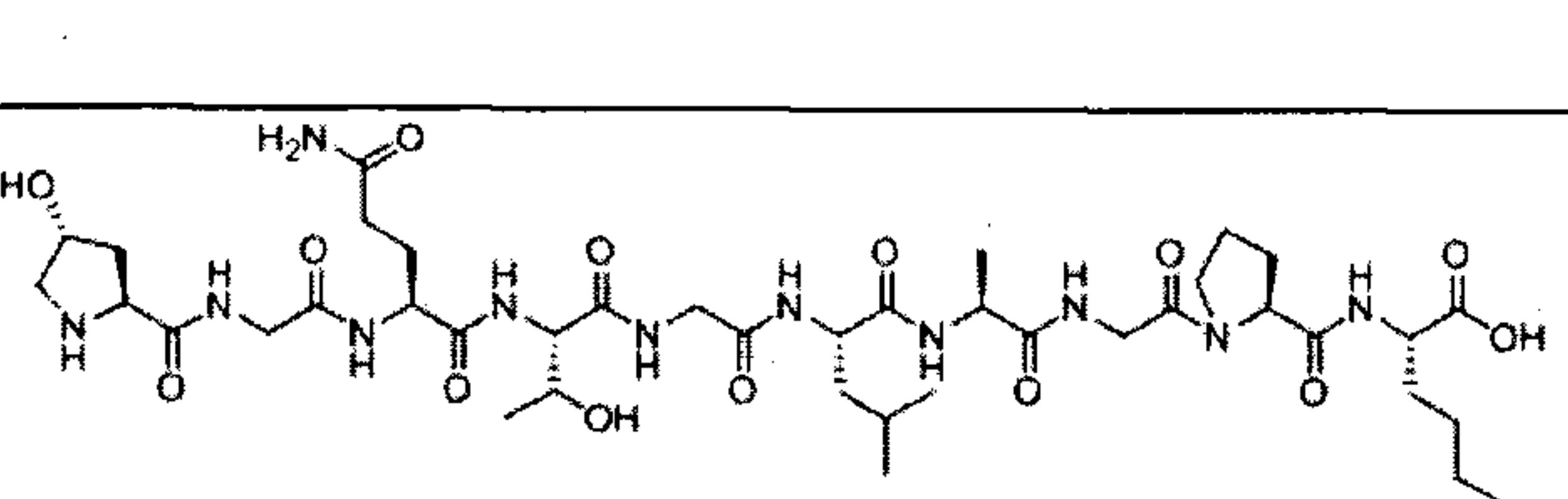
Specifically, R^1 may be one selected from the group consisting of

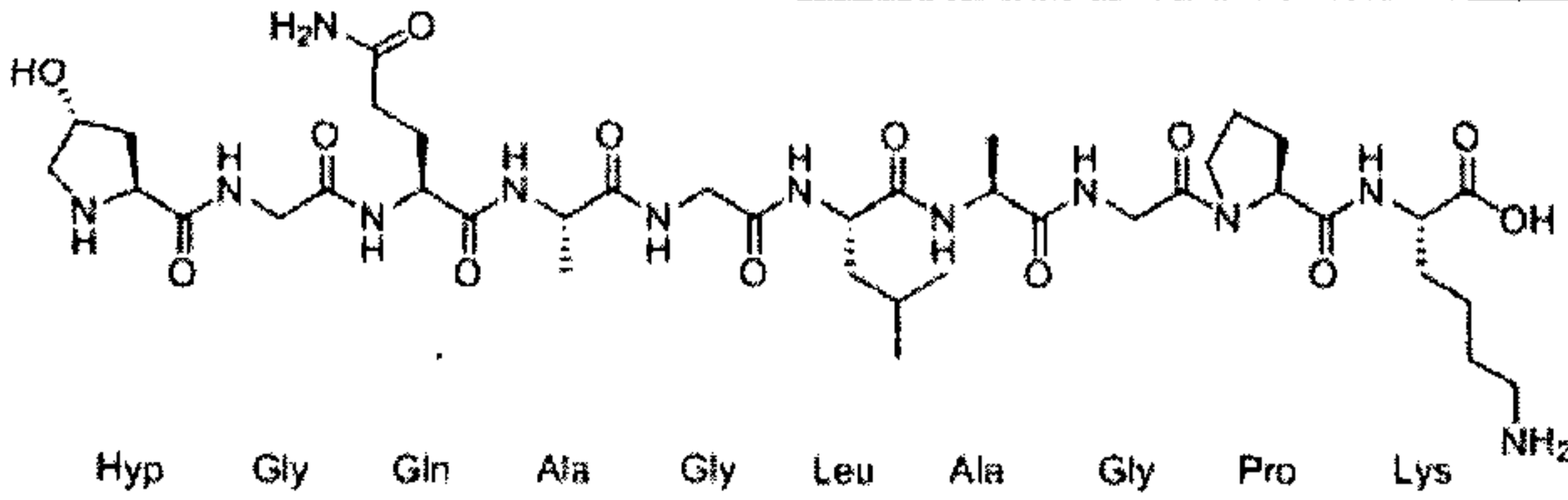
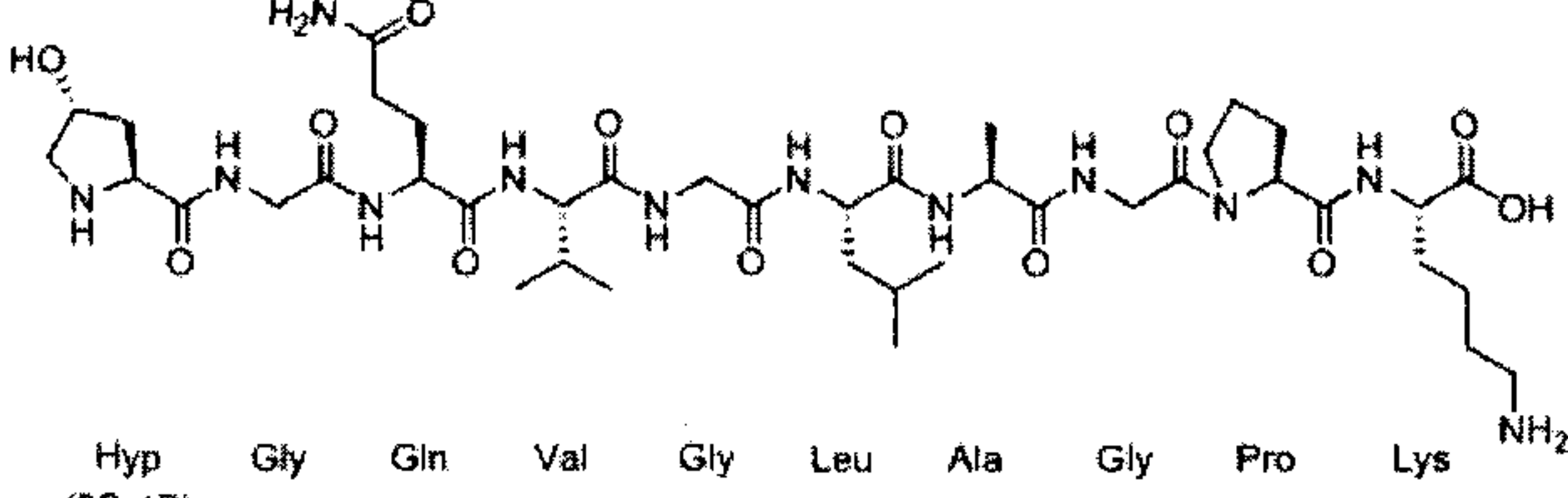
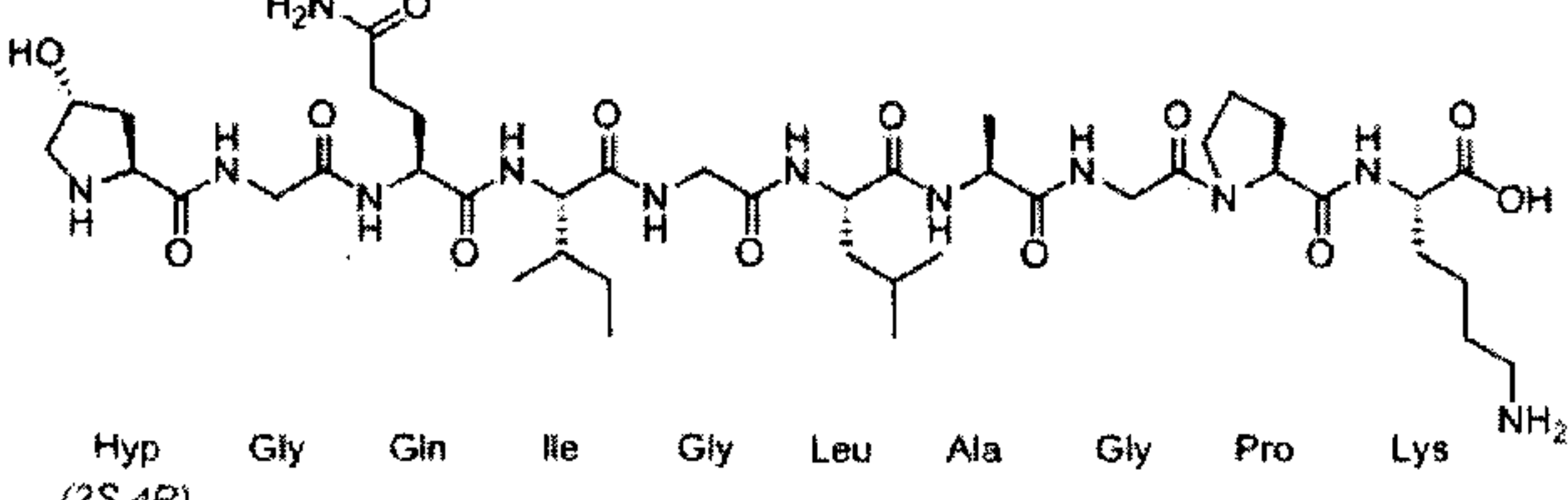
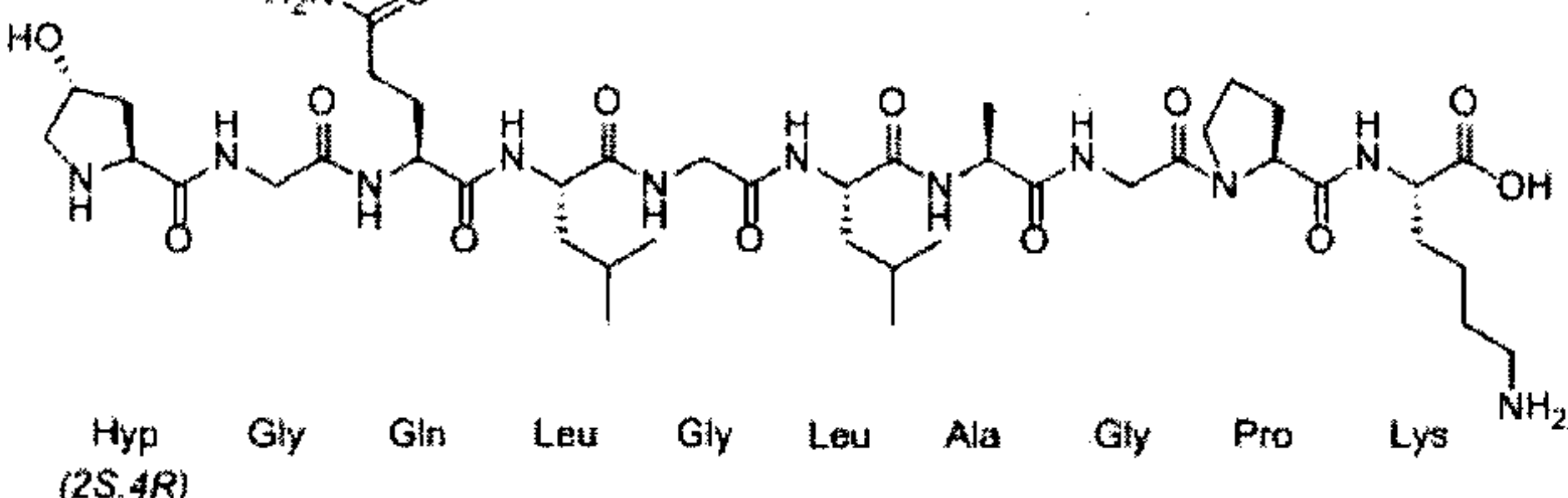
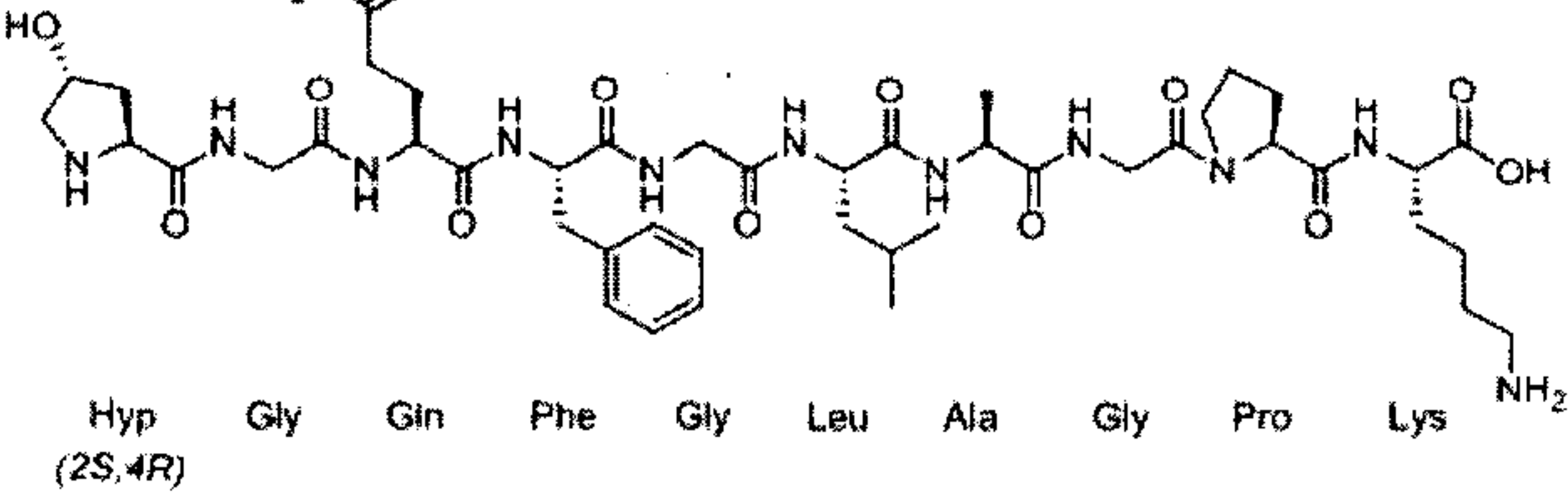
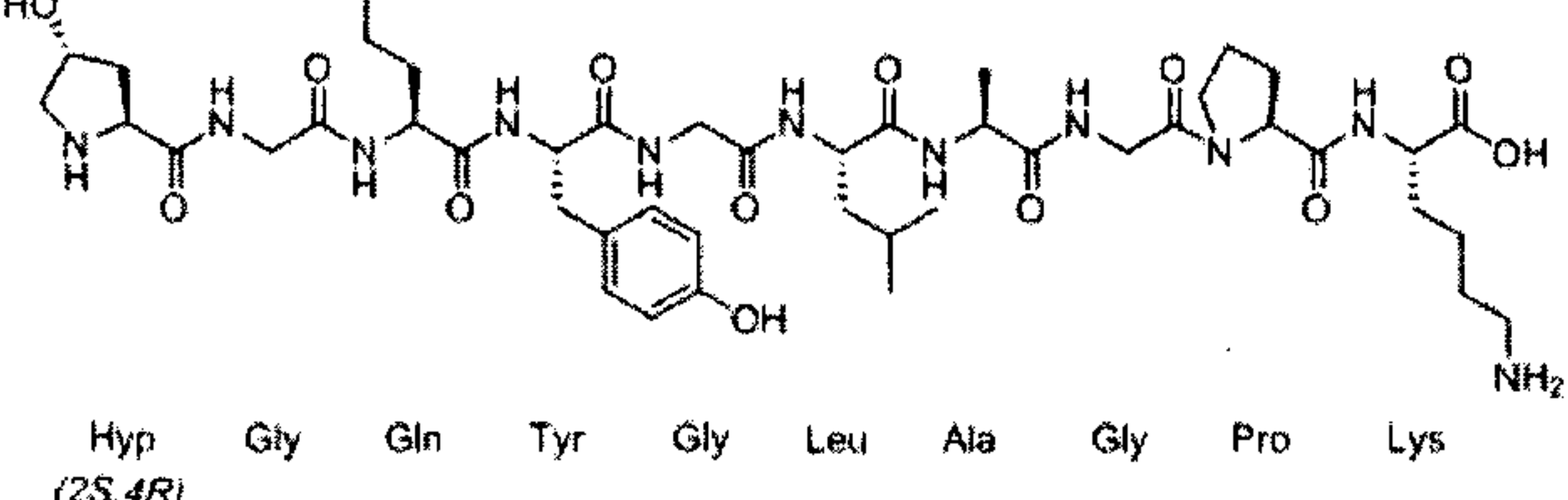


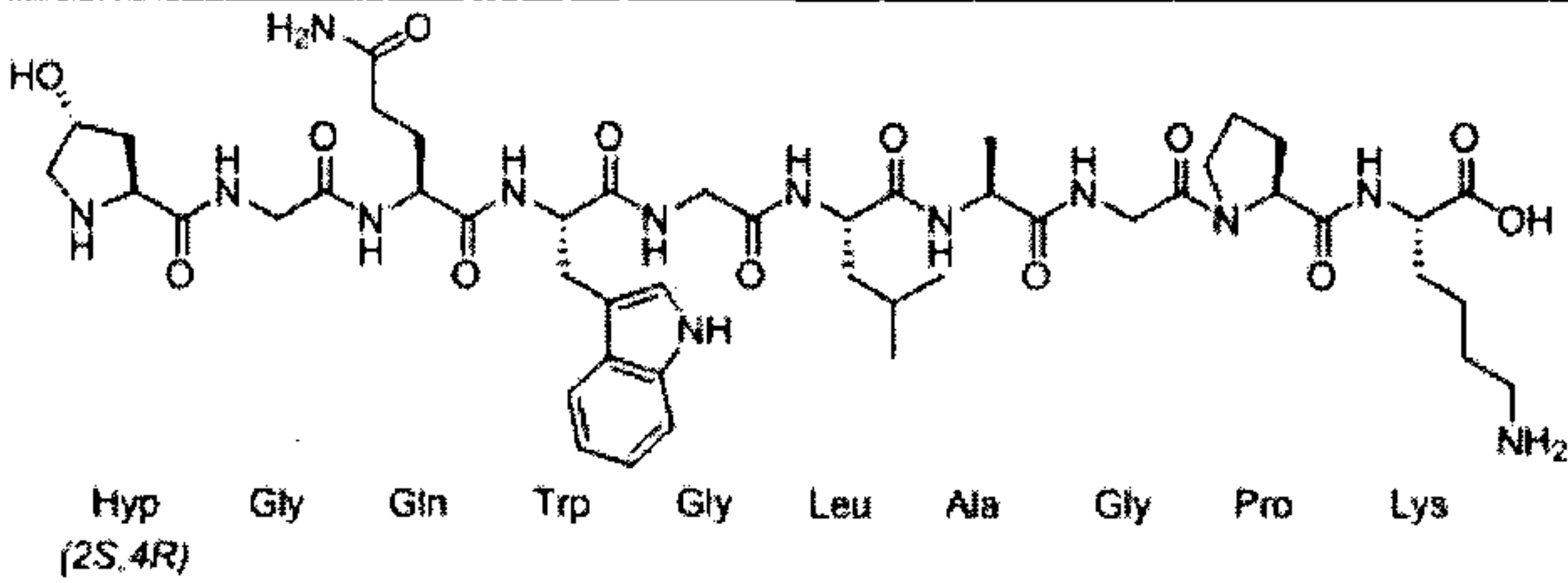
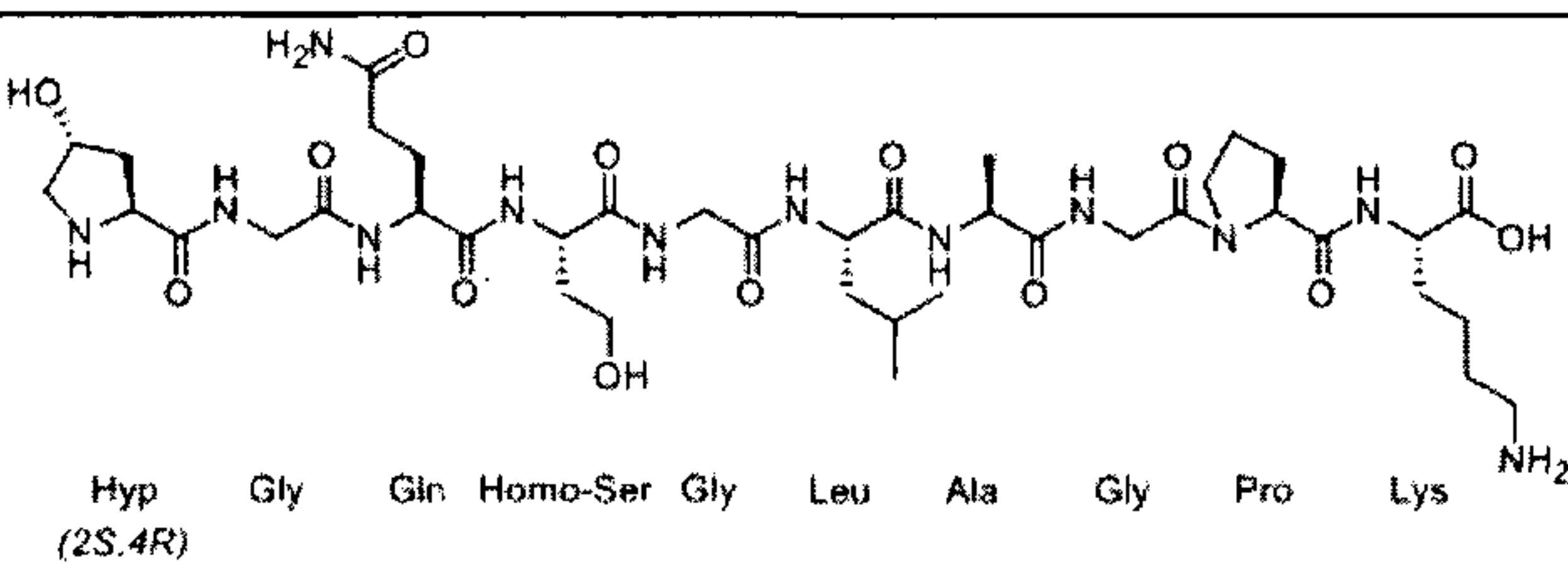
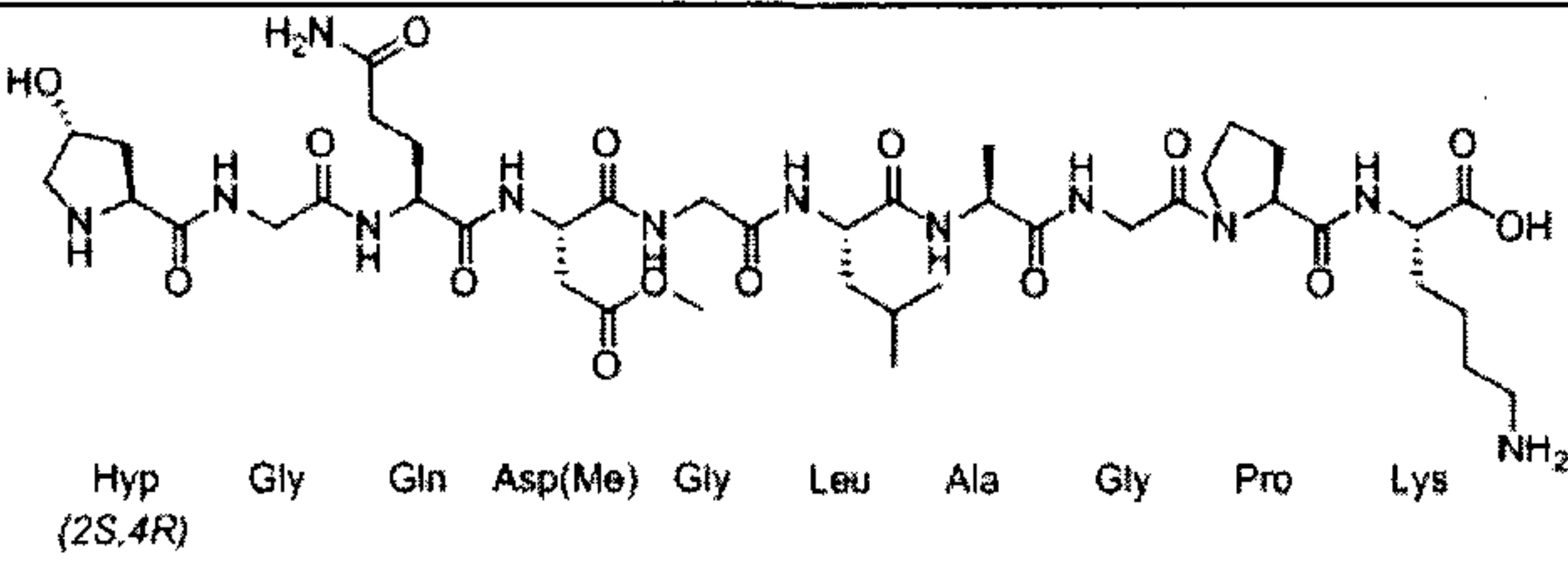
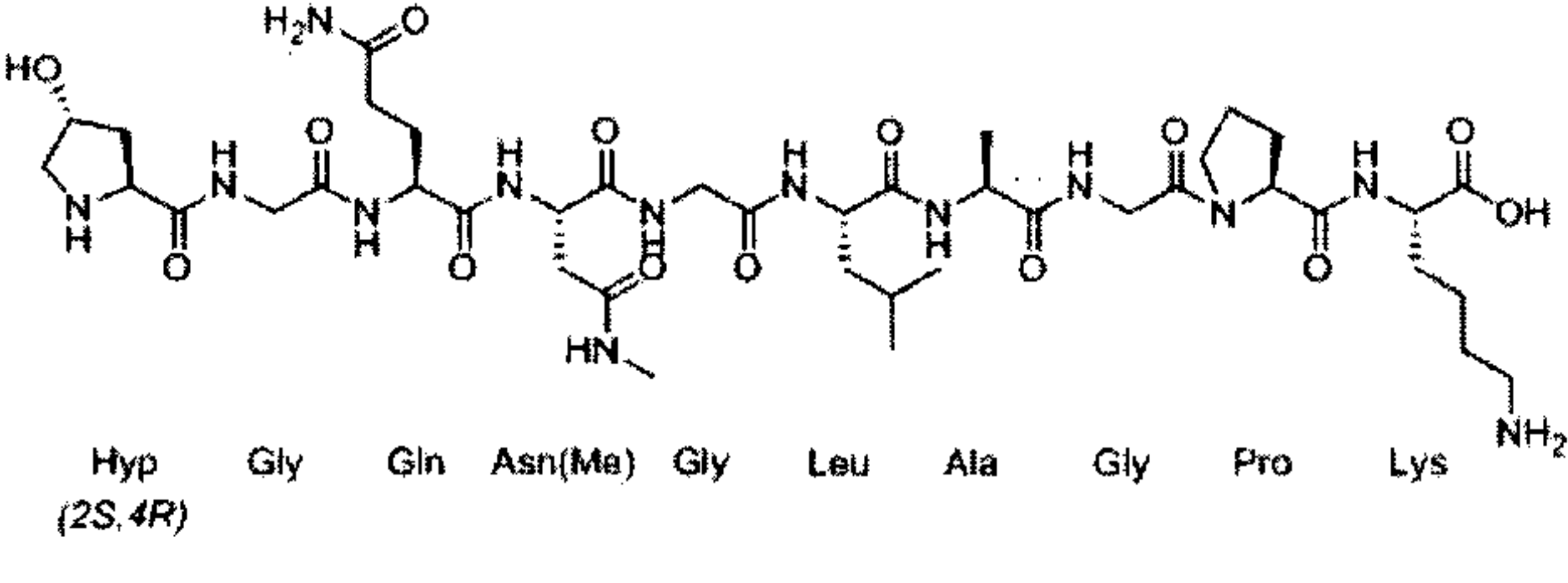
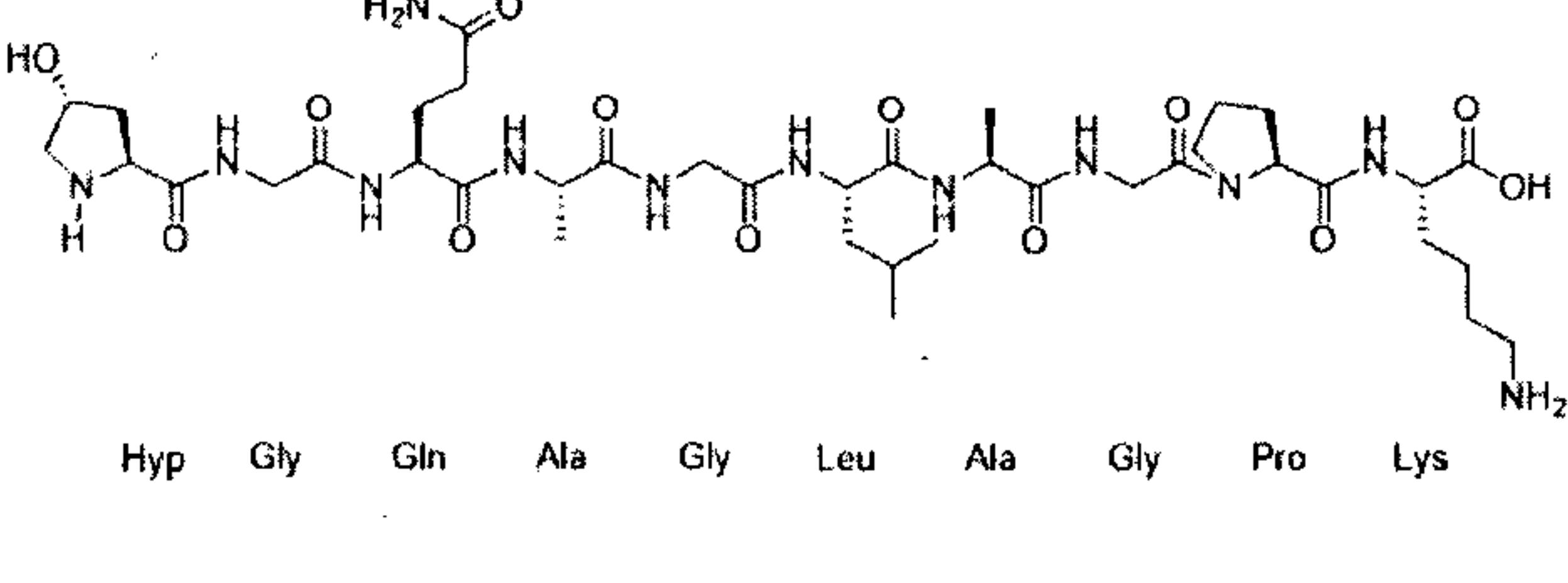
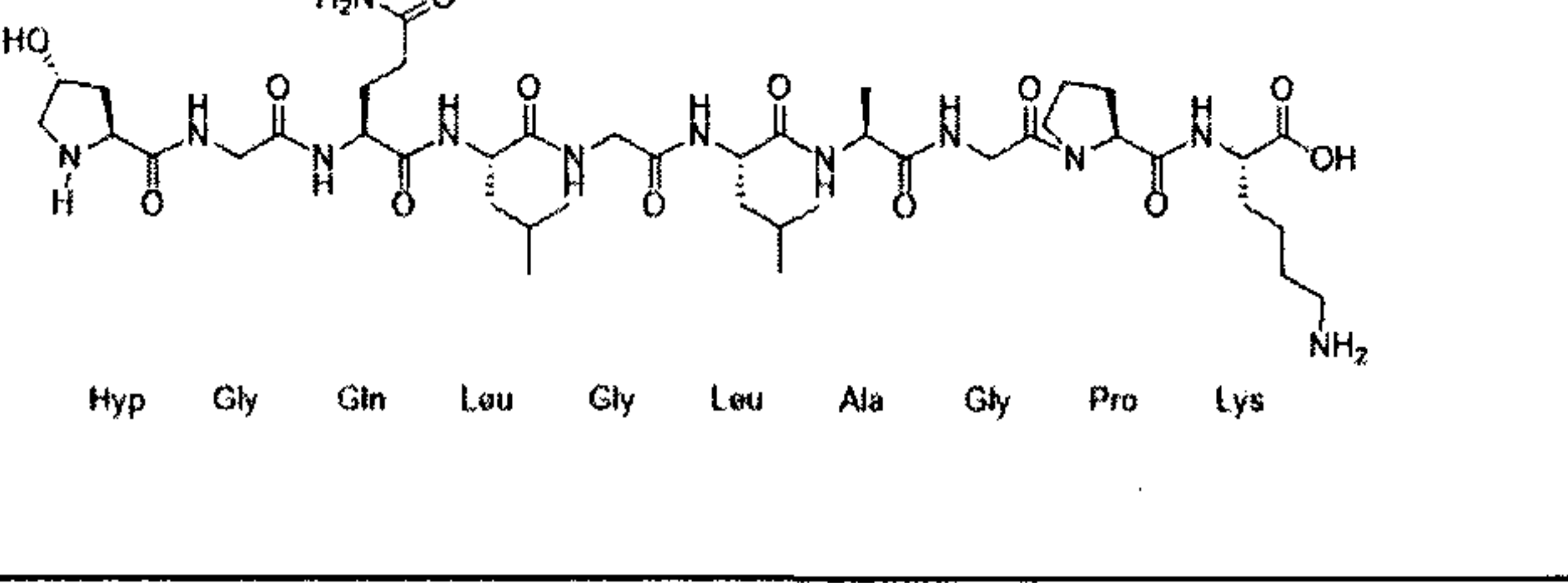
More specifically, the compound may be a compound described in Table 1 below.

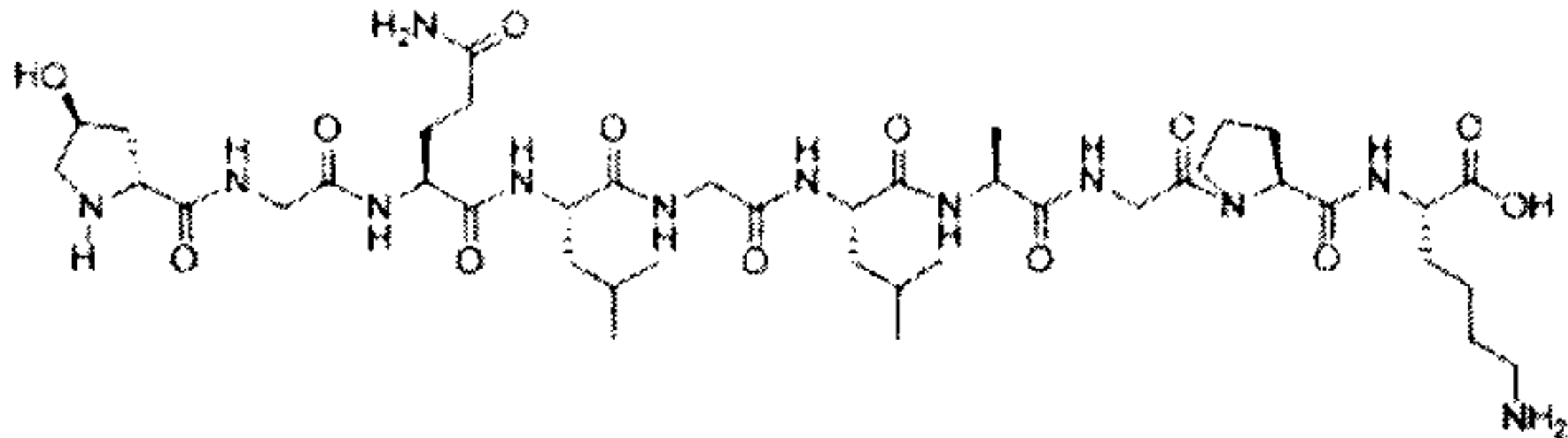
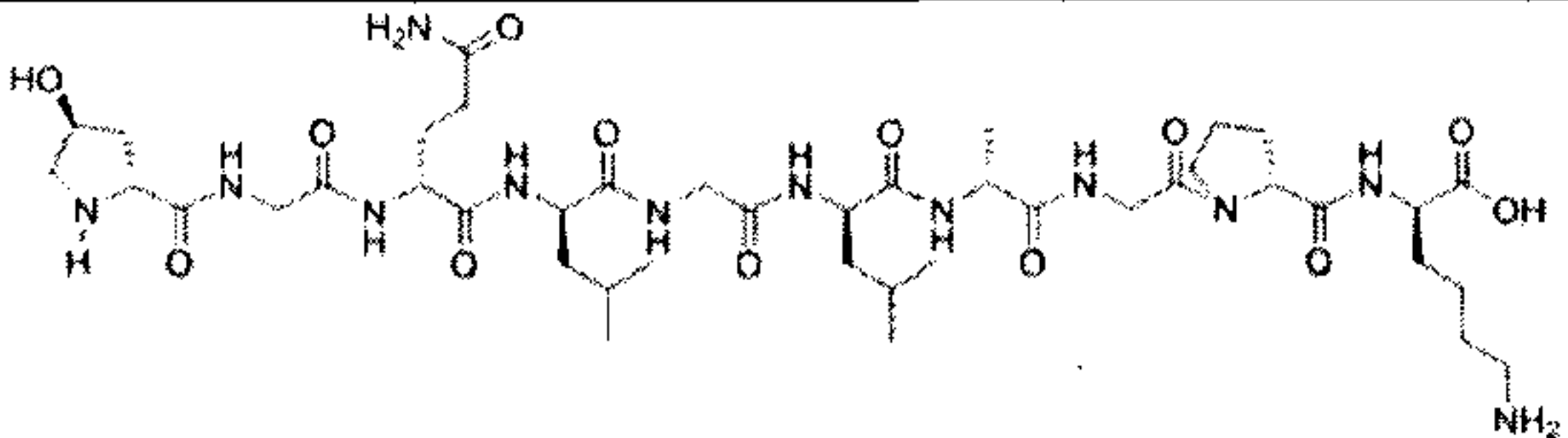
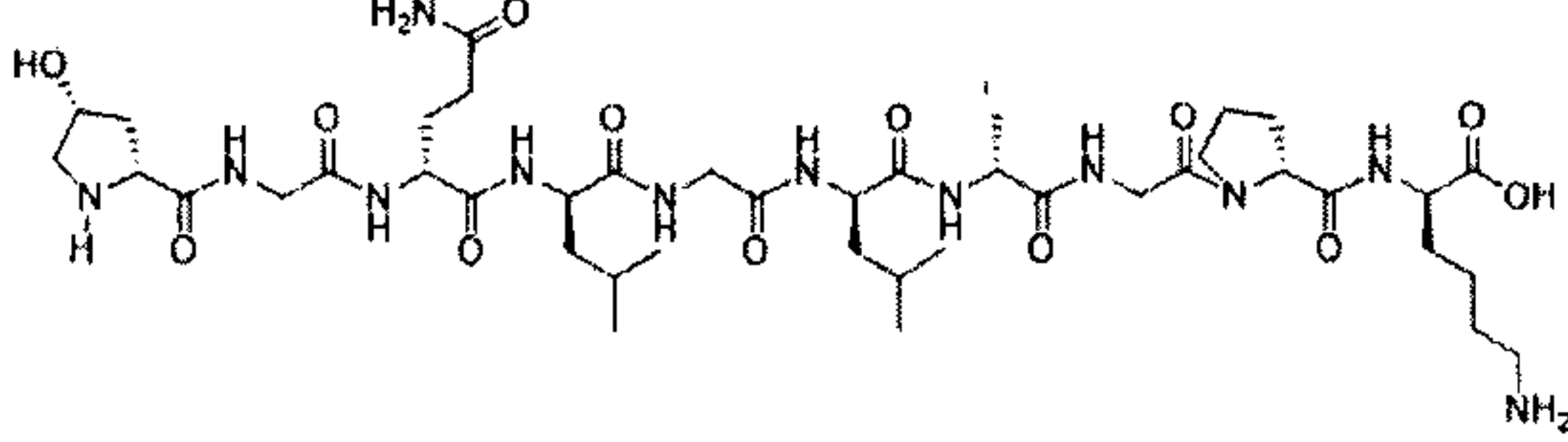
[Table 1]

YDE-001		SEQ ID NO: 1
	Hyp Gly Gln Glu Gly Leu Ala Gly Pro Lys (2S,4R)	

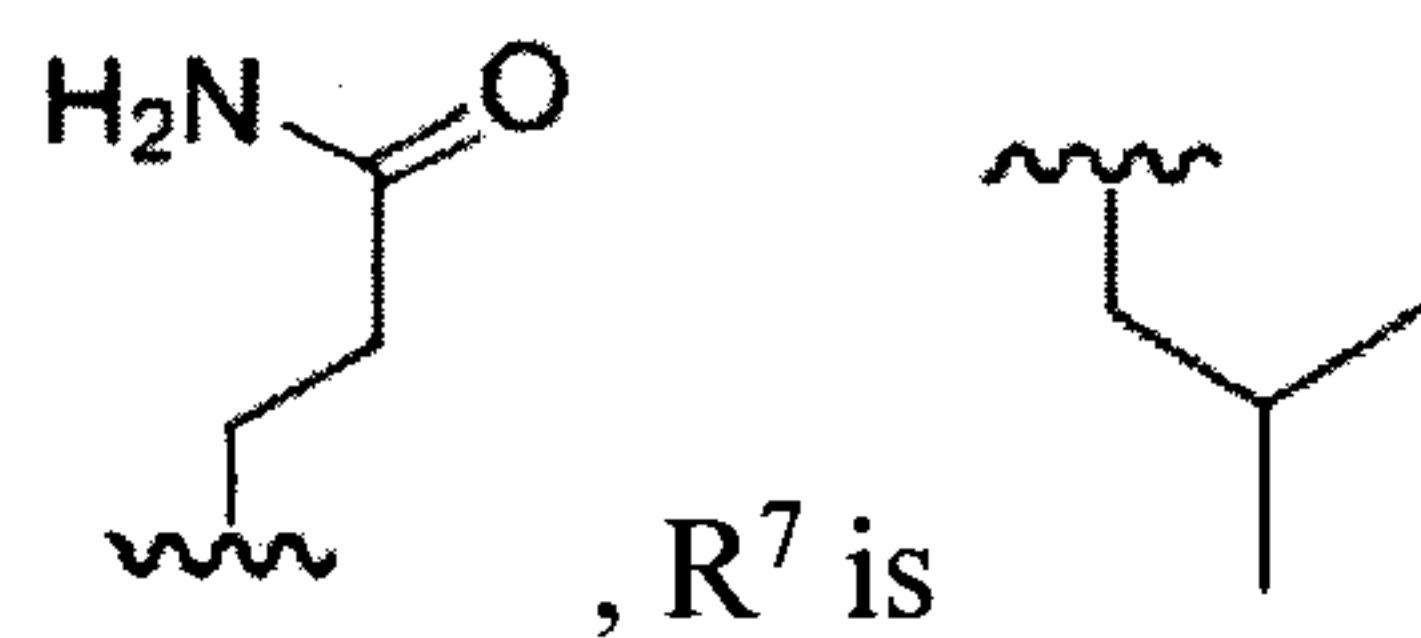
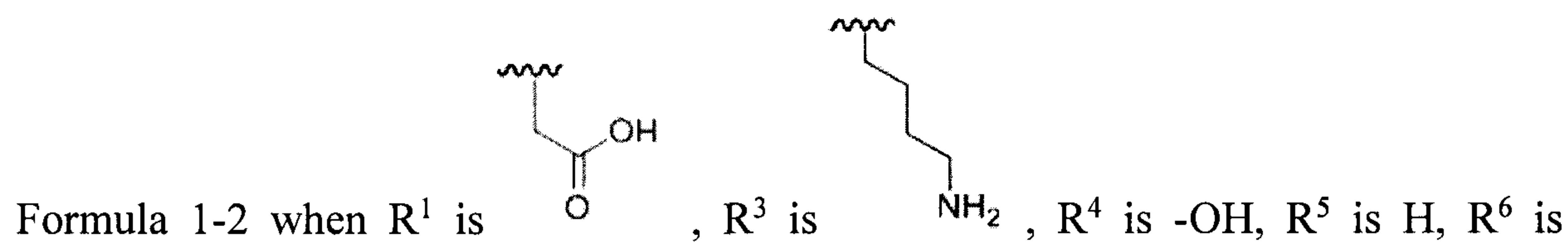
YDE-002	 Chemical structure of peptide YDE-002. The sequence is Hyp (2S,4R), Gly, Gln, Asn, Gly, Leu, Ala, Gly, Pro, Lys. The structure shows the peptide backbone with side chains and stereochemistry indicated by wedges and dashes. The N-terminus is a hydroxyl group, and the C-terminus is a carboxylic acid group. Hyp (2S,4R) Gly Gln Asn Gly Leu Ala Gly Pro Lys	SEQ ID NO: 2
YDE-003	 Chemical structure of peptide YDE-003. The sequence is Hyp (2S,4R), Gly, Gln, Gln, Gly, Leu, Ala, Gly, Pro, Lys. The structure shows the peptide backbone with side chains and stereochemistry indicated by wedges and dashes. The N-terminus is a hydroxyl group, and the C-terminus is a carboxylic acid group. Hyp (2S,4R) Gly Gln Gln Gly Leu Ala Gly Pro Lys	SEQ ID NO: 3
YDE-004	 Chemical structure of peptide YDE-004. The sequence is Hyp (2S,4R), Gly, Gln, His, Gly, Leu, Ala, Gly, Pro, Lys. The structure shows the peptide backbone with side chains and stereochemistry indicated by wedges and dashes. The N-terminus is a hydroxyl group, and the C-terminus is a carboxylic acid group. Hyp (2S,4R) Gly Gln His Gly Leu Ala Gly Pro Lys	SEQ ID NO: 4
YDE-005	 Chemical structure of peptide YDE-005. The sequence is Hyp (2S,4R), Gly, Gln, Lys, Gly, Leu, Ala, Gly, Pro, Lys. The structure shows the peptide backbone with side chains and stereochemistry indicated by wedges and dashes. The N-terminus is a hydroxyl group, and the C-terminus is a carboxylic acid group. Hyp (2S,4R) Gly Gln Lys Gly Leu Ala Gly Pro Lys	SEQ ID NO: 5
YDE-006	 Chemical structure of peptide YDE-006. The sequence is Hyp (2S,4R), Gly, Gln, Ser, Gly, Leu, Ala, Gly, Pro, Lys. The structure shows the peptide backbone with side chains and stereochemistry indicated by wedges and dashes. The N-terminus is a hydroxyl group, and the C-terminus is a carboxylic acid group. Hyp (2S,4R) Gly Gln Ser Gly Leu Ala Gly Pro Lys	SEQ ID NO: 6
YDE-007	 Chemical structure of peptide YDE-007. The sequence is Hyp (2S,4R), Gly, Gln, Thr, Gly, Leu, Ala, Gly, Pro, Lys. The structure shows the peptide backbone with side chains and stereochemistry indicated by wedges and dashes. The N-terminus is a hydroxyl group, and the C-terminus is a carboxylic acid group. Hyp (2S,4R) Gly Gln Thr Gly Leu Ala Gly Pro Lys	SEQ ID NO: 7

YDE-008	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys Hyp (2S,4R)	SEQ ID NO: 8
YDE-009	 Hyp Gly Gln Val Gly Leu Ala Gly Pro Lys Hyp (2S,4R)	SEQ ID NO: 9
YDE-010	 Hyp Gly Gln Ile Gly Leu Ala Gly Pro Lys Hyp (2S,4R)	SEQ ID NO: 10
YDE-011	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys Hyp (2S,4R)	SEQ ID NO: 11
YDE-012	 Hyp Gly Gln Phe Gly Leu Ala Gly Pro Lys Hyp (2S,4R)	SEQ ID NO: 12
YDE-013	 Hyp Gly Gln Tyr Gly Leu Ala Gly Pro Lys Hyp (2S,4R)	SEQ ID NO: 13

YDE-014	 Hyp Gly Gln Trp Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 14
YDE-026	 Hyp Gly Gln Homo-Ser Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 15
YDE-027	 Hyp Gly Gln Asp(Me) Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 16
YDE-028	 Hyp Gly Gln Asn(Me) Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 17
YDE-050	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys	SEQ ID NO: 8
YDE-053	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 11

YDE-057	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys (2R,4S)	SEQ ID NO: 18
YDE-058	 D-Hyp Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys (2R,4S)	SEQ ID NO: 19
YDE-060	 D-Hyp Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys (2R,4R)	SEQ ID NO: 20

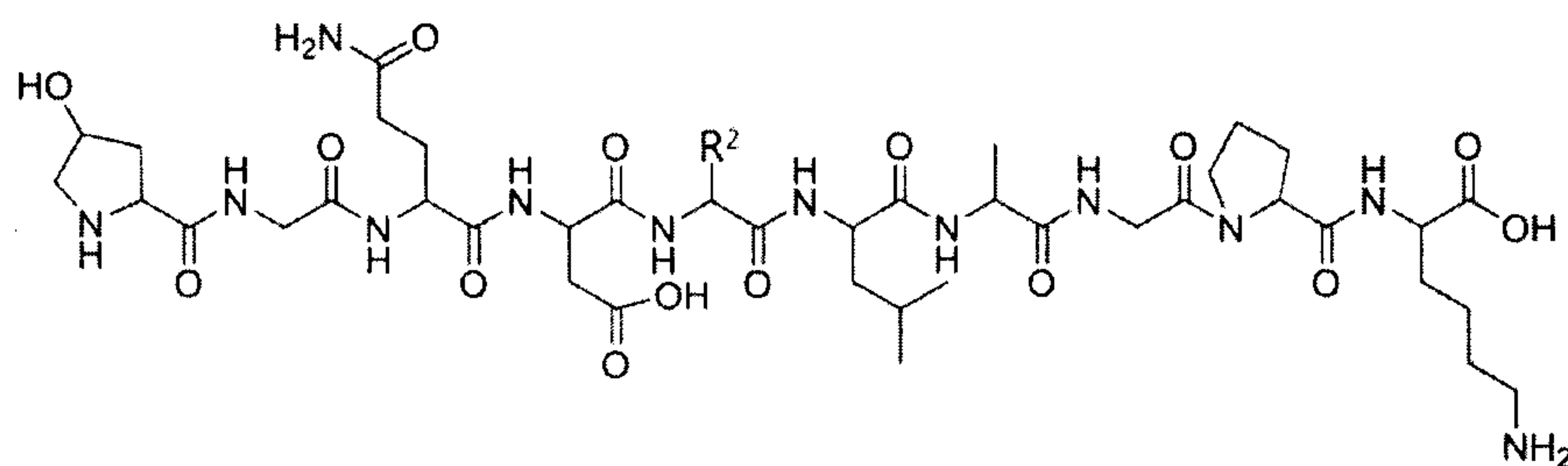
The compound represented by the above Formula 1 may be represented by



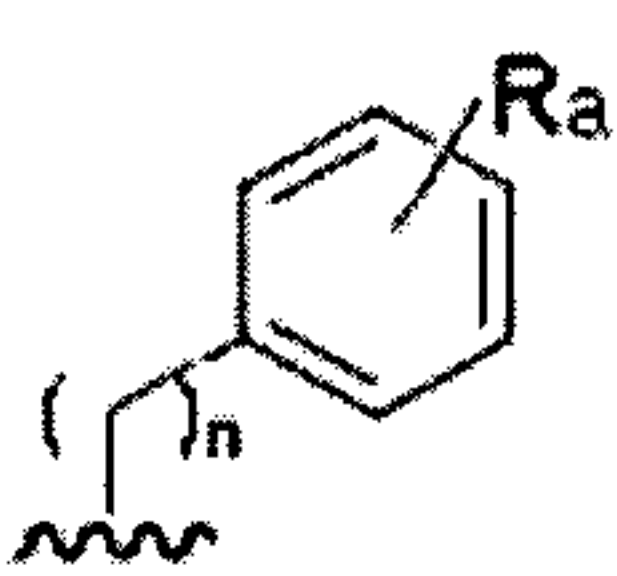
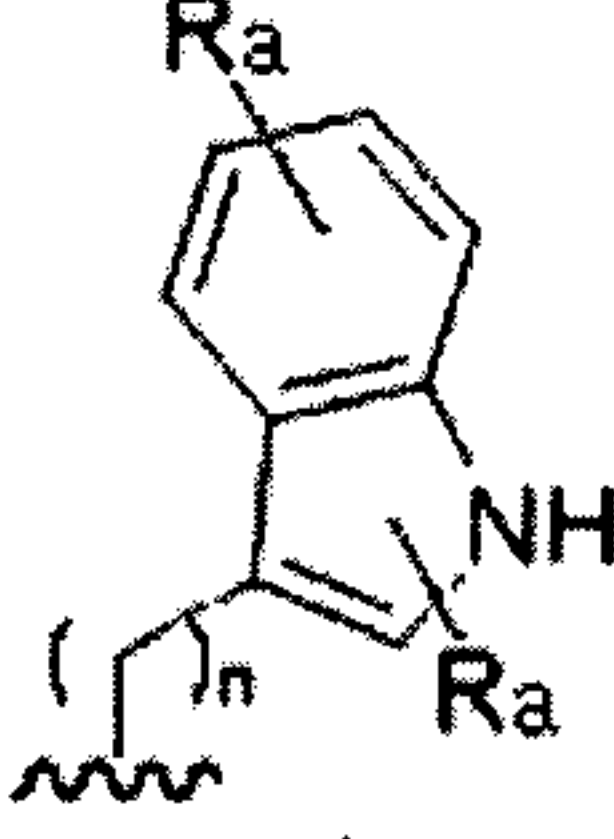
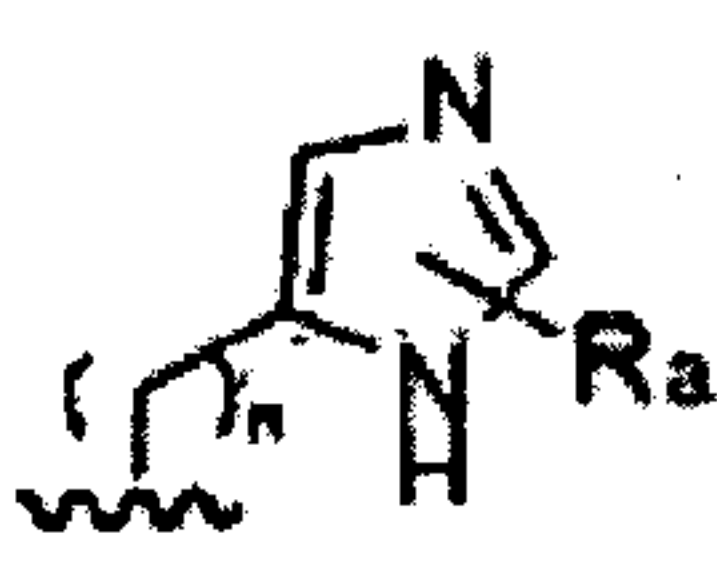
5  , R⁷ is  , R⁸ is H, and R⁹ is H. Further, the compound represented by the following Formula 1-2 may be an optical isomer type L or D.

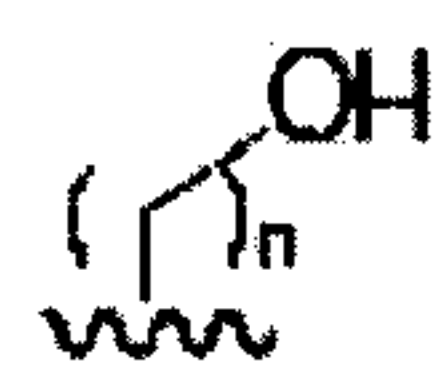
[Formula 1-2]

35



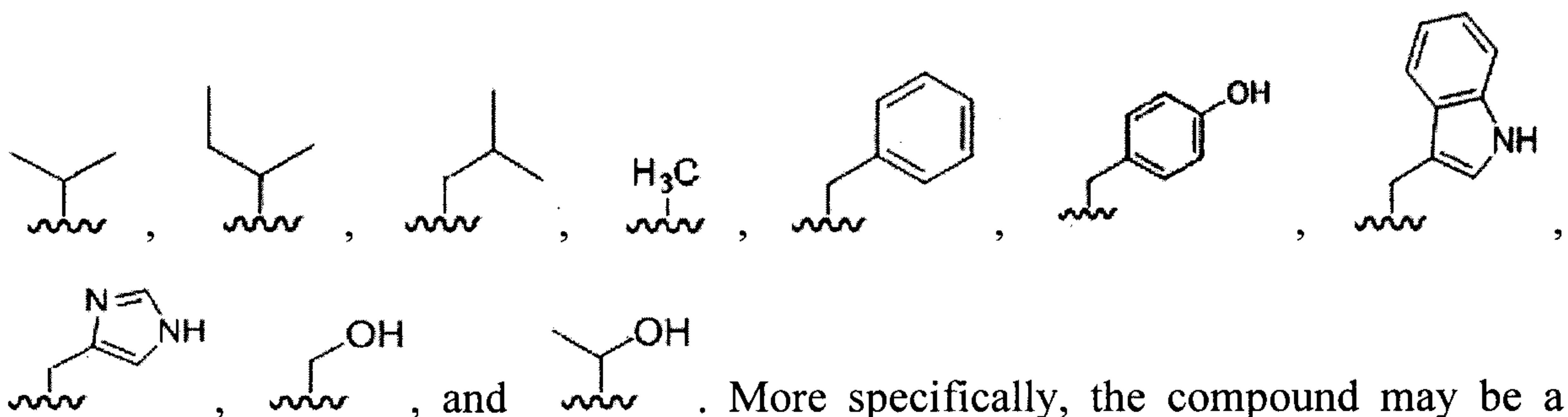
In addition, R^2 may be one selected from the group consisting of hydrogen,

substituted or unsubstituted C_{1-6} alkyl, , , , and



Here, n may be an integer of 1 to 10, but it is not limited thereto. R_a may be hydrogen or C_{1-6} alkyl.

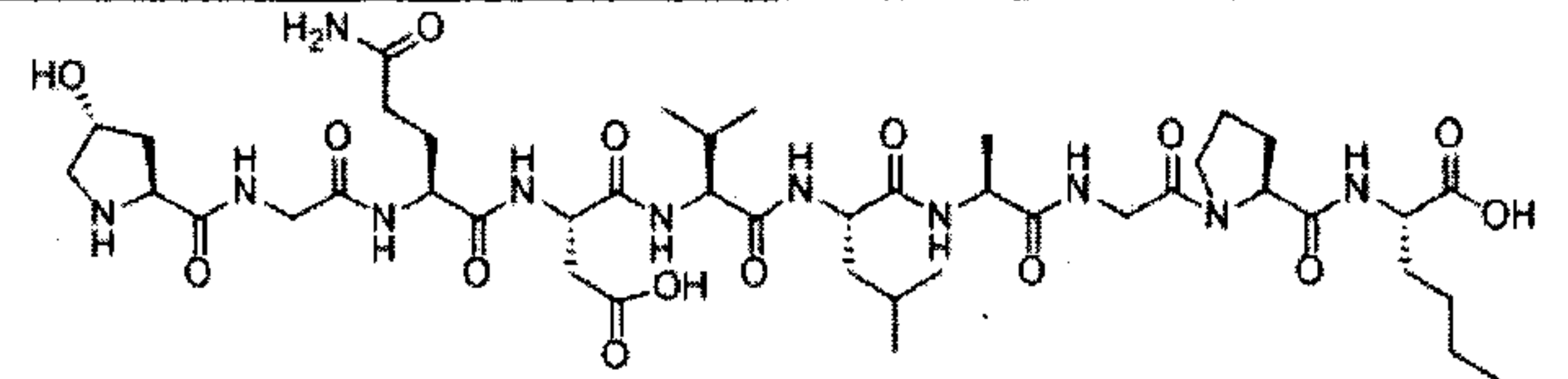
Specifically, R^2 may be one selected from the group consisting of ,

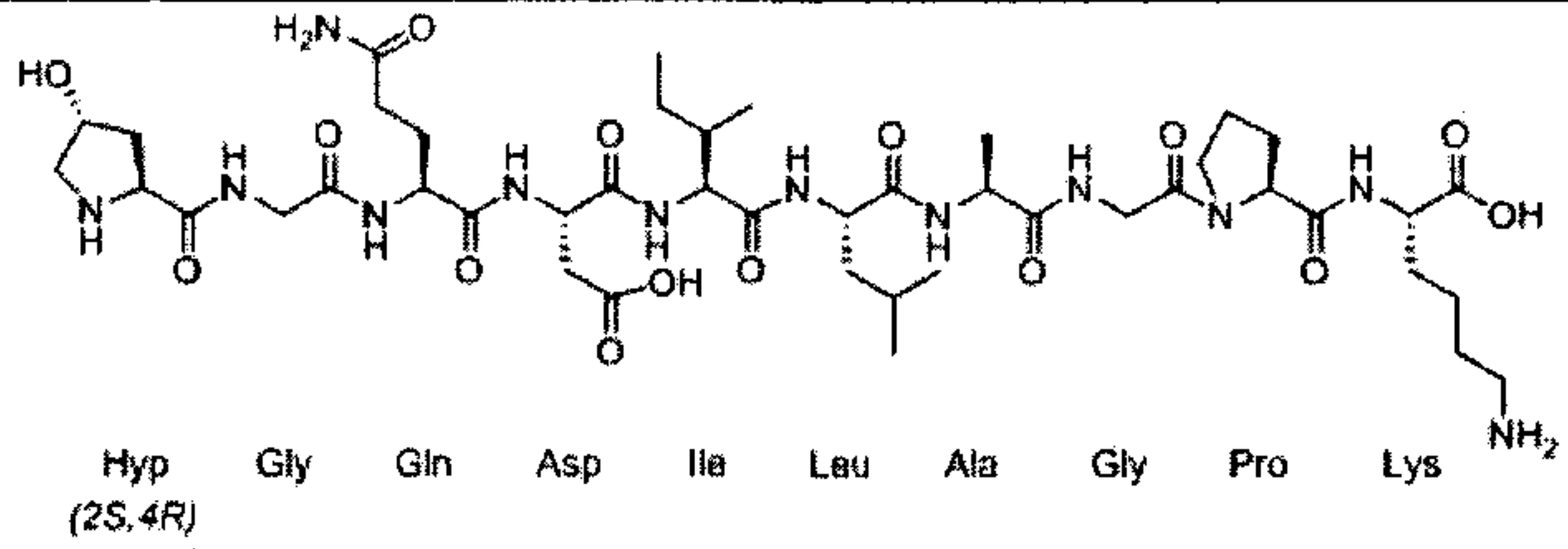
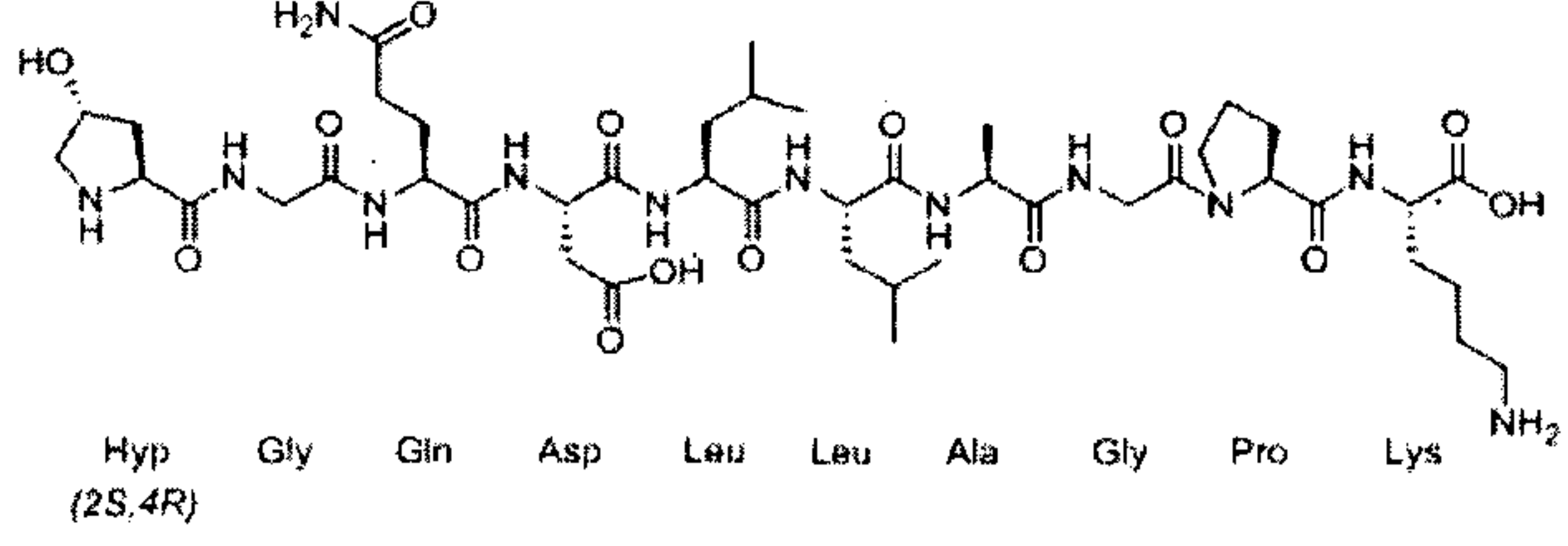
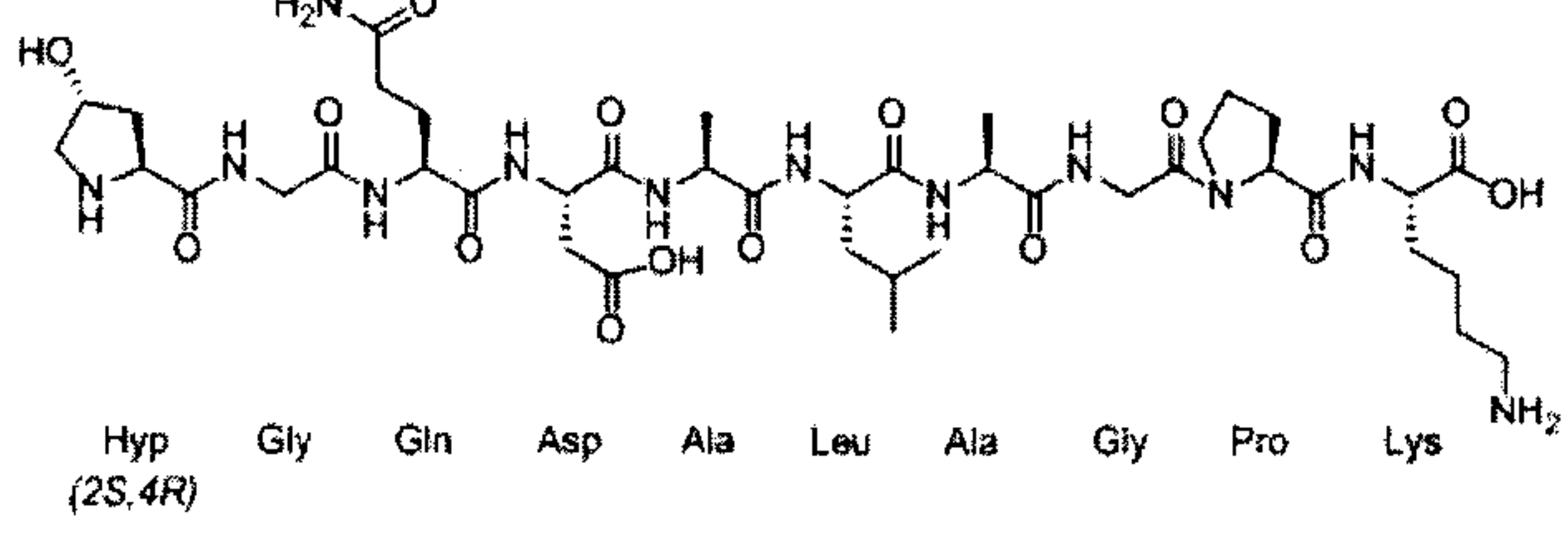
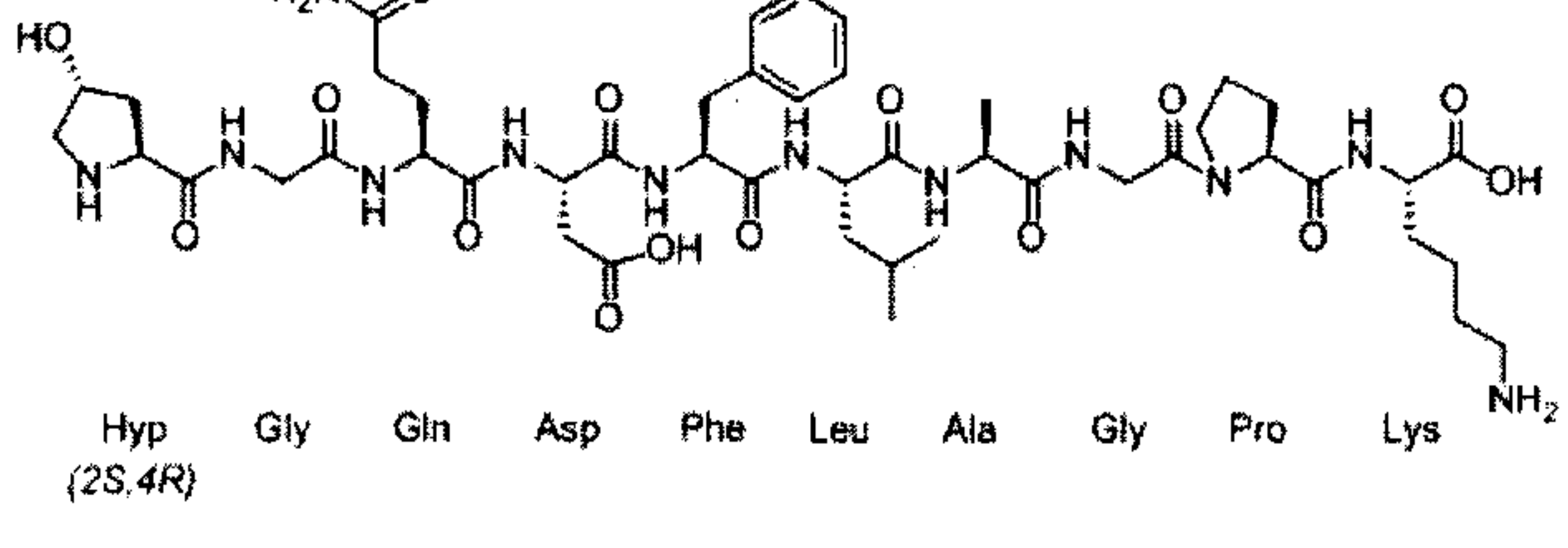
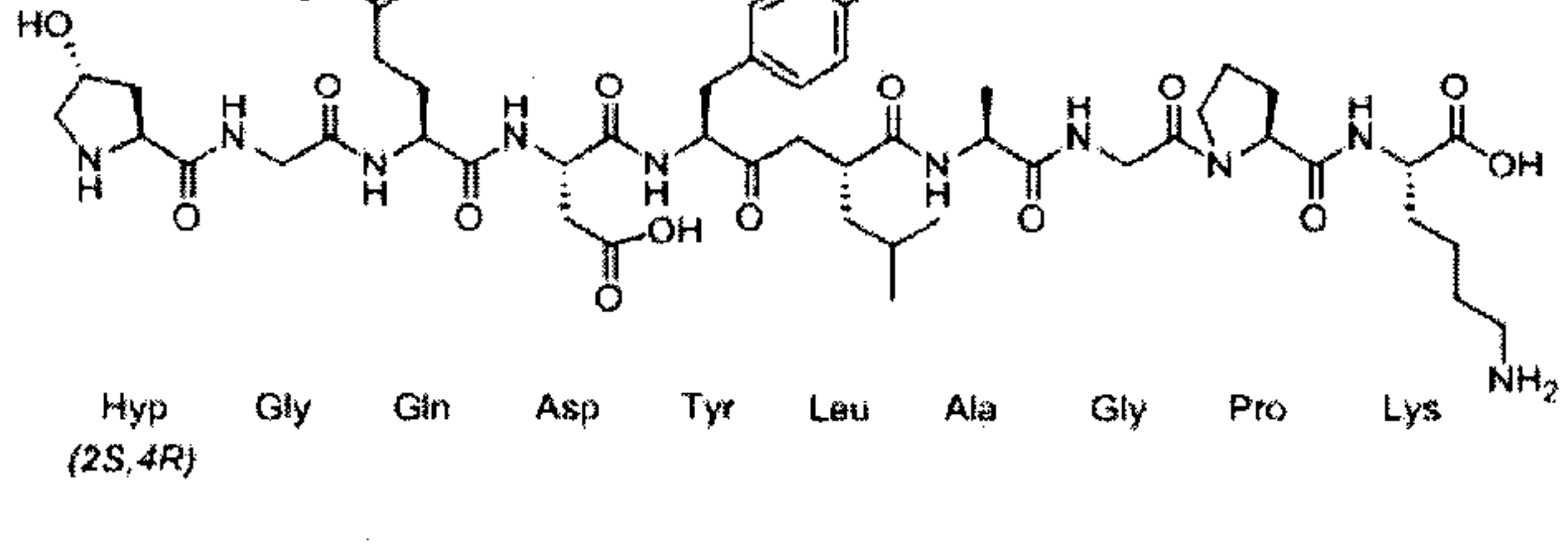
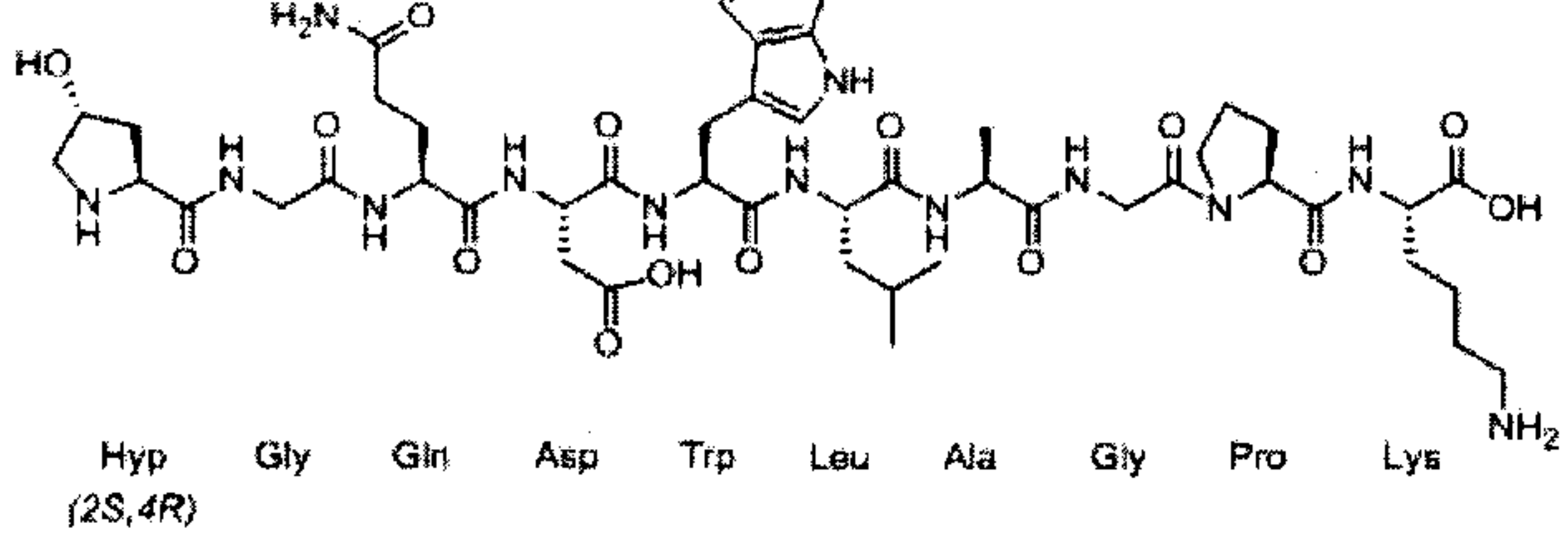


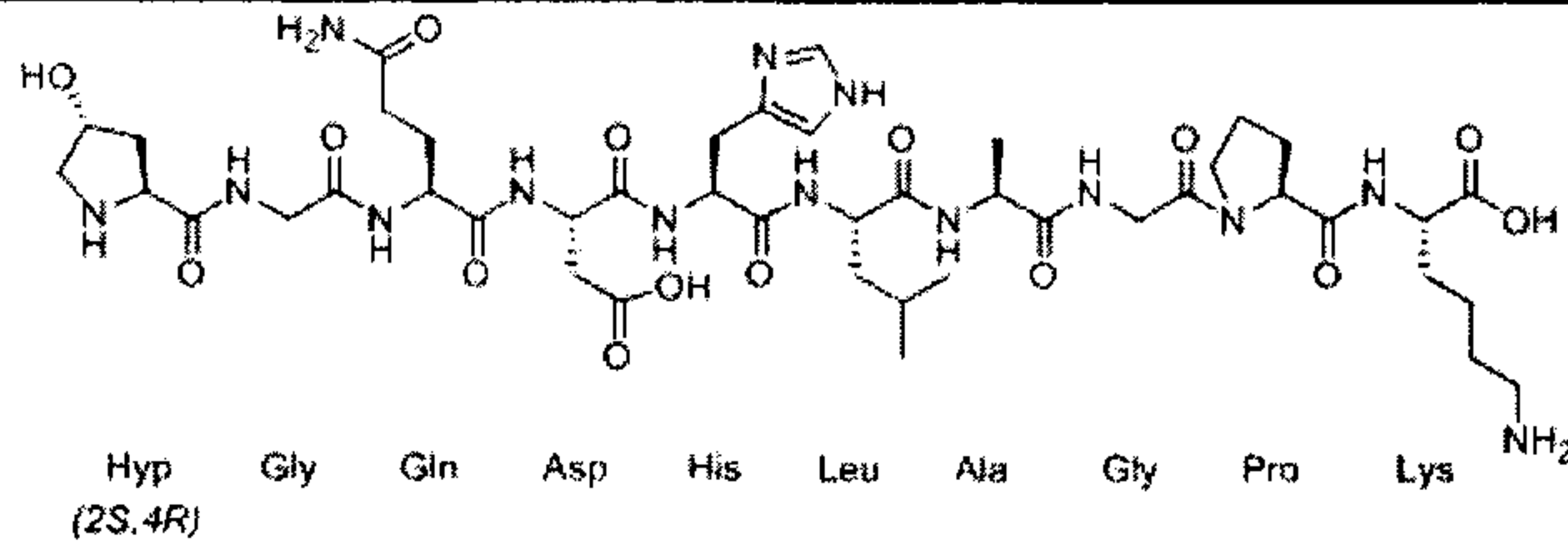
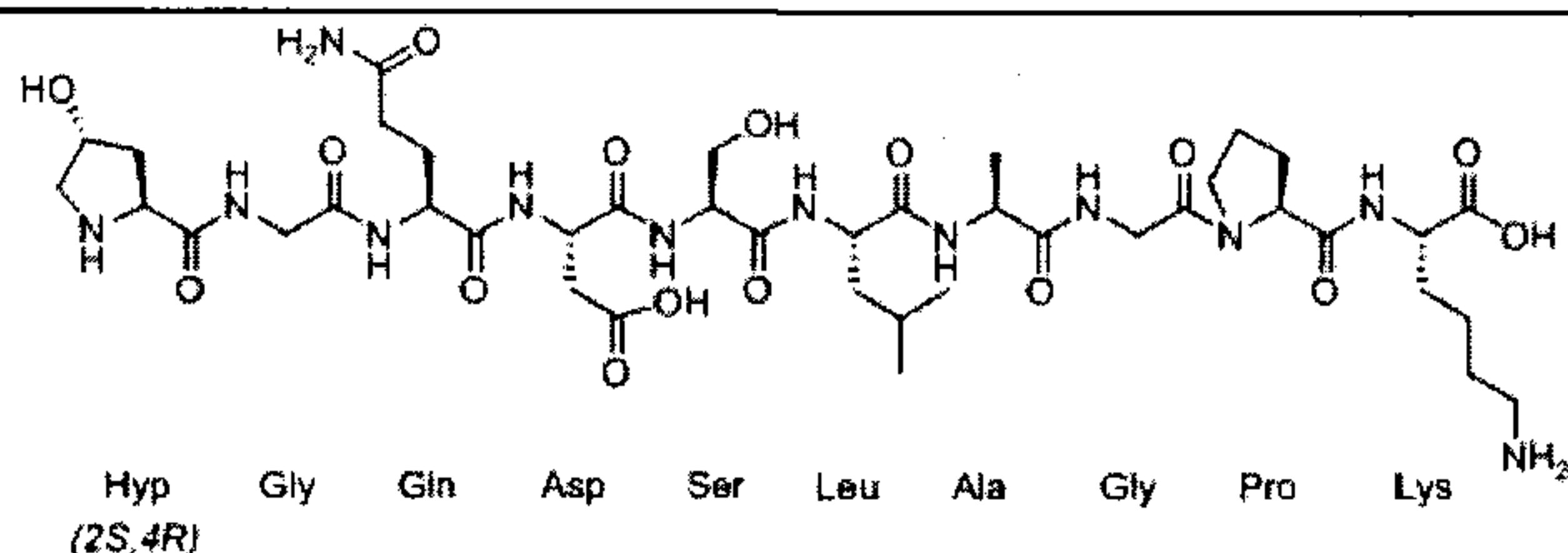
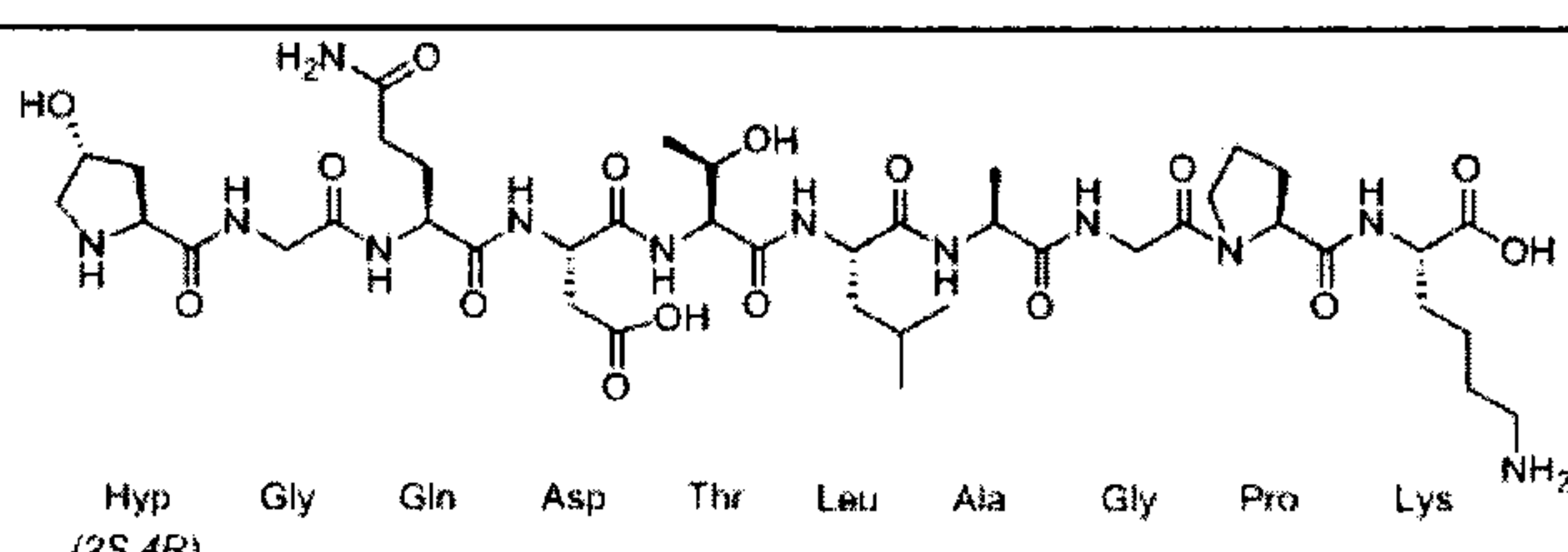
compound described in Table 2 below.

10

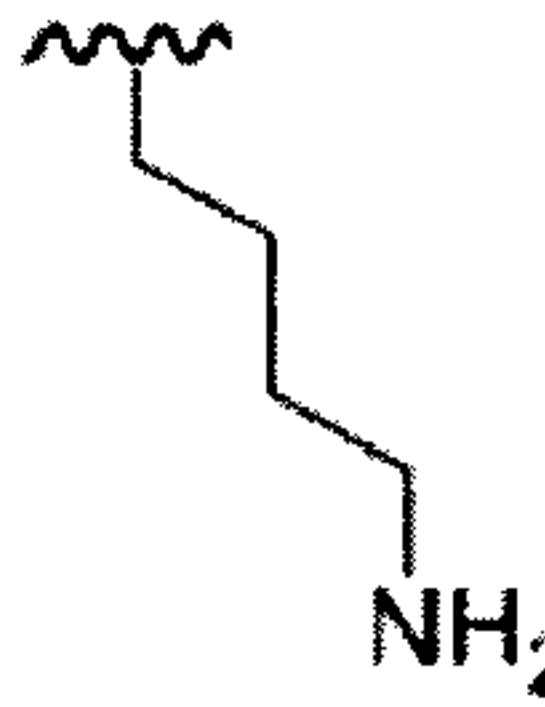
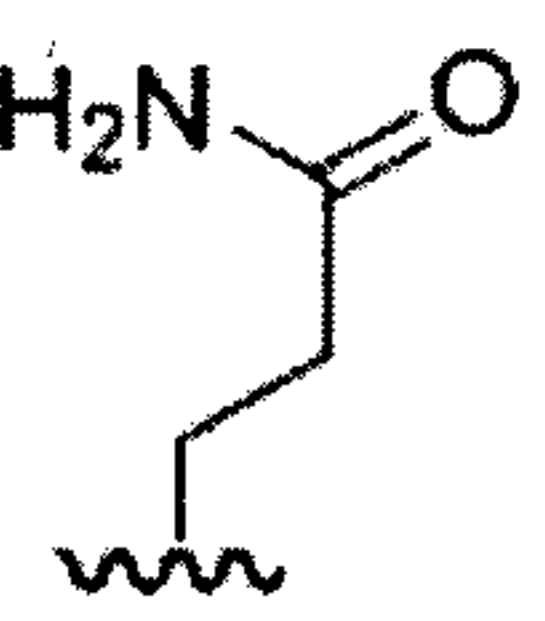
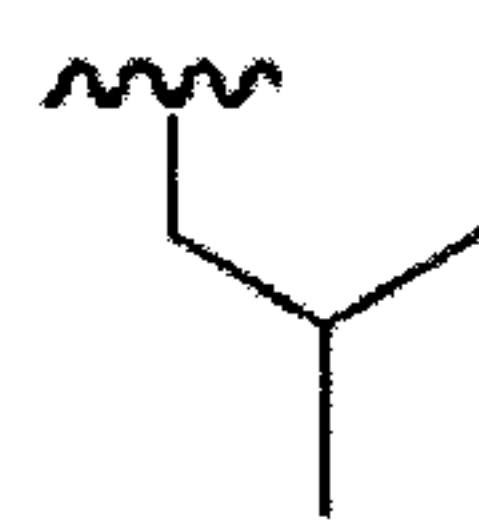
[Table 2]

YDE-015	 Hyp (2S,4R) Gly Gln Asp Val Leu Ala Gly Pro Lys	SEQ ID NO: 21
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YDE-016	 Hyp (2S,4R) Gly Gln Asp Ile Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 22
YDE-017	 Hyp (2S,4R) Gly Gln Asp Leu Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 23
YDE-018	 Hyp (2S,4R) Gly Gln Asp Ala Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 24
YDE-019	 Hyp (2S,4R) Gly Gln Asp Phe Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 25
YDE-020	 Hyp (2S,4R) Gly Gln Asp Tyr Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 26
YDE-021	 Hyp (2S,4R) Gly Gln Asp Trp Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 27

YDE-022	 Hyp (2S,4R) Gly Gln Asp His Leu Ala Gly Pro Lys	SEQ ID NO: 28
YDE-023	 Hyp (2S,4R) Gly Gln Asp Ser Leu Ala Gly Pro Lys	SEQ ID NO: 29
YDE-024	 Hyp (2S,4R) Gly Gln Asp Thr Leu Ala Gly Pro Lys	SEQ ID NO: 30

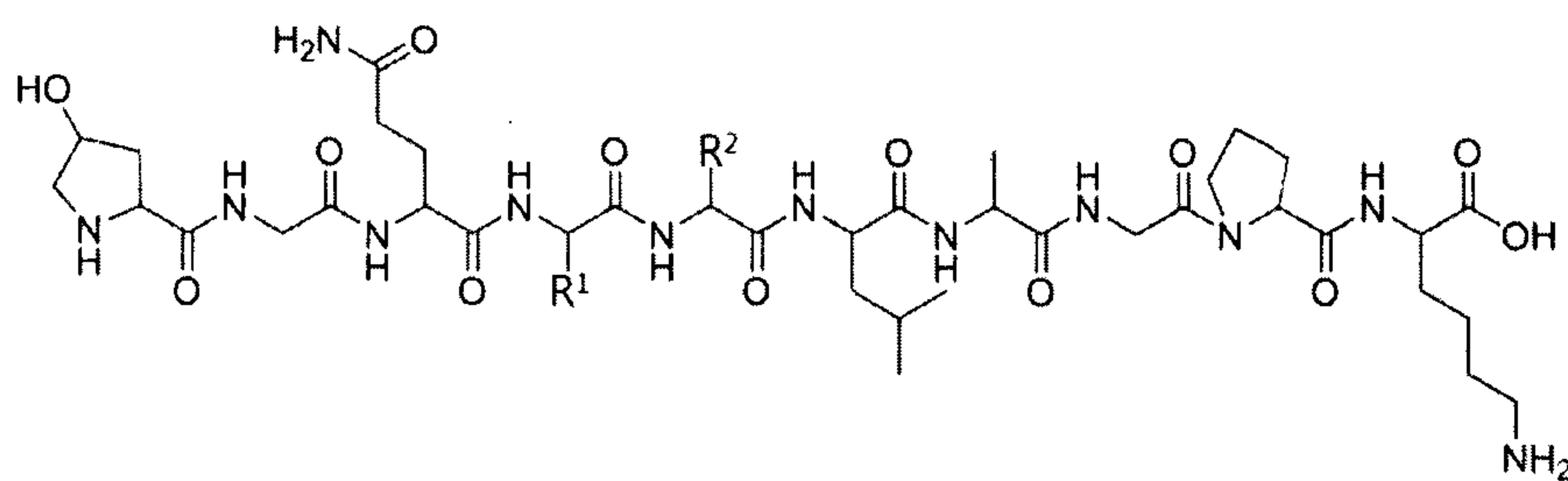
The compound represented by the above Formula 1 may be represented by

Formula 1-3 when R³ is , R⁴ is -OH, R⁵ is H, R⁶ is , R⁷ is ,

R⁸ is H, and R⁹ is H. Further, the compound represented by the following Formula 1-3

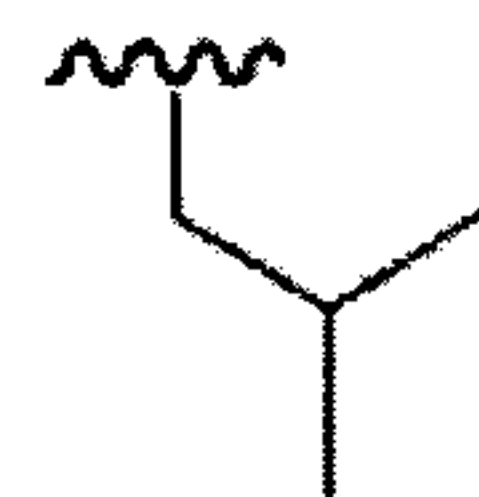
5 may be an optical isomer type L or D.

[Formula 1-3]

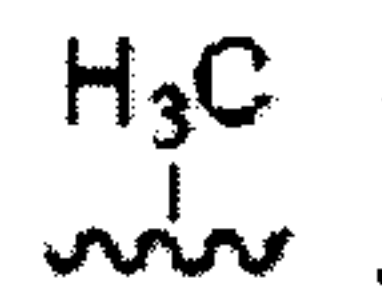


38

R^1 may be C_{1-6} alkyl. Specifically, R^1 may be



R^2 may be C_{1-6} alkyl. Specifically, R^2 may be



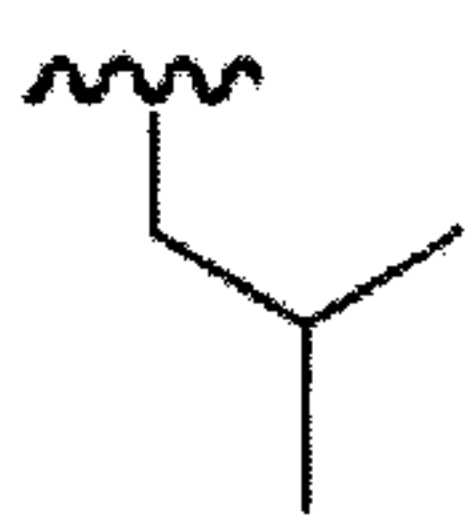
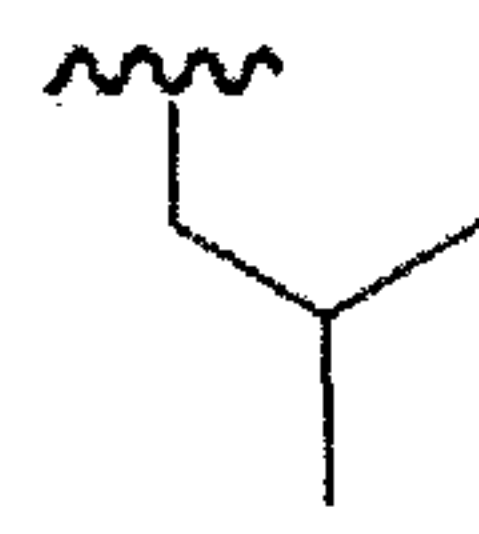
More specifically, the compound may be a compound described in Table 3 below.

[Table 3]

YDE-051	Hyp Gly Gln Leu Ala Leu Ala Gly Pro Lys	SEQ ID NO: 32
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5

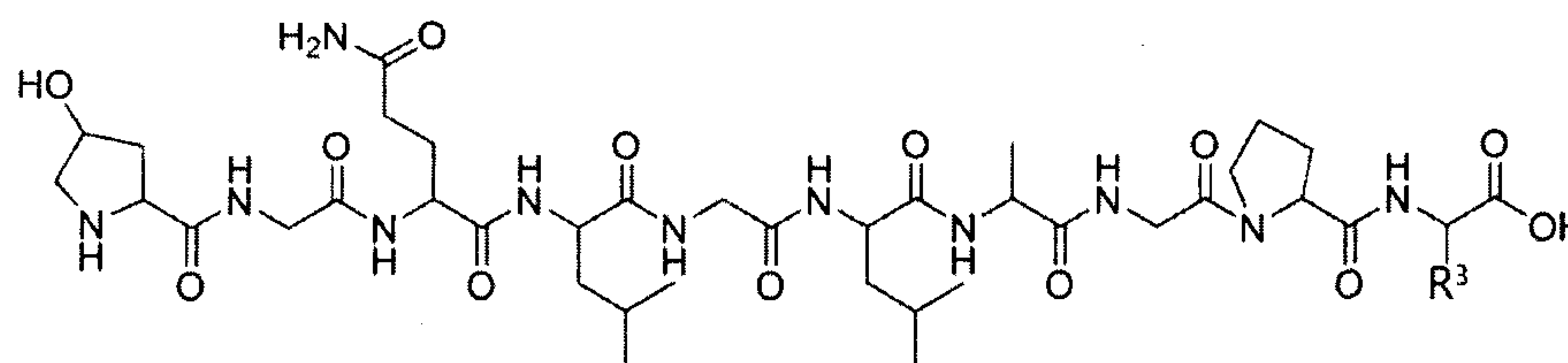
The compound represented by the above Formula 1 may be represented by

Formula 1-4 when R^1 is , R^2 is H, R^4 is -OH, R^5 is H, R^6 is , R^7 is , R^8 is H, and R^9 is H. Further, the compound represented by the following

Formula 1-4 may be an optical isomer type L or D.

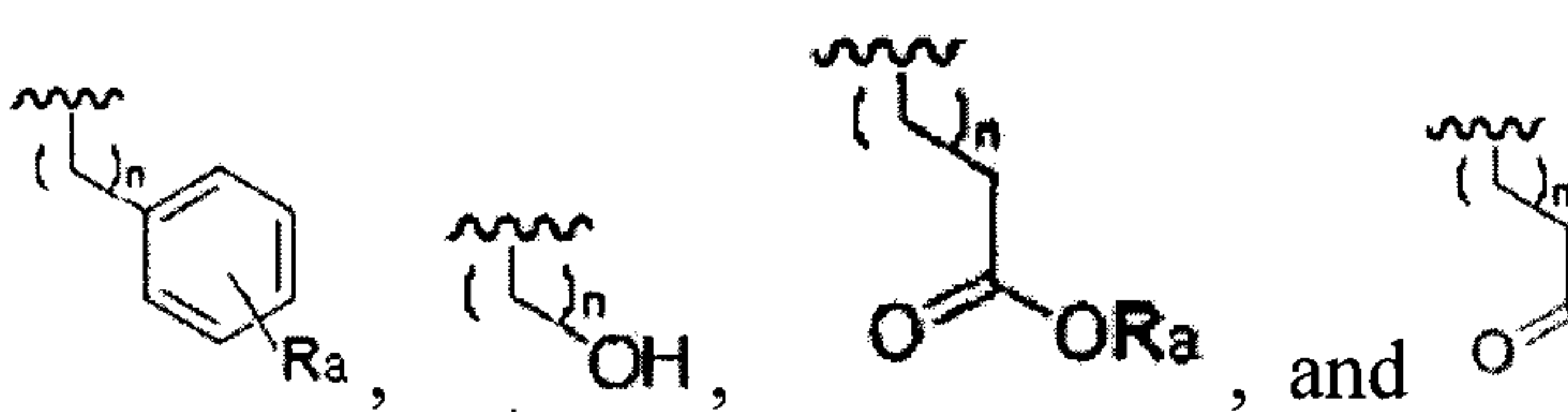
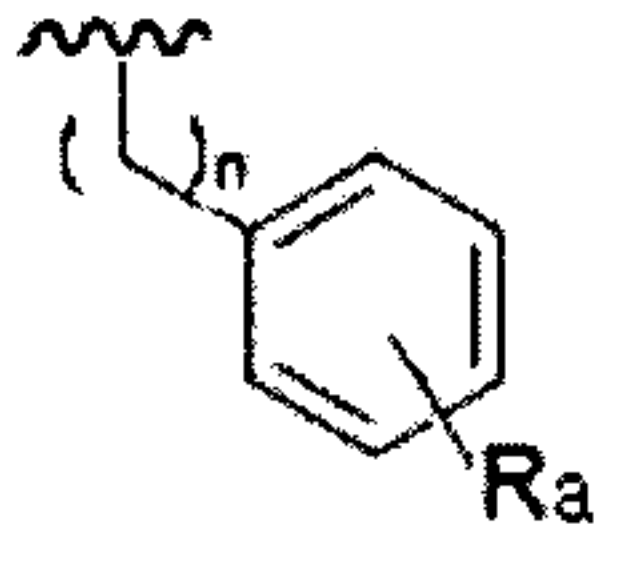
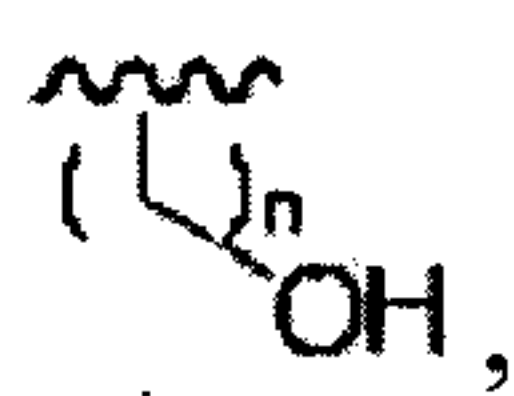
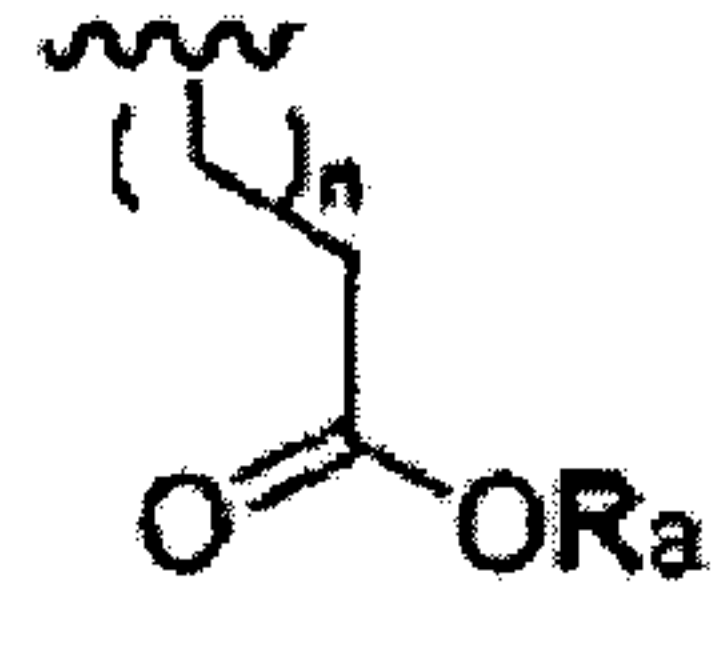
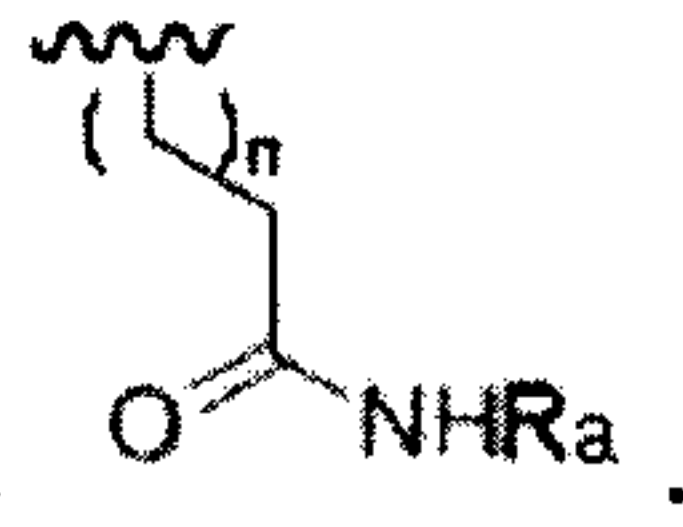
10

[Formula 1-4]

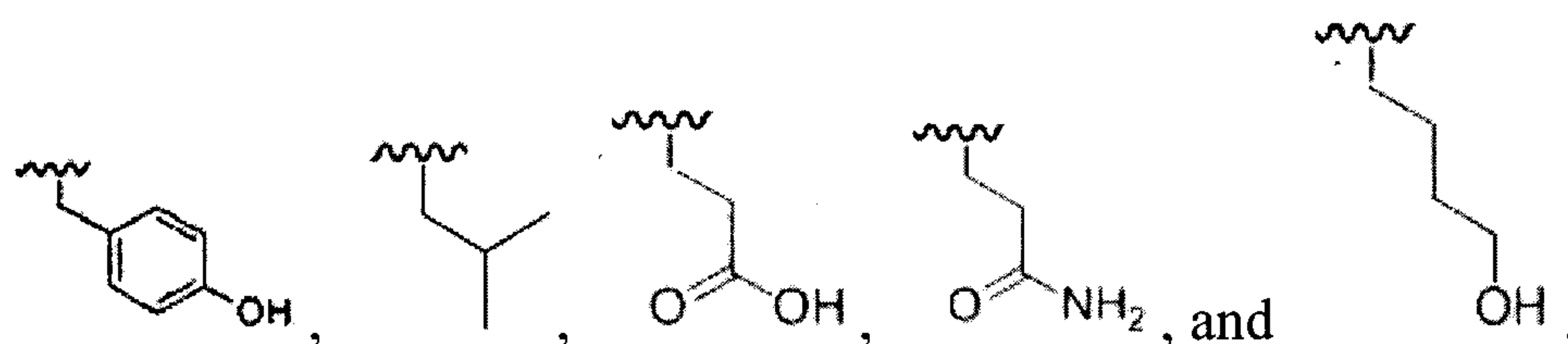


R^3 may be one selected from the group consisting of substituted or unsubstituted

39

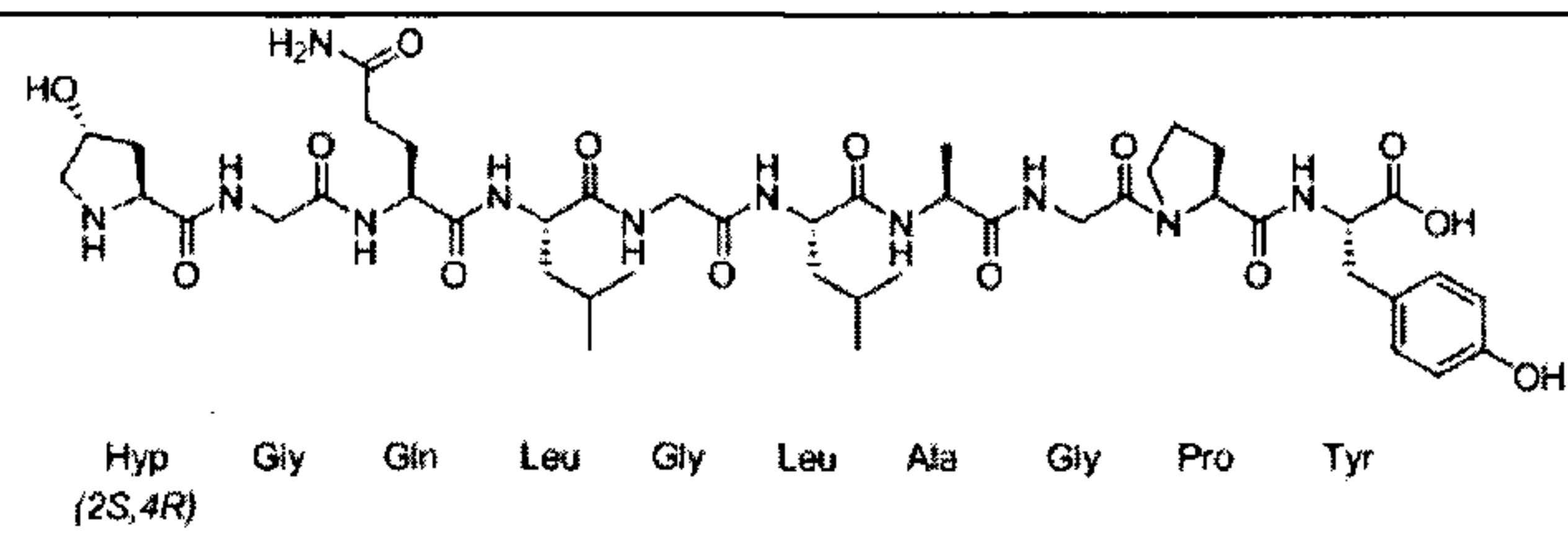
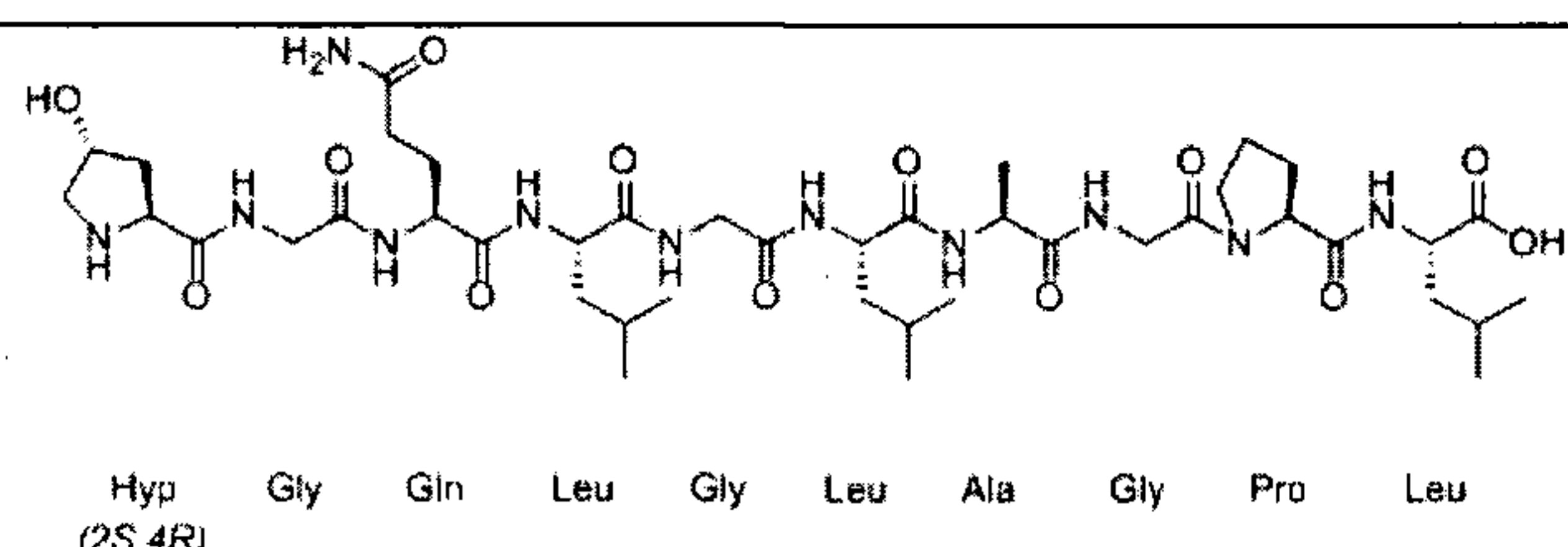

 C_{1-6} alkyl,  R_a ,  OH ,  $O-C(=O)-OR_a$, and  $O-C(=O)-NHR_a$. Here, n may be an integer of 1 to 10, but it is not limited thereto. R_a may be hydrogen or C_{1-6} alkyl.

Specifically, R^3 may be one selected from the group consisting of,

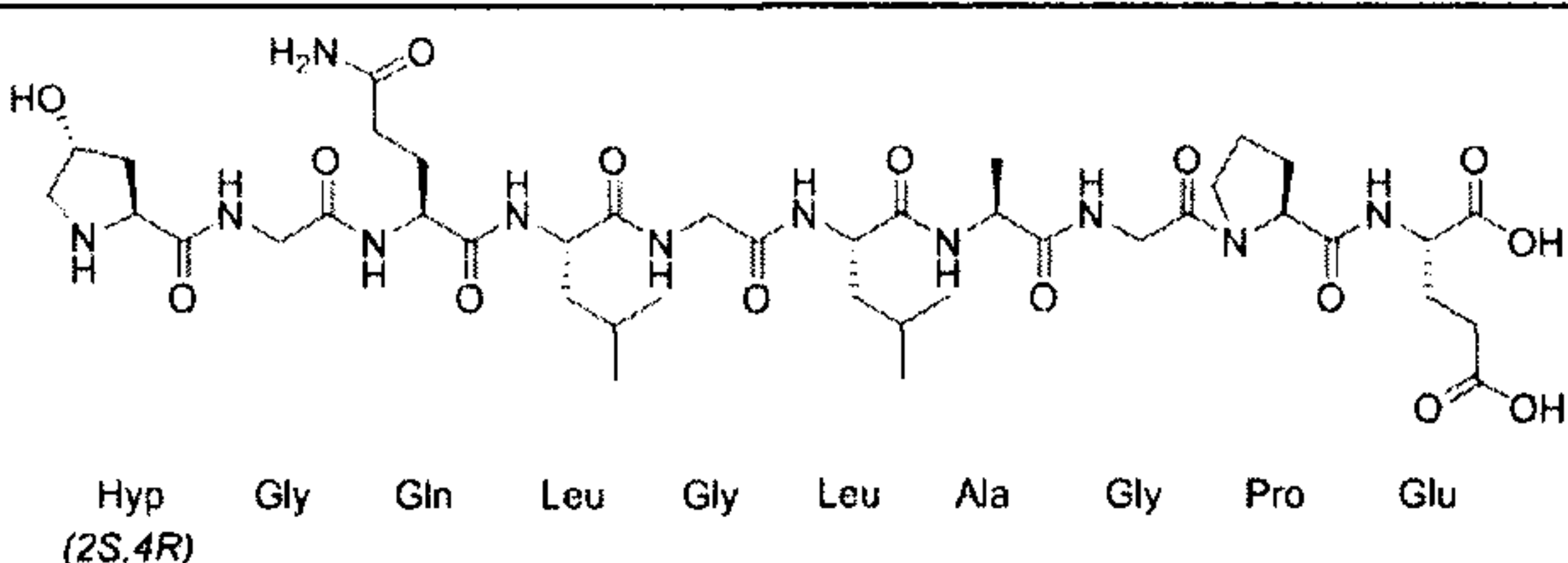
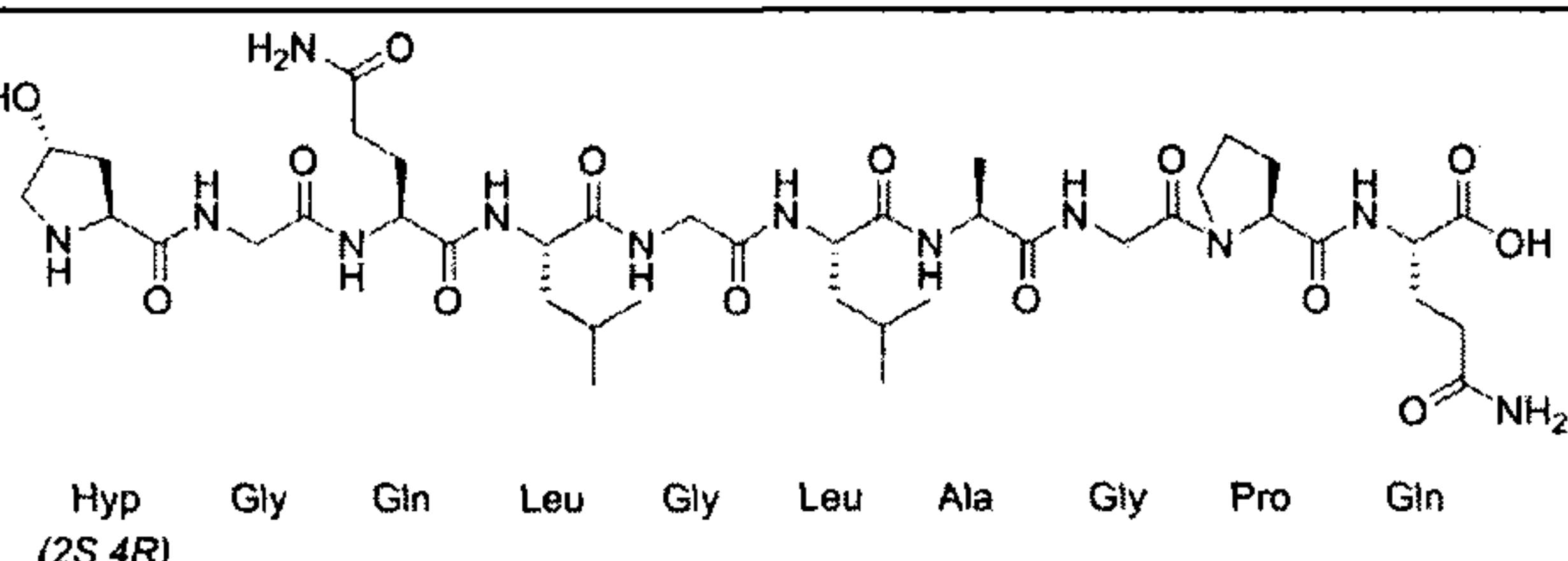
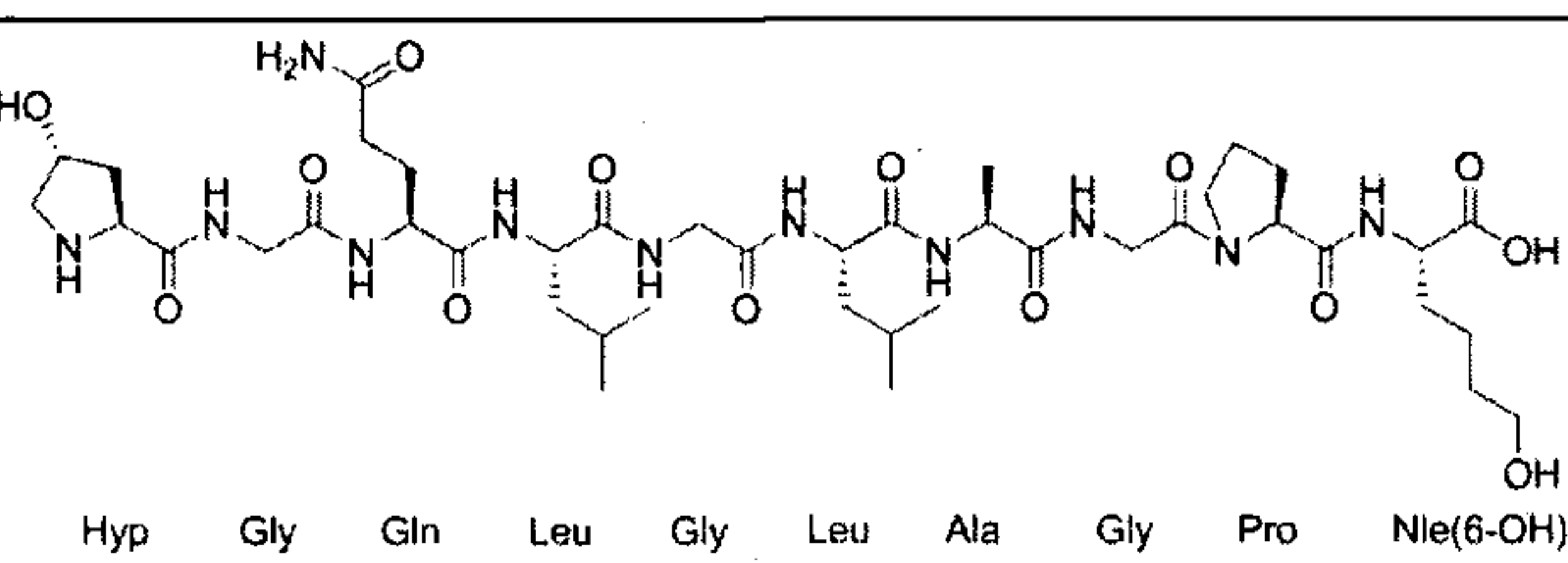
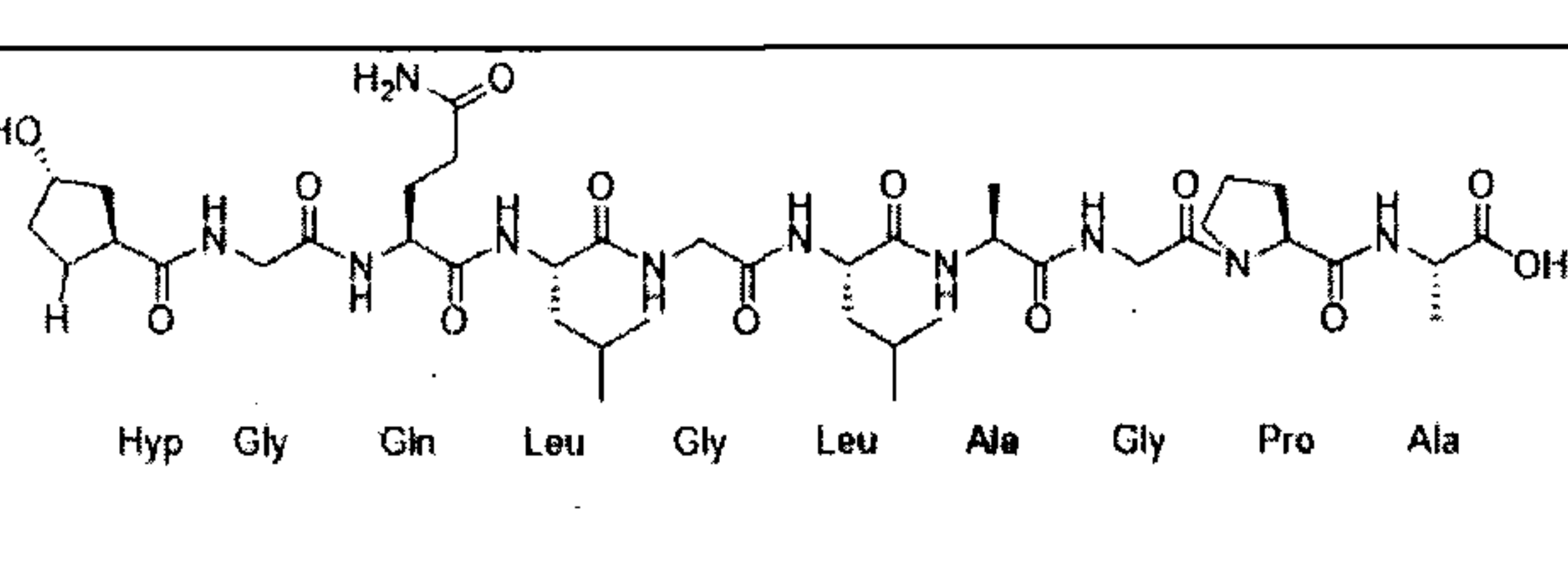
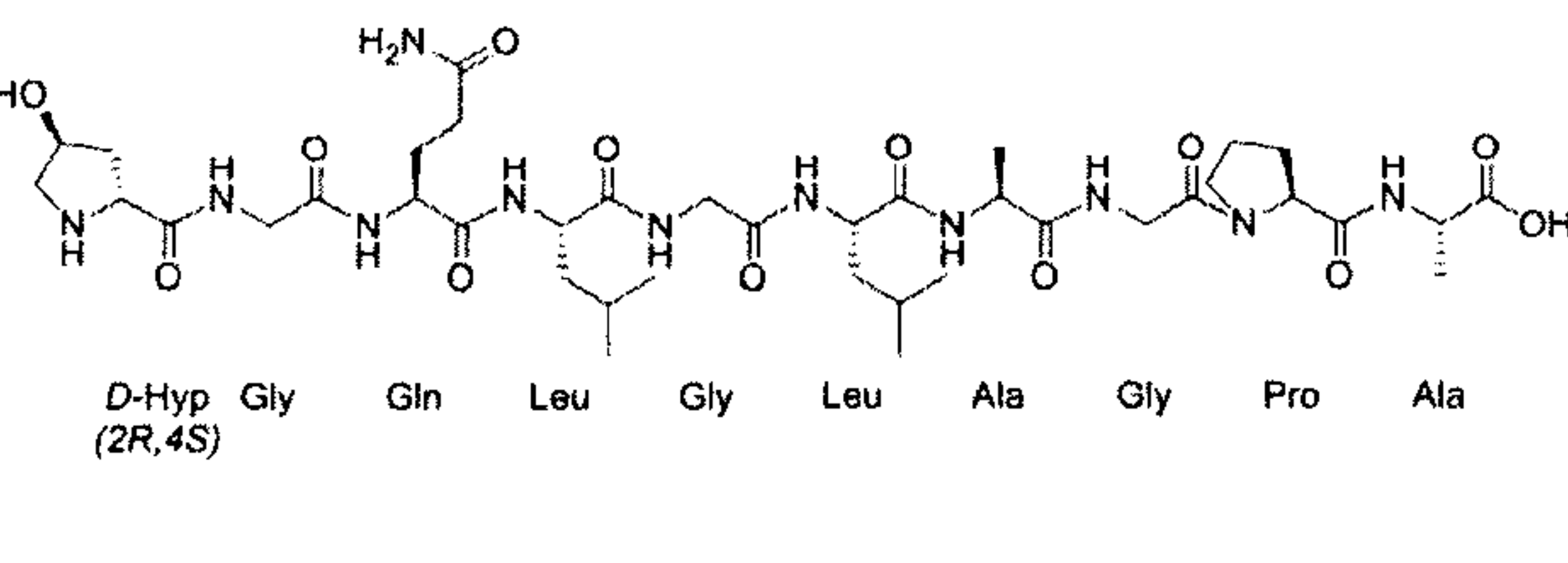


5 More specifically, the compound may be a compound described in Table 4 below.

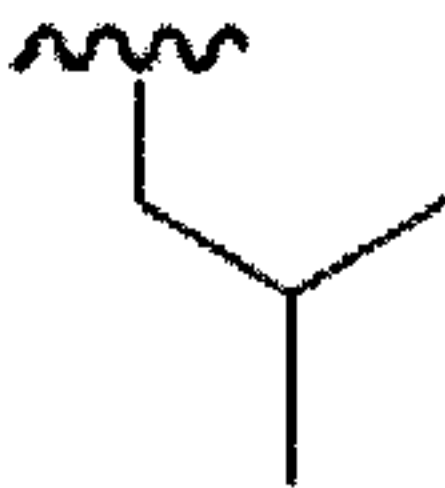
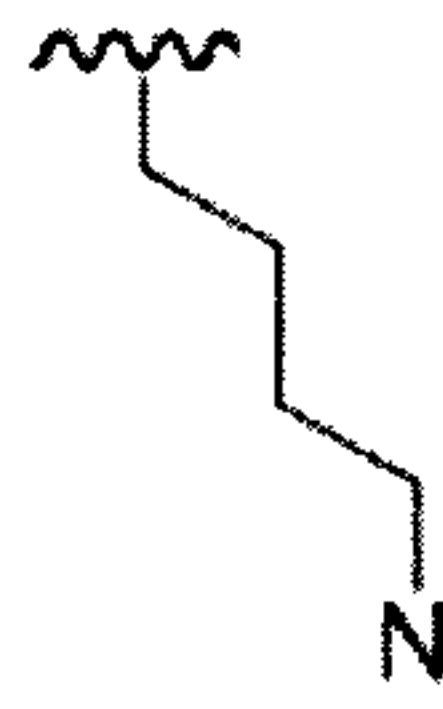
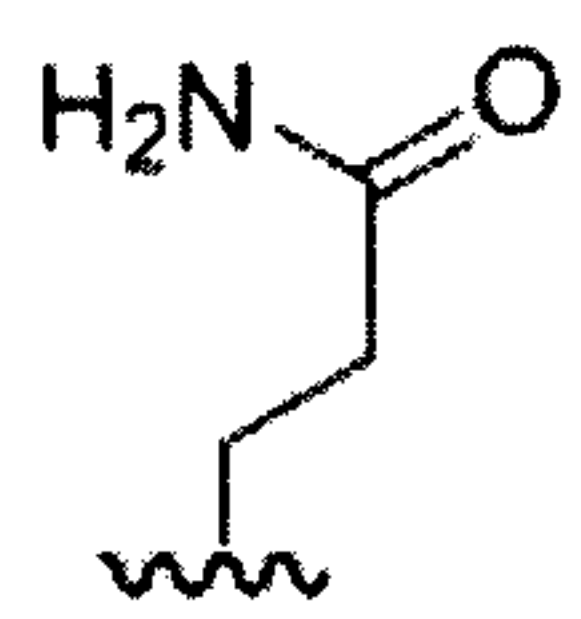
[Table 4]

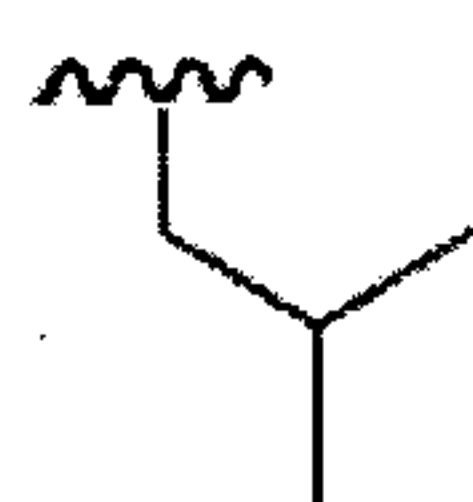
YDE-029	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Tyr (2S,4R)	SEQ ID NO: 33
YDE-030	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Leu (2S,4R)	SEQ ID NO: 34

40

YDE-031	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Glu (2S,4R)	SEQ ID NO: 35
YDE-032	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Gln (2S,4R)	SEQ ID NO: 36
YDE-033	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Nle(6-OH) (2S,4R)	SEQ ID NO: 37
YDE-056	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala	SEQ ID NO: 38
YDE-073	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala (2R,4S)	SEQ ID NO: 39

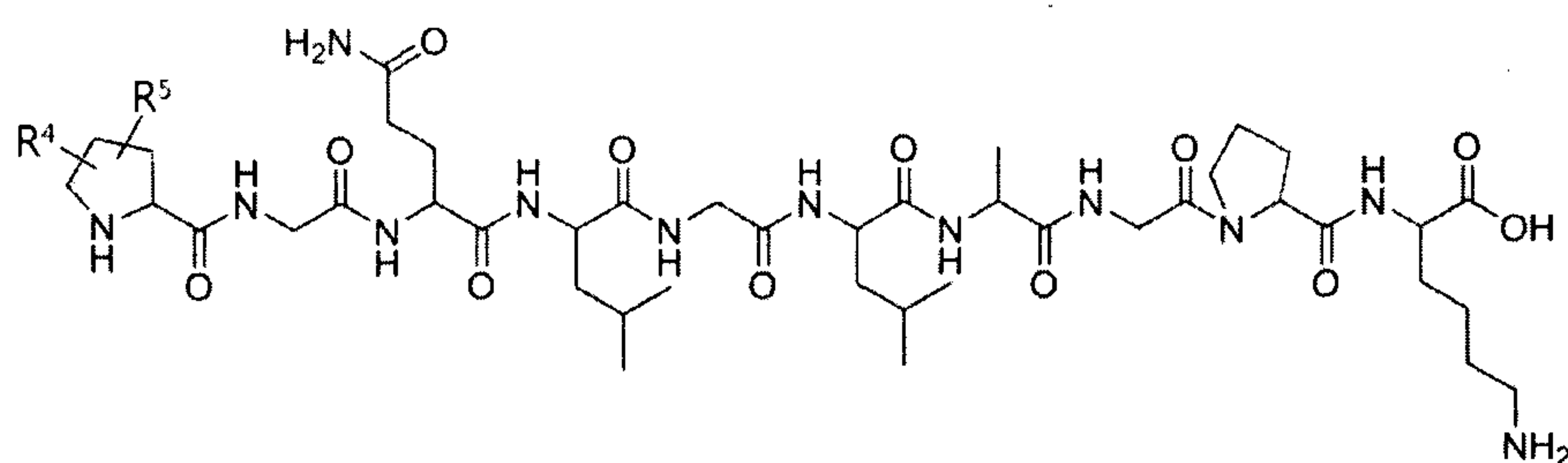
The compound represented by the above Formula 1 may be represented by

Formula 1-5 when R¹ is , R² is H, R³ is , R⁶ is , R⁷ is



, R^8 is H, and R^9 is H. Further, the compound represented by the following Formula 1-5 may be an optical isomer type L or D.

[Formula 1-5]



- 5 R^4 and R^5 may be each independently one selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, $-OR_b$, $=O$, $-CH_2OR_b$, and $-X_2$. Here, X_2 may be independently halogen such as F, Cl, Br, or I. R_b may be hydrogen or C_{1-6} alkyl.

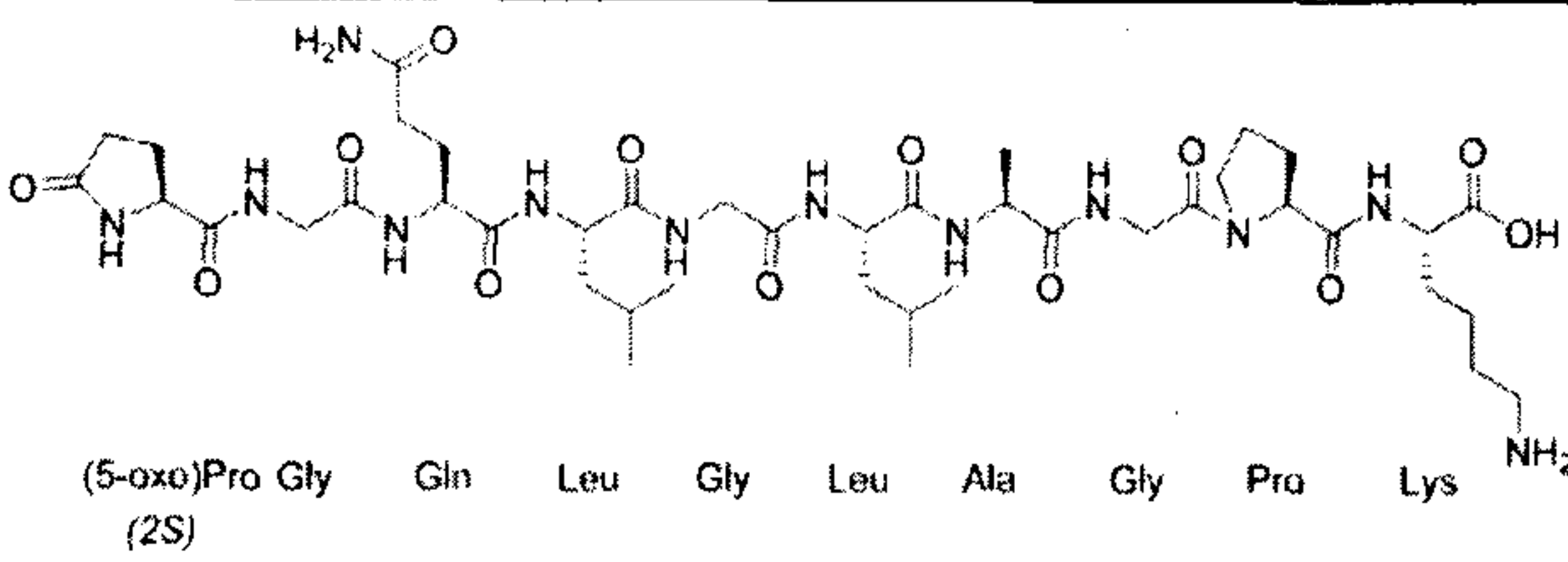
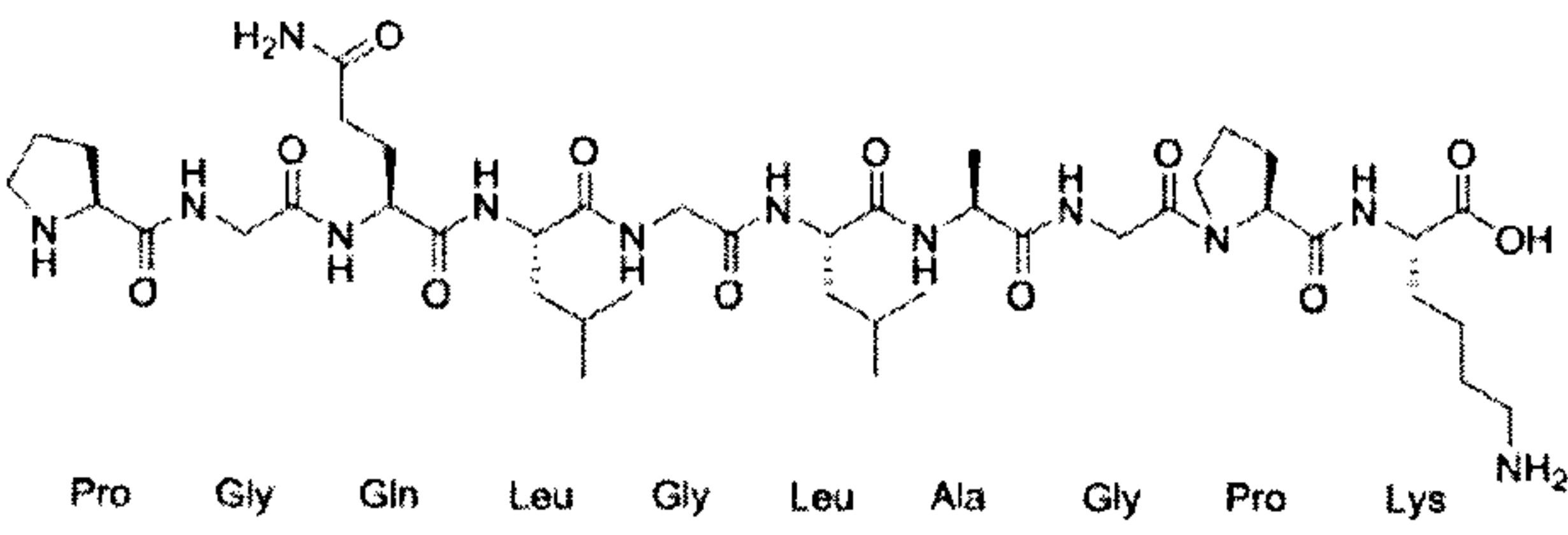
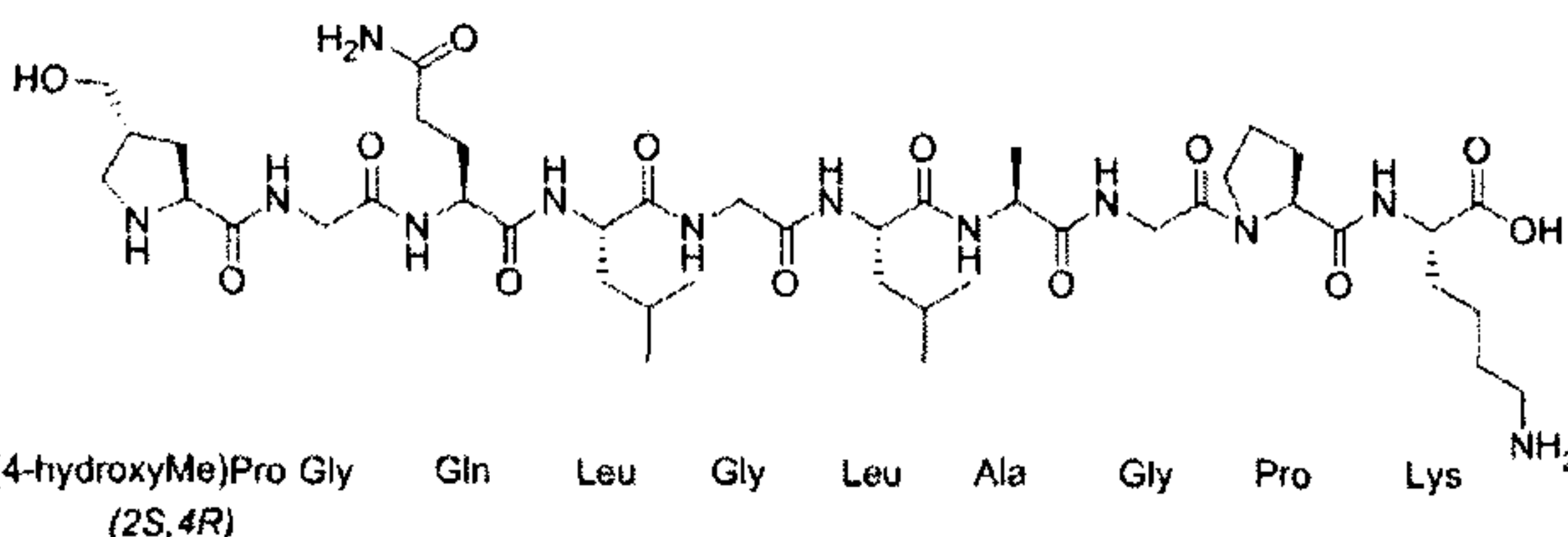
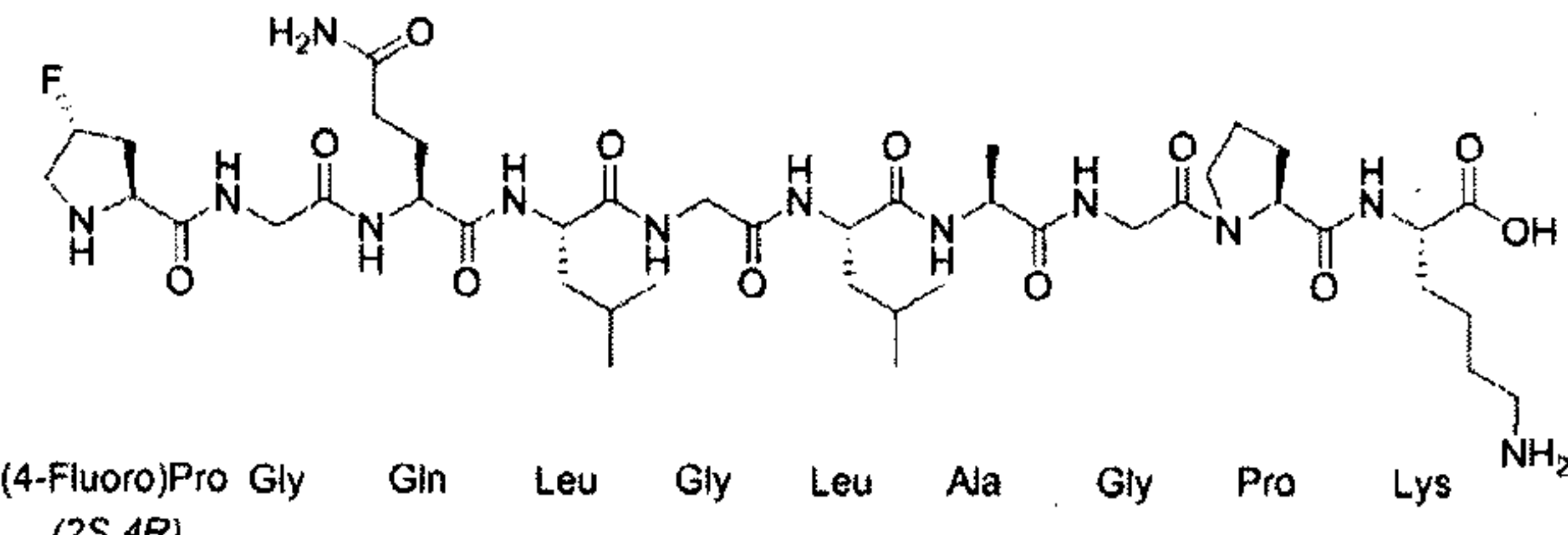
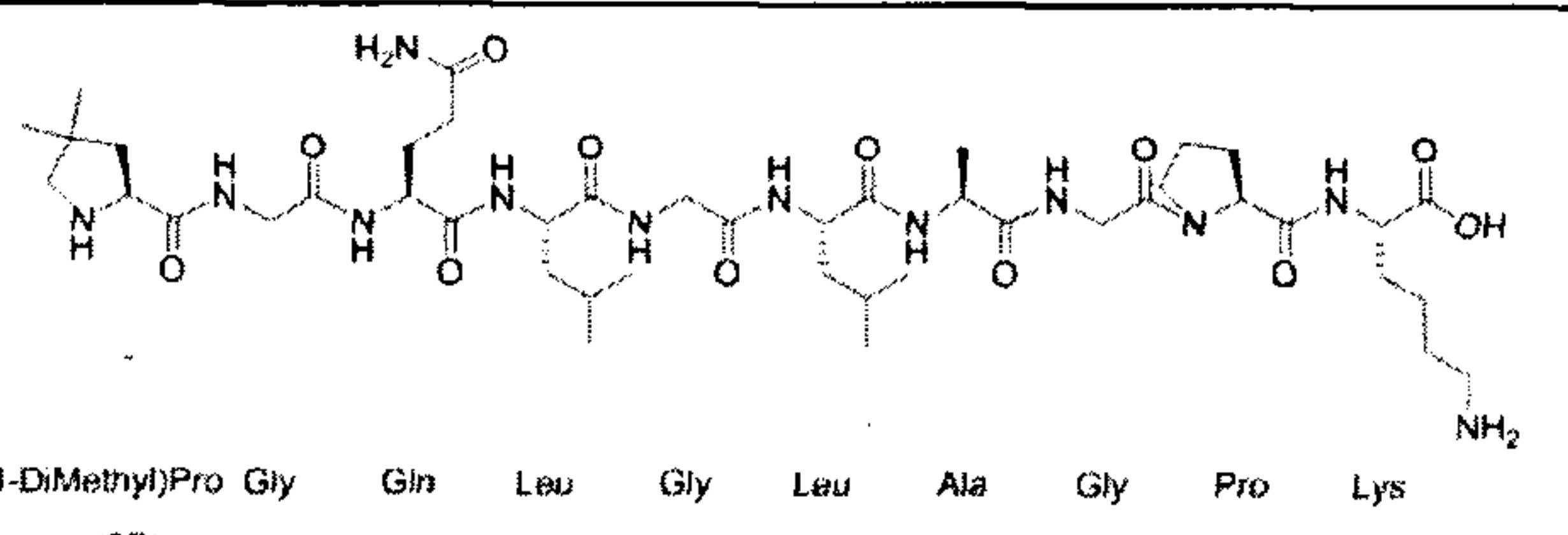
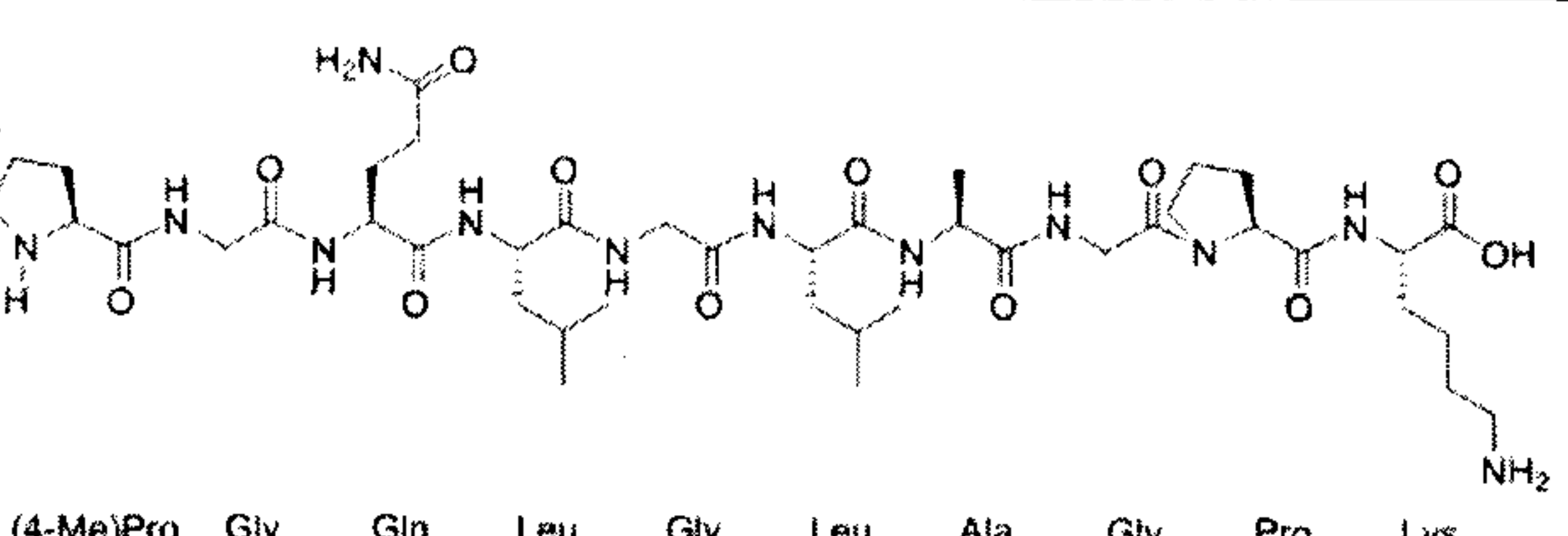
Specifically, R^4 may be one selected from the group consisting of H, $-OH$, $=O$, $-CH_2OR_b$, and F; in such event, R^5 may be H. Further, R^4 may be CH_3 ; in such event,

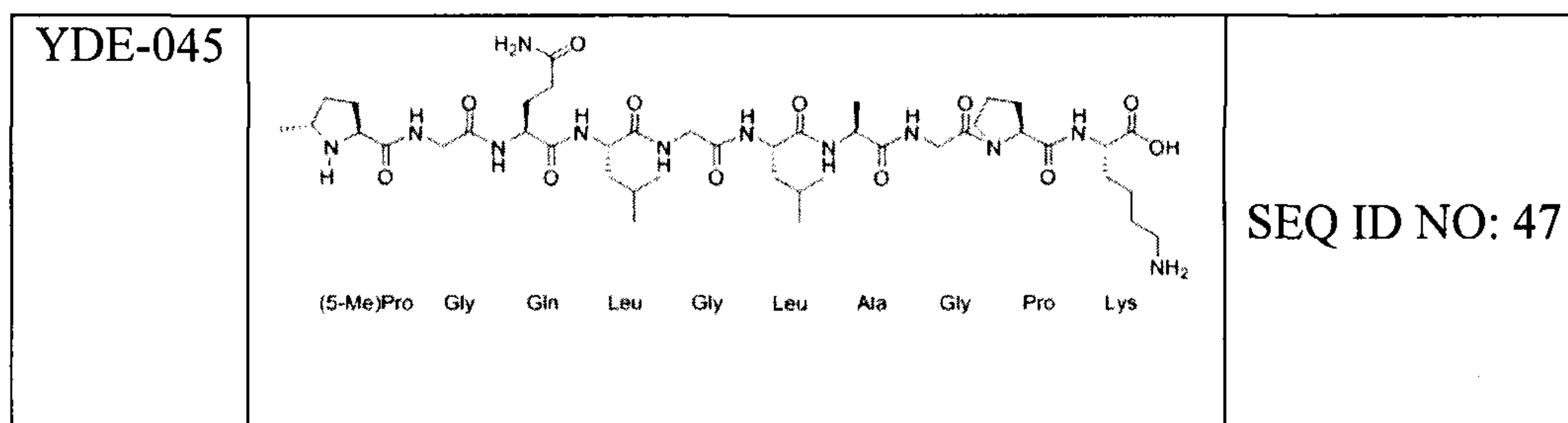
- 10 R^5 may be CH_3 .

More specifically, the compound may be a compound described in Table 5 below.

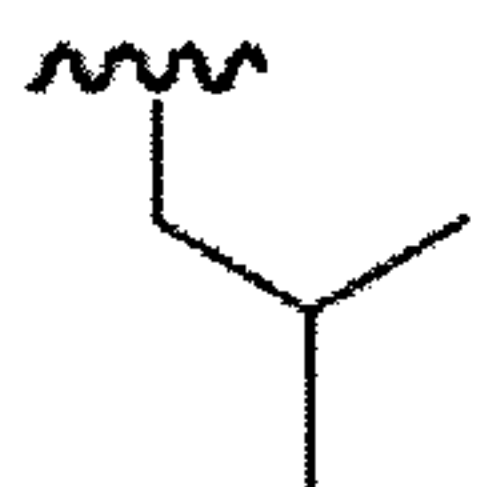
[Table 5]

YDE-034	Hyp (2S,4S) Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 63
YDE-035	(4-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 40

YDE-036	 (5-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2S)	SEQ ID NO: 41
YDE-037	 Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 42
YDE-038	 (4-hydroxyMe)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 43
YDE-039	 (4-Fluoro)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 44
YDE-040	 (4-DiMethyl)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2S)	SEQ ID NO: 45
YDE-044	 (4-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 46

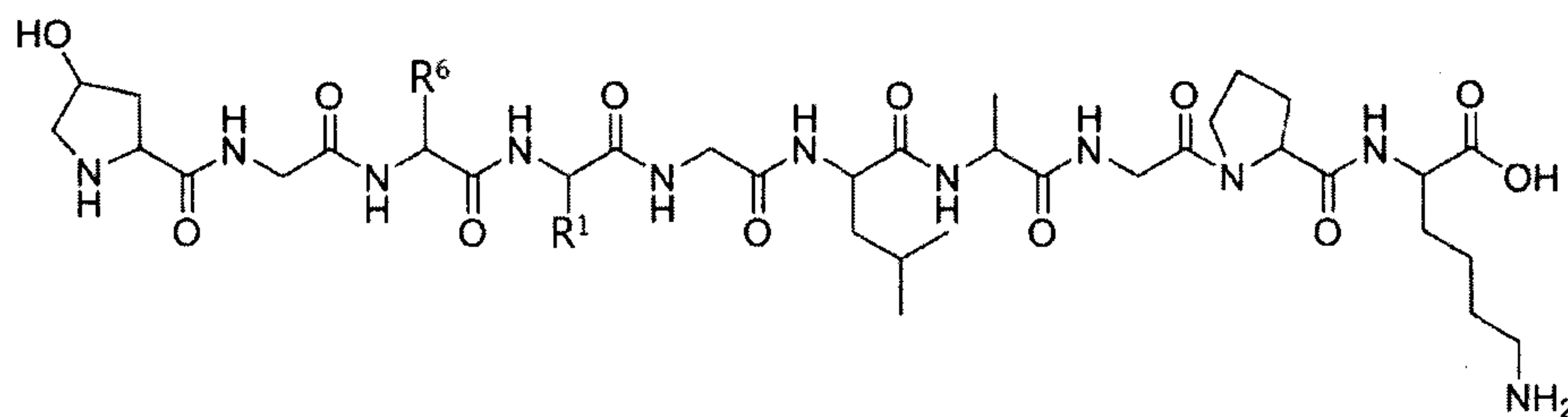


The compound represented by the above Formula 1 may be represented by

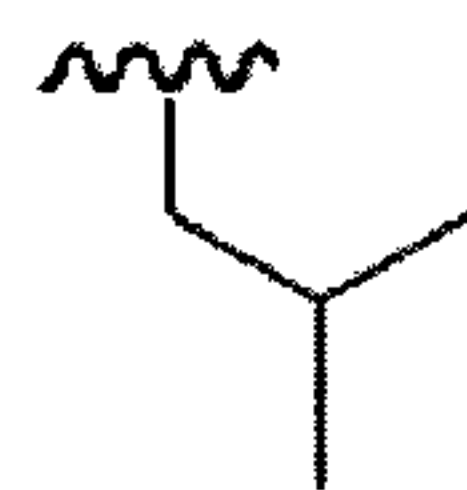
Formula 1-6 when R^2 is H, R^3 is , R^4 is -OH, R^5 is H, R^7 is , R^8 is H, and R^9 is H. Further, the compound represented by the following Formula 1-6 may be

5 an optical isomer type L or D.

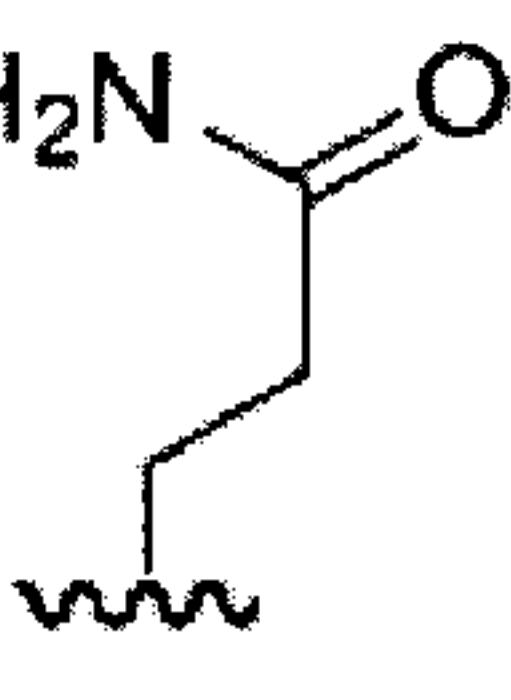
[Formula 1-6]



R^1 may be C_{1-6} alkyl. Specifically, R^1 may be



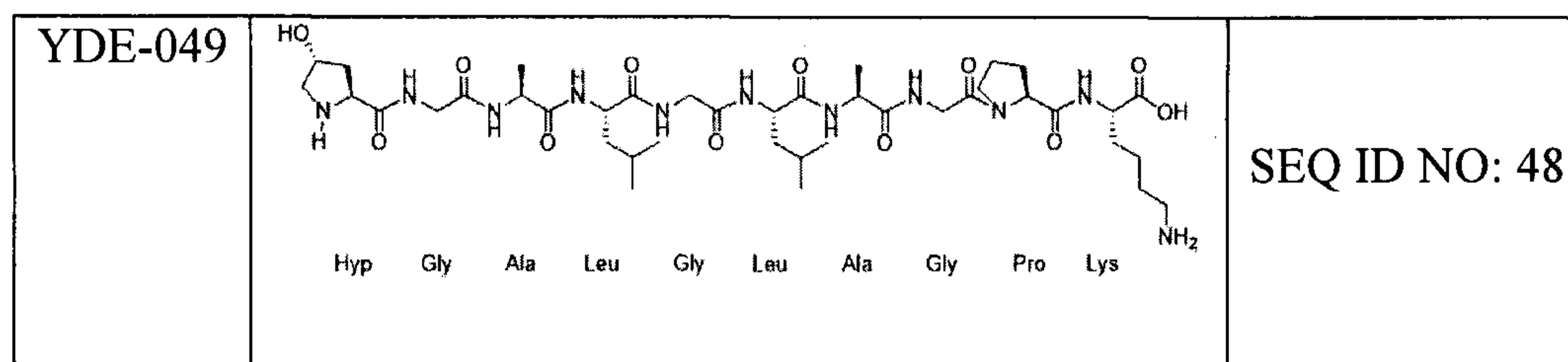
R^6 may be substituted or unsubstituted C_{1-6} alkyl, wherein the substituent may be

10 -C(=O)NH₂. Specifically, R^6 may be  or .

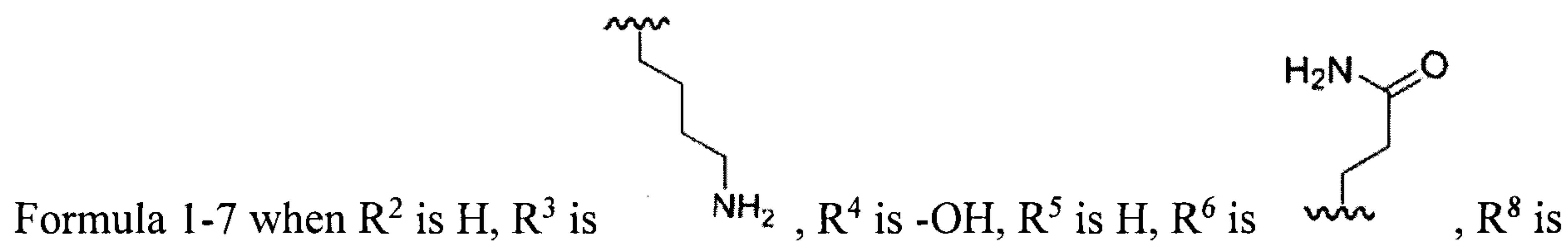
More specifically, the compound may be a compound described in Table 6 below.

[Table 6]

44



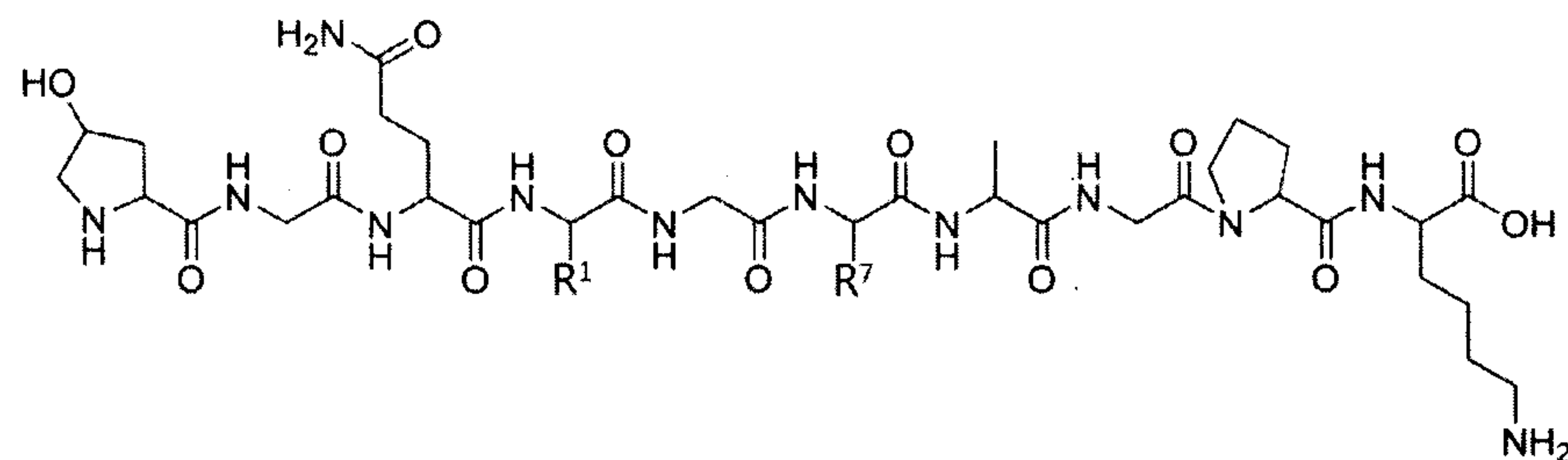
The compound represented by the above Formula 1 may be represented by



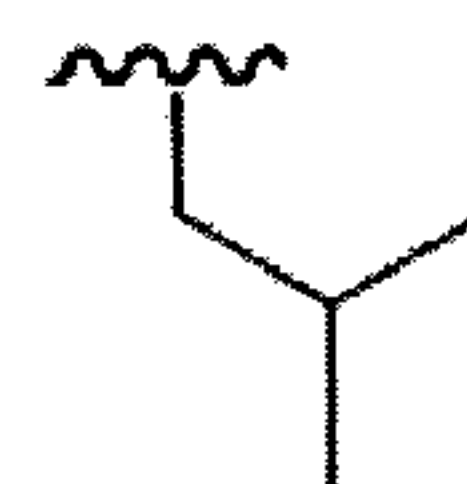
H, and R^9 is H. Further, the compound represented by the following Formula 1-7 may

5 be an optical isomer type L or D.

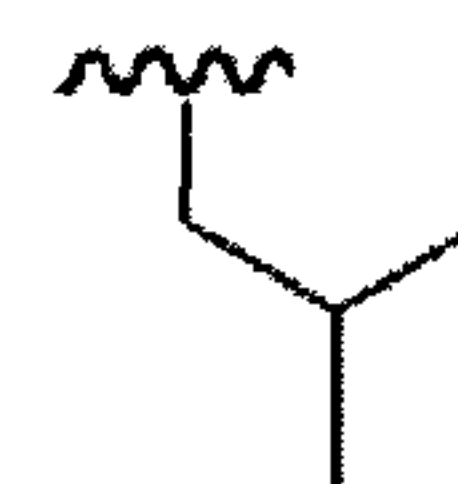
[Formula 1-7]



R^1 may be C_{1-6} alkyl. Specifically, R^1 may be



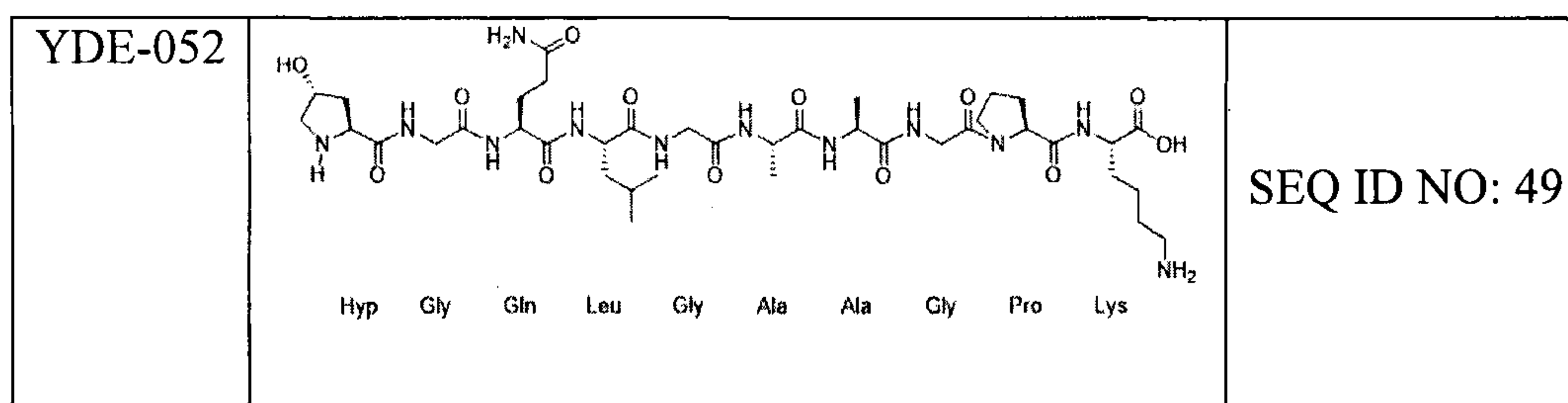
R^7 may be unsubstituted C_{1-6} alkyl. Specifically, R^7 may be



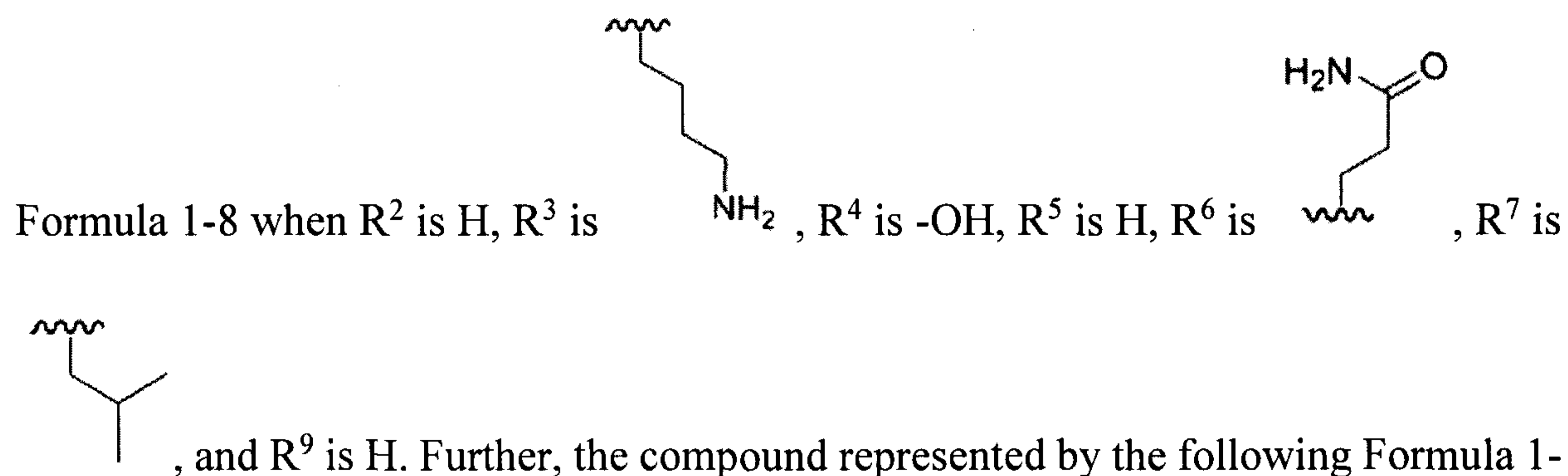
or  H_3C .

10 More specifically, the compound may be a compound described in Table 7 below.

[Table 7]

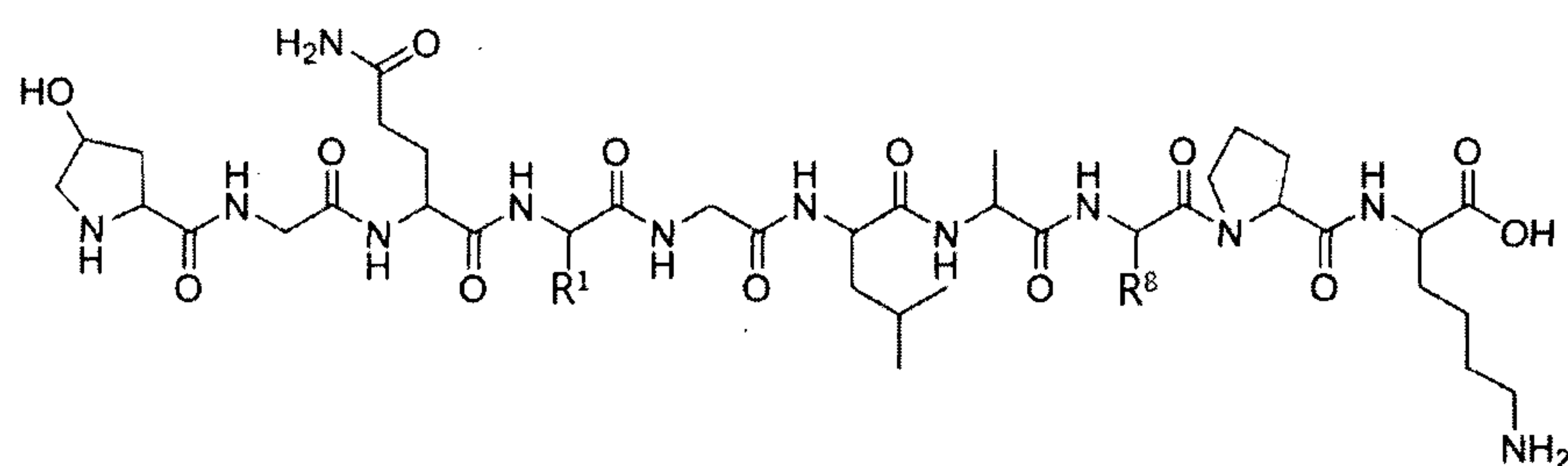


The compound represented by the above Formula 1 may be represented by



5 8 may be an optical isomer type L or D.

[Formula 1-8]



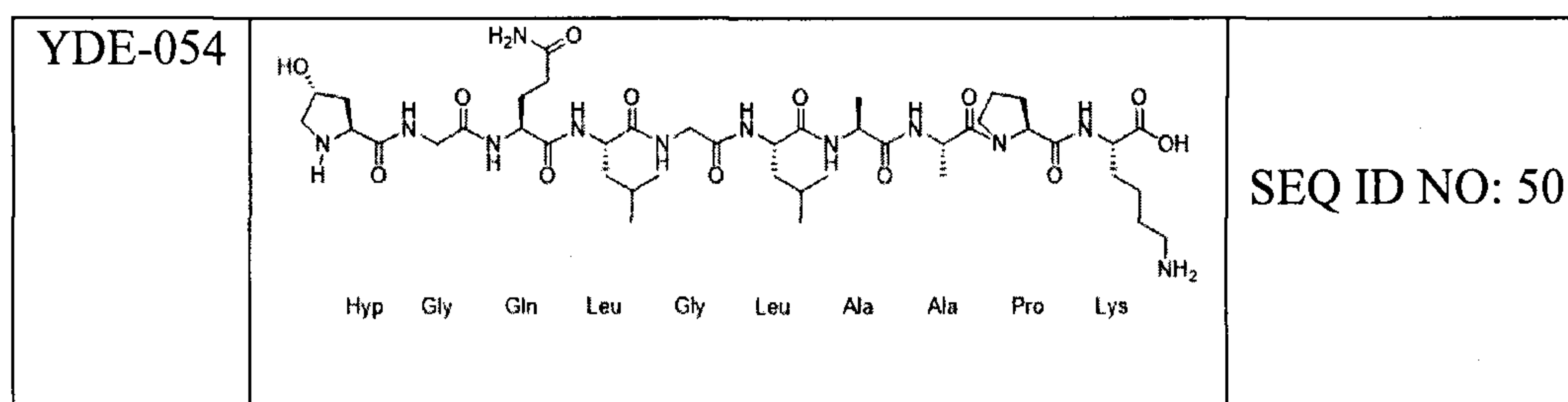
R¹ may be C₁₋₆ alkyl. Specifically, R¹ may be

R⁸ may be hydrogen or C₁₋₆ alkyl. Specifically, R⁸ may be

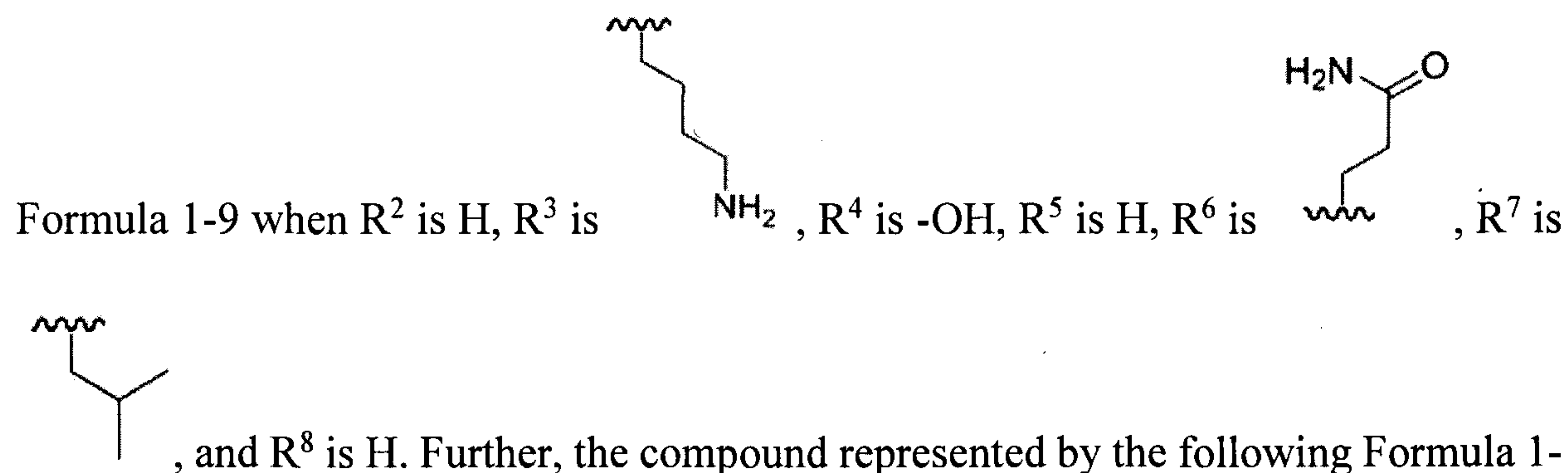
10 More specifically, the compound may be a compound described in Table 8 below.

[Table 8]

46

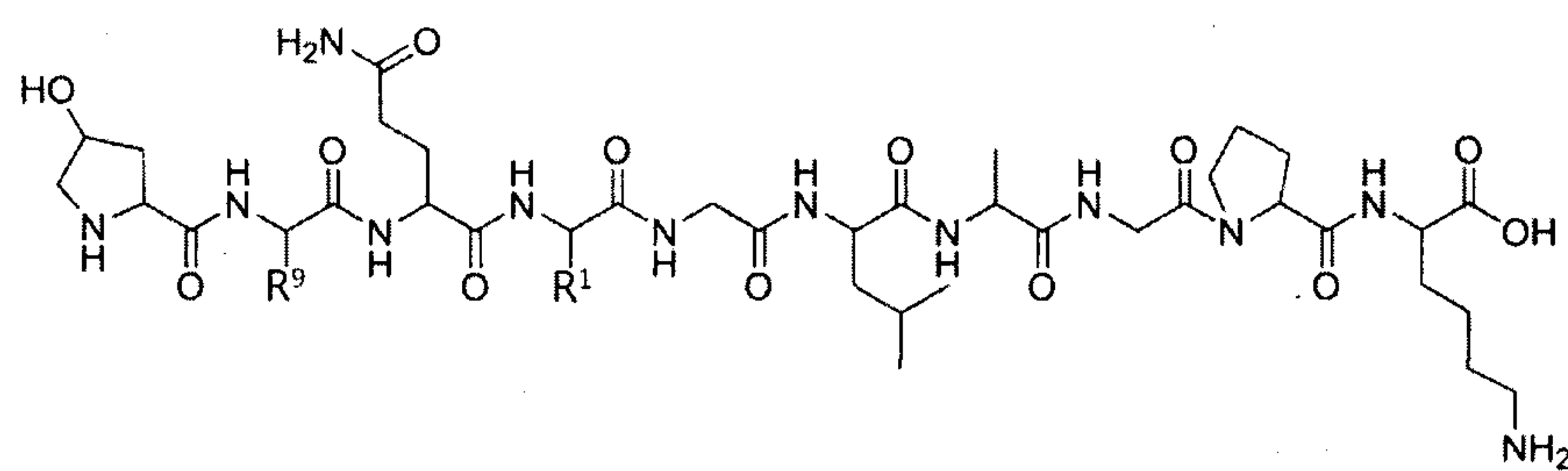


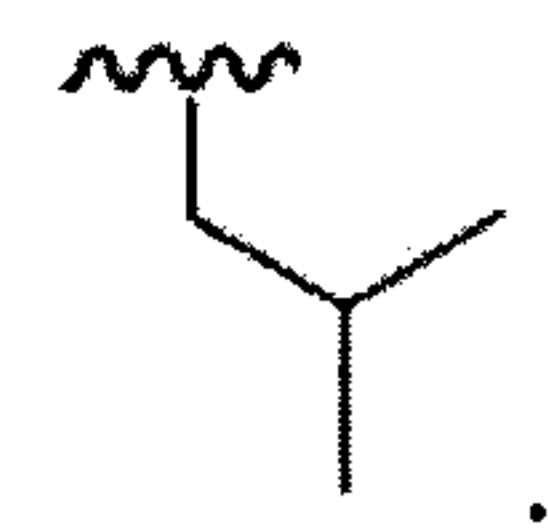
The compound represented by the above Formula 1 may be represented by

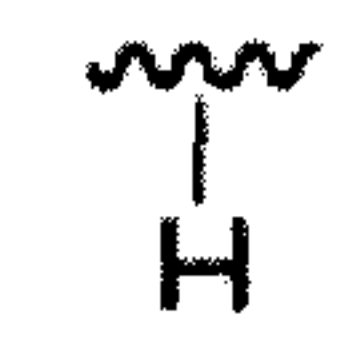
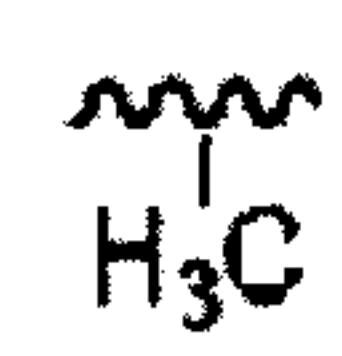


5 9 may be an optical isomer type L or D.

[Formula 1-9]



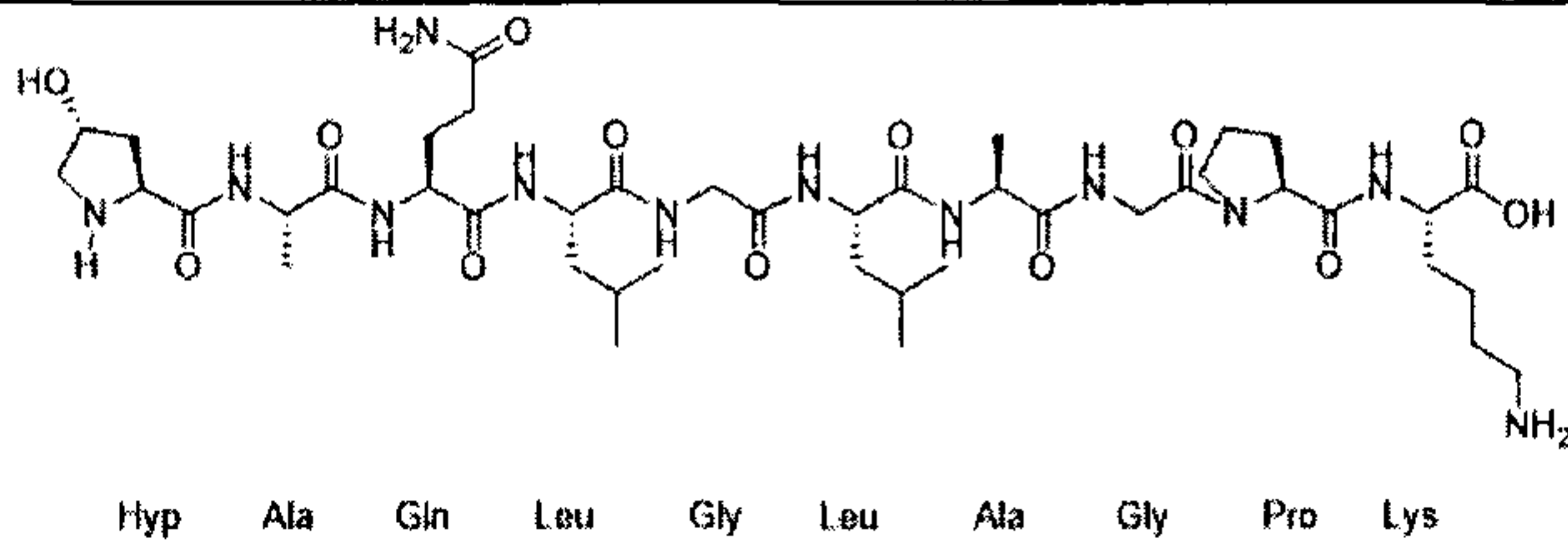
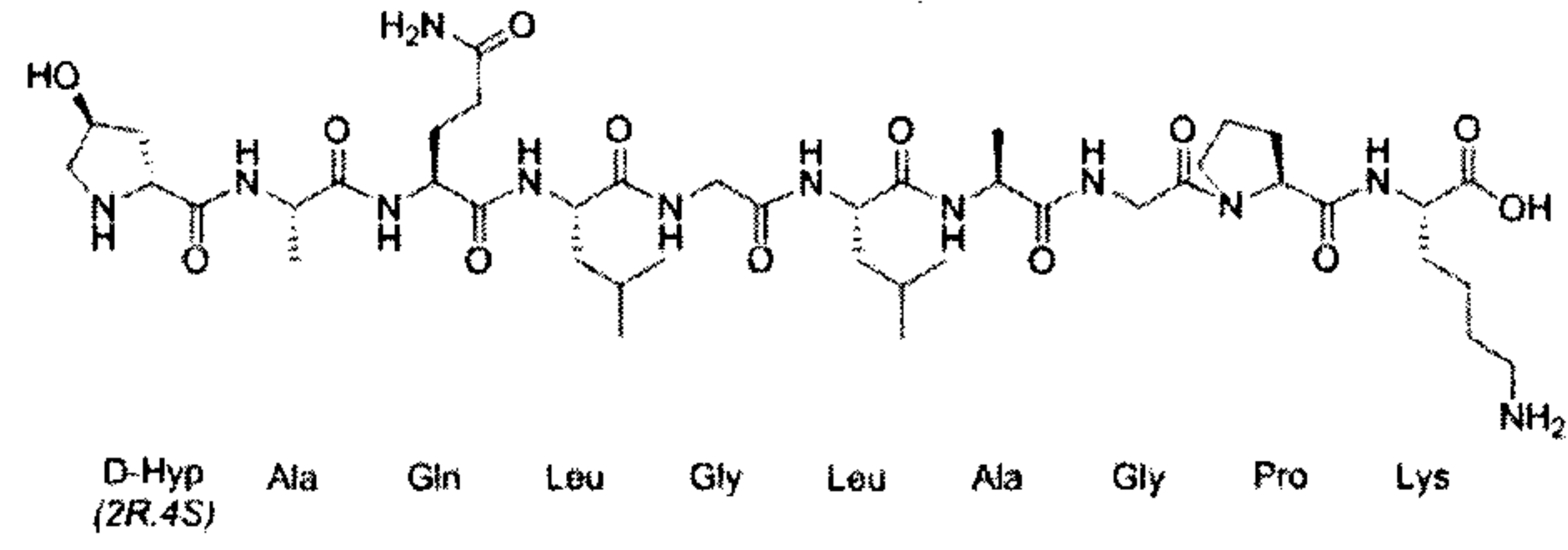
R^1 may be C_{1-6} alkyl. Specifically, R^1 may be .

R^9 may be hydrogen or C_{1-6} alkyl. Specifically, R^9 may be  or .

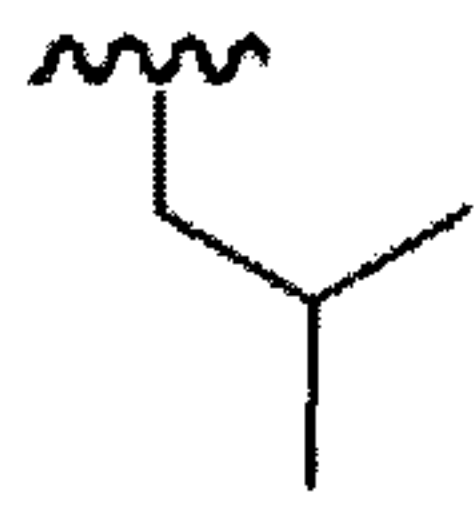
10 More specifically, the compound may be a compound described in Table 9 below.

[Table 9]

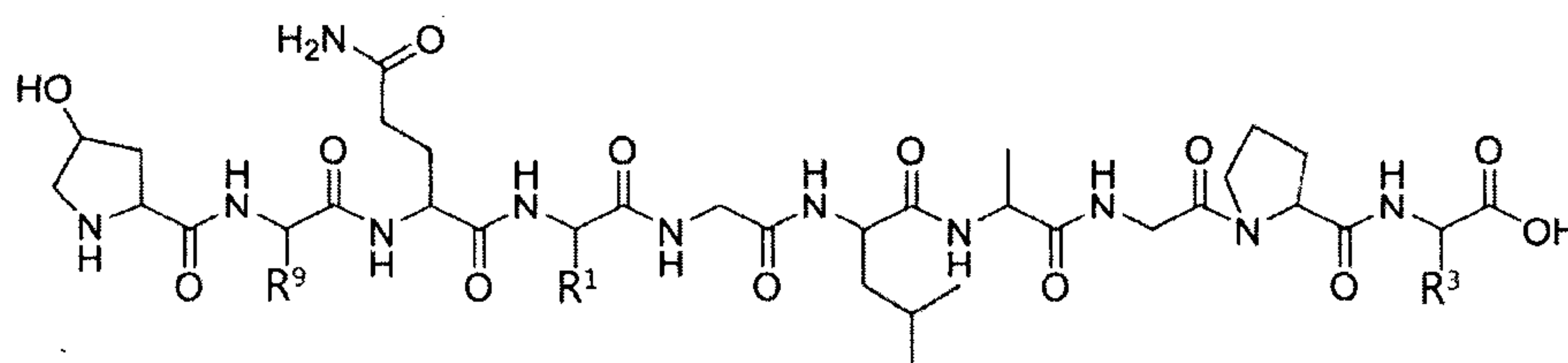
47

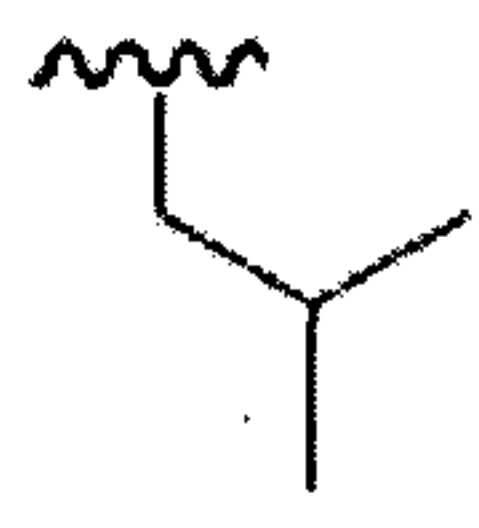
YDE-048	 Hyp Ala Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 51
YDE-072	 D-Hyp (2R,4S) Ala Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 53

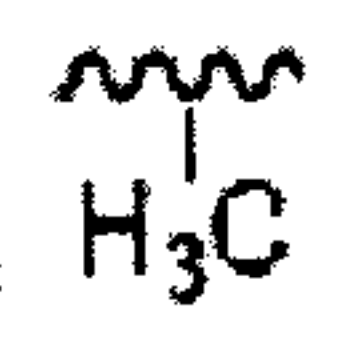
The compound represented by the above Formula 1 may be represented by

Formula 1-10 when R^2 is H, R^4 is -OH, R^5 is H, R^6 is , R^7 is , and R^8 is H. Further, the compound represented by the following Formula 1-10 may be an optical isomer type L or D.

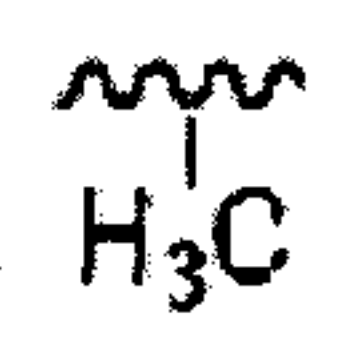
[Formula 1-10]



R^1 may be C_{1-6} alkyl. Specifically, R^1 may be .

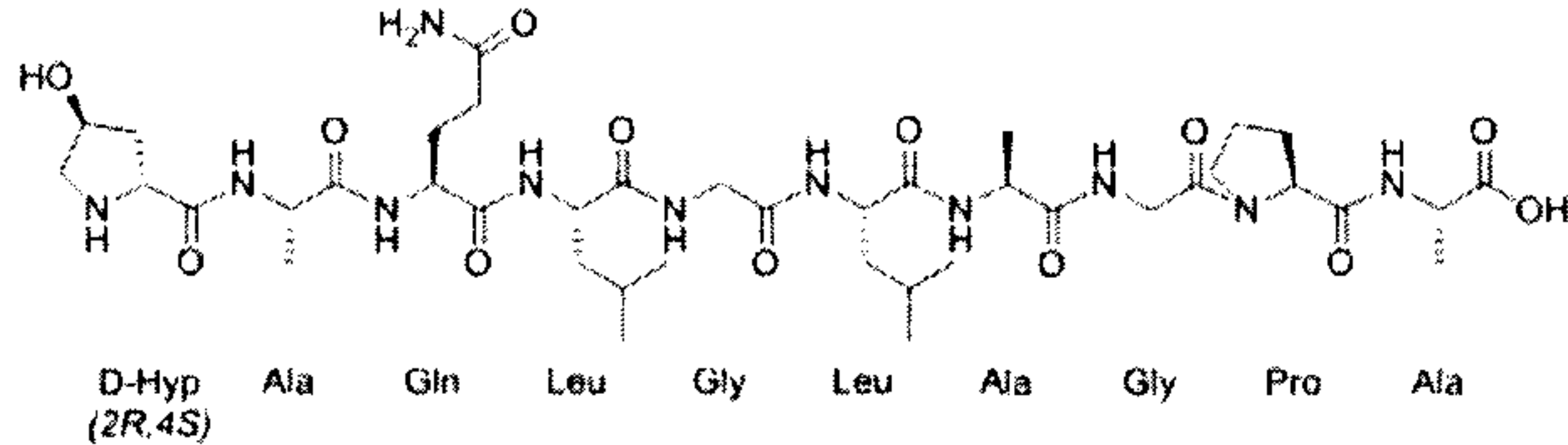
In such event, R^3 may be C_{1-6} alkyl. Specifically, R^3 may be .

10

In such event, R^9 may be C_{1-6} alkyl. Specifically, R^9 may be .

More specifically, the compound may be a compound described in Table 10 below.

[Table 10]

YDE-074	 D-Hyp (2R,4S) Ala Gln Leu Gly Leu Ala Gly Pro Ala	SEQ ID NO: 52
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5 The compounds represented by the above Formulae 1-1 to 1-10 may be any one selected from the group consisting of HyP-Gly-Gln-Glu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Gln-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-His-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Lys-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Thr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ala-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Val-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ile-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Phe-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Tyr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Trp-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser(Homo)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp(Me)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn(Me)-Gly-Leu-Ala-Gly-Pro-Lys, D-Hyp(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, D-Hyp(2R,4S)-Gly-D-Gln-D-Leu-Gly-D-Leu-D-Ala-Gly-D-Pro-D-Lys, D-Hyp(2R, 4R)-Gly-D-Gln-D-Leu-Gly-D-Leu-D-Ala-Gly-D-Pro-D-Lys,

HyP-Gly-Gln-Asp-Val-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ile-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Leu-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ala-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Phe-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Tyr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Trp-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-His-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ser-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Thr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Ala-Leu-Ala-

Gly-Pro-Lys,

HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Tyr, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Leu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Glu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Gln, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Nle(6-OH), HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala, D-HyP(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala,

Hyp(2S, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-hydroxyMe)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Fluoro)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Dimethyl)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys,

Hyp-Gly-Ala-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Ala-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Ala-Pro-Lys, Hyp-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, D-Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys and D-Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala.

Another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys. Here, Xaa may be one selected from the group consisting of Glu, Asn, Gln, His, Lys, Ser, Thr, Ala, Val, Ile, Leu, Phe, Tyr, Trp, homo-Ser, Asp(Me), and Asn(Me).

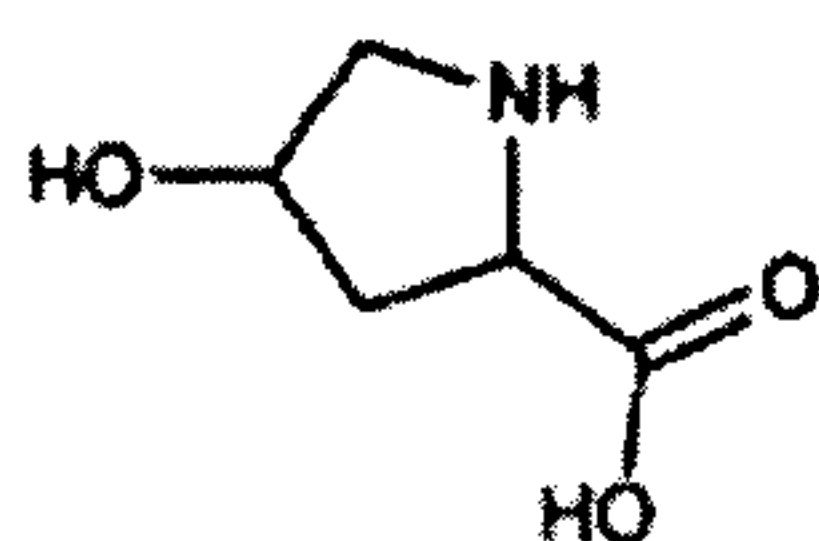
The peptide may be a variant of a collagen type II $\alpha 1$ -derived peptide. The collagen type II $\alpha 1$ may be isolated from the extracellular matrix derived from animal chondrocytes.

The term "peptide" used in the present invention refers to a compound in which two or more amino acids are linked by a peptide bond. Further, it is classified into dipeptide, tripeptide, tetrapeptide, and the like according to the number of constituent amino acids. An oligopeptide has about 10 or fewer peptide bonds, and a polypeptide

has a plurality of peptide bonds. In addition, a peptide in the present invention includes a mutated peptide in which its amino acid residue is substituted.

The term “HyP” used in the present invention refers to an amino acid called hydroxyproline, in which a hydroxyl group (-OH) is bonded to the carbon atom at the 4-position of proline. HyP has a structure of $C_5H_9NO_3$ and may be represented by the following Formula 2.

[Formula 2]

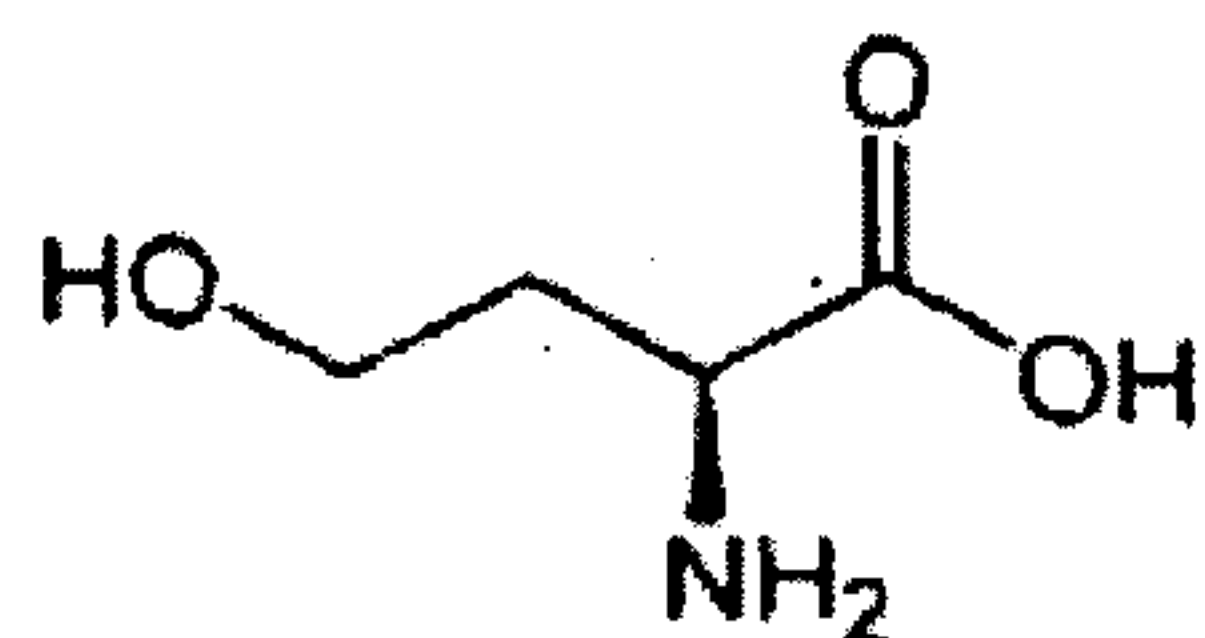


HyP may include all isomers. In addition, HyP may be an isomer represented by the stereochemistry of “2S,4R” unless otherwise specified.

The term “2S,4R” is represented by R and S that indicate a stereochemical configuration of a chiral molecule. A typical chiral molecule has a chiral center such as an asymmetric carbon atom. Since the chiral center has four different substituent groups (or substitution atoms), their priority is determined by a predetermined procedure. Once the order of the four substituents is determined by (1), (2), (3), and (4), the lowest order substituent (4) is placed farthest away from the eye direction, and the remaining substituents are arranged from the higher order to the lower order. R (or rectus in Latin, right) indicate the arrangement in which the sequence of (1) to (2) to (3) turns right. S (or sinister, left) indicates the arrangement in which this sequence turns left.

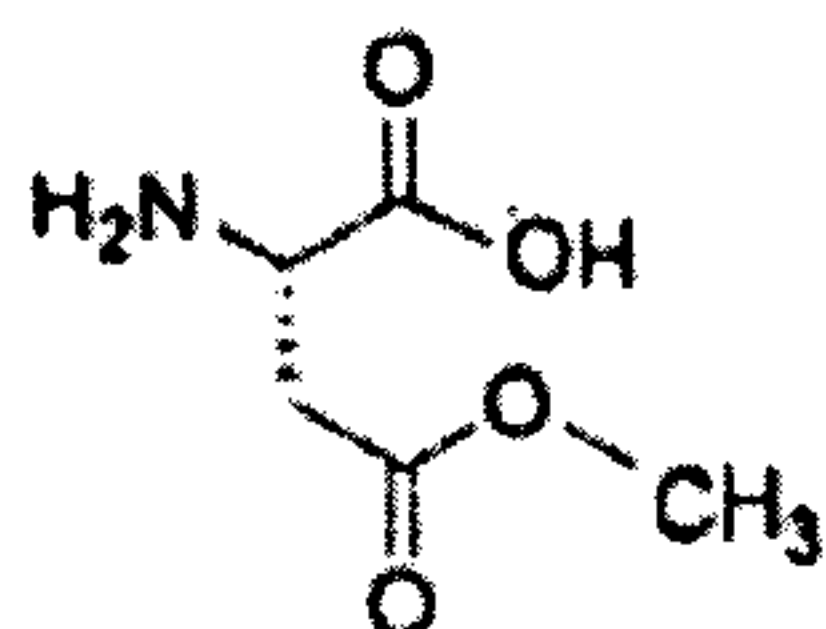
The term “homo-Ser” used in the present invention is called homoserine and refers to an α -amino acid having a hydroxyl group in the side chain. Homo-Ser is not an amino acid that constitutes a protein and is an intermediate present in the biosynthesis of threonine and methionine in microorganisms and plants. Homo-Ser may have the following Formula 3.

[Formula 3]



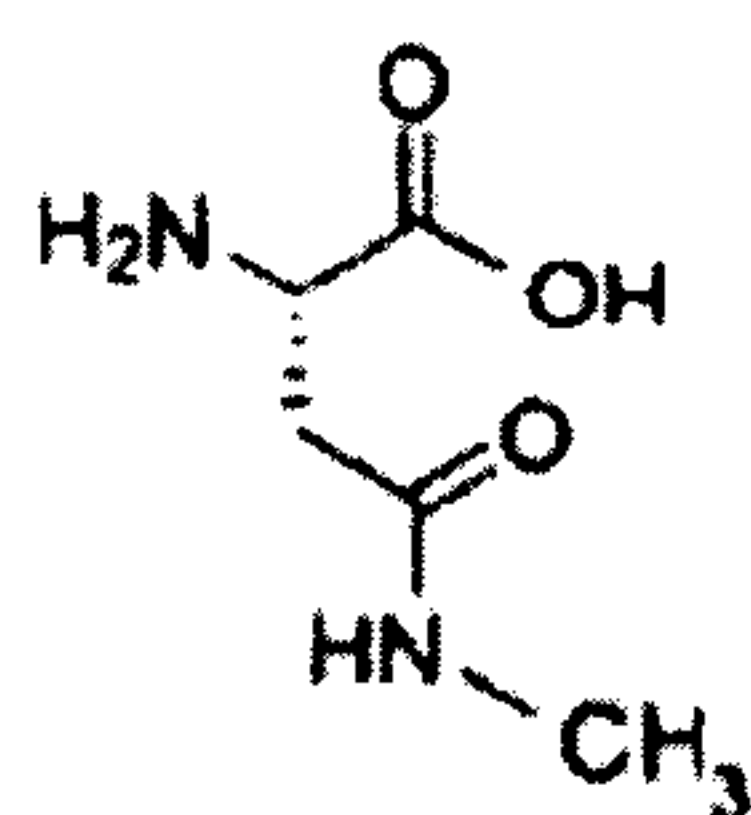
The term “Asp(Me)” used in the present invention indicates an amino acid in which the hydrogen atom of the hydroxyl group (OH) bonded to the carbon atom at the 4-position of aspartic acid is substituted by a methyl group (CH₃). Asp(Me) may have the following Formula 4.

[Formula 4]



The term “Asn(Me)” used in the present invention indicates an amino acid in which the hydrogen atom of the amine group (NH₂) bonded to the carbon atom at the 4-position of asparagine is substituted by a methyl group (CH₃). Asn(Me) may have the following Formula 5.

[Formula 5]

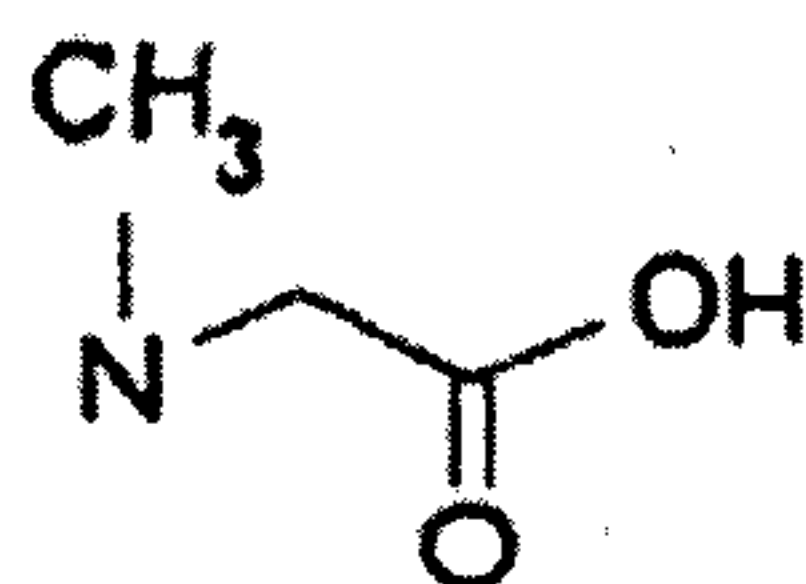


In addition, still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys. Here, Xaa may be one selected from the group consisting of Val, Ile, Leu, Ala, Phe, Tyr, Trp, Ser, Thr, and (N-Me)Gly.

The term “(N-Me)Gly” used in the present invention indicates an amino acid in which the hydrogen atom of the amine group (NH₂) bonded to the carbon atom at the

2-position of glycine is substituted by a methyl group (CH₃). (N-Me)Gly may have the following Formula 6.

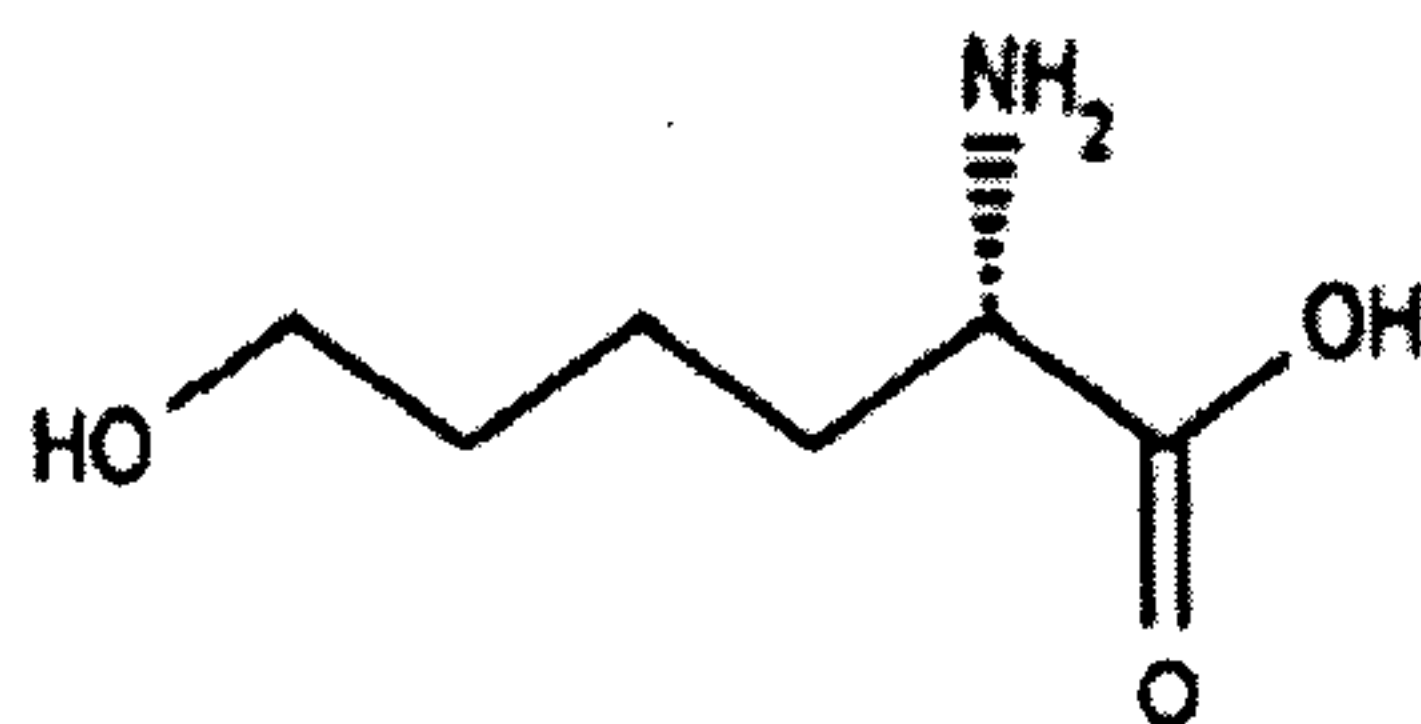
[Formula 6]



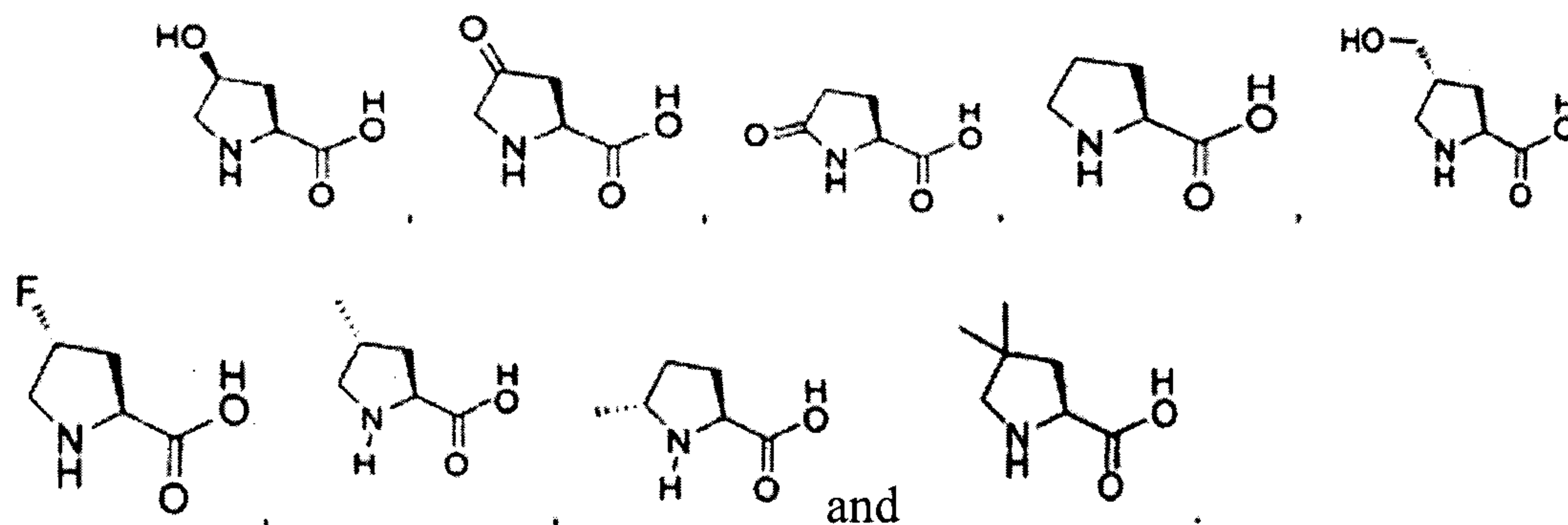
- 5 Still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa. Here, Xaa may be one selected from the group consisting of Tyr, Leu, Glu, Gln, Ala, and Nle(6-OH).

10 The term “Nle(6-OH)” used in the present invention refers to an amino acid in which a hydroxyl group (-OH) is bonded to the carbon atom at the 6-position of norleucine. Nle(6-OH) has a structure of C₅H₁₁NO₃ and may be represented by the following Formula 7.

[Formula 7]



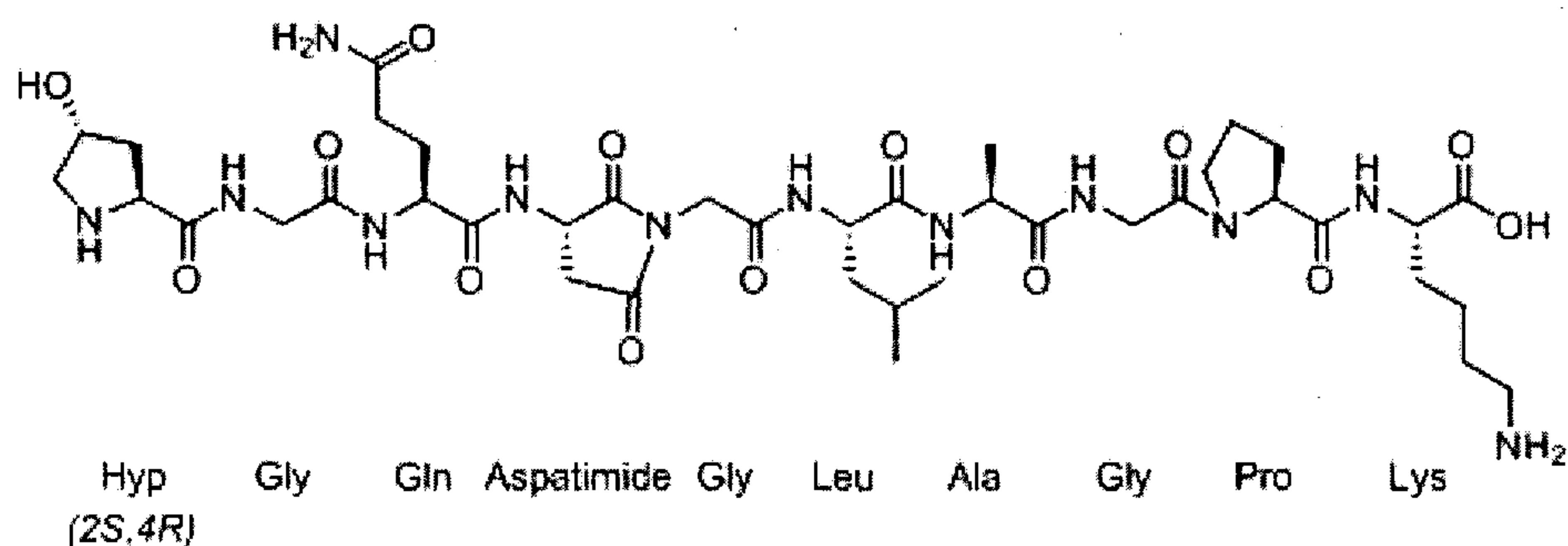
- 15 Still another aspect of the present invention provides a peptide having an amino acid sequence represented by PD-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys. Here, PD may be any one selected from the group consisting of the following formulae.



Still another aspect of the present invention provides a peptide having any one
 5 amino acid sequence selected from the group consisting of Ala-Gly-Gln-Leu-Gly-Leu-
 Ala-Gly-Pro-Lys (SEQ ID NO: 54), Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Ala-Lys
 (SEQ ID NO: 55), HyP-Gly-Gln-Leu-Gly-Leu-Ala (SEQ ID NO: 56), HyP-Gly-Gln-
 Glu-Gly-Leu-Gly (SEQ ID NO: 57), HyP-Gly-Gln-Leu-Gly-Leu (SEQ ID NO: 58), D-
 HyP(2R, 4S)-Gly-D-Gln-D-Leu-Gly-D-Leu (SEQ ID NO: 59), HyP-Gly-Gln-Leu-Gly
 10 (SEQ ID NO: 60), HyP-Gly-Gln-D-Leu-Gly (SEQ ID NO: 61), and D-HyP(2R, 4S)-Gly-
 Gln-Leu-Gly (SEQ ID NO: 62).

Still another aspect of the present invention provides a compound represented by
 Formula 8.

15 [Formula 8]

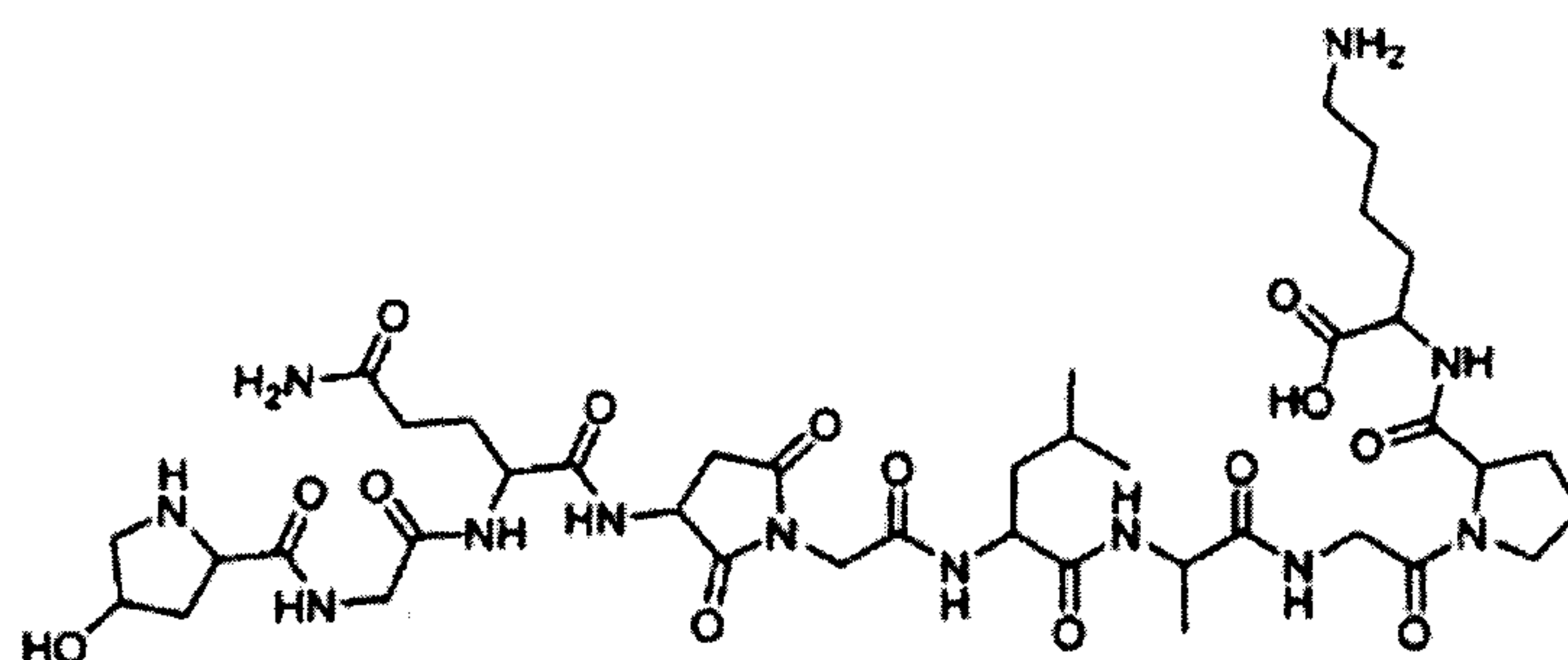


The compound represented by the above Formula 8 indicates a compound in

which Asp is modified to Aspartimide by a dehydration condensation reaction of the hydroxyl group (-OH) bonded to the carbon atom at the 4-position of Asp in the amino acid sequence represented by HyP-Gly-Gln-Asp-Gly-Leu-Ala-Gly-Pro-Lys with the Asp-Gly peptide bond.

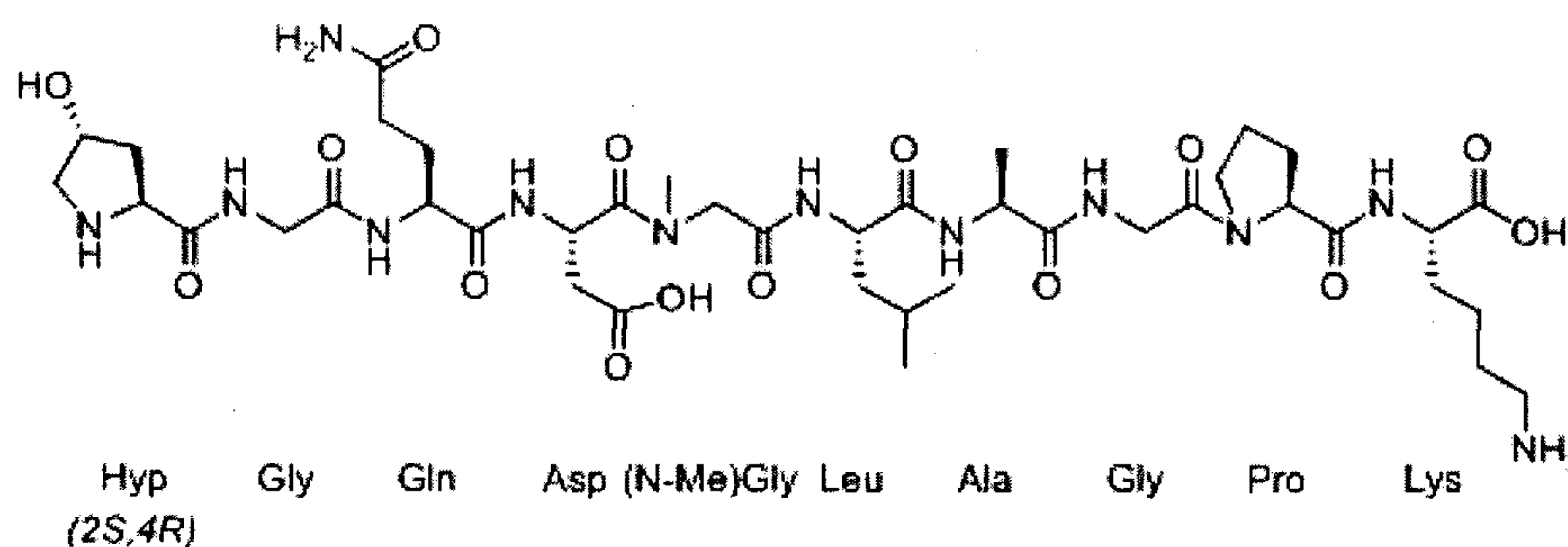
- 5 The modified compound may be a compound represented by the following Formula 9.

[Formula 9]



- 10 Still another aspect of the present invention provides a compound represented by Formula 10.

[Formula 10]



- 15 The compound represented by Formula 10 may be a compound represented by the amino acid sequence of SEQ ID NO: 31.

Further, the present invention provides a pharmaceutical composition for treating an eye disease, which comprises the compound or the peptide as an active pharmaceutical ingredient.

Specifically, the eye disease may be one selected from the group consisting of retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, keratoconjunctival epithelium disorder, proliferative vitreoretinopathy, pigmentary retinopathy, diabetic retinopathy, retinopathy of prematurity, retinopathy
5 of immaturity, proliferative retinopathy, ischemic retinopathy, epidemic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, phlyctenular keratoconjunctivitis, scleritis, corneal transplant rejection, choroidal neovascularization, neovascular glaucoma, ischemic optic neuropathy, retrolental fibroplasias, diabetic macula, neovascular iris disease, erythrosis, myopia, Von Hippel-
10 Lindau syndrome, ocular histoplasmosis, central retinal vein occlusion, Sjogren syndrome and Stevens-Johnson syndrome. Preferably, the eye disease may be one selected from the group consisting of retinopathy, keratitis, macular degeneration, dry eye syndrome and keratoconjunctival epithelium disorder.

The keratoconjunctival epithelium disorder may be due to post-operative surgery,
15 drug, trauma or contact lens wear.

Specifically, the composition for treating an eye disease, which comprises the compound or the peptide as an active pharmaceutical ingredient, may further comprise at least one additive selected from the group consisting of a carrier, an excipient, a disintegrant, a sweetener, a coating agent, a swelling agent, a lubricant, a slip agent, a
20 flavor, an antioxidant, a buffer, a bacteriostat, a diluent, a dispersant, a surfactant, and a binder. Specifically, a formulation for parenteral administration may be a sterilized aqueous solution, a non-aqueous solution, a suspension, an emulsion, a lyophilized preparation, a suppository, or the like.

Still another aspect of the present invention provides a method for treating an eye
25 disease, which comprises administering the compound or the peptide to a subject.

The dose of the compound or the peptide may be adjusted depending on such various factors as the kind of the disease, the severity of the disease, the kinds and amounts of the active pharmaceutical ingredient and other ingredients contained in the

pharmaceutical composition, the type of the formulation, the age, body weight, general health condition, sex, and diet of the patient, the time and the route of administration, the duration of treatment, and the drugs concurrently used.

However, for the desired effect, the effective amount of the compound or the peptide contained in the pharmaceutical composition may be 0.0001 $\mu\text{g/day}$ to 100 $\mu\text{g/day}$. In such event, the administration may be carried out once a day, or divided into several doses. Specifically, the concentration of the compound or the peptide contained in the pharmaceutical composition may be 1000 μM to 0.001 μM . Also, the concentration of the compound or the peptide contained in the pharmaceutical composition may be 100 μM to 0.005 μM or 50 μM to 0.02 μM .

In addition, if necessary, the concentration of the compound or the peptide contained in the pharmaceutical composition may be 30 μM to 1 μM . Further, the concentration of the compound or the peptide contained in the pharmaceutical composition may be 0.01 μM to 1 μM .

In addition, the subject may be a mammal, particularly a human. The administration route may be appropriately selected by a person skilled in the art in consideration of the administration method, the volume and viscosity of the body fluid, and the like. Specifically, the administration may be carried out through any one route selected from the group consisting of an application, intravenous, intraarterial, intraperitoneal, intramuscular, intrasternal, percutaneous, intranasal, inhalation, topical, rectal, oral, intraocular, and intradermal. In particular, it may preferably be applied to the eye for use as an eye drop.

Still another aspect of the present invention provides the use of the compound or the peptides for the treatment of an eye disease.

Still another aspect of the present invention provides the use of the compound or the peptides for the preparation of a pharmaceutical composition for treating an eye disease.

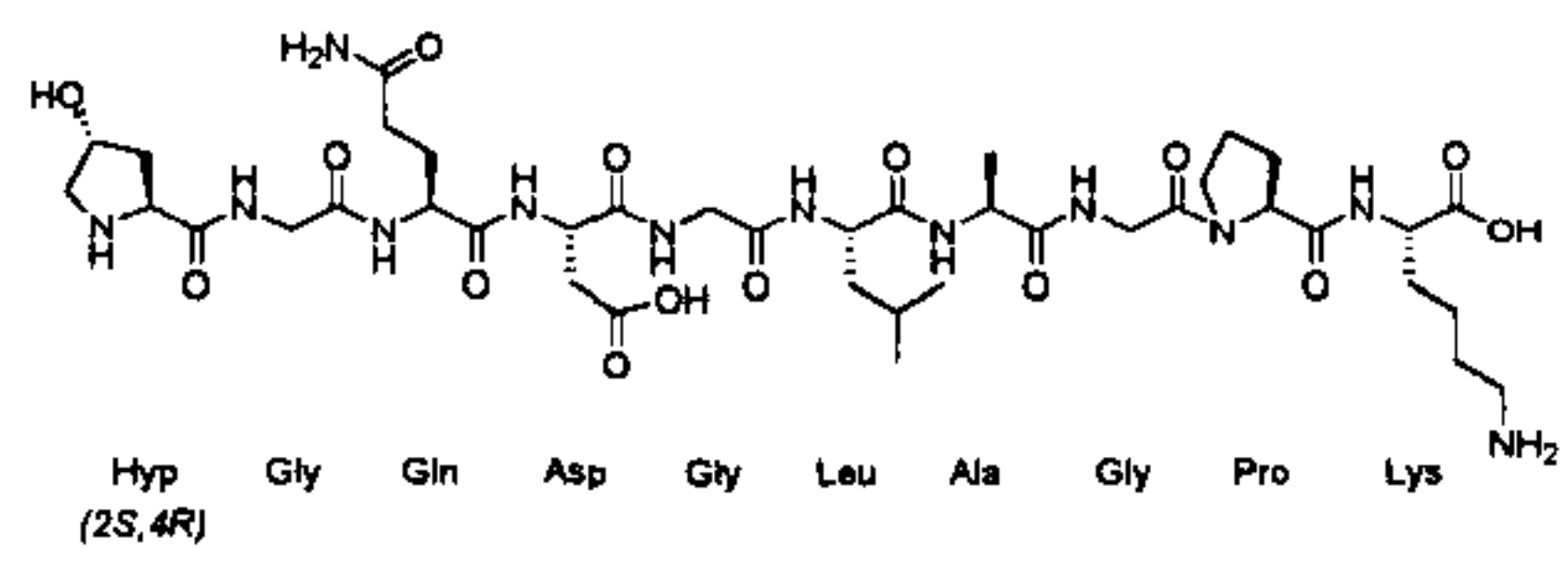
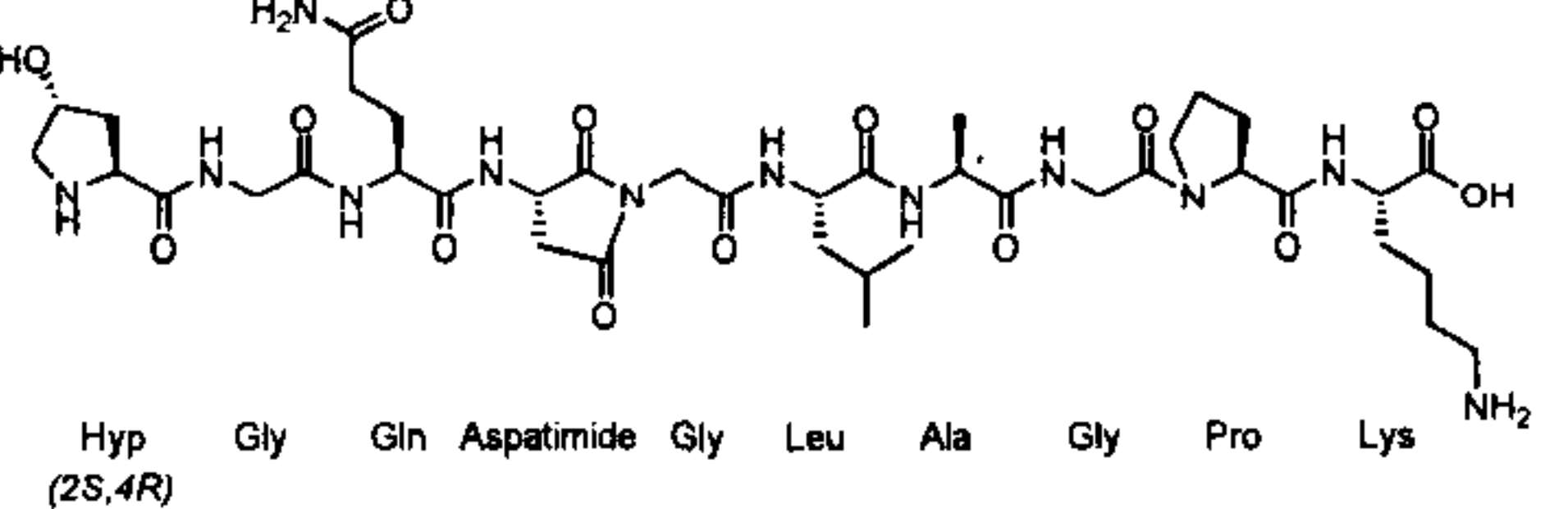
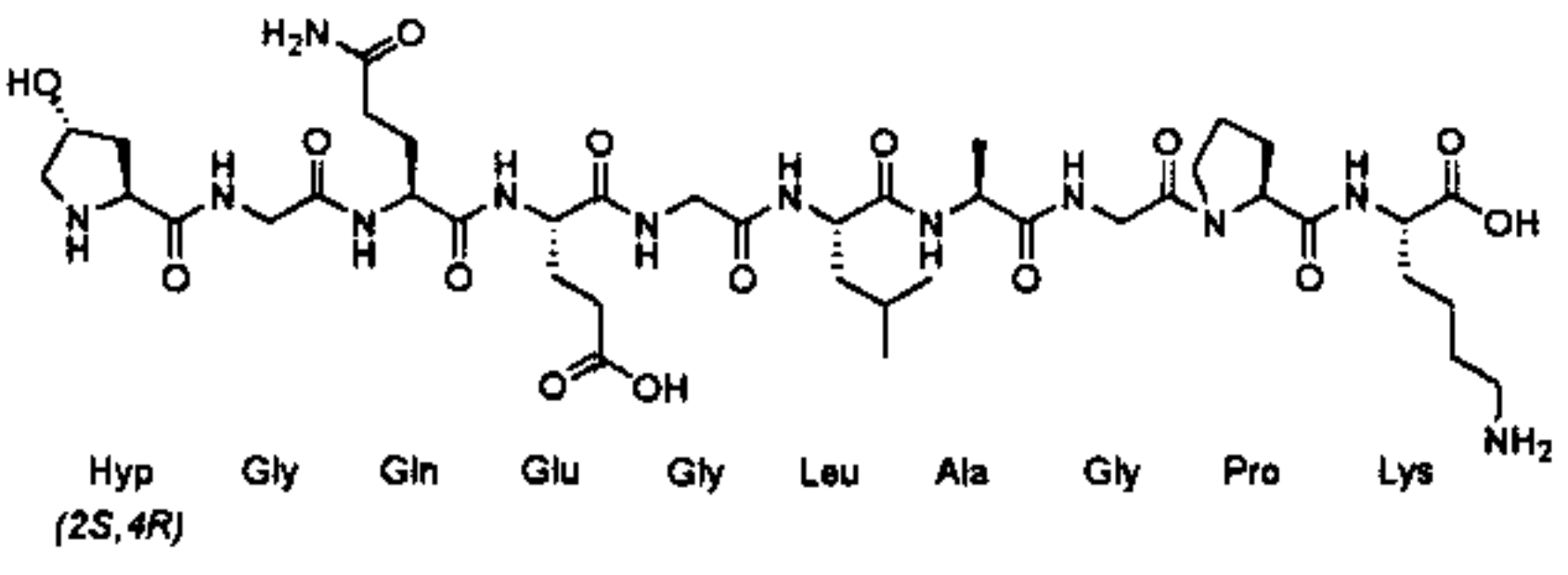
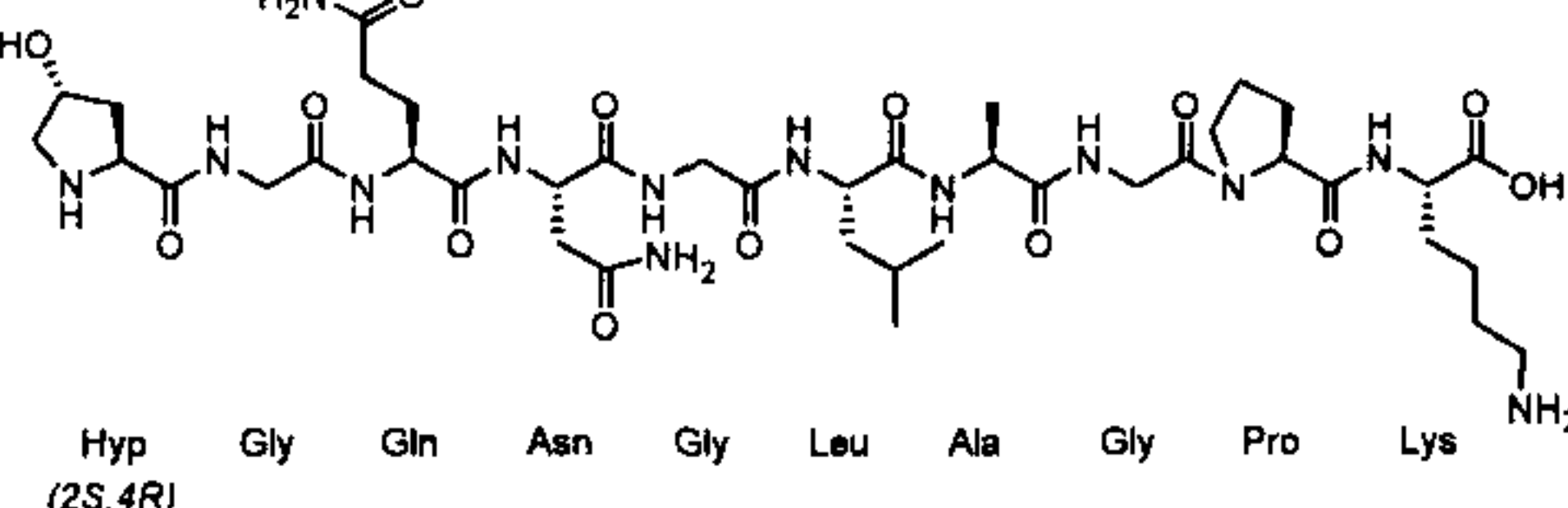
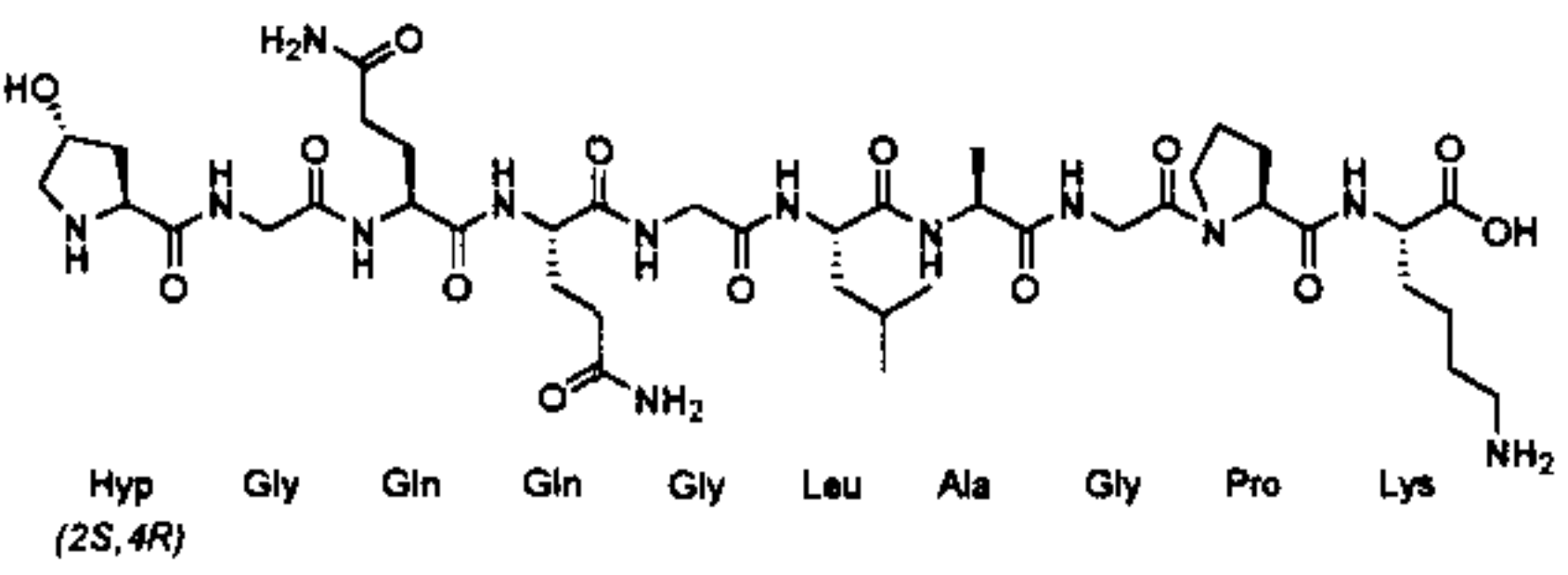
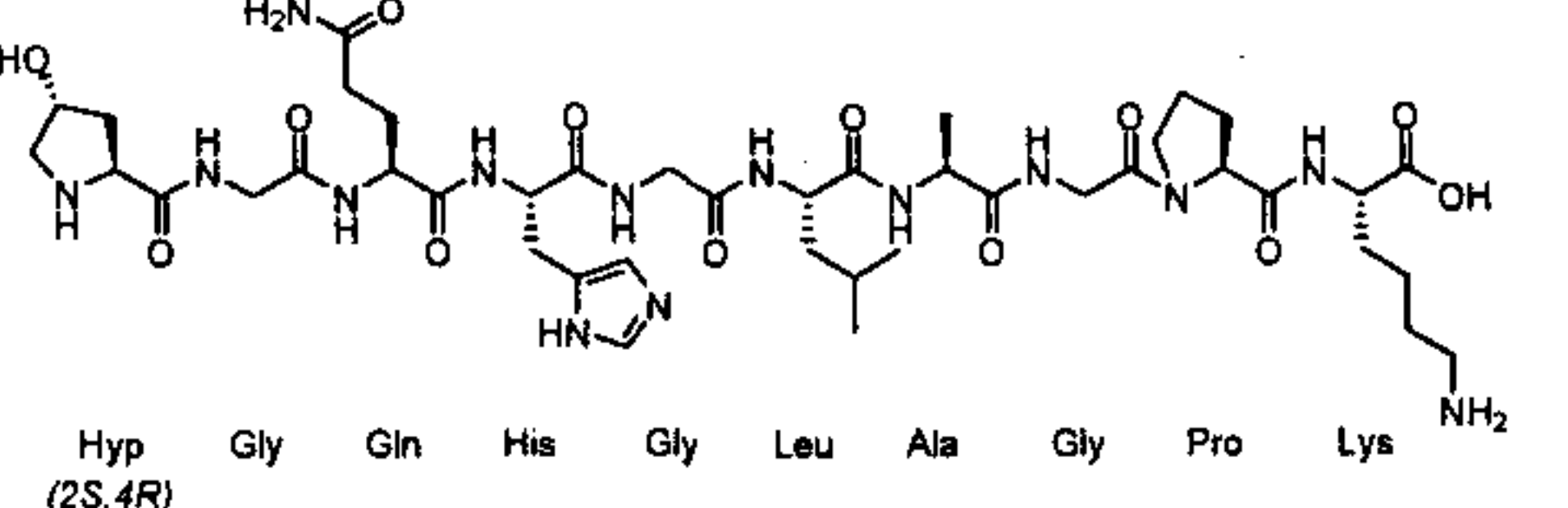
Hereinafter, the present invention is explained in more detail by the following working examples. However, the following working examples are intended to further illustrate the present invention. The scope of the present invention is not limited thereby.

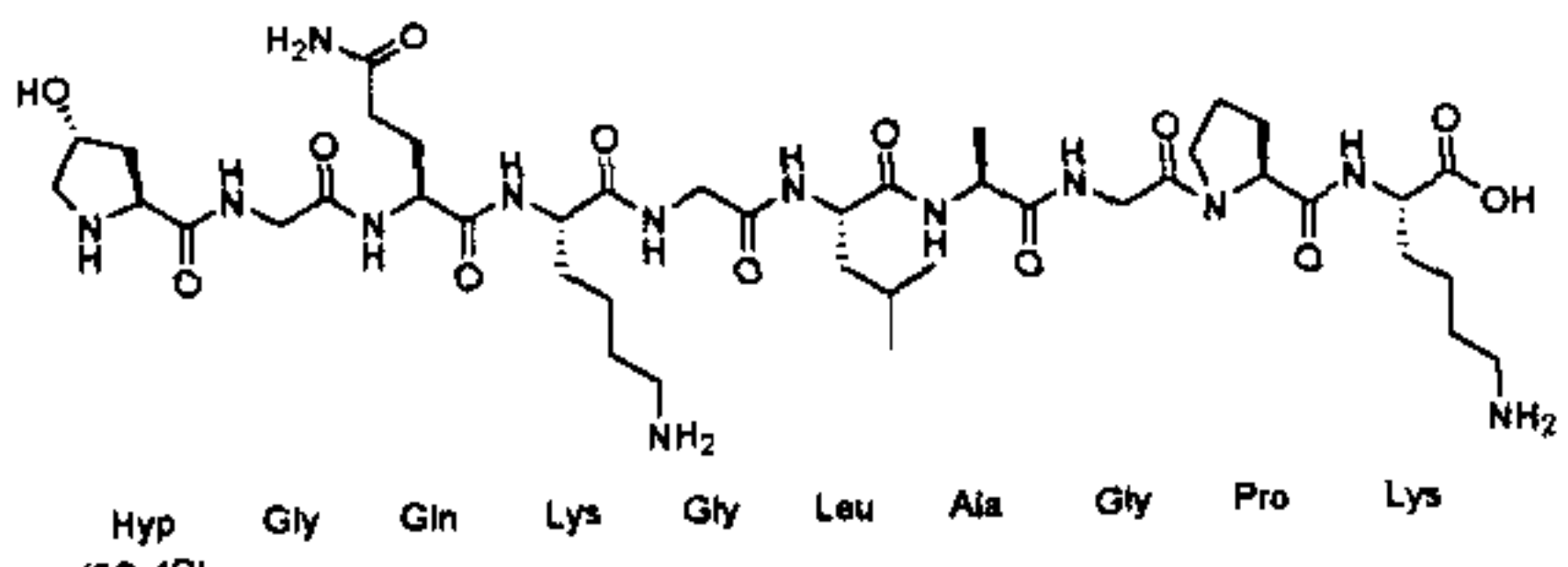
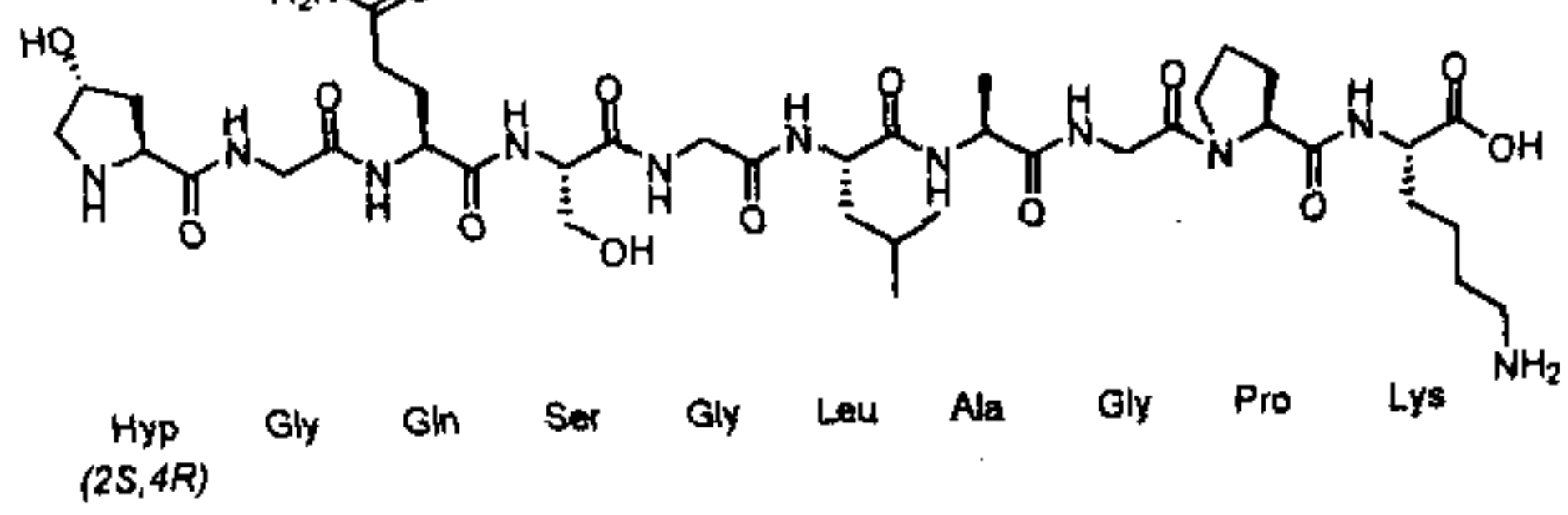
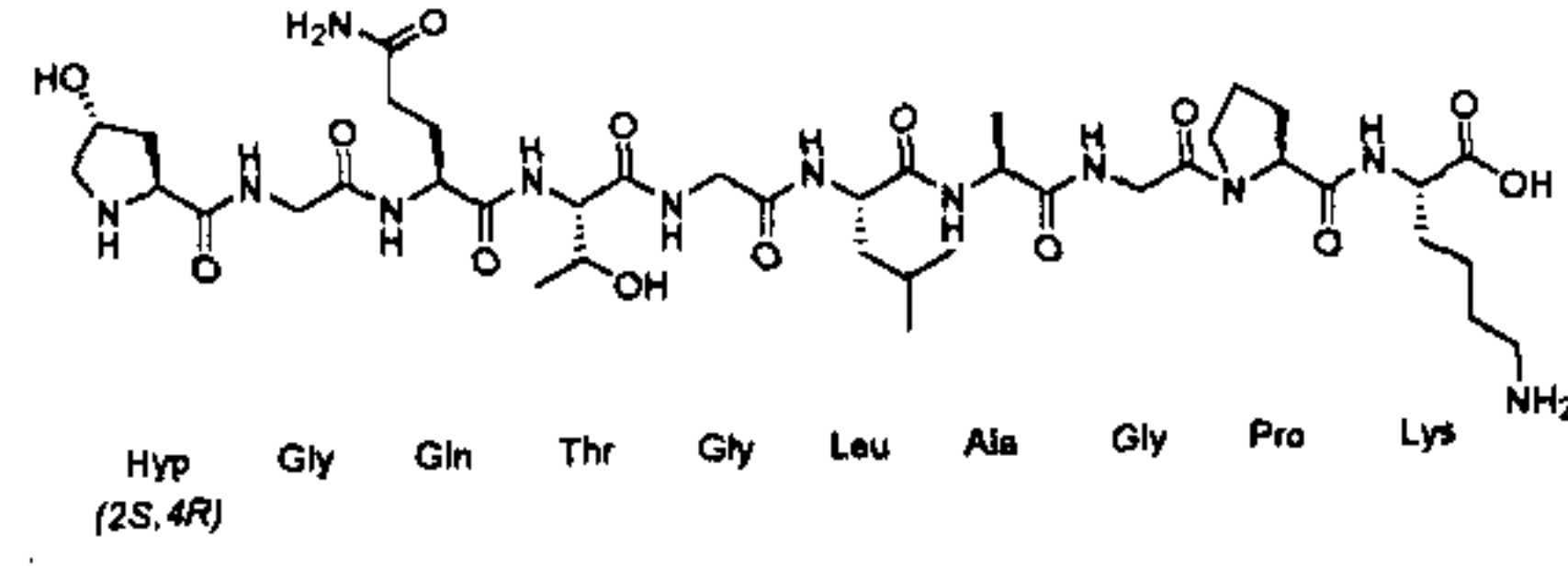
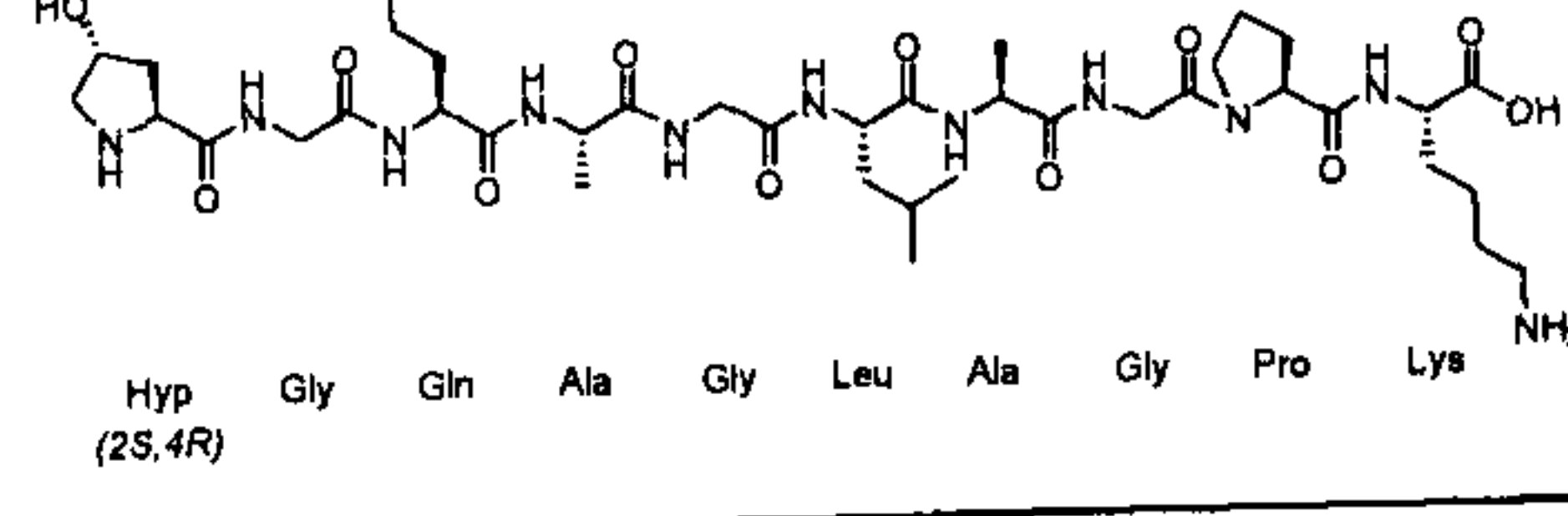
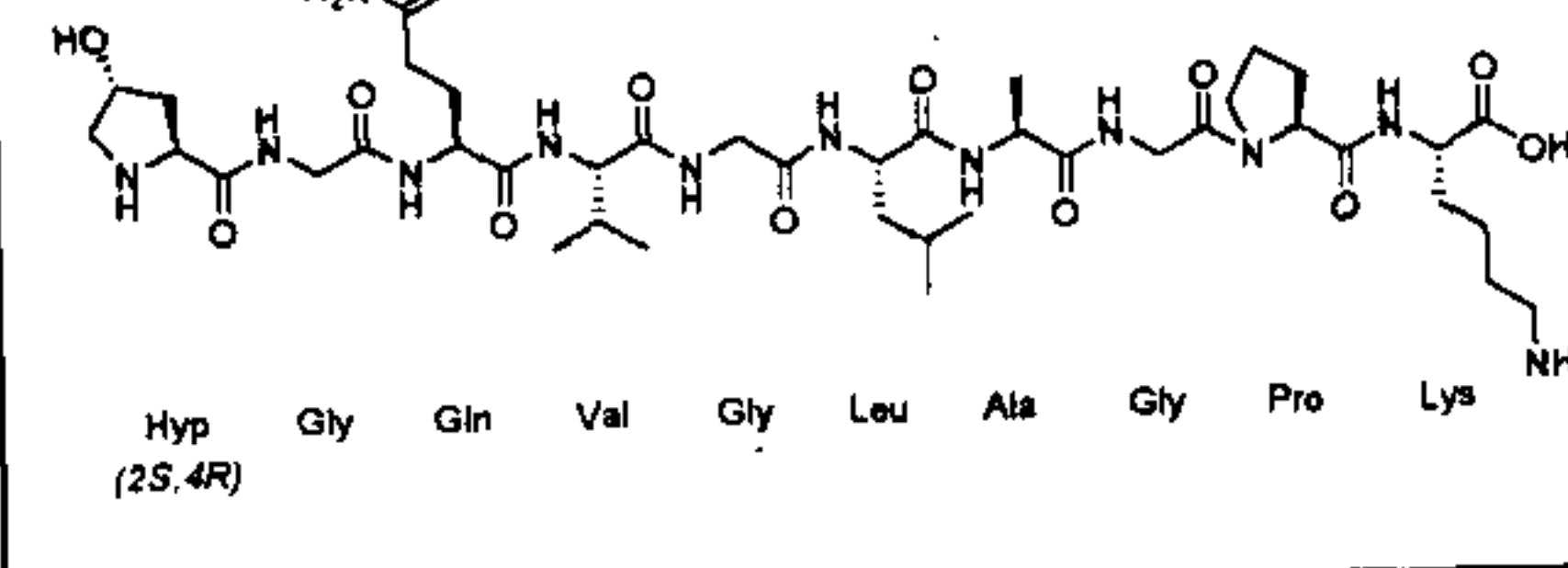
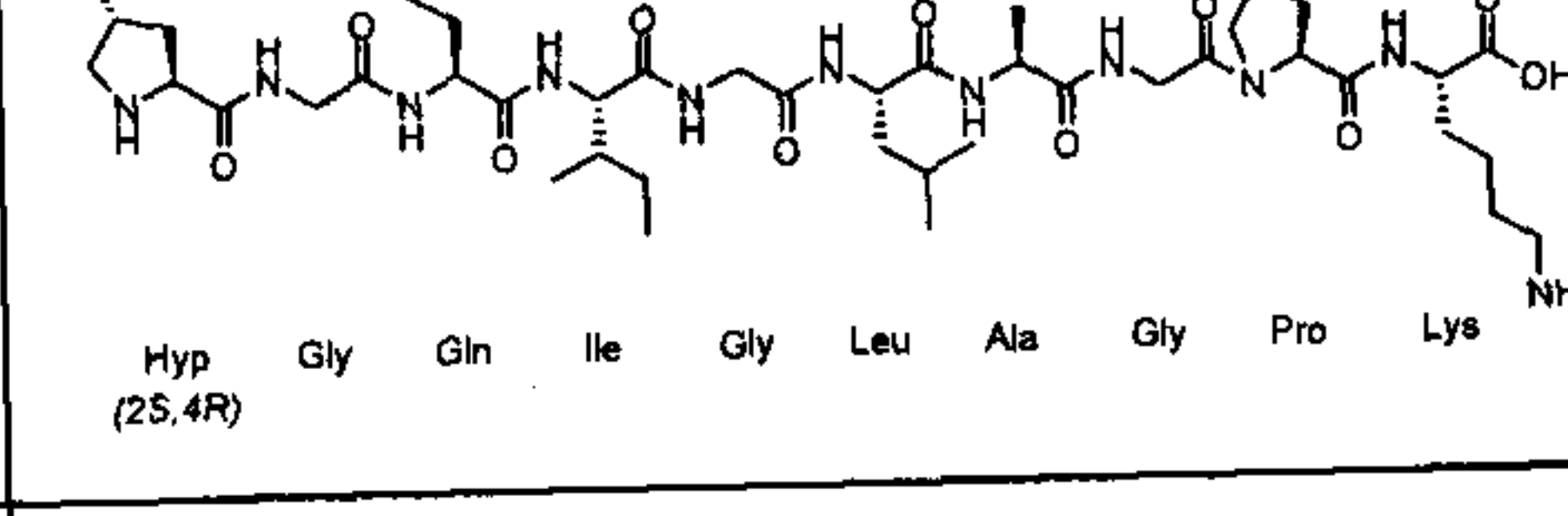
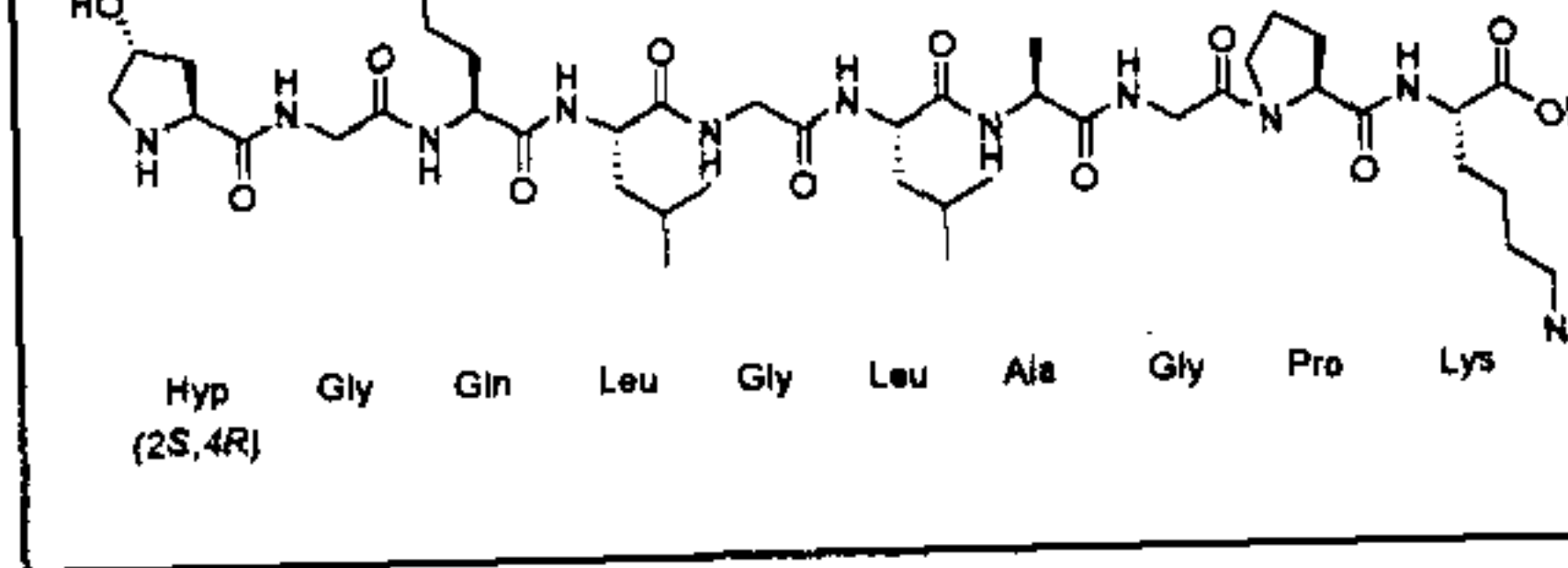
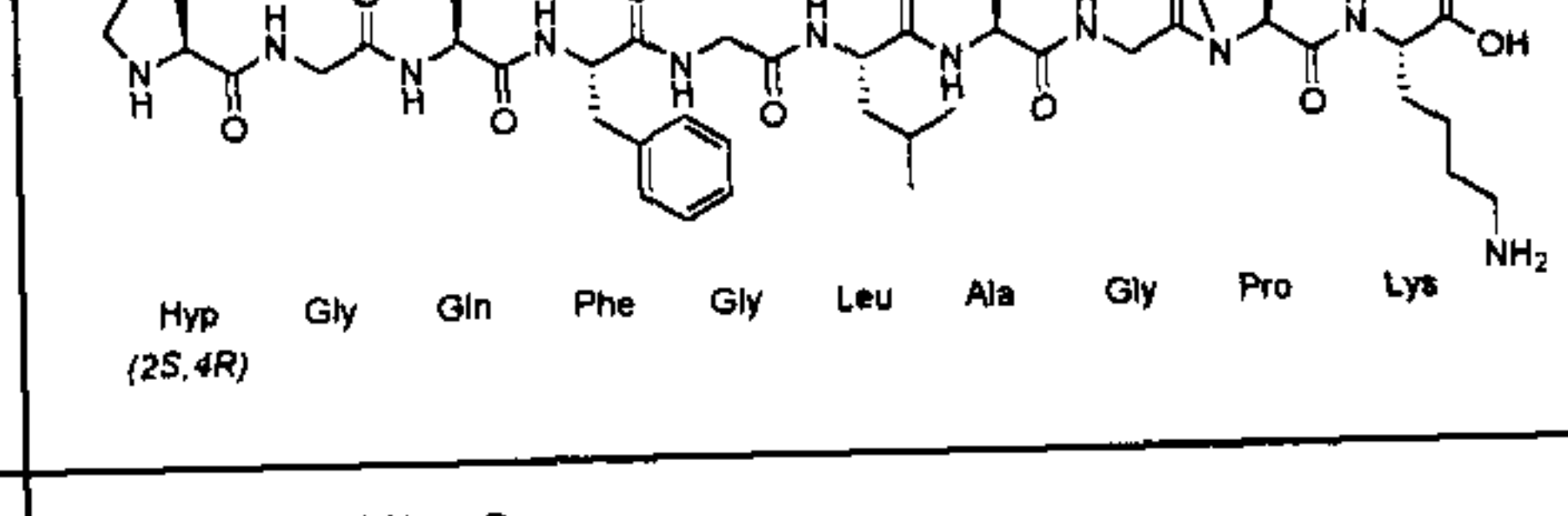
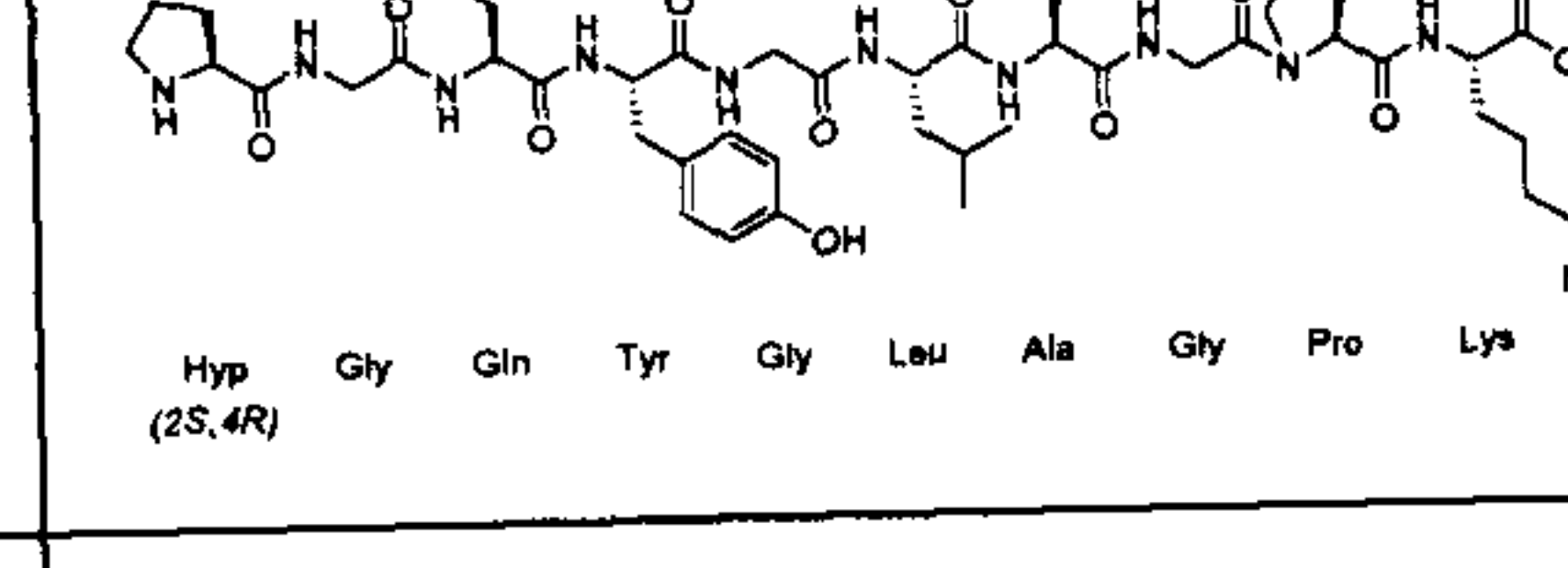
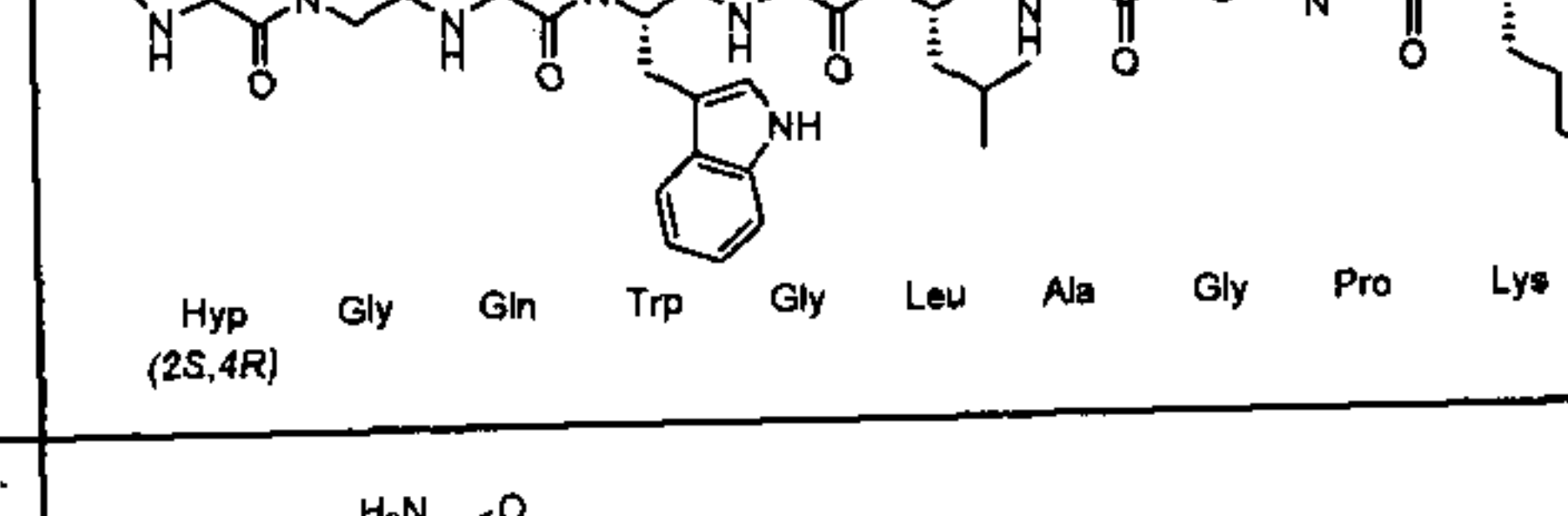
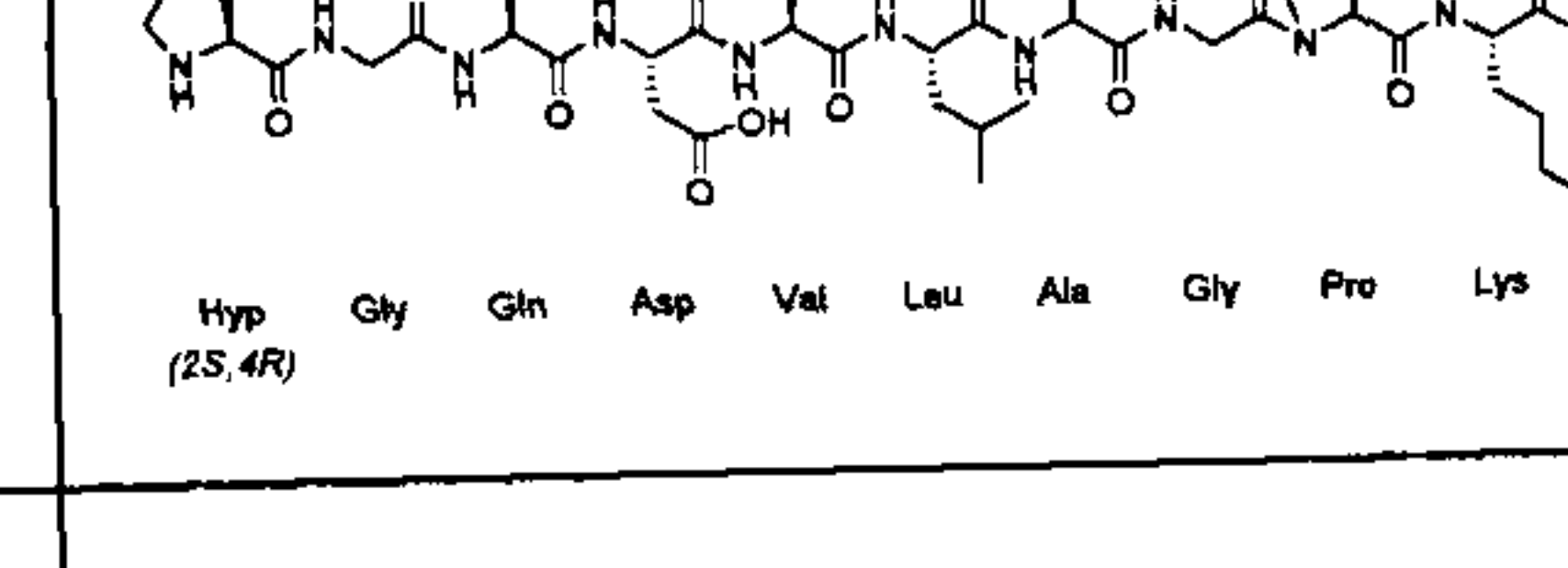
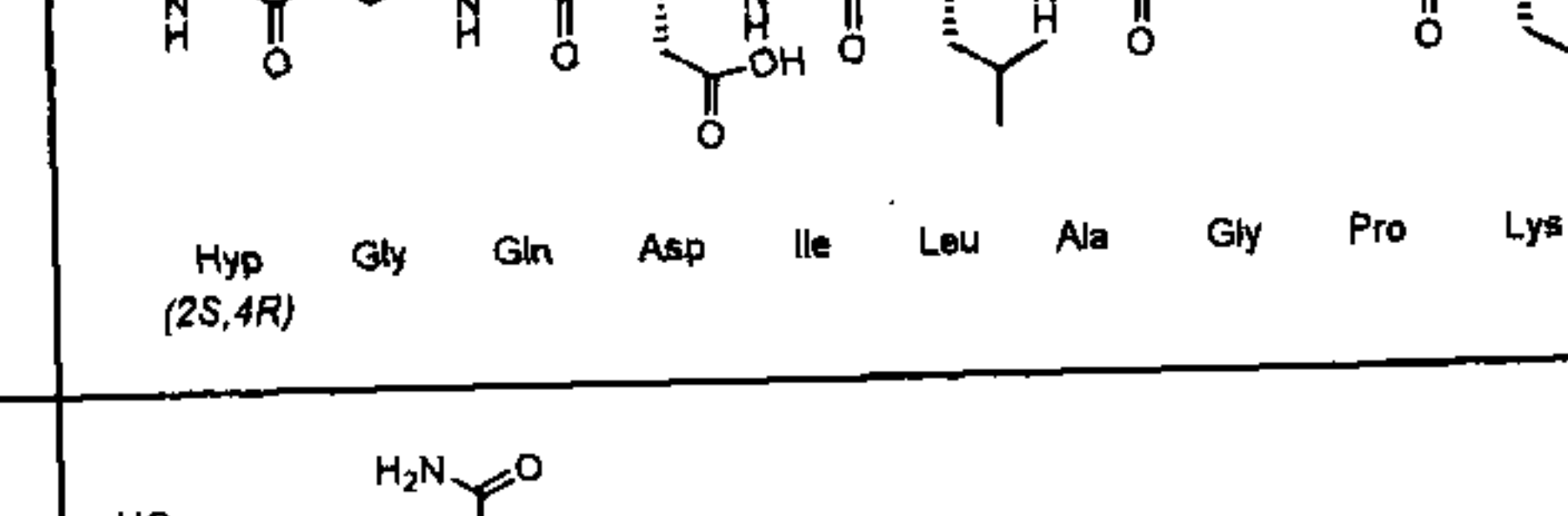
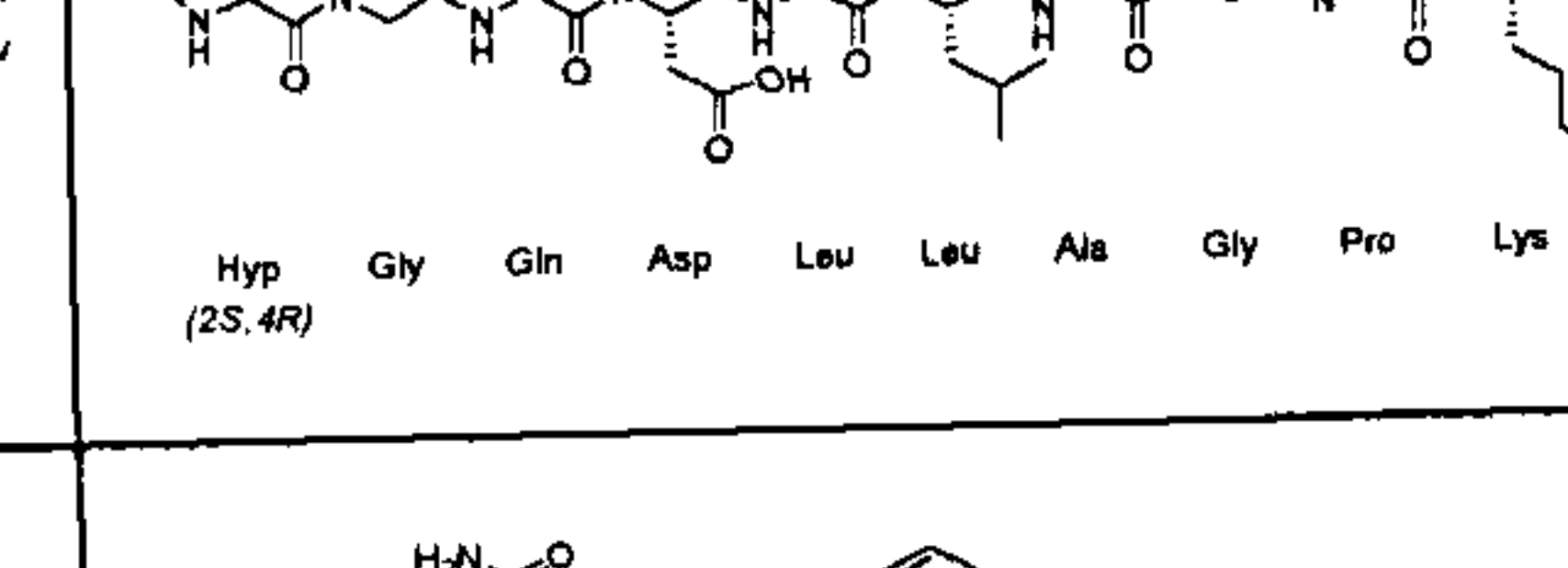
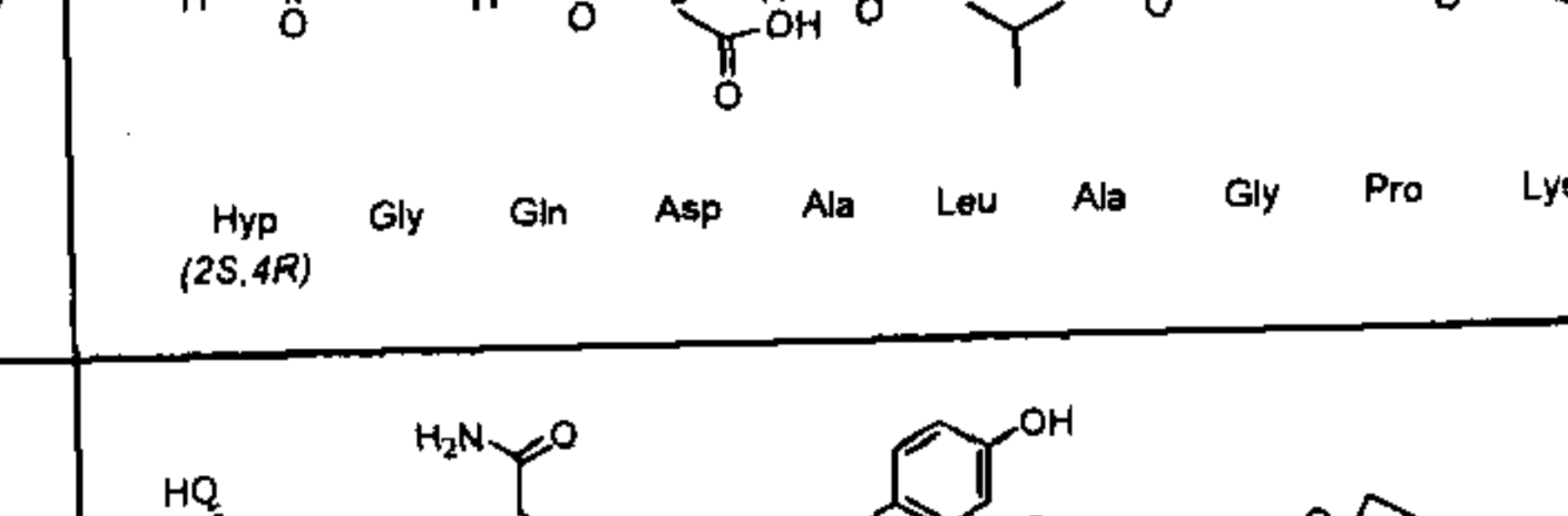
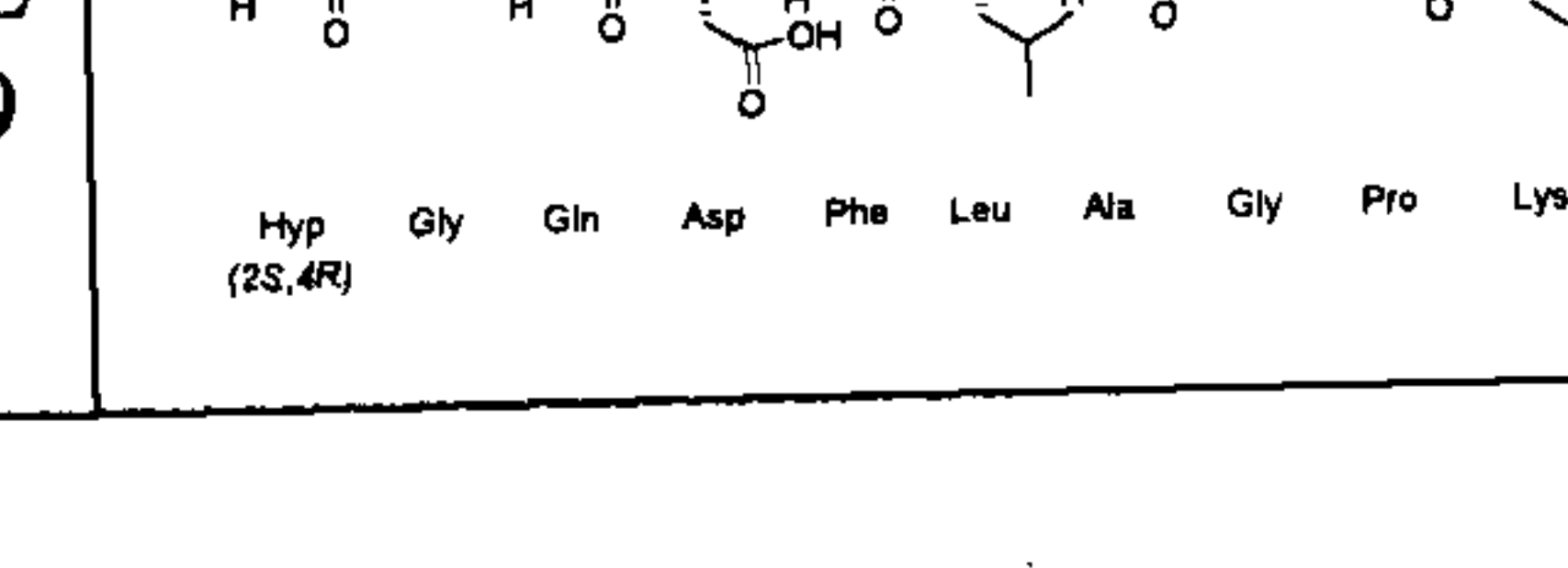
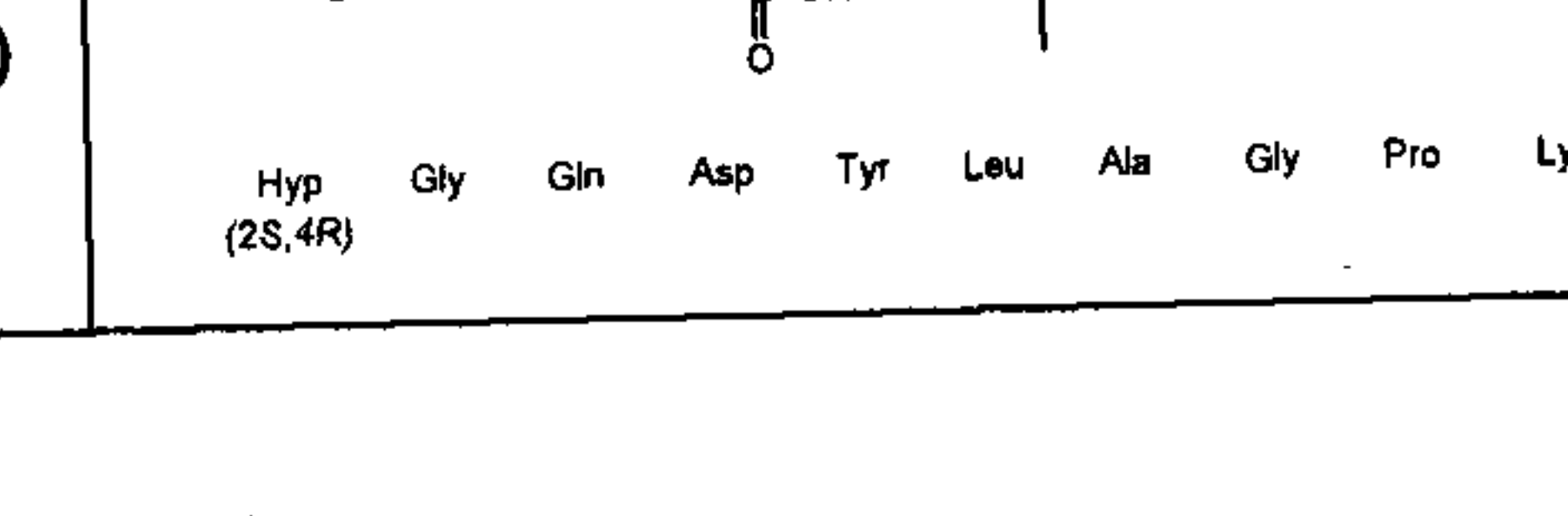
5 **Working Example 1: Preparation of YDE derivatives**

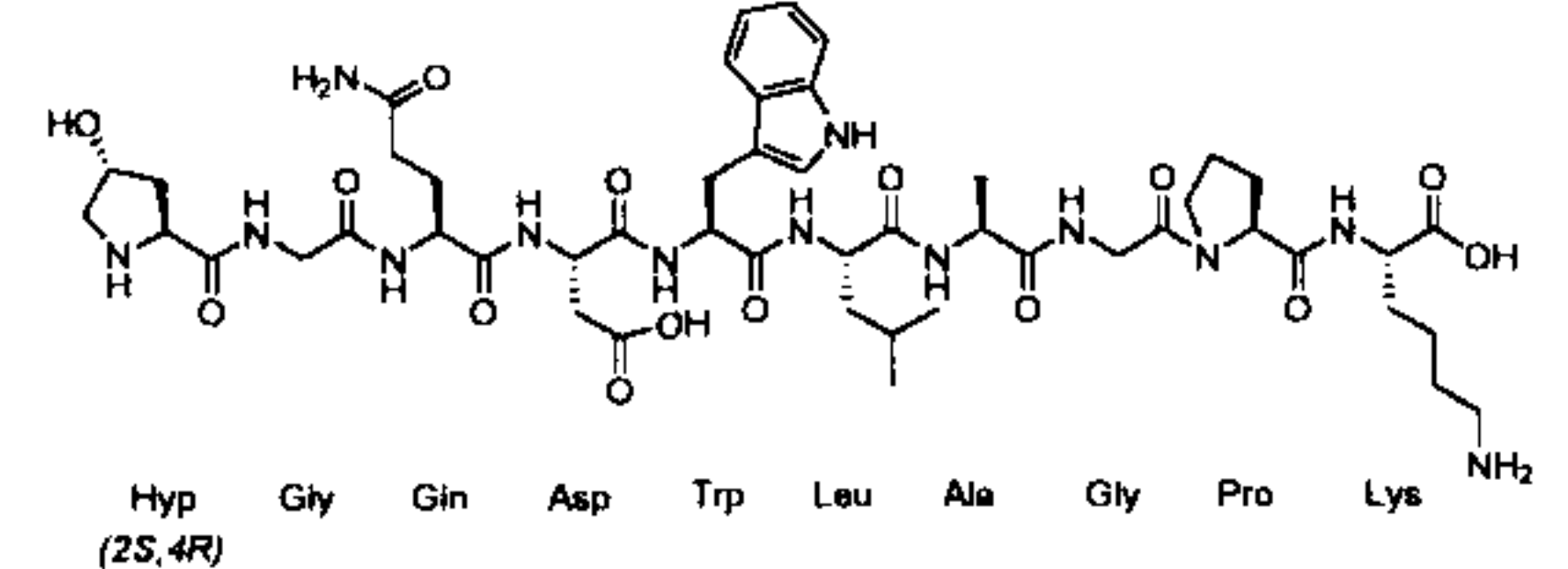
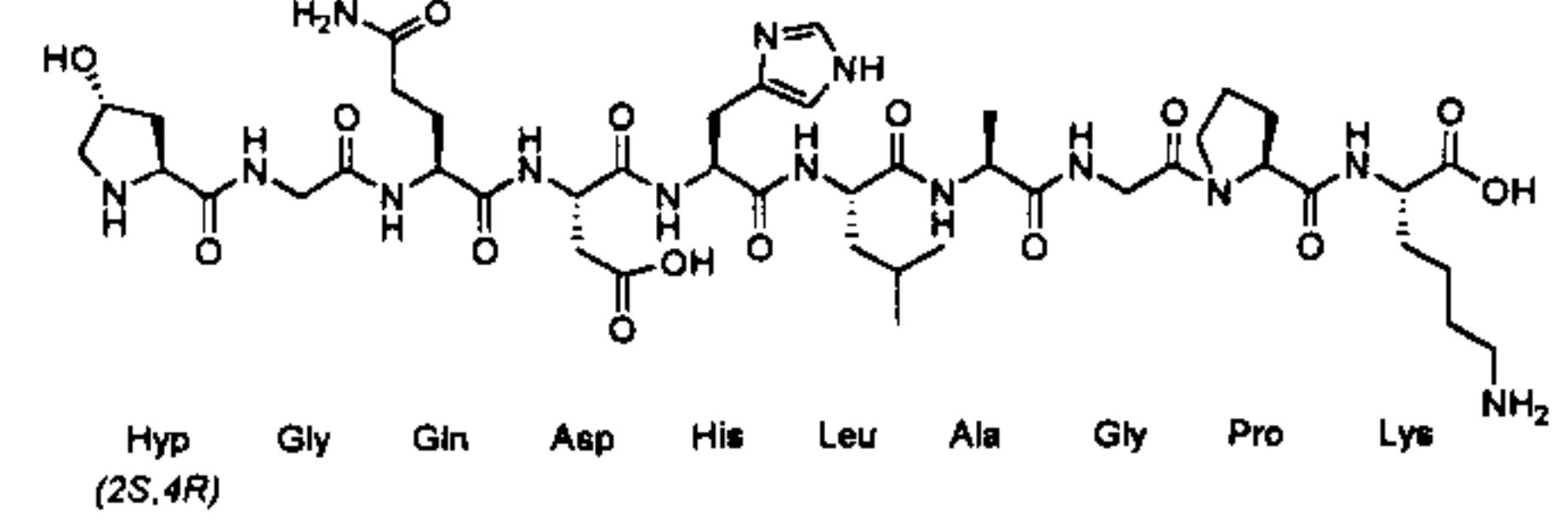
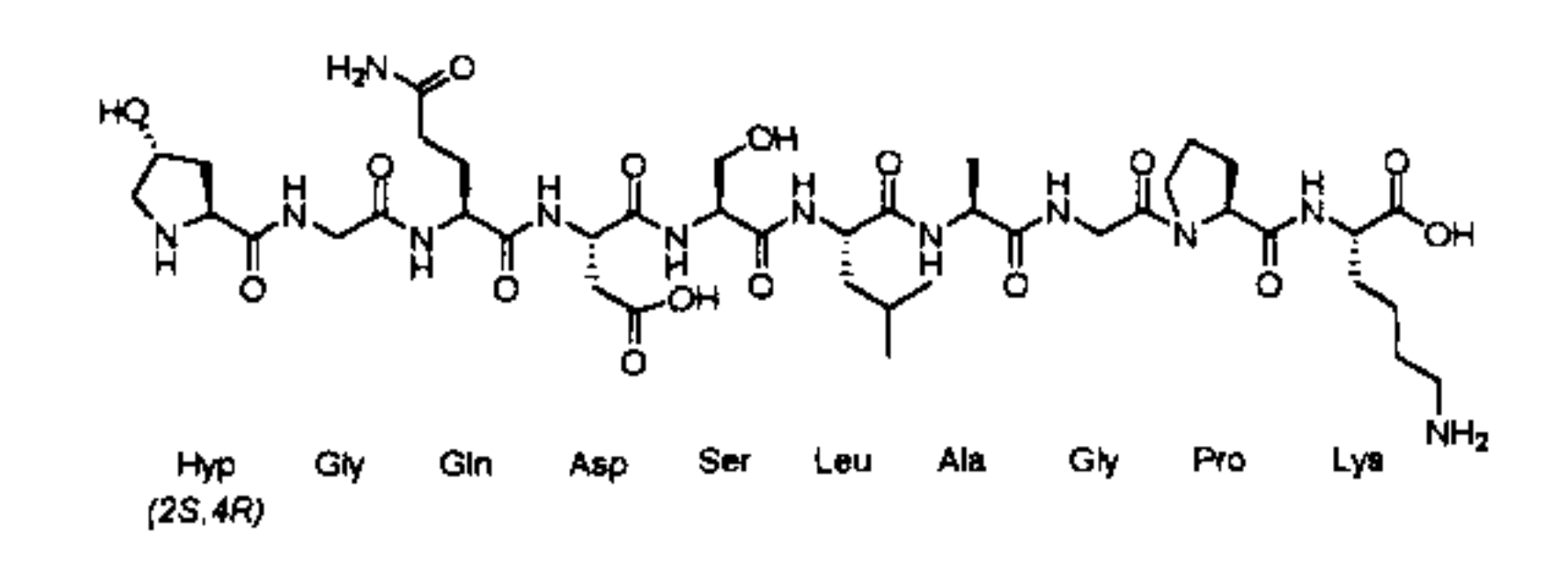
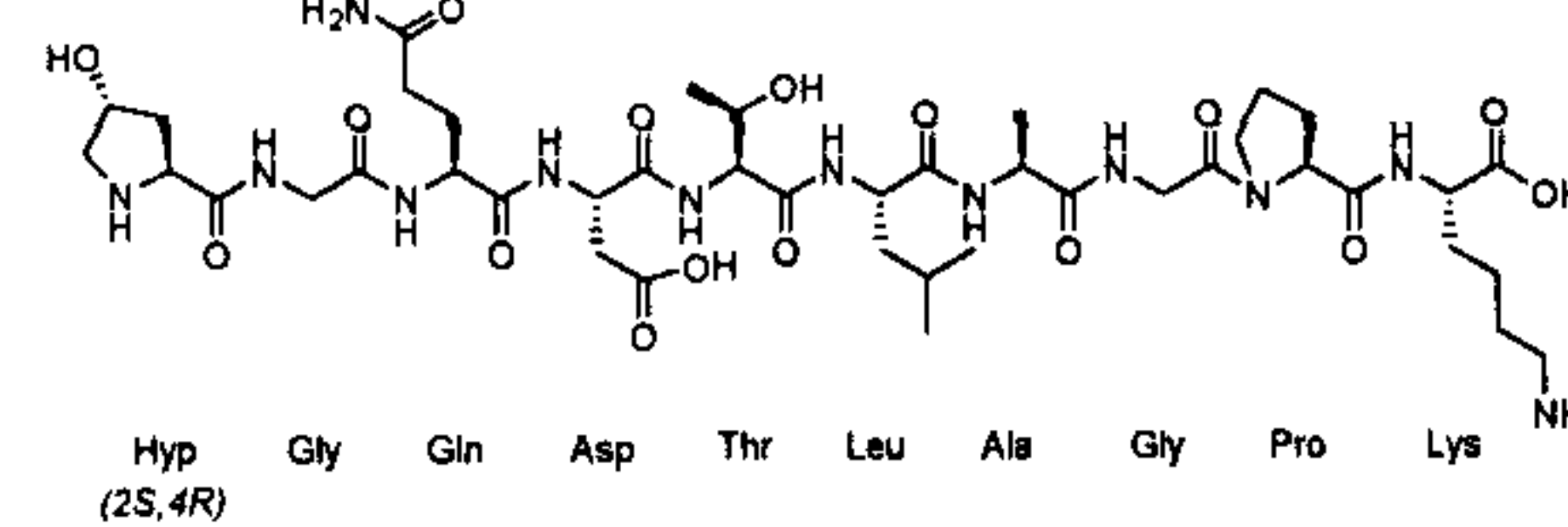
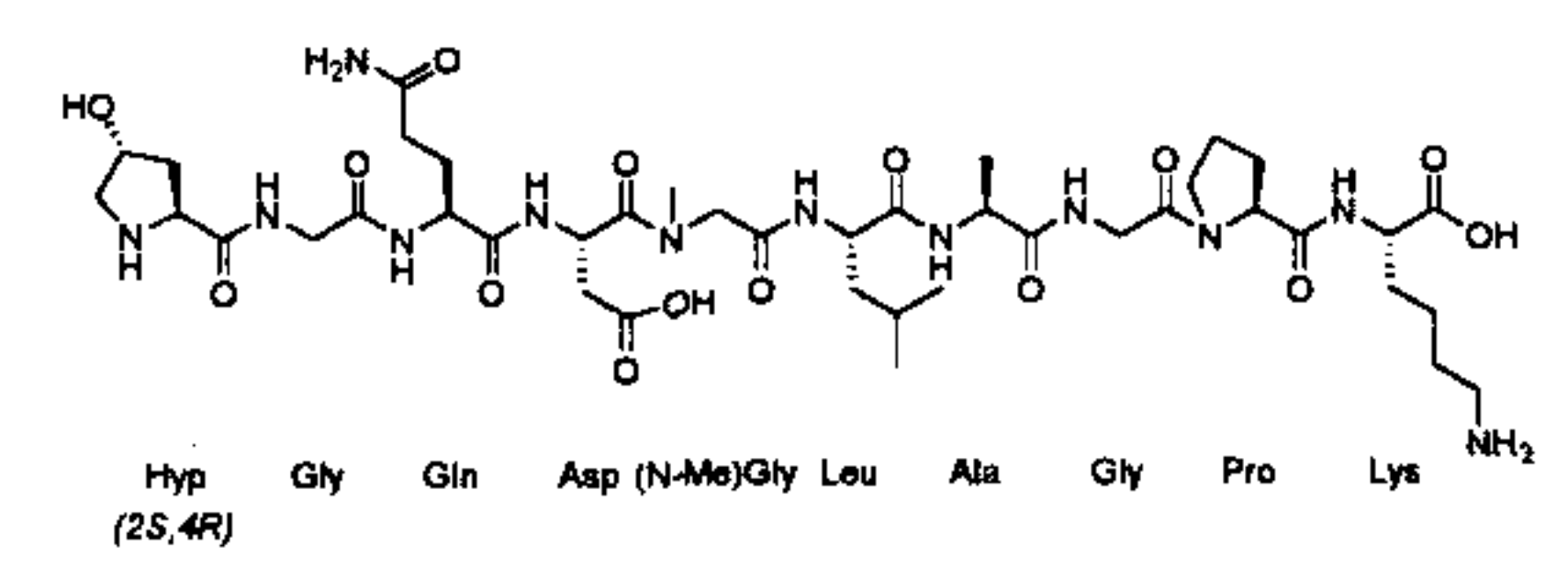
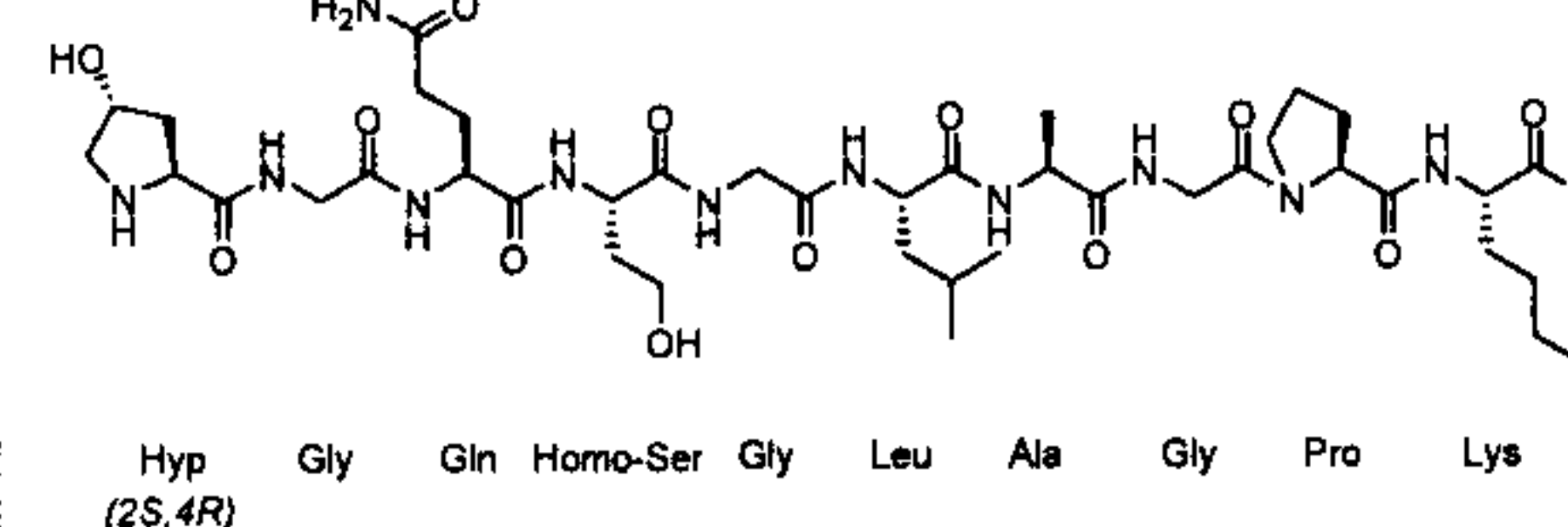
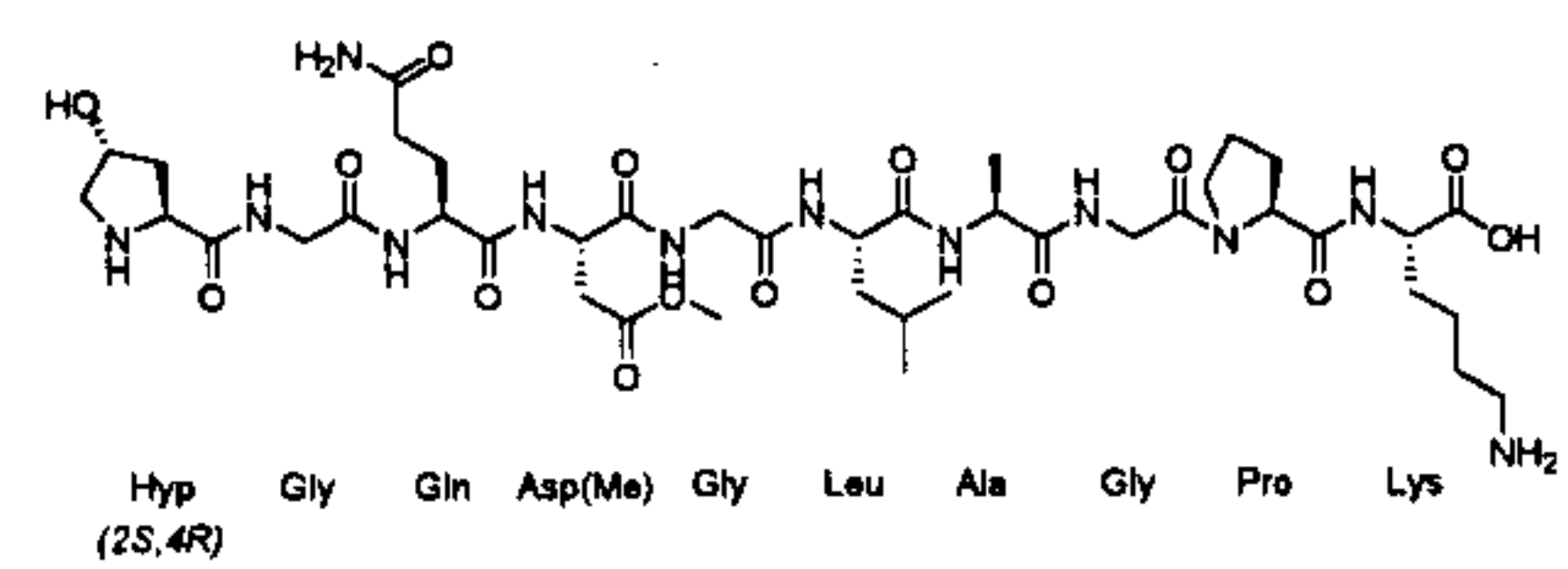
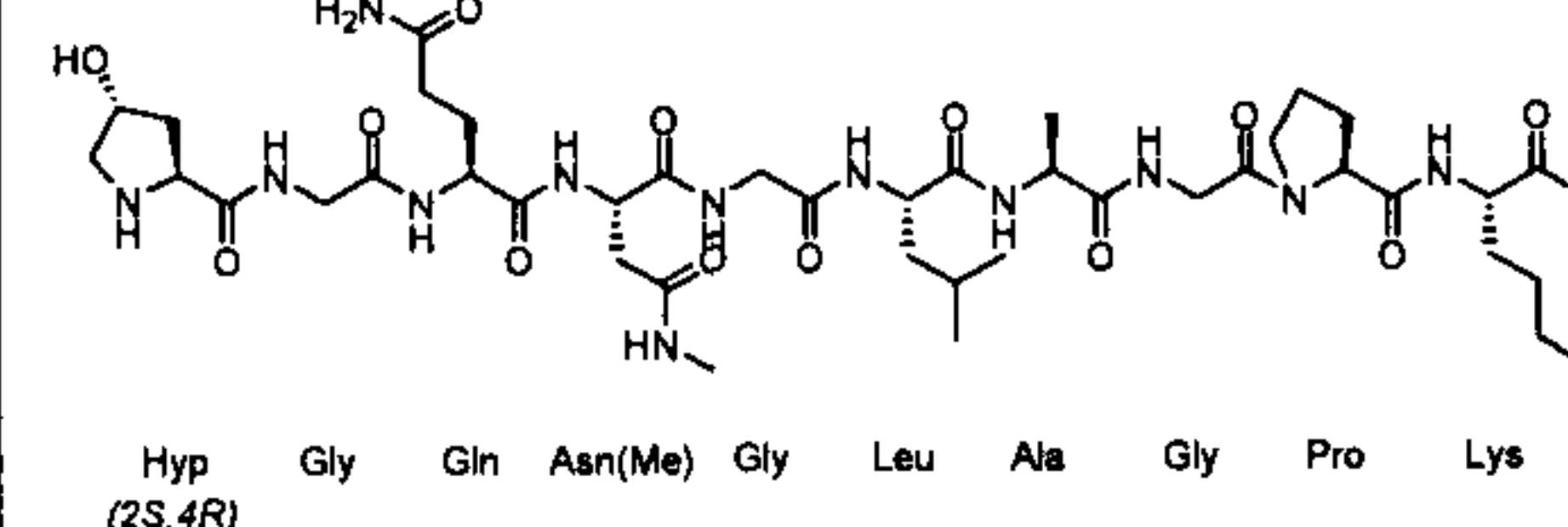
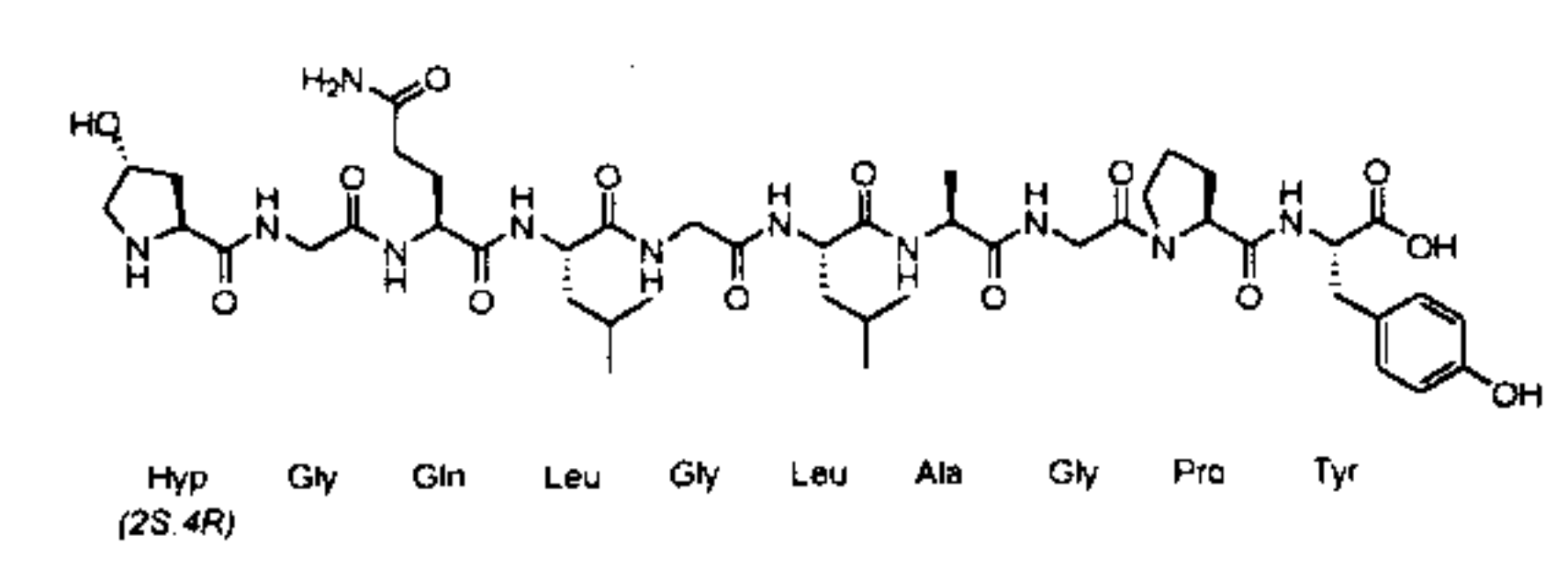
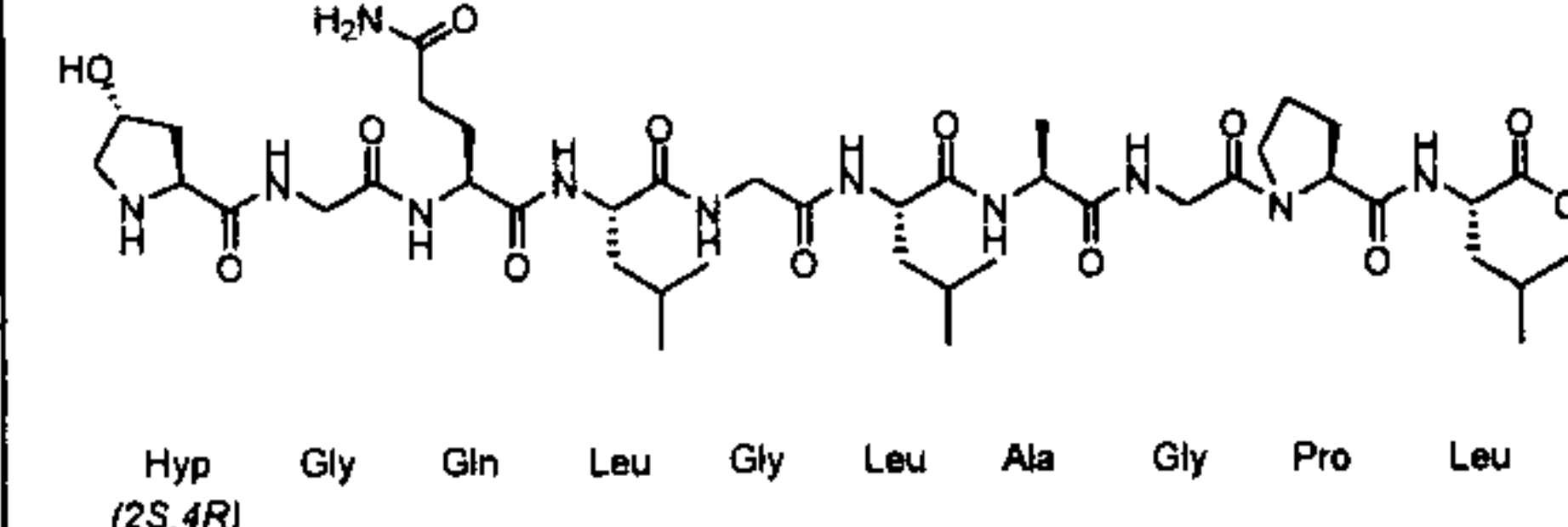
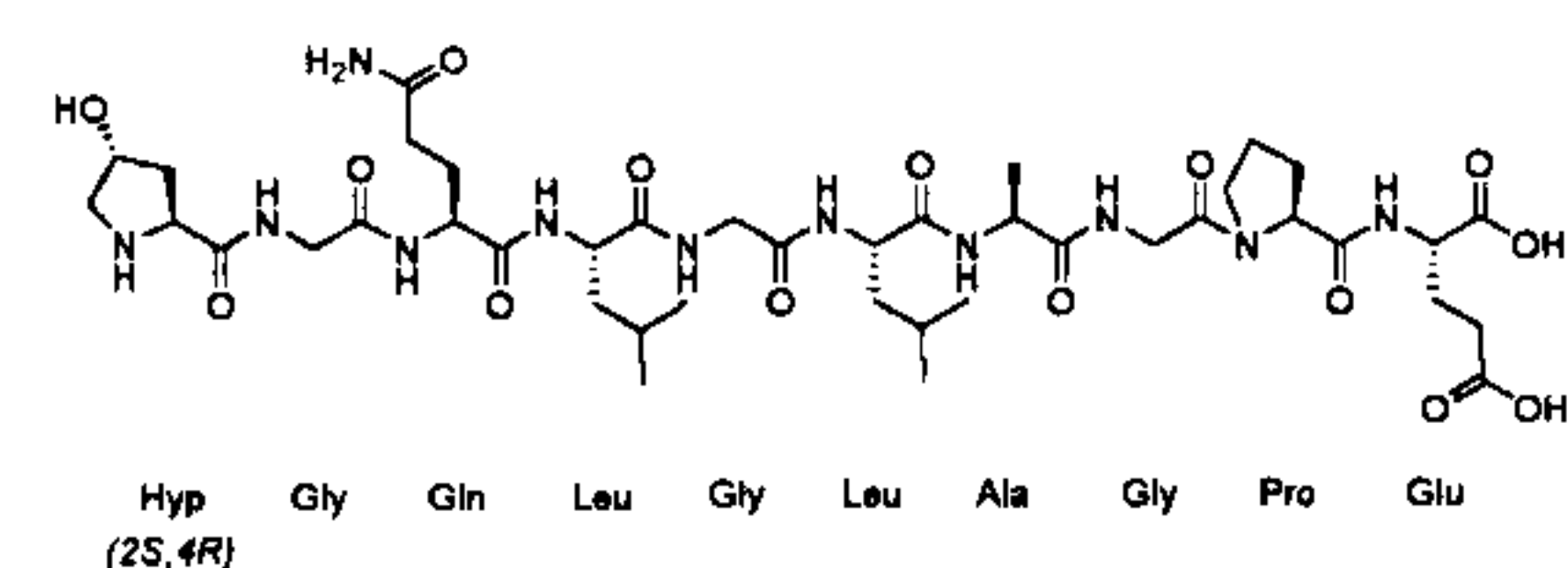
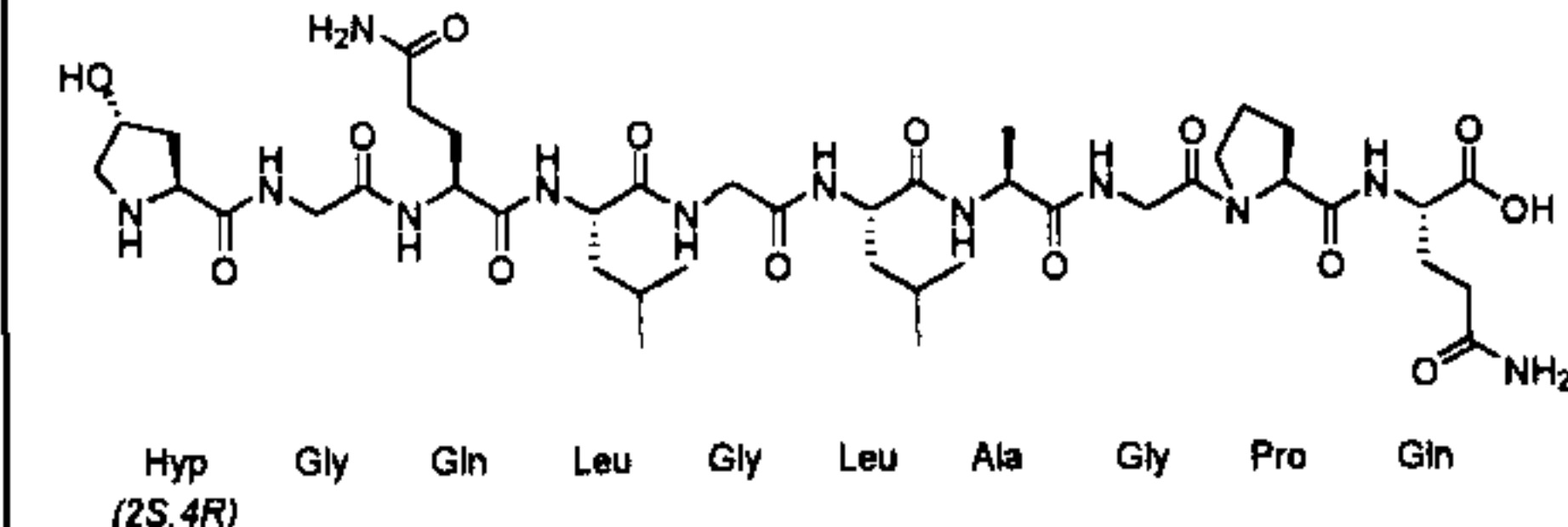
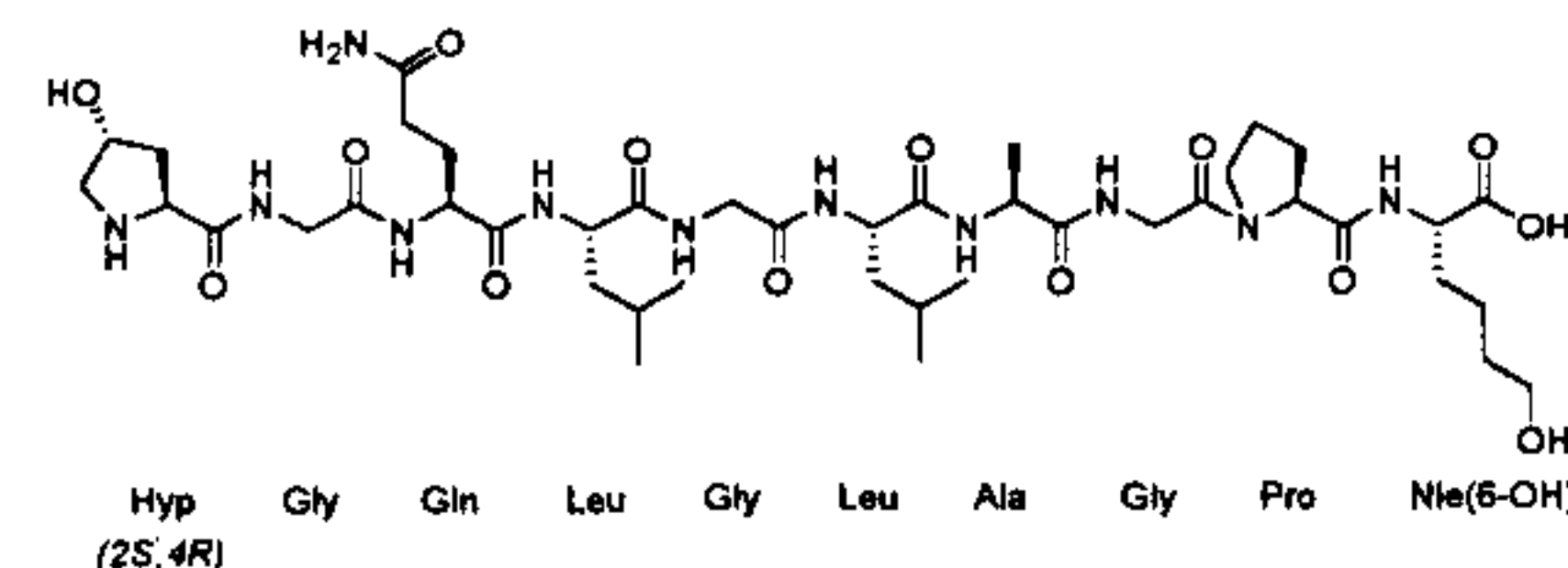
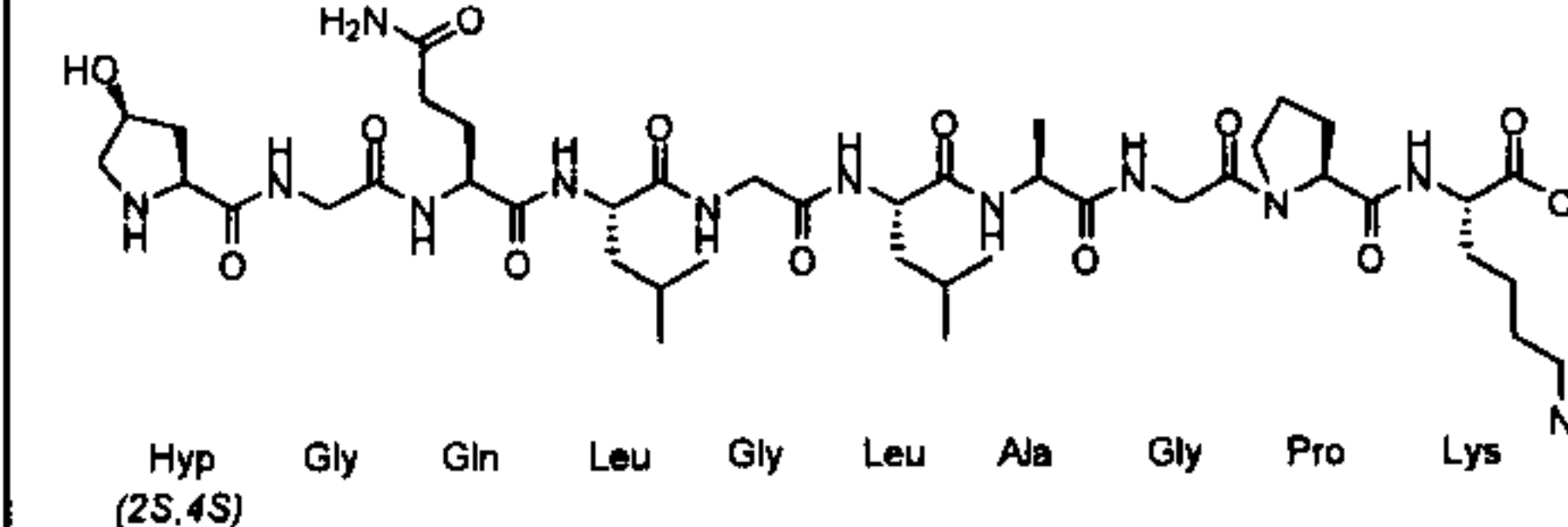
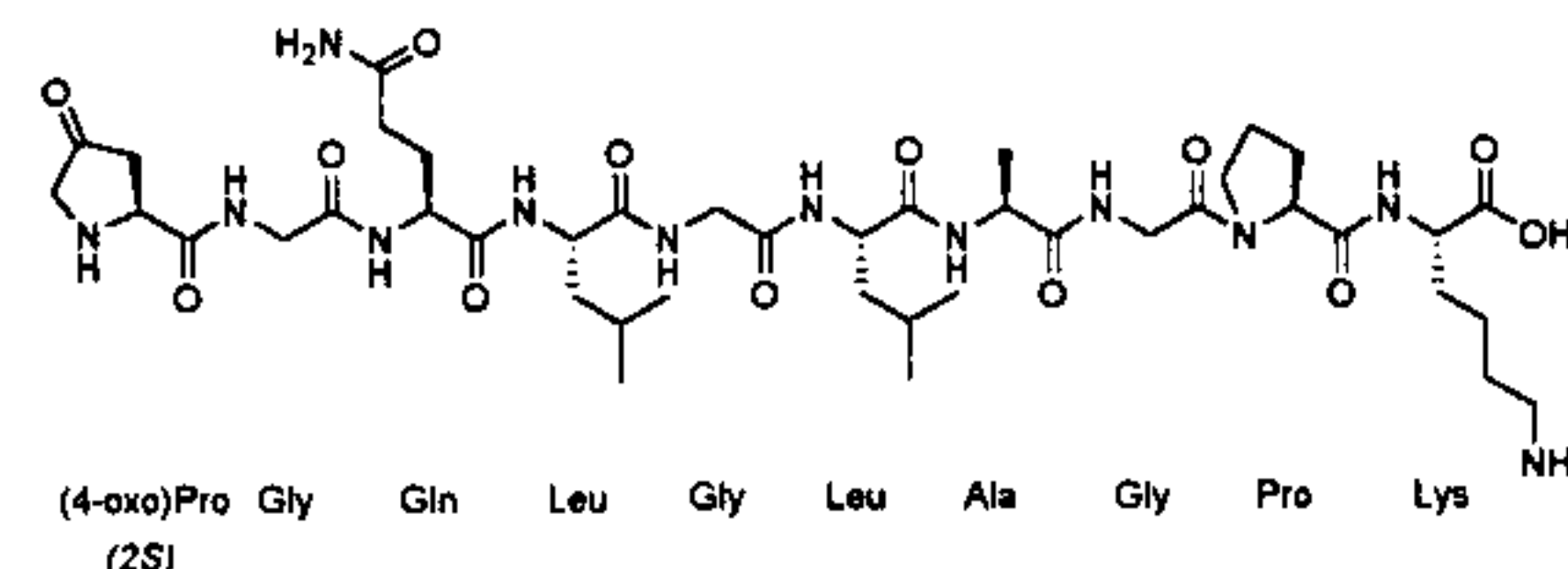
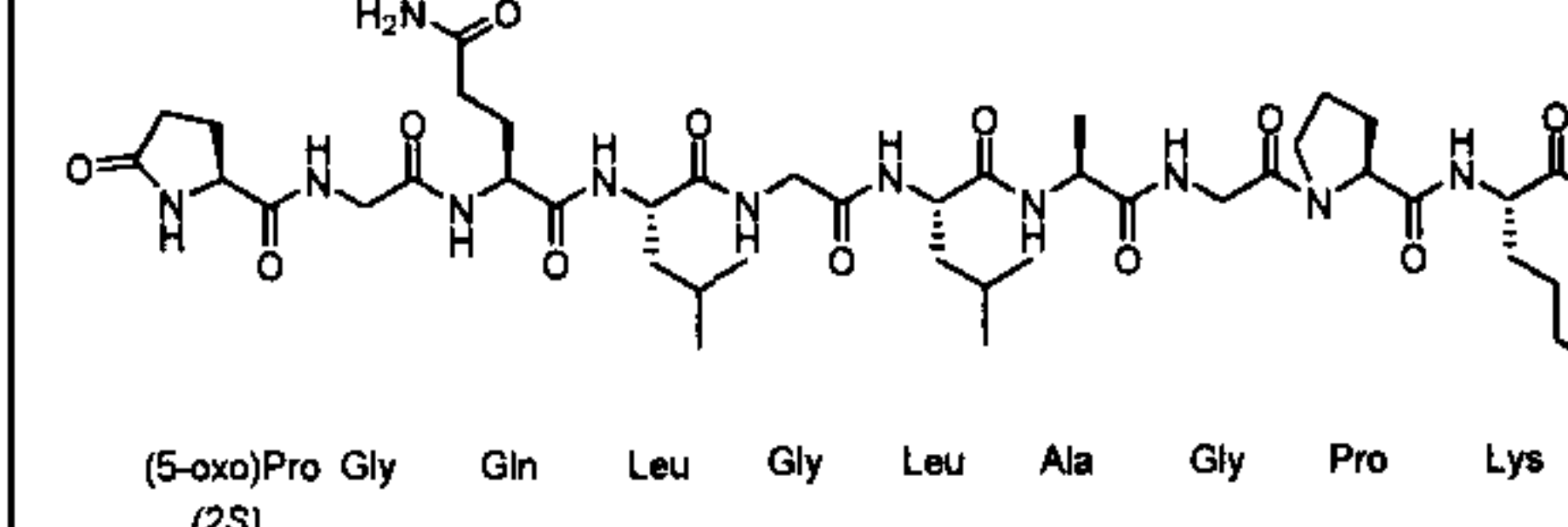
10 A protein analysis of the extracellular matrix derived from animal chondrocytes was performed in Baek's group of Center of Biomedical Mass Spectrometry (Diatech Korea Co., Ltd., Seoul, Korea). Proline-GQDGLAGPK (P-GQDGLAGPK), which is a part of the amino acid sequence of the collagen type II $\alpha 1$ protein, was obtained through the above protein analysis. YDE-001 to YDE-075 peptides were synthesized by ANYGEN (Gwangju, Korea) by substituting a part of the above peptide (Fig. 1 and Table 11).

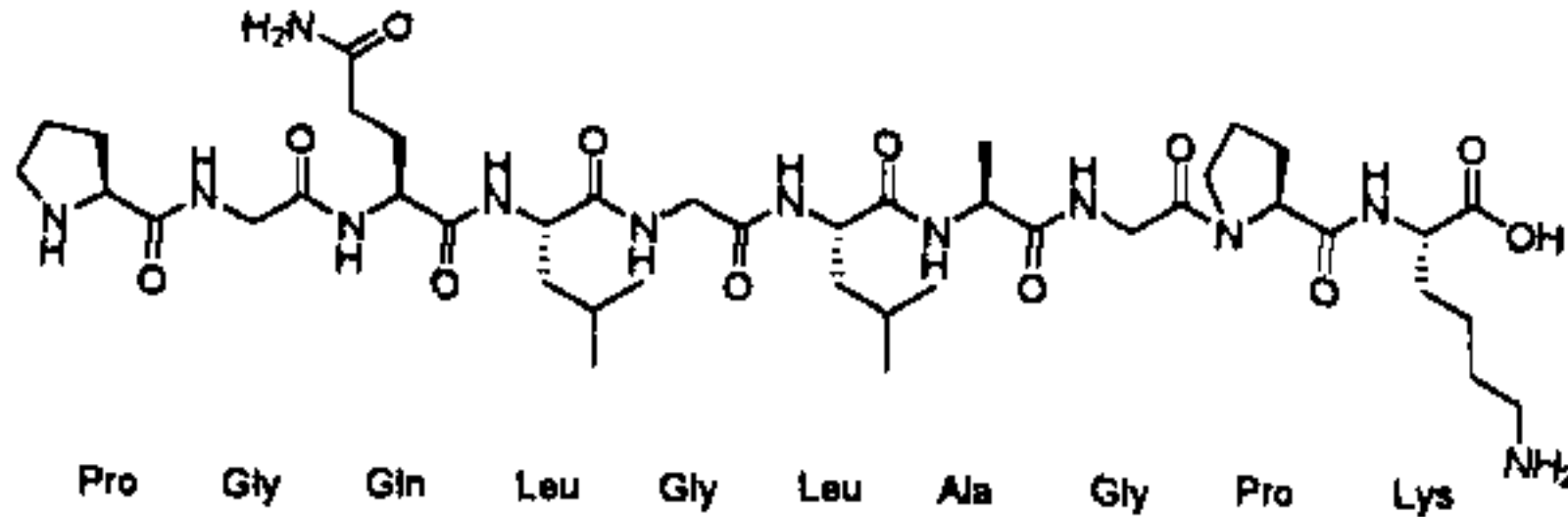
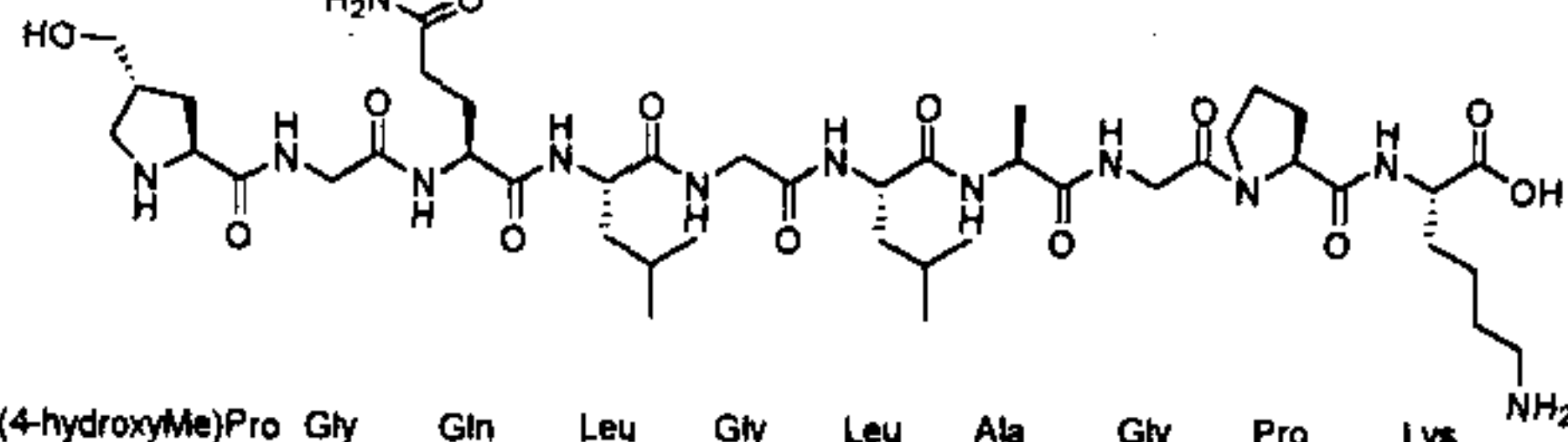
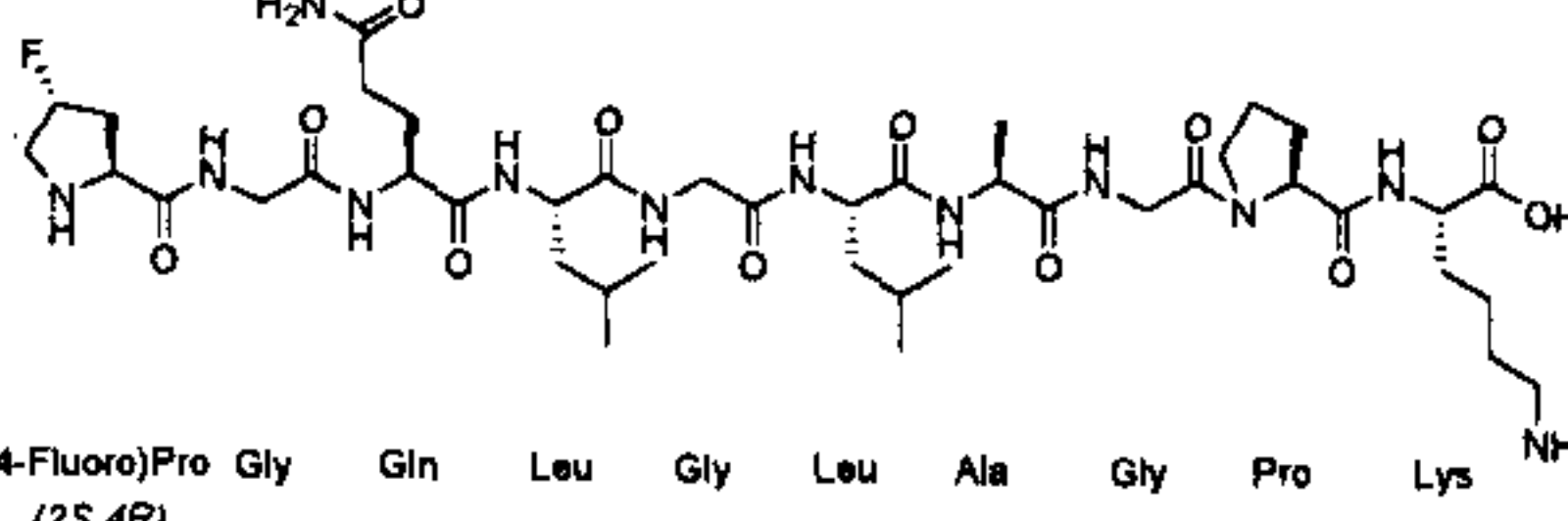
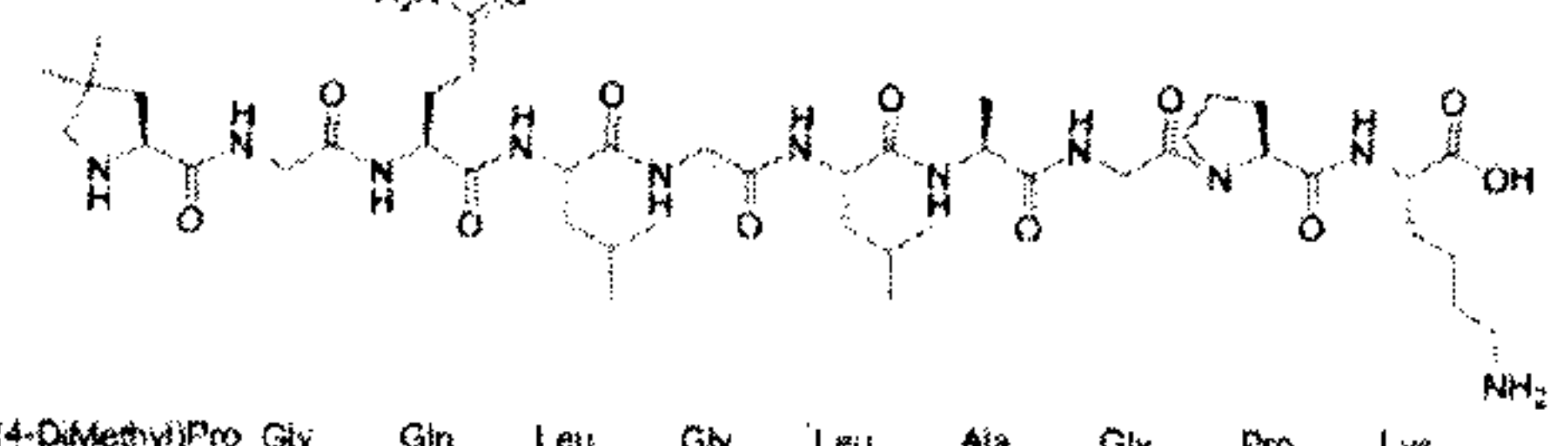
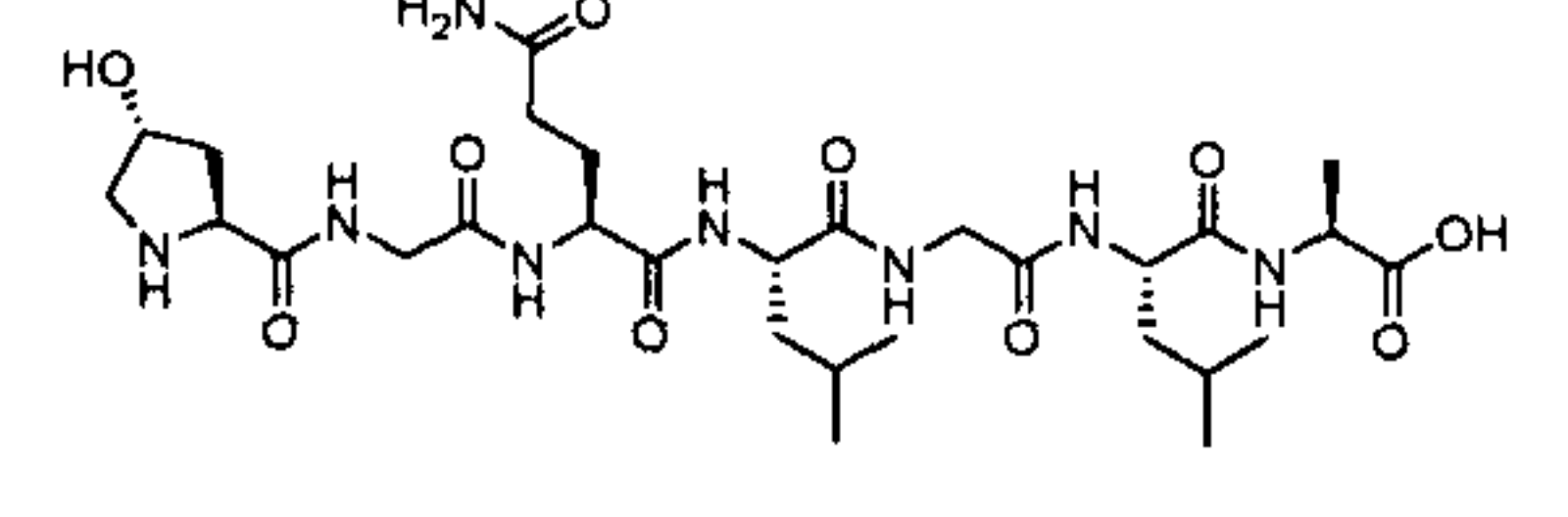
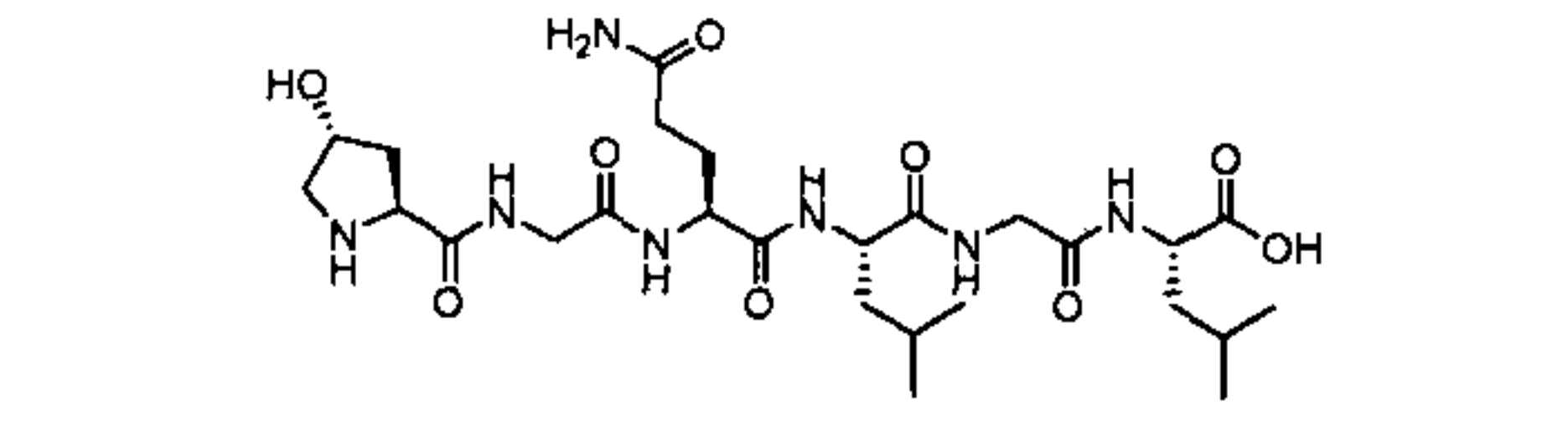
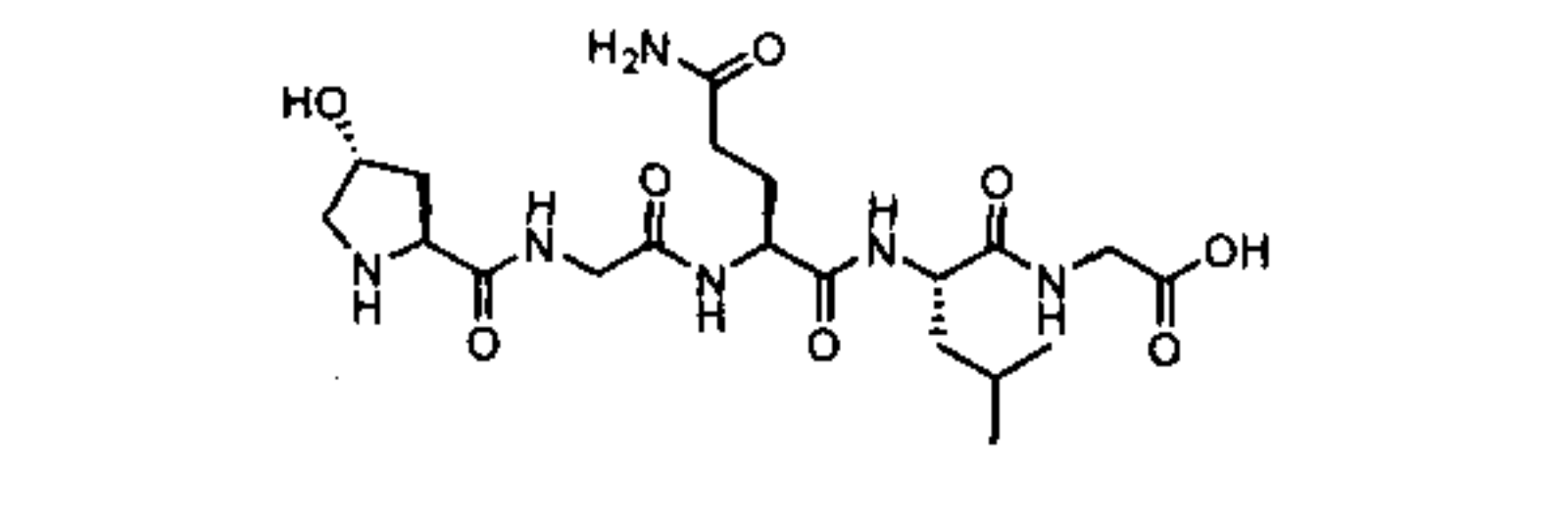
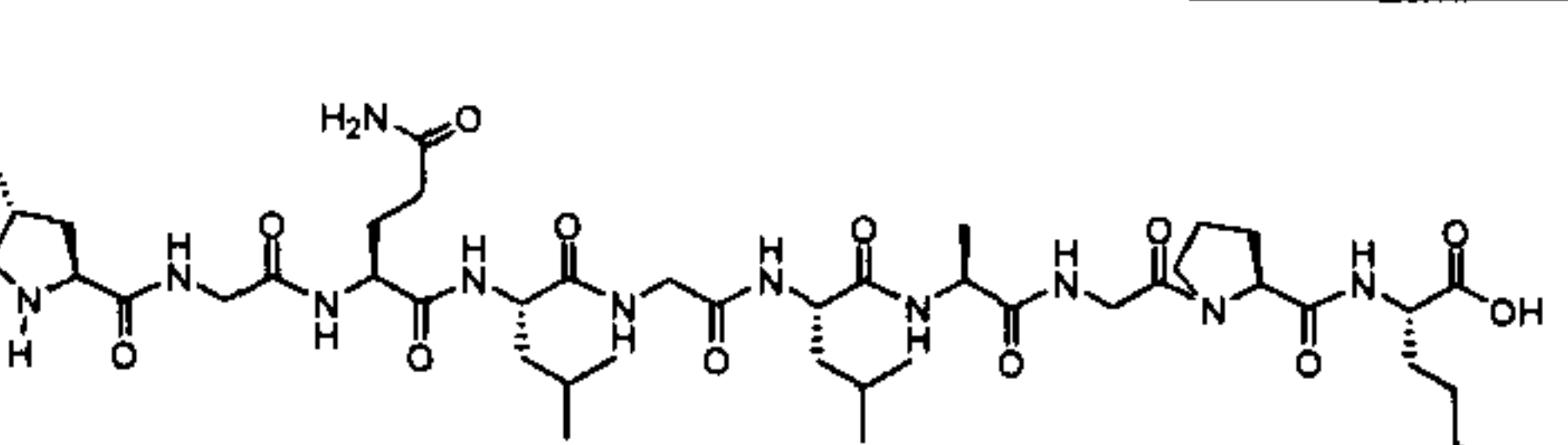
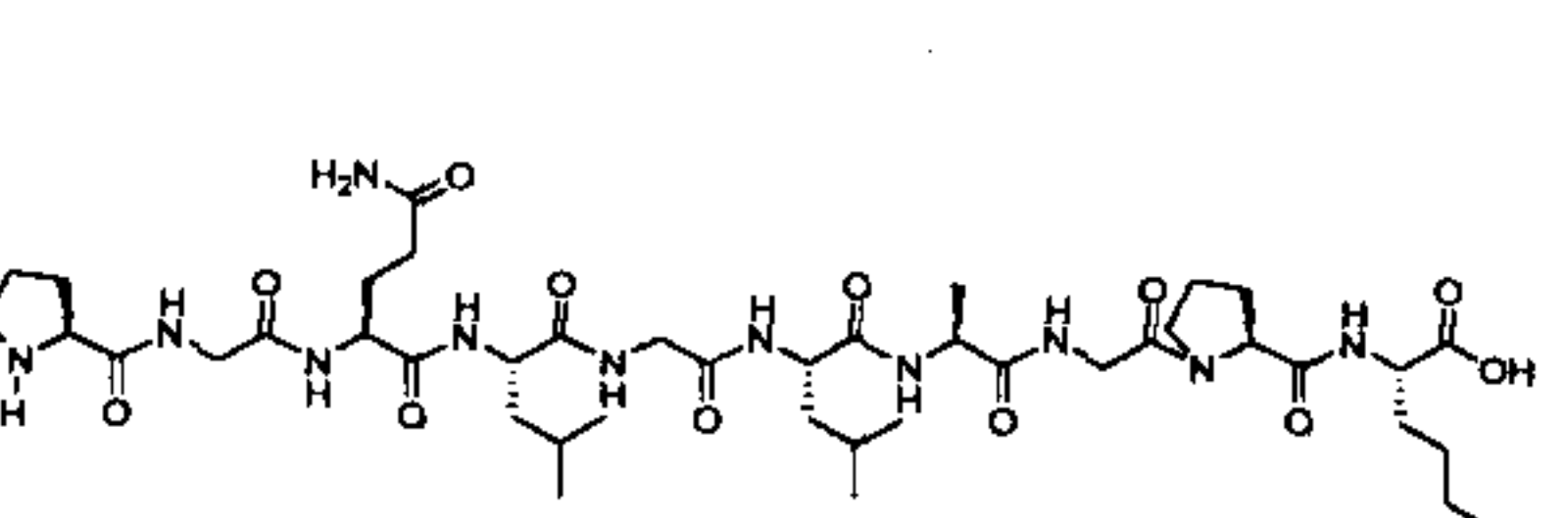
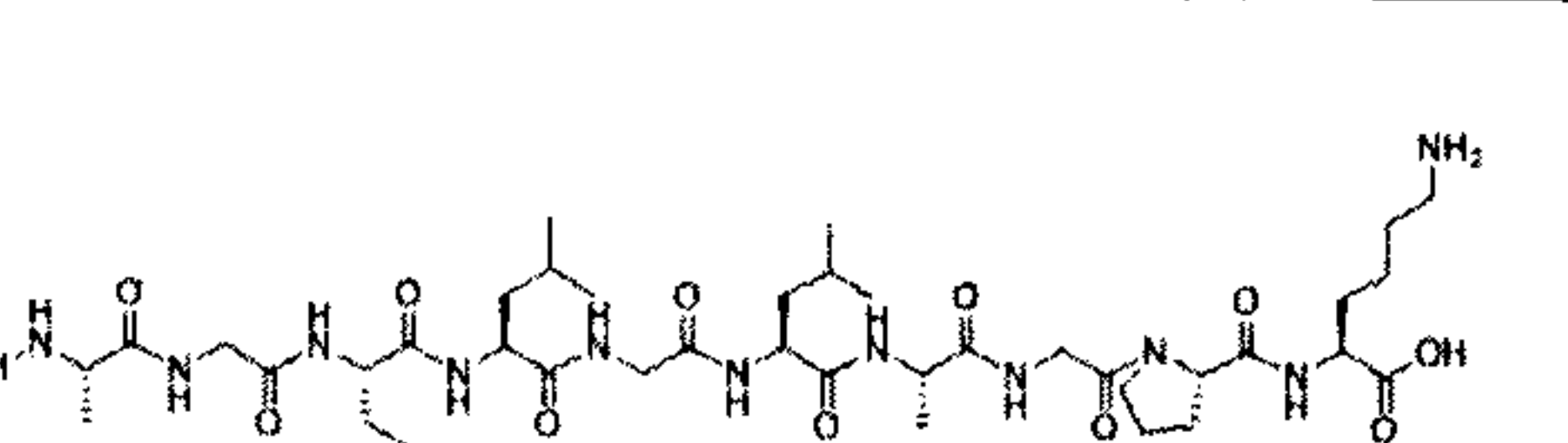
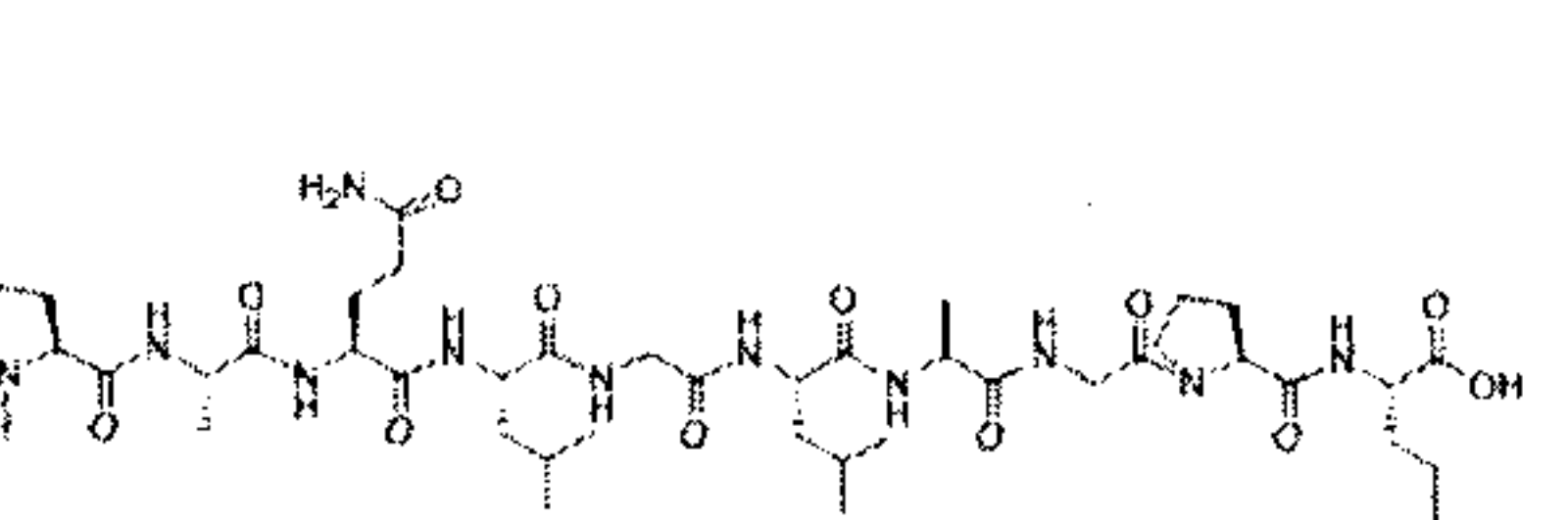
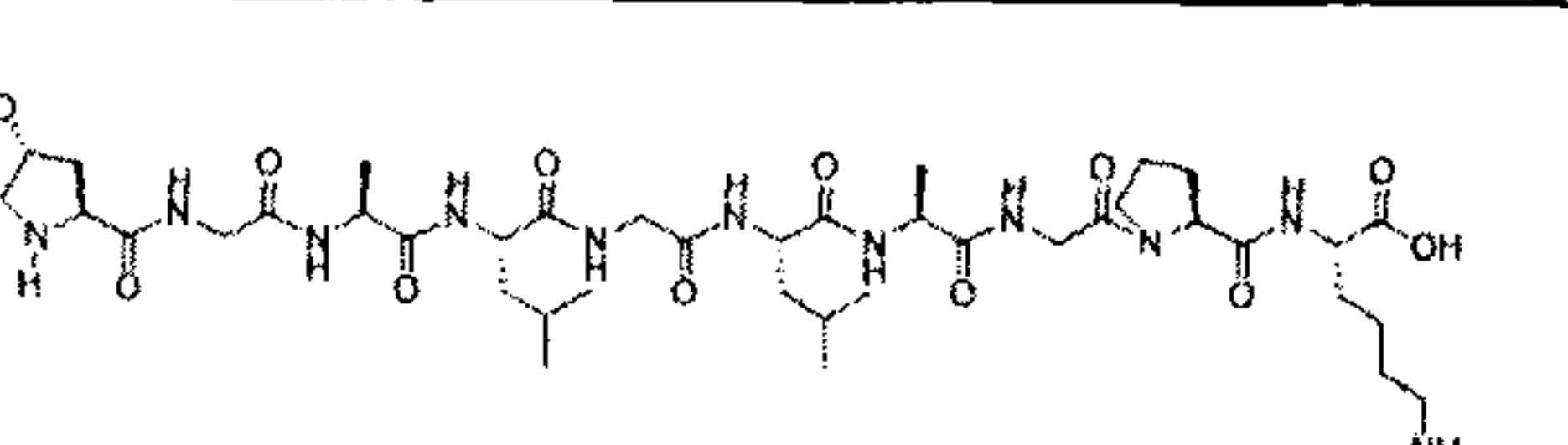
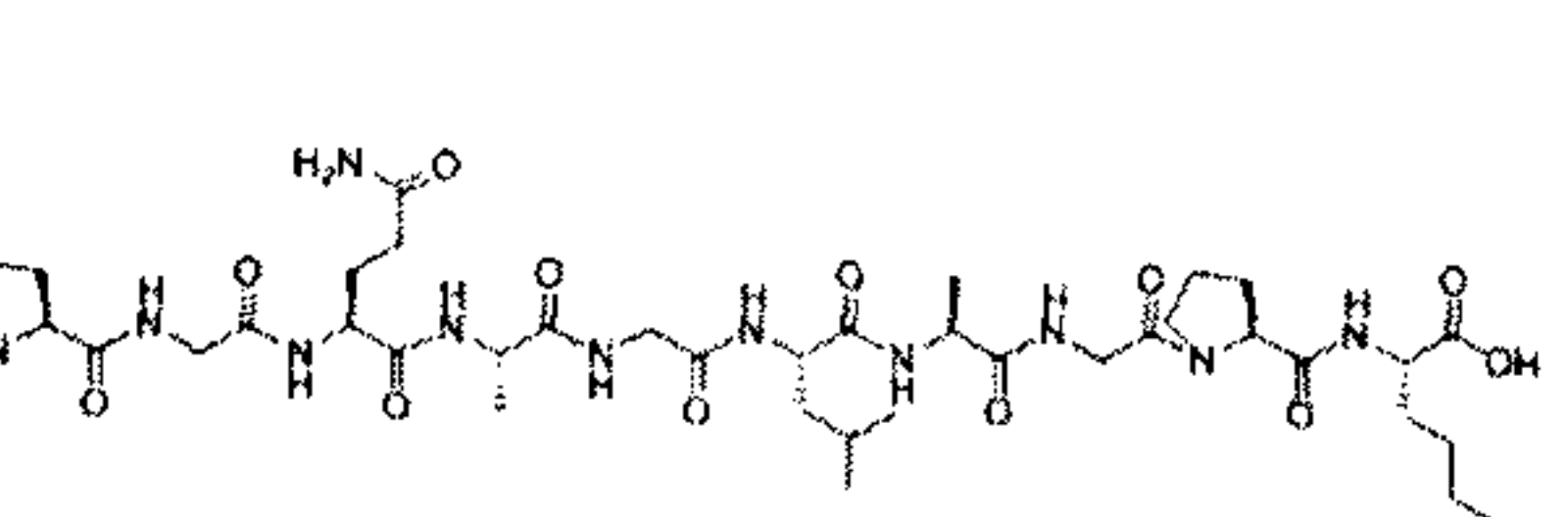
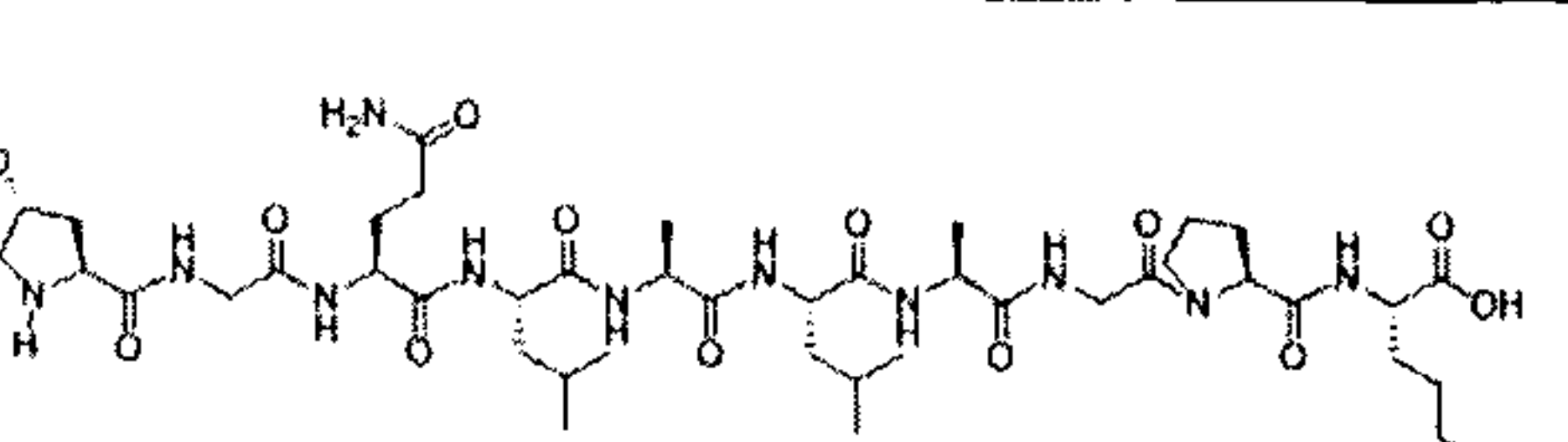
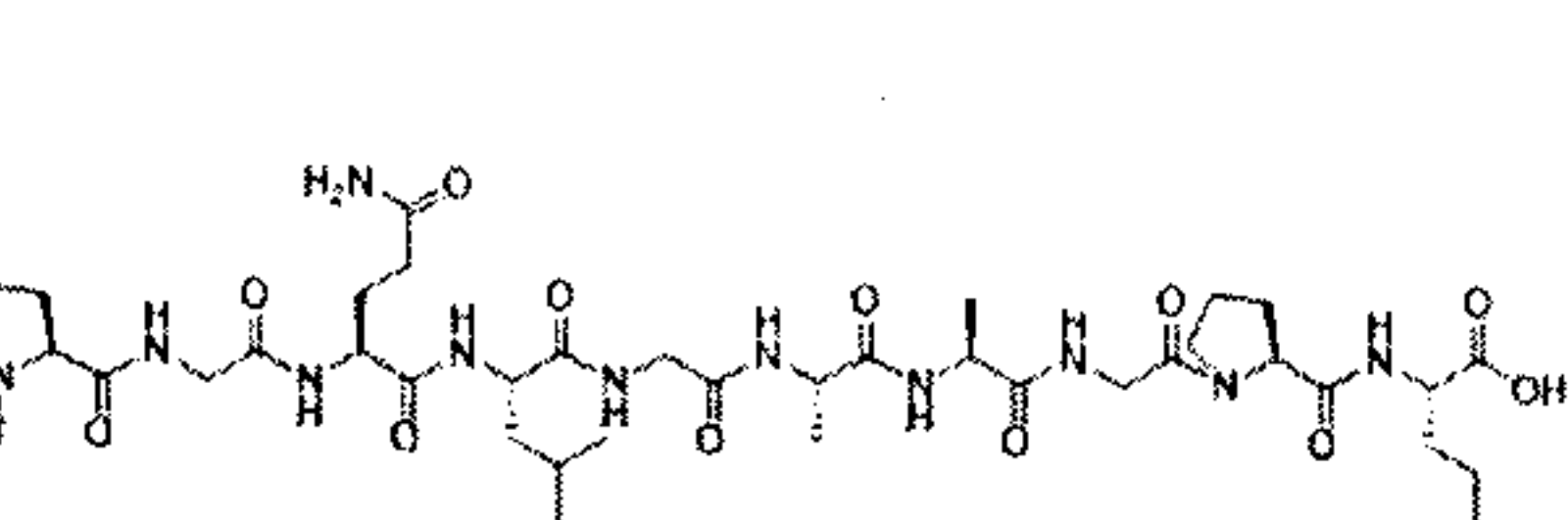
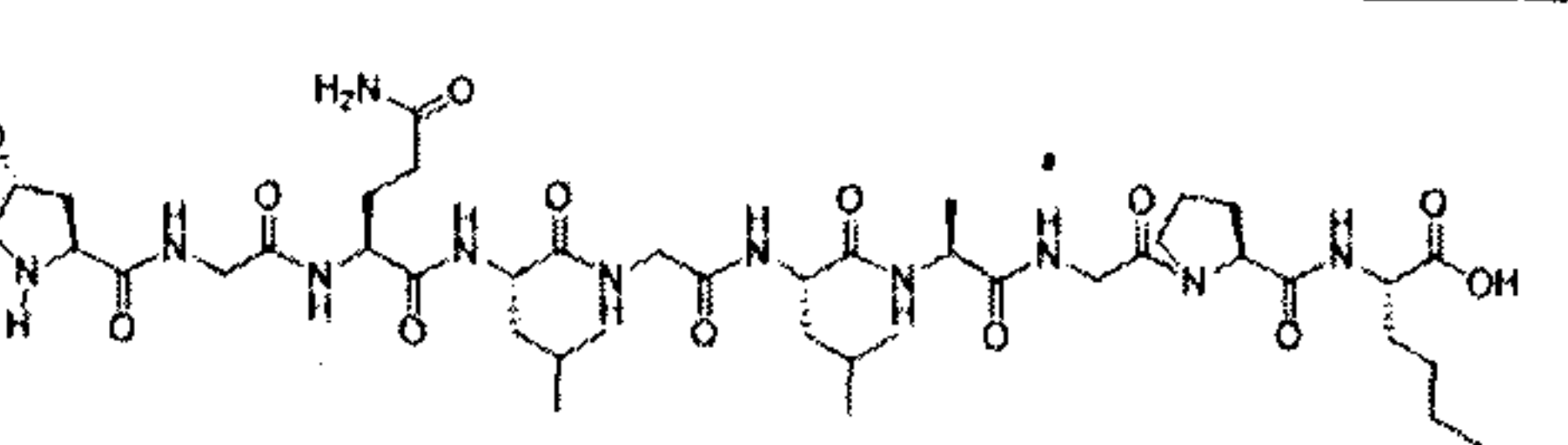
 The process for synthesizing the YDE-001 to YDE-075 peptides and the purification procedure thereof conducted by ANYGEN were depicted in Figs. 2 and 3.

15 [Table 11]

No.	Structure of compound	No.	Structure of compound
YY-101		YY-102	
YDE-001		YDE-002	
YDE-003		YDE-004	

YDE -005		YDE -006	
YDE -007		YDE -008	
YDE -009		YDE -010	
YDE -011		YDE -012	
YDE -013		YDE -014	
YDE -015		YDE -016	
YDE -017		YDE -018	
YDE -019		YDE -020	

YDE -021	 Hyp (2S,4R) Gly Gln Asp Trp Leu Ala Gly Pro Lys NH ₂	YDE -022	 Hyp (2S,4R) Gly Gln Asp His Leu Ala Gly Pro Lys NH ₂
YDE -023	 Hyp (2S,4R) Gly Gln Asp Ser Leu Ala Gly Pro Lys NH ₂	YDE -024	 Hyp (2S,4R) Gly Gln Asp Thr Leu Ala Gly Pro Lys NH ₂
YDE -025	 Hyp (2S,4R) Gly Gln Asp (N-Me) Leu Ala Gly Pro Lys NH ₂	YDE -026	 Hyp (2S,4R) Gly Gln Homo-Ser Gly Leu Ala Gly Pro Lys NH ₂
YDE -027	 Hyp (2S,4R) Gly Gln Asp (Me) Gly Leu Ala Gly Pro Lys NH ₂	YDE -028	 Hyp (2S,4R) Gly Gln Asn (Me) Gly Leu Ala Gly Pro Lys NH ₂
YDE -029	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Tyr	YDE -030	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Leu
YDE -031	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Glu	YDE -032	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Gln
YDE -033	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Nie(6-OH)	YDE -034	 Hyp (2S,4S) Gly Gln Leu Gly Leu Ala Gly Pro Lys NH ₂
YDE -035	 (4-oxo)Pro (2S) Gly Gln Leu Gly Leu Ala Gly Pro Lys NH ₂	YDE -036	 (5-oxo)Pro (2S) Gly Gln Leu Gly Leu Ala Gly Pro Lys NH ₂

YDE -037	 Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	YDE -038	 (4-hydroxyMe)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -039	 (4-Fluoro)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	YDE -040	 (4-DiMethyl)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -041	 Hyp Gly Gln Leu Gly Leu Ala	YDE -042	 Hyp Gly Gln Leu Gly Leu
YDE -043	 Hyp Gly Gln Leu Gly	YDE -044	 (4-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -045	 (5-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	YDE -047	 Ala Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -048	 Hyp Ala Gln Leu Gly Leu Ala Gly Pro Lys	YDE -049	 Hyp Gly Ala Leu Gly Leu Ala Gly Pro Lys
YDE -050	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys	YDE -051	 Hyp Gly Gln Leu Ala Leu Ala Gly Pro Lys
YDE -052	 Hyp Gly Gln Leu Gly Ala Ala Gly Pro Lys	YDE -053	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys

YDE -054	 Hyp Gly Gln Leu Gly Leu Ala Ala Pro Lys	YDE -055	 Hyp Gly Gln Leu Gly Leu Ala Gly Ala Lys
YDE -056	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala	YDE -057	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys (2R,4S)
YDE -058	 D-Hyp Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys (2R,1S)	YDE -059	 Hyp Gly Gln Glu Gly Lys Gly
YDE -060	 D-Hyp Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys (2R,4R)	YDE -064	 D-Hyp Gly D-Gln D-Leu Gly D-Leu (2R,4S)
YDE -066	 Hyp Gly Gln D-Leu Gly	YDE -072	 D-Hyp Ala Gln Leu Gly Leu Ala Gly Pro Lys (2R,4S)
YDE -073	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala (2R,4S)	YDE -074	 D-Hyp Ala Gln Leu Gly Leu Ala Gly Pro Ala (2R,4S)
YDE -075	 D-Hyp Gly Gln Leu Gly (2R,4S)		

Experimental Example 1: Analysis of YDE derivatives

The YDE derivatives prepared in Working Example 1 were analyzed by HPLC. As a result, it was confirmed that the purities of synthesized YDE-001, YDE-002, YDE-003, YDE-004, YDE-005, YDE-006, YDE-007, YDE-008, YDE-009, YDE-010,

YDE-011, YDE-012, YDE-013, YDE-014, YDE-015, YDE-016, YDE-017, YDE-018, YDE-019, YDE-020, YDE-021, YDE-022, YDE-023, YDE-024, YDE-025, YDE-026, YDE-027, YDE-028, YDE-029, YDE-030, YDE-031, YDE-032, YDE-033, YDE-034, YDE-035, YDE-036, YDE-037, YDE-038, YDE-039, YDE-040, YDE-041, YDE-042, 5 YDE-043, YDE-044, YDE-045, YDE-047, YDE-048, YDE-049, YDE-050, YDE-051, YDE-052, YDE-053, YDE-054, YDE-055, YDE-056, YDE-057, YDE-058, YDE-059, YDE-060, YDE-064, YDE-066, YDE-072, YDE-073, YDE-074, and YDE-075 were 99.7%, 99.7%, 99.7%, 99.7%, 99.5%, 98.9%, 98.0%, 98.8%, 98.1%, 99.0%, 98.3%, 98.9%, 98.7%, 98.5%, 99.1%, 99.4%, 98.0%, 99.6%, 99.6%, 99.2%, 98.1%, 98.3%, 10 96.1%, 98.9%, 95.1%, 98.6%, 96.9%, 99.5%, 98.0%, 98.1%, 98.8%, 98.2%, 97.2%, 98.6%, 98.8%, 98.7%, 99.2%, 98.7%, 98.1%, 97.5%, 96.5%, 97.4%, 98.7%, 97.8%, 95.5%, 97.5%, 97.2%, 96.9%, 99.3%, 98.0%, 99.4%, 96.4%, 95.1%, 98.6%, 97.4%, 98.8%, 97.4%, 95.8%, 98.9%, 96.9%, 98.8%, 97.7%, 95.0%, 97.9%, and 96.3%, respectively (Figs. 4 to 68).

15 In addition, the YDE derivatives prepared in Working Example 1 were analyzed by Ion-Mass. As a result, it was confirmed that the molecular weights of synthesized YDE-001, YDE-002, YDE-003, YDE-004, YDE-005, YDE-006, YDE-007, YDE-008, YDE-009, YDE-010, YDE-011, YDE-012, YDE-013, YDE-014, YDE-015, YDE-016, YDE-017, YDE-018, YDE-019, YDE-020, YDE-021, YDE-022, YDE-023, YDE-024, 20 YDE-025, YDE-026, YDE-027, YDE-028, YDE-029, YDE-030, YDE-031, YDE-032, YDE-033, YDE-034, YDE-035, YDE-036, YDE-037, YDE-038, YDE-039, YDE-040, YDE-041, YDE-042, YDE-043, YDE-044, YDE-045, YDE-047, YDE-048, YDE-049, YDE-050, YDE-051, YDE-052, YDE-053, YDE-054, YDE-055, YDE-056, YDE-057, YDE-058, YDE-059, YDE-060, YDE-064, YDE-066, YDE-072, YDE-073, YDE-074, 25 and YDE-075 were 969.6, 954.8, 967.7, 977.1, 968.1, 926.9, 941.1, 910.7, 939.7, 953.0, 953.7, 987.8, 1003.8, 1025.9, 996.7, 1011.0, 1011.4, 968.7, 1044.4, 1061.4, 1084.5, 1035.0, 984.9, 999.1, 969.7, 942.0, 937.6, 967.3, 988.1, 960.6, 954.2, 991.1, 954.4, 990.7, 950.9, 937.6, 968.1, 955.4, 966.0, 709.3, 622.2, 486.8, 951.3, 951.3, 911.4,

967.5, 896.5, 911.0, 967.3, 911.2, 953.2, 967.2, 927.4, 896.4, 952.8, 953.4, 670.1, 953.3, 599.7, 486.5, 966.1, 895.8, 909.1, and 486.4, respectively (Figs. 69 to 133).

Experimental Example 2: Evaluation of the eye protection effect on dry eye syndrome by the YDE derivatives

Experimental Example 2.1: Preparation of rats with dry eye syndrome

In order to evaluate the eye protection effect on dry eye syndrome by YDE-001 to YDE-028 prepared in Working Example 1, a total of 320 Sprague-Dawley-type male rats (OrientBio, Seungnam, Korea) were adapted for 7 days. Thereafter, dry eye syndrome was induced in 264 test rats through extraorbital lacrimal gland excision (hereinafter, ELGE). 8 test rats without the eye abnormality were subjected to a sham operation as a control group.

The rats were systemically anesthetized by inhaling a mixed gas of 2% to 3% of isoflurane (Hana Pharm. Co., Hwasung, Korea), 70% of N₂O, and 28.6% of O₂ using a rodent anesthesia machine (Surgivet, Waukesha, Wis., USA) and a ventilator (Model 687, Harvard Apparatus, Cambridge, UK). Thereafter, the extraorbital lacrimal gland located in the subdermal area above the masseter muscle and under the optic nerve was excised through a transverse incision in a size of 10 mm on the anterior part of the left ear tragus. The skin was sutured by a general method. The ELGE operation time did not exceed 5 minutes for each rat. After 6 days following the ELGE operation, confirmation was performed through the Schirmer test by measuring the amount of tear secretion whether dry eye syndrome had been induced. Meanwhile, each rat of the control group with the sham operation was checked for the presence and location of the extraorbital lacrimal gland through a skin incision, and the skin was then sutured without the excision thereof (Fig. 134).

The average weight of the ELGE test group measured before the ELGE operation was 241.59 ± 13.56 g, and the average weight measured after 6 days from the ELGE operation was 297.38 ± 34.02 g. The average weight of the control group measured

before the sham operation was 240.13 ± 25.63 g, and the average weight measured after 6 days from the sham operation was 297.38 ± 34.02 g (Fig. 135).

The average amount of tear secretion of the control group was 8.34 ± 0.73 mm³, and the average amount of tear secretion of the ELGE test group was 3.55 ± 0.70 mm³.

5 8 rats per group and a total of 32 groups were selected based on the average amount of tear secretion.

As a reference drug, 3% diquafosol sodium (Santen, Tokyo, Japan; hereinafter, DS), which is currently on the market, was used.

10 The present animal tests were conducted with a prior approval of the Animal Experimental Ethics Committee of Daegu Haany University (Approval No. DHU2017-003, January 12, 2017). All test animals were caused to fast for 18 hours before the ELGE operation and final sacrifice except for feeding water.

The 32 groups were summarized in Table 12.

[Table 12]

Group classification	32 groups in total; 8 rats per group
Sham control group	Group administered with physiological saline after the sham operation
ELGE control group	Group administered with physiological saline after the ELGE operation
Reference	Group administered with DS after the ELGE operation
YY-102	Group administered with a 0.3% YY-102 solution after the ELGE operation
YDE series	Group administered with any of 0.3% YDE-01 to YDE-28 solutions (28 groups in total)

15

In addition, in order to evaluate the eye protection effect on dry eye syndrome by YDE-029 to YDE-043 prepared in Working Example 1, a total of 200 Sprague-Dawley-type male rats (OrientBio, Seungnam, Korea) were adapted for 7 days. Dry eye syndrome was induced in 165 test rats through the ELGE. 8 test rats without the eye abnormality were subjected to the sham operation as a control group. The ELGE was carried out as described above.

20

The average weight of the ELGE test group measured before the ELGE operation was 264.09 ± 11.53 g, and the average weight measured after 6 days from the ELGE operation was 316.13 ± 15.77 g. The average weight of the control group measured before the sham operation was 263.50 ± 9.24 g, and the average weight measured after 5 6 days from the sham operation was 315.25 ± 10.85 g (Fig. 136).

The average amount of tear secretion of the control group was 10.90 ± 1.69 mm³, and the average amount of tear secretion of the ELGE test group was 4.83 ± 0.99 mm³. 8 rats per group and a total of 20 groups were selected based on the average amount of tear secretion.

10 As a reference drug, 3% DS, which is currently on the market, was used.

The present animal tests were conducted with prior approval of the Animal Experimental Ethics Committee of Daegu Haany University (Approval No. DHU2017-050, June 08, 2017). All test animals were caused to fast for 18 hours before the ELGE operation and final sacrifice except for feeding water.

15 The 20 groups were summarized in Table 13.

[Table 13]

Group classification	20 groups in total; 8 rats per group
Sham control group	Group administered with physiological saline after the sham operation
ELGE control group	Group administered with physiological saline after the ELGE operation
Reference	Group administered with DS after the ELGE operation
YY-101	Group administered with a 0.3% YY-101 solution after the ELGE operation
YY-102	Group administered with a 0.3% YY-102 solution after the ELGE operation
YDE series	Group administered with any of 0.3% YDE-01 to YDE-28 solutions (15 groups in total)

Experimental Example 2.2: Administration of the YDE derivatives

For YDE-001 to YDE-028, YY-102 and the 28 YDE-series were each dissolved 20 in physiological saline at a concentration of 3 mg/ml and administered at a dose of 5

μl/eye at 9:30 am and 3:30 pm daily for 14 days after 7 days from the ELGE operation for a total of 28 times. The DS solution was dissolved in physiological saline at a concentration of 30 mg/ml and administered at a dose of 5 μl/eye twice a day for 14 days after 7 days from the ELGE operation for a total of 28 times. For the sham control and the ELGE control groups, the same stimulation as the administration was applied. In order to prevent excessive eye dryness, the same volume of physiological saline was applied in the same manner in place of the test substances.

Further, For YDE-029 to YDE-043, YY-102 and the 15 YDE-series were each dissolved in physiological saline at a concentration of 3 mg/ml and administered at a dose of 5 μl/eye at 9:30 am and 3:30 pm daily for 14 days after 7 days from the ELGE operation for a total of 28 times. The DS solution was dissolved in physiological saline at a concentration of 30 mg/ml and administered at a dose of 5 μl/eye twice a day for 14 days after 7 days from the ELGE operation for a total of 28 times. For the sham control and the ELGE control groups, the same stimulation as the administration was applied. In order to prevent excessive eye dryness, the same volume of physiological saline was applied in the same manner in place of the test substances (Fig. 137).

Test Example 2.3: Confirmation of the changes in the amount of tear secretion by the YDE derivatives

After 6 days from the ELGE surgery, the changes in the amount of tear secretion were measured at day 7 and day 14 after the administration of YDE-001 to YDE-043. The amount of tear secretion was measured by the decrease in the travel distance of tears absorbed by cobalt chloride paper in a size of 1 x 15 mm (Toyo Roshi Kaisha, Japan).

The cobalt chloride paper was placed in the lateral canthus of a rat for 60 seconds to absorb tears (Fig. 139). The length of the area absorbed from the corner of the cobalt chloride paper was measured with an electronic digital caliper (Mytutoyo, Tokyo, Japan) (Fig. 138).

Fig. 139 shows the results of the test, wherein A is for the sham control group, B is for the ELGE control group, C is for the DS reference group, D is for the YY-102 administered group, and E to AF are for the YDE-001 to YDE-028 administered groups in order.

5 As a result, it was confirmed that the amount of tear secretion was decreased after 6 days from the ELGE operation at days 7 and 14 after the application of physiological saline in the ELGE control group as compared with the sham control group. In the groups treated with YDE derivatives and the DS reference group, the amount of tear secretion was increased as compared with the ELGE control group, except for the
10 groups treated with a 0.3% solution of YDE-9, YDE-10, YDE-17, YDE-19, YDE-20, YDE-21, YDE-22, YDE-25, YDE-27, and YDE-28, which did not show any significant changes in the amount of tear secretion after the administration thereof for 14 days. Especially, the amount of tear secretion was increased by more than 20% in the groups treated with a 0.3% solution of YDE-15, YDE-11, YDE-08, YDE-26, YDE-16, YDE-
15 01, YDE-23, and YY-102 as compared with the DS reference group.

The specific amounts of tear secretion are shown in Fig. 140 and Table 14.

[Table 14]

No.	Tear Volumes (mm ³)	
	Day 7	Day 14
YY-101	7.66±0.61	6.00±0.69
YY-102	4.59±1.43	5.77±1.99
YDE-001	4.88±1.62	5.92±2.19
YDE-002	3.84±1.16	5.01±1.67
YDE-003	4.13±1.76	4.88±1.57
YDE-004	3.42±1.06	5.19±1.84
YDE-005	3.85±0.93	5.08±1.91
YDE-006	3.44±1.69	5.35±1.68
YDE-007	3.91±1.28	5.45±1.26
YDE-008	4.57±1.25	6.10±2.36
YDE-009	3.76±1.21	4.54±1.11
YDE-010	3.42±1.31	4.35±1.36
YDE-011	4.22±1.45	6.16±2.16
YDE-012	3.68±0.99	5.67±1.86
YDE-013	5.27±1.50	5.49±1.92

YDE-014	3.81±1.21	5.62±1.85
YDE-015	4.03±2.19	6.65±2.13
YDE-016	4.59±1.13	5.98±2.27
YDE-017	4.00±1.22	4.89±1.50
YDE-018	3.75±1.54	4.99±1.60
YDE-019	4.84±1.39	4.52±1.07
YDE-020	3.41±1.47	4.20±1.35
YDE-021	4.08±1.33	4.90±1.13
YDE-022	3.19±0.67	4.10±0.95
YDE-023	5.32±2.30	5.78±2.23
YDE-024	3.85±1.30	5.72±1.36
YDE-025	3.21±0.72	4.72±2.19
YDE-026	4.32±1.47	6.01±1.83
YDE-027	2.82±0.86	3.95±1.52
YDE-028	4.04±0.99	4.73±1.18

Fig. 141 shows the results of the test, wherein A is for the sham control group, B is for the ELGE control group, C is for the DS reference group, D is for the YY-102 administered group, and E to S are for the YDE-029 to YDE-043 administered groups in order.

As a result, it was confirmed that the amount of tear secretion was decreased after 6 days from the ELGE operation at days 7 and 14 after the application of physiological saline in the ELGE control group as compared with the sham control group. In the groups treated with YDE derivatives and the DS reference group, the amount of tear secretion was increased as compared with the ELGE control group, except for the groups treated with a 0.3% solution of YDE-029, YDE-030, YDE-032, YDE-033, YDE-034, YDE-036, and YDE-41, which did not show any significant changes in the amount of tear secretion after the administration thereof for 14 days. Especially, the amount of tear secretion increased by more than 20% in the groups treated with a 0.3% solution of YDE-040, YDE-043, and YDE-042 in order as compared with the DS reference group.

The specific amounts of tear secretion are shown in Fig. 142 and Table 15.

[Table 15]

No.	Tear Volumes (mm ³)	
	Day 7	Day 14
YY-101	5.36±0.68	6.25±0.68
YY-102	5.77±1.01	6.60±0.64
YDE-029	5.33±1.43	6.03±1.71
YDE-030	5.69±1.79	6.65±2.17
YDE-031	5.63±1.97	5.91±0.85
YDE-032	5.58±0.80	5.03±0.93
YDE-033	4.99±1.20	4.54±1.16
YDE-034	6.16±1.01	6.43±1.86
YDE-035	4.96±0.96	6.25±0.79
YDE-036	4.95±1.05	5.13±1.03
YDE-037	4.98±0.66	5.80±0.90
YDE-039	6.04±1.01	6.44±1.96
YDE-040	5.77±1.05	8.63±1.53
YDE-041	5.01±1.26	6.25±2.15
YDE-042	6.30±1.08	7.97±1.48
YDE-043	5.90±1.06	8.16±1.42

Experimental Example 2.4: Confirmation of the changes in the corneal damage by the YDE derivatives

After YDE-001 to YDE-028 were each administered to the eyes 14 times, the changes in the corneal permeability were checked.

In order to measure the corneal permeability, Zoletyl 50TM (Virbac Lab., Carros, France), an animal anesthetic, was intraperitoneally injected at a dose of 25 mg/kg. Thereafter, saline containing a 1% (v/v) fluorescent solution (fluorescein sodium salt, Tokyo Kasei Kogyo Co., Tokyo, Japan) was applied to the eyes at a dose of 5 µl/eye. The eyes thus treated were closed and fixed with a tape. After 1 hour, the remaining fluorescent solution was removed using a cotton swab (Fig. 142). After 12 hours to 24 hours, the corneal permeability was measured using a blue light tungsten lamp and an ophthalmic slit lamp table top model biomicroscope (Model SM-70N; Takaci Seiko Co., Nakano, Japan) (Fig. 143).

Fig. 144 shows the results of the test, wherein A is for the sham control group, B is for the ELGE control group, C is for the DS reference group, D is for the YY-102

administered group, and E to AF are for the YDE-001 to YDE-028 administered groups in order.

As a result, the permeability of the fluorescent dye was increased in the ELGE control group as compared with the sham control group. The permeability of the fluorescent dye was not decreased in the groups treated with a 0.3% solution of YDE-10, YDE-20, YDE-22, YDE-25, YDE-27, and YDE-28 as compared with the ELGE control group at day 14 after the administration. In the groups treated with YDE derivatives and the DS reference group, the corneal permeability of the fluorescent dye was decreased as compared with the ELGE control group, except for the groups treated with a 0.3% solution of YDE-10, YDE-20, YDE-22, YDE-25, YDE-27, and YDE-28. Especially, the permeability of the fluorescent dye was decreased by more than 20% in the groups treated with a 0.3% solution of YDE-15, YDE-11, YDE-08, YDE-26, YDE-16, YDE-01, YDE-23, and YY-102, as compared with the DS reference group.

The specific permeabilities of the fluorescent dye are shown in Fig. 145 and Table 16.

[Table 16]

No.	Permeability of fluorescent dye (%)
YY-101	27.53±5.62
YY-102	27.48±14.37
YDE-001	25.49±11.62
YDE-002	38.26±11.25
YDE-003	40.45±6.46
YDE-004	35.05±11.74
YDE-005	37.98±11.53
YDE-006	33.23±13.26
YDE-007	32.79±10.77
YDE-008	20.32±11.87
YDE-009	41.50±7.86
YDE-010	49.29±12.06
YDE-011	18.11±11.61
YDE-012	31.01±11.38
YDE-013	32.24±7.84
YDE-014	31.15±10.87
YDE-015	15.95±6.48

YDE-016	24.57±10.34
YDE-017	39.76±7.42
YDE-018	38.19±10.96
YDE-019	40.39±12.57
YDE-020	47.84±13.47
YDE-021	37.00±10.49
YDE-022	47.82±10.01
YDE-023	26.51±8.18
YDE-024	30.63±10.41
YDE-025	47.10±11.45
YDE-026	22.63±11.23
YDE-027	50.24±11.94
YDE-028	41.17±10.25

In addition, YDE-029 to YDE-043 were each administered to the eyes 14 times, and the changes in the corneal permeability were then checked. The measurement of the corneal permeability was carried out in the same manner as described above (Fig. 146).

As a result, the permeability of the fluorescent dye was increased in the ELGE control group as compared with the sham control group. The permeability of the fluorescent dye was not decreased in the groups treated with a 0.3% solution of YDE-29, YDE-32, YDE-33, YDE-36, and YDE-41 as compared with the ELGE control group at day 14 after the administration. In the groups treated with YDE derivatives and the DS reference group, the corneal permeability of the fluorescent dye was decreased as compared with the ELGE control group, except for the groups treated with a 0.3% solution of YDE-29, YDE-32, YDE-33, YDE-36, and YDE-41. Especially, the permeability of the fluorescent dye was decreased by more than 20% in the groups treated with a 0.3% solution of YDE-40, YDE-43, and YDE-42, as compared with the DS reference group.

The specific permeabilities of the fluorescent dye are shown in Fig. 147 and Table 17.

[Table 17]

No.	Permeability of fluorescent dye (%)
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YY-101	33.80±11.11
YY-102	27.89±7.10
YDE-029	63.45±11.57
YDE-030	30.60±13.61
YDE-031	33.35±11.01
YDE-032	58.90±19.81
YDE-033	60.55±21.22
YDE-034	32.17±12.94
YDE-035	27.62±6.51
YDE-036	57.87±22.91
YDE-037	36.30±9.75
YDE-039	29.94±11.40
YDE-040	18.33±9.41
YDE-041	46.38±26.65
YDE-042	20.72±11.37
YDE-043	19.04±7.36

Experimental Example 3: Evaluation of the stability of the YDE derivatives

In order to confirm the stability of each test substance in an aqueous solution, 10 mg of each sample was dissolved in 1 ml of water to a concentration of 1 mg/ml, which was then charged to a glass vial, plugged with a rubber cap, sealed with an aluminum cap, and stored under long-term storage conditions (25°C, 75% RH). The stability of the test substance was evaluated by measuring the amount of related substances at the time of one week, two weeks, four weeks, eight weeks, and twelve weeks under the long-term storage conditions.

As a result, 66.5% of related substances was generated in YY-101 after two weeks. In contrast, 1.1% to 30.6% of related substances was generated in YDE-001 to YDE-028 after 12 weeks. The specific amounts are shown in Table 18.

[Table 18]

No.	Amount of related substances (%; after 12 weeks)
YY-101	66.51 (after 2 weeks)
YDE-001	3.92
YDE-002	4.93
YDE-003	6.86
YDE-004	2.11

YDE-005	2.97
YDE-006	3.67
YDE-007	3.76
YDE-008	4.42
YDE-009	4.71
YDE-010	4.39
YDE-011	3.83
YDE-012	3.57
YDE-013	5.92
YDE-014	6.72
YDE-015	13.05
YDE-016	11.33
YDE-017	11.88
YDE-018	25.39
YDE-019	13.43
YDE-020	21.54
YDE-021	21.33
YDE-022	19.23
YDE-023	30.66
YDE-024	20.59
YDE-025	5.17
YDE-026	10.15
YDE-027	12.74
YDE-028	1.15

Test Example 4: Evaluation of recovery of corneal damage by the YDE derivatives

In order to confirm whether the YDE derivatives could recover corneal damage, the cellular growth rate of human primary corneal epithelial cells was checked.

Specifically, primary corneal epithelial cells (ATCC, ATCC PCS-700-010) were seeded on a 96-well culture plate (Perkin Elmer, 6005680) containing the Corneal Epithelial Cell Basal Medium (ATCC, ATCC PCS-700-030) in the Corneal Epithelial Cell Growth Kit (ATCC, ATCC PCS-700-040) in an amount of 5×10^3 cells per well, which was then cultured for 24 hours under the conditions of 37°C and 5% CO₂.

YDE-001 to YDE-075 were each dissolved in 100% DMSO (Sigma, D2660) to a concentration of 10 mM, which was then diluted with 100% DMSO to a concentration

of the compound of 6, 1.9, 0.6, 0.2, 0.06, 0.02, 0.006, and 0.002 mM. 20 μ l of the diluted YDE derivative was added to a 96-well microplate (Greiner Bio-One, 651201) containing 380 μ l of the Corneal Epithelial Cell Basal Medium such that the concentration of DMSO was diluted to 5%.

5 After 24 hours, 20 μ l of each of the YDE derivatives diluted in the 96-well microplate was added to the 96-well culture plate containing the cells. As a control group, hEGF (Sigma, E9644) was treated at the same concentration as the YDE derivatives. The cells treated with the YDE-derivatives or hEGF were cultured for 48 hours and 72 hours under the conditions of 37°C and 5% CO₂ (Figs. 148 to 155).

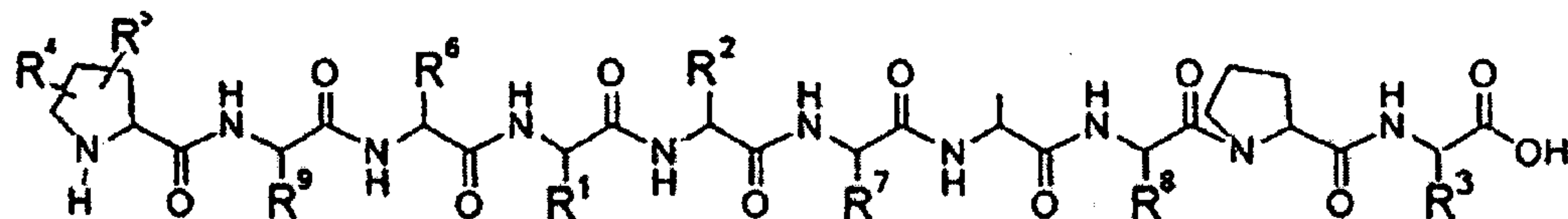
10 The cultured cells were treated with the CellTiter-Glo luminescent reagent (Promega, G7573) according to the manufacturer's instructions and reacted for 30 minutes at room temperature. Thereafter, the fluorescent signal (or luminescence signal) was checked using an Envision 2014 Multi-label plate reader. The measured values were normalized using a vehicle control (100% proliferation cell).

15 As a result, the cell proliferation was observed at concentrations of 0.3 μ M or less in YY-101, YY-102, YDE-011, YDE-038, YDE-042, YDE-043, YDE-044, YDE-045, YDE-049, YDE-054, YDE-057, YDE-058, YDE-059, and YDE-060. Especially, a high cell proliferation rate was shown in YY-102, YDE-011, YDE-045, YDE-057, and YDE-060 (Figs. 156 to 173).

CLAIMS:

1. A compound represented by Formula 1:

5 [Formula 1]



wherein R^1 to R^3 are each independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-10} alkoxy, substituted or unsubstituted C_{1-10} haloalkyl, substituted or unsubstituted C_{2-10} alkenyl, substituted or unsubstituted C_{2-10} alkynyl, substituted or unsubstituted C_{1-10} alkylene, substituted or unsubstituted C_{1-10} alkenylene, substituted or unsubstituted C_{1-10} alkynylene, substituted or unsubstituted C_{5-12} aryl, substituted or unsubstituted C_{7-12} arylalkyl, substituted or unsubstituted C_{5-14} arylalkynyl, substituted or unsubstituted C_{8-16} arylalkenyl, substituted or unsubstituted C_{3-10} heteroalkyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{3-10} heterocycloalkyl, or substituted or unsubstituted C_{5-12} heteroaryl, the heteroalkyl, heterocycloalkyl, or heteroaryl containing at least one of N, O, and S,

the substitution refers to a substitution with a non-hydrogen substituent, the non-hydrogen substituent may be at least one selected from the group consisting of $-X_1$, $-R_a$, $-O^-$, $=O$, $-OR_a$, $-SR_a$, $-S^-$, $-N(R_a)_2$, $-N^+(R_a)_3$, $=NR_a$, $-C(X_1)_3$, $-CN$, $-OCN$, $-SCN$, $-N=C=O$, $-NCS$, $-NO$, $-NO_2$, $=N-OH$, $=N_2$, $-N_3$, $-NHC(=O)R_a$, $-C(=O)R_a$, $-C(=O)NR_aR_a$, $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R_a$, $-OS(=O)_2OR_a$, $-S(=O)_2NR_a$, $-S(=O)R_a$, $-OP(=O)(OR_a)_2$, $-C(=O)R_a$, alkylene- $C(=O)R_a$, $-C(=S)R_a$, $-C(=O)OR_a$, alkylene- $C(=O)OR_a$, $-C(=O)O^-$, alkylene- $C(=O)O^-$, $-C(=S)OR_a$, $-C(=O)SR_a$, $-C(=S)SR_a$, $-C(=O)NR_aR_a$, alkylene- $C(=O)NR_aR_a$, $-C(=S)NR_aR_a$, and $-C(-NR_a)NR_aR_a$, X_1 is F, Cl, Br, or I, R_a is hydrogen, C_{1-6} alkyl, C_{5-12} aryl, C_{7-12} arylalkyl, or heterocycle,

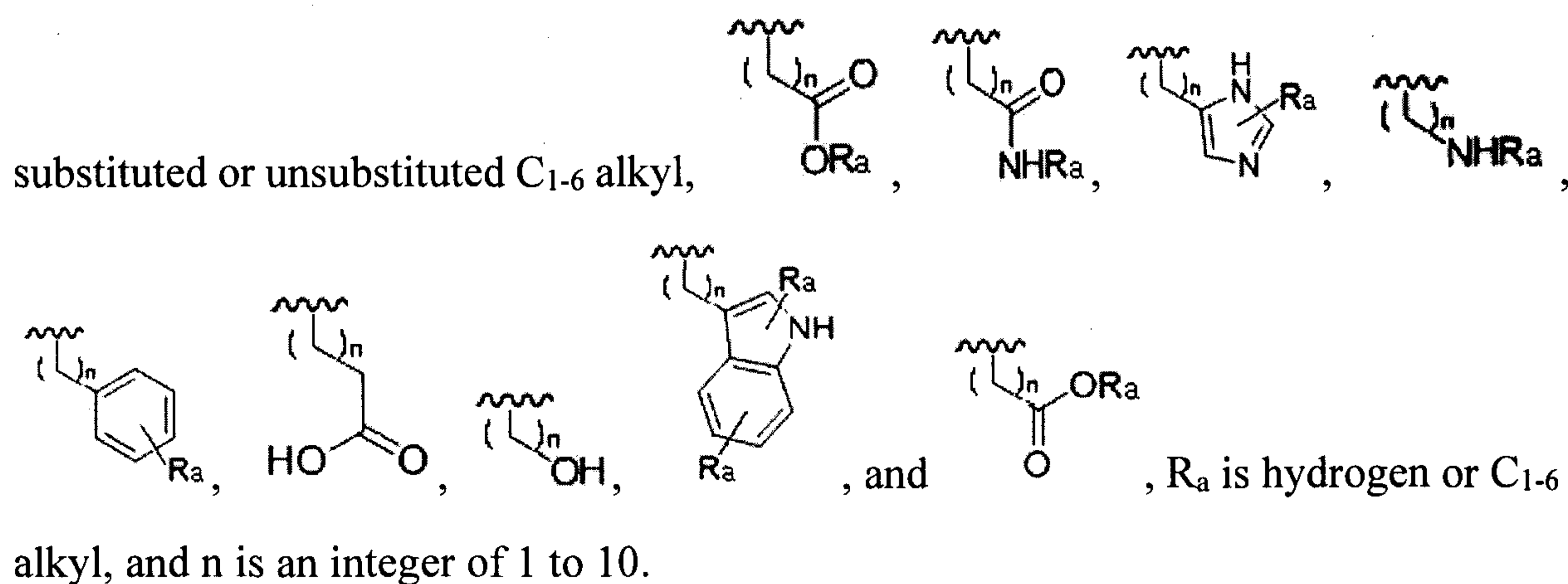
R^4 and R^5 are each independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, $-X_2$, $-R_b$, $-O^-$, $=O$, $-CH_2OR_b$, or $-OR_b$, X_2 is F, Cl, Br, or I, R_b is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{5-12} aryl, substituted or unsubstituted C_{7-12} arylalkyl, or substituted or unsubstituted heterocycle,

5 R^6 is hydrogen or substituted or unsubstituted C_{1-6} alkyl, the substituent being $-C(=O)NH_2$,

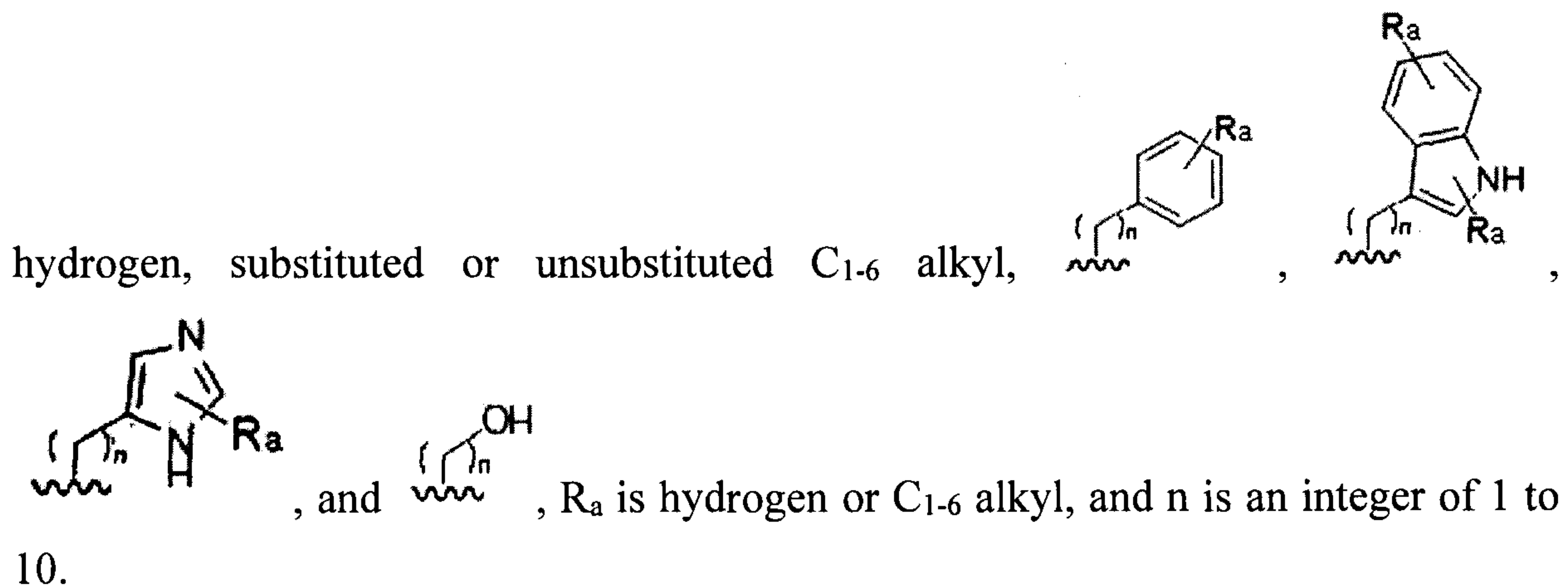
R^7 is hydrogen or C_{1-6} alkyl, and

R^8 and R^9 are hydrogen or unsubstituted C_{1-6} alkyl.

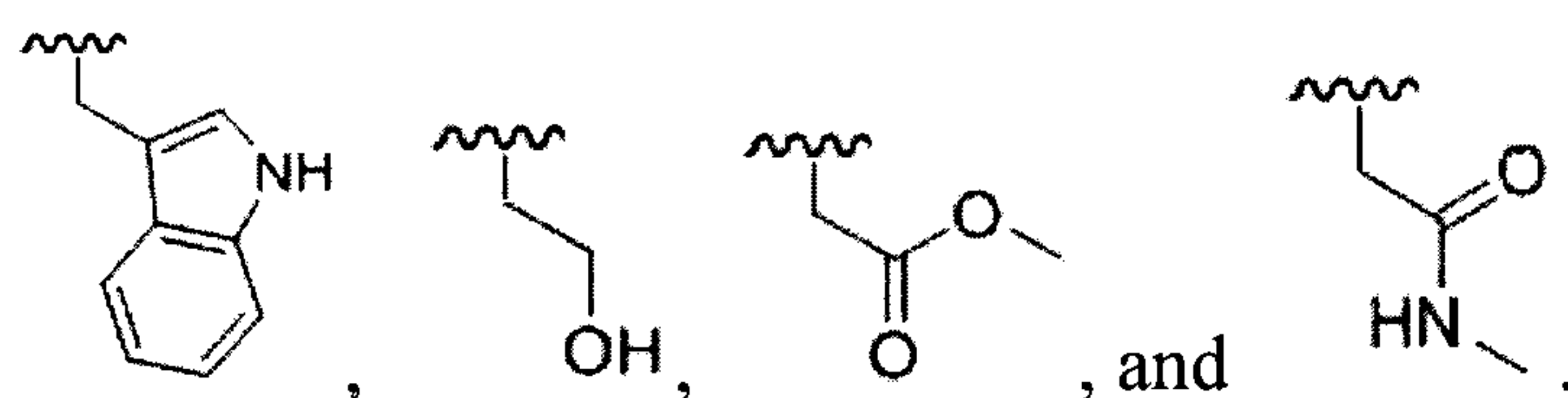
10 2. The compound of claim 1, wherein R^1 is selected from the group consisting of



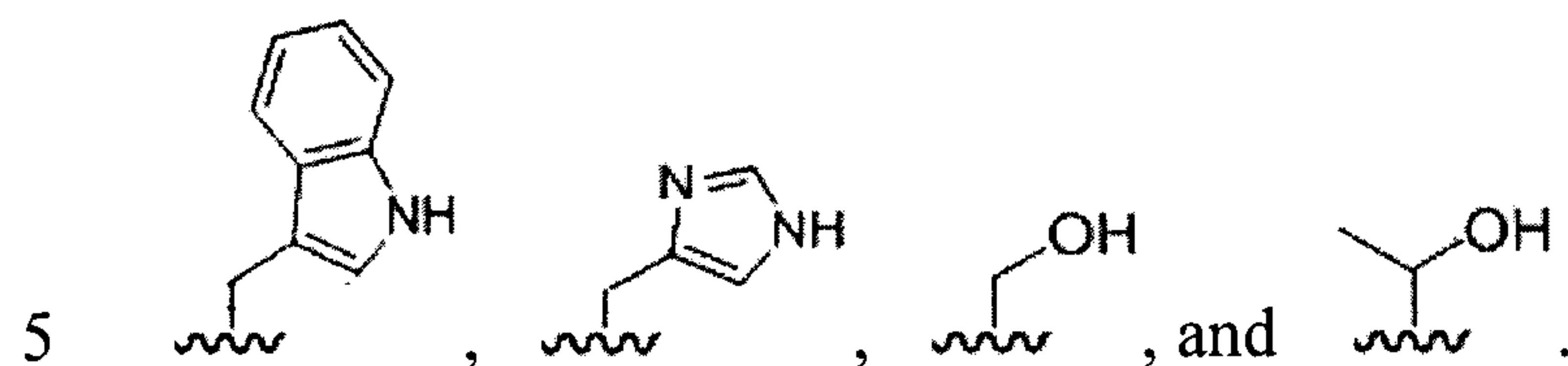
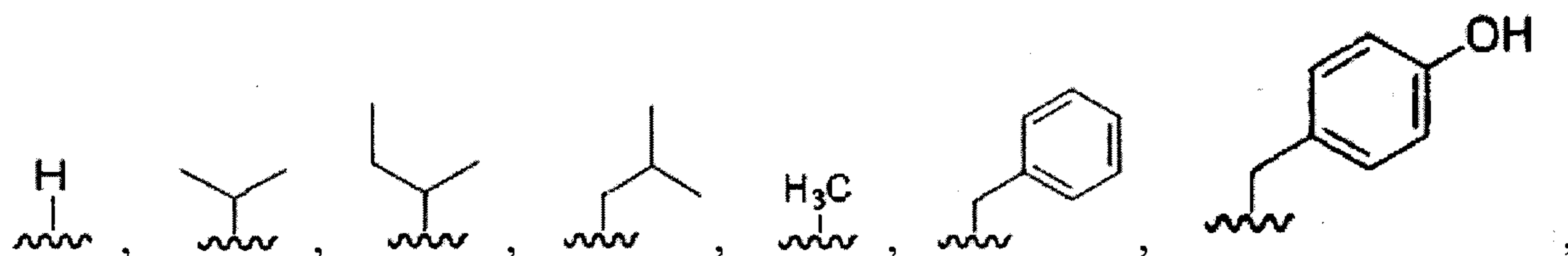
15 3. The compound of claim 1, wherein R^2 is selected from the group consisting of



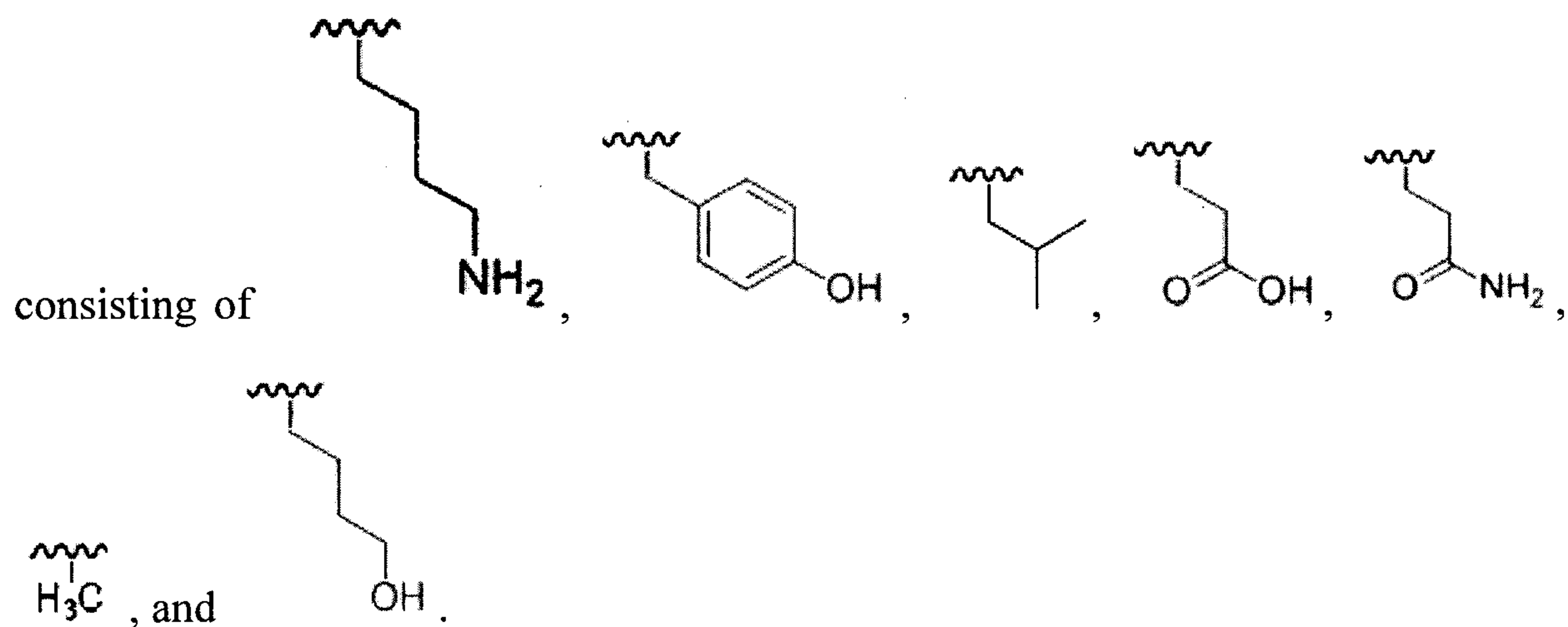
78



9. The compound of claim 3, wherein R^2 is selected from the group consisting of



10. The compound of claim 4, wherein R^3 is one selected from the group



10

11. The compound of claim 6, wherein R^4 is selected from the group consisting of H, -OH, =O, and -CH₃.

12. The compound of claim 1, which is any one selected from the group consisting of HyP-Gly-Gln-Glu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Gln-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-His-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Lys-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Thr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ala-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Val-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ile-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Phe-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Tyr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Trp-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser(Homo)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp(Me)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn(Me)-Gly-Leu-Ala-Gly-Pro-Lys, D-HyP(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, D-Hyp(2R,4S)-Gly-D-Gln-D-Leu-Gly-D-Leu-D-Ala-Gly-D-Pro-D-Lys, D-Hyp(2R, 4R)-Gly-D-Gln-D-Leu-Gly-D-Leu-D-Ala-Gly-D-Pro-D-Lys, HyP-Gly-Gln-Asp-Val-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ile-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Leu-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ala-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Phe-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Tyr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Trp-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-His-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ser-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Thr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Ala-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Tyr, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Leu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Glu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Gln, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Nle(6-OH), HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala, D-HyP(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala, Hyp(2S, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-hydroxyMe)Pro-Gly-Gln-Leu-Gly-Leu-

Ala-Gly-Pro-Lys, (4-Fluoro)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Dimethyl)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys,

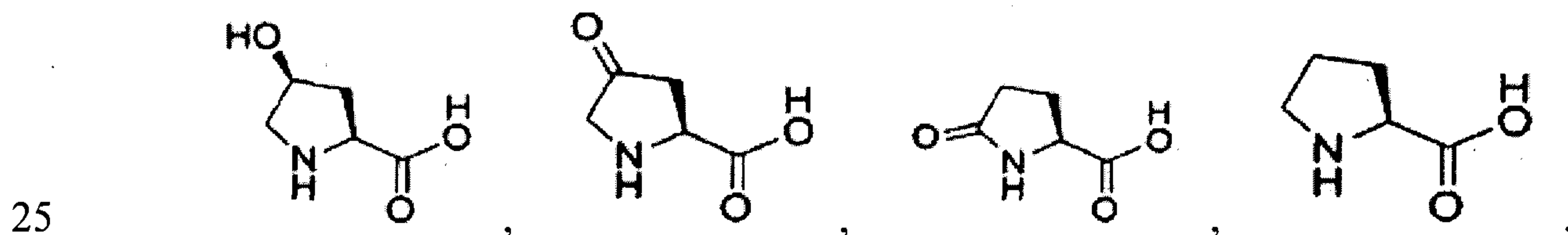
Hyp-Gly-Ala-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Ala-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Ala-Pro-Lys, Hyp-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, D-Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, and D-Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala.

13. A peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys, wherein Xaa is selected from the group consisting of Glu, Asn, Gln, His, Lys, Ser, Thr, Ala, Val, Ile, Leu, Phe, Tyr, Trp, homo-Ser, Asp(Me), and Asn(Me).

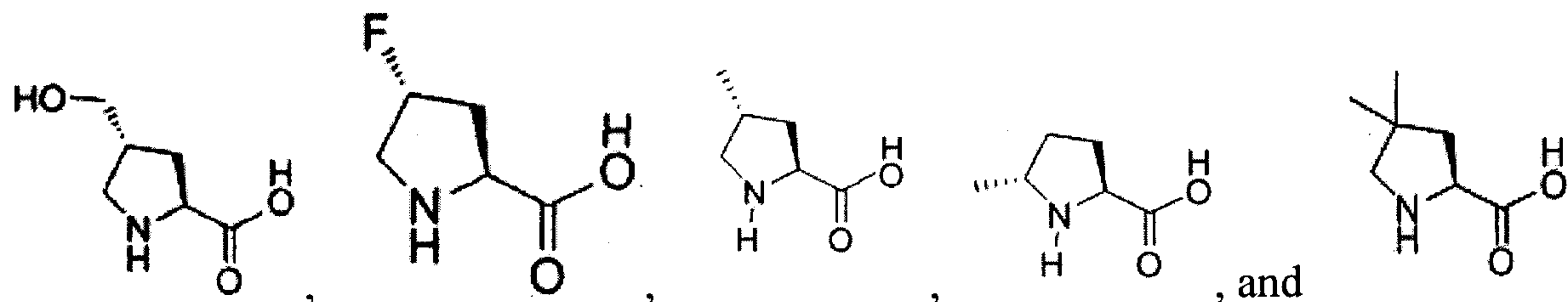
14. A peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys, wherein Xaa is selected from the group consisting of Val, Ile, Leu, Ala, Phe, Tyr, Trp, Ser, Thr, and (N-Me)Gly.

15. A peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa, wherein Xaa is selected from the group consisting of Tyr, Leu, Glu, Gln, Ala, and Nle(6-OH).

16. A peptide having an amino acid sequence represented by PD-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, wherein PD is any one selected from the group consisting of the following formulae:



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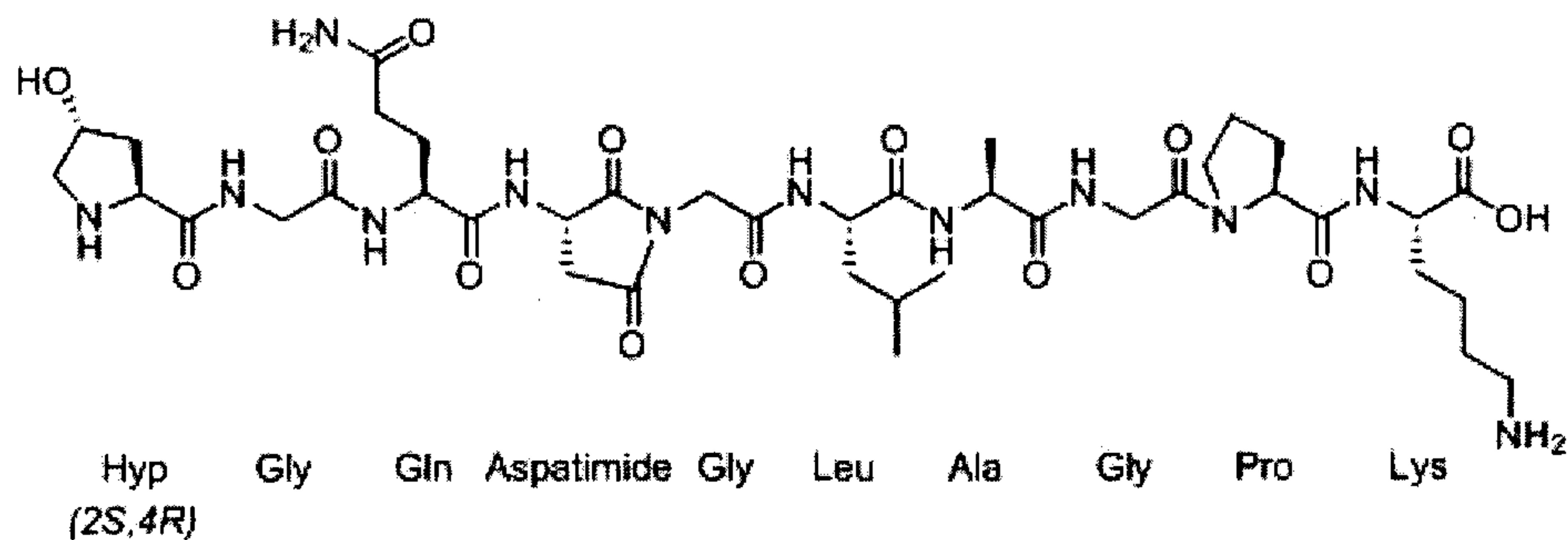


17. A peptide having any one amino acid sequence selected from the group consisting of Ala-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Ala-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala, HyP-Gly-Gln-Glu-Gly-Leu-Gly, HyP-Gly-Gln-Leu-Gly-Leu, *D*-HyP(2R, 4S)-Gly-*D*-Gln-*D*-Leu-Gly-*D*-Leu, HyP-Gly-Gln-Leu-Gly, HyP-Gly-Gln-*D*-Leu-Gly, and *D*-HyP(2R, 4S)-Gly-Gln-Leu-Gly.

18. A compound represented by Formula 8:

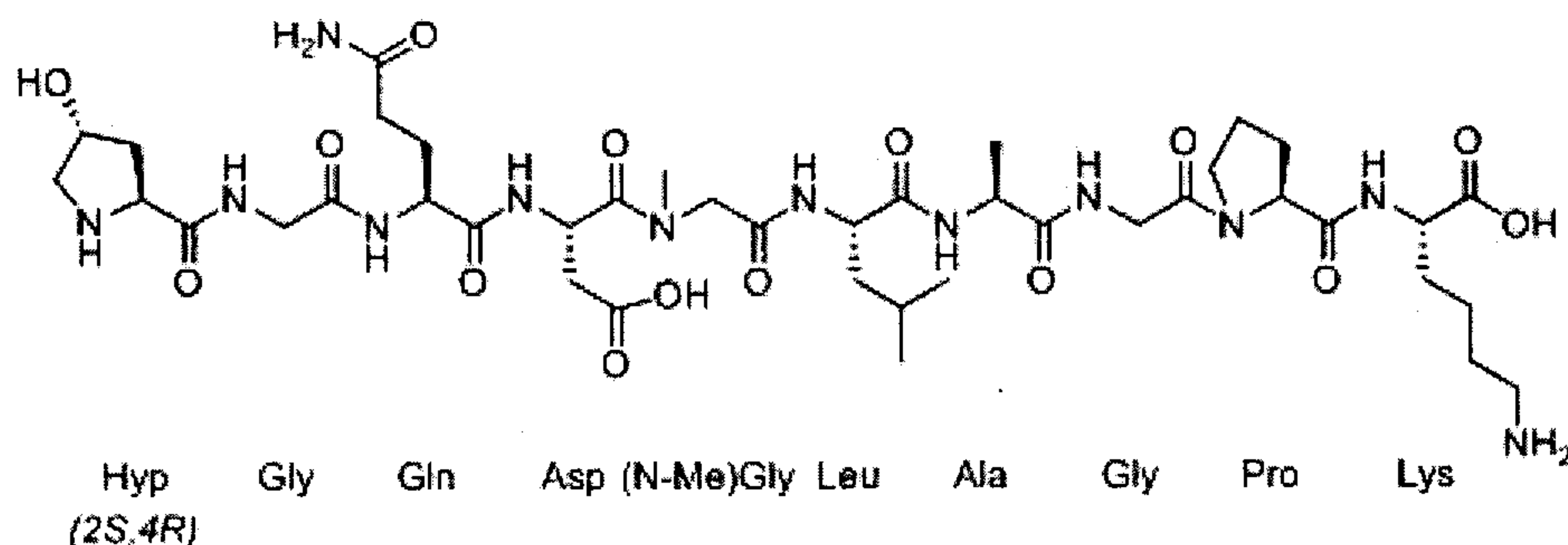
10

[Formula 8]



19. A compound represented by Formula 10:

[Formula 10]



20. A pharmaceutical composition for treating an eye disease, which comprises the compound according to any one of claims 1 to 12, 18, and 19, or the peptide according to any one of claims 13 to 17, as an active pharmaceutical ingredient.

21. The pharmaceutical composition of claim 20, wherein eye disease is one selected from the group consisting of retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, heratoconjunctivitis sicca and keratoconjunctival epithelium disorder.

22. A method for treating an eye disease, which comprises administering the compound according to any one of claims 1 to 12, 18, and 19, or the peptide according to any one of claims 13 to 17, to a subject.

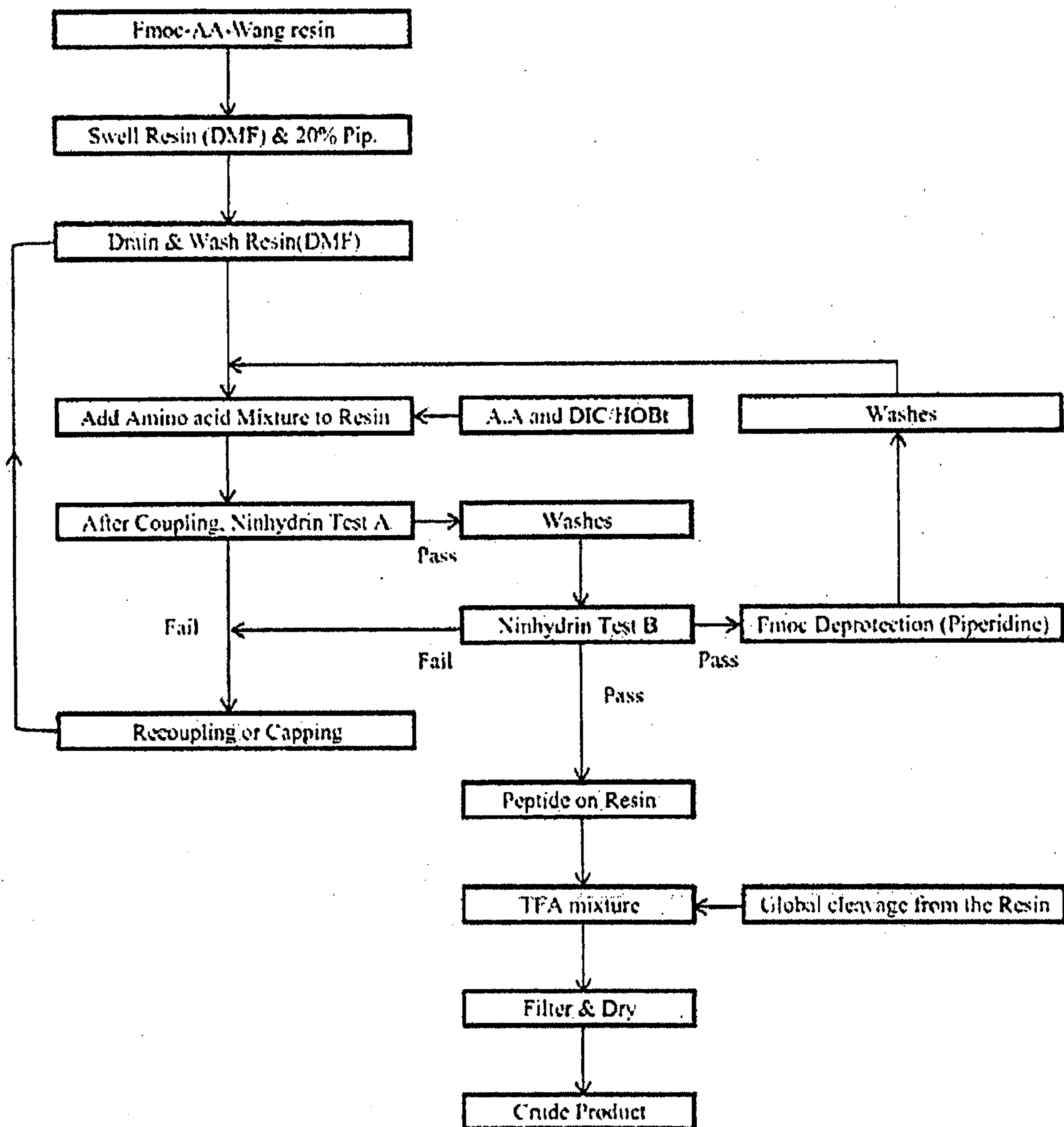
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FIG 1

No.	Lot Number	Peptide Name	Sequence	M.W.	Purity (%)	Amount (mg)	Solubility (0.5mg/ml)
1	K161389	YDE-001	OGQEGLAGPK (O : Hydroxyproline)	969.1	>99.7%	5.0mg 10.0mg	Water
2	K161390	YDE-002	OGQNGLAGPK (O : Hydroxyproline)	954.0	>99.7%	5.0mg 10.0mg	Water
3	K161391	YDE-003	OGQQGLAGPK (O : Hydroxyproline)	968.1	>99.7%	5.0mg 10.0mg	Water
4	K161392	YDE-004	OGQHGLAGPK (O : Hydroxyproline)	977.1	>99.7%	5.0mg 10.0mg	Water
5	K161393	YDE-005	OGQKGLAGPK (O : Hydroxyproline)	968.1	>99.5%	5.0mg 10.0mg	Water
6	K161394	YDE-006	OGQSGLAGPK (O : Hydroxyproline)	927.0	>98.9%	5.0mg 10.0mg	Water
7	K161395	YDE-007	OGQTGLAGPK (O : Hydroxyproline)	941.0	>98.0%	5.0mg 10.0mg	Water
8	K161396	YDE-008	OGQAGLAGPK (O : Hydroxyproline)	911.0	>98.8%	5.0mg 10.0mg	Water
9	K161397	YDE-009	OGQVGLAGPK (O : Hydroxyproline)	939.1	>98.1%	5.0mg 10.0mg	Water
10	K161398	YDE-010	OGQIGLAGPK (O : Hydroxyproline)	953.1	>99.0%	5.0mg 10.0mg	Water
11	K161399	YDE-011	OGQIGLAGPK (O : Hydroxyproline)	953.1	>98.3%	5.0mg 10.0mg	Water
12	K161400	YDE-012	OGQKGLAGPK (O : Hydroxyproline)	987.1	>98.9%	5.0mg 10.0mg	Water
13	K161401	YDE-013	OGQYGLAGPK (O : Hydroxyproline)	1003.1	>98.7%	5.0mg 10.0mg	Water
14	K161402	YDE-014	OGQWGLAGPK (O : Hydroxyproline)	1026.2	>98.5%	5.0mg 10.0mg	Water
15	K161403	YDE-015	OGQDVLGAPK (O : Hydroxyproline)	997.1	>99.1%	5.0mg 10.0mg	Water
16	K161404	YDE-016	OGQDILAGPK (O : Hydroxyproline)	1011.1	>99.4%	5.0mg 10.0mg	Water
17	K161405	YDE-017	OGQDLLAGPK (O : Hydroxyproline)	1011.1	>98.0%	5.0mg 10.0mg	Water
18	K161406	YDE-018	OGQDALAGPK (O : Hydroxyproline)	969.1	>99.6%	5.0mg 10.0mg	Water
19	K161407	YDE-019	OGQDFLAGPK (O : Hydroxyproline)	1045.2	>99.6%	5.0mg 10.0mg	Water
20	K161408	YDE-020	OGQDYLAGPK (O : Hydroxyproline)	1061.2	>99.2%	5.0mg 10.0mg	Water
21	K161409	YDE-021	OGQDWLAGPK (O : Hydroxyproline)	1084.2	>98.1%	5.0mg 10.0mg	Water
22	K161410	YDE-022	OGQOHLAGPK (O : Hydroxyproline)	1035.1	>98.3%	5.0mg 10.0mg	Water
23	K161411	YDE-023	OGQDSLAPK (O : Hydroxyproline)	985.1	>96.1%	5.0mg 10.0mg	Water
24	K161412	YDE-024	OGQDTLAGPK (O : Hydroxyproline)	999.1	>98.9%	5.0mg 10.0mg	Water
25	K161413	YDE-025	OGQD-Sar-LAGPK (Sar : me-Gly) (O : Hydroxyproline)	969.1	>95%	5.0mg 10.0mg	Water
26	K161414	YDE-026	OGQS*GLAGPK (S* : homo-Ser) (O : Hydroxyproline)	941.1	>95%	5.0mg 10.0mg	Water
27	K161415	YDE-027	OGQD*GLAGPK (D* : D(OMe)) (O : Hydroxyproline)	969.1	>95%	5.0mg 10.0mg	Water
28	K161416	YDE-028	OGQN*GLAGPK (N* : N(NMe)) (O : Hydroxyproline)	968.1	>95%	5.0mg 10.0mg	Water

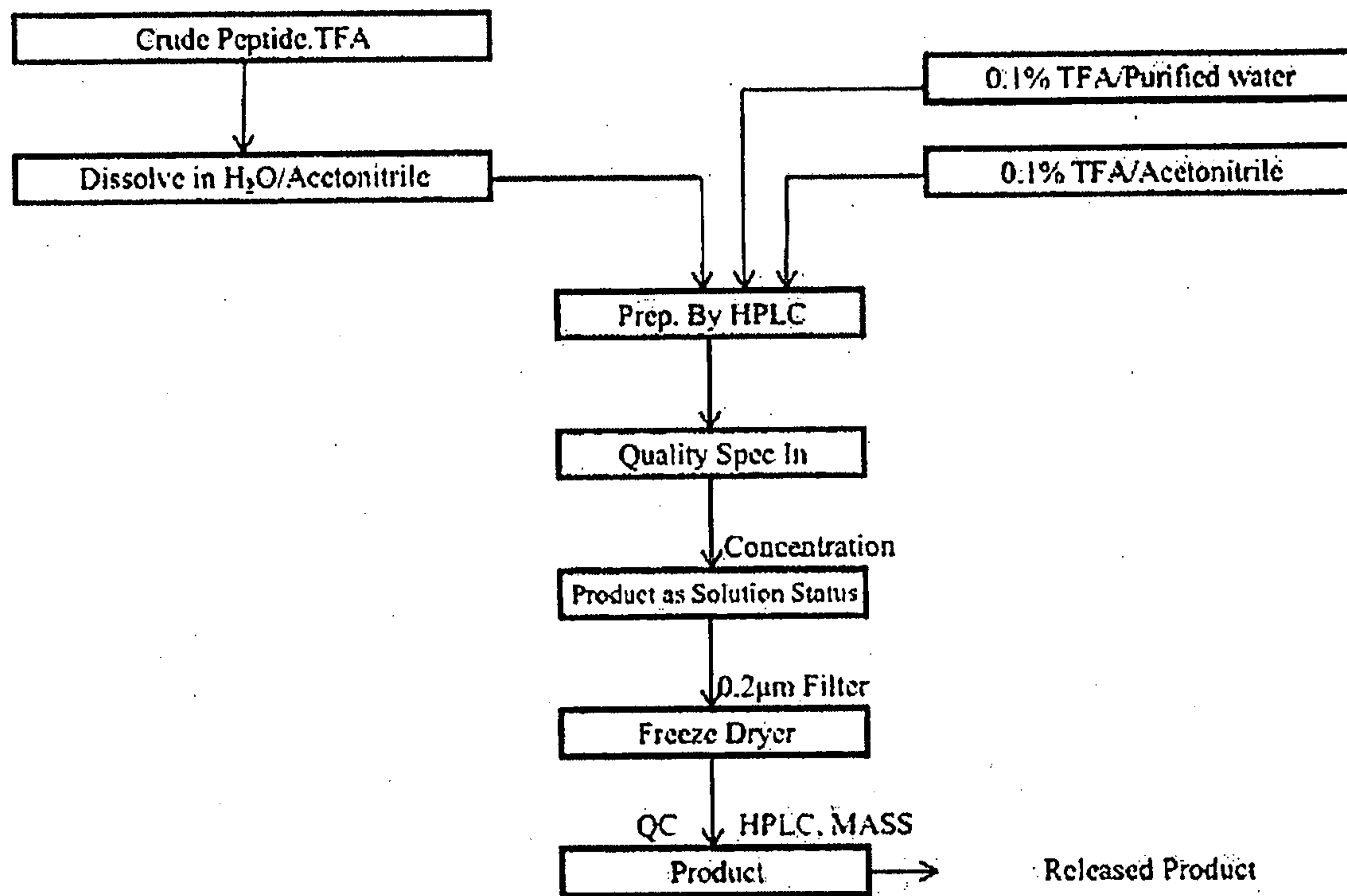
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FIG 2



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FIG 3



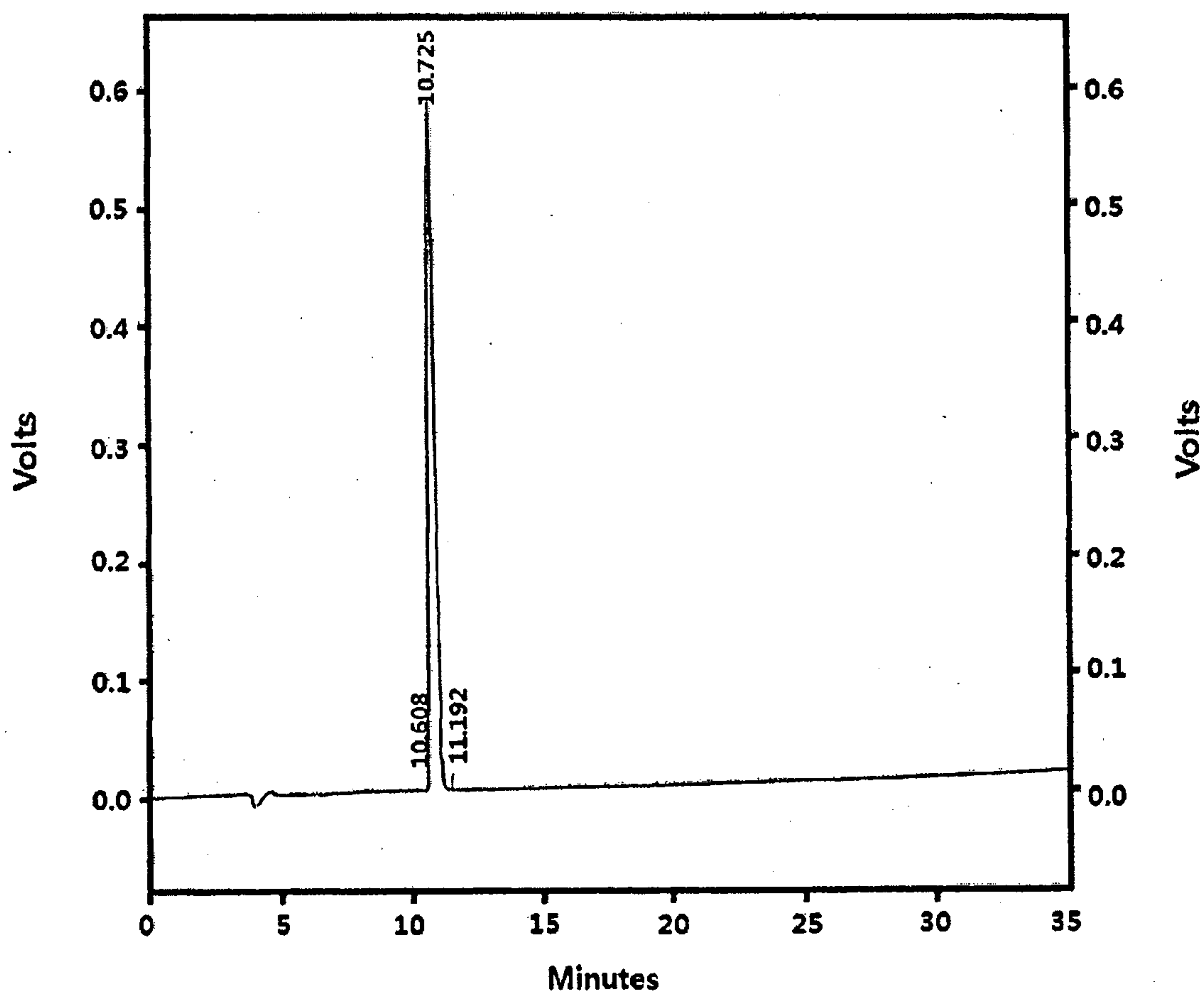
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FIG 4

Shimadzu CLASS-VP V6.14 SP1 manual

Area % Report

Sample ID : K161389 (YDE-001)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	10.608	783	0.008
2	10.725	10120624	99.730
3	11.192	26596	0.262
Totals		10148003	100.000

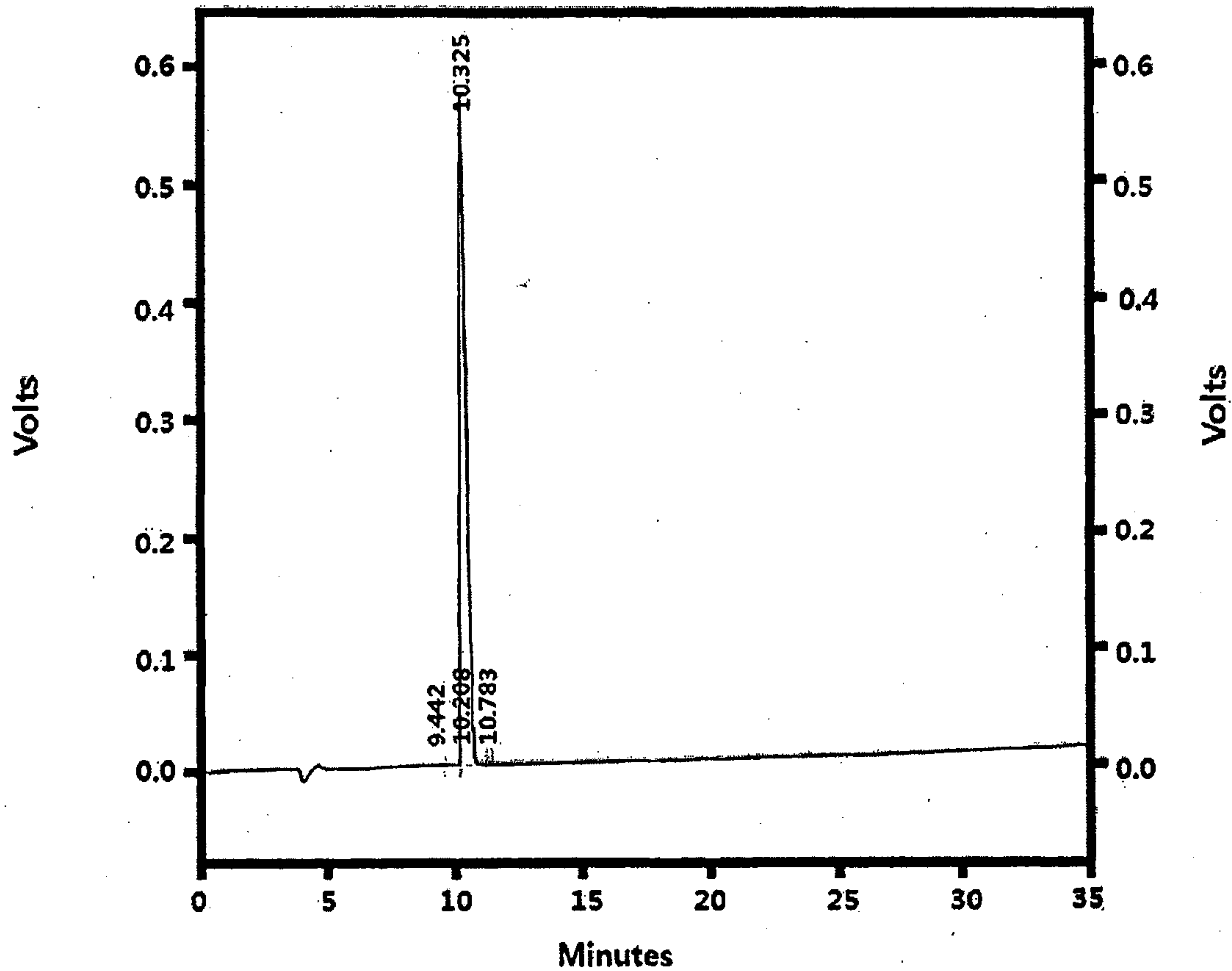
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FIG 5

Shimadzu CLASS-VP V6.14 SP1 manual

Area % Report

Sample ID : K161390 (YDE-002)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	9.442	290	0.003
2	10.208	456	0.005
3	10.325	9921099	99.715
4	10.783	27655	0.278
Totals		9949500	100.000

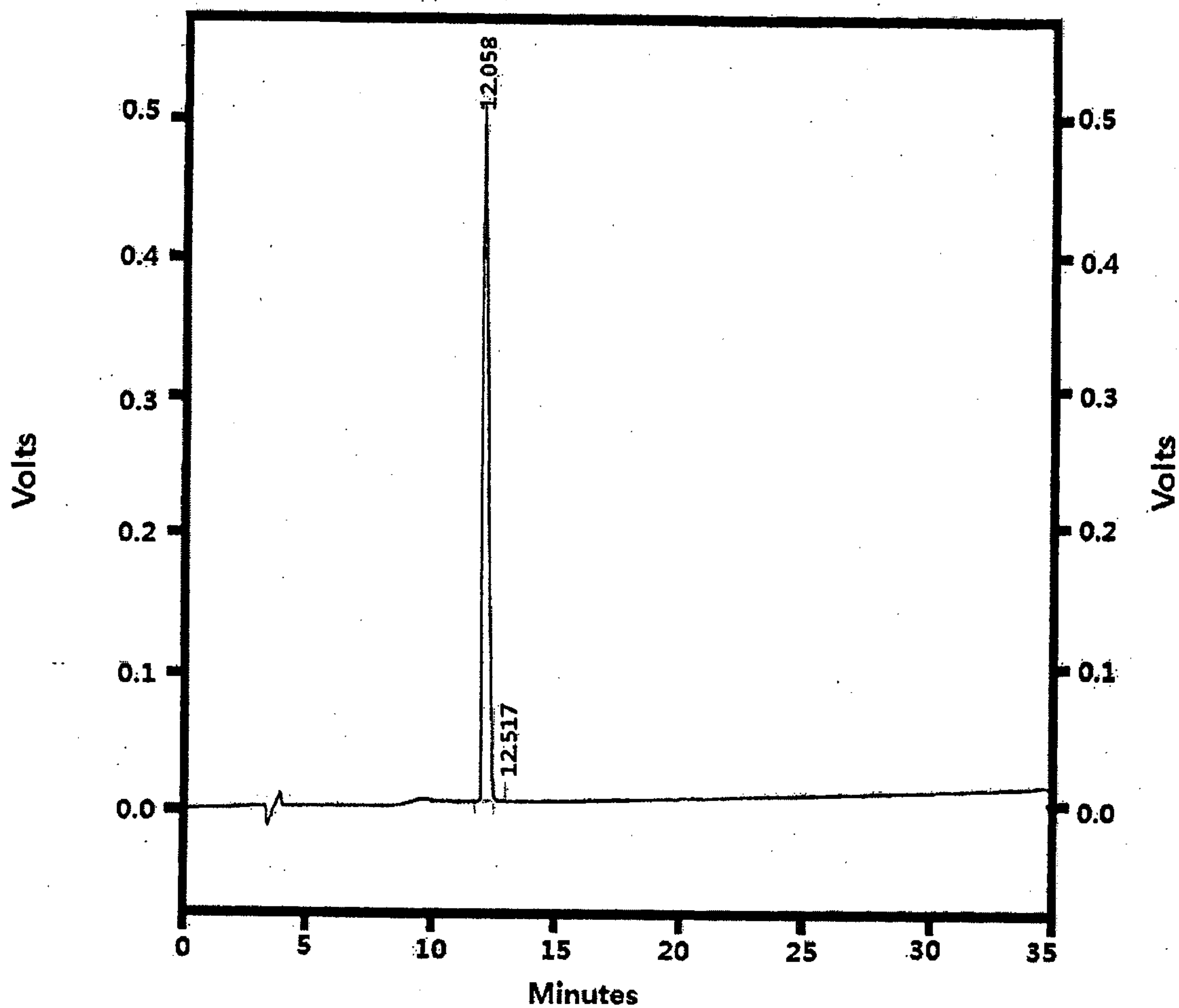
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FIG 6

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161391 (YDE-003)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	12.058	7863599	99.774
2	12.517	17816	0.226
Totals		7881415	100.000

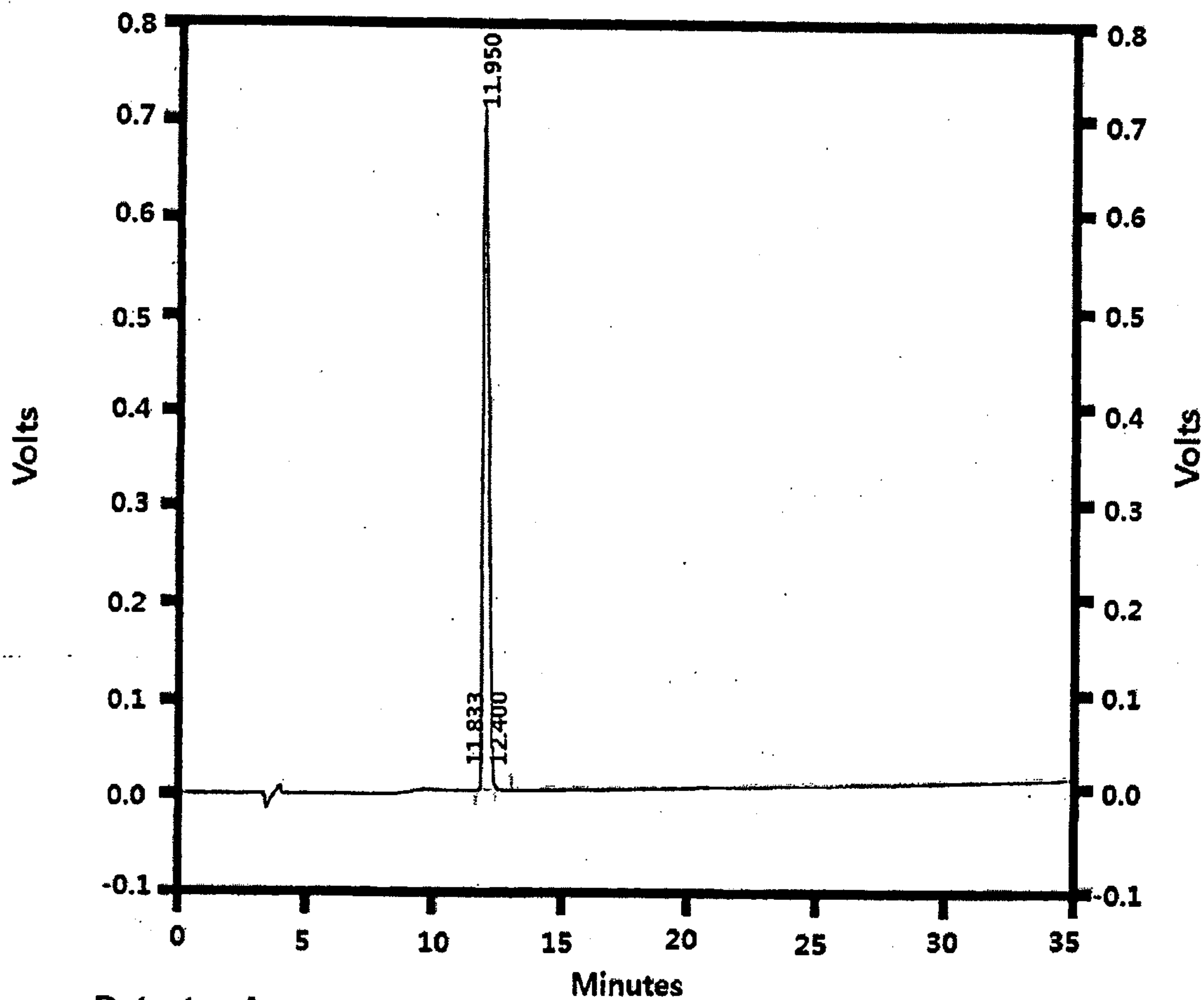
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FIG 7

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161392 (YDE-004)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	11.833	4175	0.038
2	11.950	10864330	99.735
3	12.400	24696	0.227
Totals		10893201	100.000

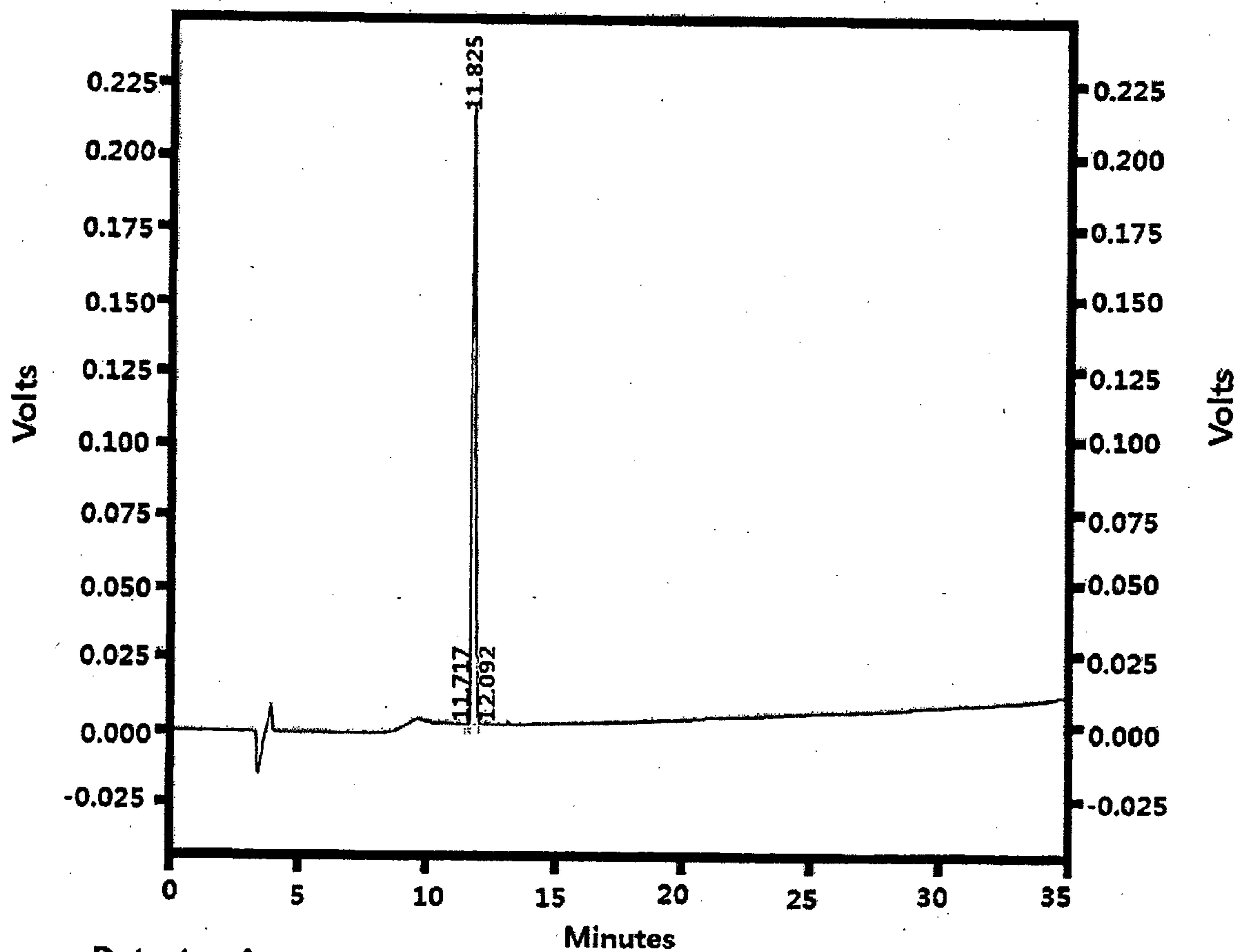
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FIG 8

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161393 (YDE-005)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	11.717	2003	0.102
2	11.825	1950157	99.552
3	12.092	6778	0.346
Totals		1958938	100.000

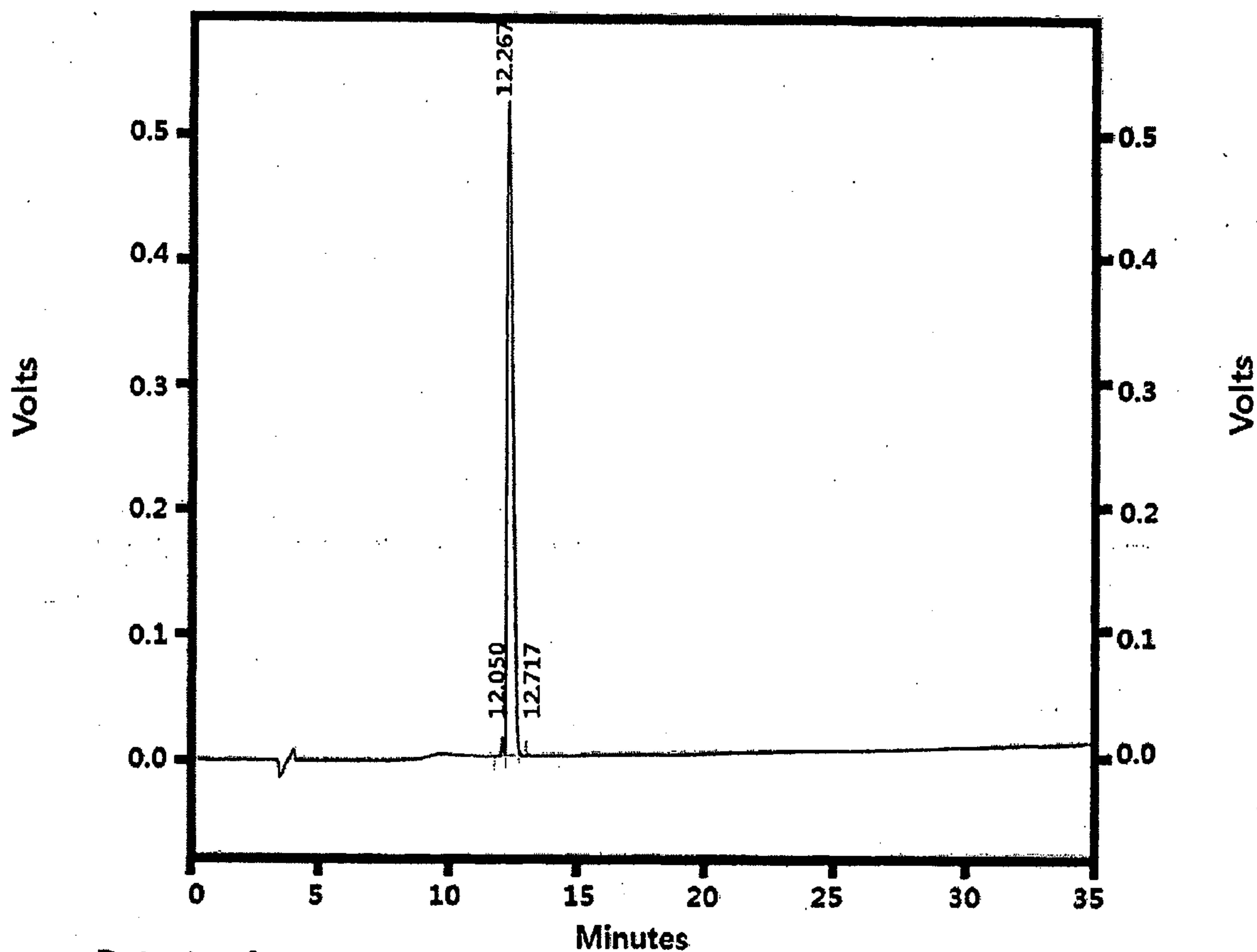
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FIG 9

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161394 (YDE-006)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	12.050	78741	0.961
2	12.267	8100790	98.903
3	12.717	11116	0.136
Totals		8190647	100.000

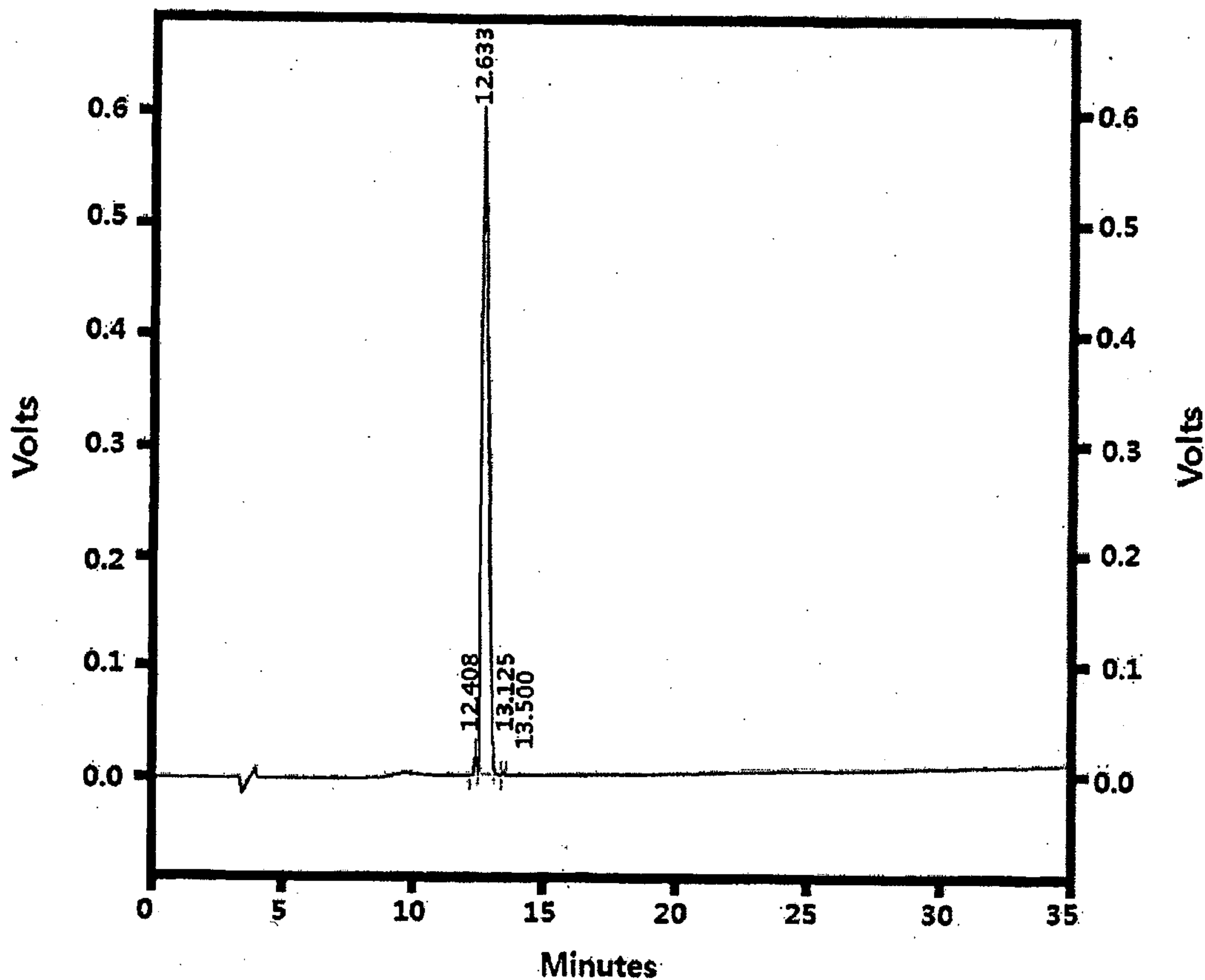
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FIG 10

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161395 (YDE-007)



Detector A

(230nm) Pk #	Retention Time	Area	Area %
1	12.408	171422	1.618
2	12.633	10390868	98.067
3	13.125	18102	0.171
4	13.500	15280	0.144

Totals		10595672	100.000
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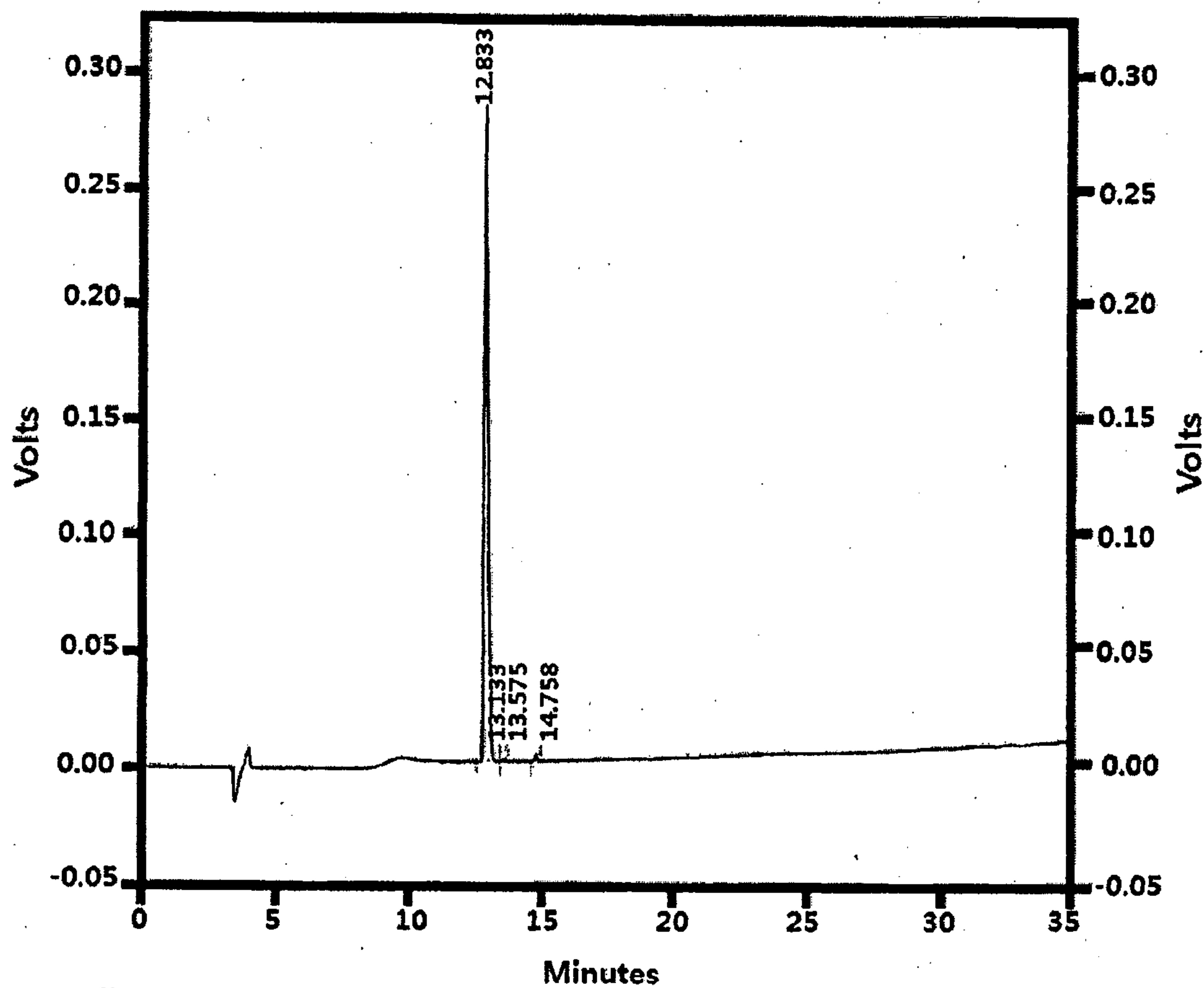
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FIG 11

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161396 (YDE-008)



Detector A

(230nm) Pk #

Retention Time

Area

Area %

1

12.833

2920911

98.891

2

13.133

11156

0.378

3

13.575

6889

0.233

4

14.758

14724

0.498

Totals

2953680

100.000

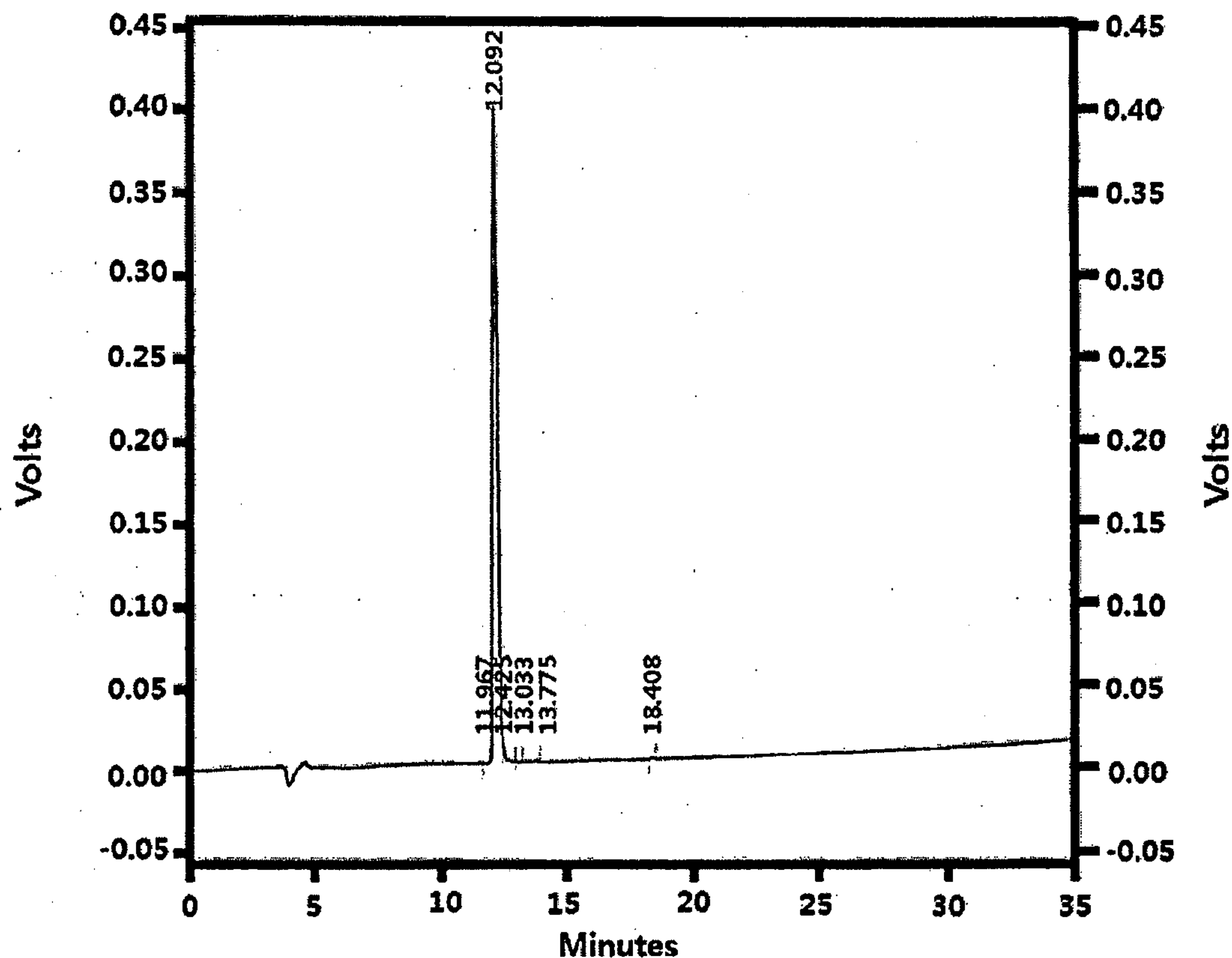
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FIG 12

Shimadzu CLASS-VP V6.14 SP1 manual

Area % Report

Sample ID : K161397 (YDE-009)



Detector A

(230nm) Pk #

Retention Time

Area

Area %

1	11.967	1118	0.020
2	12.092	5394758	98.184
3	12.425	87049	1.584
4	13.033	706	0.013
5	13.775	5416	0.099
6	18.408	5476	0.100
Totals		5494523	100.000

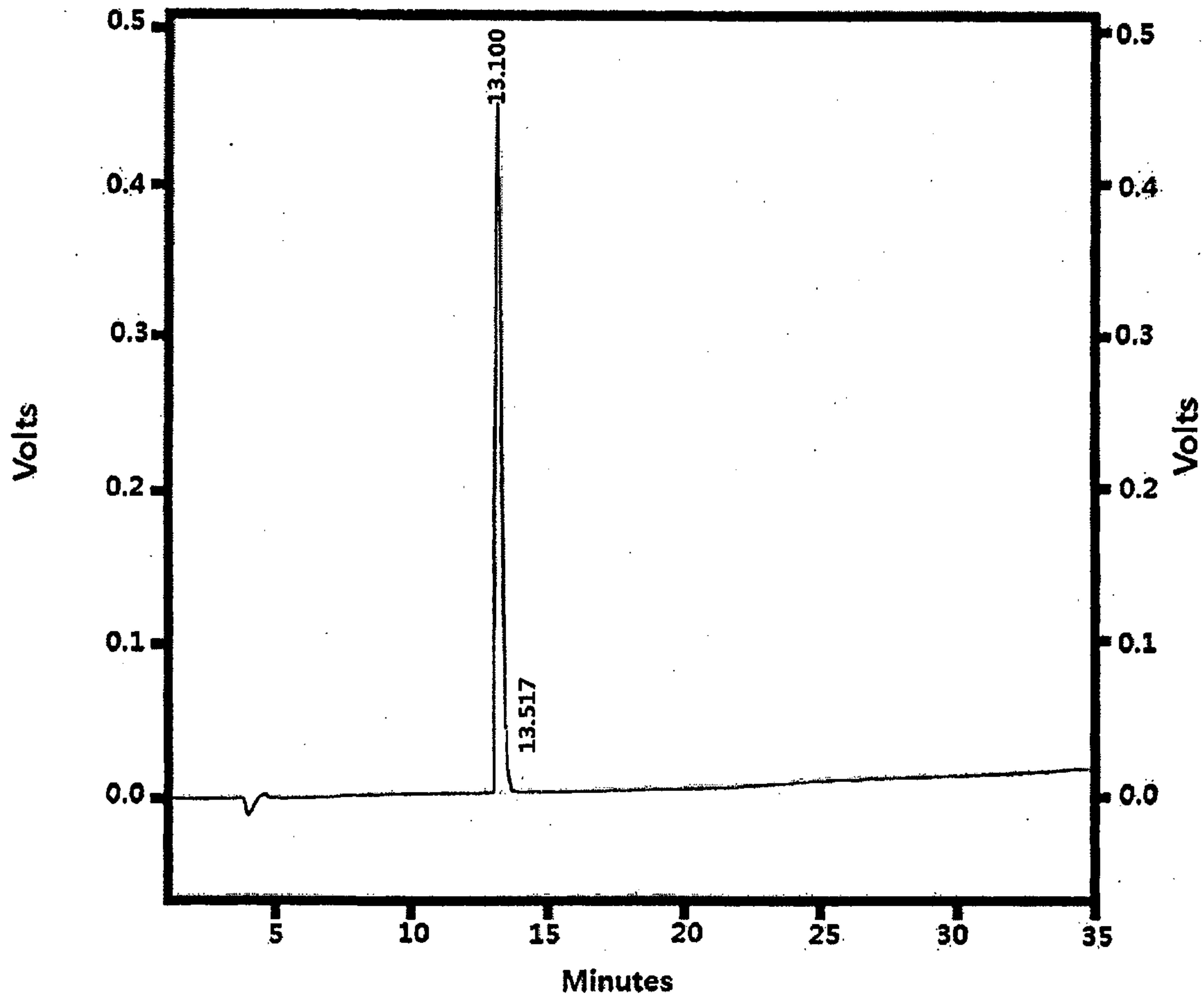
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FIG. 13

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161398 (YDE-010)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	13.100	6966383	99.047
2	13.517	67028	0.953
Totals		7033411	100.000

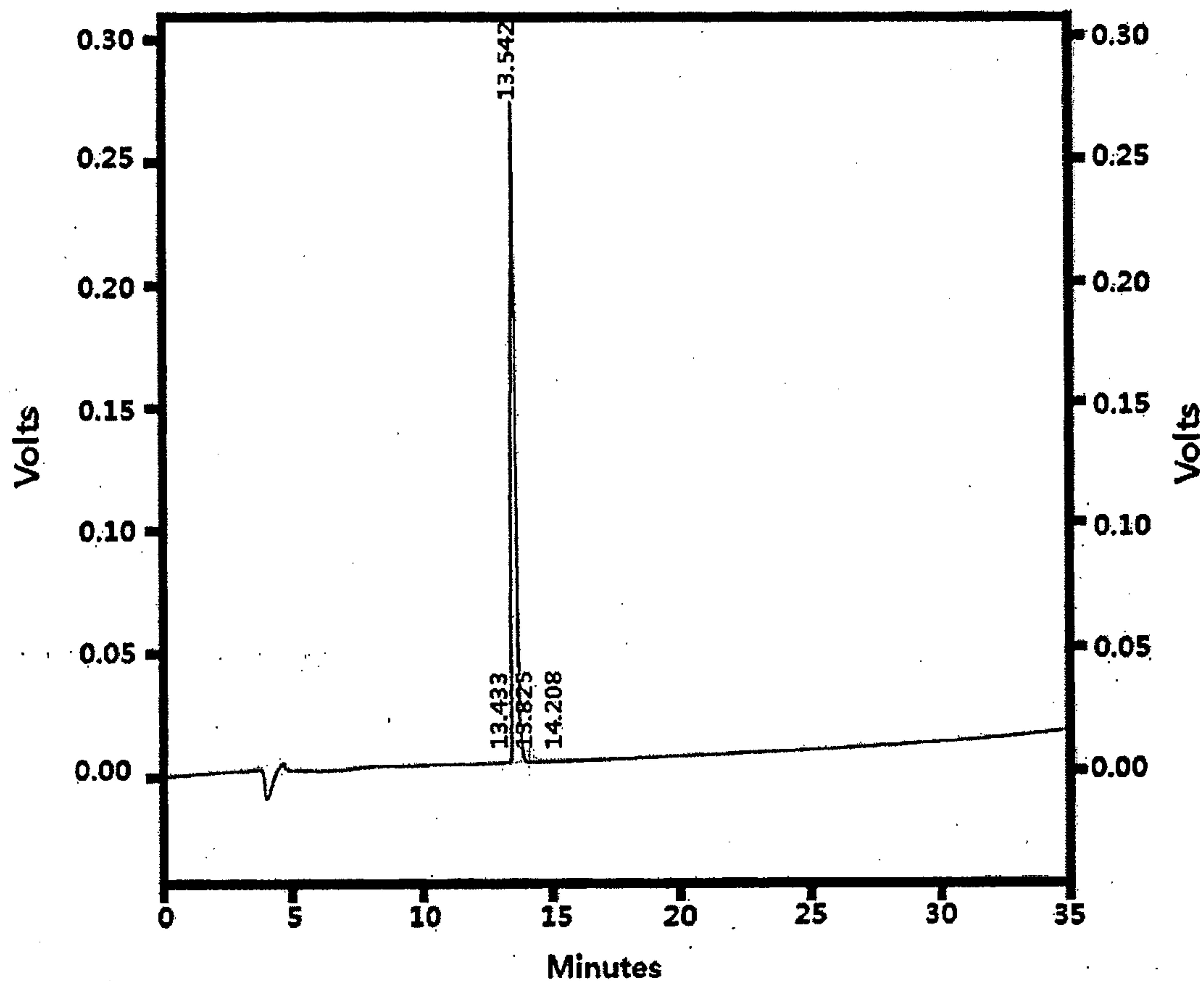
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FIG 14

Shimadzu CLASS-VP V6.14 SP1 manual

Area % Report

Sample ID : K161399 (YDE-011)



Detector A

(230nm) Pk #	Retention Time	Area	Area %
1	13.433	857	0.027
2	13.542	3082773	98.389
3	13.825	48609	1.551
4	14.208	1010	0.032

Totals		3133249	100.000
--------	--	---------	---------

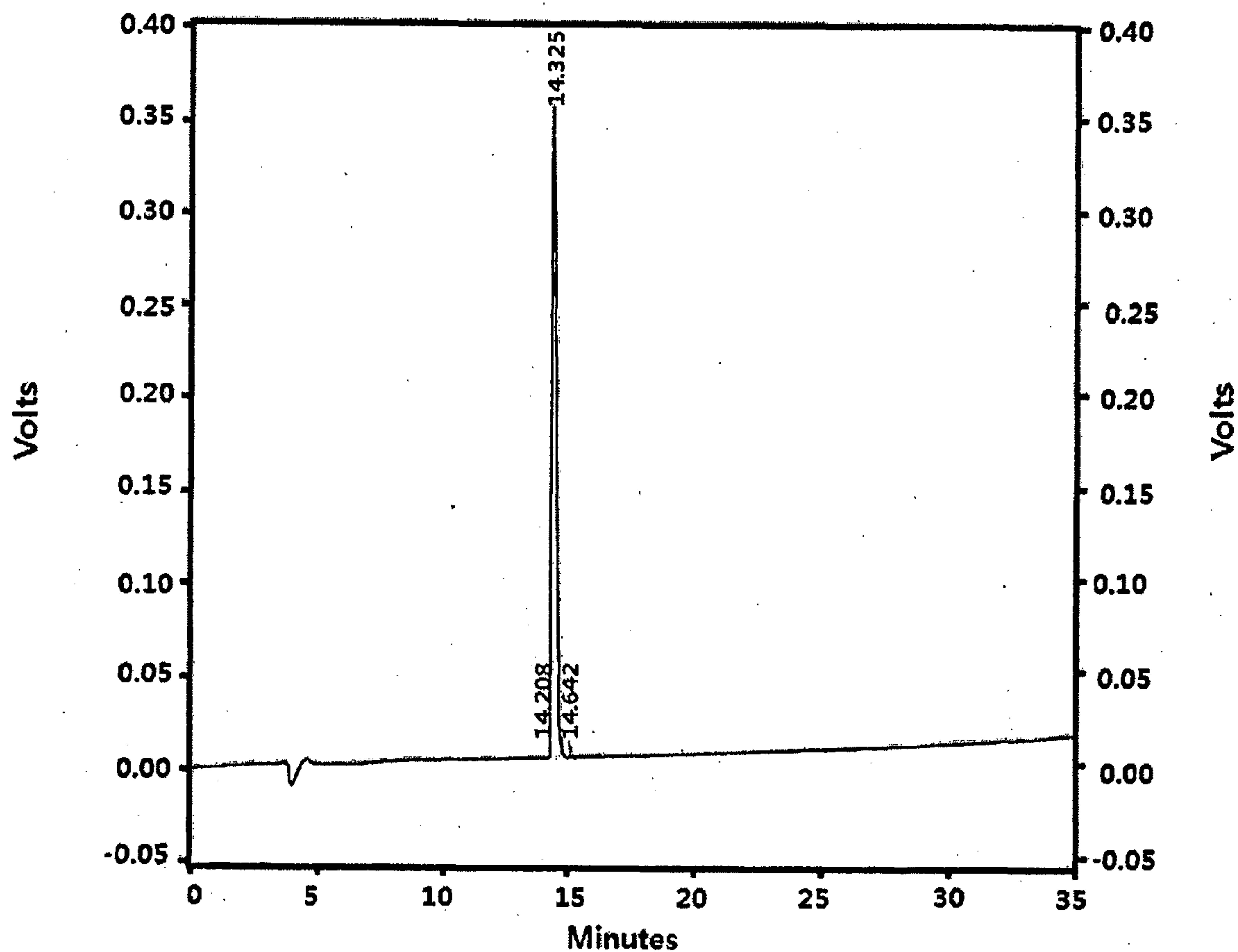
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FIG 15

Shimadzu CLASS-VP V6.14 SP1 manual

Area % Report

Sample ID : K161400 (YDE-012)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	14.208	534	0.012
2	14.325	4465205	98.962
3	14.642	46297	1.026
Totals		4512036	100.000

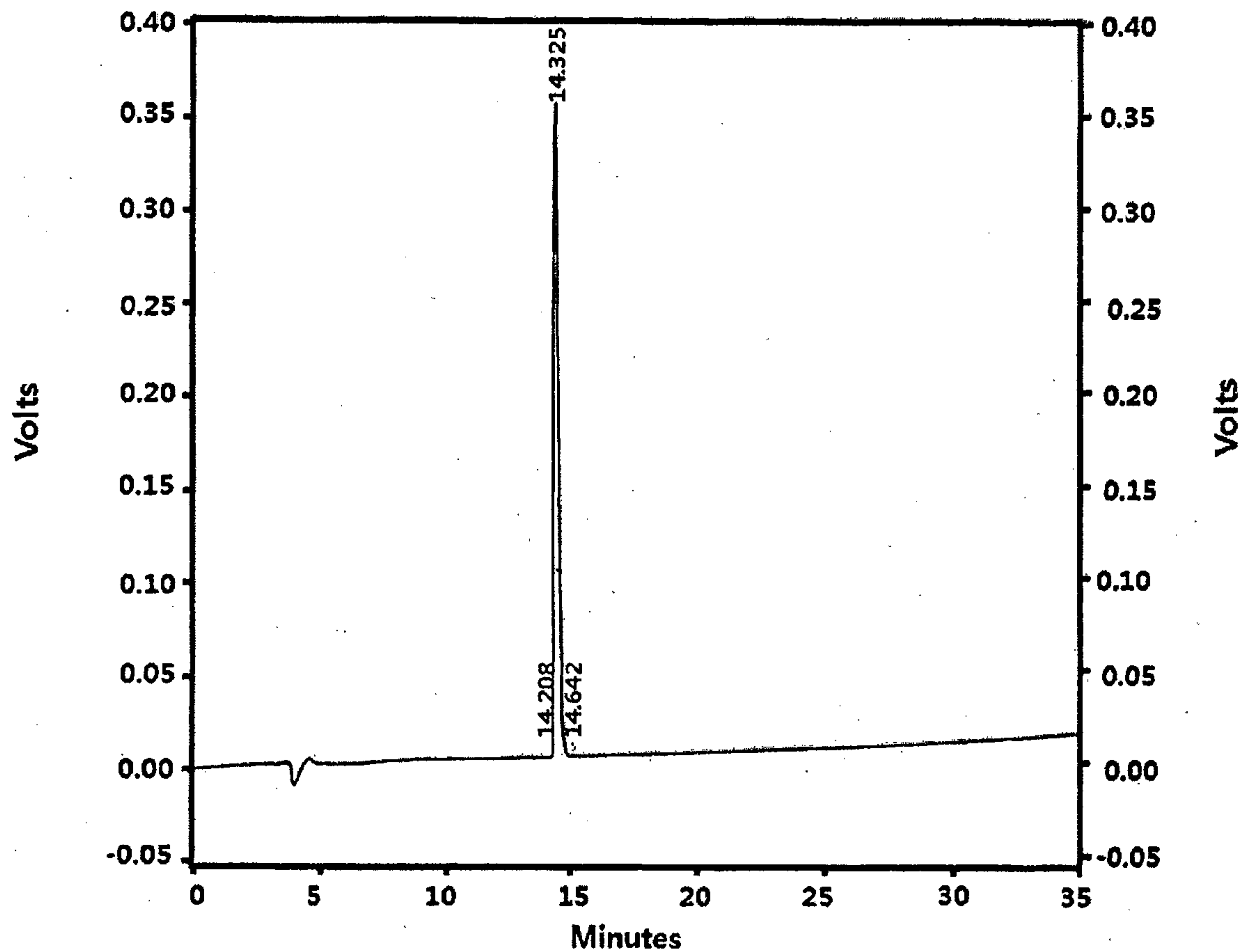
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FIG 16

Shimadzu CLASS-VP V6.14 SP1 manual

Area % Report

Sample ID : K161400 (YDE-012)



Detector A

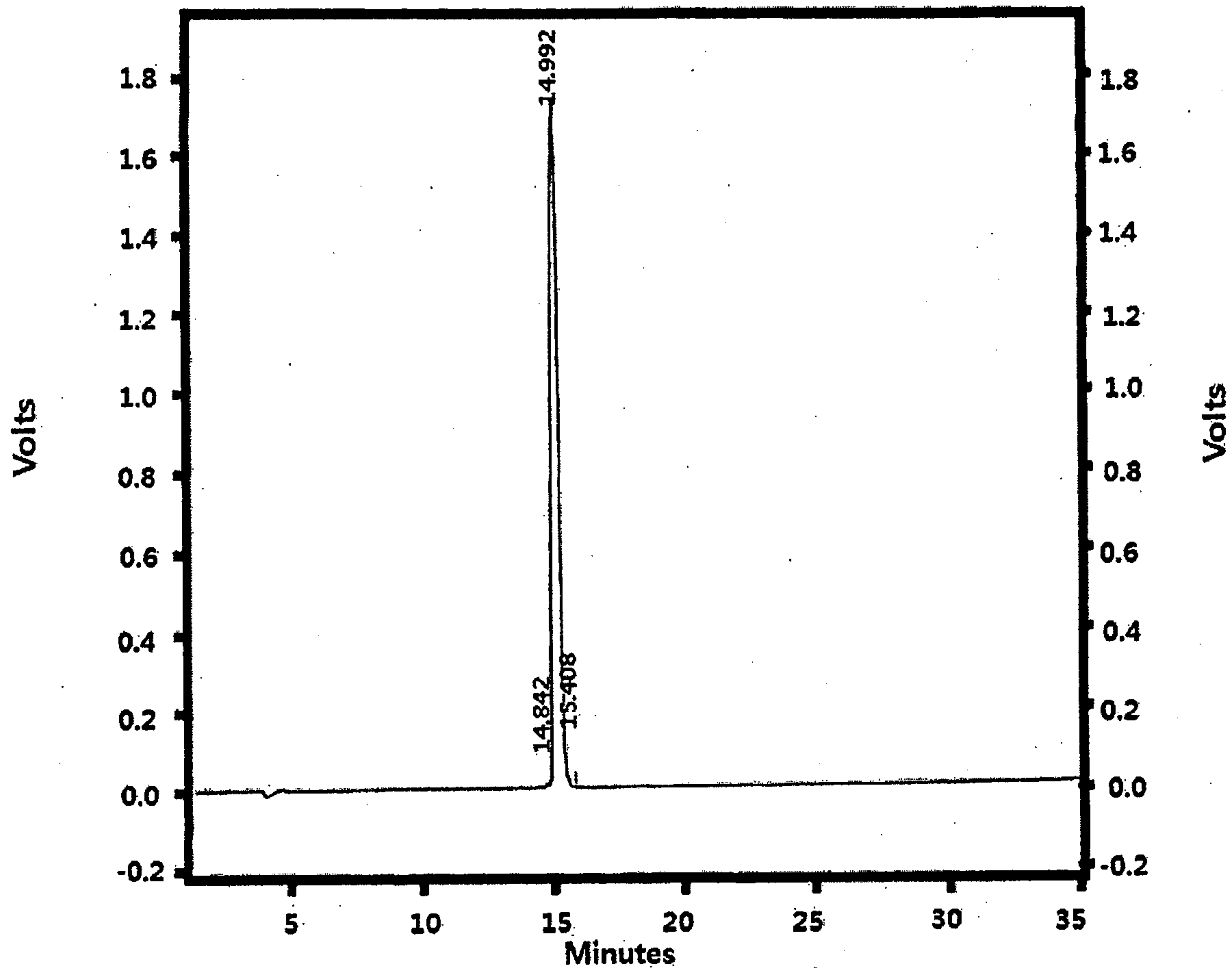
(230nm)

Pk #	Retention Time	Area	Area %
1	14.208	534	0.012
2	14.325	4465205	98.962
3	14.642	46297	1.026
Totals		4512036	100.000

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FIG 17

Sample ID : K161402 (YDE-014)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	14.842	78055	0.241
2	14.992	31942847	98.537
3	15.408	396165	1.222
Totals		32417067	100.000

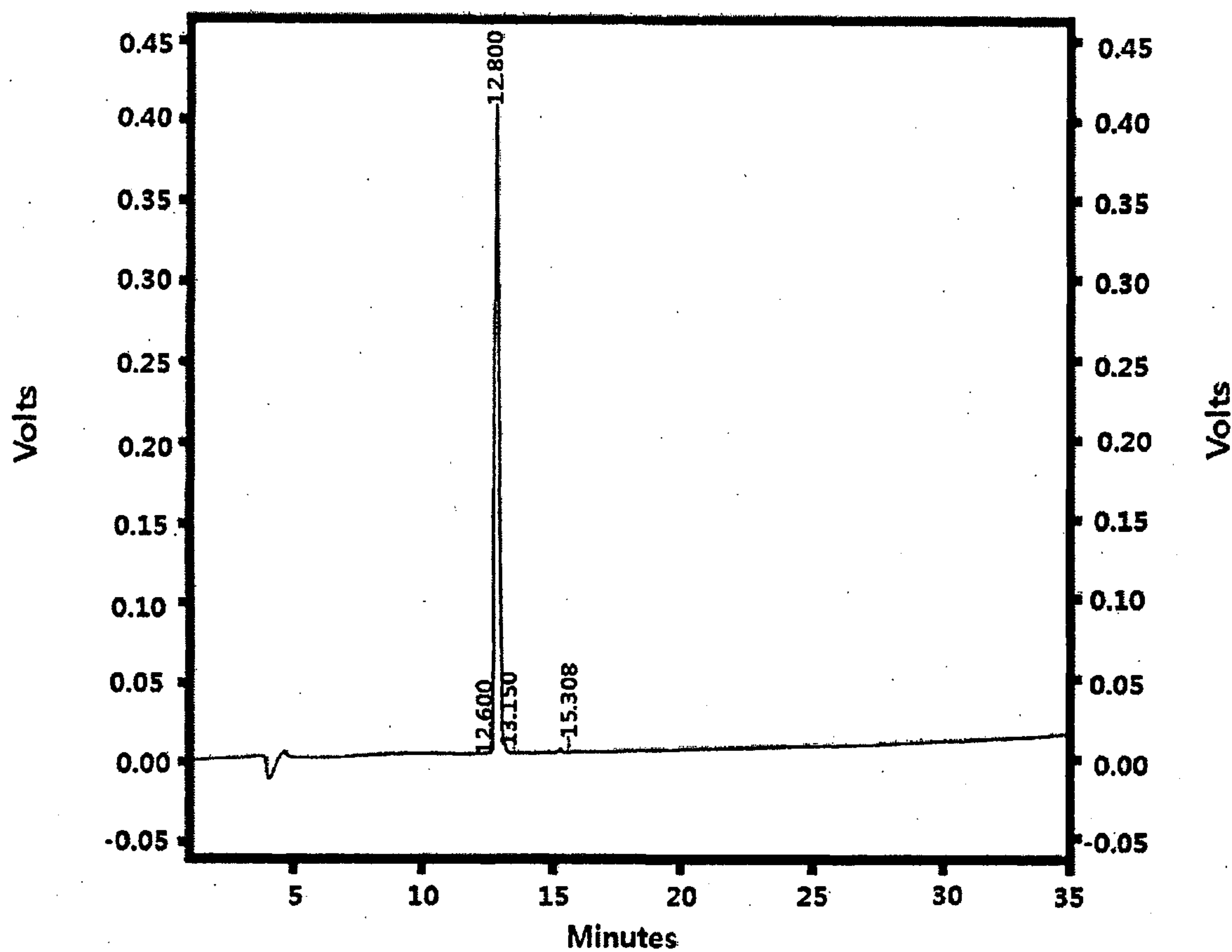
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FIG 18

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161403 (YDE-015)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	12.600	3628	0.074
2	12.800	4859852	99.167
3	13.150	23016	0.470
4	15.308	14170	0.289
Totals		4900666	100.000

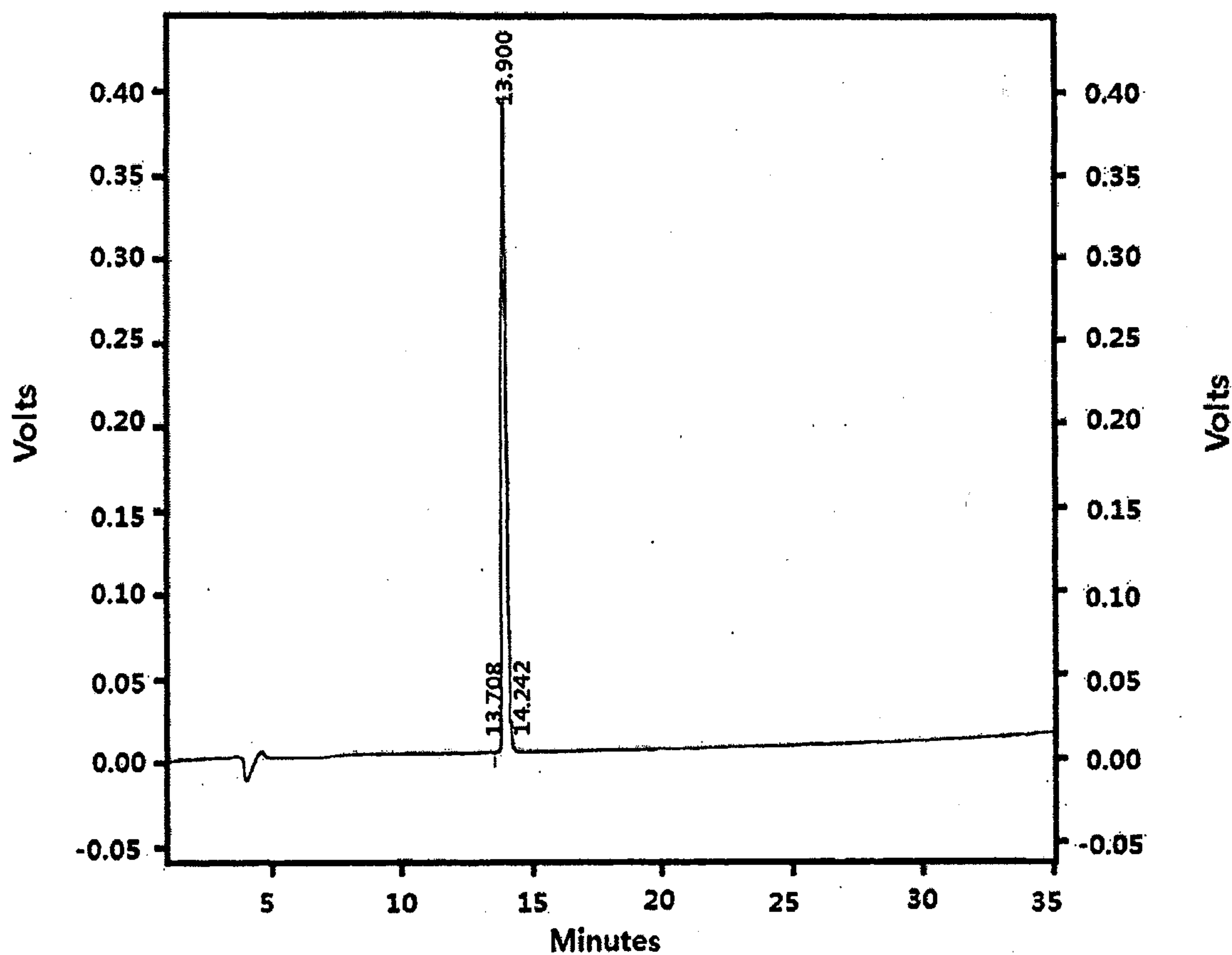
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FIG. 19

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161404 (YDE-016)



Detector A				
(230nm)				
	Pk #	Retention Time	Area	Area %
	1	13.708	6002	0.126
	2	13.900	4752700	99.407
	3	14.242	22362	0.468
Totals			4781064	100.000

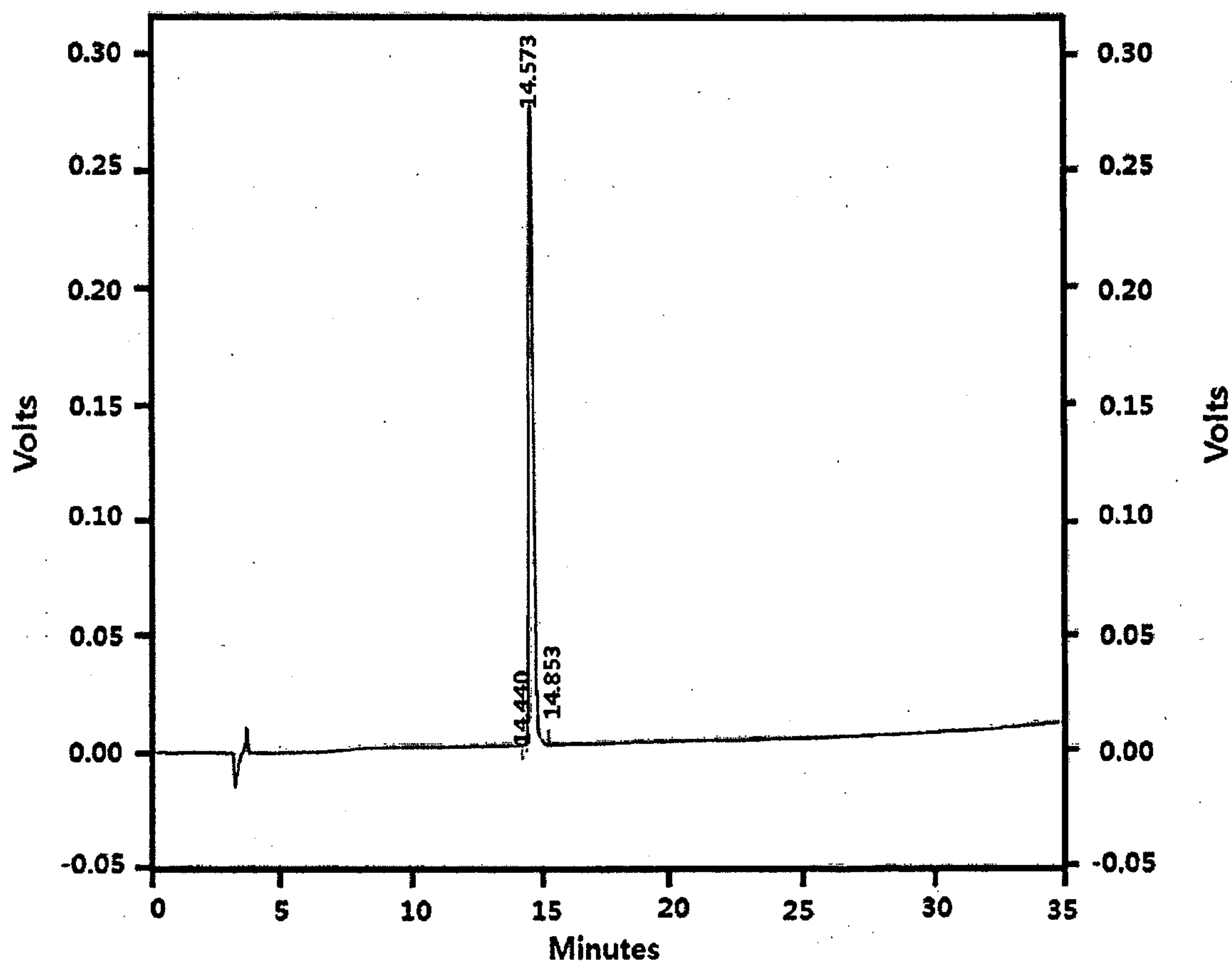
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FIG 20

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161405 (YDE-017)



Detector A				
(230nm)	Pk #	Retention Time	Area	Area %
	1	14.440	5413	0.163
	2	14.573	3259531	98.058
	3	14.853	59145	1.779
Totals			3324089	100.000

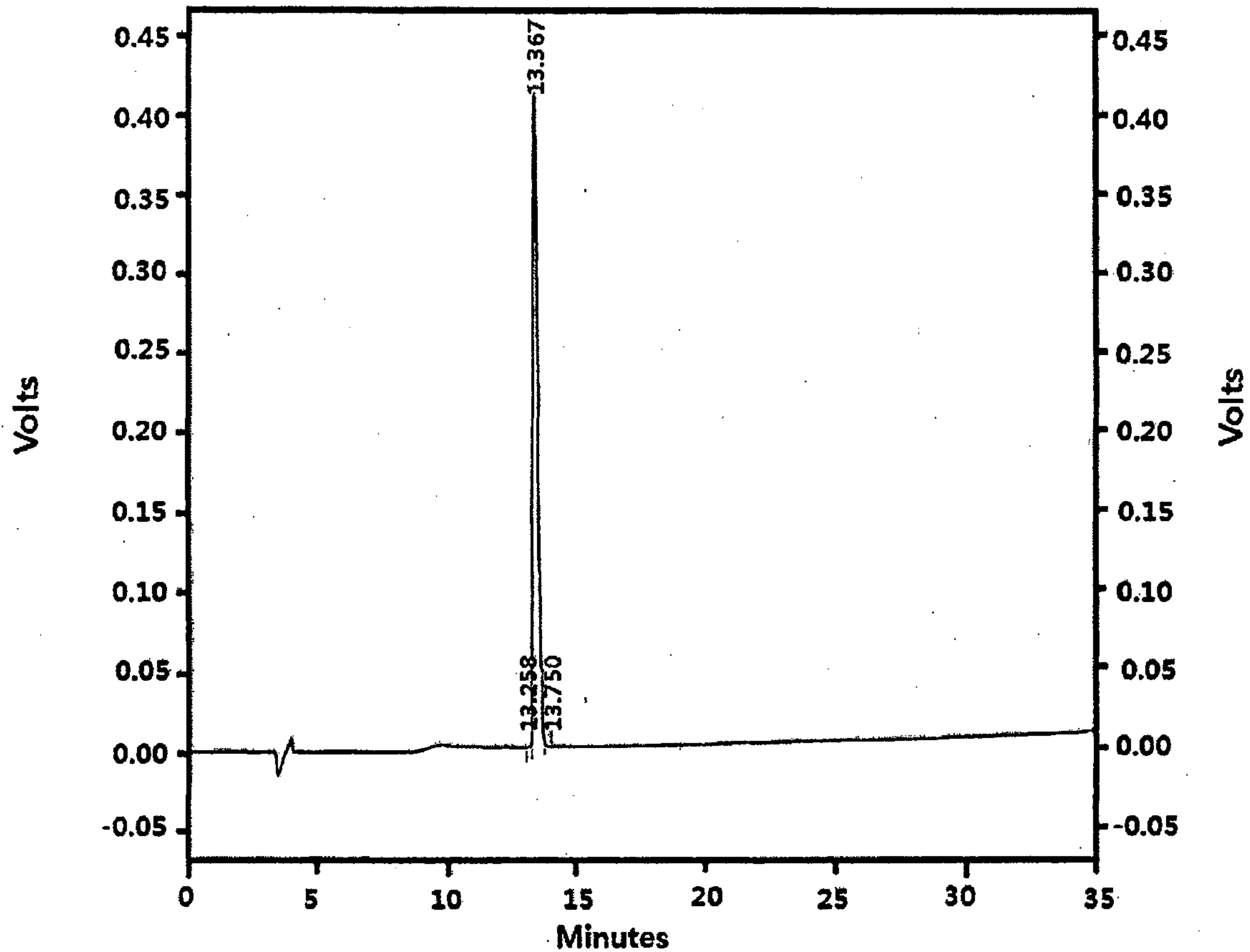
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FIG. 21

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161406 (YDE-018)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	13.258	4690	0.089
2	13.367	5263105	99.679
3	13.750	12277	0.233
Totals		5280072	100.000

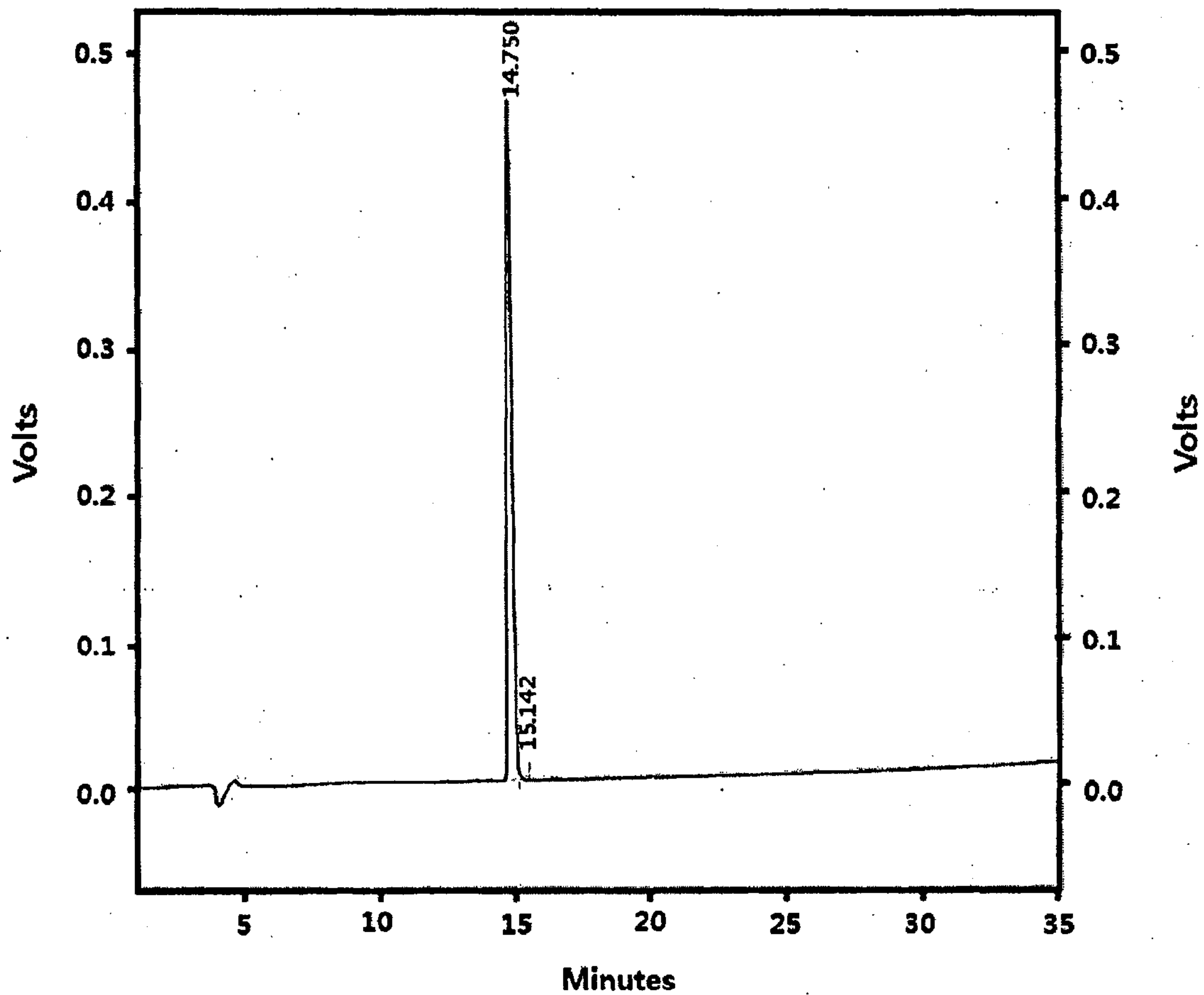
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FIG 22

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161407 (YDE-019)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	14.750	6335299	99.670
2	15.142	20958	0.330
Totals		6356257	100.000

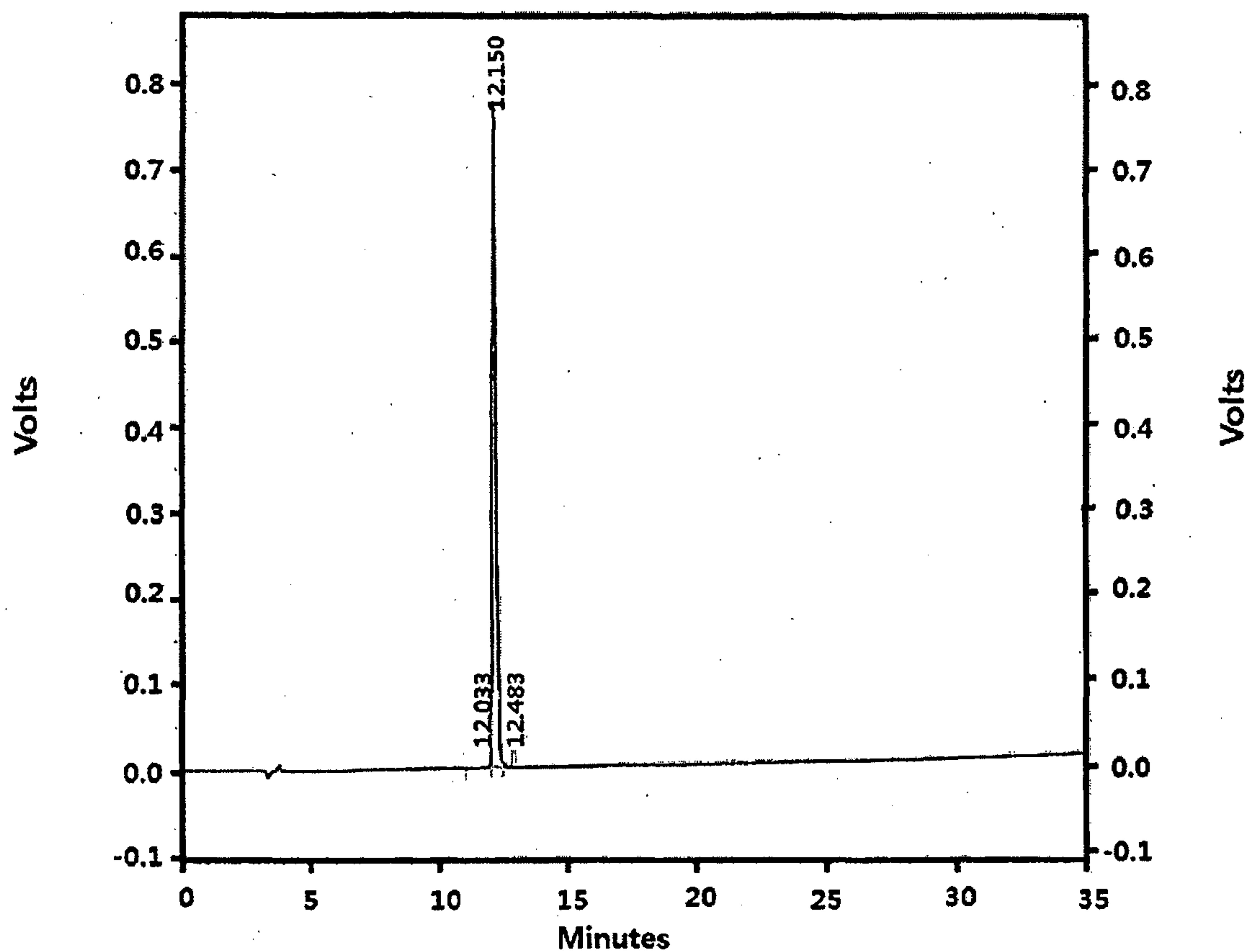
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FIG 23

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161408 (YDE-020)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	12.033	23465	0.300
2	12.150	7757581	99.214
3	12.483	38002	0.486
Totals		7819048	100.000

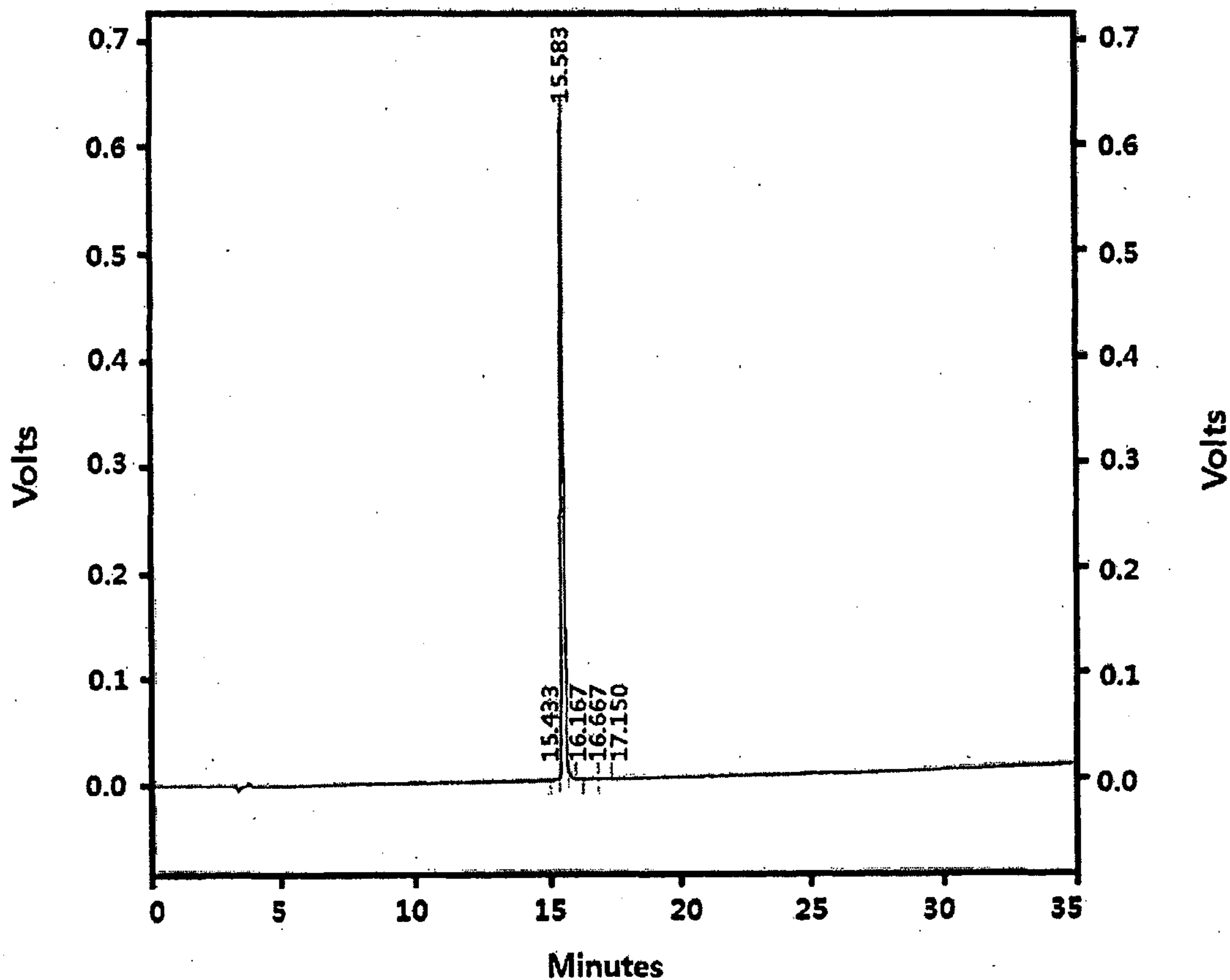
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FIG 24

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161409 (YDE-021)



Detector A

(230nm) Pk #	Retention Time	Area	Area %
1	15.433	12207	0.250
2	15.583	4793036	98.162
3	16.167	61475	1.259
4	16.667	8052	0.165
5	17.150	8010	0.164
Totals		4882780	100.000

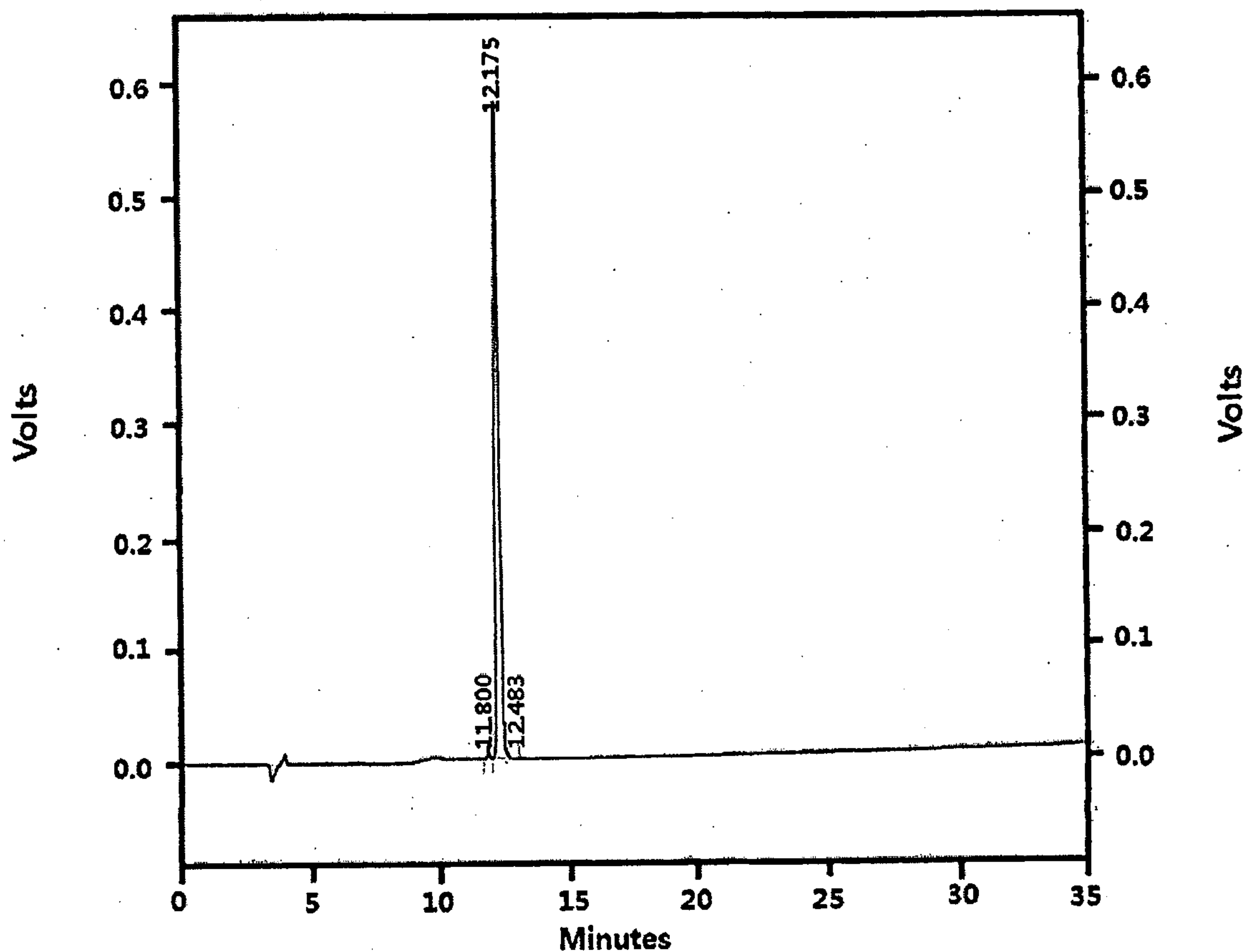
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FIG 25

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K161410 (YDE-022)



Detector A				
(230nm)				
Pk #	Retention Time	Area	Area %	
1	11.800	67819	1.041	
2	12.175	6405639	98.306	
3	12.483	42551	0.653	
Totals		6516009	100.000	

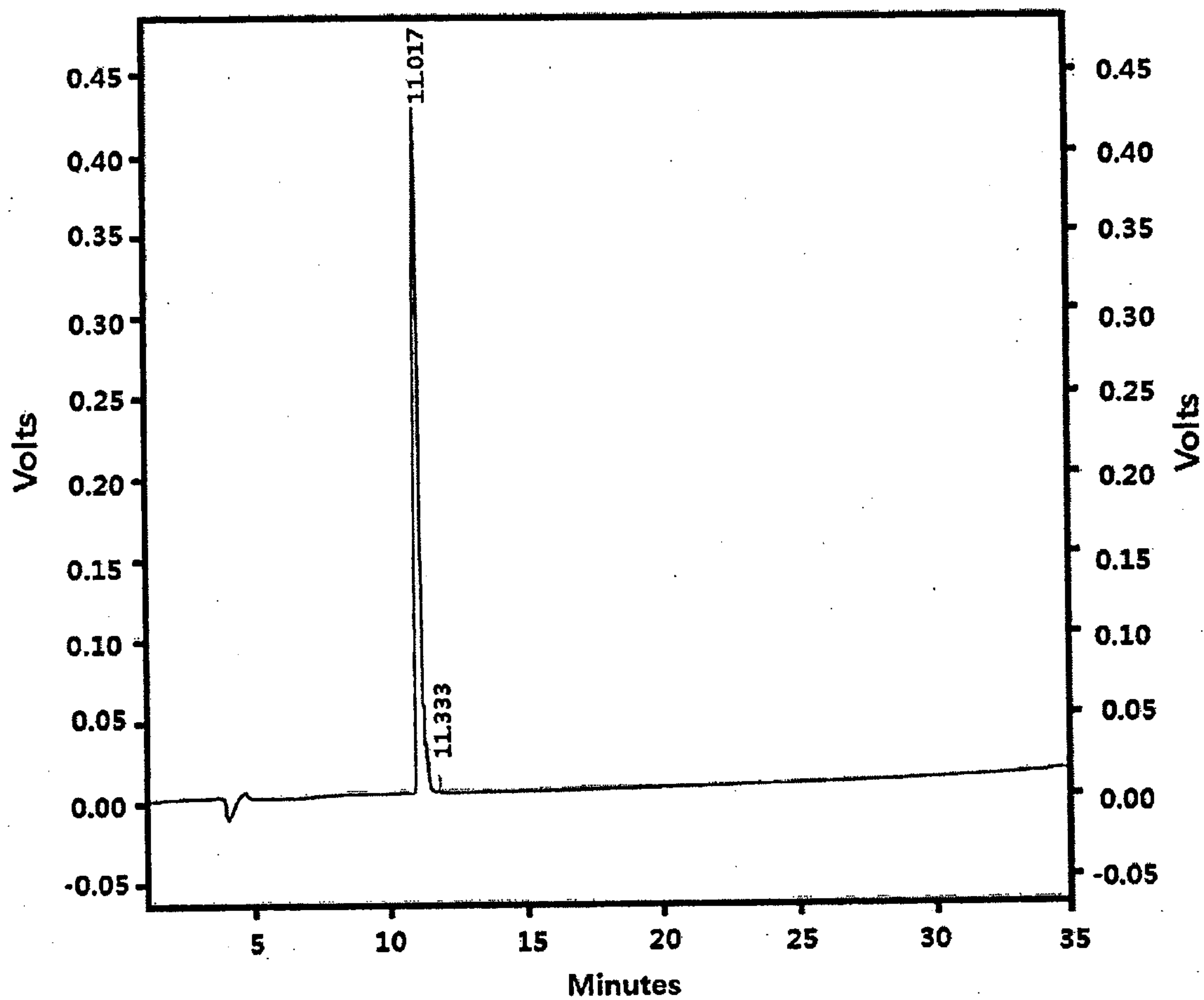
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FIG. 26

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161411 (YDE-023)



Detector A (230nm)		Pk #	Retention Time	Area	Area %
		1	11.017	5051126	96.145
		2	11.333	202520	3.855
Totals				5253646	100.000

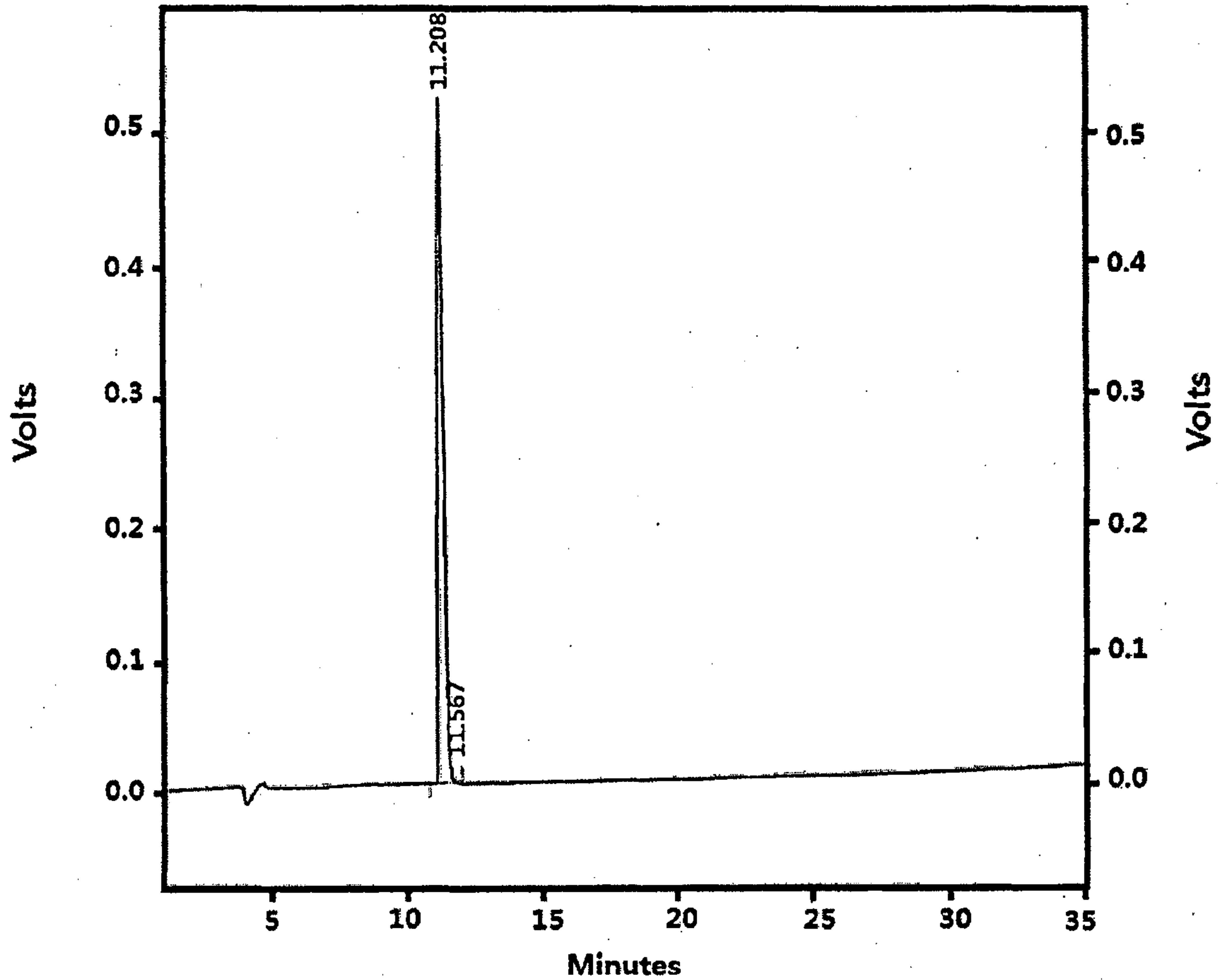
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FIG 27

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161412 (YDE-024)



Detector A				
(230nm)				
Pk #	Retention Time	Area	Area %	
1	11.208	7214585	98.998	
2	11.567	73036	1.002	
Totals		7287621	100.000	

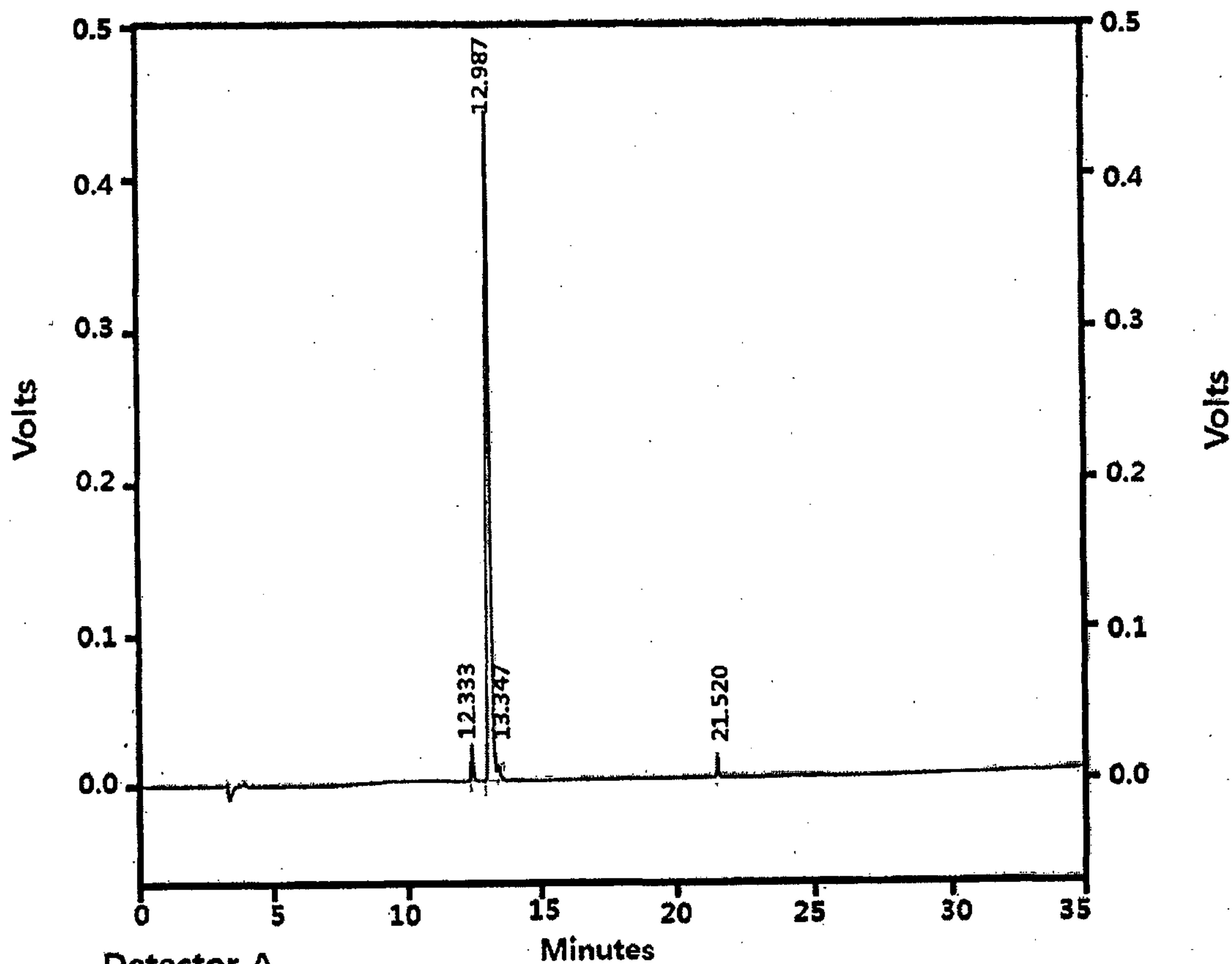
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FIG 28

Shimadzu CLASS-VP V6.14 SPI 20A_prep

Area % Report

Sample ID : K161413 (YDE-025)



Detector A

(230nm) Pk #

Retention Time

Area

Area %

1	12.333	89208	2.157
2	12.987	3936279	95.167
3	13.347	61019	1.475
4	21.520	49664	1.201

Totals

4136170

100.000

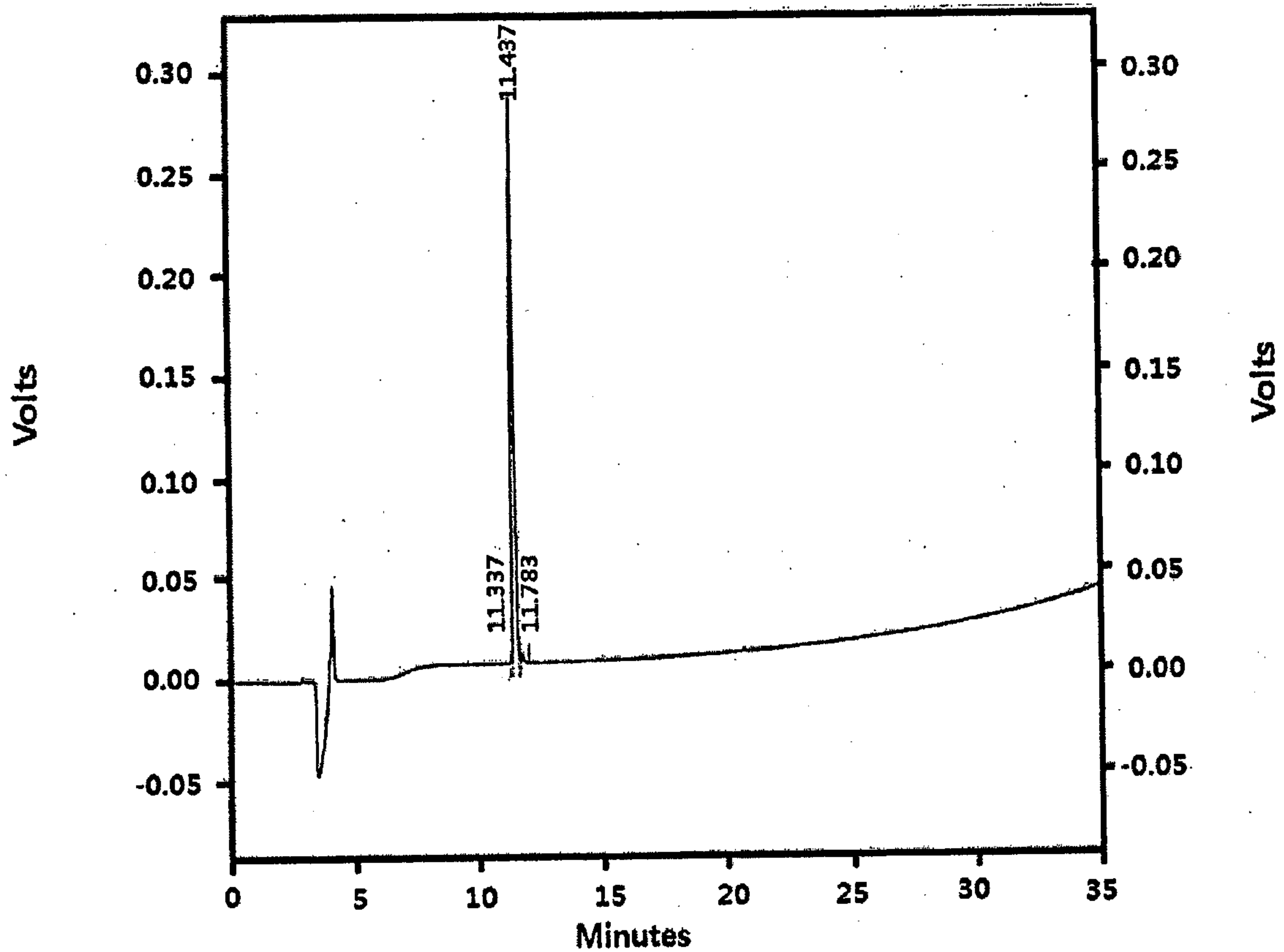
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FIG 29

Shimadzu CLASS-VP V6.14 SP1 new 10AVP

Area % Report Page of 1

Sample ID : K161414 (YDE-026)



Detector A

(230nm)	Pk #	Retention Time	Area	Area %
	1	11.337	1455	0.068
	2	11.437	2109578	98.675
	3	11.783	26862	1.256
Totals			2137895	100.000

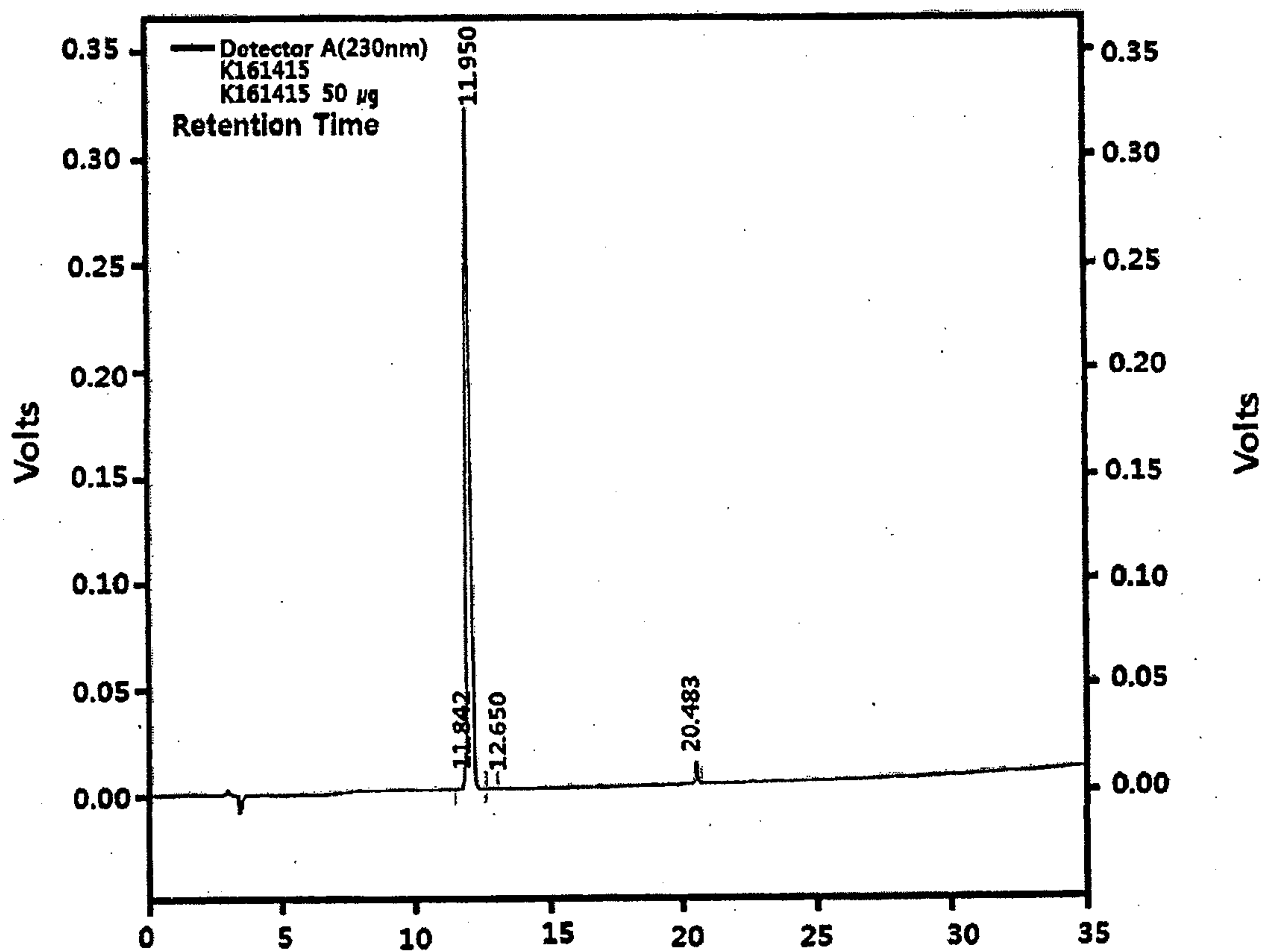
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FIG 30

Shimadzu CLASS-VP V6.14 SP1 Manual(AUTO Sampler)

Area % Report

Sample ID : K161415 (YDE-027)



Detector A		Minutes	
(230nm) Pk #	Retention Time	Area	Area %
1	11.842	41052	1.200
2	11.950	3316998	96.933
3	12.650	4962	0.145
4	20.483	58920	1.722
Totals		3421932	100.000

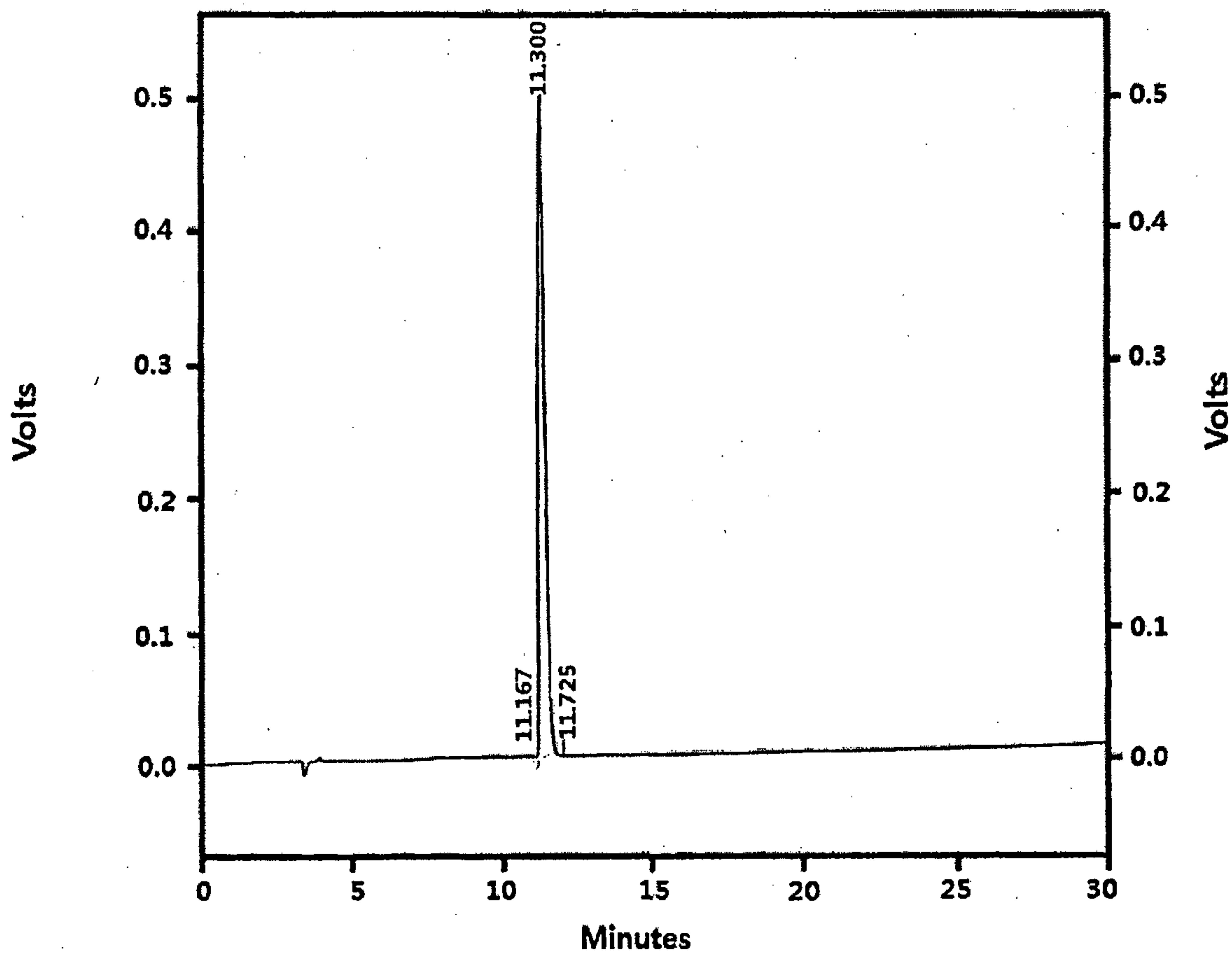
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FIG 31

Shimadzu CLASS-VP V6.14 SP1 MANUAL

Area % Report

Sample ID : K161416 (YDE-028)



Detector A

(230nm)

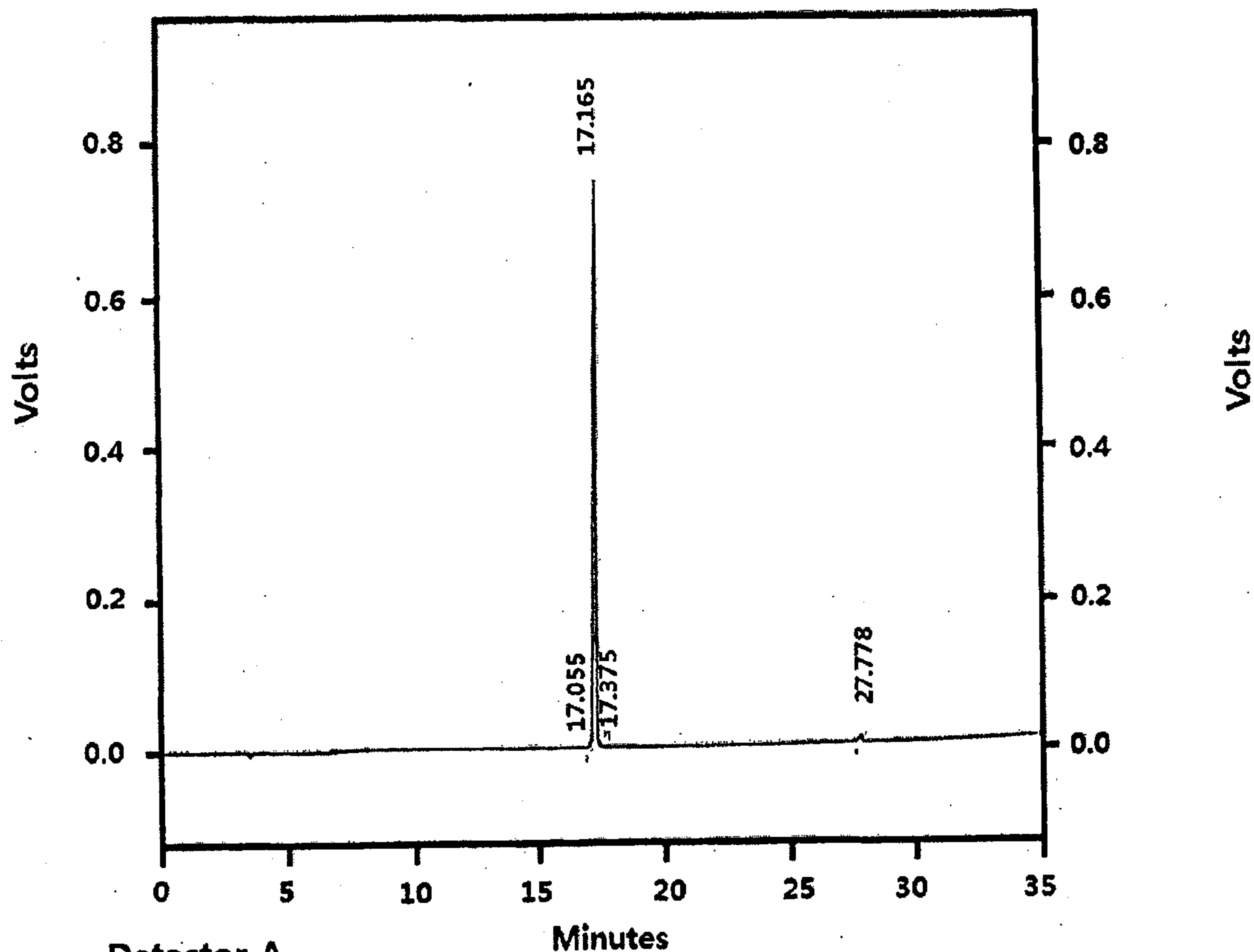
Pk #	Retention Time	Area	Area %
1	11.167	150	0.002
2	11.300	7430217	99.528
3	11.725	35093	0.470
Totals		7465460	100.000

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FIG. 32

Shimadzu CLASS-VP V6.14 SP1 new 10AVP *Area % Report* *Page of 1*

Sample ID : K170461 (YDE-029)



Detector A

Minutes

(230nm) Pk #	Retention Time	Area	Area %
1	17.055	22757	0.455
2	17.165	4899267	98.005
3	17.375	14310	0.286
4	27.778	62641	1.253

Totals		4998975	100.000
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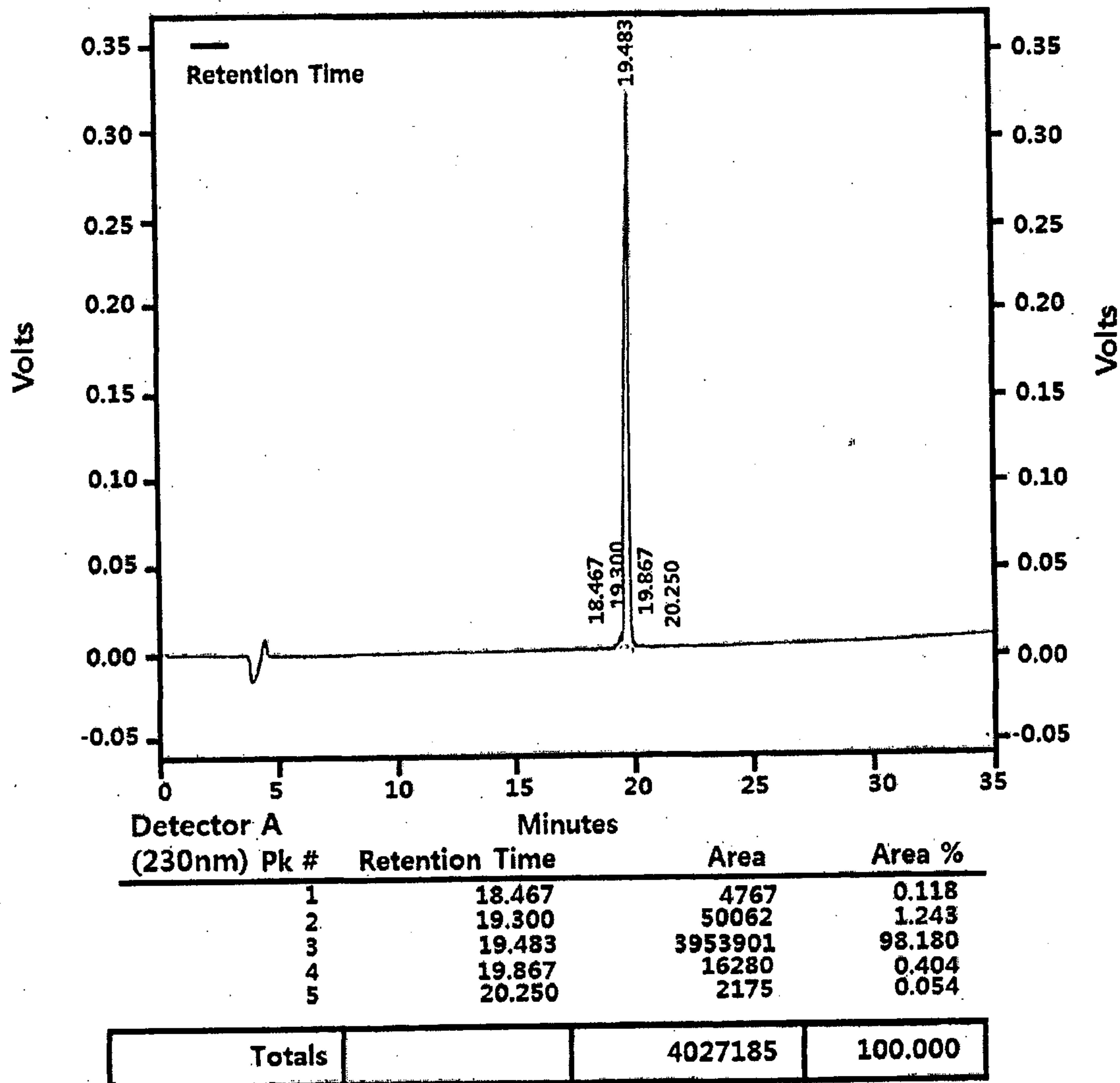
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FIG 33

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K170462 (YDE-030)



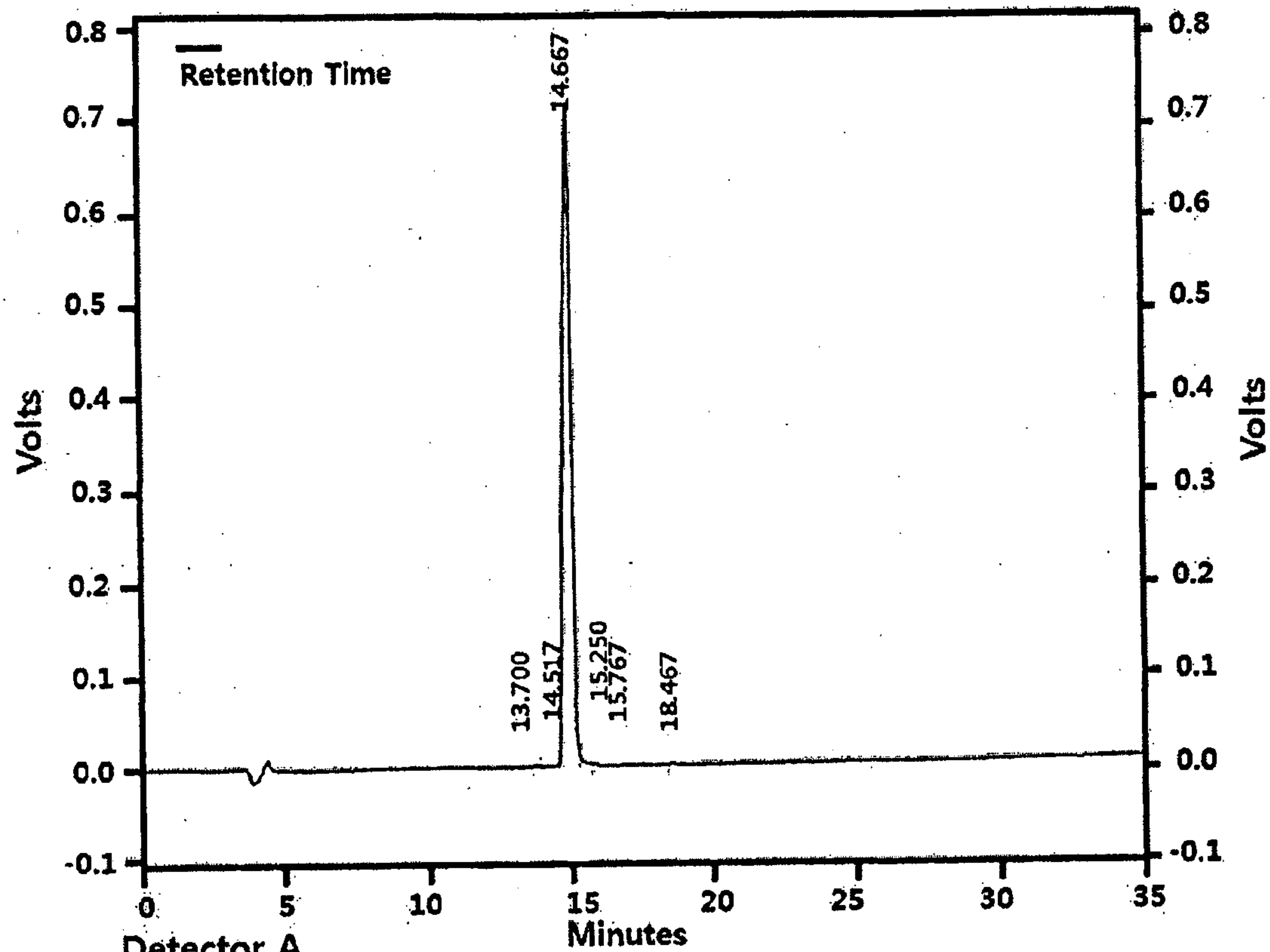
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FIG 34

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K170463 (YDE-031)



Detector A (230nm) Pk #	Retention Time	Area	Area %
1	13.700	9470	0.066
2	14.517	5967	0.041
3	14.667	14223947	98.895
4	15.250	102756	0.714
5	15.767	25707	0.179
6	18.467	15003	0.104
Totals		14382850	100.000

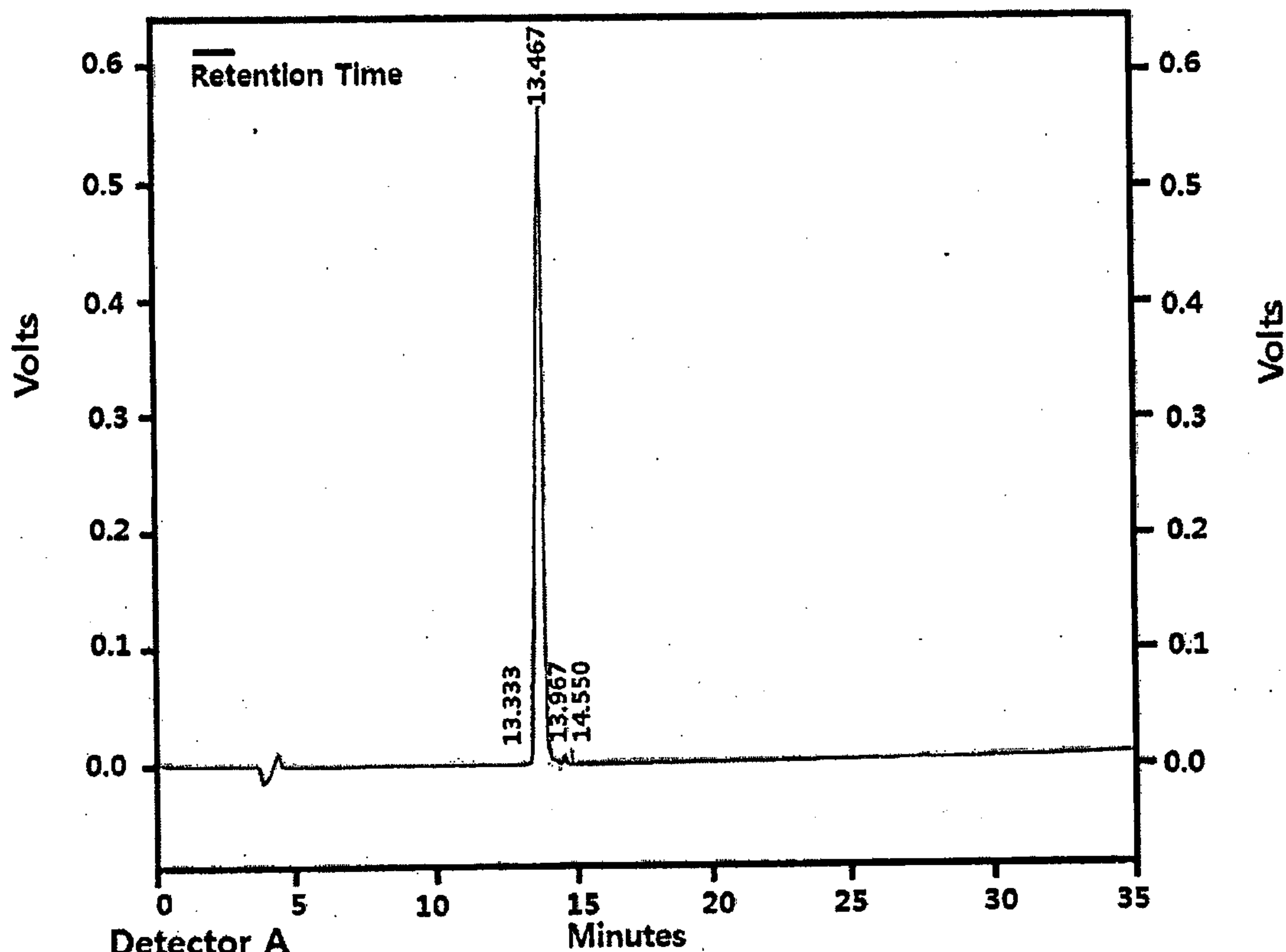
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FIG 35

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K170464 (YDE-032)



Detector A

(230nm) Pk #

Retention Time

Area

Area %

1	13.333	9786	0.099
2	13.467	9733951	98.224
3	13.967	118058	1.191
4	14.550	48177	0.486

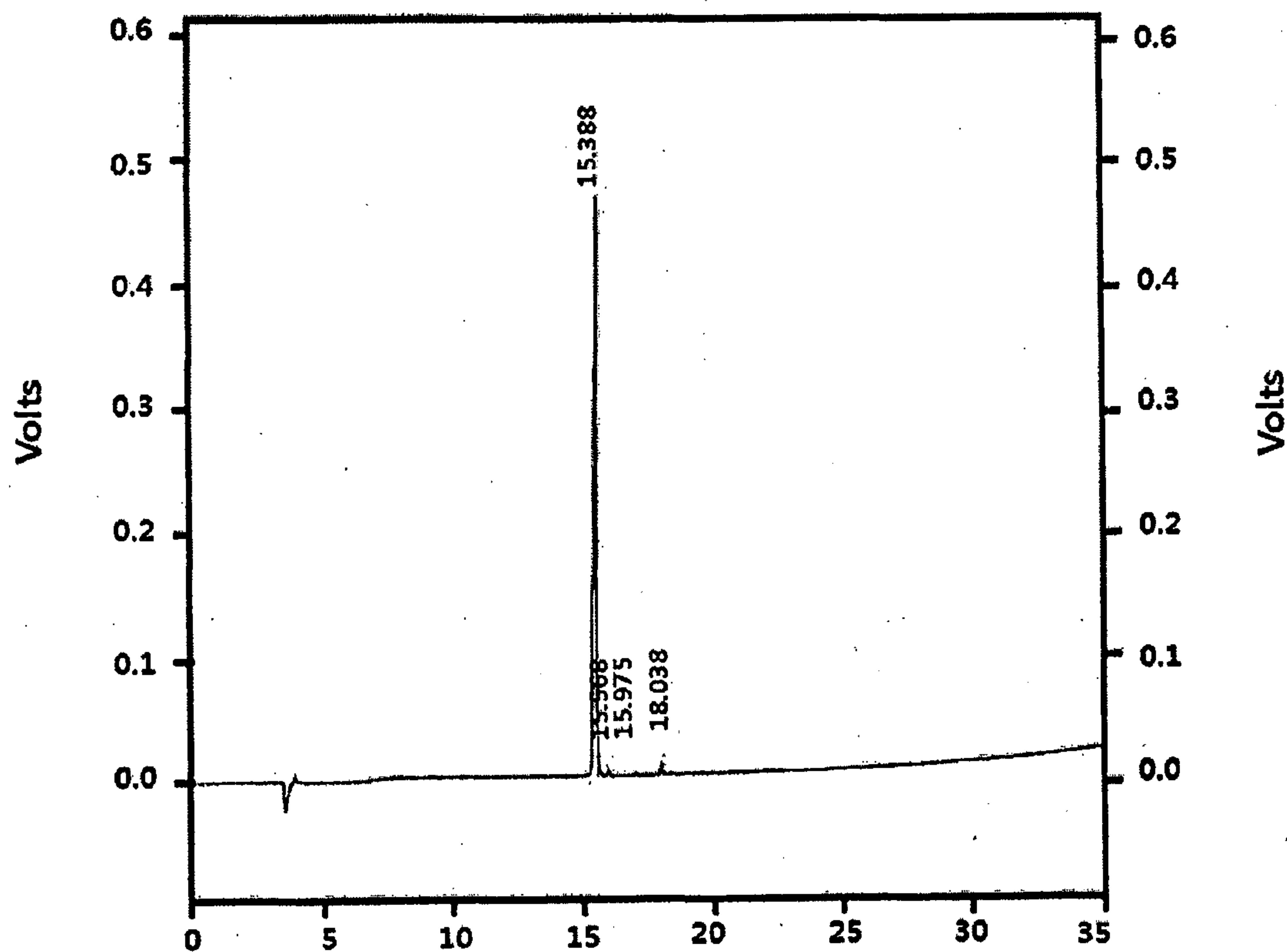
Totals		9909972	100.000
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FIG 36

Shimadzu CLASS-VP V6.14 SP1 new 10AVP Area % Report Page of 1

Sample ID : K170465 (YDE-033)



Detector A		Minutes		
(230nm) Pk #	Retention Time	Area	Area %	
1	15.388	3503595	97.229	
2	15.568	36015	0.999	
3	15.975	25007	0.694	
4	18.038	38811	1.077	
Totals		3603428	100.000	

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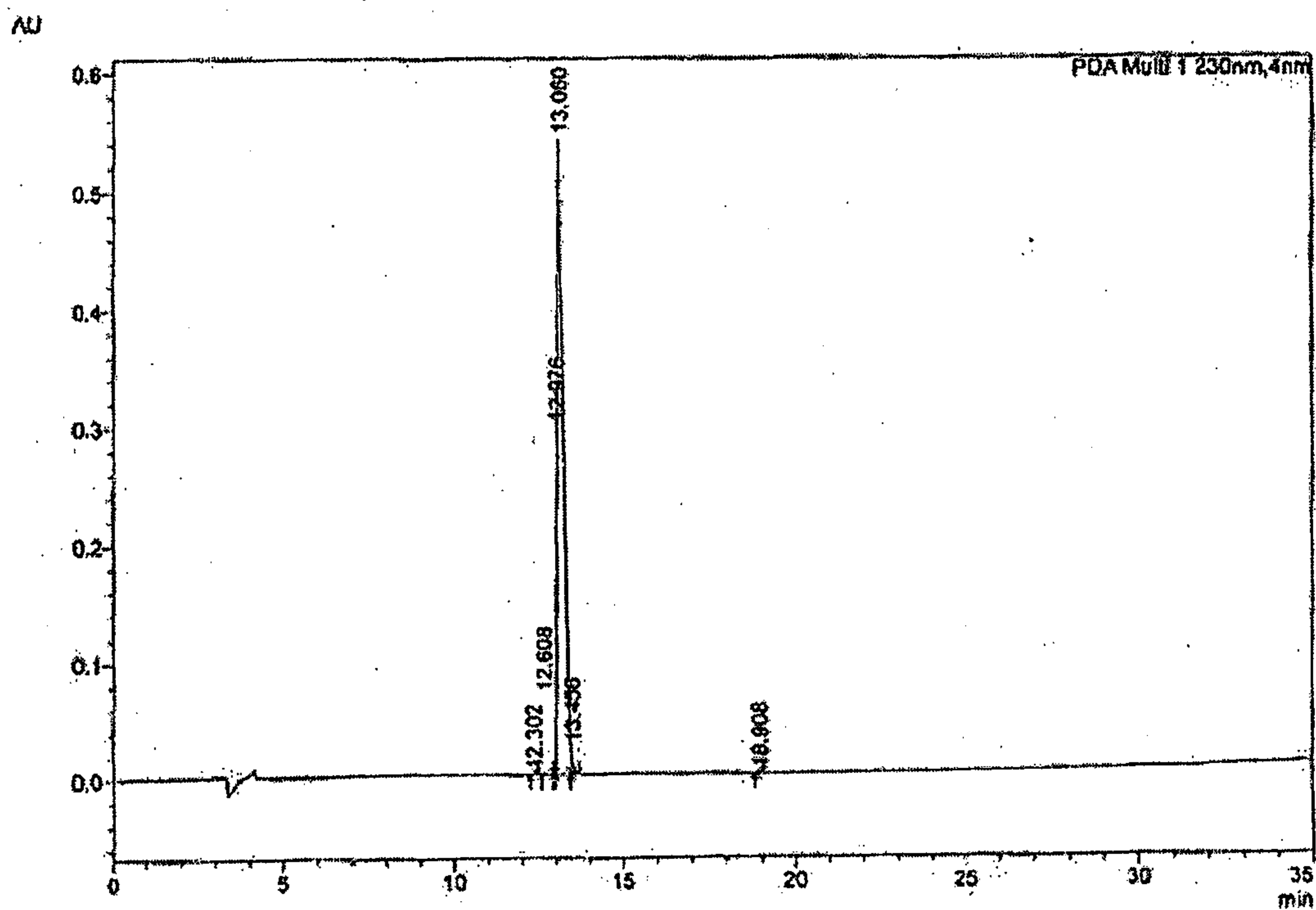
FIG 37

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name :K170467 (YDE-034)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.302	3679	0.049
2	12.608	6351	0.084
3	12.976	21634	0.287
4	13.060	7431450	98.885
5	13.456	62871	0.835
6	18.908	4490	0.060
Total		7530474	100.000

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FIG 38

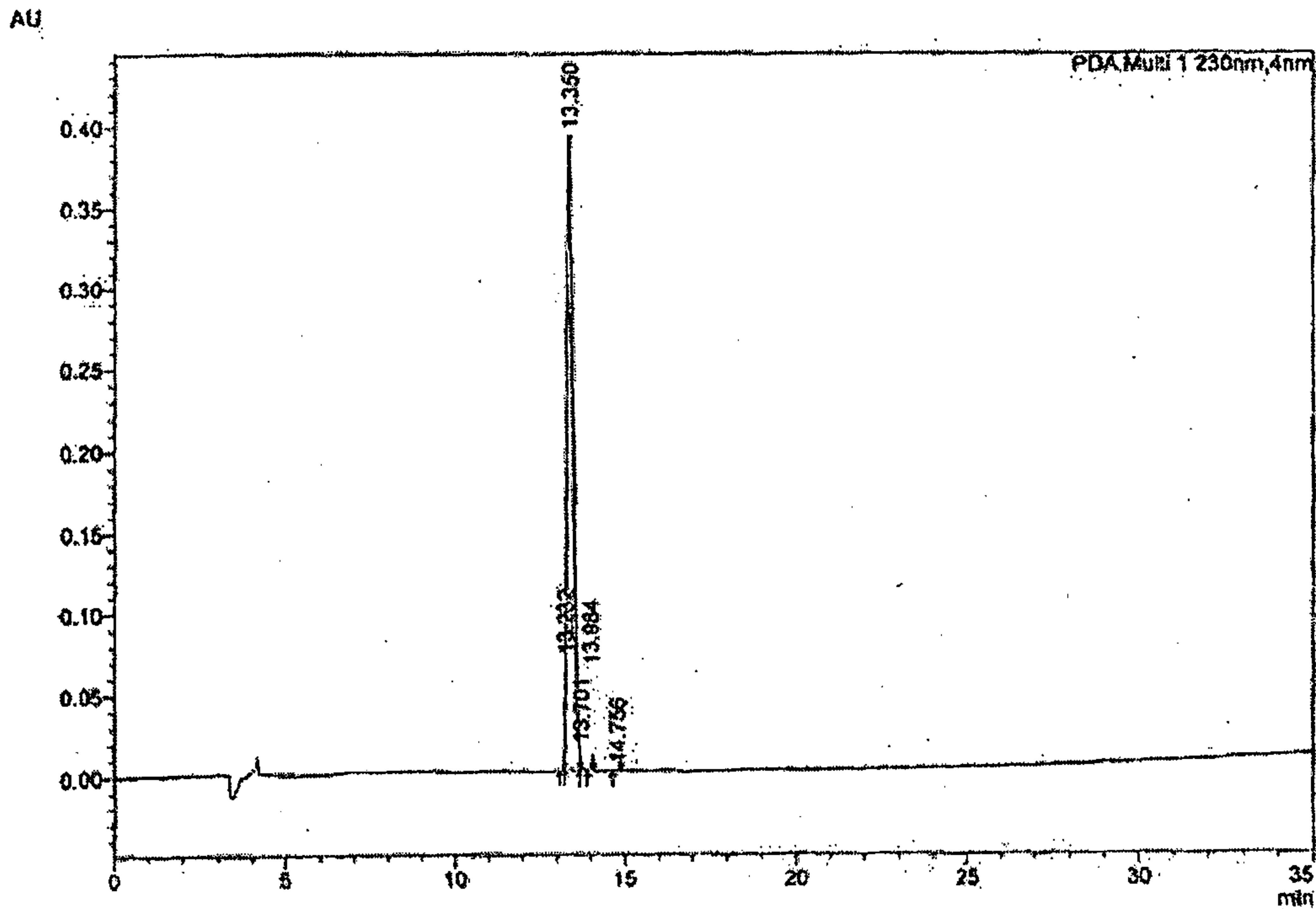
 SHIMADZU
LabSolutions

Analysis Report

<Sample Information>

Sample Name :K170468 (YDE-035)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	13.232	12349	0.252
2	13.350	4845696	98.818
3	13.701	38529	0.786
4	13.984	2572	0.052
5	14.756	4526	0.092
Total		4903673	100.000

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FIG 39



SHIMADZU

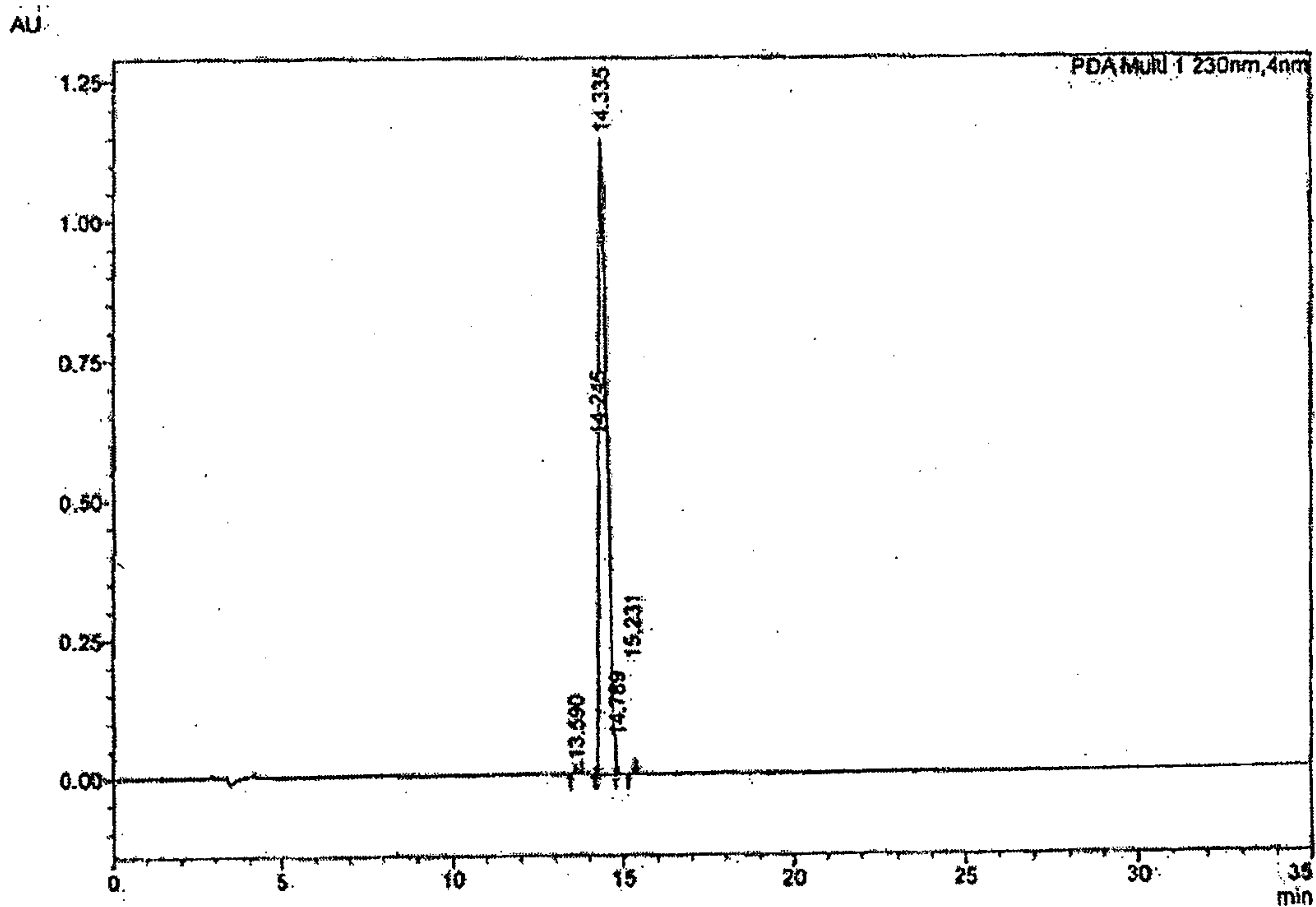
LabSolutions

Analysis Report

<Sample Information>

Sample Name :K170469 (YDE-036)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	13.590	95741	0.502
2	14.245	21037	0.110
3	14.335	18844050	98.765
4	14.789	113179	0.593
5	15.231	5631	0.030
Total		19079638	100.000

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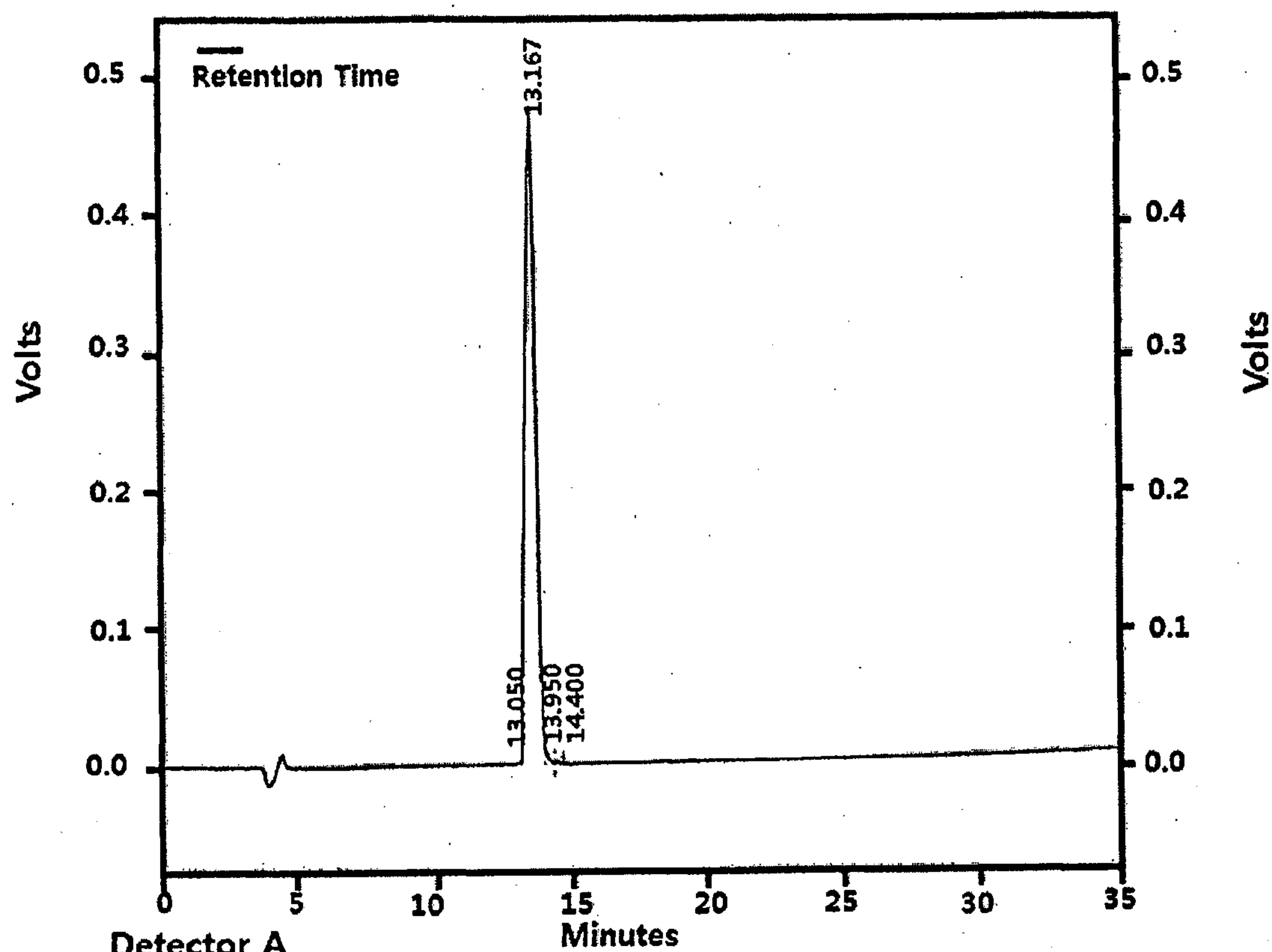
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FIG 40

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K170470 (YDE-037)



Detector A

Minutes

(230nm) Pk #	Retention Time	Area	Area %
--------------	----------------	------	--------

1	13.050	18320	0.148
2	13.167	12318048	99.237
3	13.950	60854	0.490
4	14.400	15548	0.125

Totals		12412770	100.000
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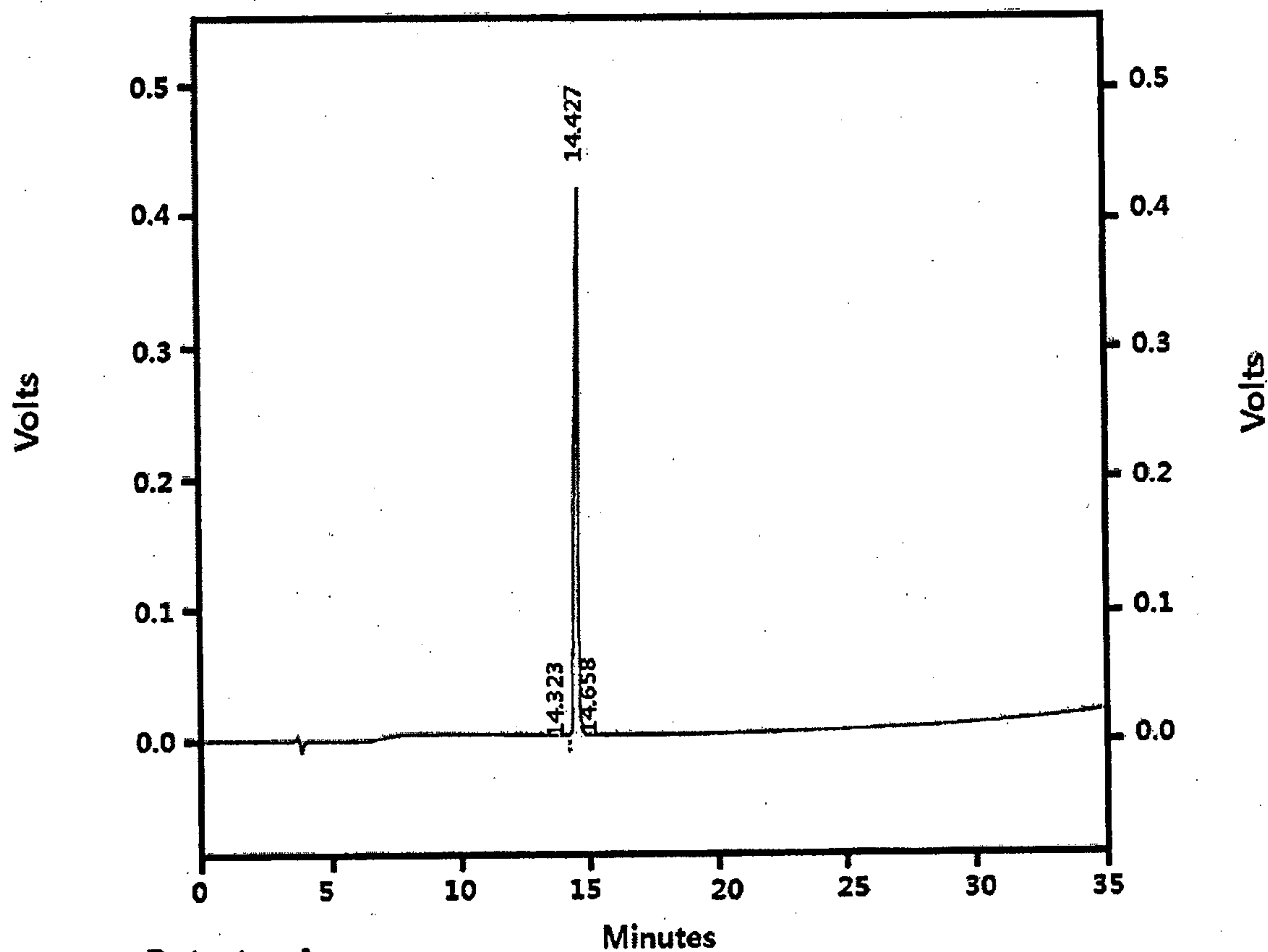
FIG 41

Shimadzu CLASS-VP V6.14 SP1 new 10AVP

Area % Report

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Sample ID : K170471 (YDE-038)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	14.323	7412	0.197
2	14.427	3716173	98.767
3	14.658	38987	1.036
Totals		3762572	100.000

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FIG 42



SHIMADZU

LabSolutions

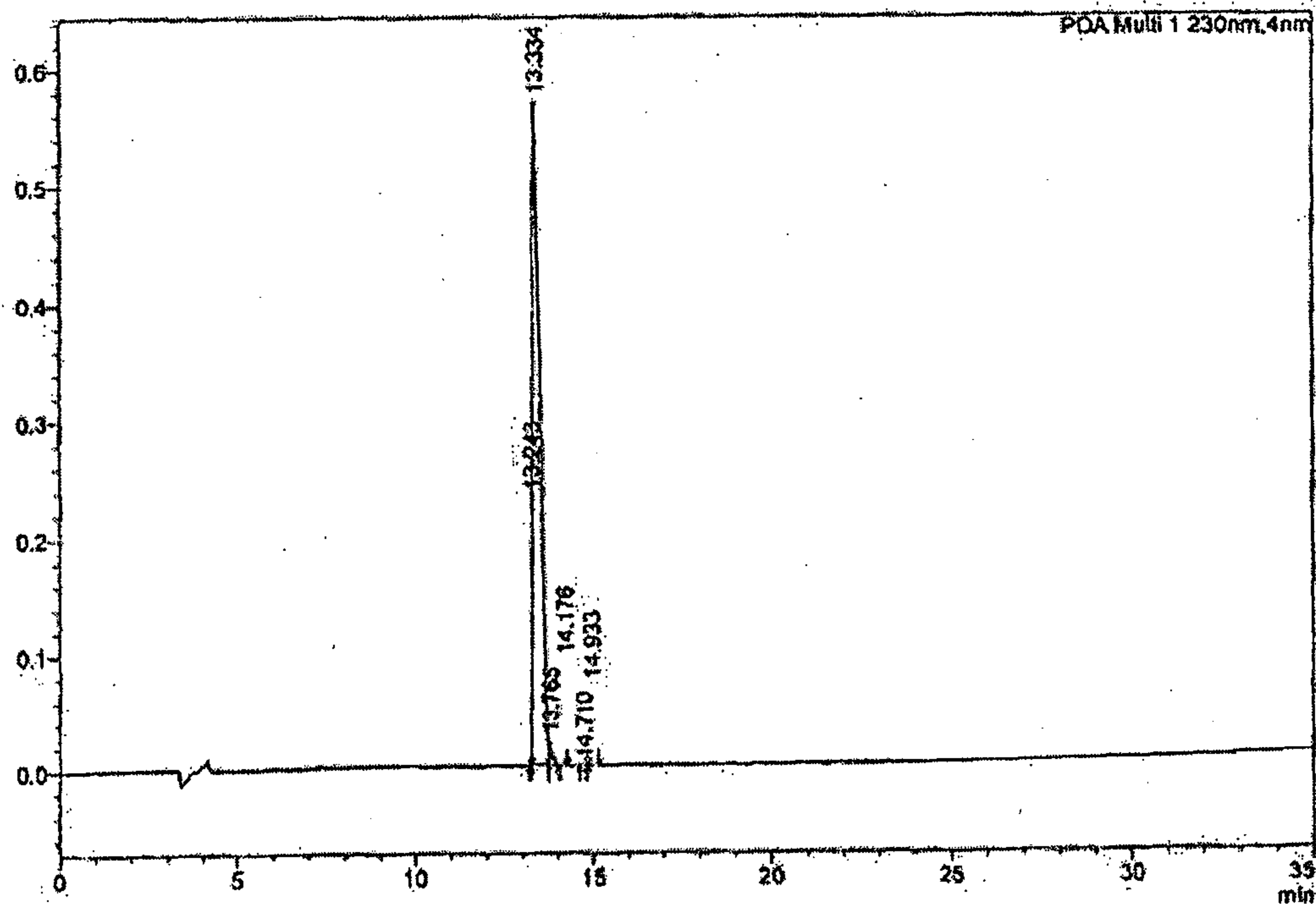
Analysis Report

<Sample Information>

Sample Name :K170484 (YDE-039)

<Chromatogram>

AU



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	13.243	10337	0.120
2	13.334	8471164	98.101
3	13.765	141934	1.644
4	14.176	1883	0.022
5	14.710	3097	0.036
6	14.933	6746	0.078
Total		8635161	100.000

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FIG 43

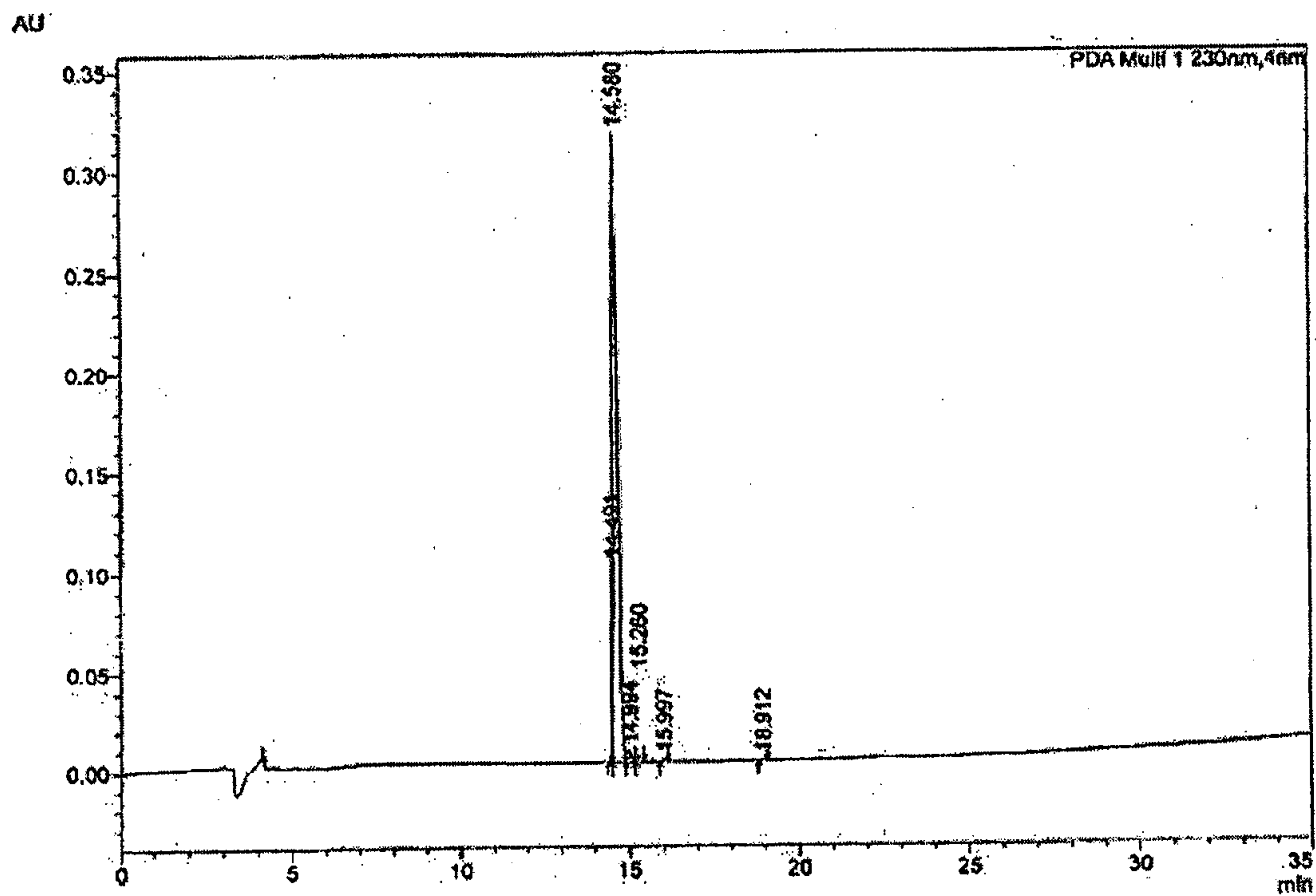


Analysis Report

<Sample Information>

Sample Name : K170485 (YDE-040)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	14.491	8575	0.268
2	14.580	3145995	97.580
3	14.994	43744	1.357
4	15.260	10665	0.331
5	15.997	9068	0.281
6	18.912	5968	0.185
Total		3224014	100.000

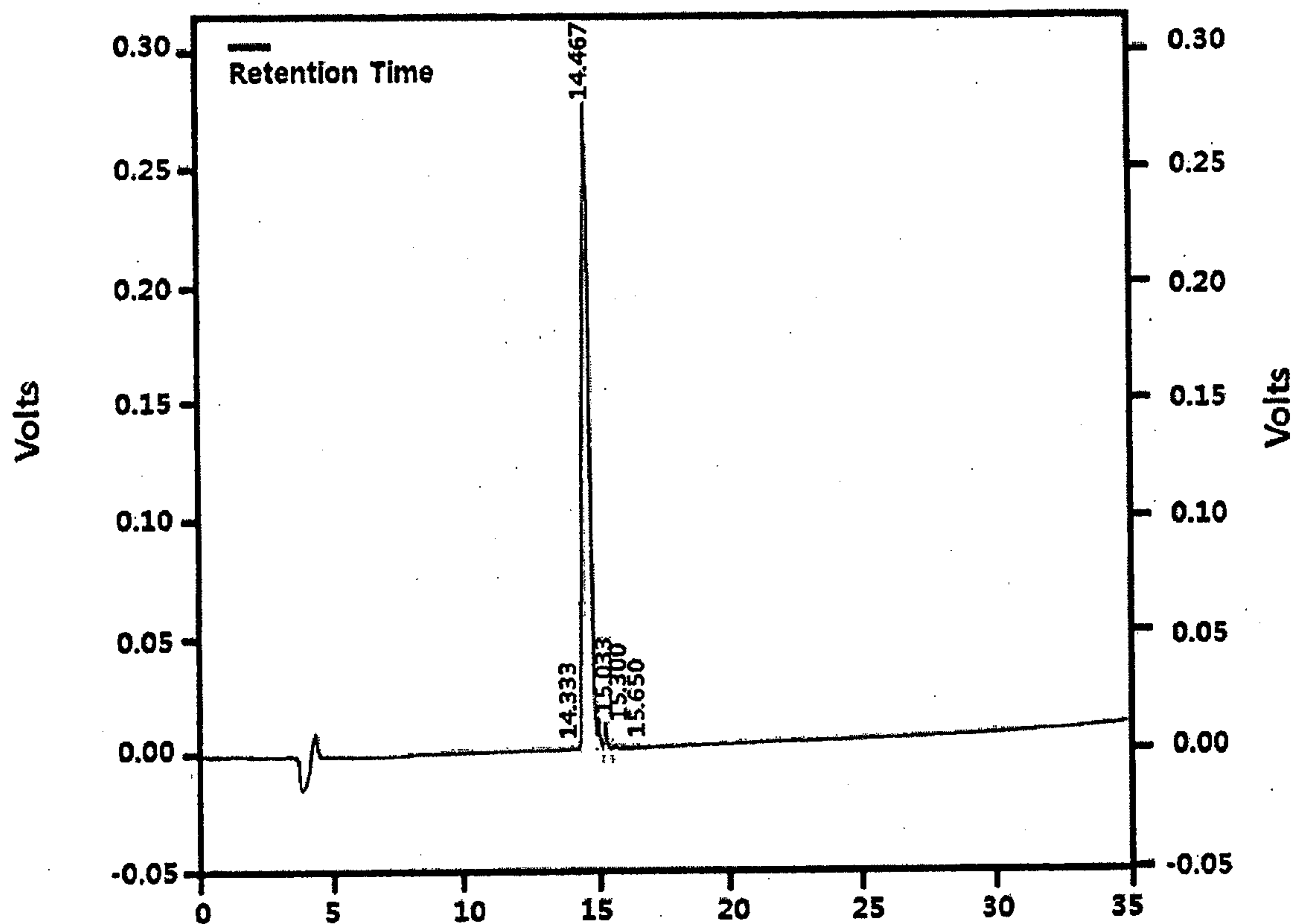
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FIG 44

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K170466 (YDE-041)



Detector A		Minutes			
(230nm) Pk #	Retention Time	Area	Area %		
1	14.333	8213	0.167		
2	14.467	4742455	96.577		
3	15.033	84778	1.726		
4	15.300	67385	1.372		
5	15.650	7689	0.157		
Totals		4910520	100.000		

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FIG 45

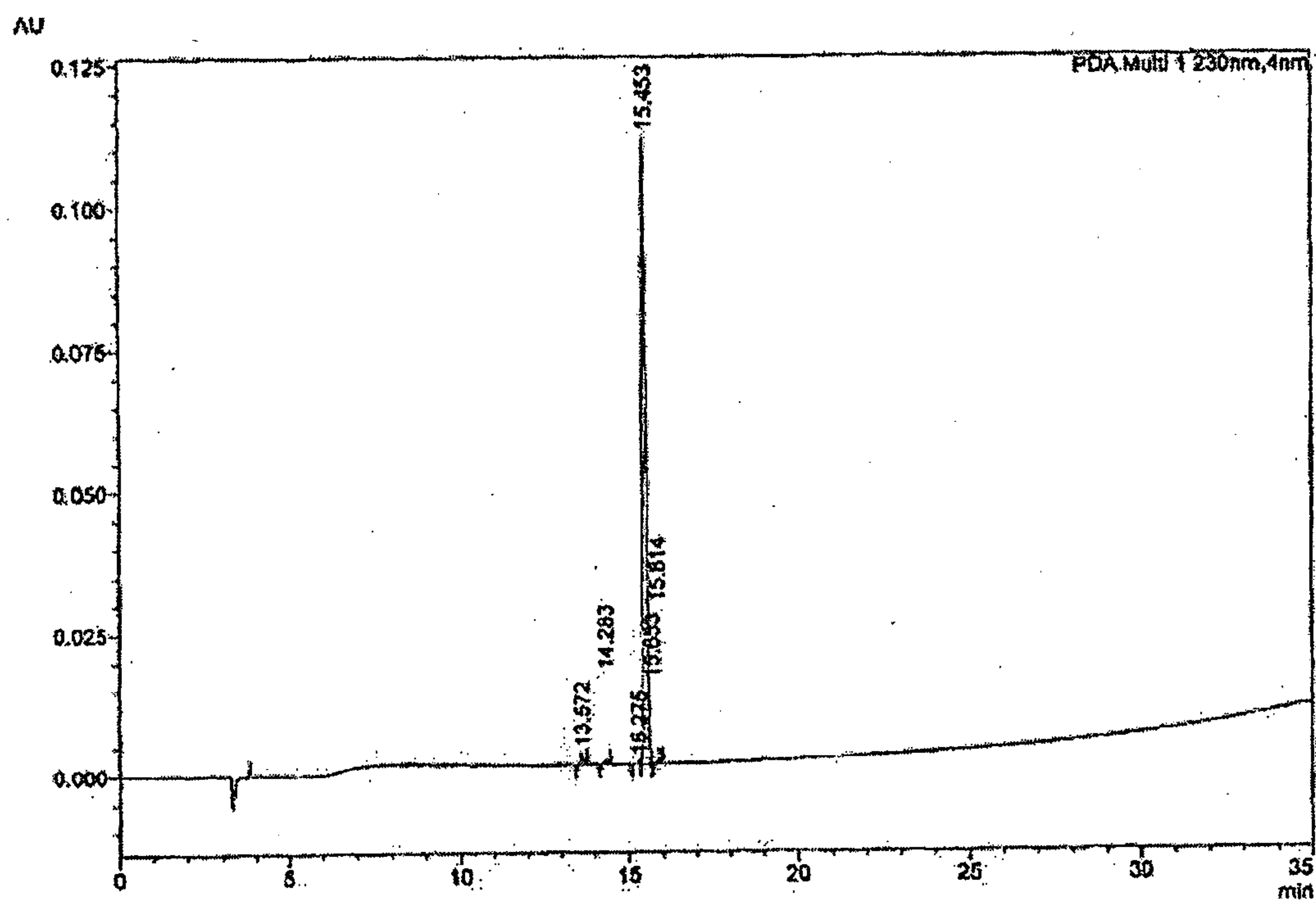
SHIMADZU
LabSolutions

Analysis Report

<Sample Information>

Sample Name :K170696 (YDE-042)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	13.572	10672	1.287
2	14.283	3251	0.392
3	15.275	1984	0.239
4	15.453	808105	97.478
5	15.653	3981	0.480
6	15.814	1036	0.125
Total		829028	100.000

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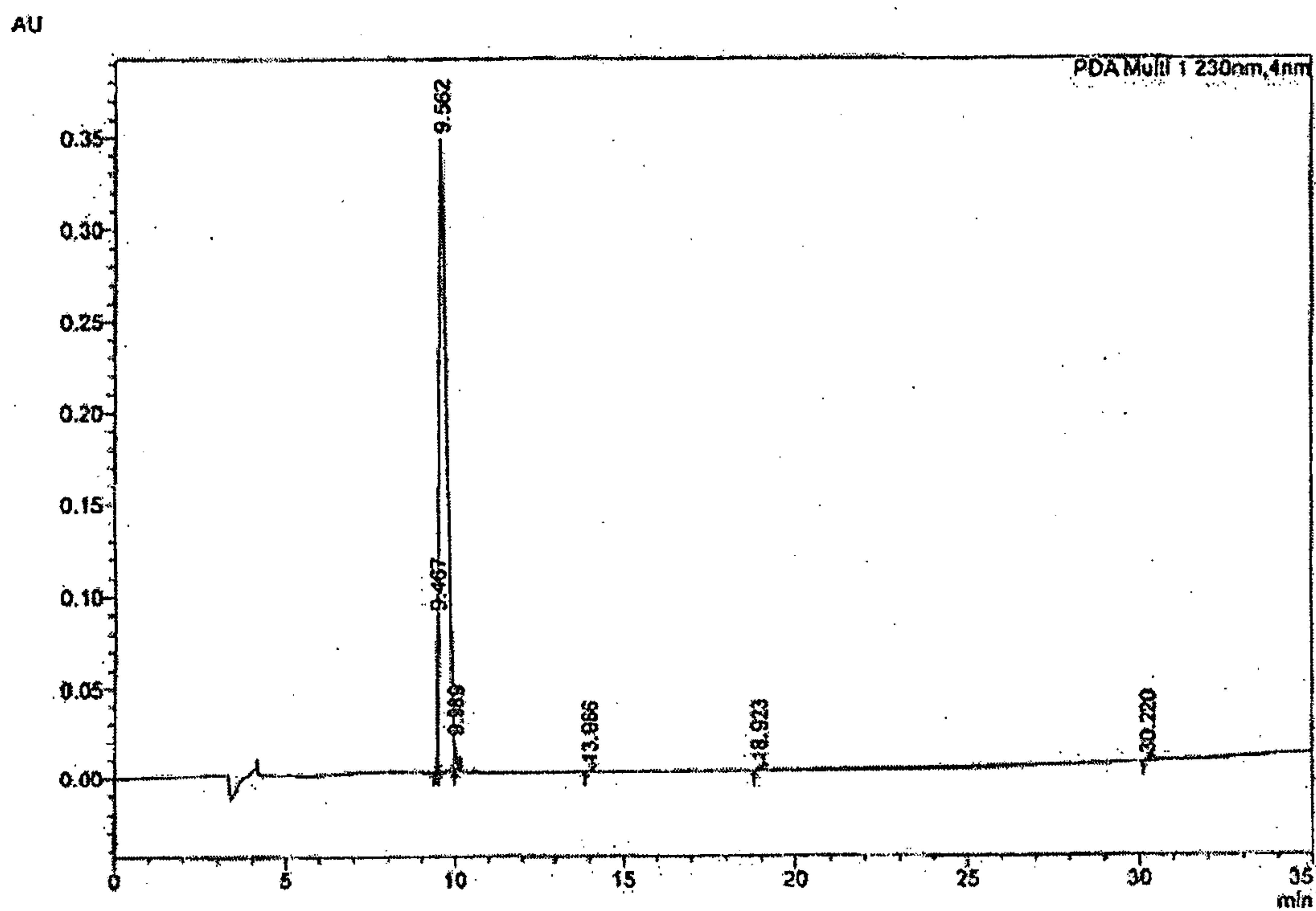
FIG 46

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name :K170695 (YDE-043)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	9.467	2371	0.045
2	9.562	5211379	98.719
3	9.989	47144	0.893
4	13.966	4274	0.081
5	18.923	8330	0.158
6	30.220	5506	0.104
Total		5279004	100.000

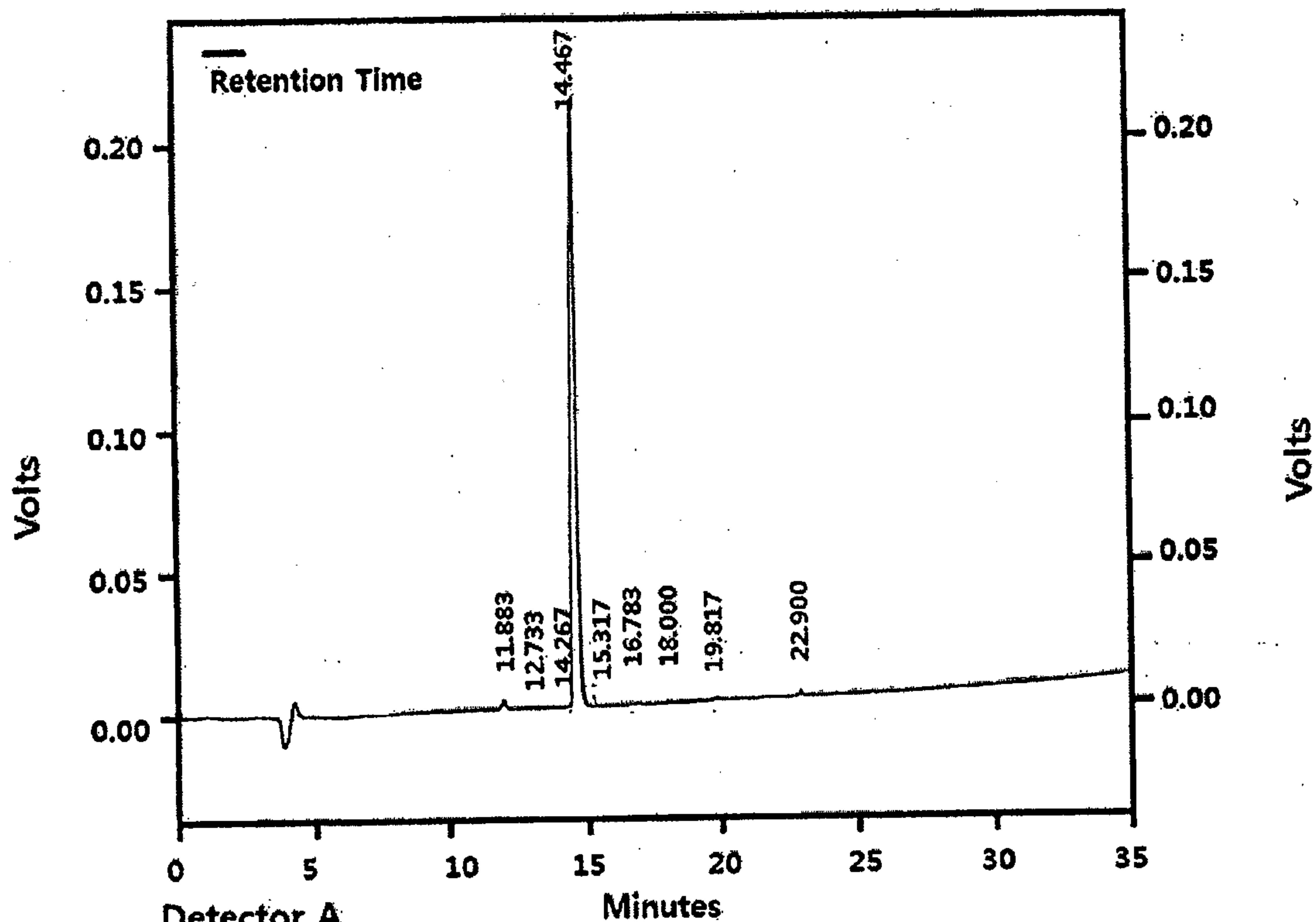
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FIG 47

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K171020 (YDE-044)



Detector A (230nm)	Retention Time	Area	Area %
1	11.883	27993	1.012
2	12.733	1286	0.047
3	14.267	2811	0.102
4	14.467	2704866	97.828
5	15.317	10992	0.398
6	16.783	4363	0.158
7	18.000	887	0.032
8	19.817	3279	0.119
9	22.900	8453	0.306
Totals		2764930	100.000

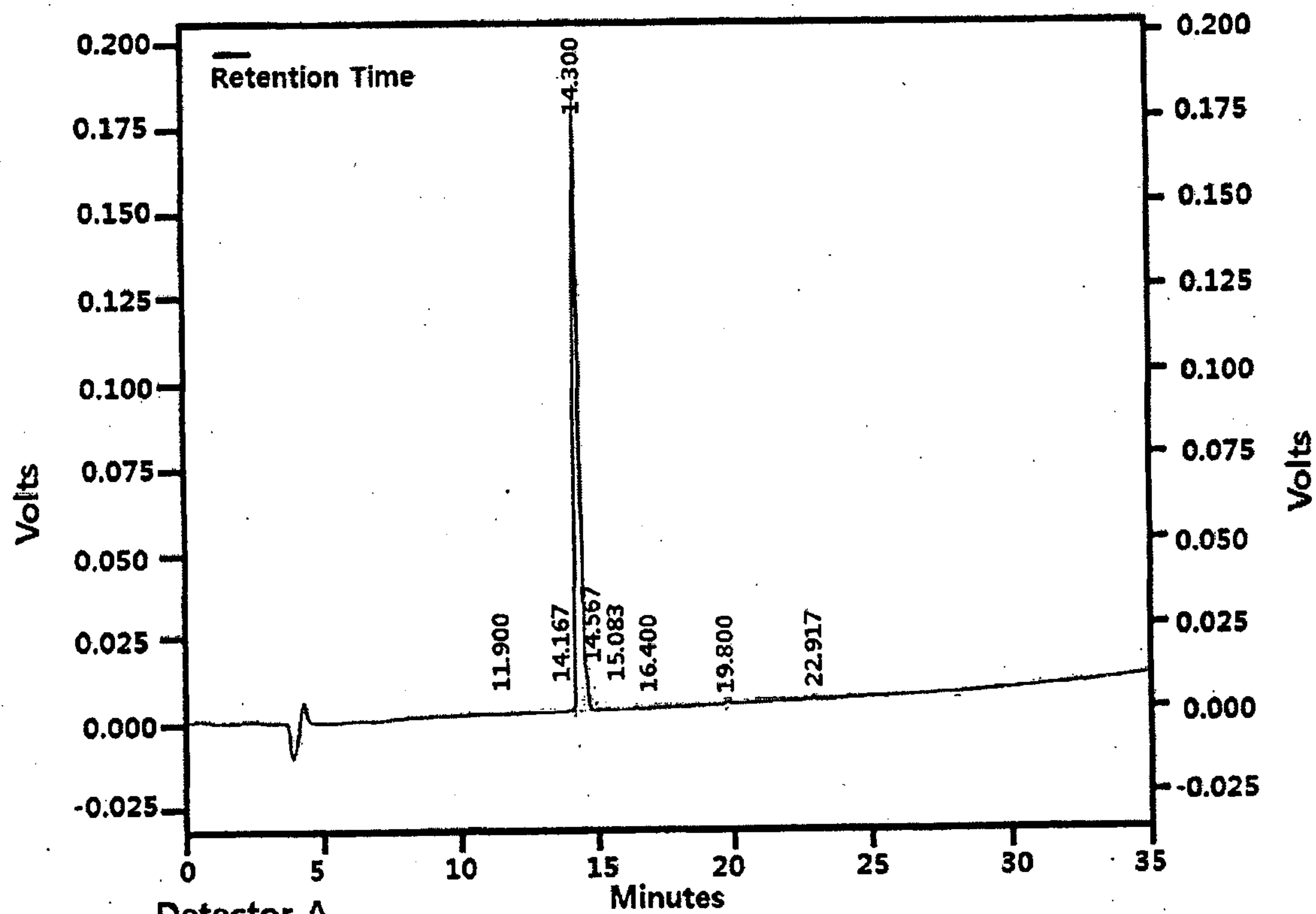
48/133

FIG 48

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K171021 (YDE-045)



Detector A (230nm) Pk #	Retention Time	Area	Area %
1	11.900	636	0.029
2	14.167	5291	0.242
3	14.300	2089275	95.561
4	14.567	80787	3.695
5	15.083	1596	0.073
6	16.400	2393	0.109
7	19.800	2986	0.137
8	22.917	3361	0.154
Totals		2186325	100.000

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FIG 49

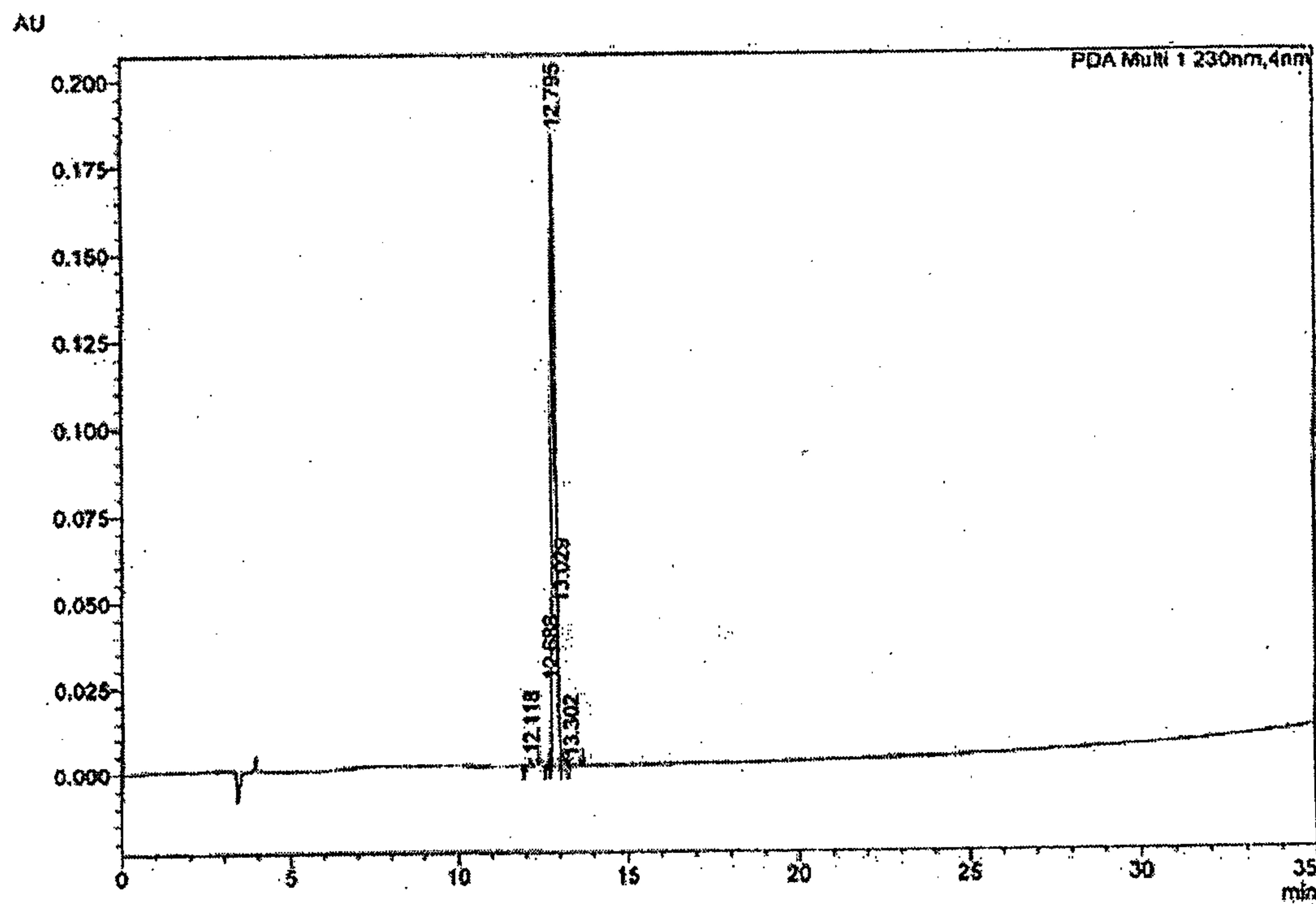
SHIMADZU
LabSolutions

Analysis Report

<Sample Information>

Sample Name :K171849 (YDE-047)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.118	8416	0.566
2	12.688	3751	0.252
3	12.795	1449638	97.513
4	13.029	22365	1.504
5	13.302	2443	0.164
Total		1486612	100.000

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FIG 50

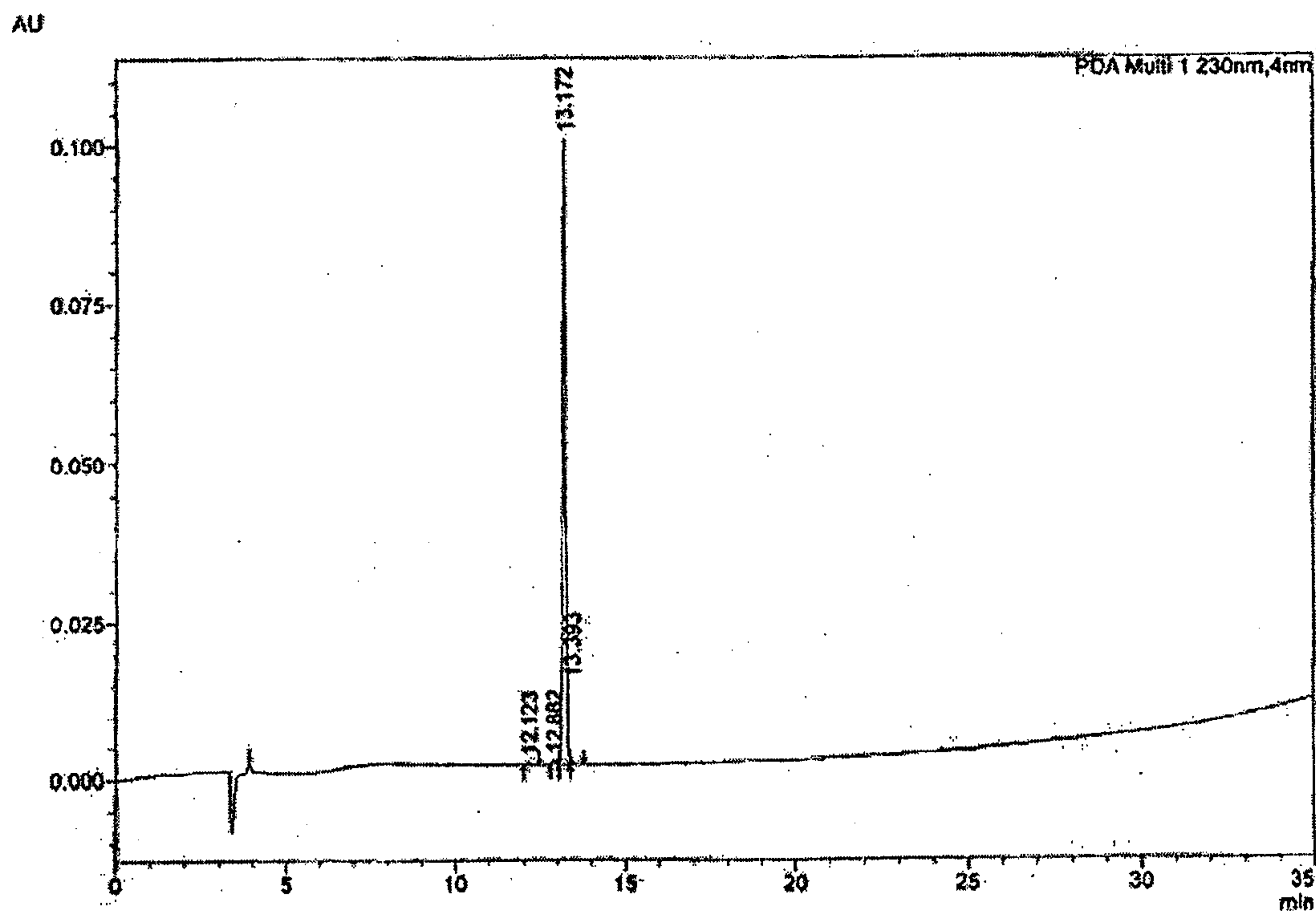


Analysis Report

<Sample Information>

Sample Name :K171850 (YDE-048)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.123	3743	0.600
2	12.882	7696	1.234
3	13.172	606751	97.254
4	13.393	5695	0.913
Total		623885	100.000

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FIG 51



SHIMADZU

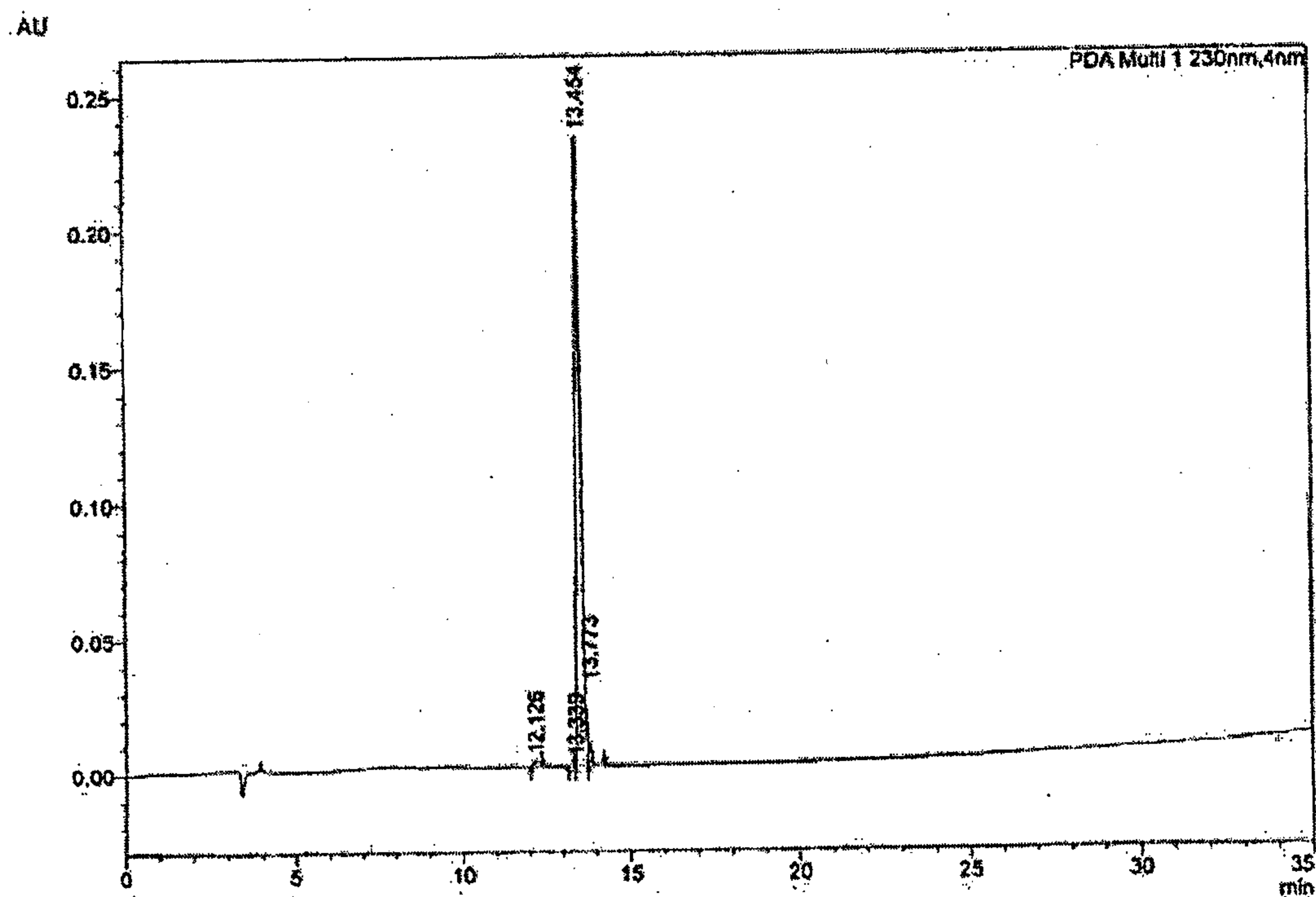
LabSolutions

Analysis Report

<Sample Information>

Sample Name :K171851 (YDE-049)

<Chromatogram>



<Peak Table>

PDA Ch1,230nm

Peak#	Ret. Time	Area	Area%
1	12.126	12891	0.539
2	13.339	1756	0.073
3	13.454	2318972	96.924
4	13.773	58958	2.464
Total		2392577	100.000

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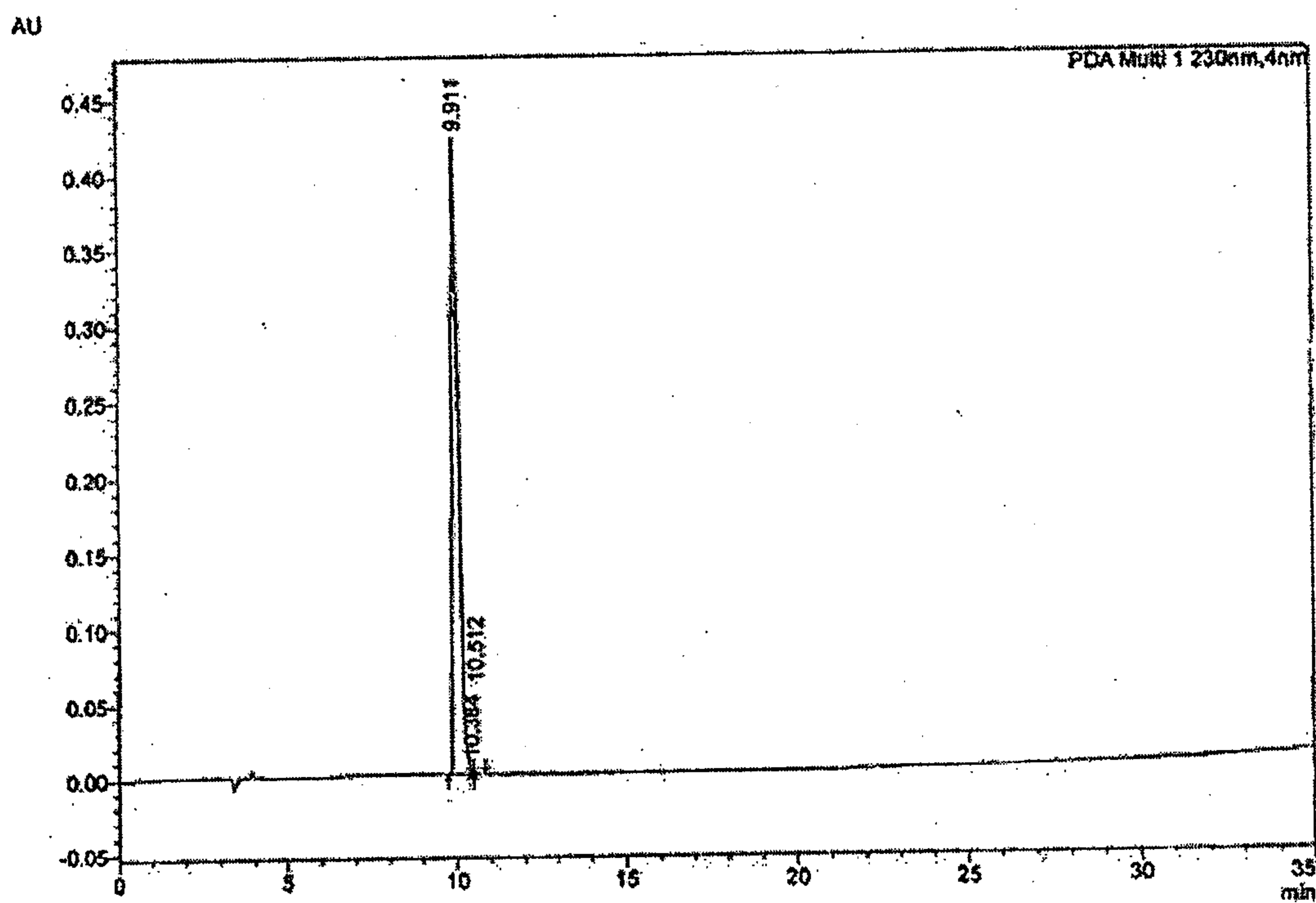
FIG 52

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name : K171852 (YDE-050)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	9.911	5450324	99.329
2	10.384	20990	0.383
3	10.512	15843	0.289
Total		5487158	100.000

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FIG 53



SHIMADZU

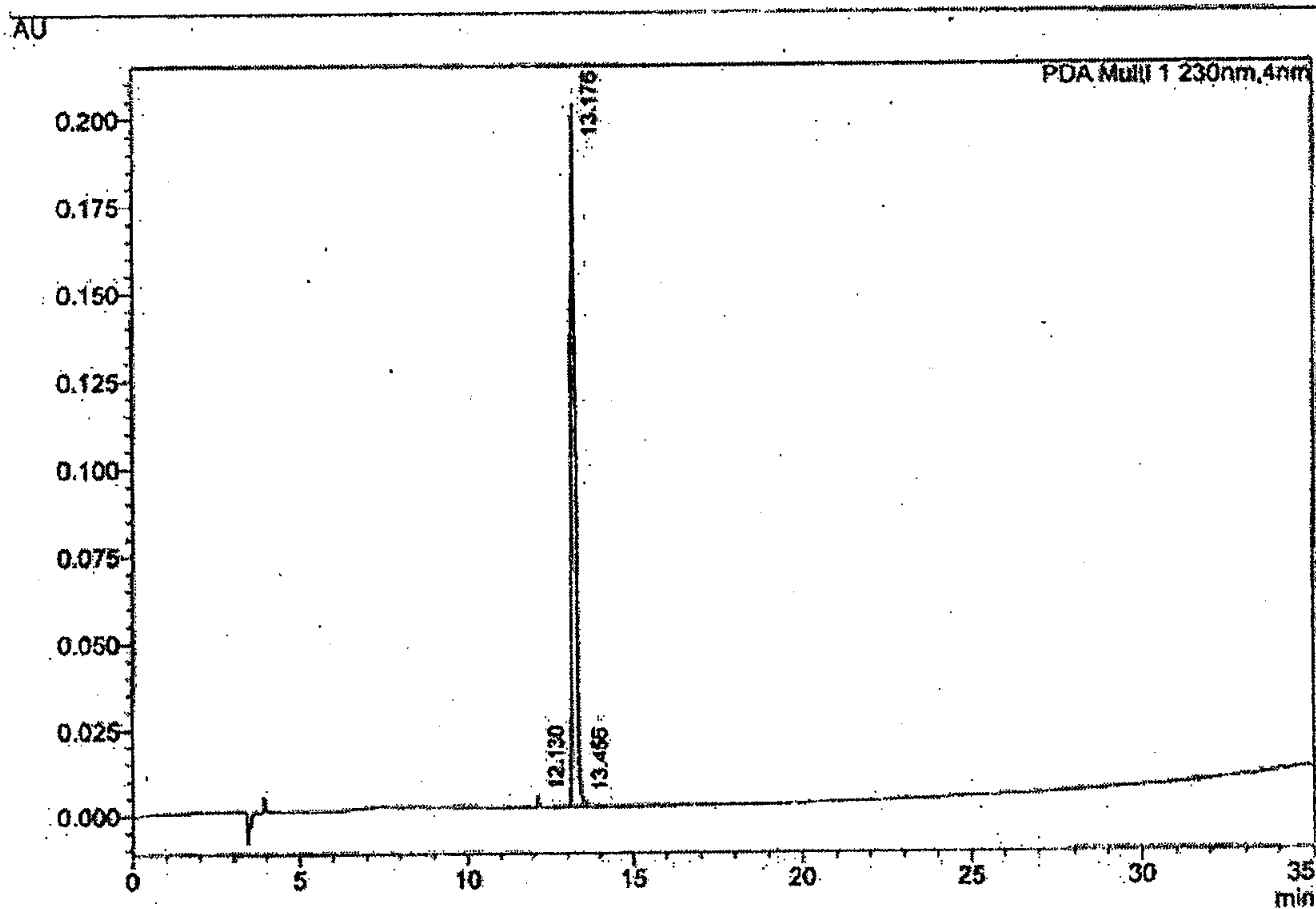
LabSolutions

Analysis Report

<Sample Information>

Sample Name : K171853 (YDE-051)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.130	18605	1.120
2	13.176	1627394	98.011
3	13.458	14421	0.869
Total		1660420	100.000

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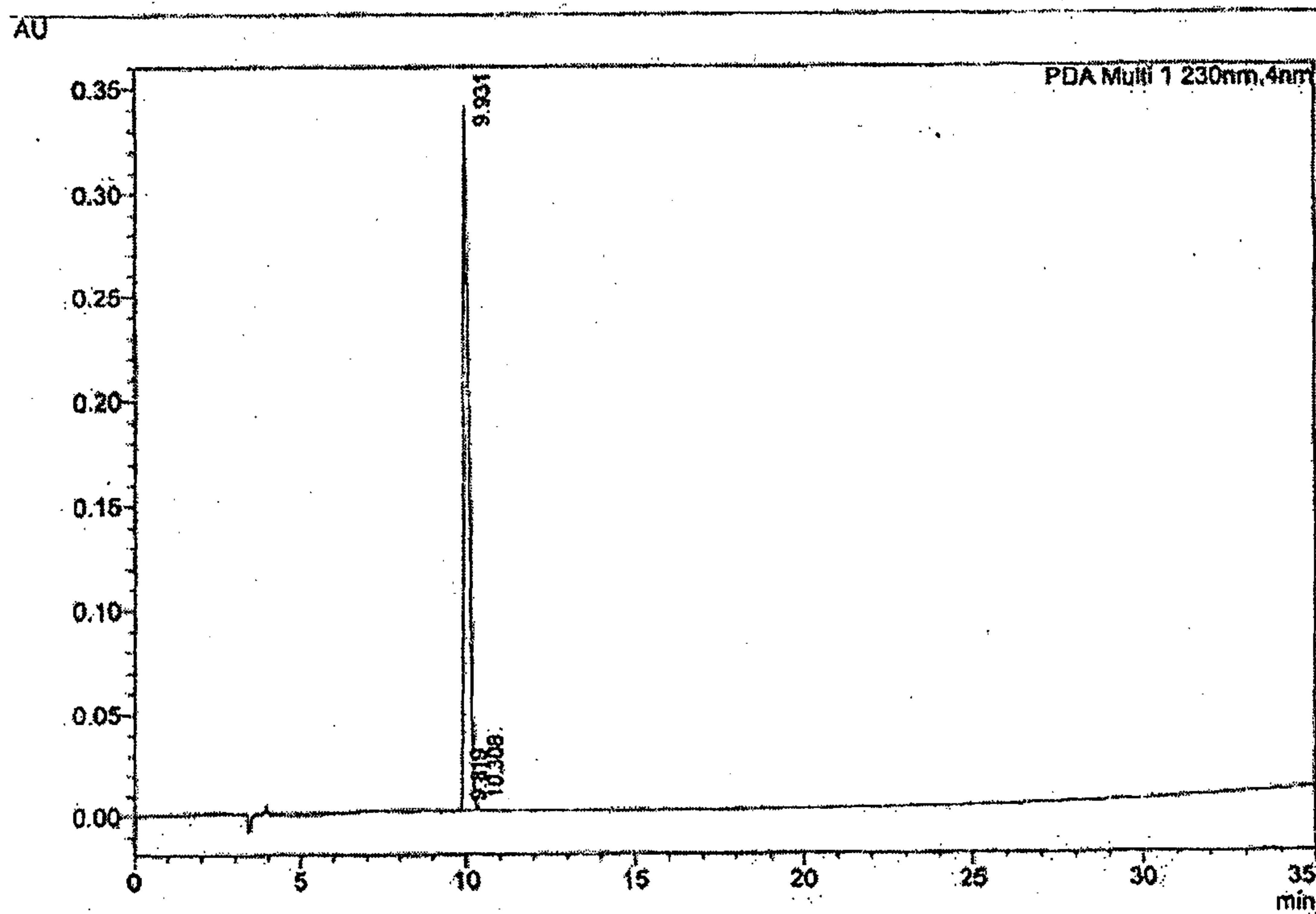
FIG 54

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name : K171854 (YDE-052)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	9.819	2280	0.065
2	9.831	3486152	99.456
3	10.308	16804	0.479
Total		3505236	100.000

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FIG 55

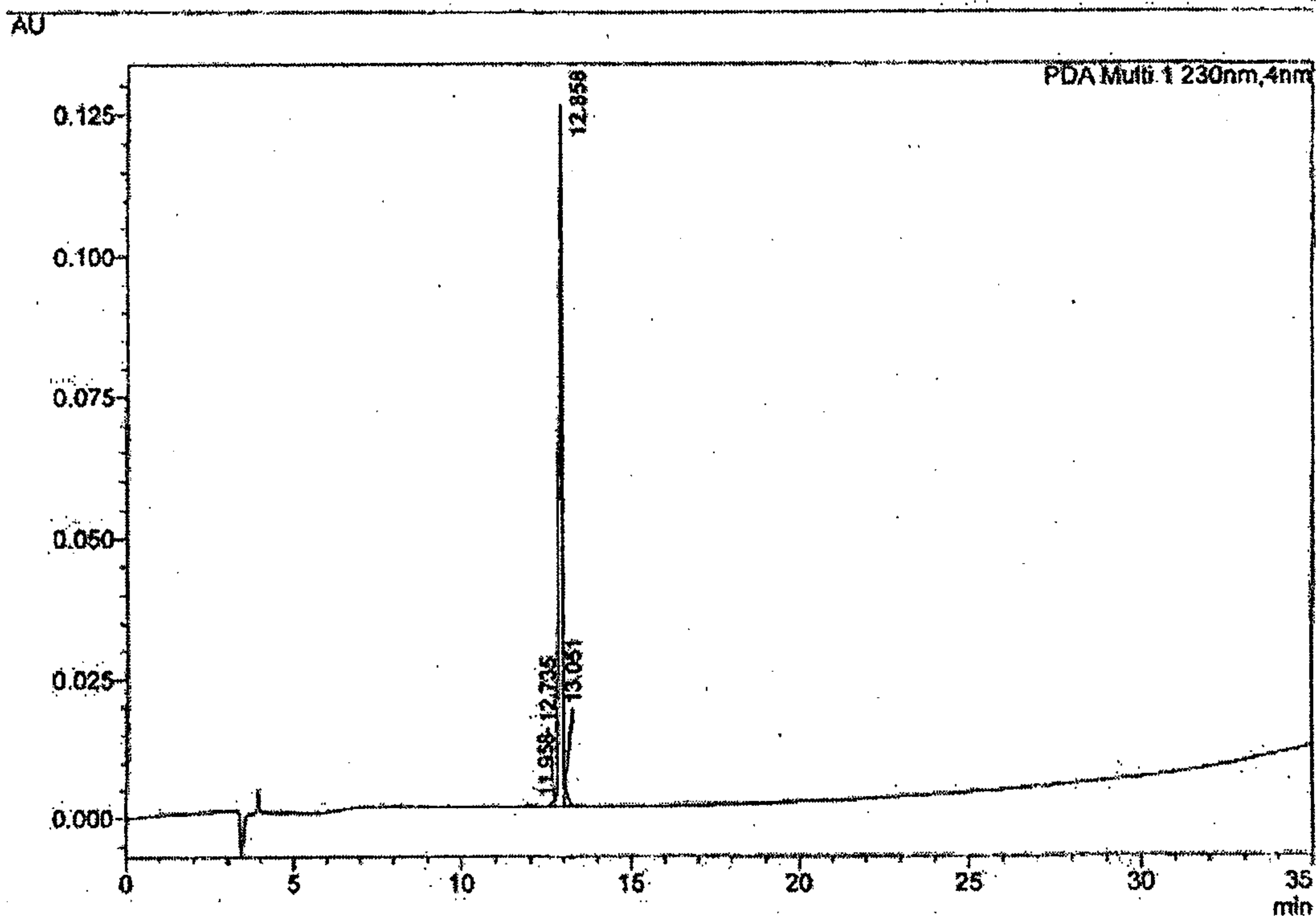
SHIMADZU
LabSolutions

Analysis Report

<Sample Information>

Sample Name : K171855 (YDE-053)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	11.958	3827	0.441
2	12.735	7134	0.822
3	12.858	836814	96.428
4	13.051	20034	2.309
Total		867809	100.000

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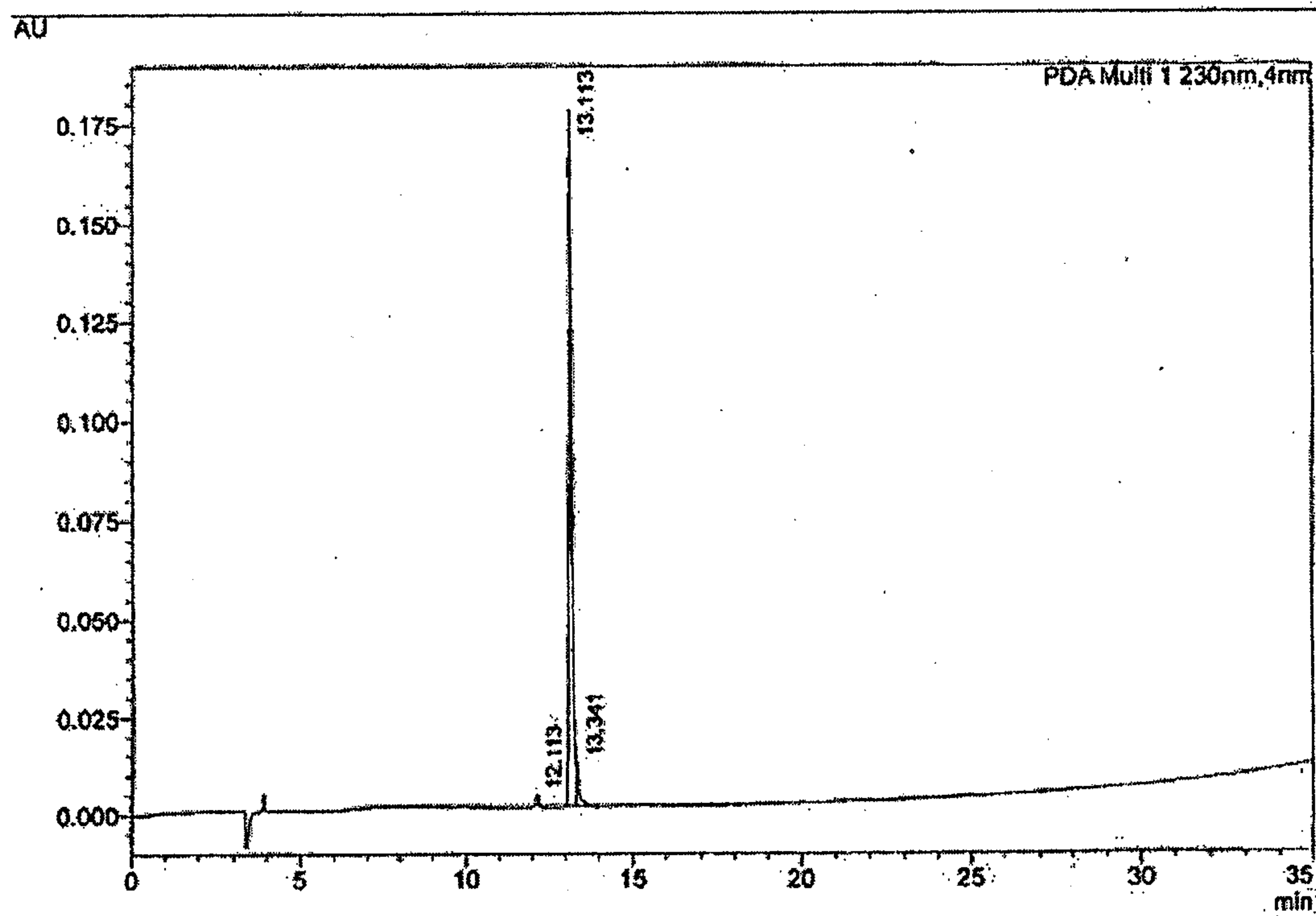
FIG 56

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name : K171856 (YDE-054)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.113	9831	0.724
2	13.113	1291332	95.112
3	13.341	56534	4.164
Total		1357696	100.000

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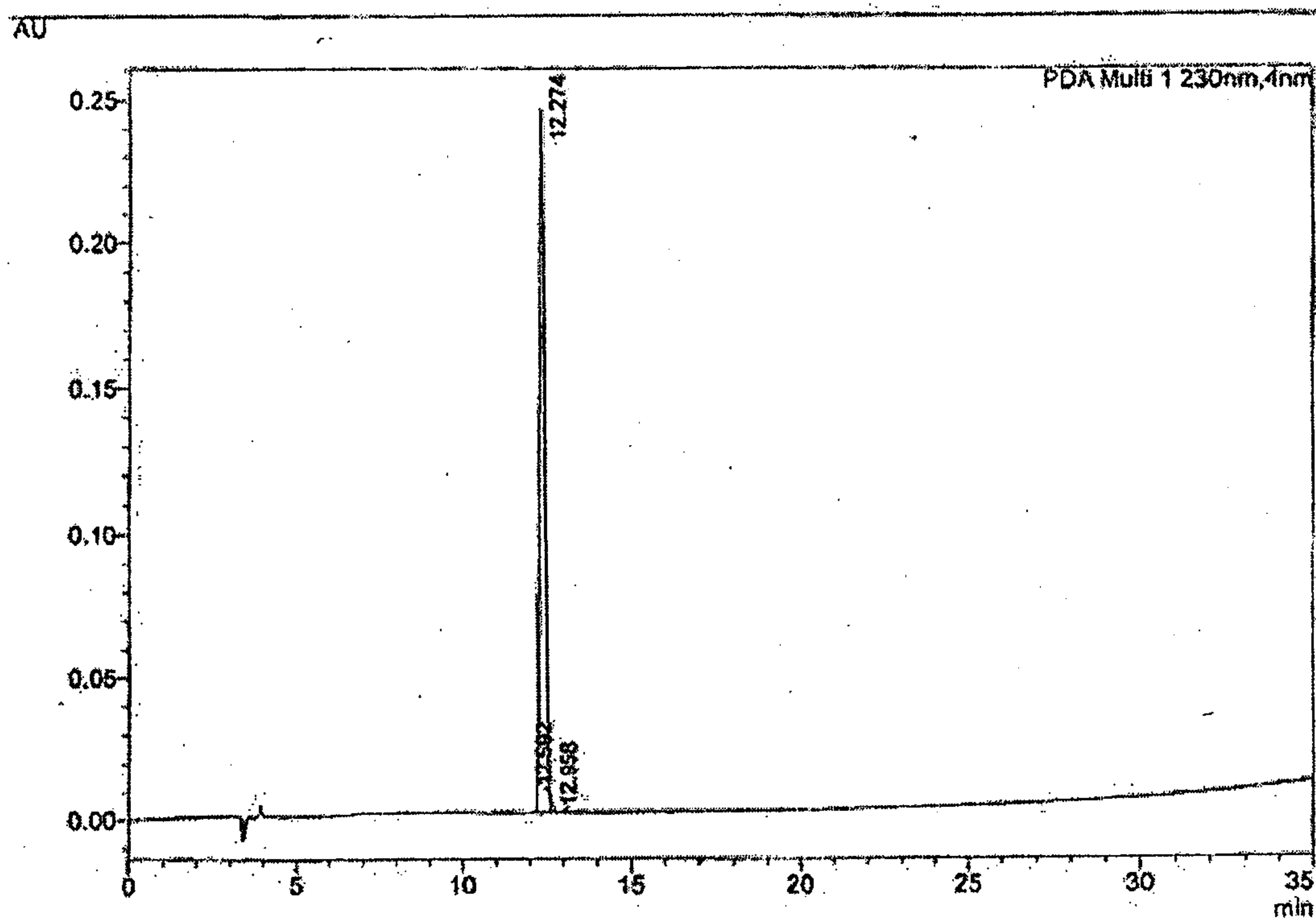
FIG 57

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name : K171857 (YDE-055)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.274	2627179	98.689
2	12.592	31720	1.192
3	12.958	3175	0.119
Total		2662073	100.000

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FIG 58

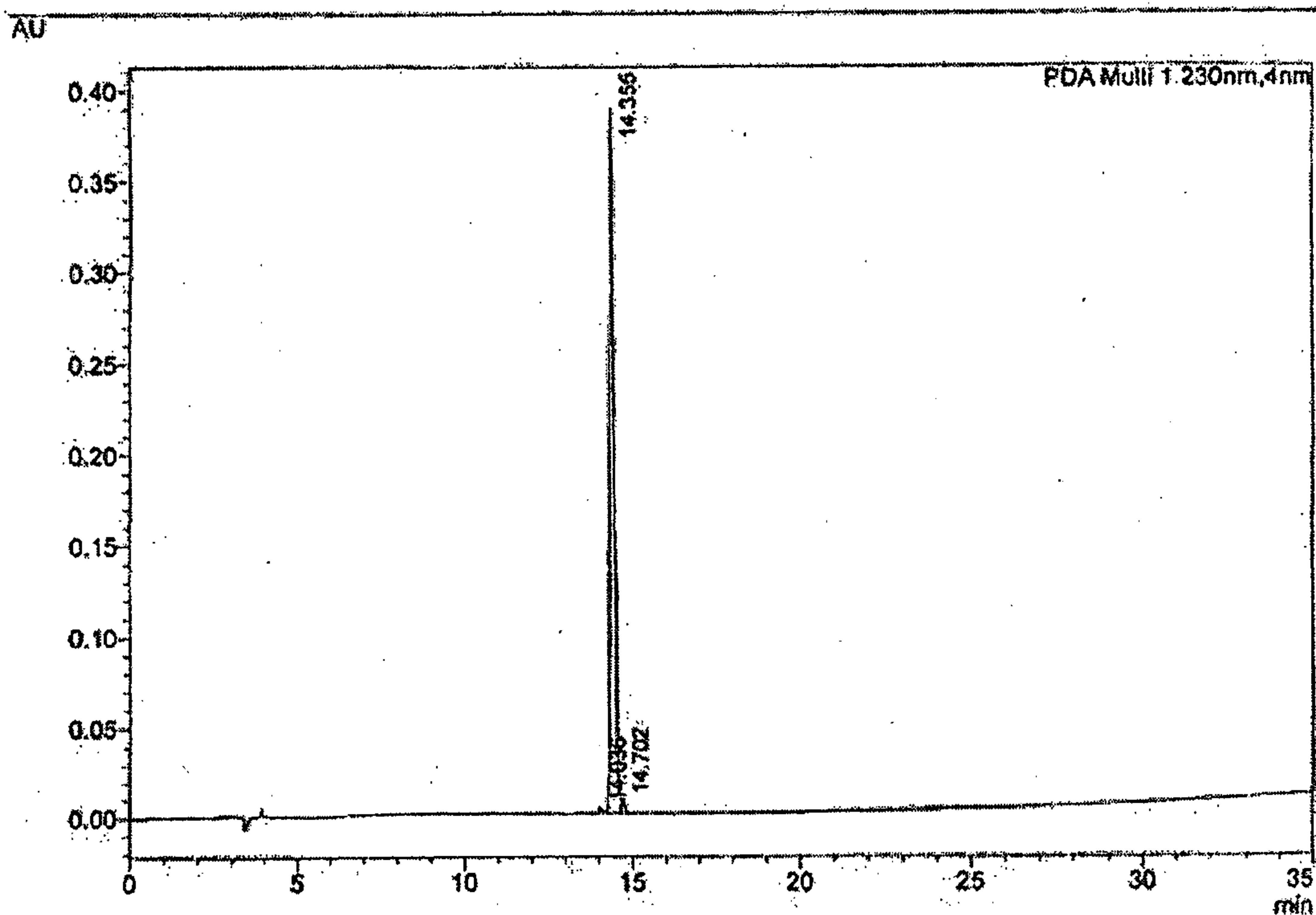


Analysis Report

<Sample Information>

Sample Name : K171858 (YDE-056)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	14.036	36272	0.999
2	14.355	3637845	97.433
3	14.702	56951	1.568
Total		3631088	100.000

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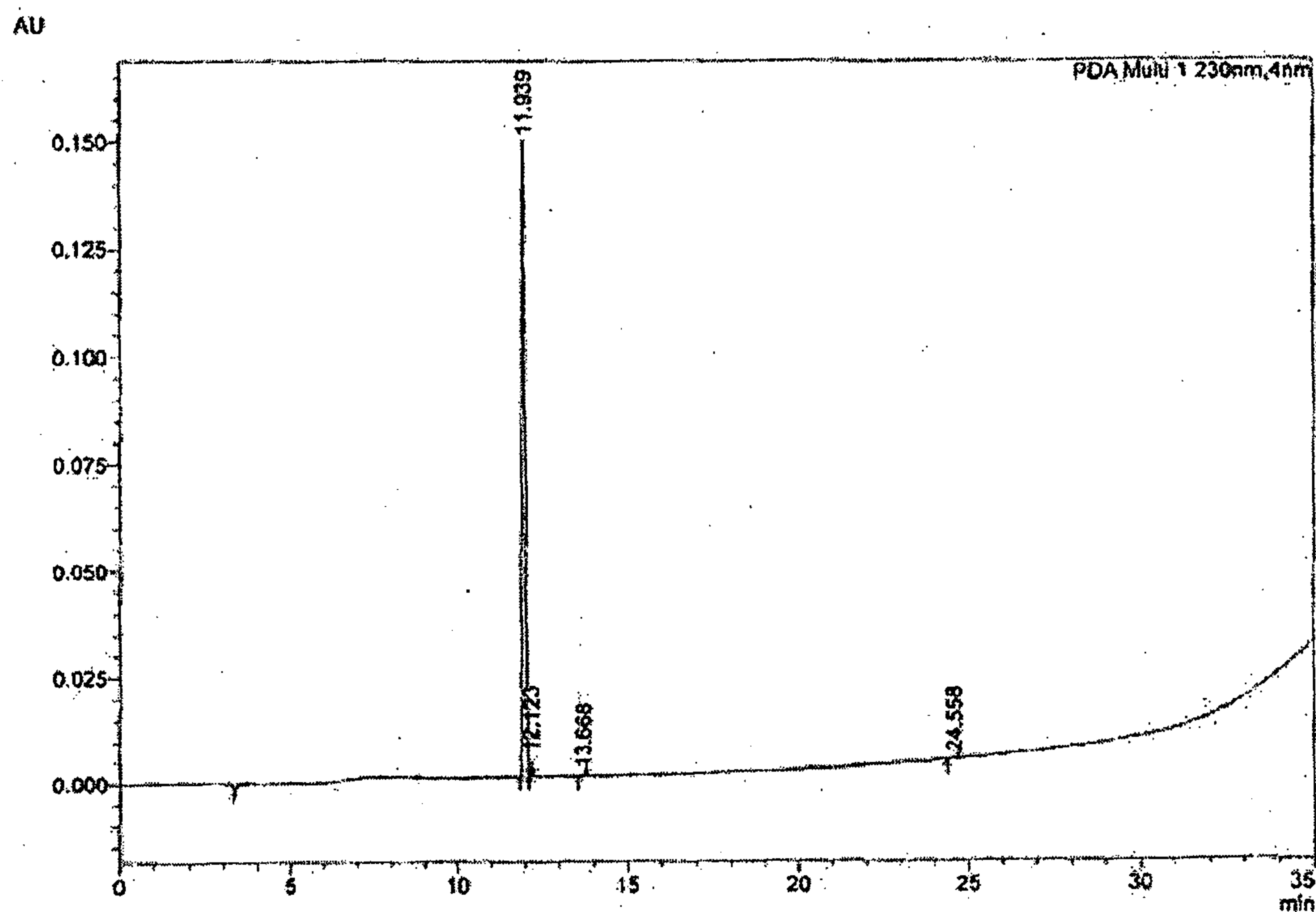
FIG 59

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name : K171869 (YDE-057)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	11.939	945100	98.813
2	12.123	6524	0.682
3	13.668	2176	0.227
4	24.558	2651	0.277
Total		956452	100.000

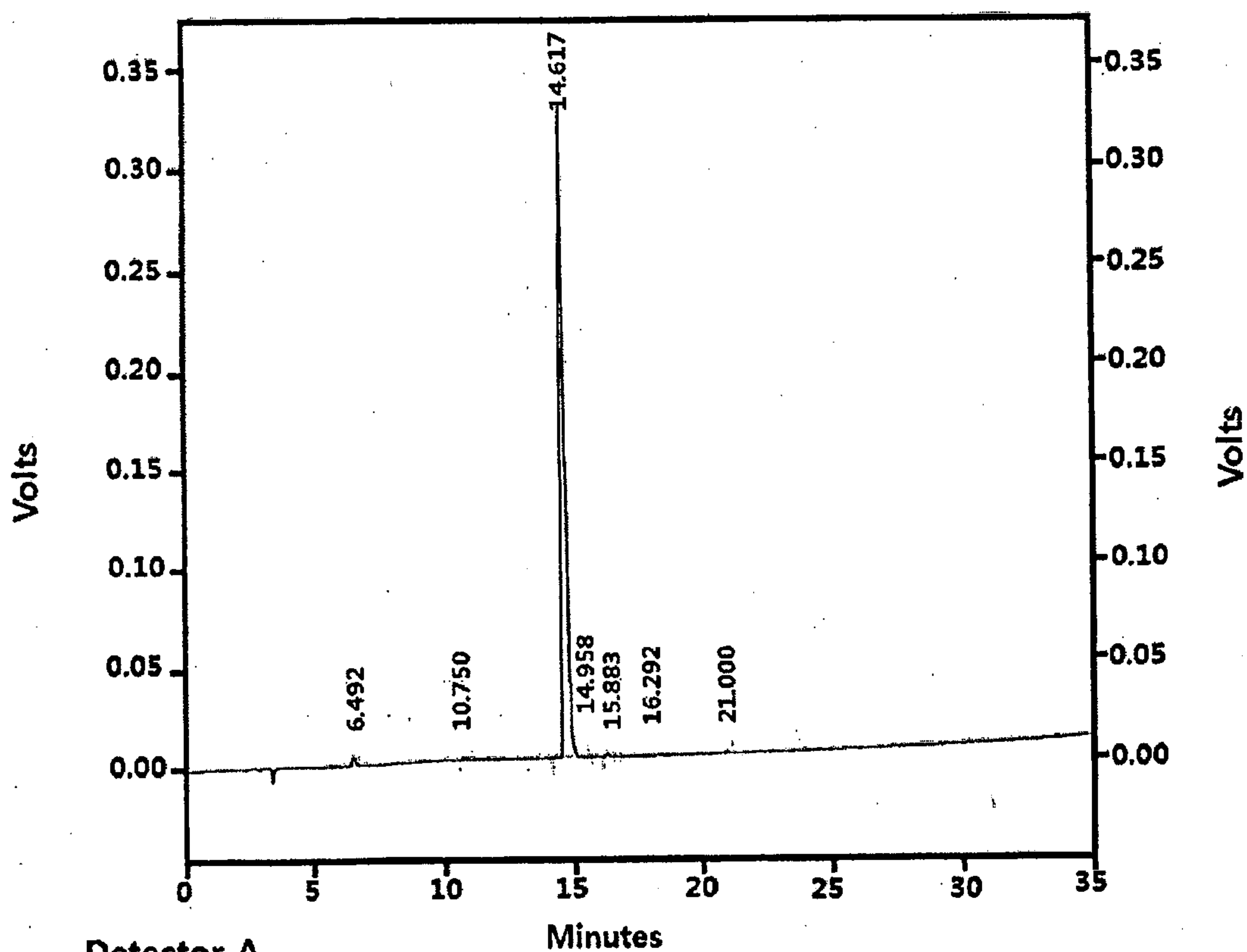
60/133

FIG 60

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K171870 (YDE-058)



Detector A

(230nm) Pk #

Retention Time

Area

Area %

1	6.492	36263	0.915
2	10.750	9609	0.243
3	14.617	3861560	97.473
4	14.958	33751	0.852
5	15.883	2210	0.056
6	16.292	13260	0.335
7	21.000	5001	0.126
Totals		3961654	100.000

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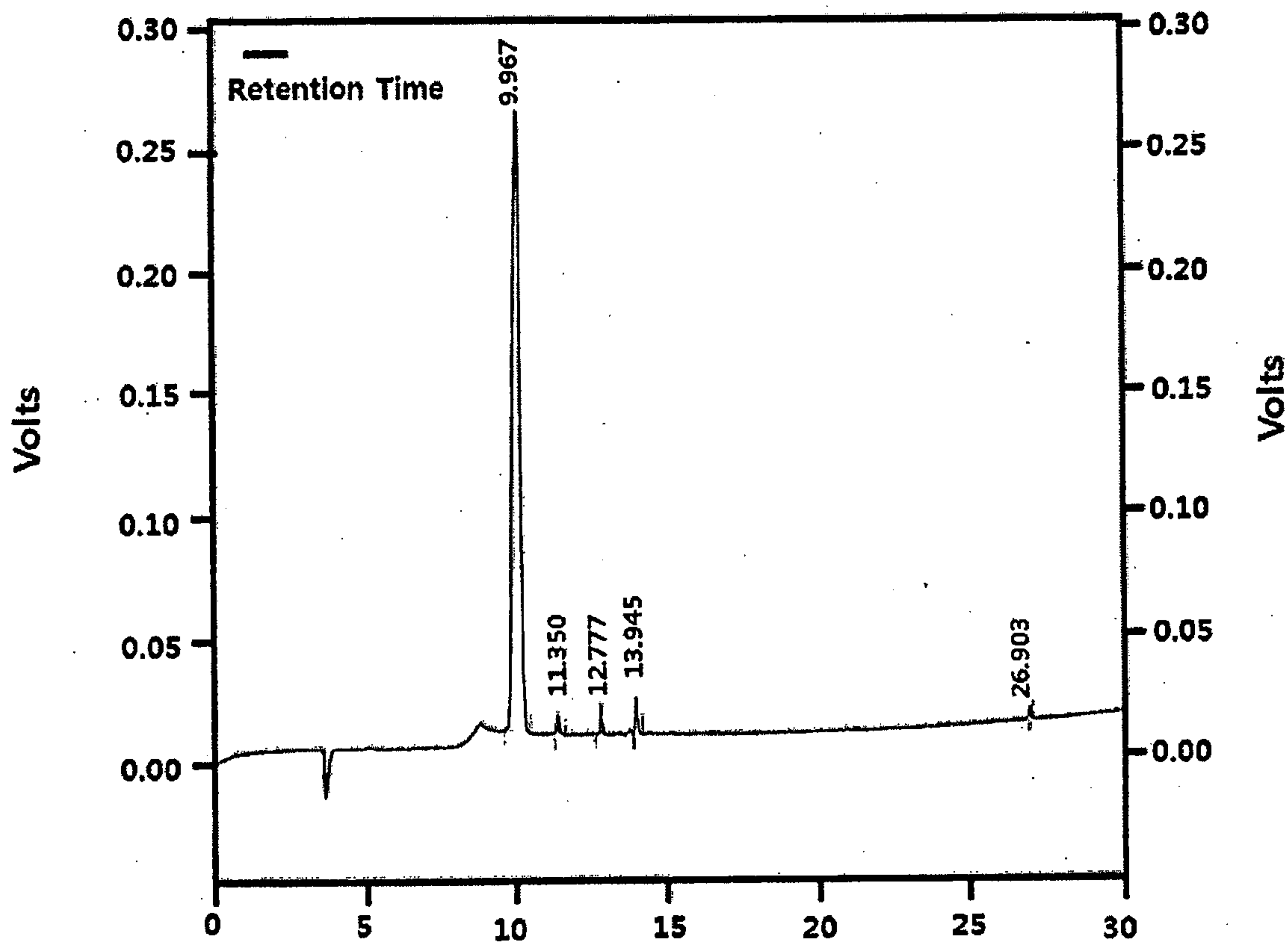
FIG 61

Shimadzu CLASS-VP V6.14 SP1 new 10AVP

Area % Report

Page of 1

Sample ID : K171871 (YDE-059)



Detector A (230nm) Pk #	Minutes Retention Time	Area	Area %
1	9.967	4241746	95.874
2	11.350	40399	0.913
3	12.777	52325	1.183
4	13.945	74918	1.693
5	26.903	14911	0.337
Totals		4424299	100.000

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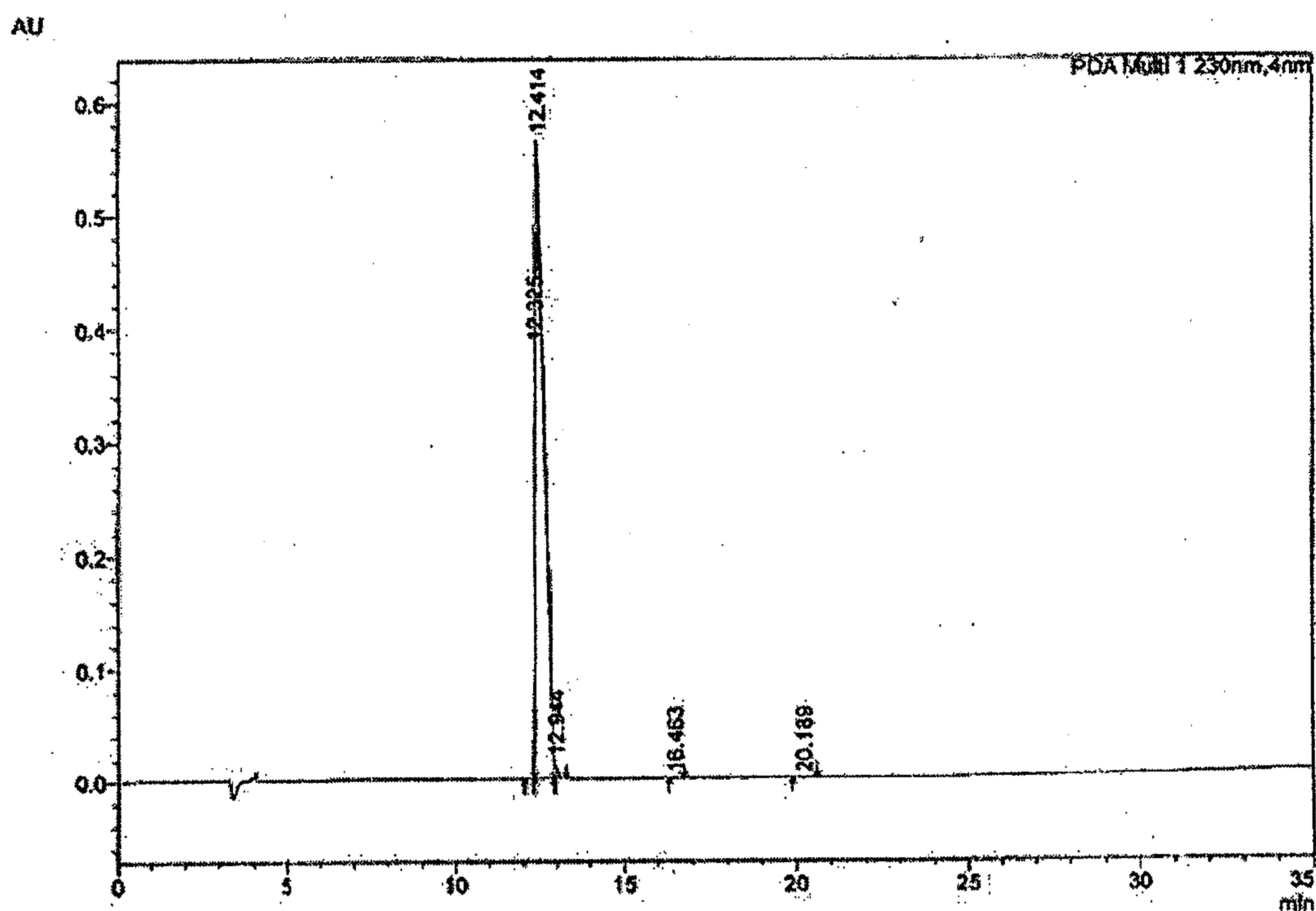
FIG 62

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name K171872 (YDE-060)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	12.325	21419	0.202
2	12.414	10477432	98.960
3	12.944	77001	0.727
4	16.463	6326	0.060
5	20.189	5396	0.051
Total		10587574	100.000

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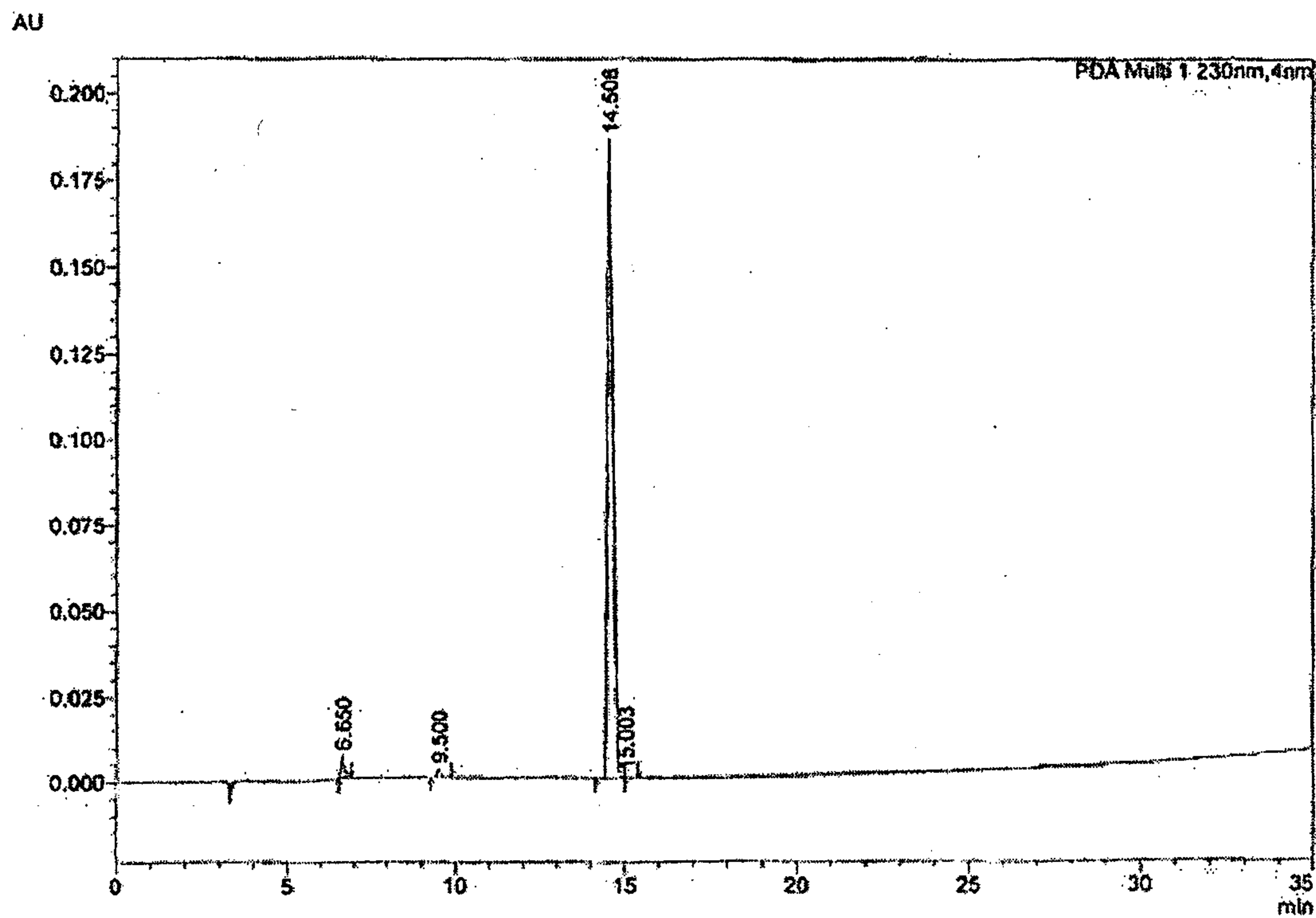
FIG 63

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name :K171987(YDE-064)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	6.650	45425	2.187
2	9.500	15738	0.758
3	14.508	2014246	96.975
4	15.003	1669	0.080
Total		2077077	100.000

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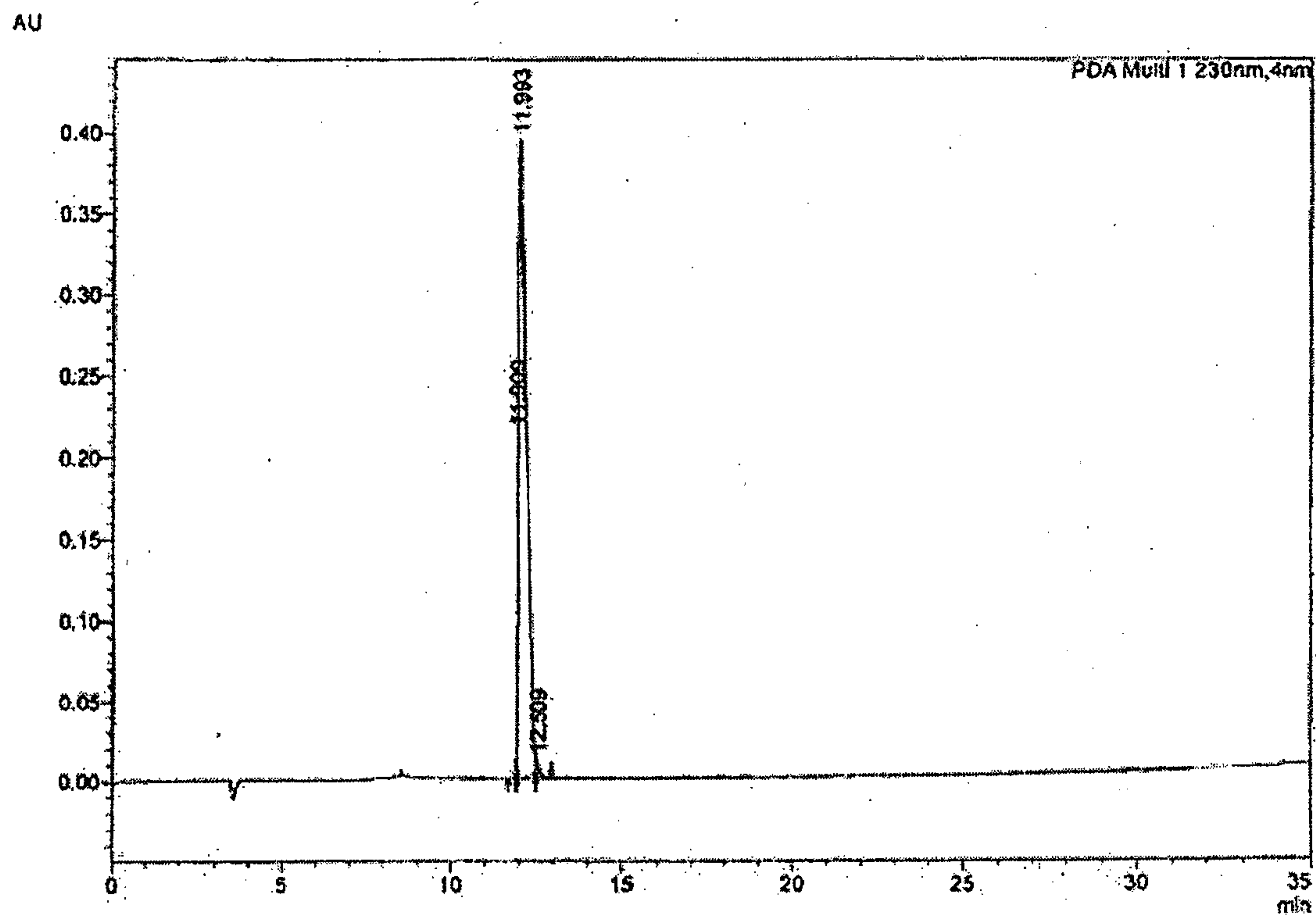
FIG 64

SHIMADZU
LabSolutions Analysis Report

<Sample Information>

Sample Name :K171989 (YDE-066)

<Chromatogram>



<Peak Table>

PDA Ch1.230nm

Peak#	Ret. Time	Area	Area%
1	11.909	1016	0.016
2	11.993	6411284	98.801
3	12.509	76758	1.183
Total		6489058	100.000

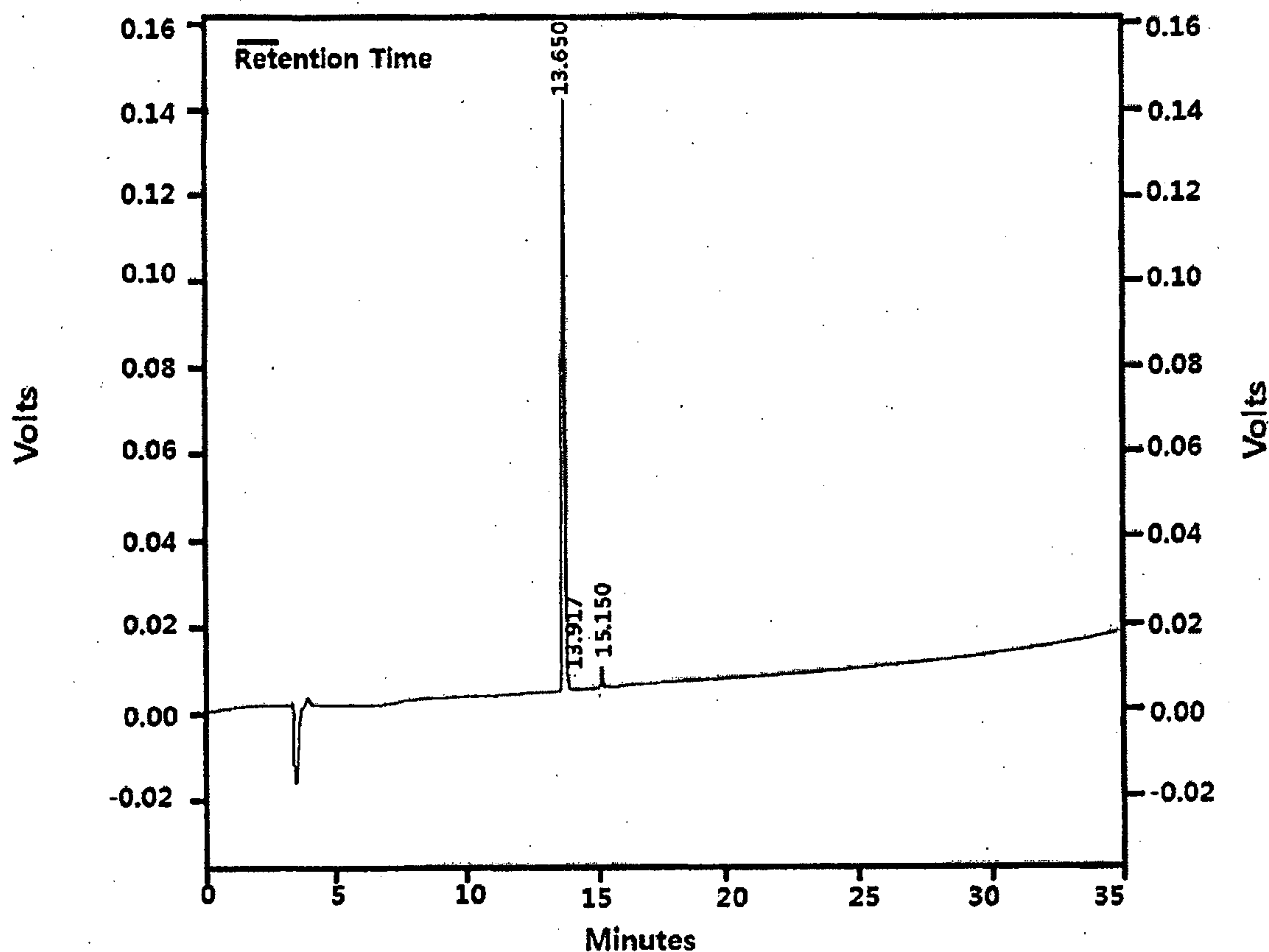
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FIG 65

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K180115 (YDE-072)



Detector A

(230nm)

Pk #	Retention Time	Area	Area %
1	13.650	1120198	97.732
2	13.917	1749	0.153
3	15.150	24243	2.115
Totals		1146190	100.000

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FIG 66

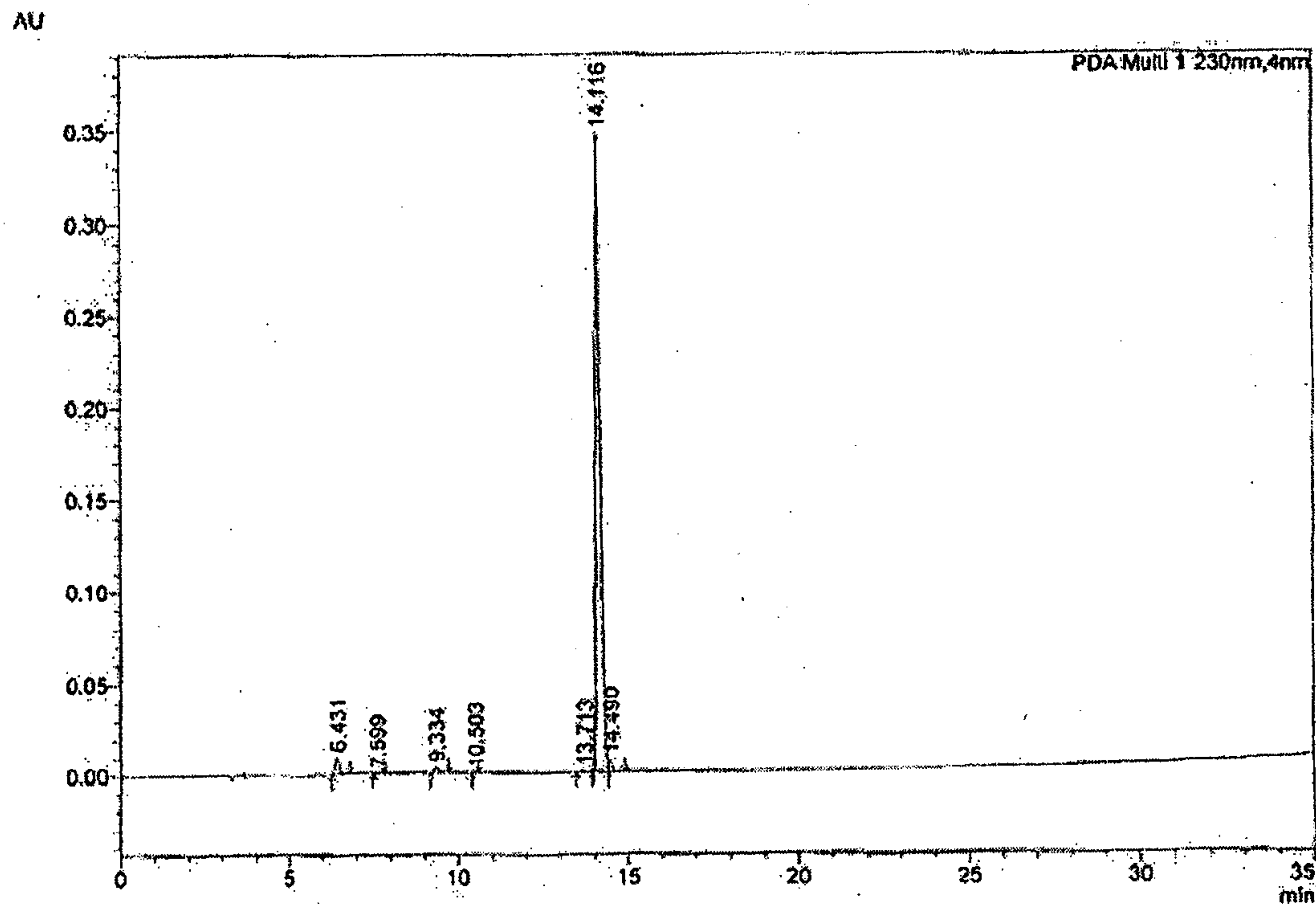


Analysis Report

<Sample Information>

Sample Name :K180116 (YDE-073)

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	6.431	84808	2.497
2	7.599	2612	0.077
3	9.334	26801	0.789
4	10.503	2243	0.066
5	13.713	11180	0.329
6	14.116	3228240	95.033
7	14.490	41081	1.209
Total		3396964	100.000

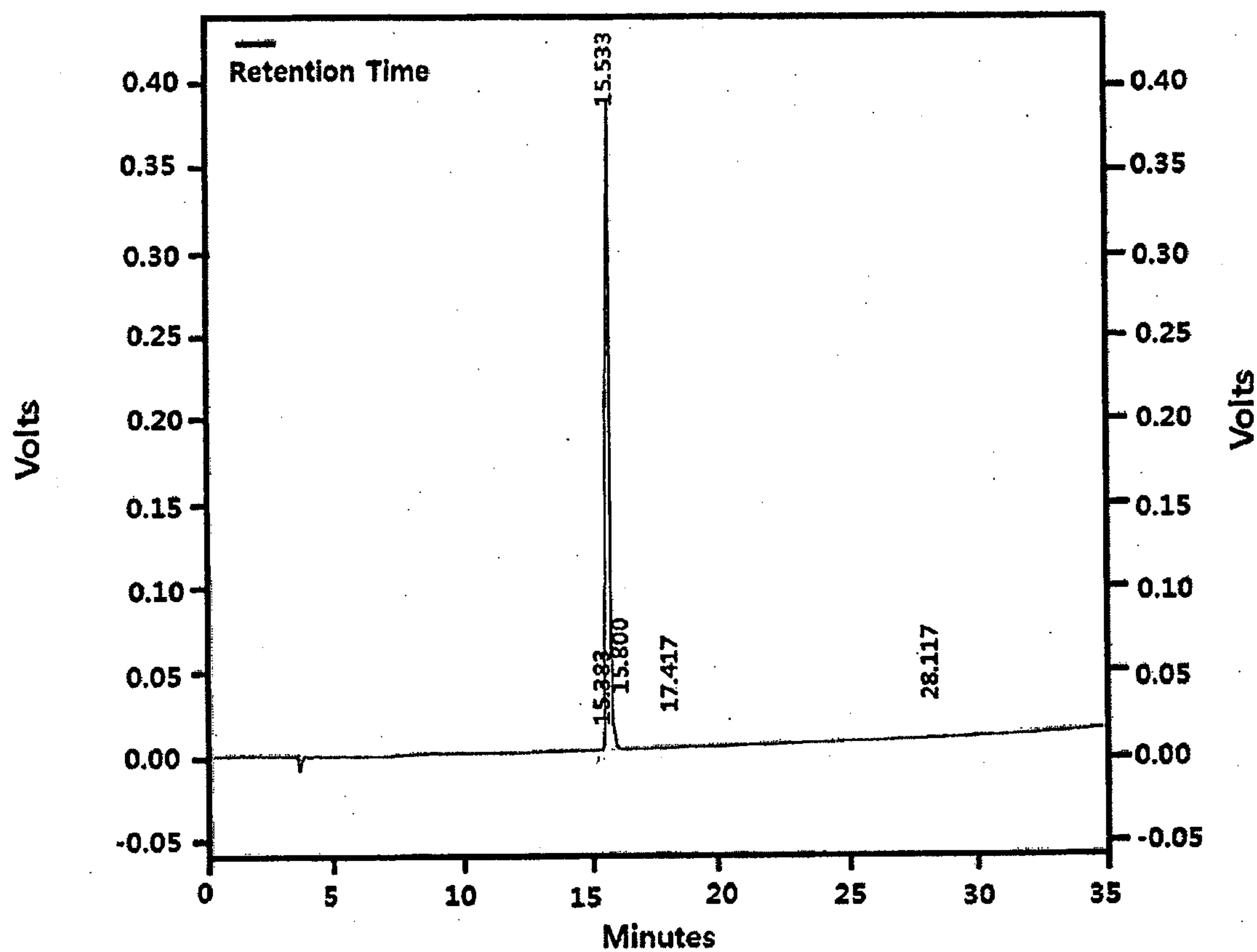
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FIG 67

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K180117 (YDE-074)



Detector A

(230nm) Pk #	Retention Time	Area	Area %
1	15.383	1715	0.042
2	15.533	3991816	97.947
3	15.800	78057	1.915
4	17.417	1505	0.037
5	28.117	2389	0.059
Totals		4075482	100.000

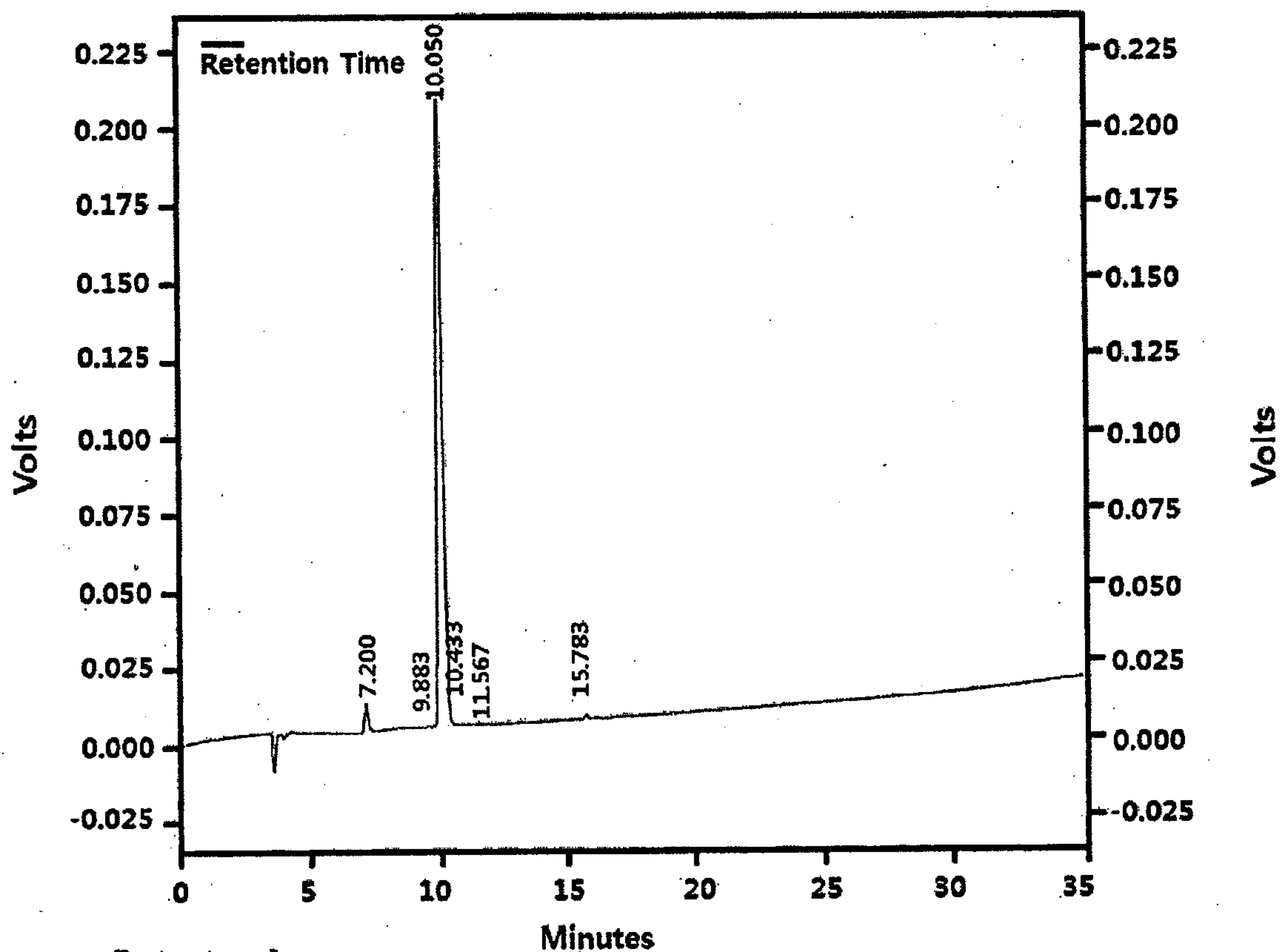
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FIG 68

Shimadzu CLASS-VP V6.14 SP1 20A_prep

Area % Report

Sample ID : K180118 (YDE-075)



Detector A

(230nm) pk #

Retention Time

Area

Area %

1	7.200	87289	2.762
2	9.883	1976	0.063
3	10.050	3045468	96.361
4	10.433	11869	0.376
5	11.567	3797	0.120
6	15.783	10067	0.319

Totals		3160466	100.000
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FIG 69

Anygen
K161389
Data: <Untitled> L9[c] 26 Sep 2016 12:56 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 29, P.Ext. @ 1000 (bin 56)
%Int. 223 mV Profiles 1-7: Threshold 25% Centroid [Adaptive]

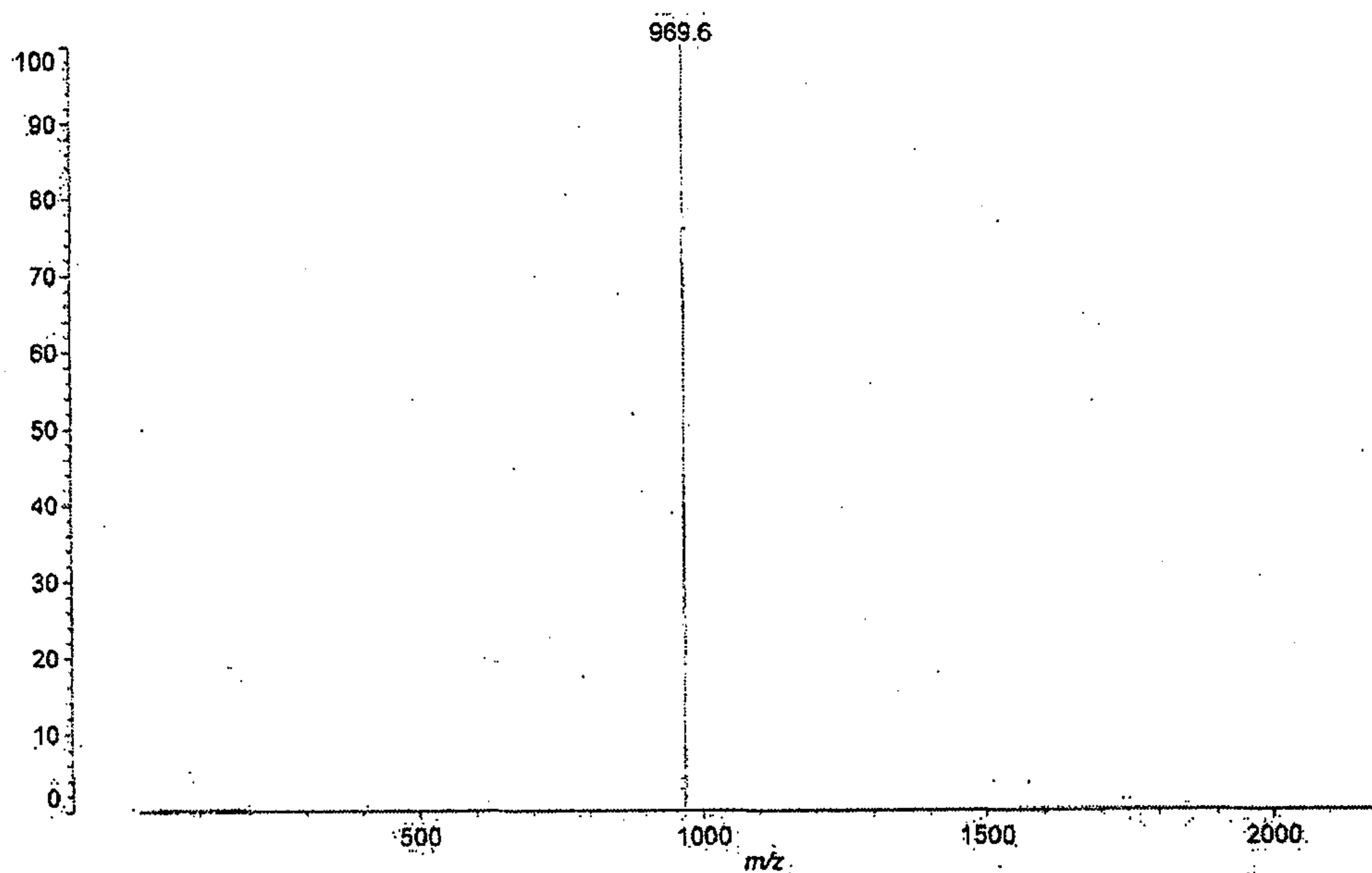
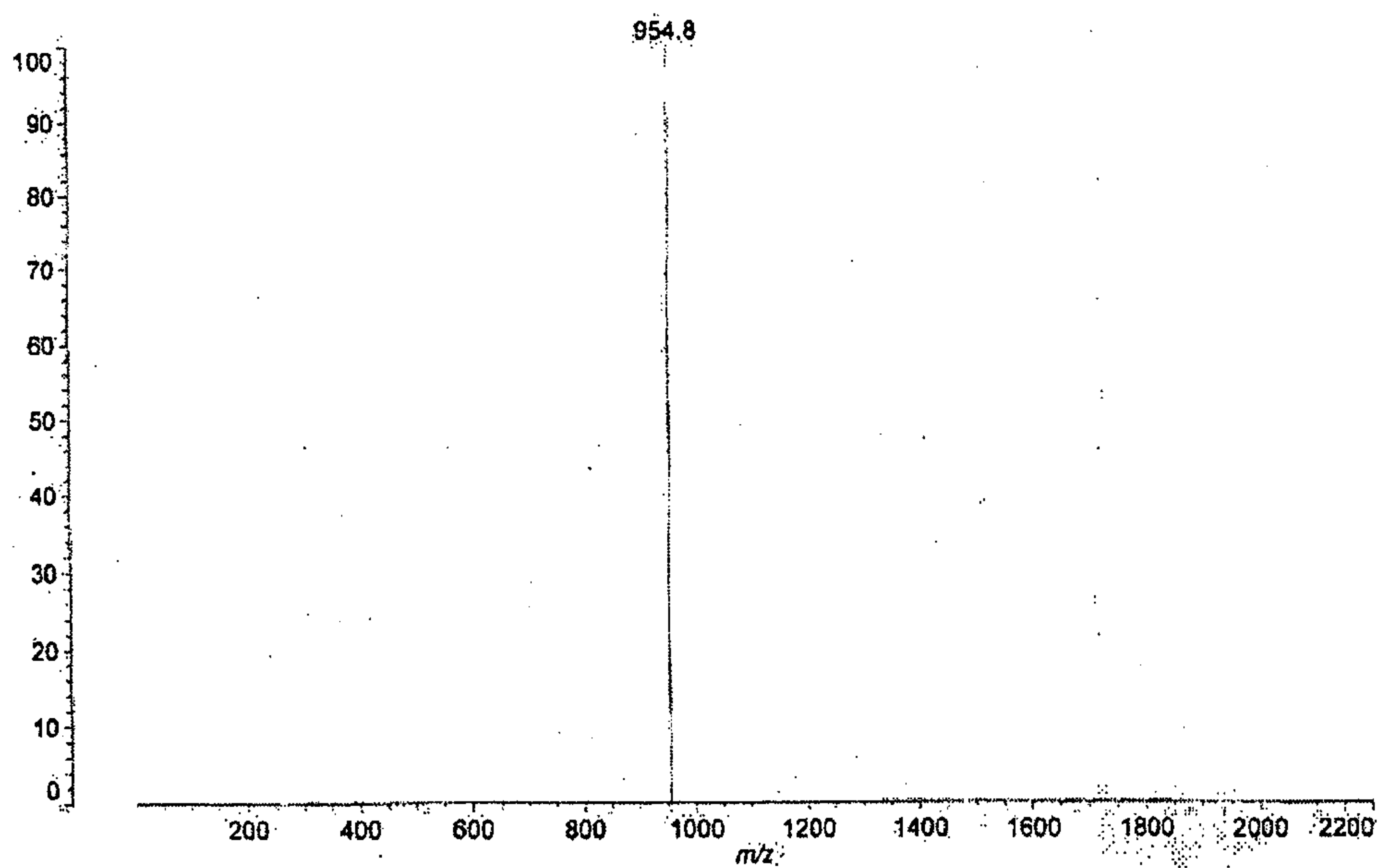


FIG 70

Anygen
K161390
Data: <Untitled> K9[c] 26 Sep 2016 12:56 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 29, P.Ext. @ 1000 (bin 56)
%Int. 196 mV Profiles 1-14: Threshold 25% Centroid [Adaptive]



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FIG 71

Anygen
K161391
Data: <Untitled>.E13[c] 27-Sep-2016 10:13 Cal: 7-Apr-2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 30, P.Ext. @ 1000 (bin 56)
%Int. 117 mV Profiles 1-15: Threshold 25% Centroid [Adaptive]

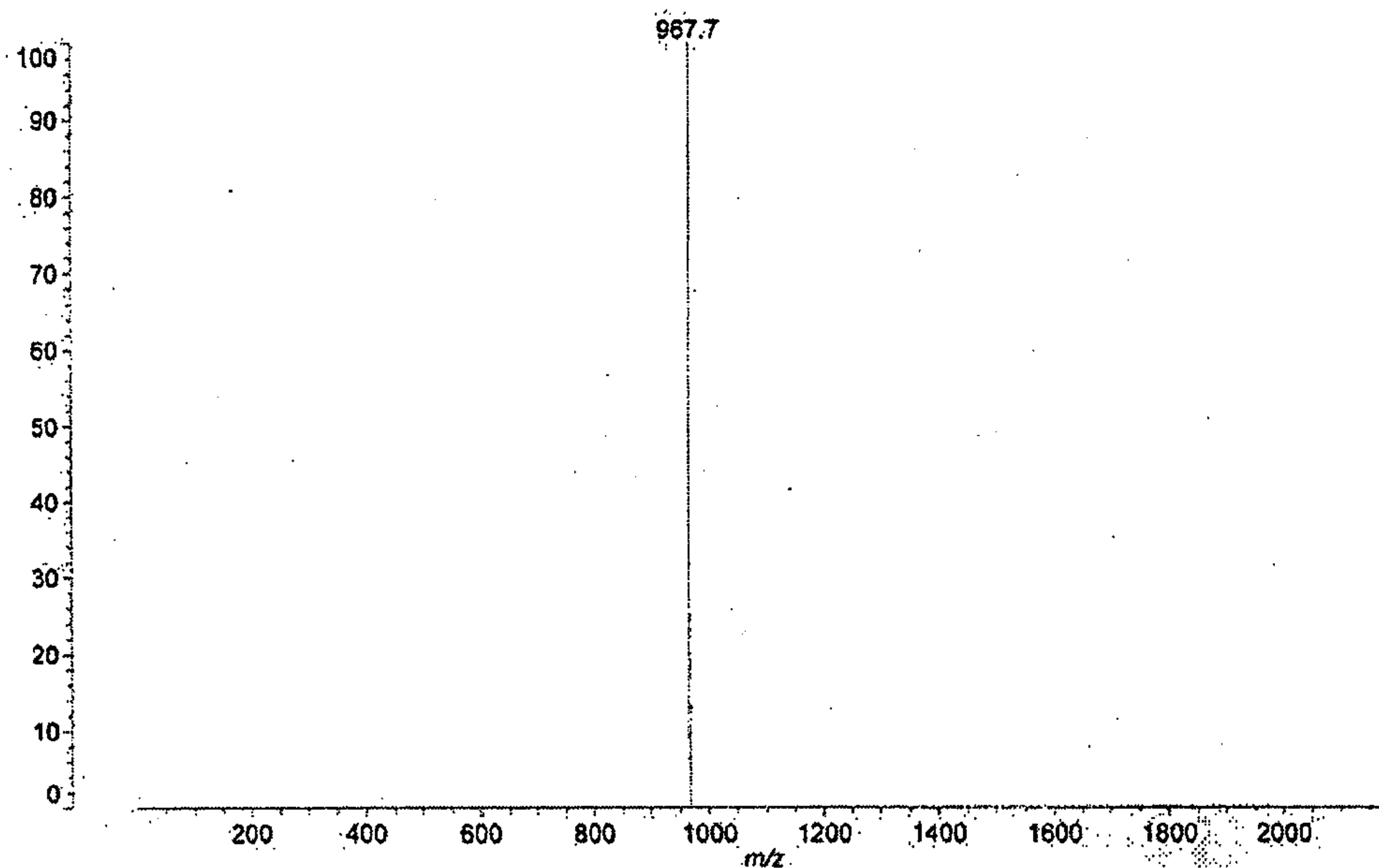
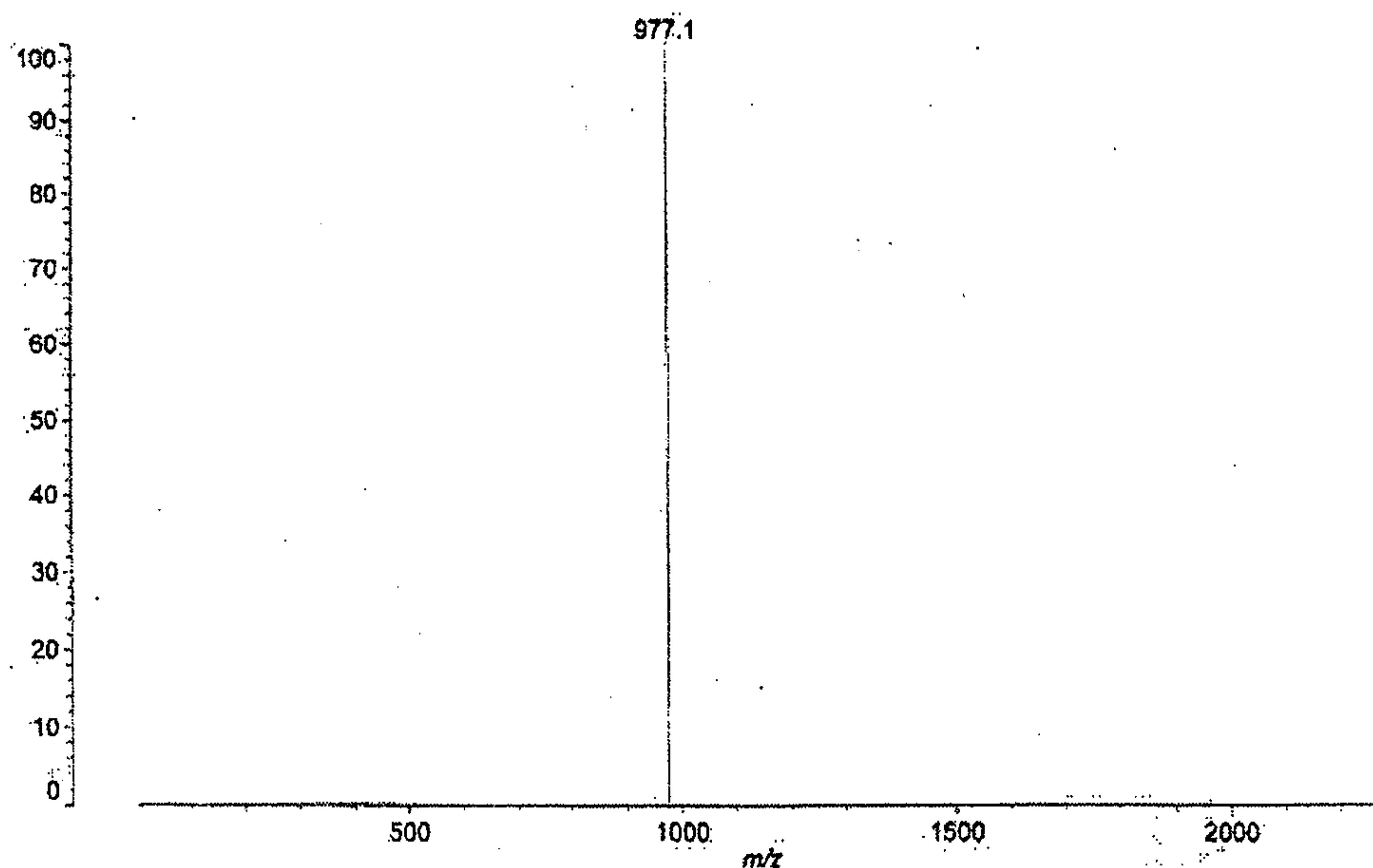


FIG 72

Anygen
K161392
Data: <Untitled>.F13[c] 27-Sep-2016 10:15 Cal: 7-Apr-2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 30, P.Ext. @ 1000 (bin 56)
%Int. 1974 mV Profiles 1-6: Threshold 25% Centroid [Adaptive]



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FIG 73

Anygen
K161393
Data: K161393-0002.G13[c] 27 Sep 2016 10:15 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 30, P.Ext. @ 1000 (bin 56)
%Int. 147 mV Profiles 1-24: Threshold 25% Centroid [Adaptive]

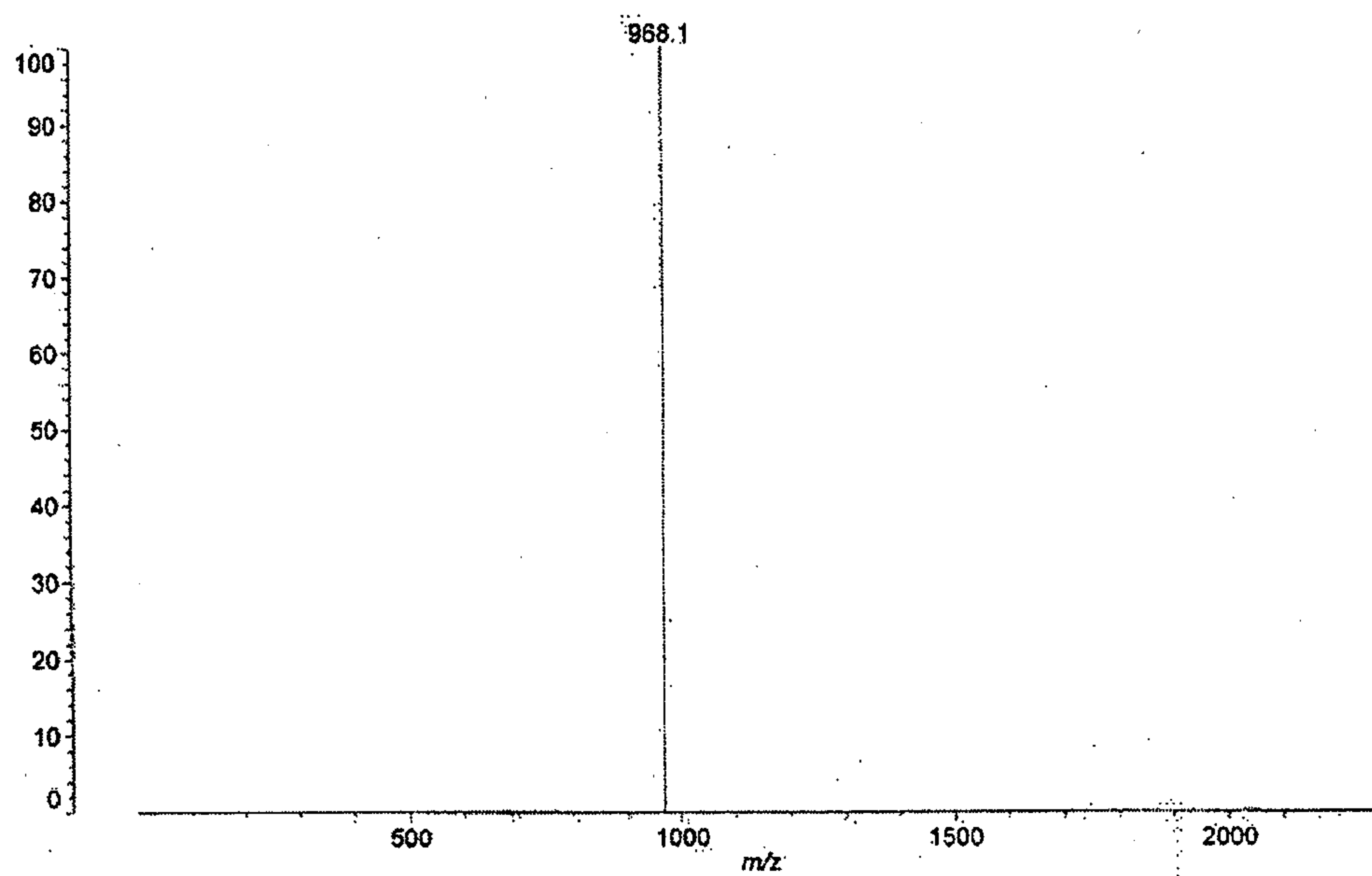
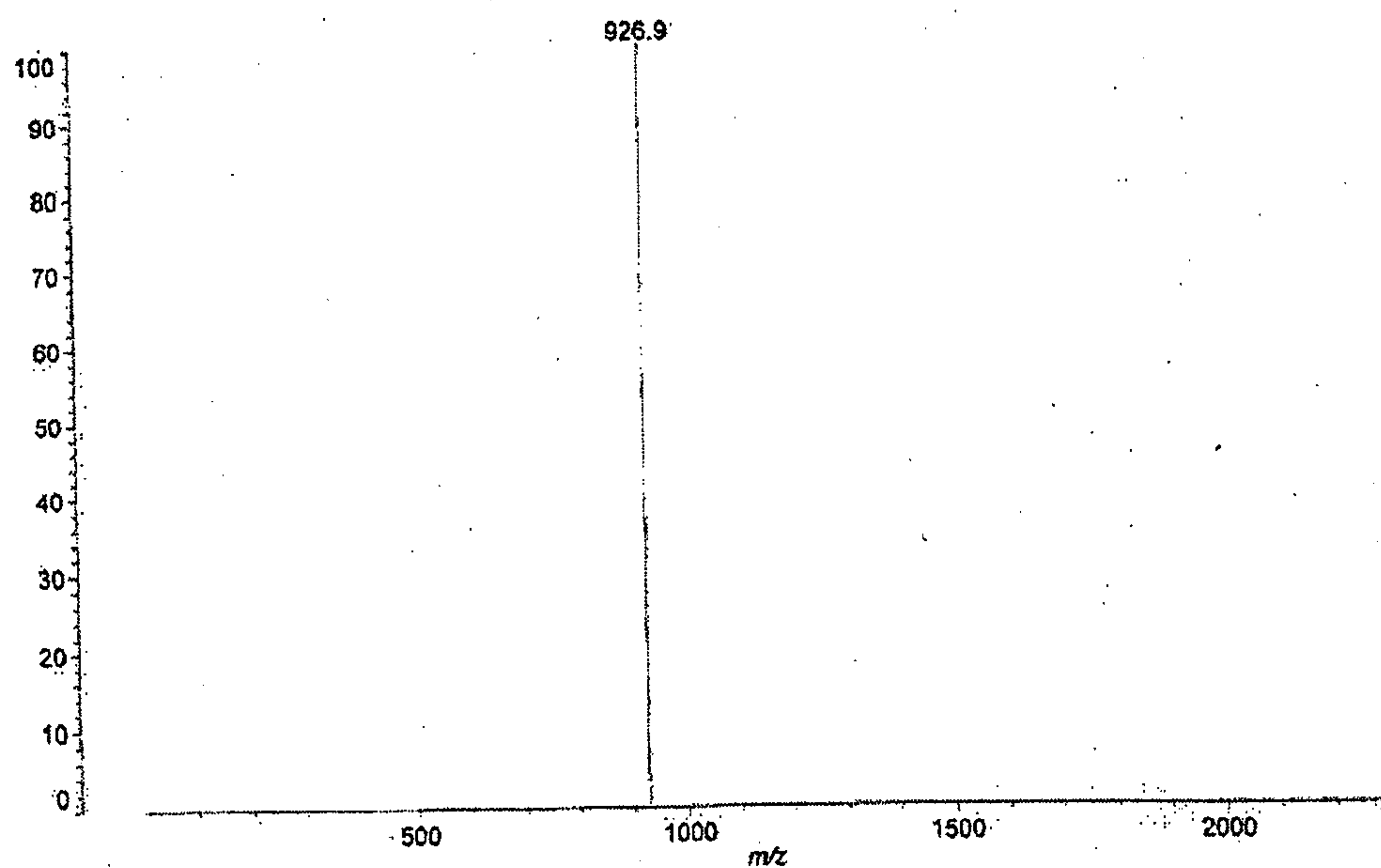


FIG 74

Anygen
K161394
Data: K161394-0002.H13[c] 27 Sep 2016 10:16 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 39, P.Ext. @ 1000 (bin 56)
%Int. 168 mV Profiles 1-51: Threshold 25% Centroid [Adaptive]



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FIG 75

Anygen
K161395
Data: K161395-0002.I13[c] 27 Sep 2016 10:16 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 39, P.Ext. @ 1000 (bin 56)
%Int. 303 mV Profiles 1-56: Threshold 25% Centroid [Adaptive]

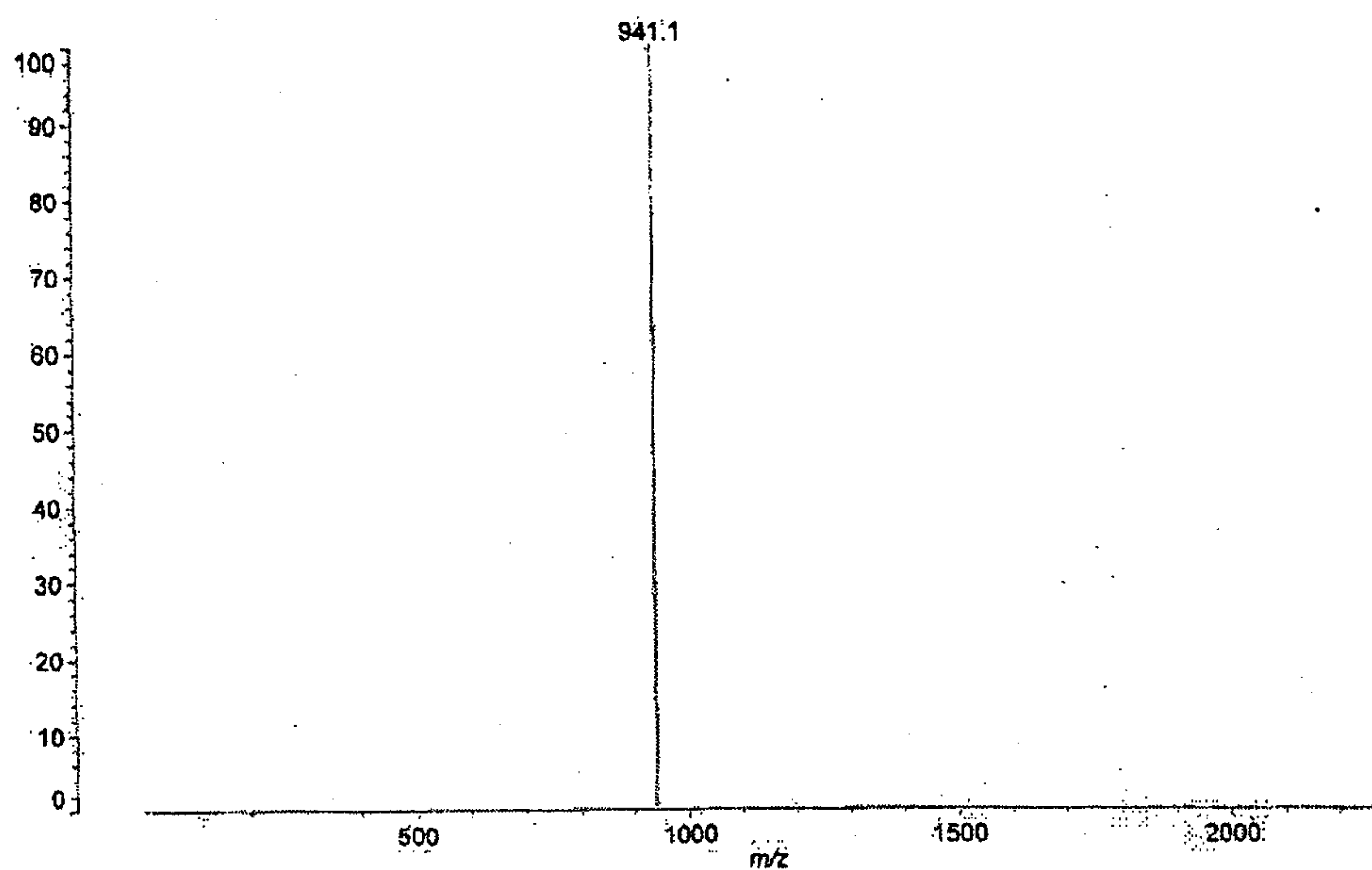
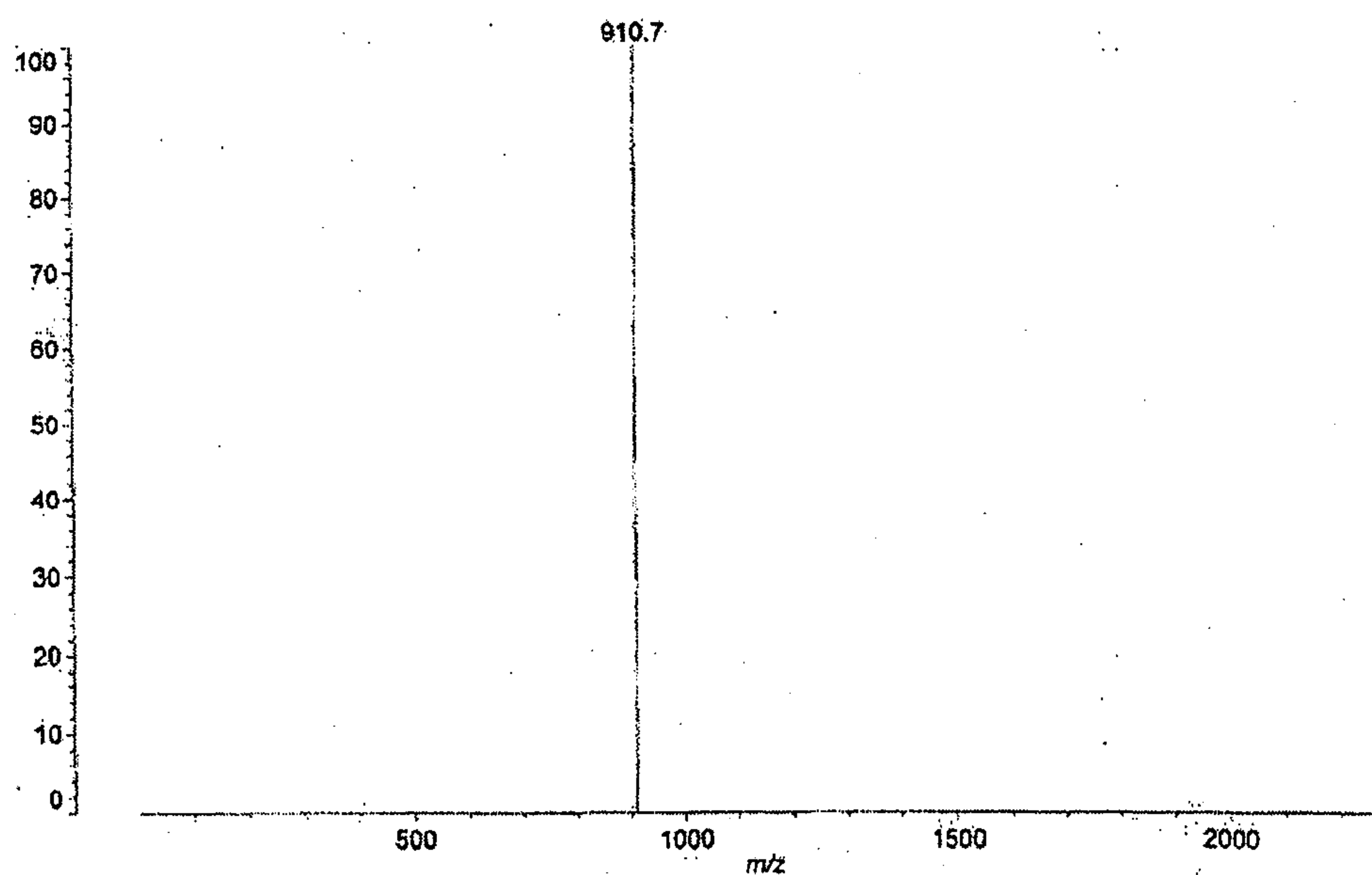


FIG 76

Anygen
K161396
Data: K161396-0002.J13[c] 27 Sep 2016 10:17 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 39, P.Ext. @ 1000 (bin 56)
%Int. 510 mV Profiles 1-10: Threshold 25% Centroid [Adaptive]



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FIG 77

Anygen
K161397
Data: <Untitled>.J9[c] 26 Sep 2016 12:56 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 29, P.Ext. @ 1000 (bin 56)
%Int. 55 mV Profiles 1-14: Threshold 25% Centroid [Adaptive]

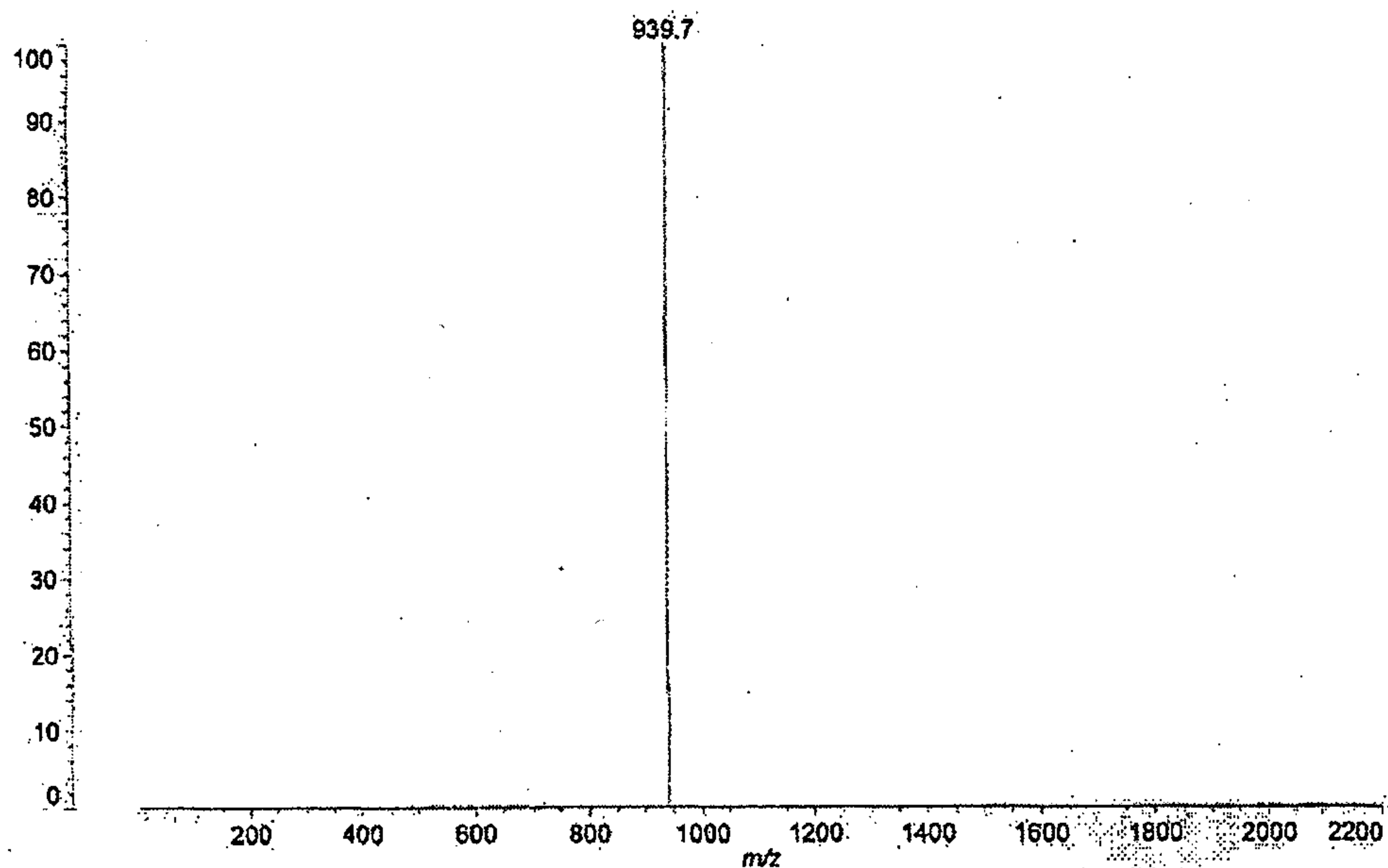
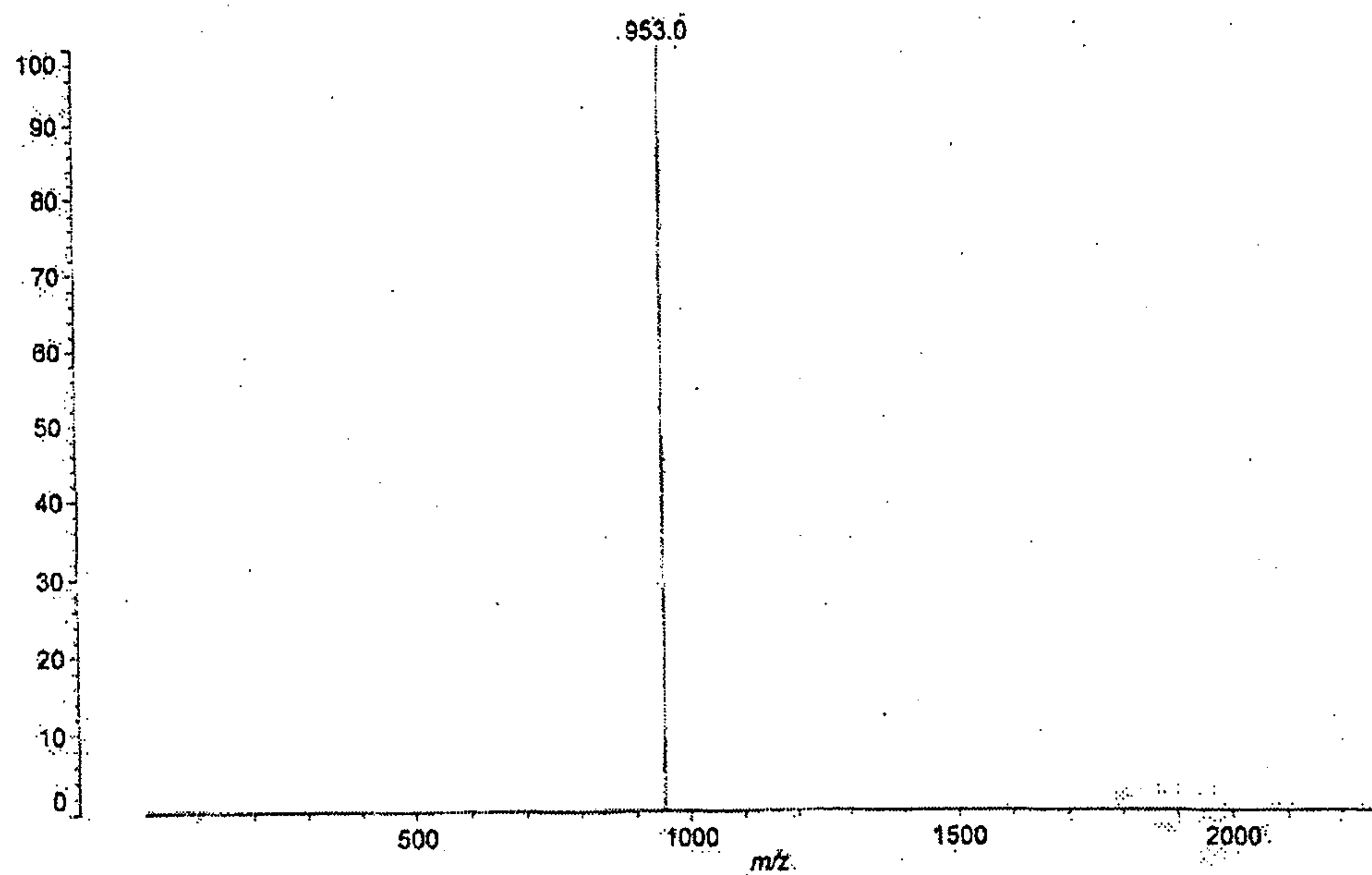


FIG. 78

Anygen
K161398
Data: K161398-0001:K13[c] 27 Sep 2016 10:18 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 31, P.Ext. @ 1000 (bin 56)
%Int. 30 mV Profiles 1-53: Threshold 25% Centroid [Adaptive]



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FIG 79

Anygen
K161399
Data: <Untitled>.I9[c] 26 Sep 2016 12:55 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 29, P.Ext. @ 1000 (bin 56)
%Int. 11 mV Profiles 1-52: Threshold 25% Centroid [Adaptive]

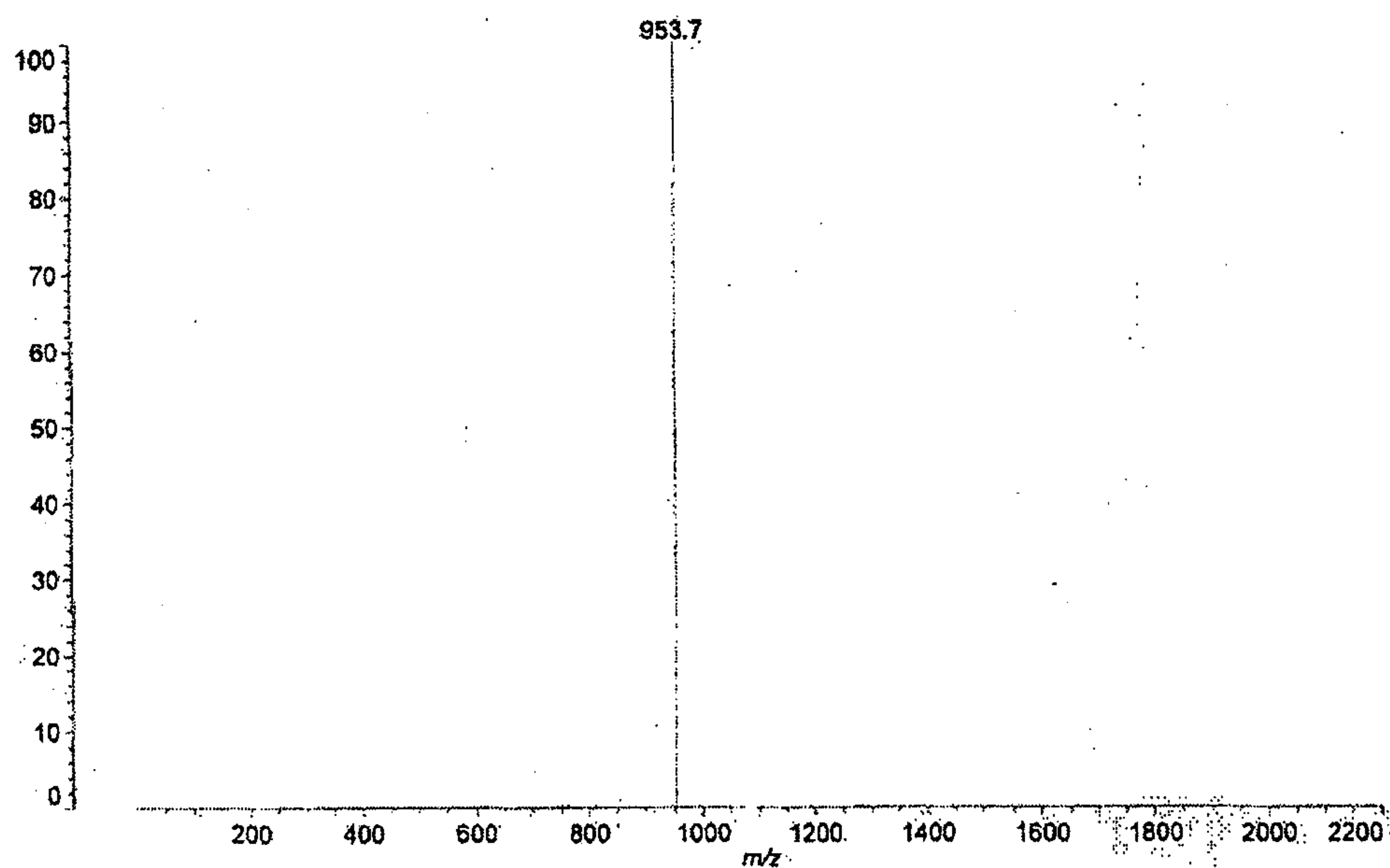
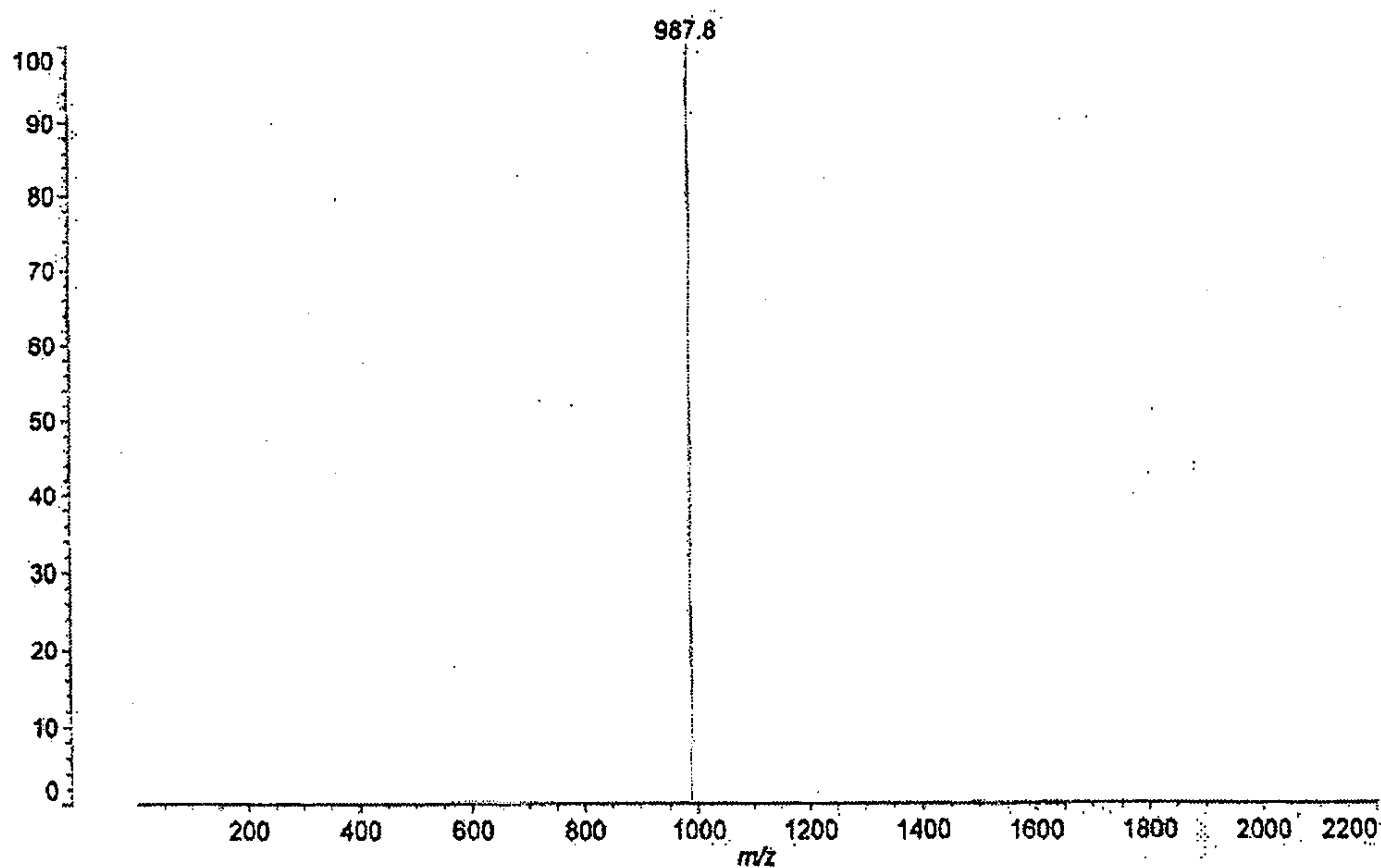


FIG 80

Anygen
K161400
Data: <Untitled>.H9[c] 26 Sep 2016 12:55 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 29, P.Ext. @ 1000 (bin 56)
%Int. 179 mV Profiles 1-73: Threshold 25% Centroid [Adaptive]



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FIG 81

Anygen
K161401
Data: <Untitled>.G9[c] 26 Sep 2016 12:54 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 29, P.Ext. @ 1000 (bin 56)
%Int. 295 mV Profiles 1-7: Threshold 25% Centroid [Adaptive]

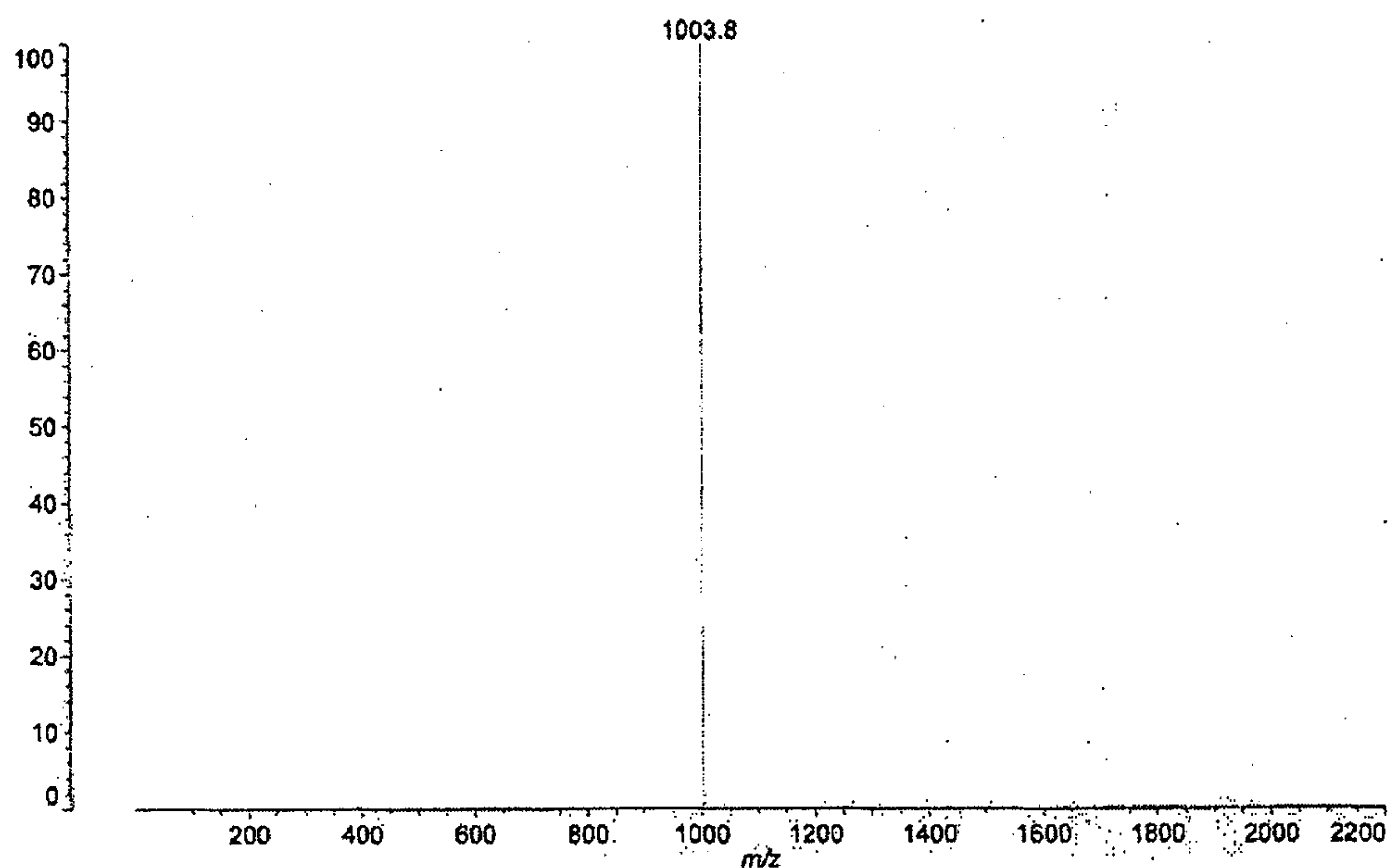
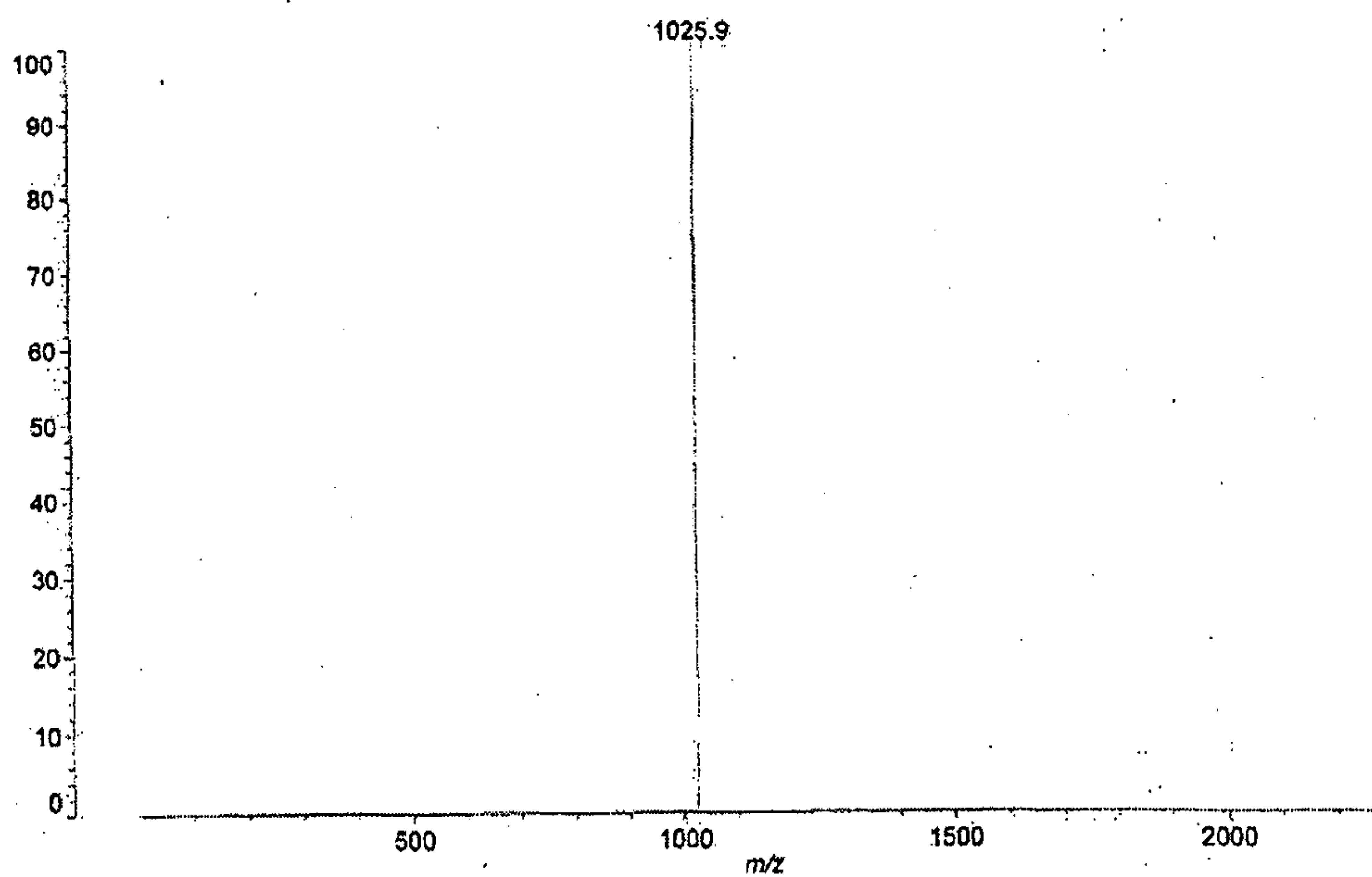


FIG 82

Anygen
K161402
Data: K161402-0001.L13[c] 27 Sep 2016 10:18 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 34, P.Ext. @ 1000 (bin 56)
%Int. 309 mV Profiles 1-7: Threshold 25% Centroid [Adaptive]



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FIG 83

Anygen
K161403
Data: <Untitled>.M13[c] 27 Sep 2016 10:18 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 34, P.Ext. @ 1000 (bin 56)
%Int. 19 mV Profiles 1-101: Threshold 25% Centroid [Adaptive]

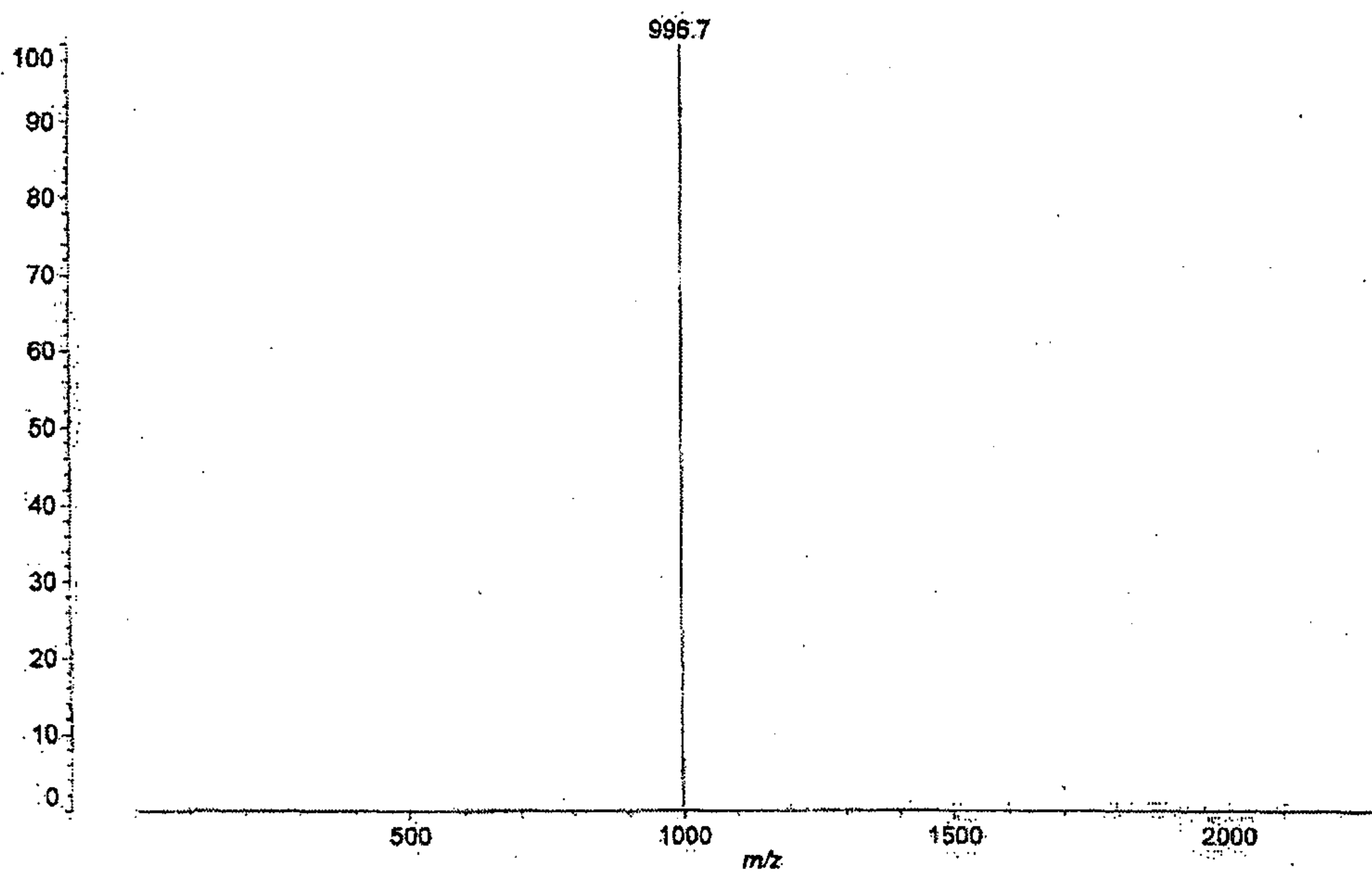
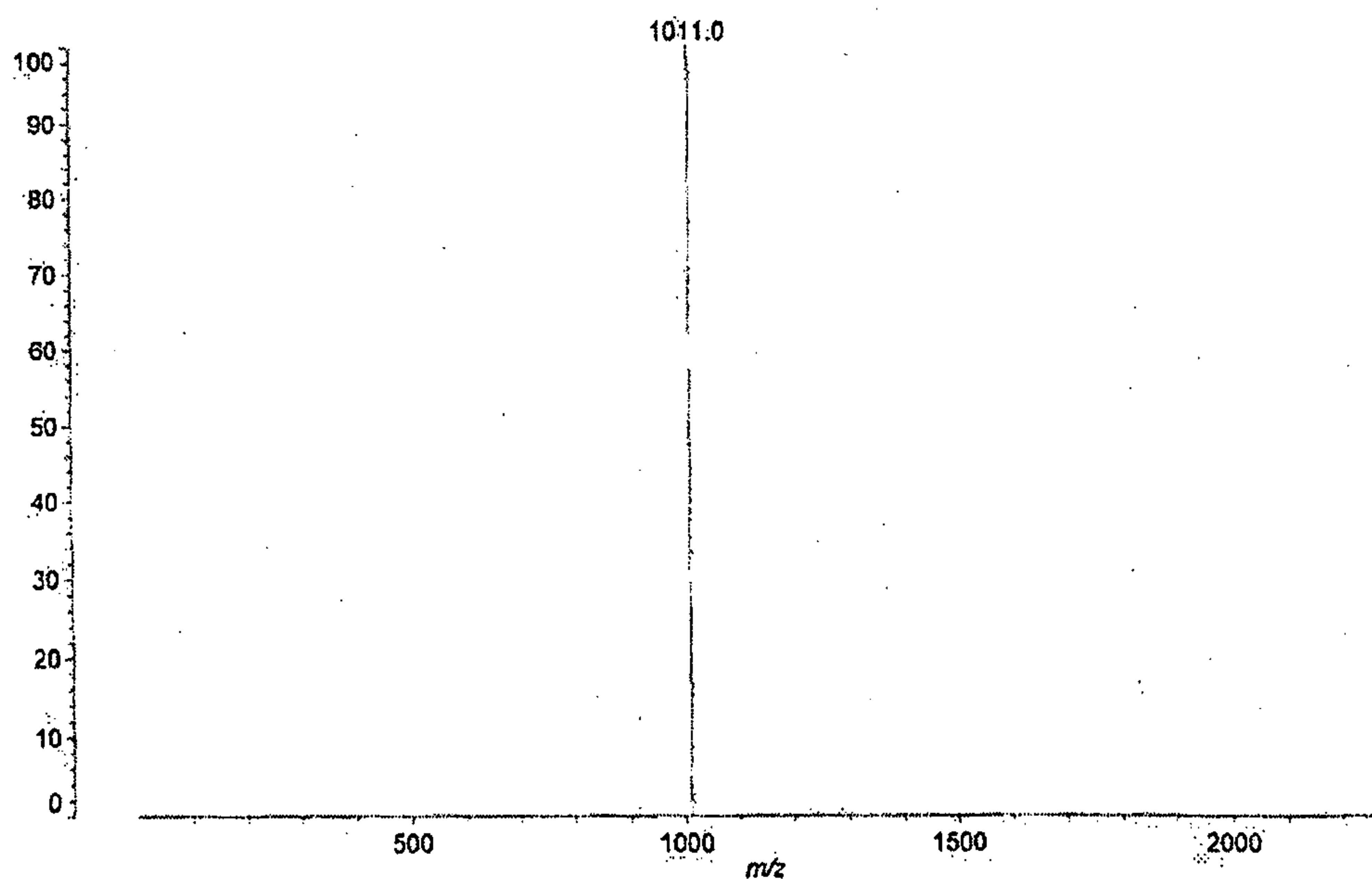


FIG 84

Anygen
K161404
Data: K161404-0001.N13[c] 27 Sep 2016 10:19 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 40, P.Ext. @ 1000 (bin 56)
%Int. 162 mV Profiles 1-85: Threshold 25% Centroid [Adaptive]



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FIG 85

Anygen
K161405
Data: <Untitled>.M16[c] 28 Sep 2016 13:09 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 22, P.Ext. @ 1000 (bin 56)
%Int. 64 mV Profiles 1-106: Threshold 25% Centroid [Adaptive]

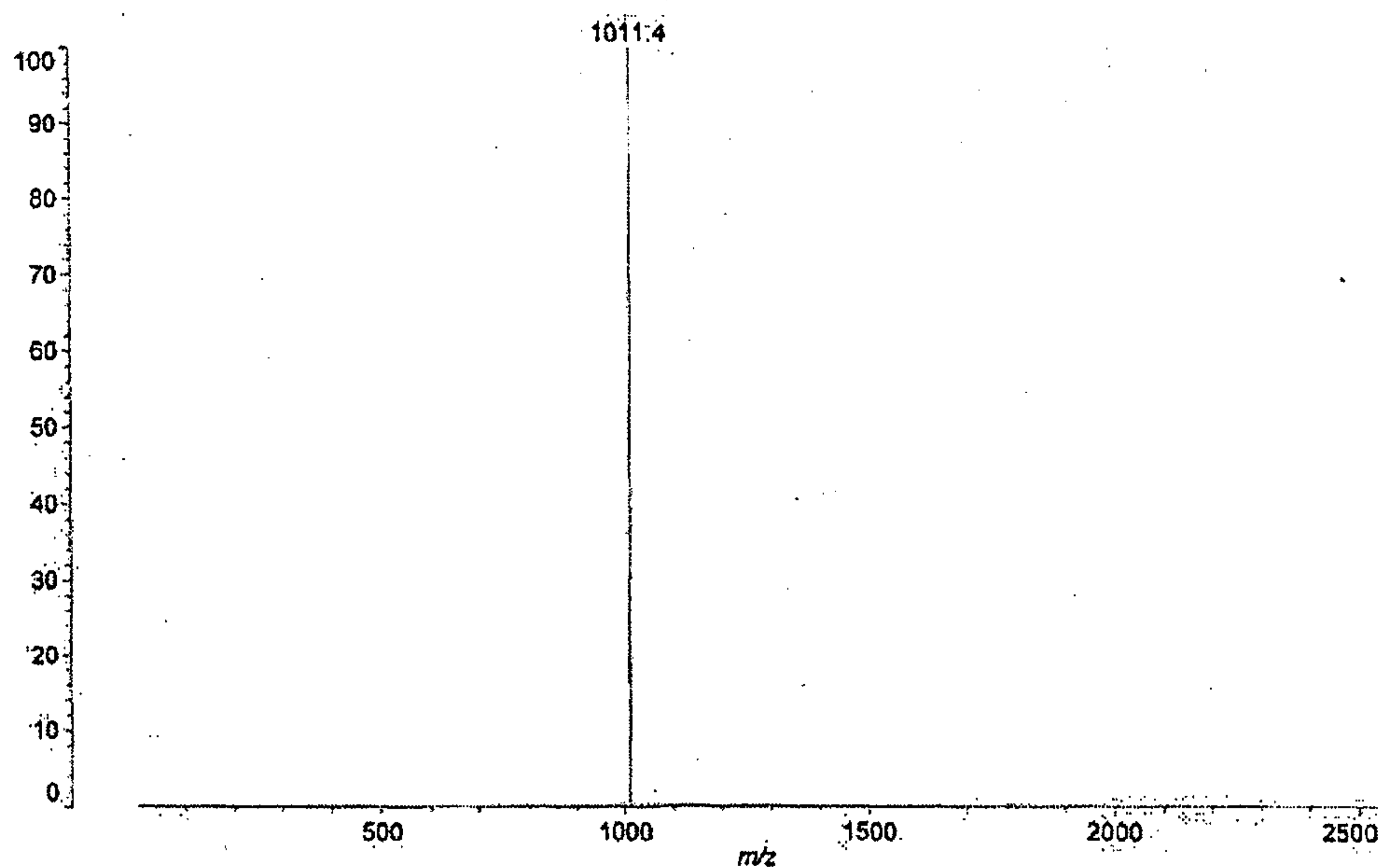
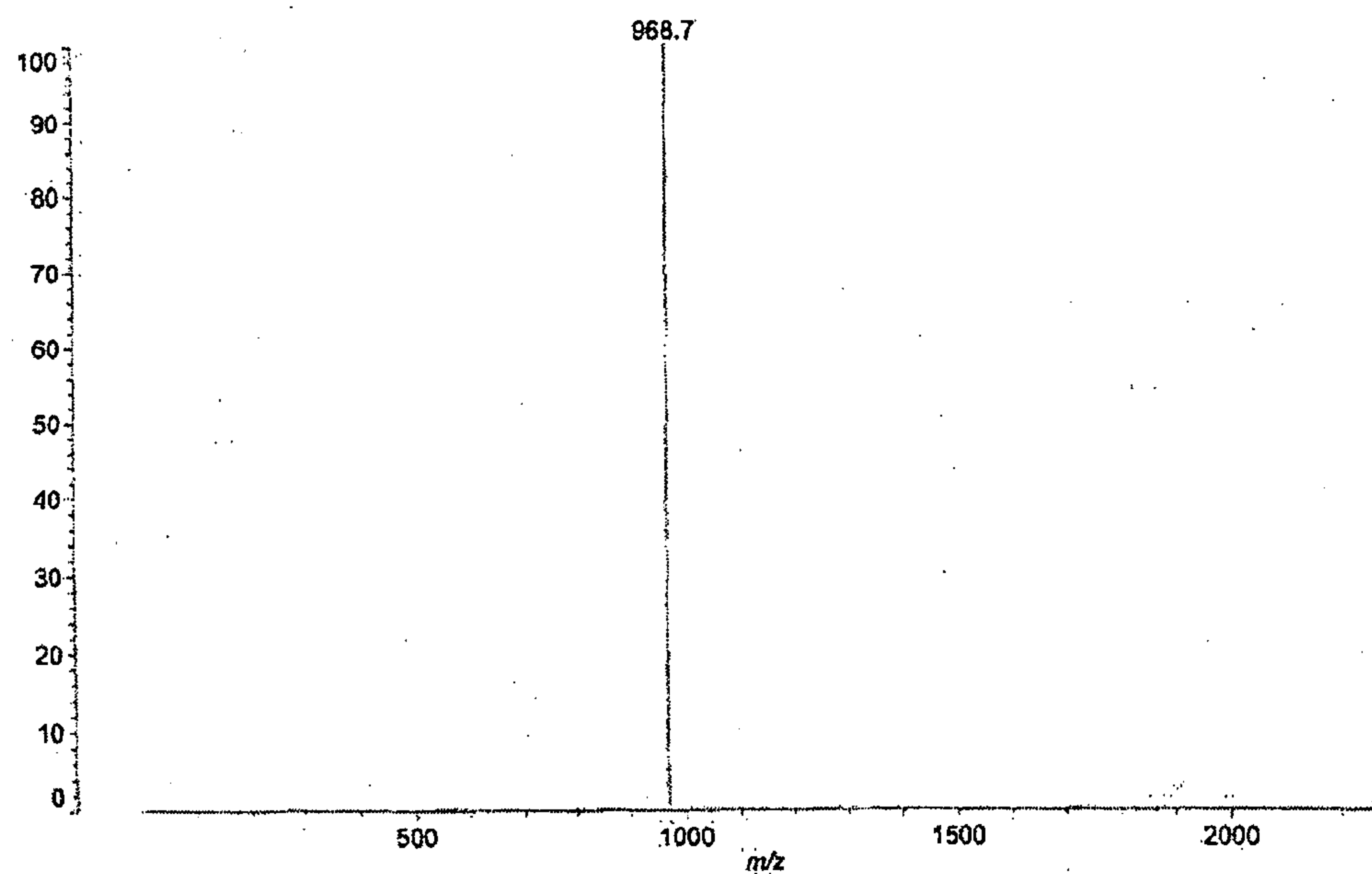


FIG 86

Anygen
K161406
Data: <Untitled>.O13[c] 27 Sep 2016 10:20 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 37, P.Ext. @ 1000 (bin 56)
%Int. 25 mV Profiles 1-55: Threshold 25% Centroid [Adaptive]



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FIG 87

Anygen
K161407
Data: <Untitled>.P13(c) 27 Sep 2016 10:20 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 37, P.Ext. @ 1000 (bin 56)
%Int. 337 mV Profiles 1-132: Threshold 25% Centroid [Adaptive]

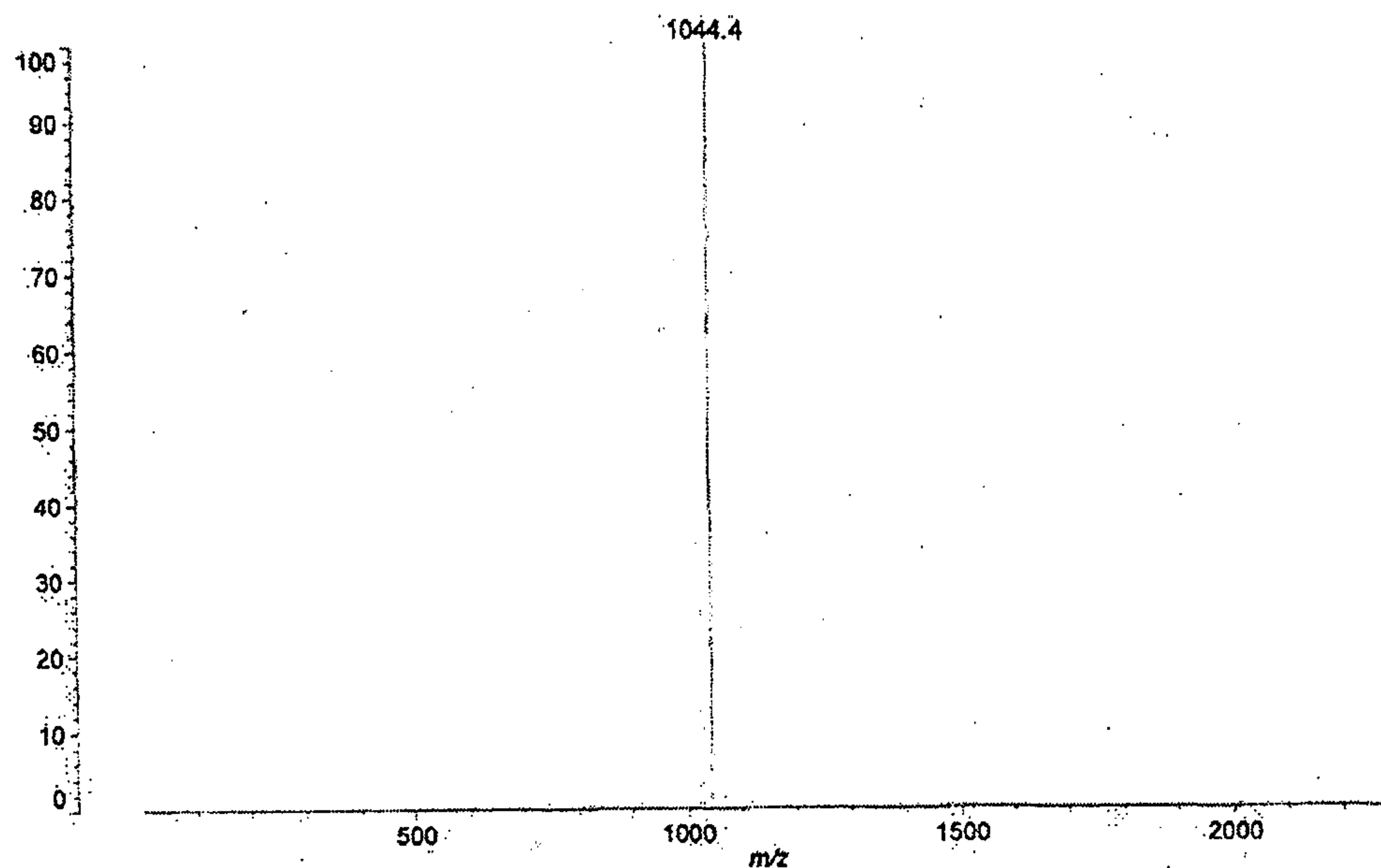
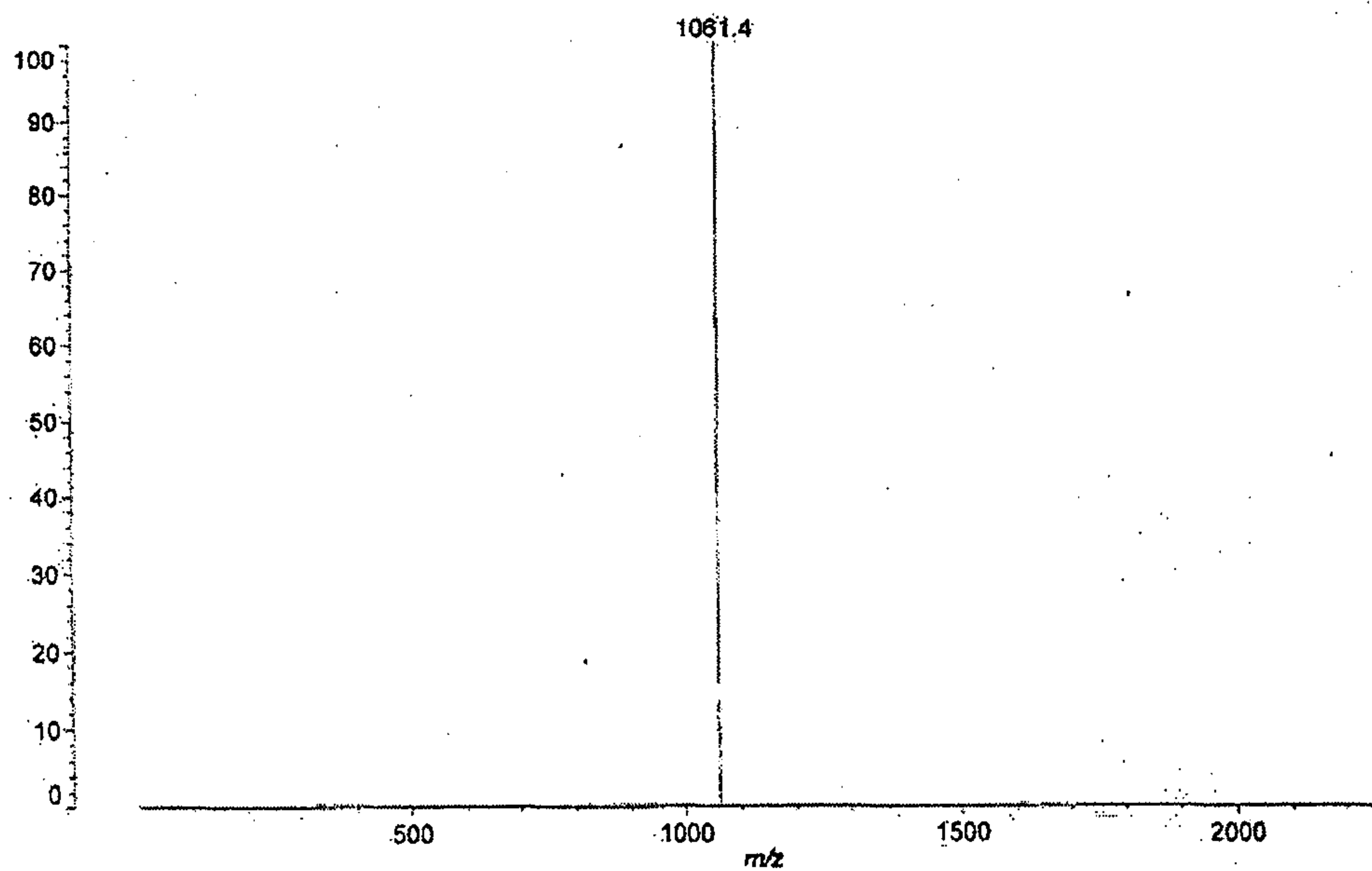


FIG. 88

Anygen
K161408
Data: <Untitled>.O7(c) 26 Sep 2016 12:48 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 33, P.Ext. @ 1000 (bin 56)
%Int. 405 mV Profiles 1-40: Threshold 25% Centroid [Adaptive]



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FIG 89

Anygen
K161409
Data: <Untitled>.N7[c] 26 Sep 2016 12:48 Cal: 7 Apr 2016 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624; Mode Linear, Power: 33, P.Ext. @ 1000 (bin 56)
%Int. 432 mV Profiles 1-25: Threshold 25% Centroid [Adaptive]

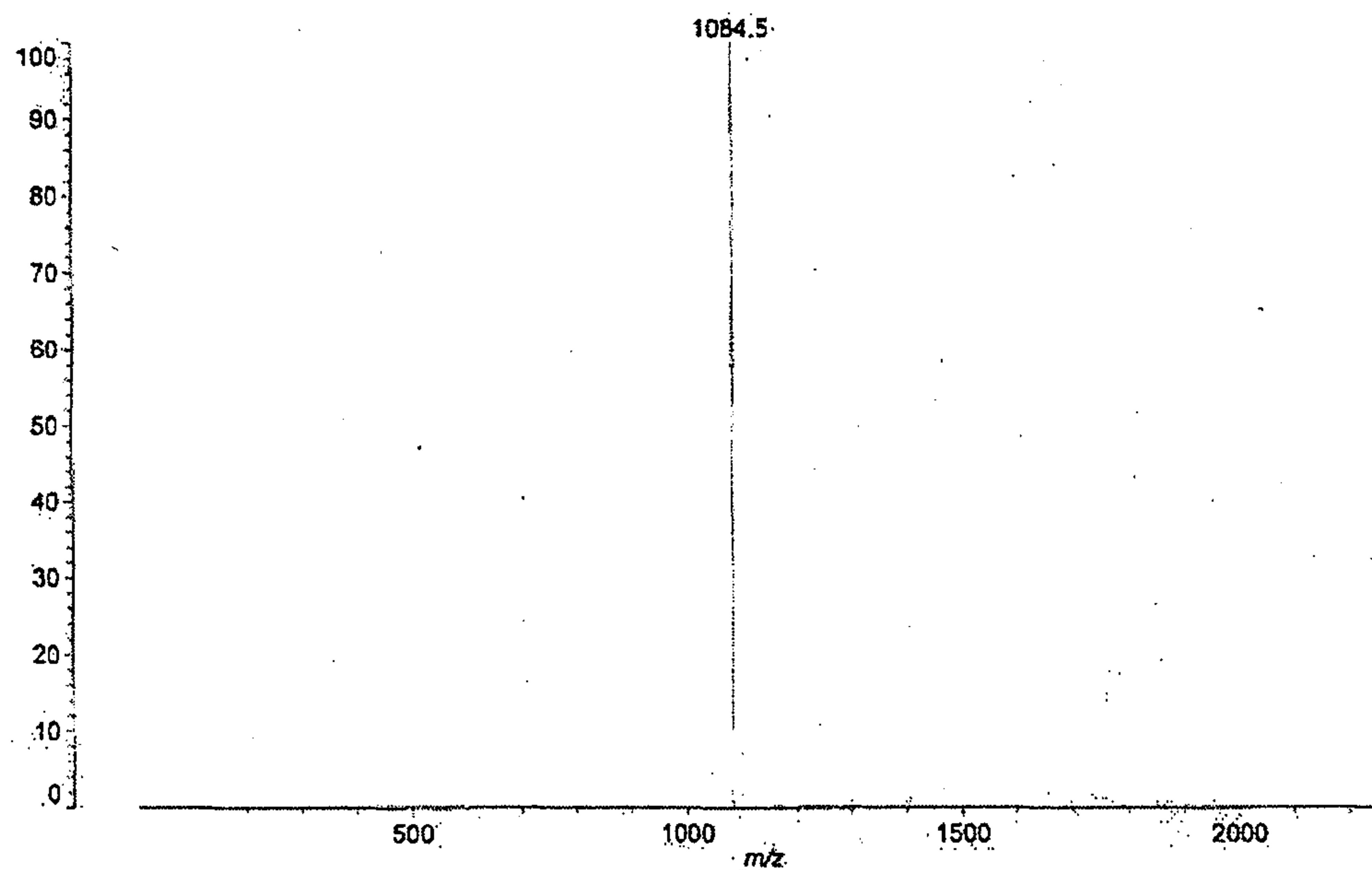
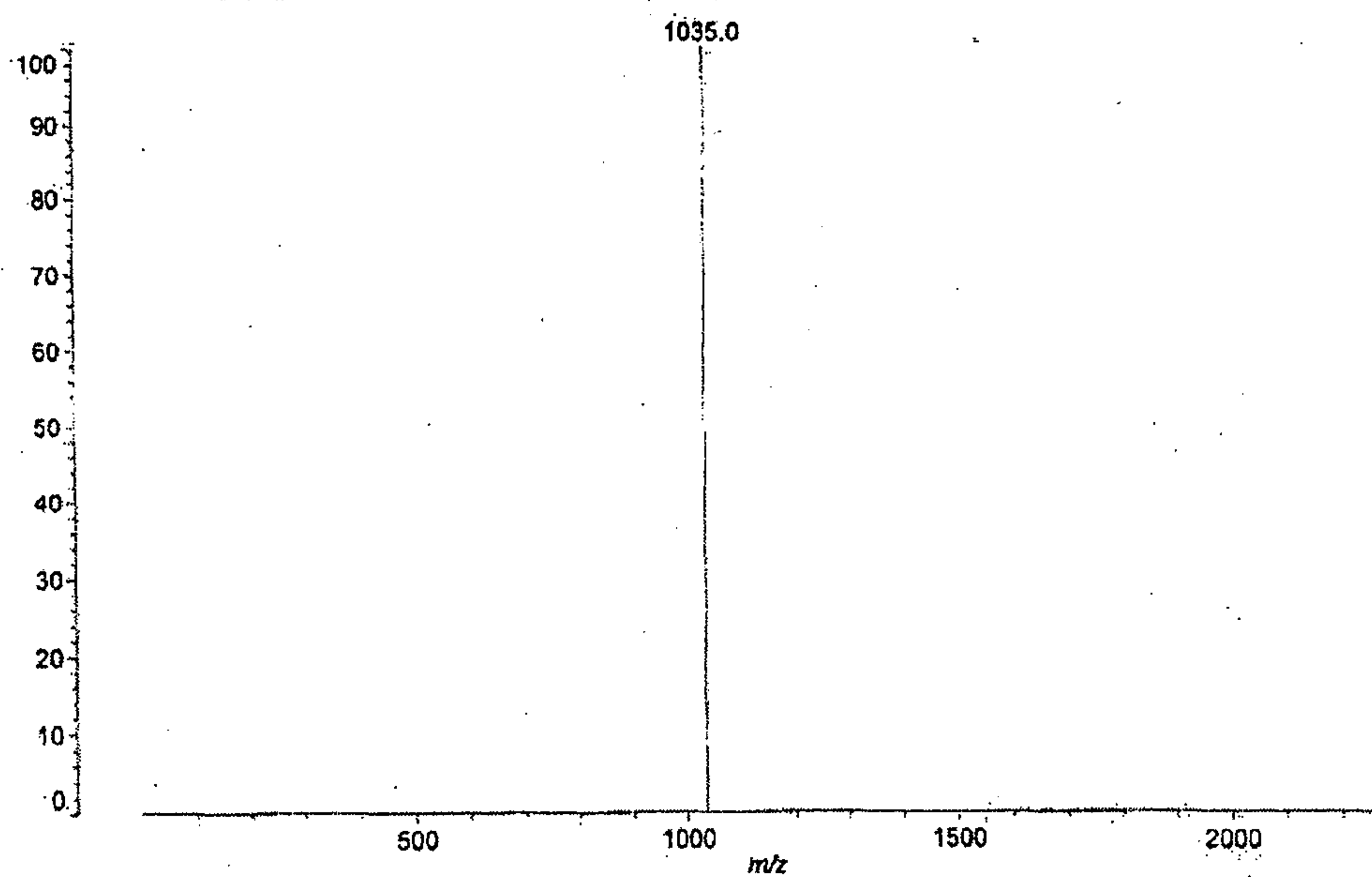


FIG 90

Anygen
K161410
Data: <Untitled>.E14[c] 27 Sep 2016 10:21 Cal: 7 Apr 2016 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624; Mode Linear, Power: 37, P.Ext. @ 1000 (bin 56)
%Int. 1132 mV Profiles 1-9: Threshold 25% Centroid [Adaptive]



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FIG 91

Anygen
K161411
Data: <Untitled> F14[c] 27 Sep 2016 10:22 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 37, P.Ext. @ 1000 (bin 56)
%Int. 45 mV Profiles 1-64: Threshold 25% Centroid [Adaptive]

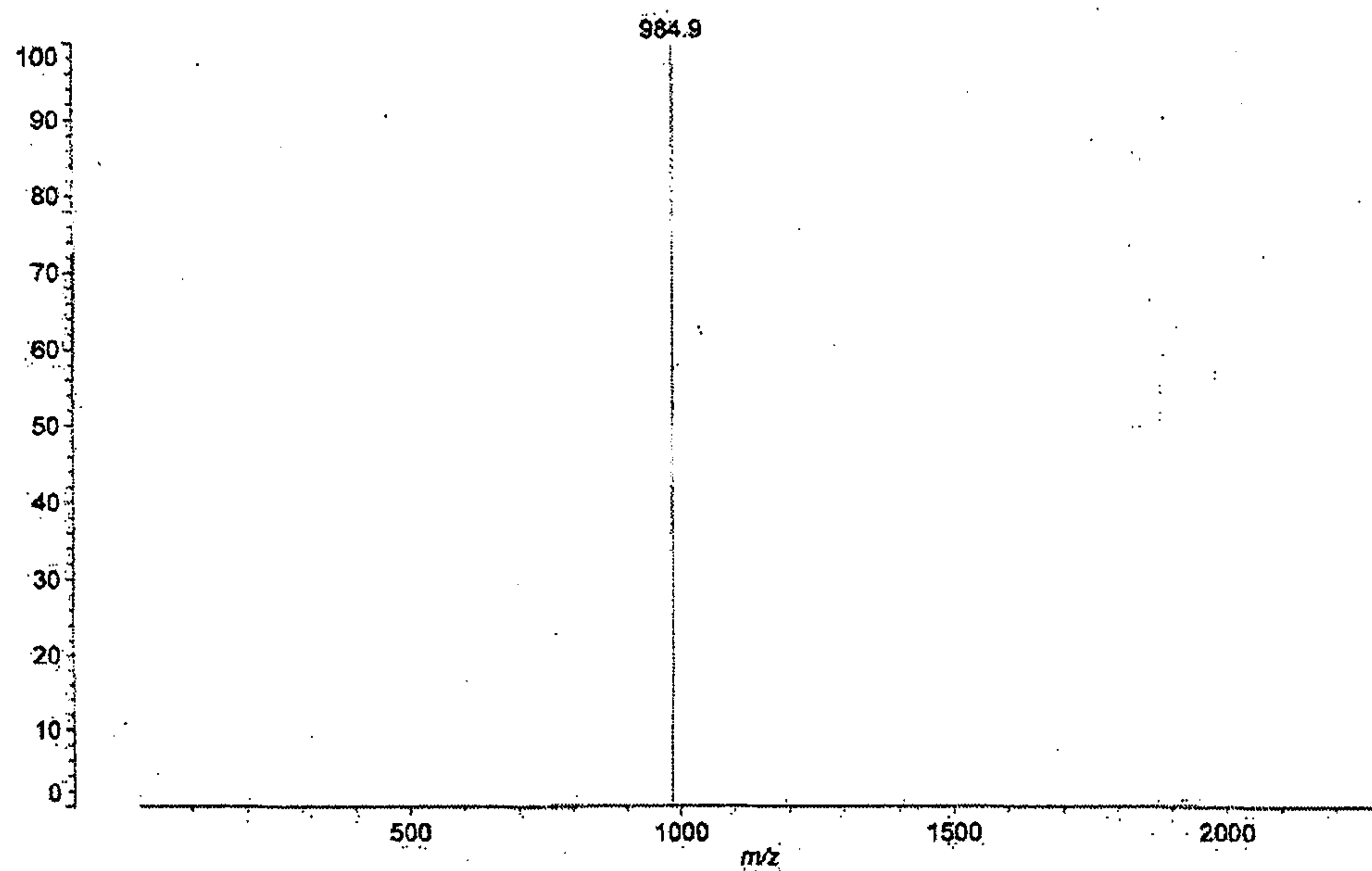
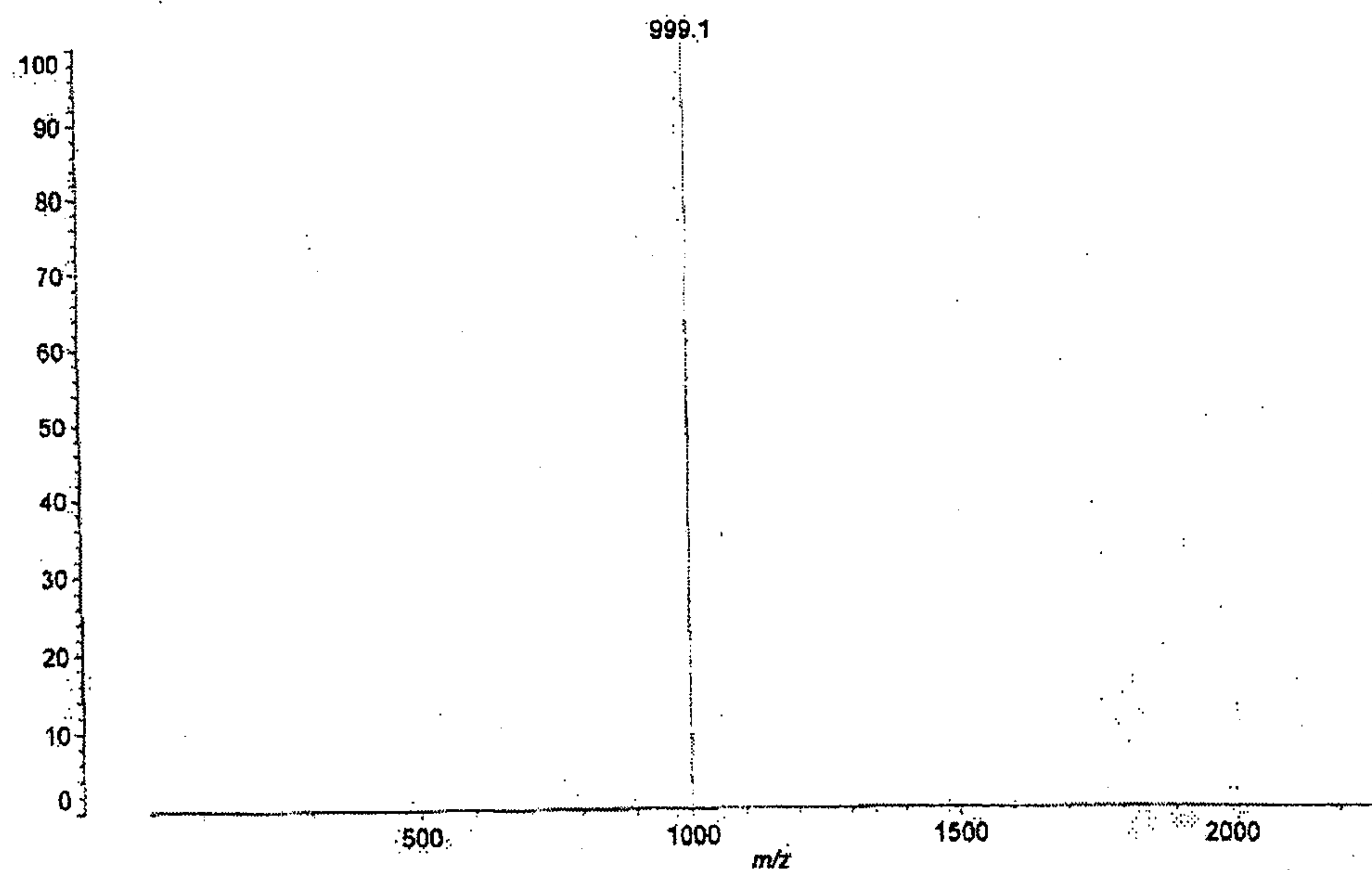


FIG 92

Anygen
K161412
Data: <Untitled> G14[c] 27 Sep 2016 10:22 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 37, P.Ext. @ 1000 (bin 56)
%Int. 134 mV Profiles 1-71: Threshold 25% Centroid [Adaptive]



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FIG 93

Anygen
K161413
Data: <Untitled>.I21[c] 13 Oct 2016 14:40 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 35, P.Ext. @ 1000 (bin 56)
%Int. 33 mV Profiles 1-46: Threshold 25% Centroid [Adaptive]

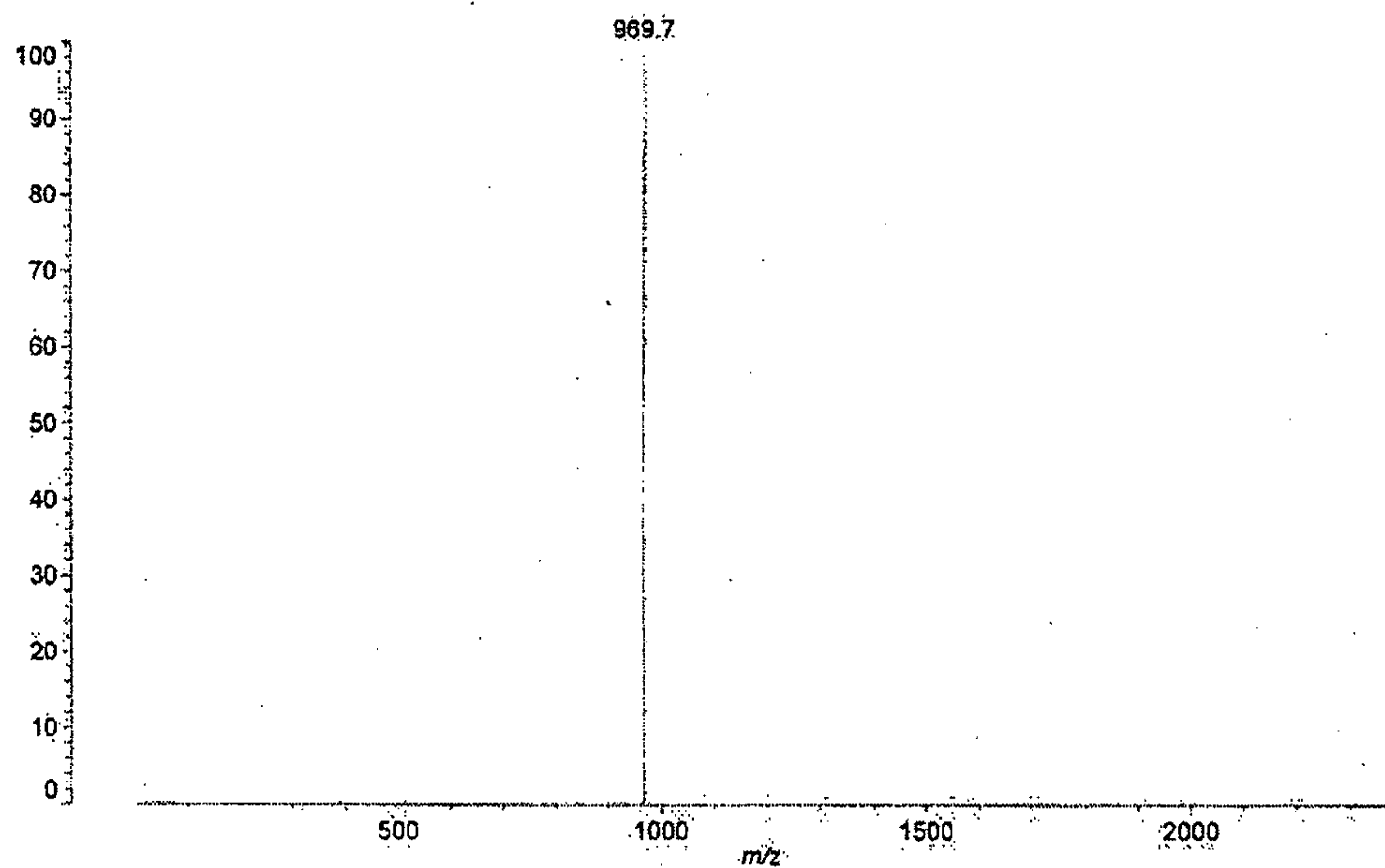
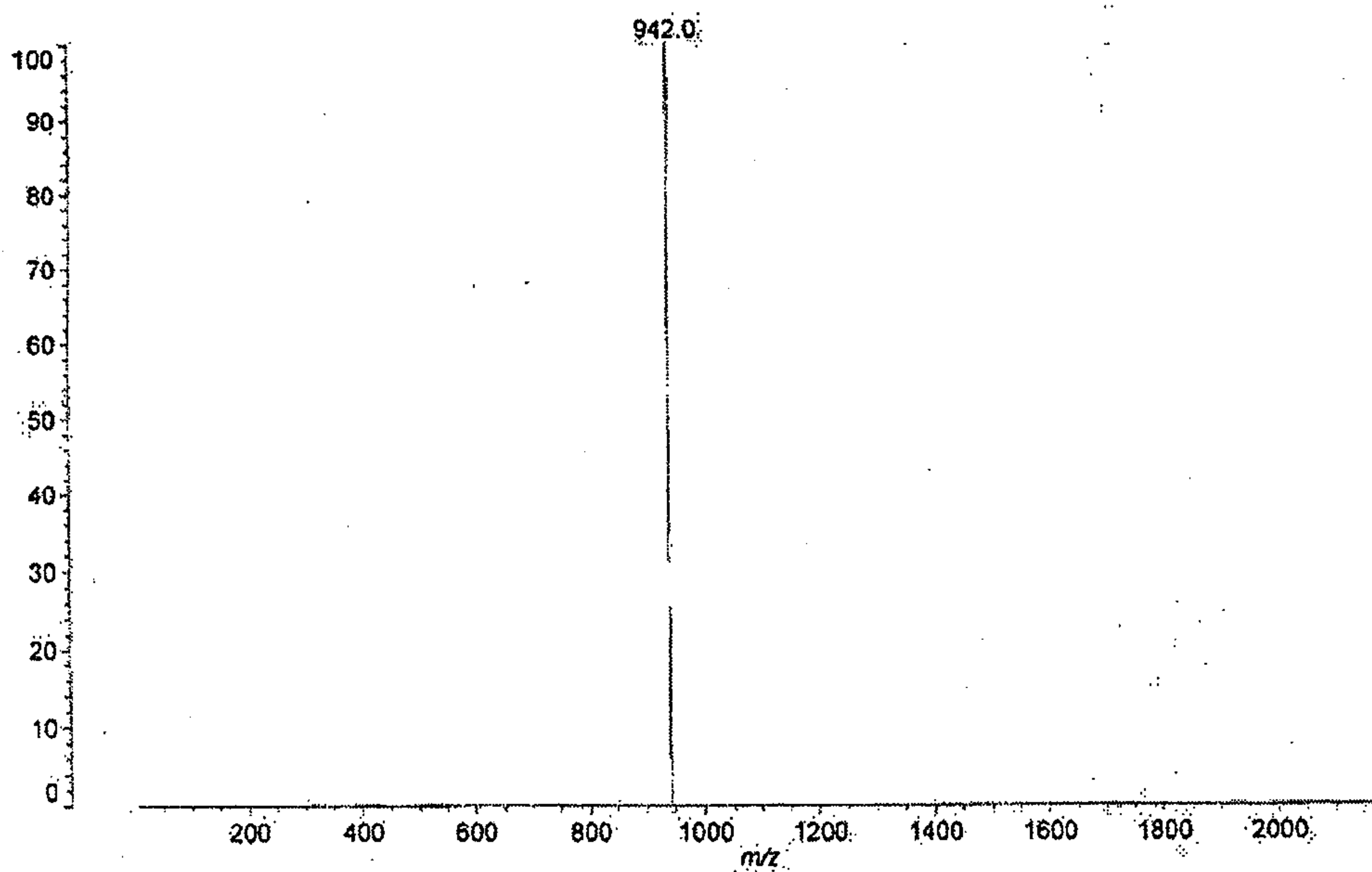


FIG 94

Anygen
K161414
Data: <Untitled>.M18[c] 27 Oct 2016 14:10 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 37, Blanked, P.Ext. @ 2000 (bin 64)
%Int. 11 mV Profiles 1-27: Threshold 25% Centroid [Adaptive]



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FIG 95

Anygen
K161415
Data: <Untitled> A20[c] 3 Nov 2016 15:16 Cal: peptide 25 Oct 2016 15:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 22, P.Ext. @ 1000 (bin 56)
%Int. 422 mV Profiles 1-90: Threshold 25% Centroid [Adaptive]

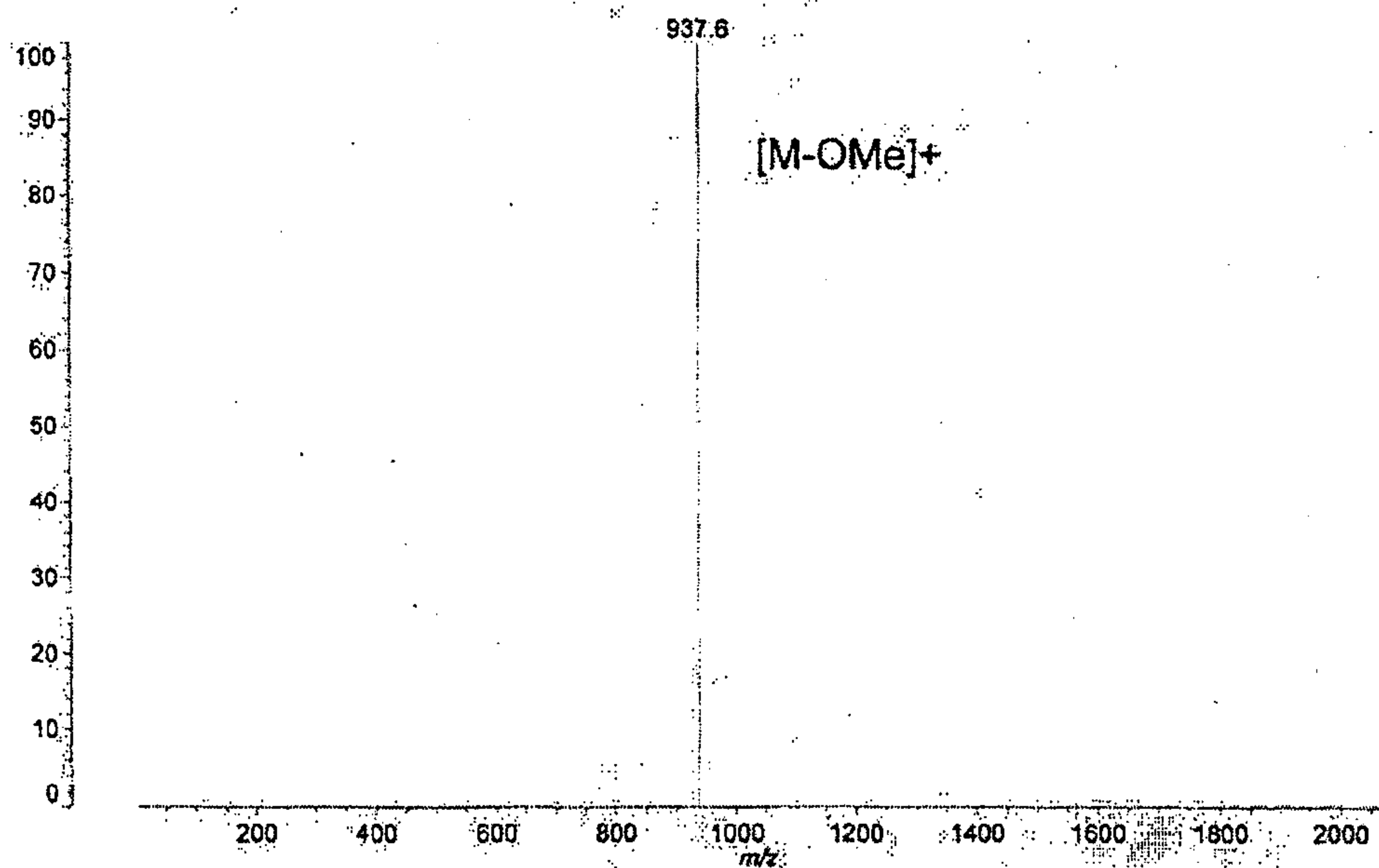
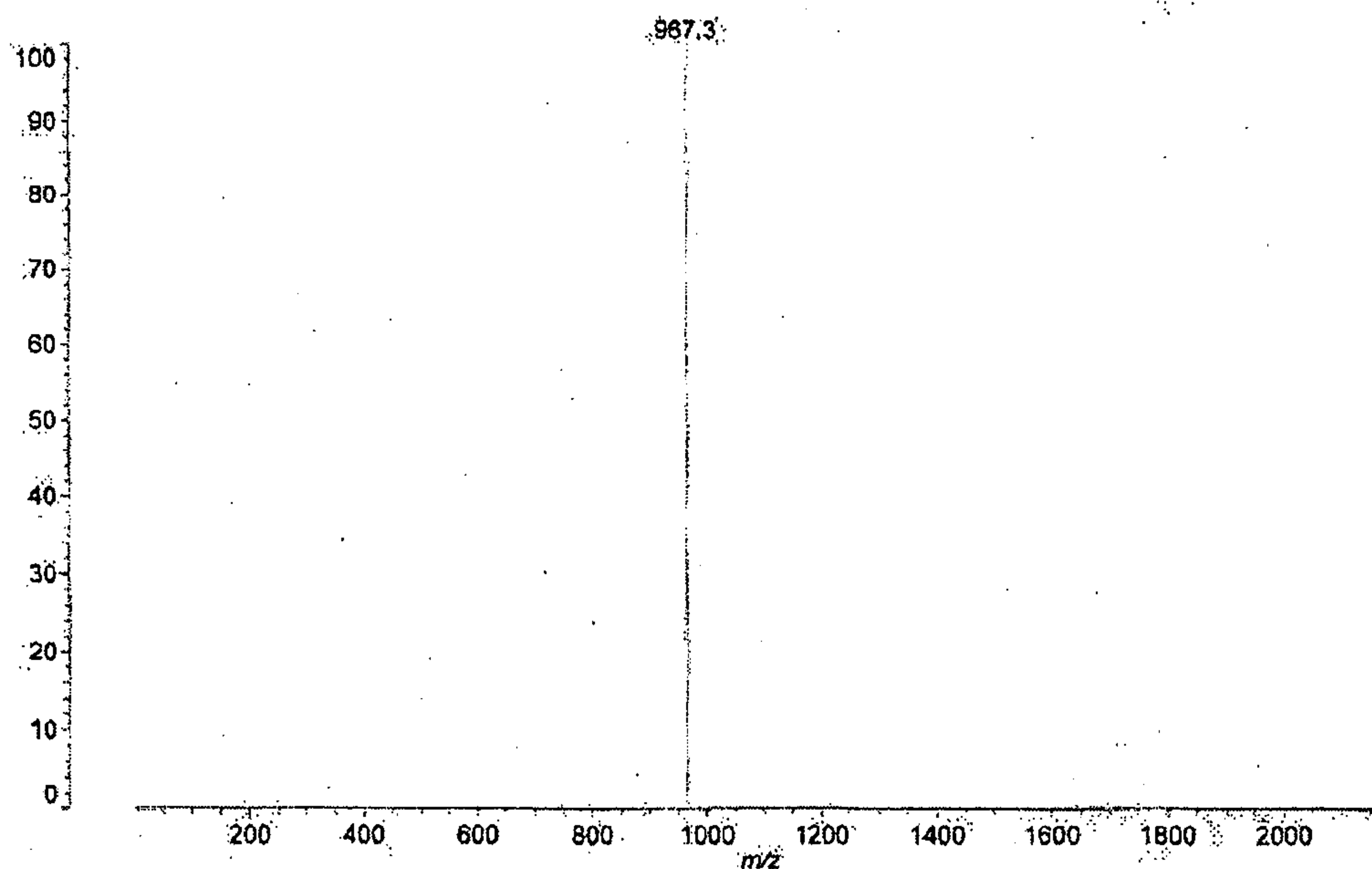


FIG 96

Anygen
K161416
Data: <Untitled> N18[c] 27 Oct 2016 14:10 Cal: 400-4000 24 Jun 2015 9:11
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 32, Blanked, P.Ext. @ 2000 (bin 64)
%Int. 166 mV Profiles 1-39: Threshold 25% Centroid [Adaptive]



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FIG 97

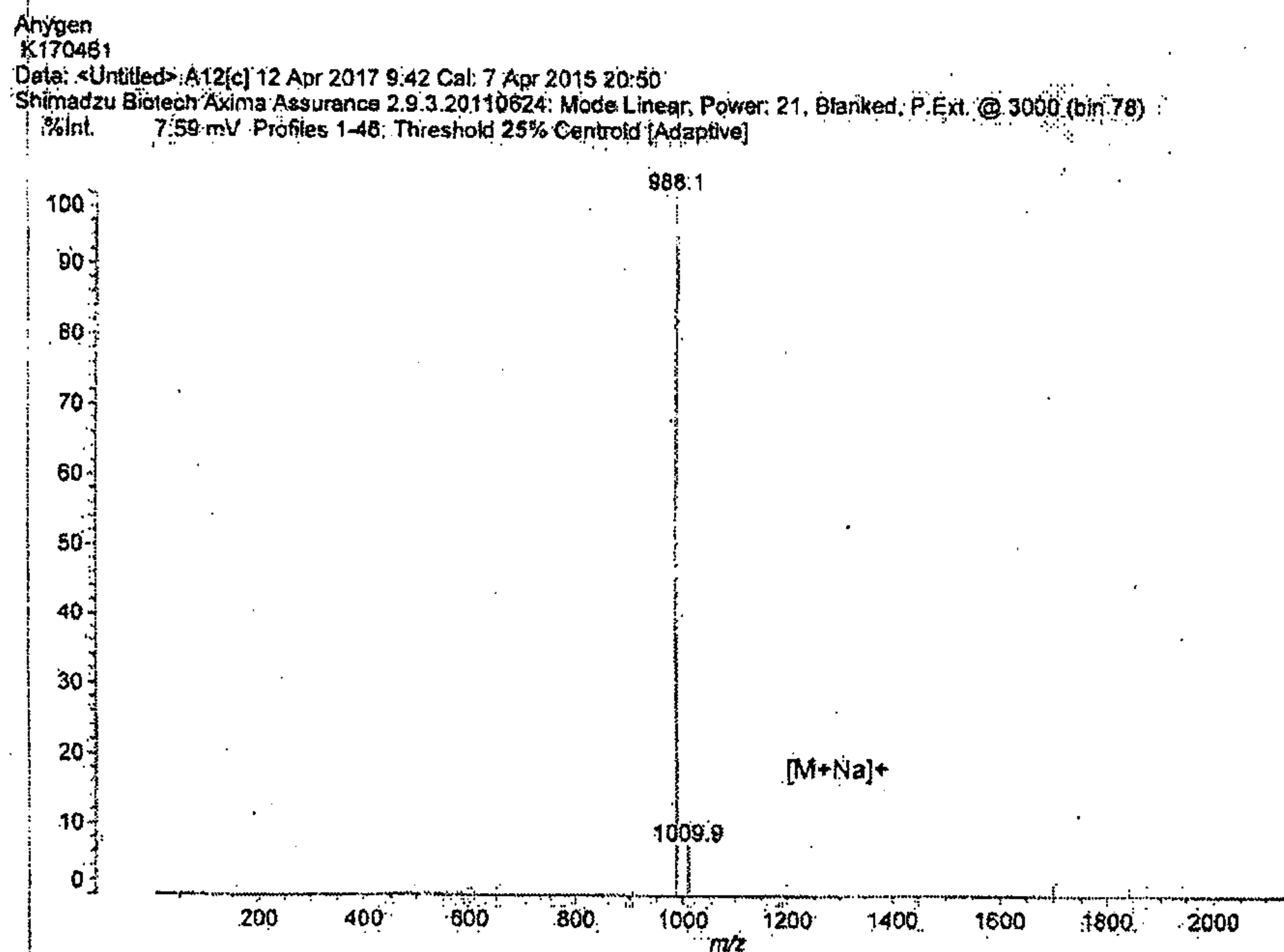
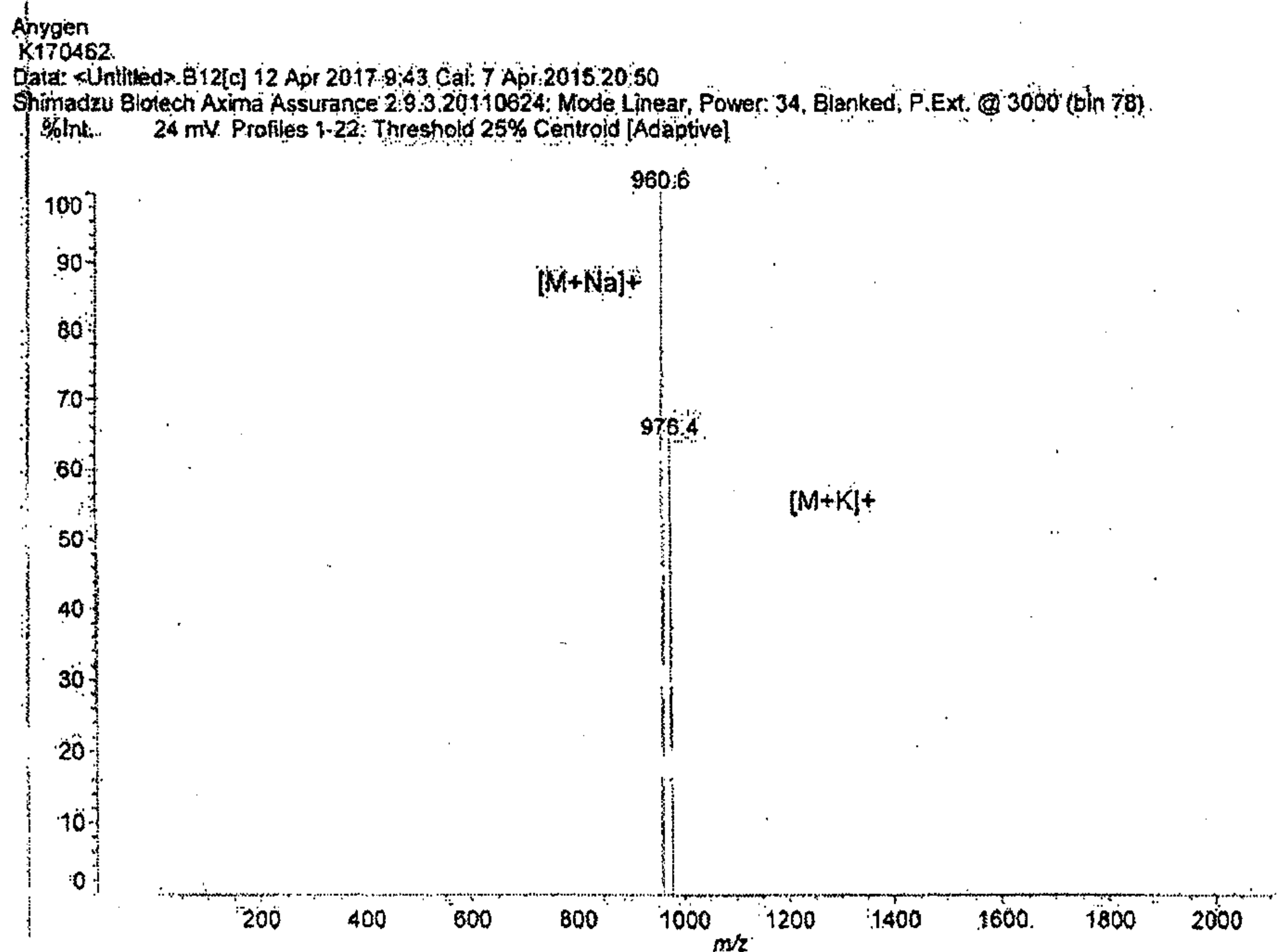


FIG 98



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FIG 99

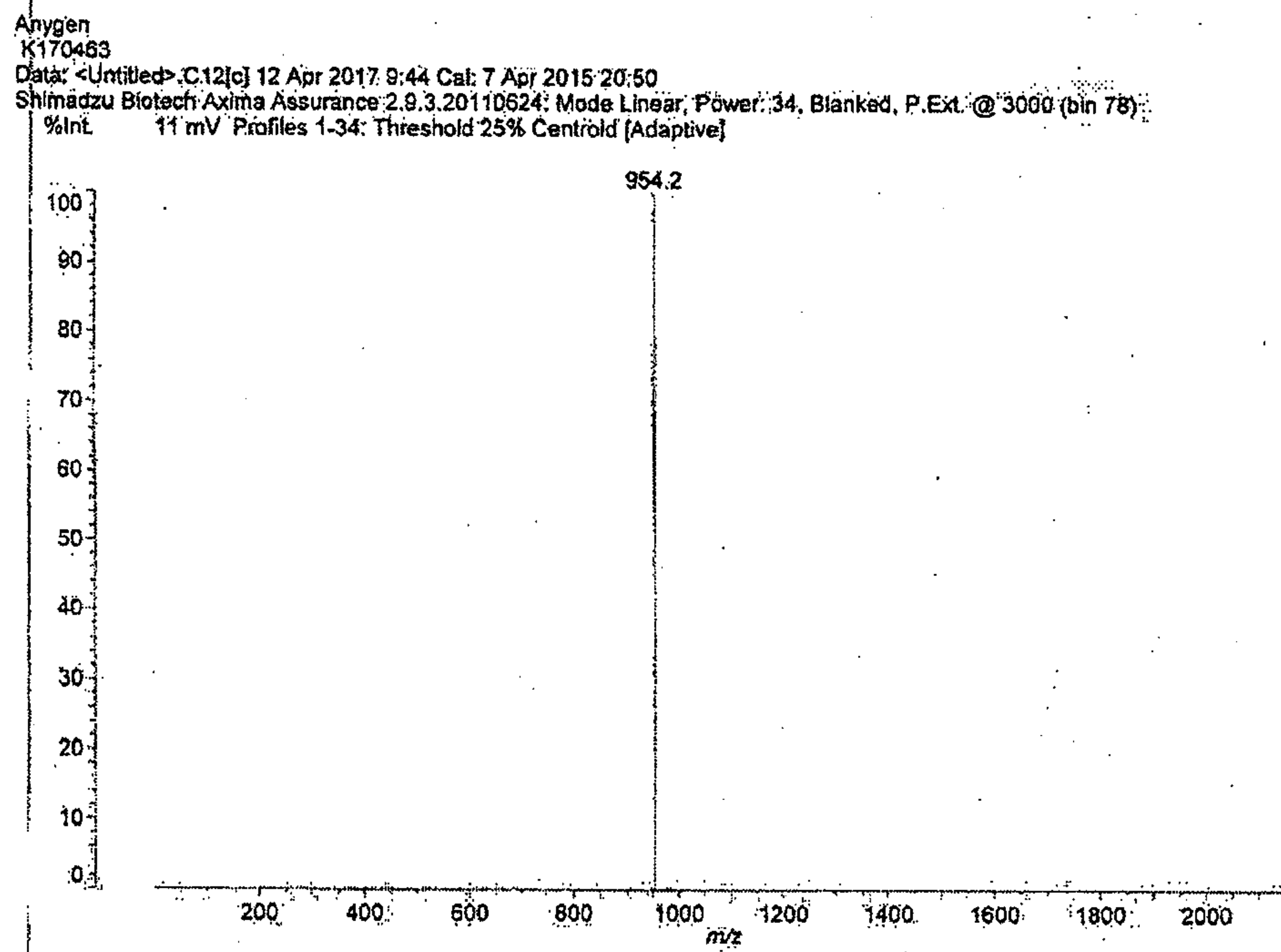
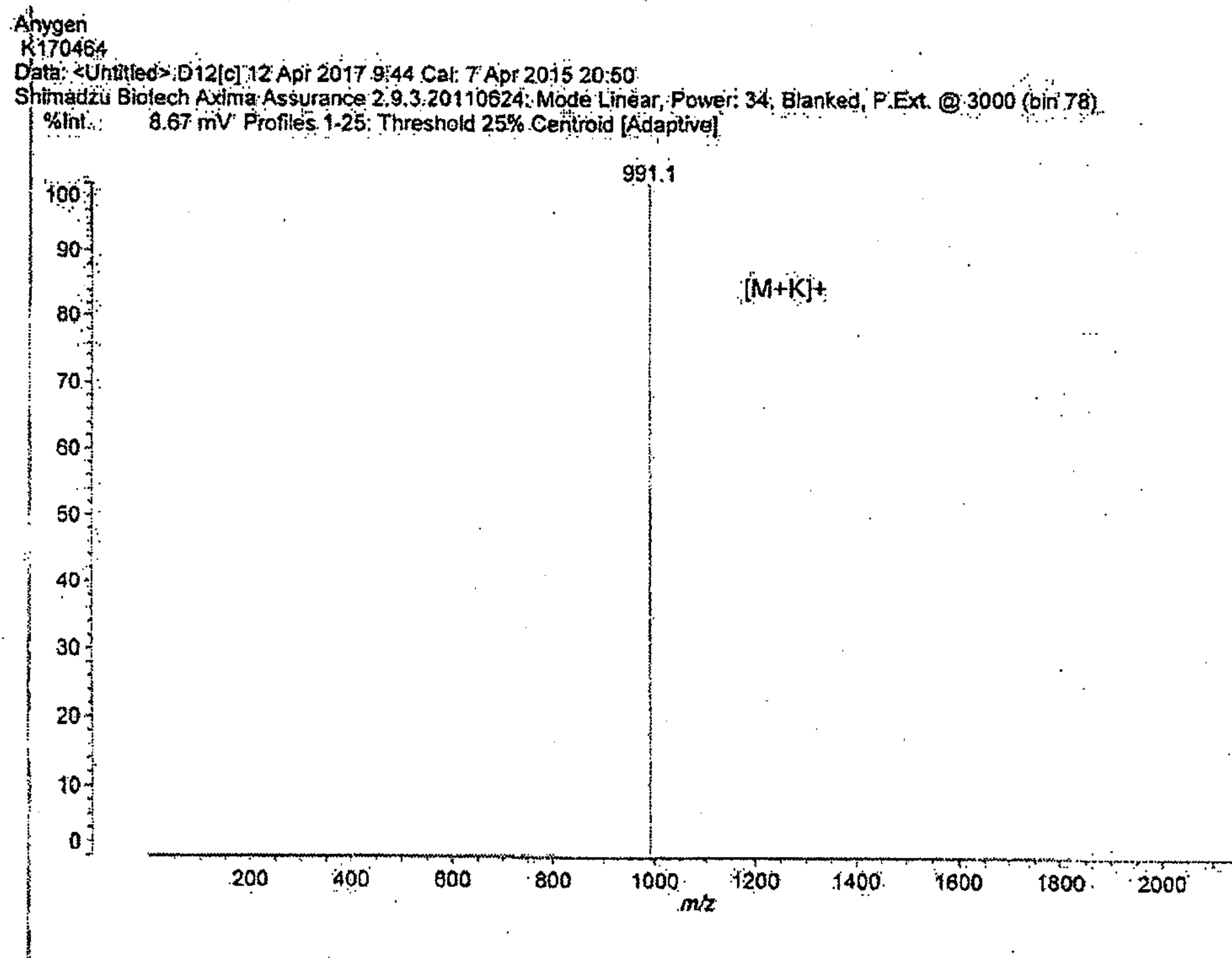


FIG 100



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FIG 101

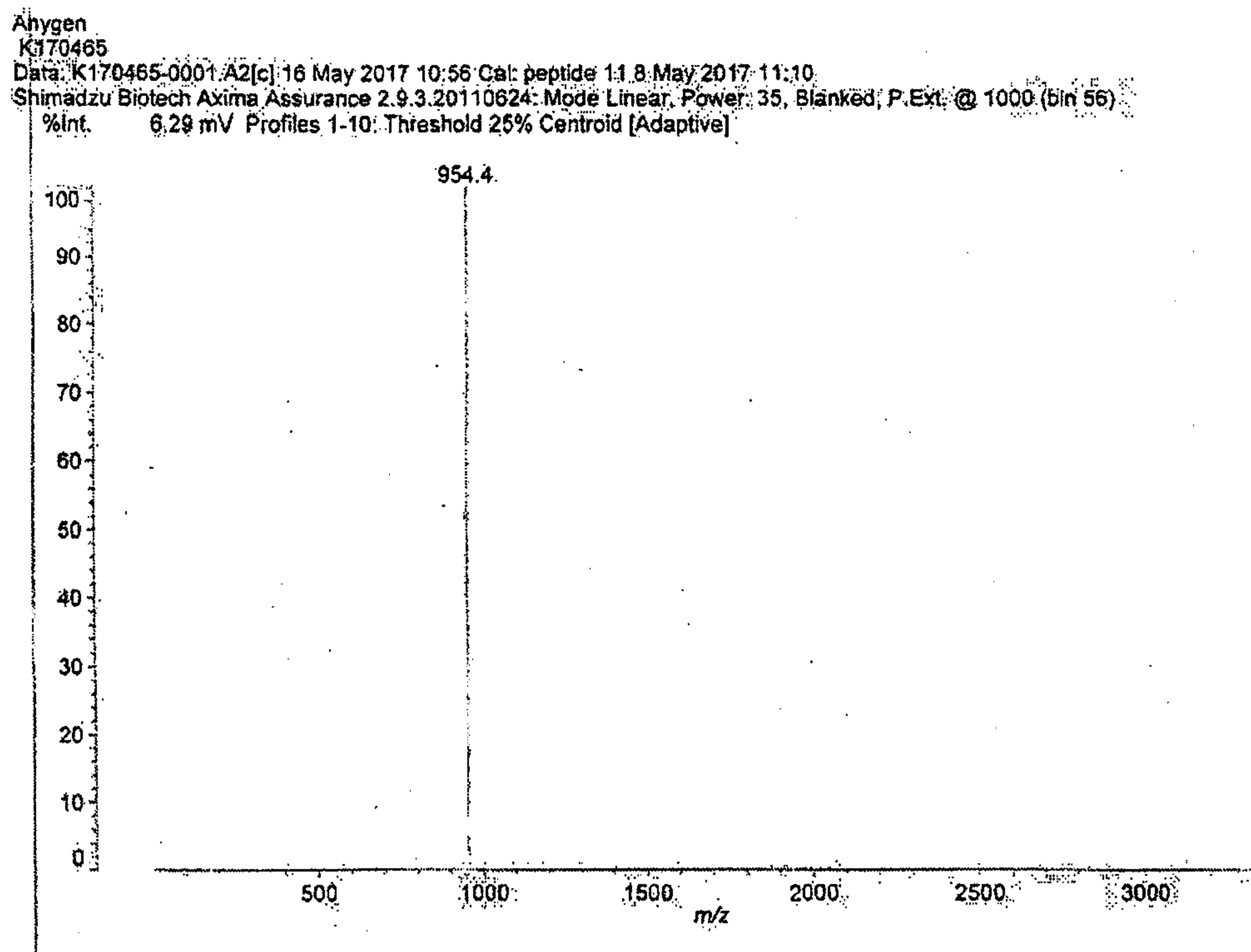
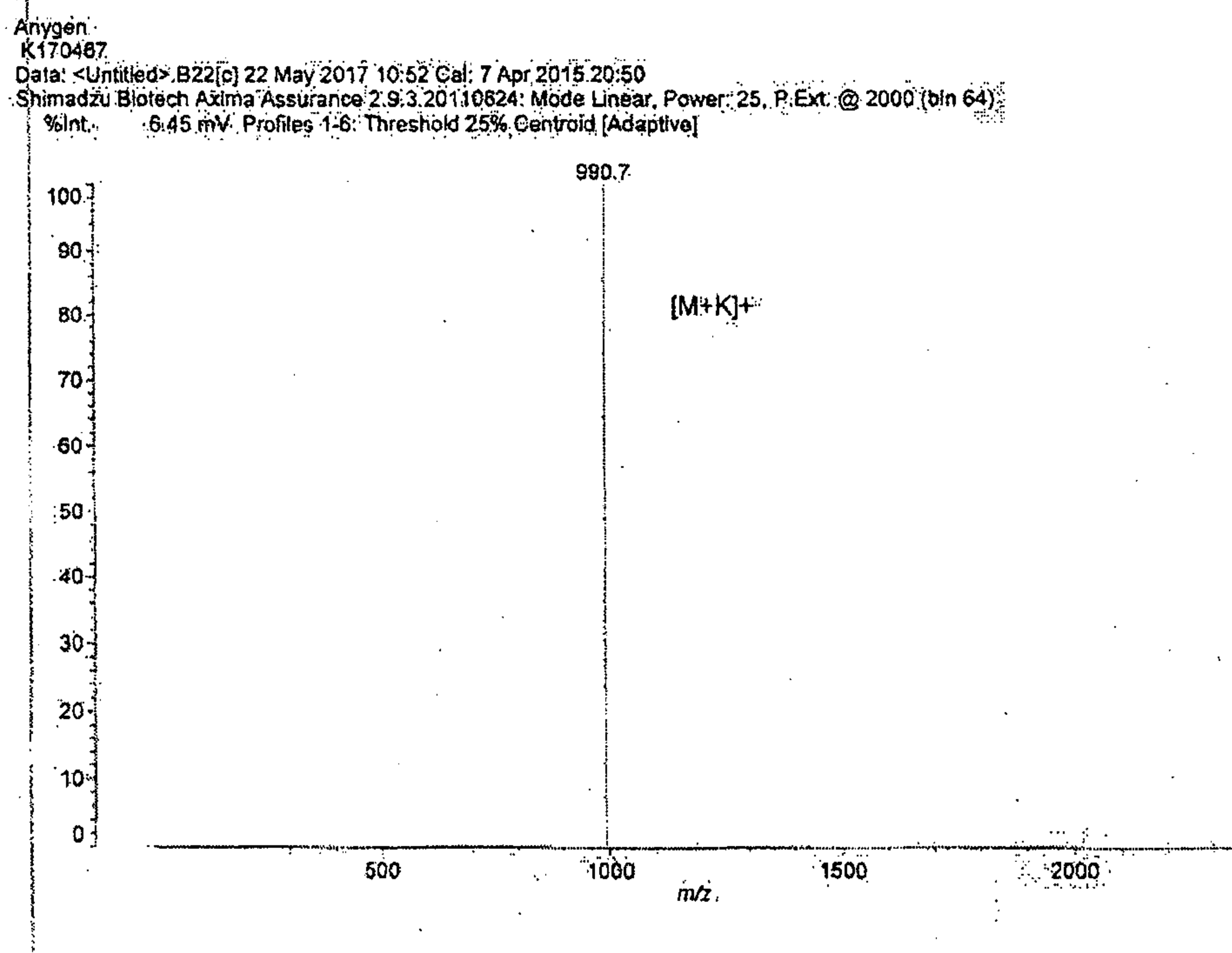


FIG 102



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FIG 103

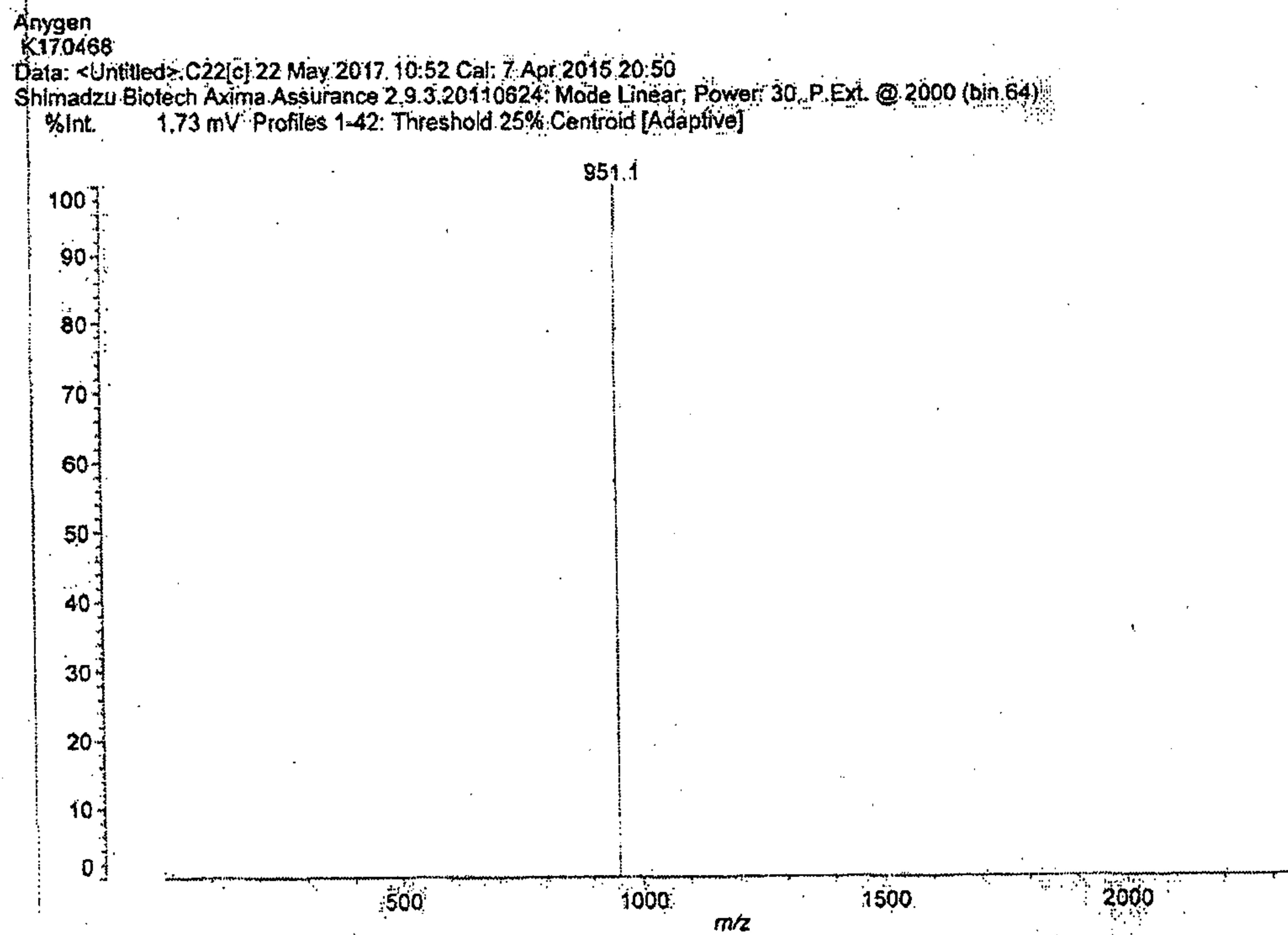
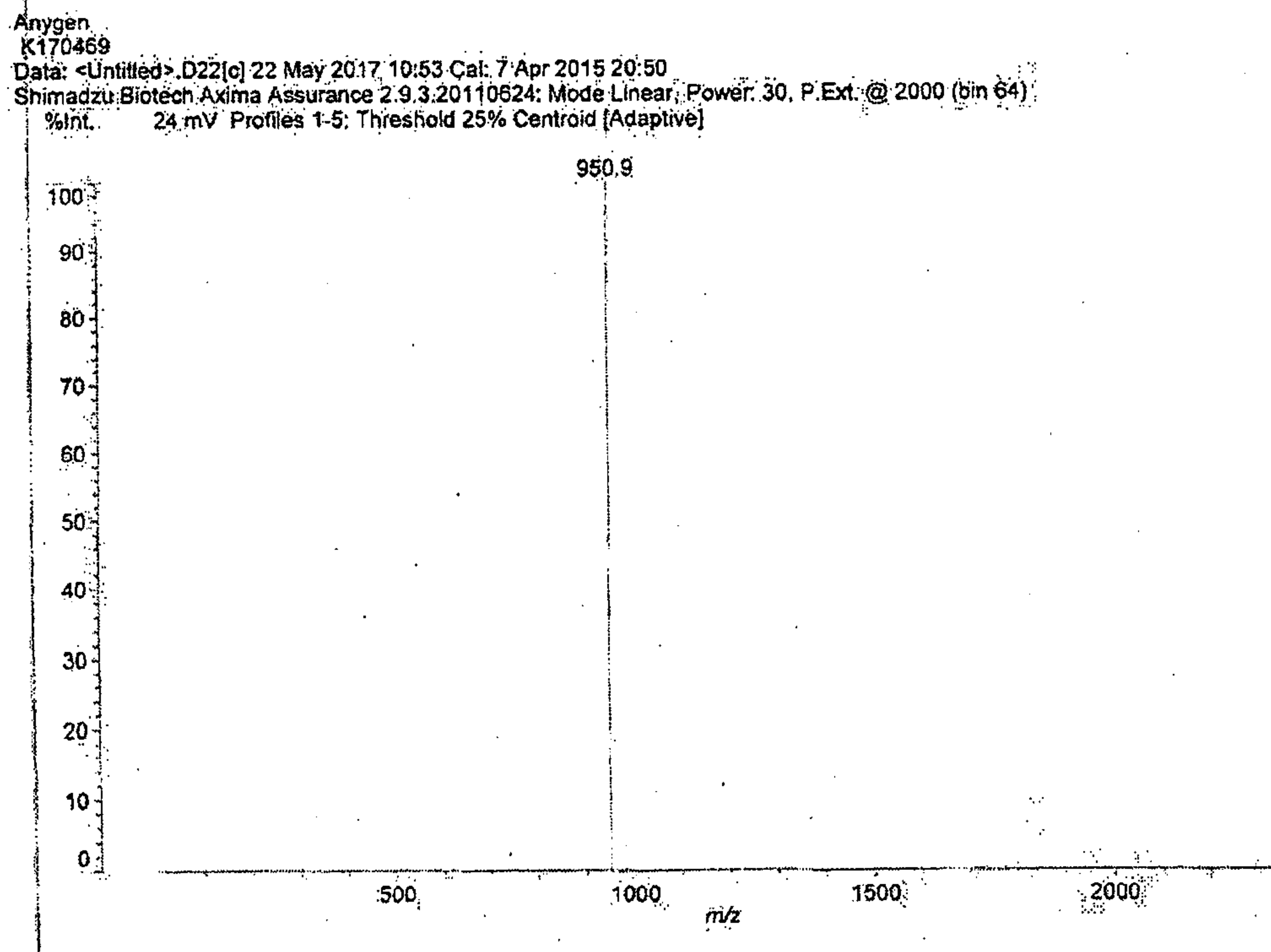


FIG 104



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FIG 105

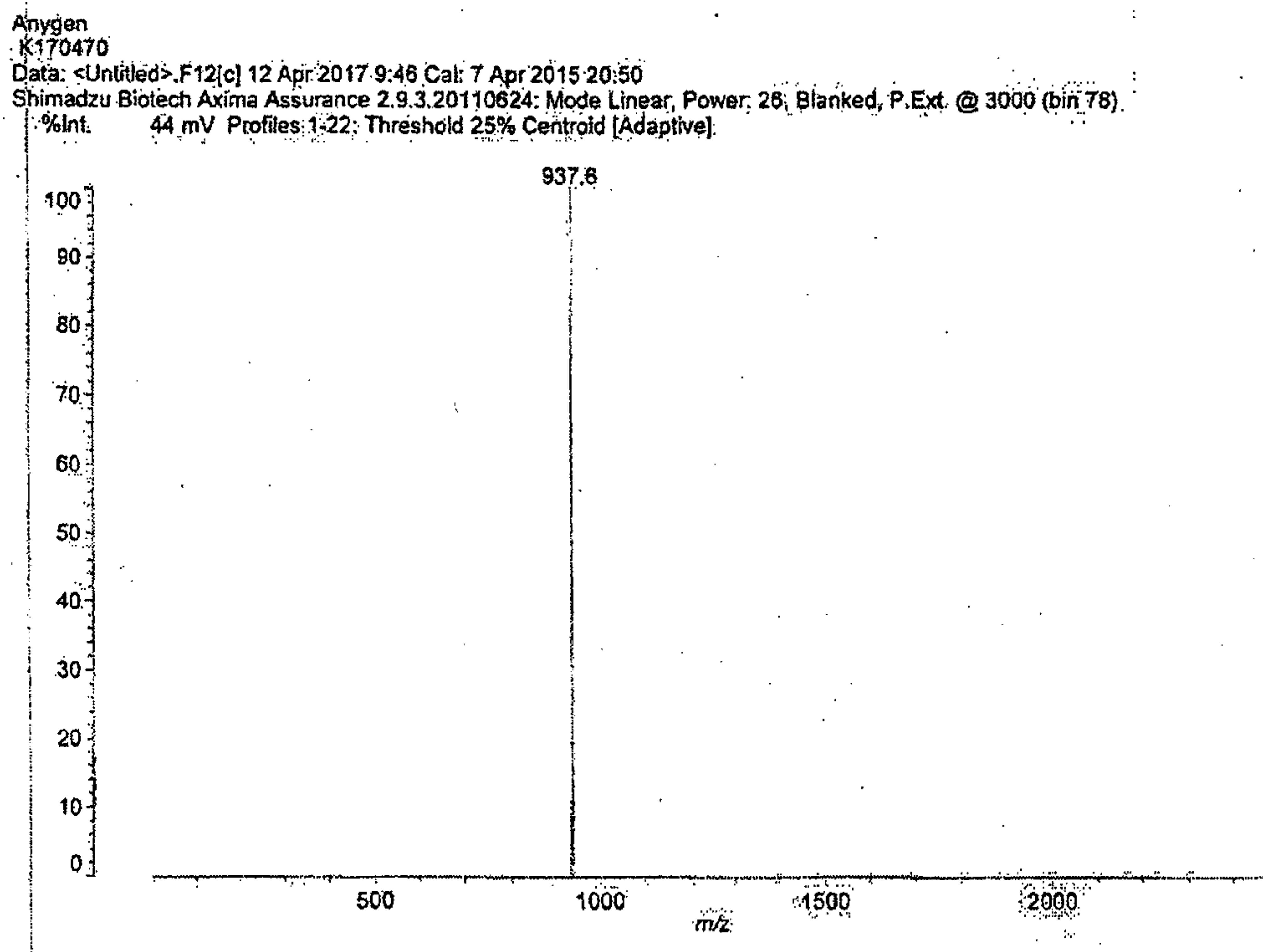
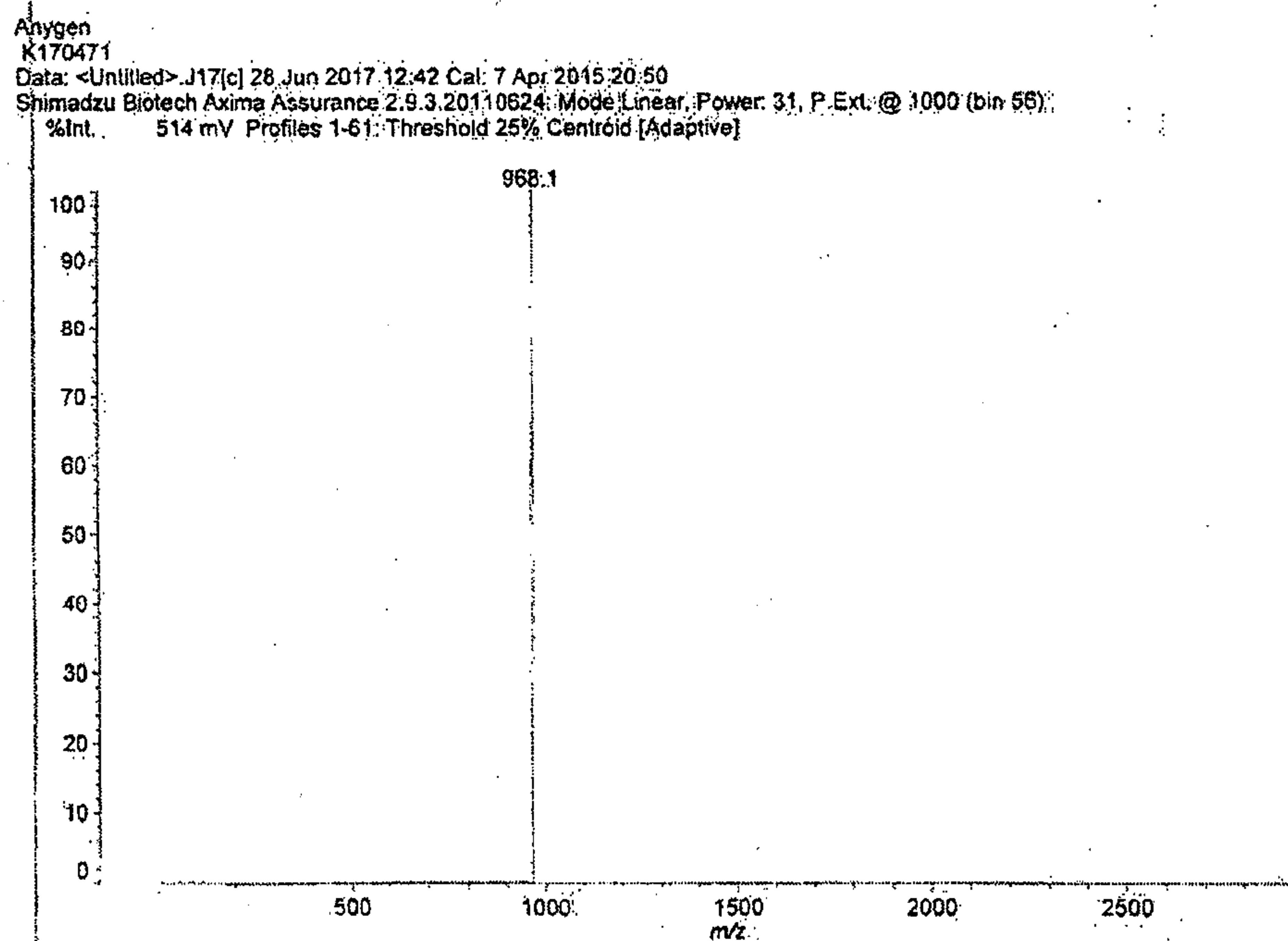


FIG 106



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FIG 107

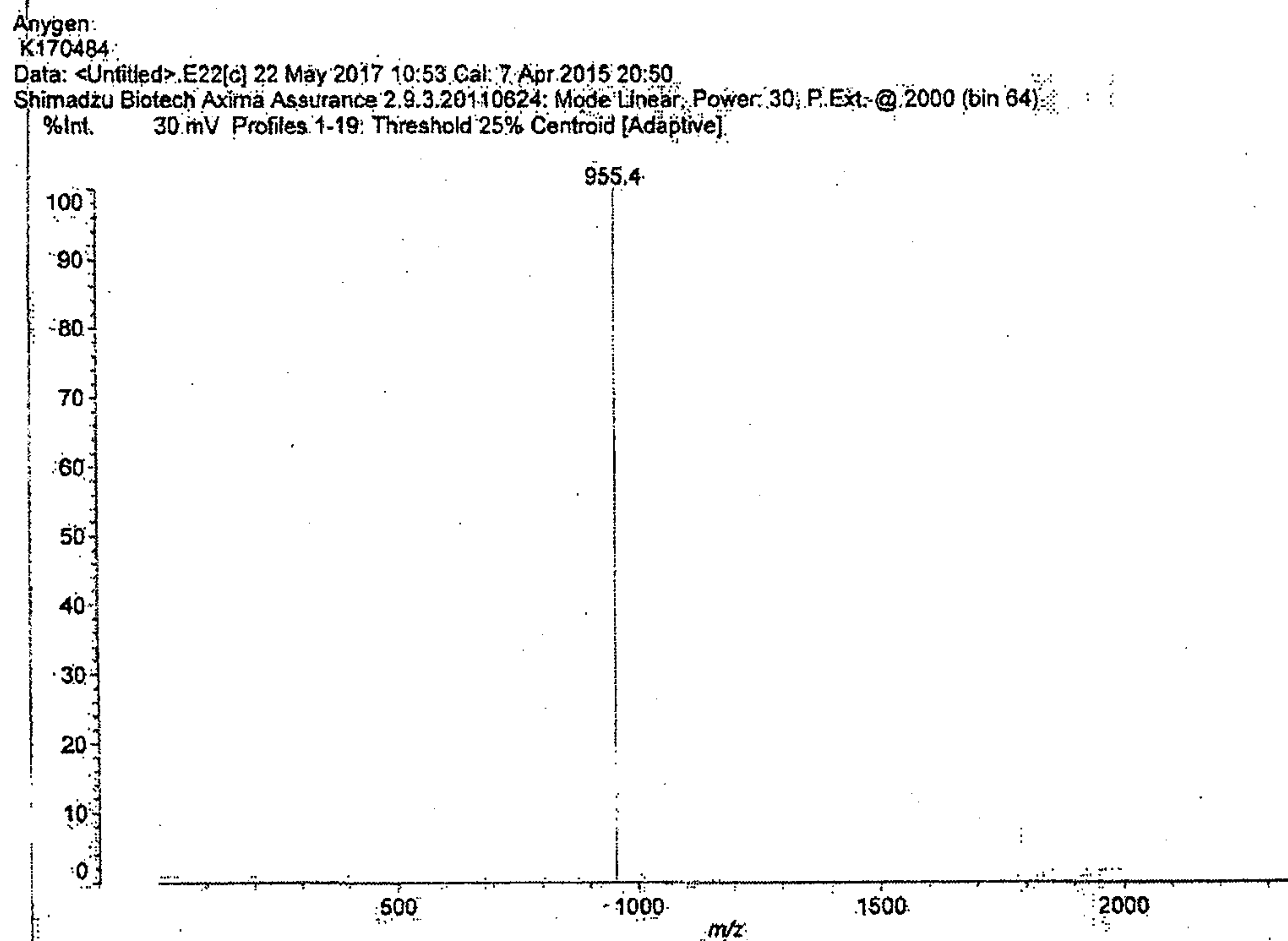
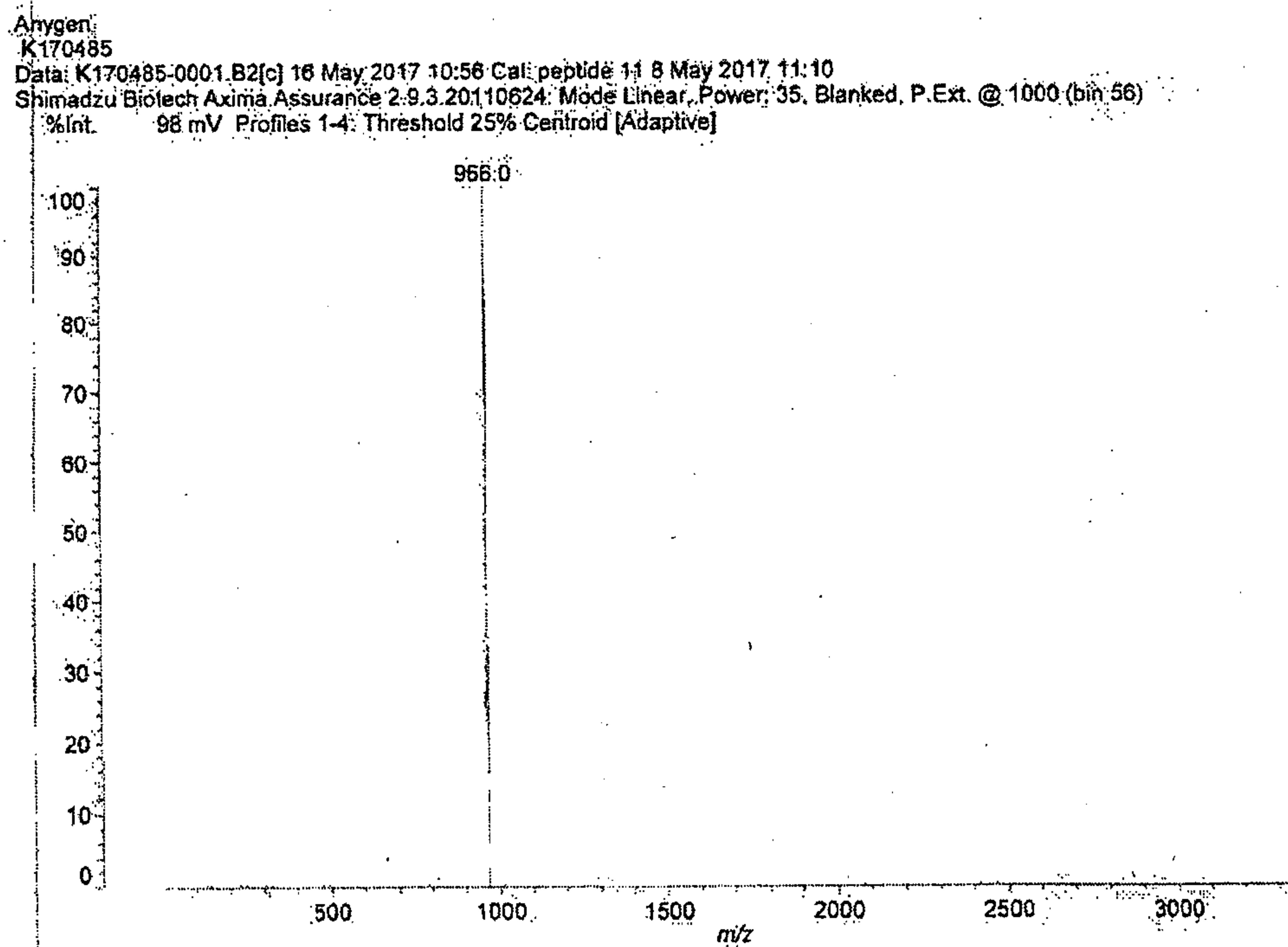


FIG 108



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FIG 109

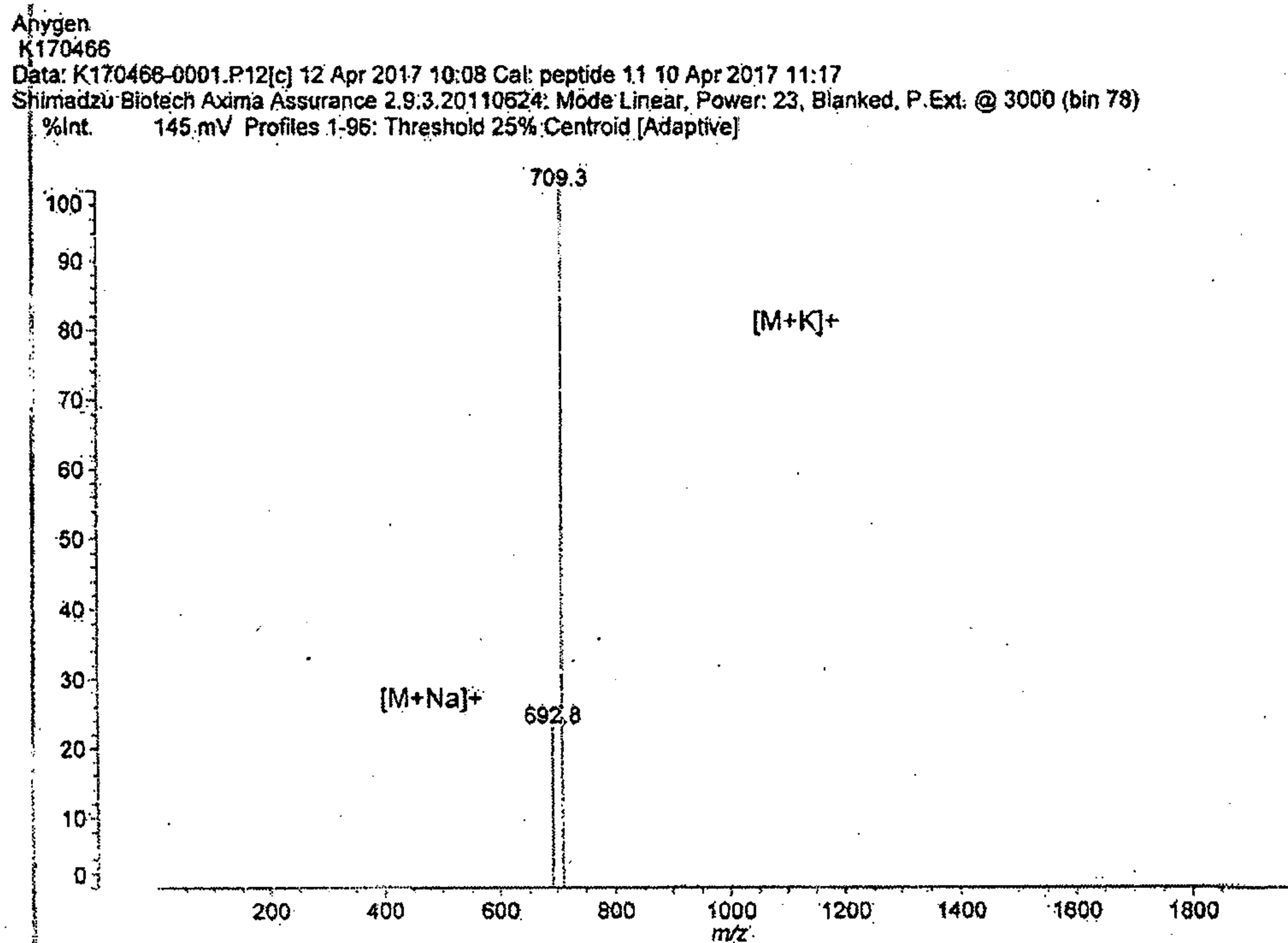
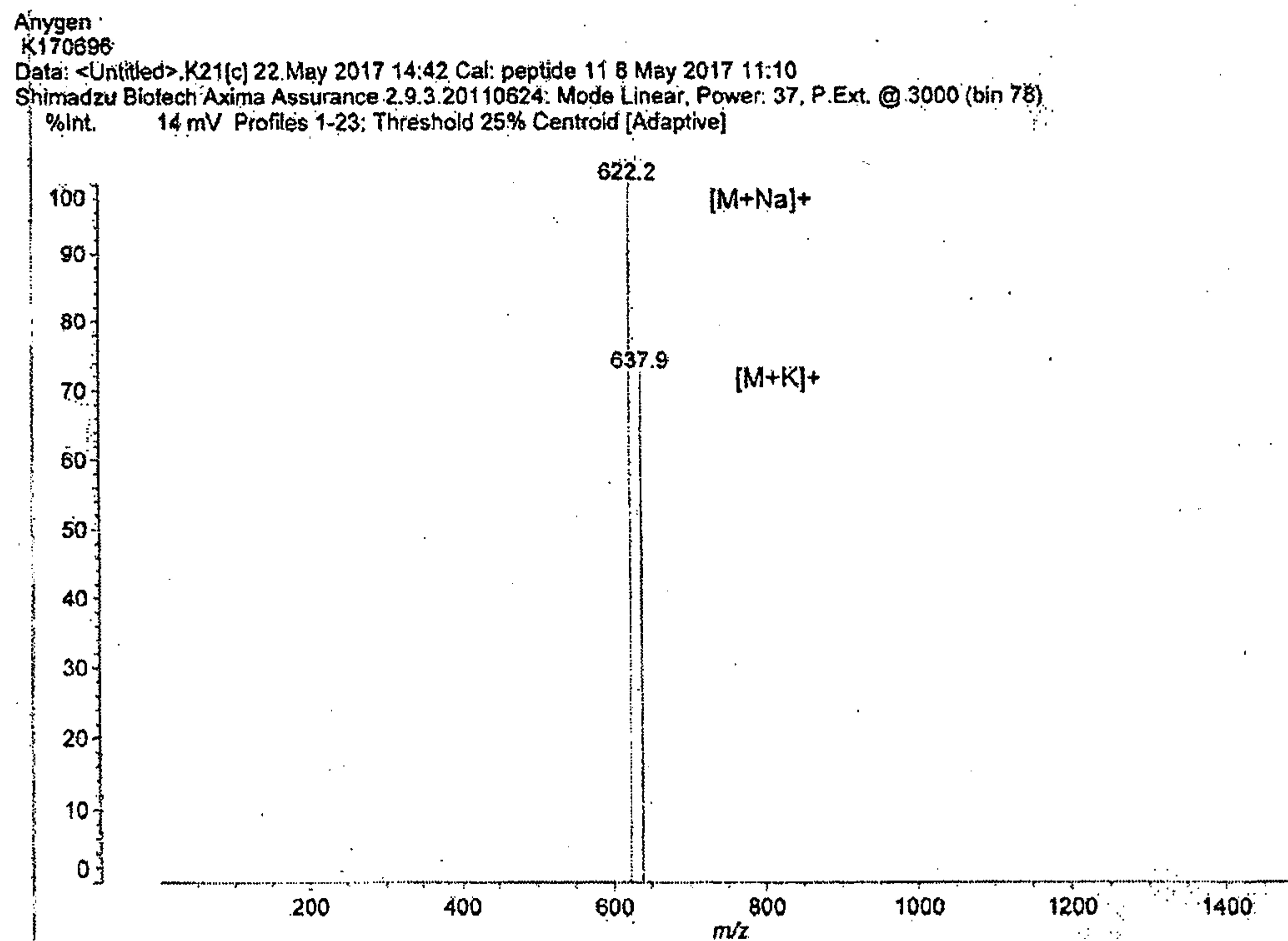


FIG 110



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FIG 111

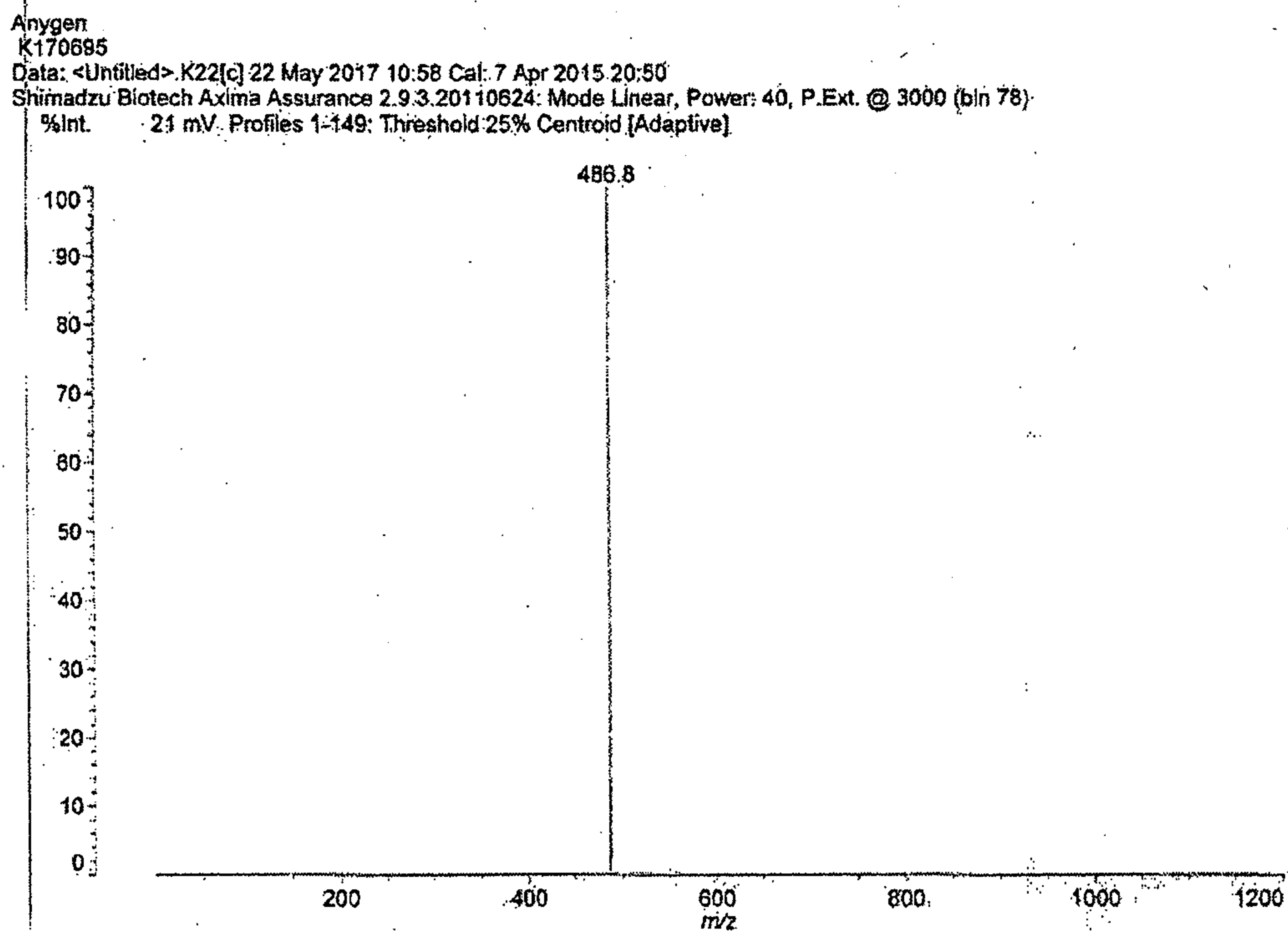
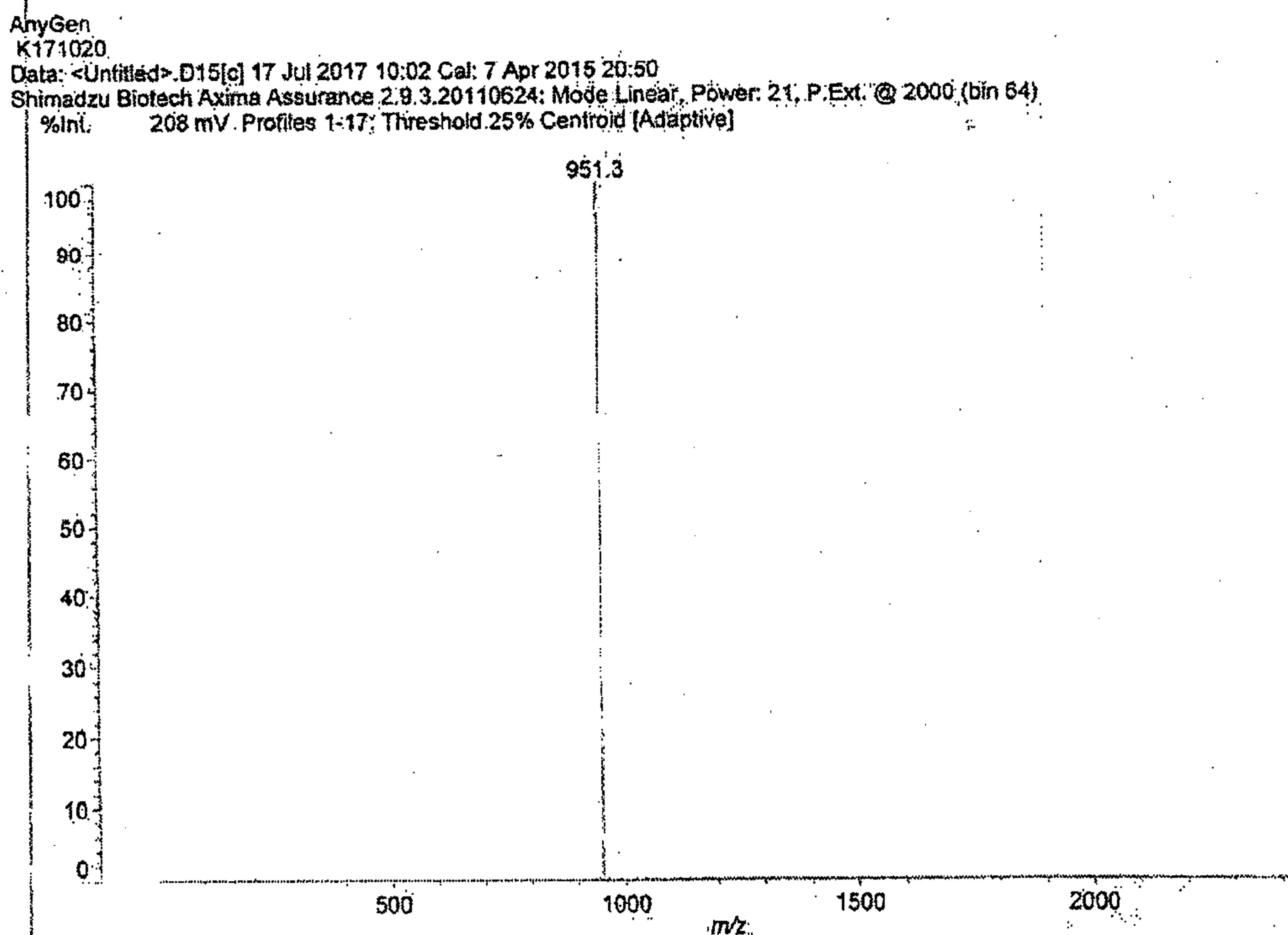


FIG 112



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FIG 113

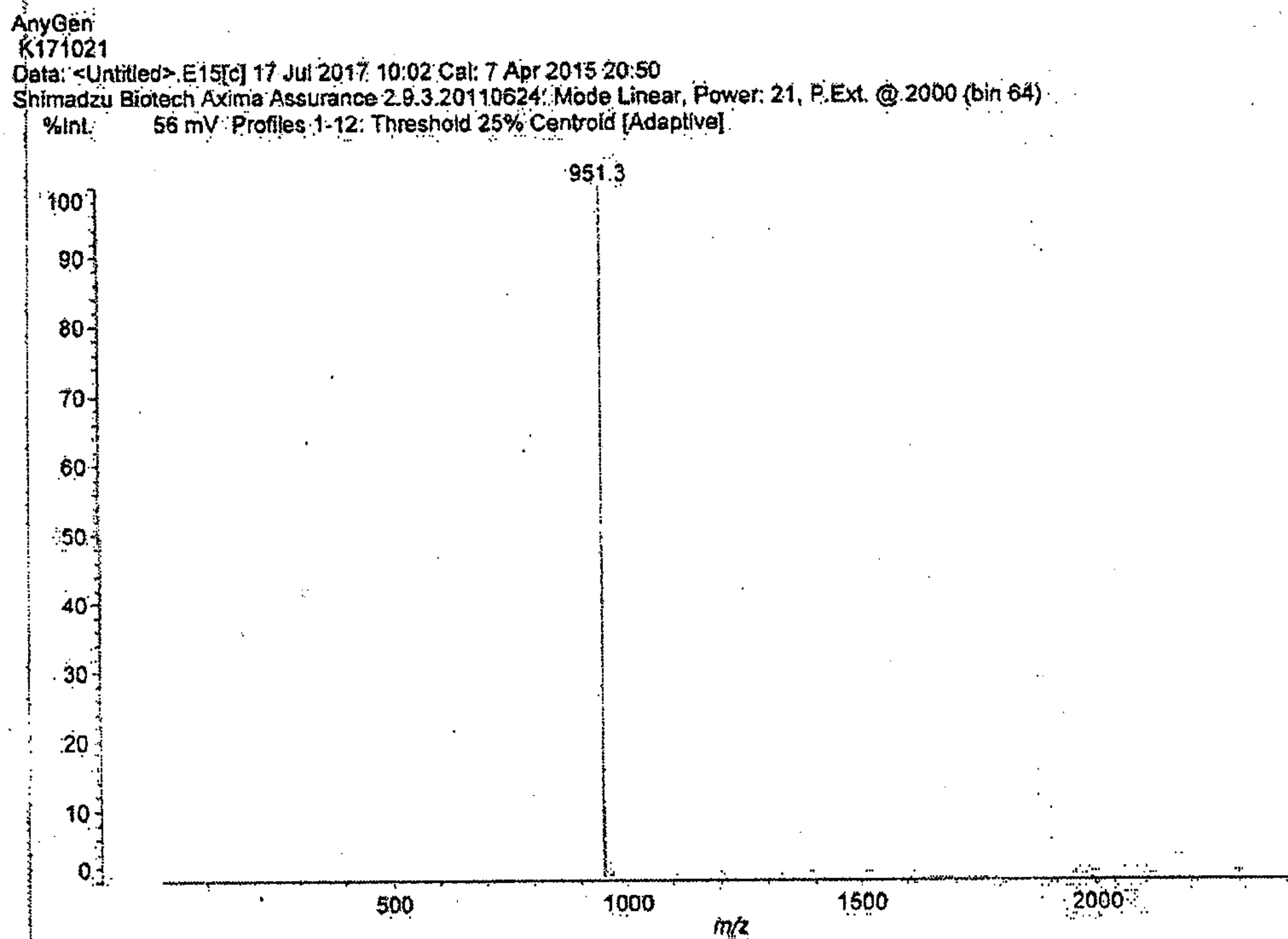
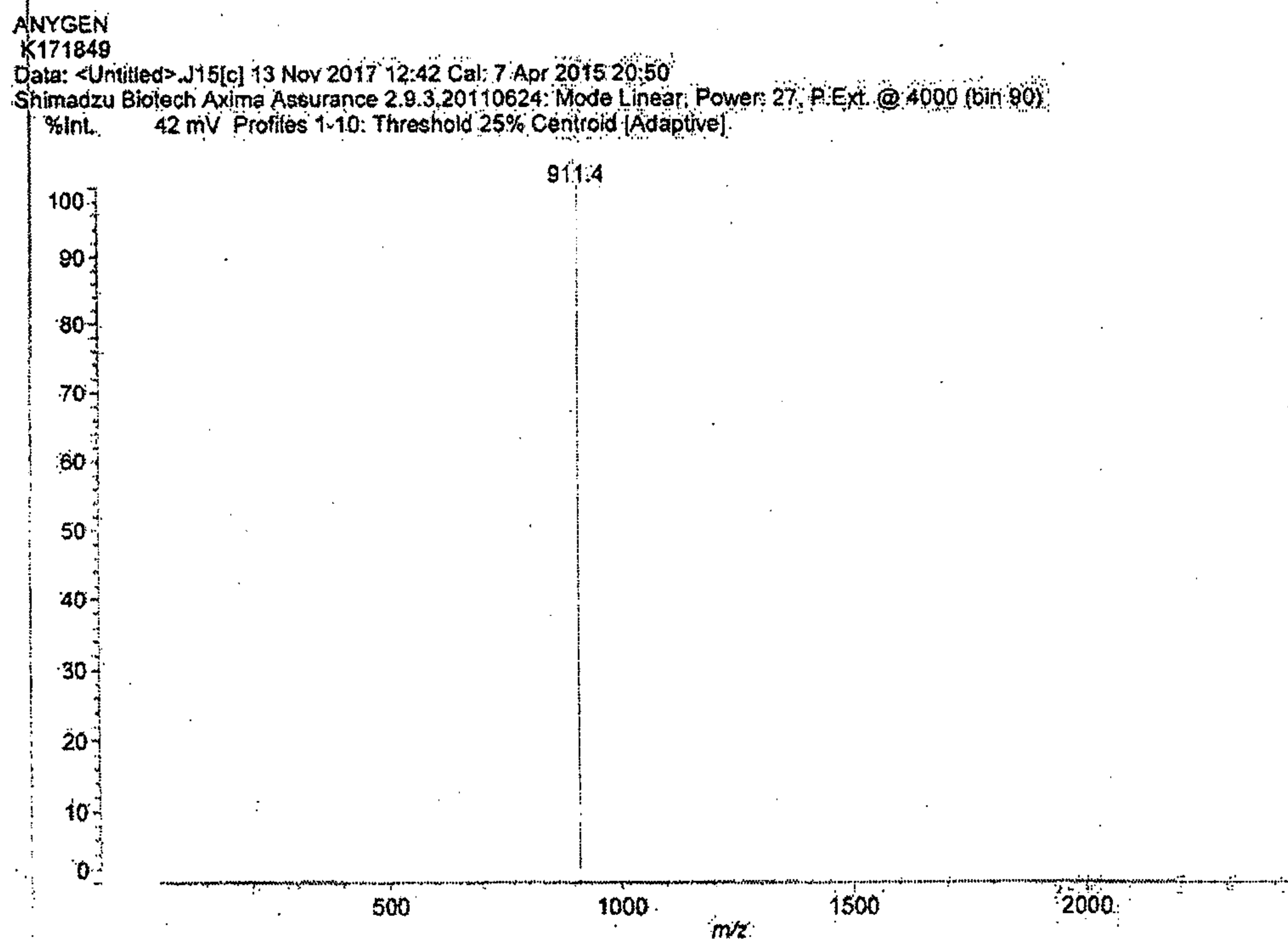


FIG 114



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FIG 115

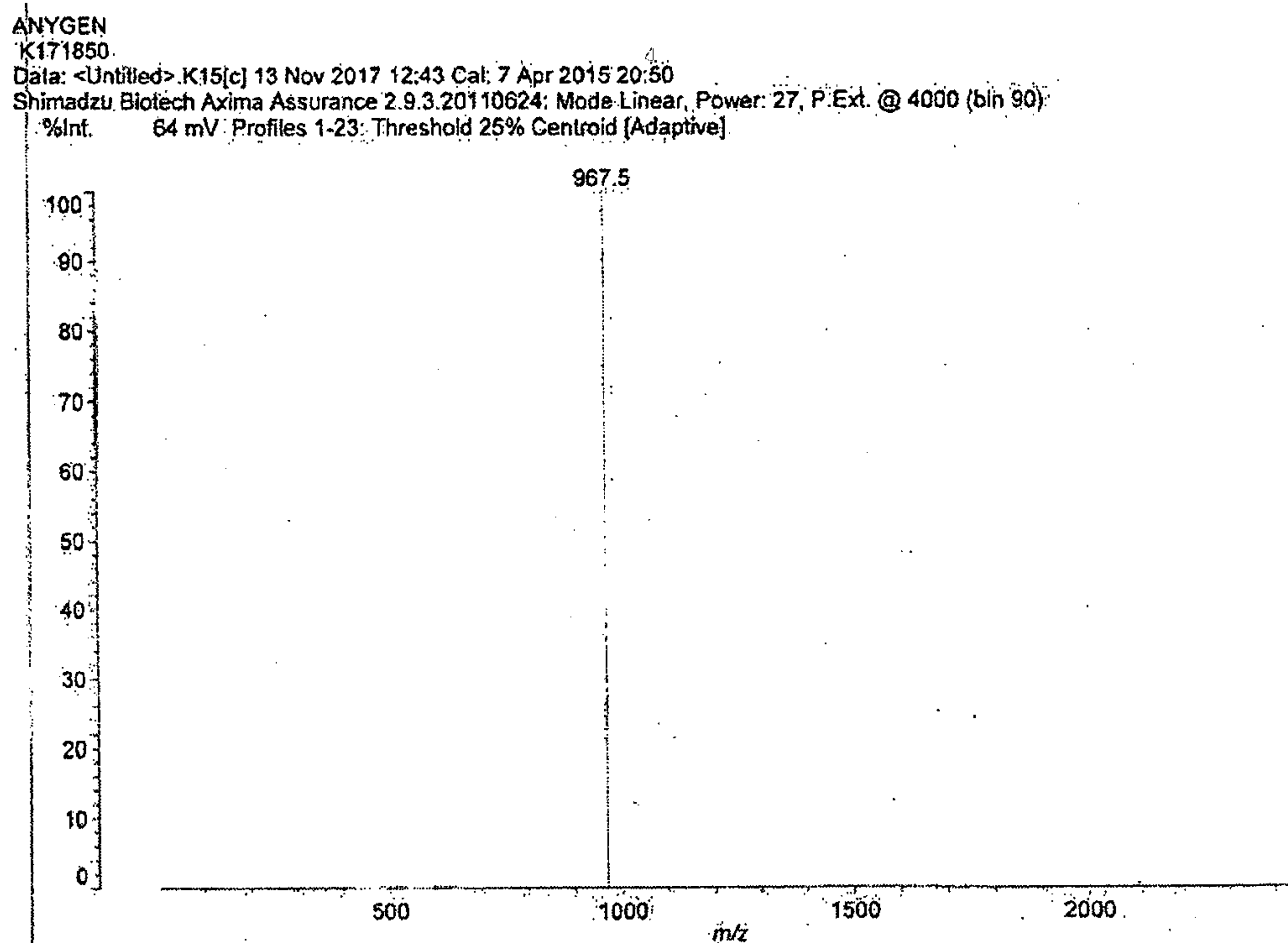
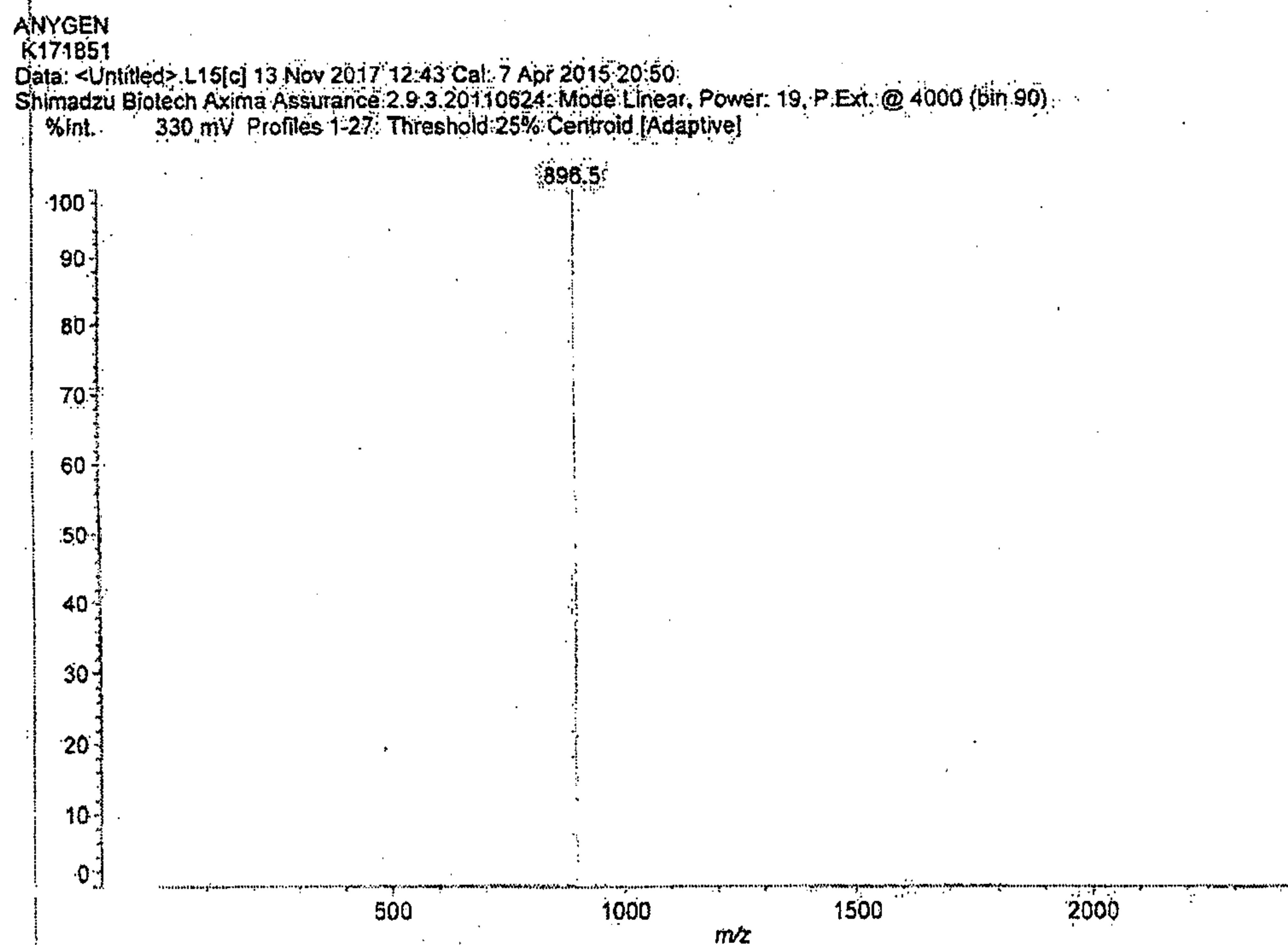


FIG 116



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FIG 117

ANYGEN
K171852
Data: <Untitled>.A16[c] 13 Nov 2017 12:44 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int: 168 mV Profiles 1-24; Threshold 25% Centroid [Adaptive]

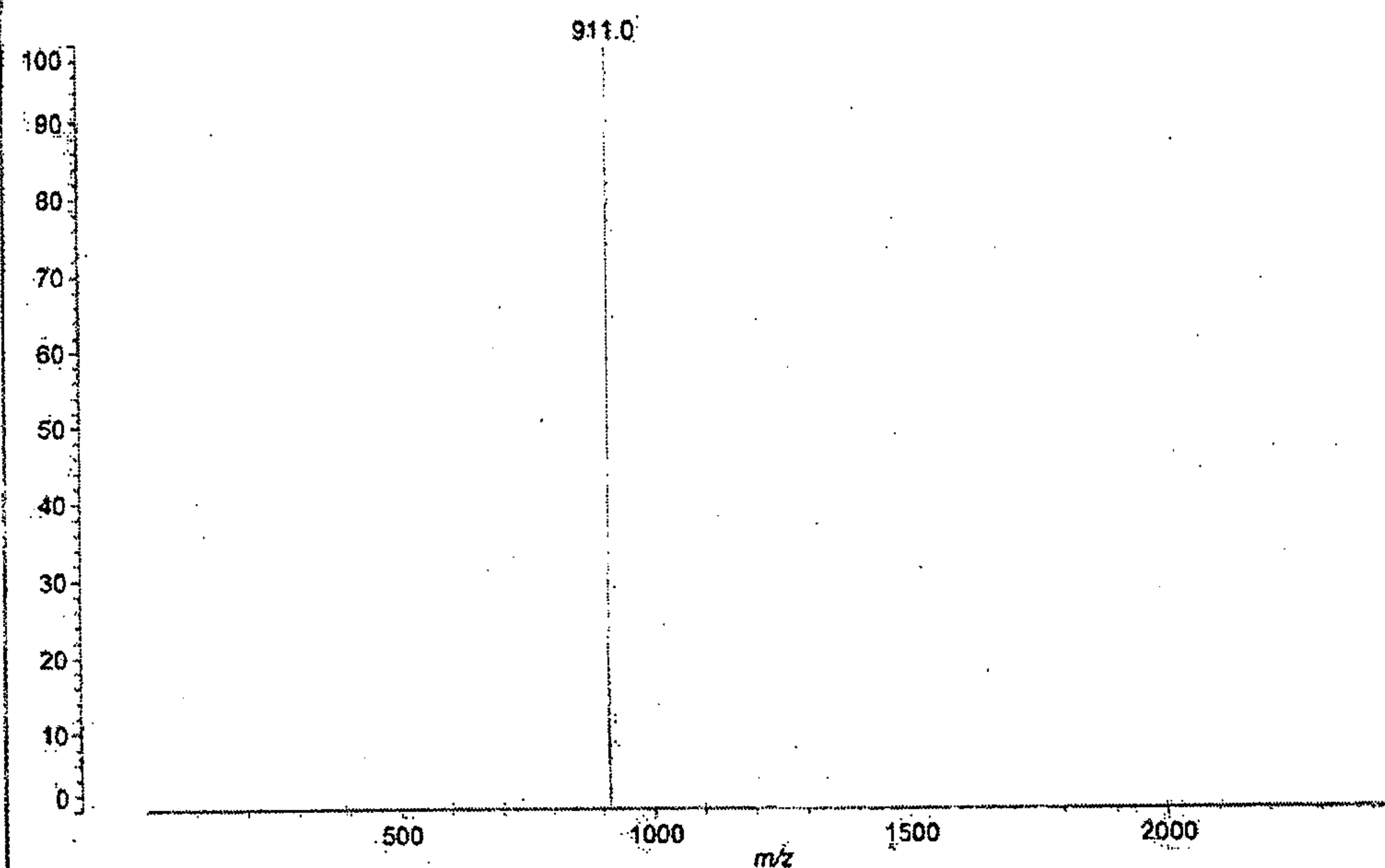
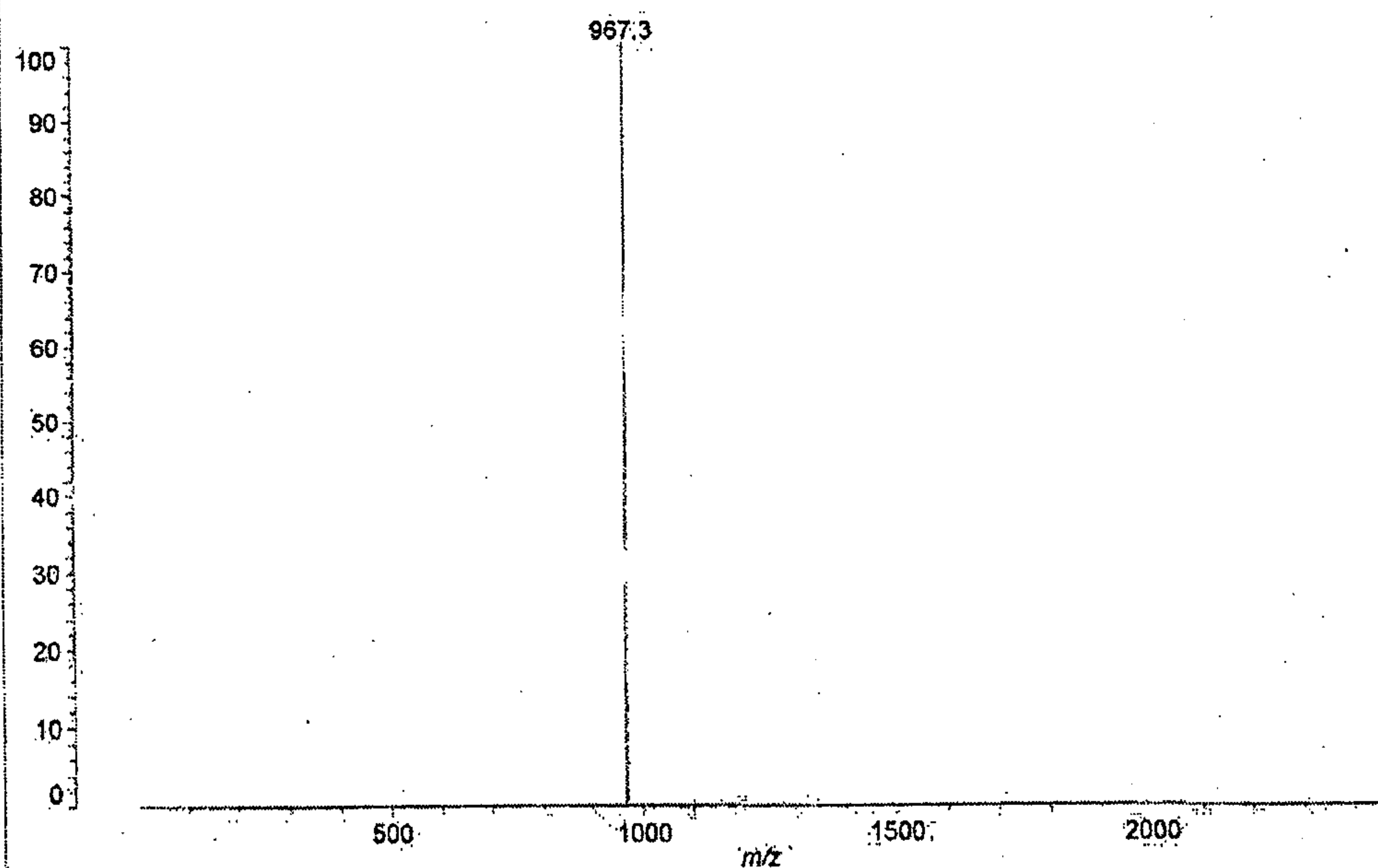


FIG 118

ANYGEN
K171853
Data: <Untitled>.B16[c] 13 Nov 2017 12:44 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int: 189 mV Profiles 1-19; Threshold 25% Centroid [Adaptive]



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FIG. 119

ANYGEN

K171854

Data: <Untitled>.C16[c] 13 Nov 2017 12:44 Cal: 7 Apr 2015 20:50

Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)

%Int. 580 mV. Profiles 1-17: Threshold 25% Centroid [Adaptive]

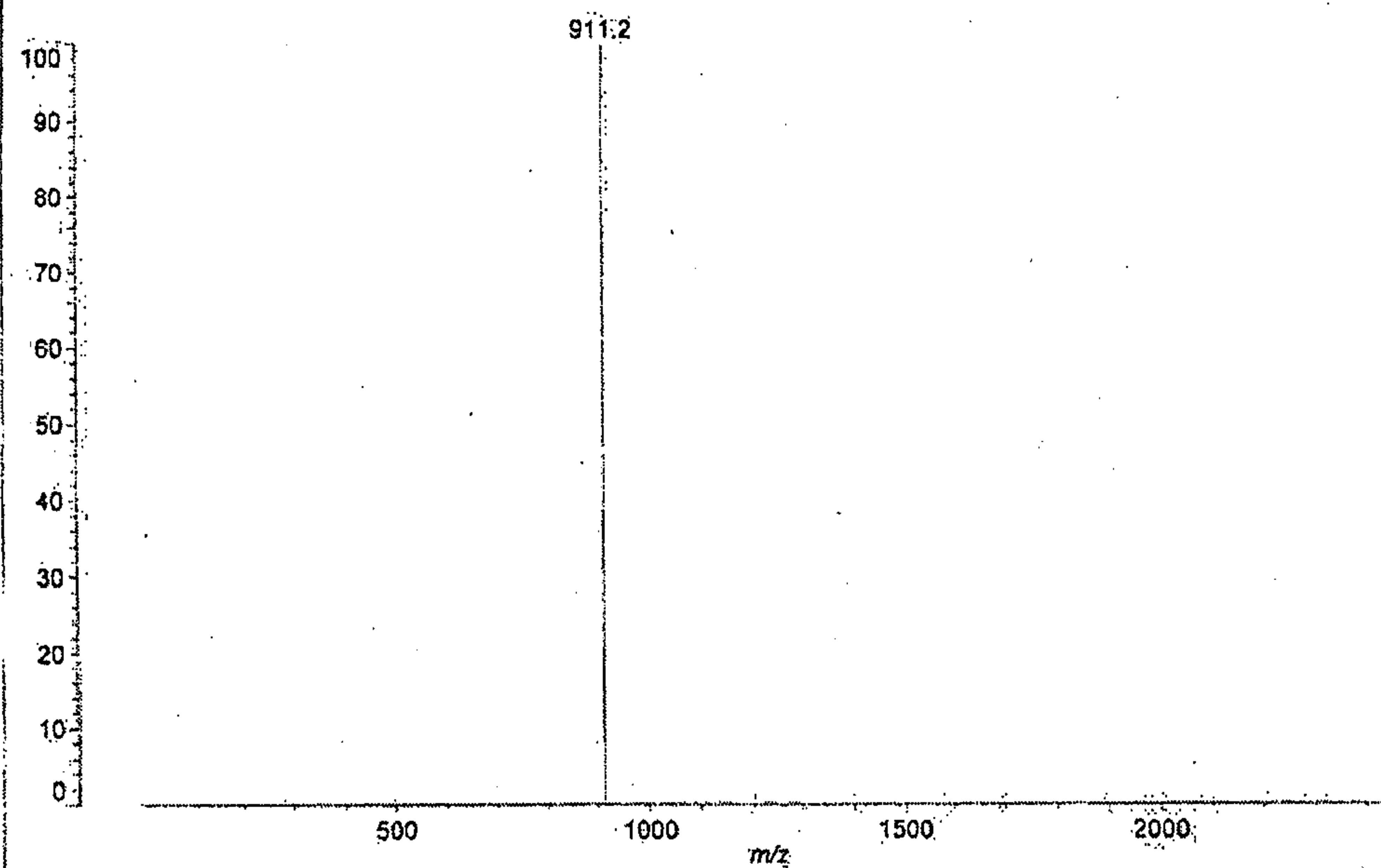


FIG 120

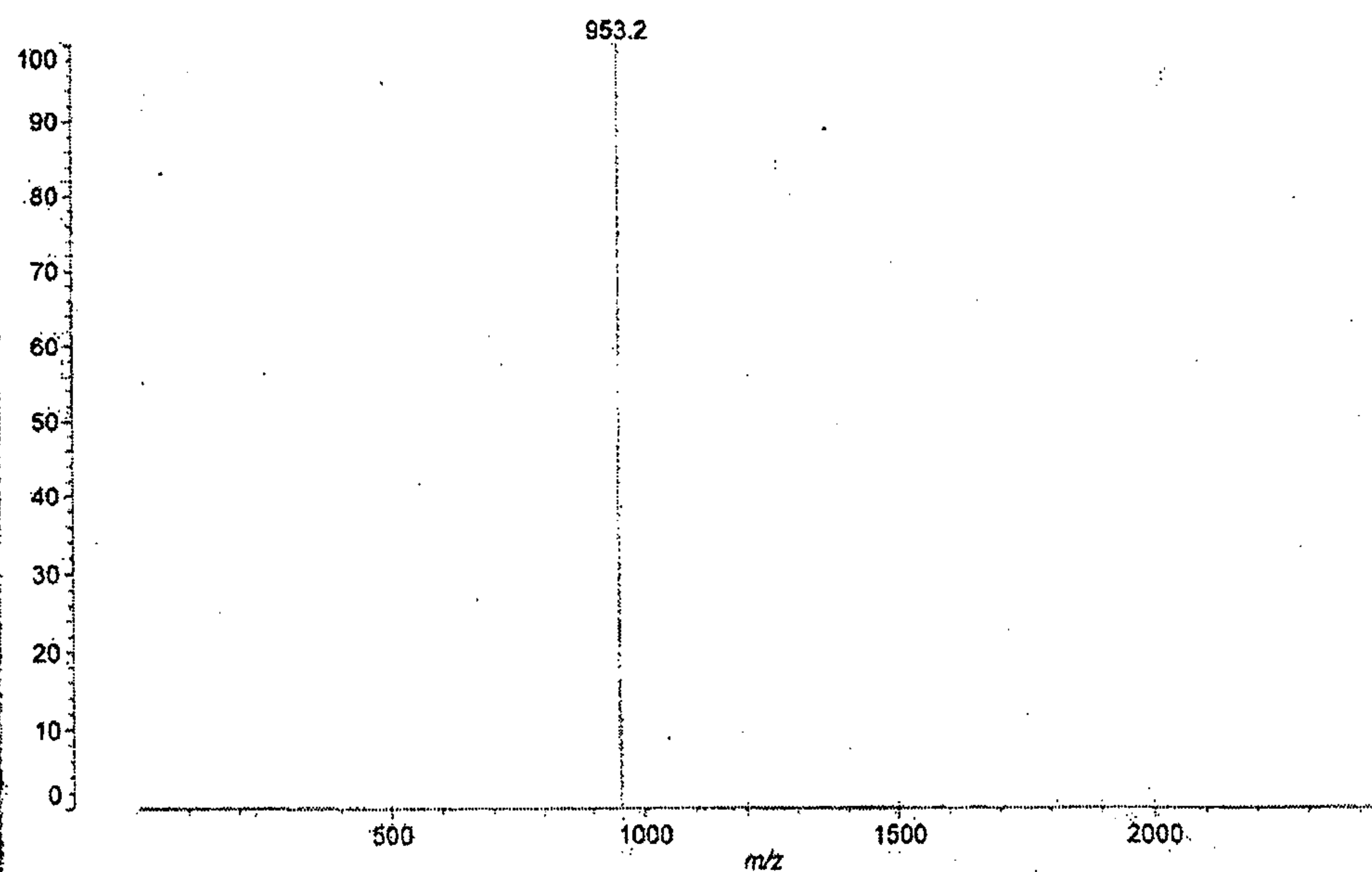
ANYGEN

K171855

Data: <Untitled>.D16[c] 13 Nov 2017 12:45 Cal: 7 Apr 2015 20:50

Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)

%Int. 108 mV Profiles 1-8: Threshold 25% Centroid [Adaptive]



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FIG 121

ANYGEN
K171856
Data: <Untitled>.E16[c] 13-Nov-2017 12:45 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int. 46 mV Profiles 1-6; Threshold 25% Centroid [Adaptive]

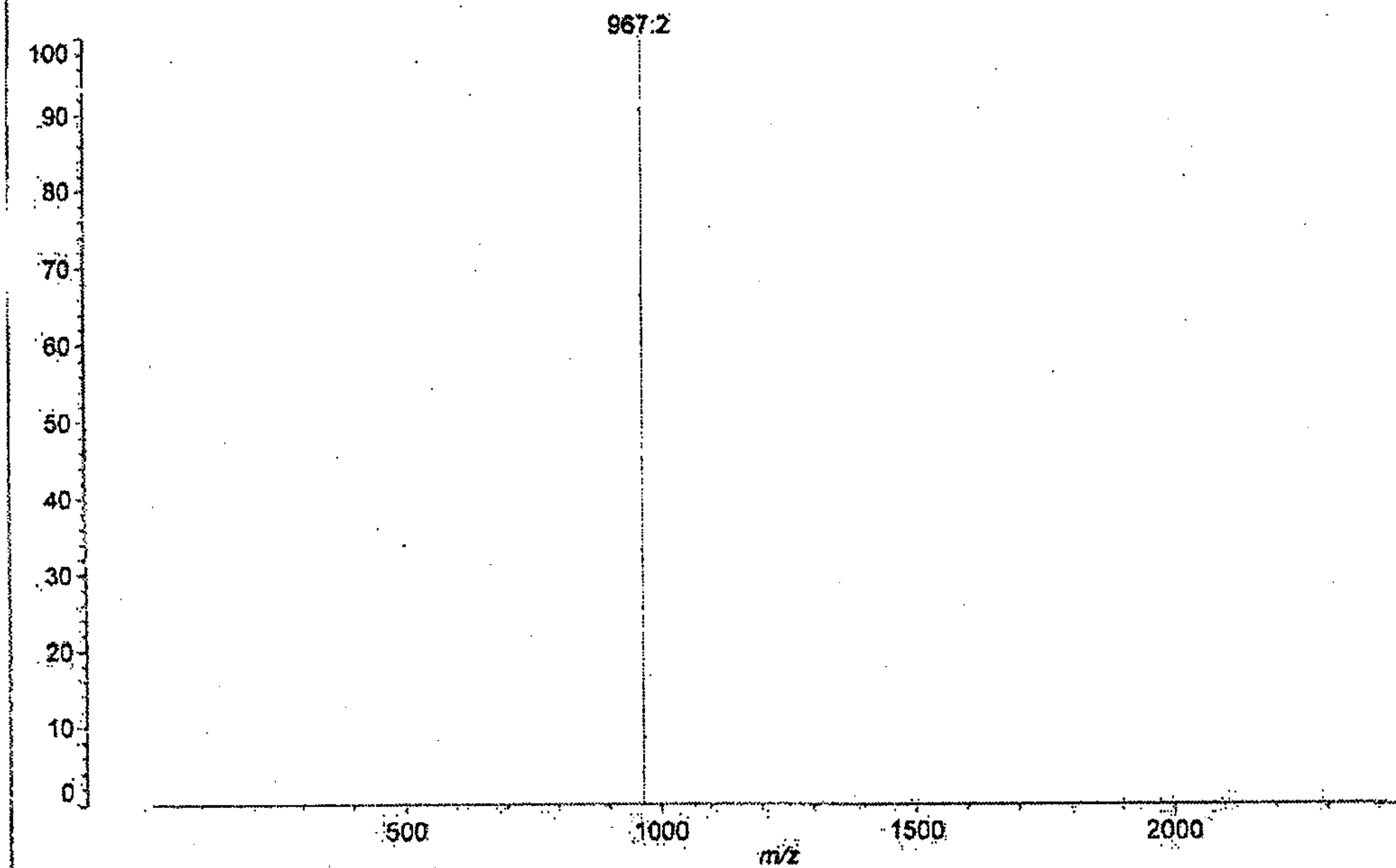
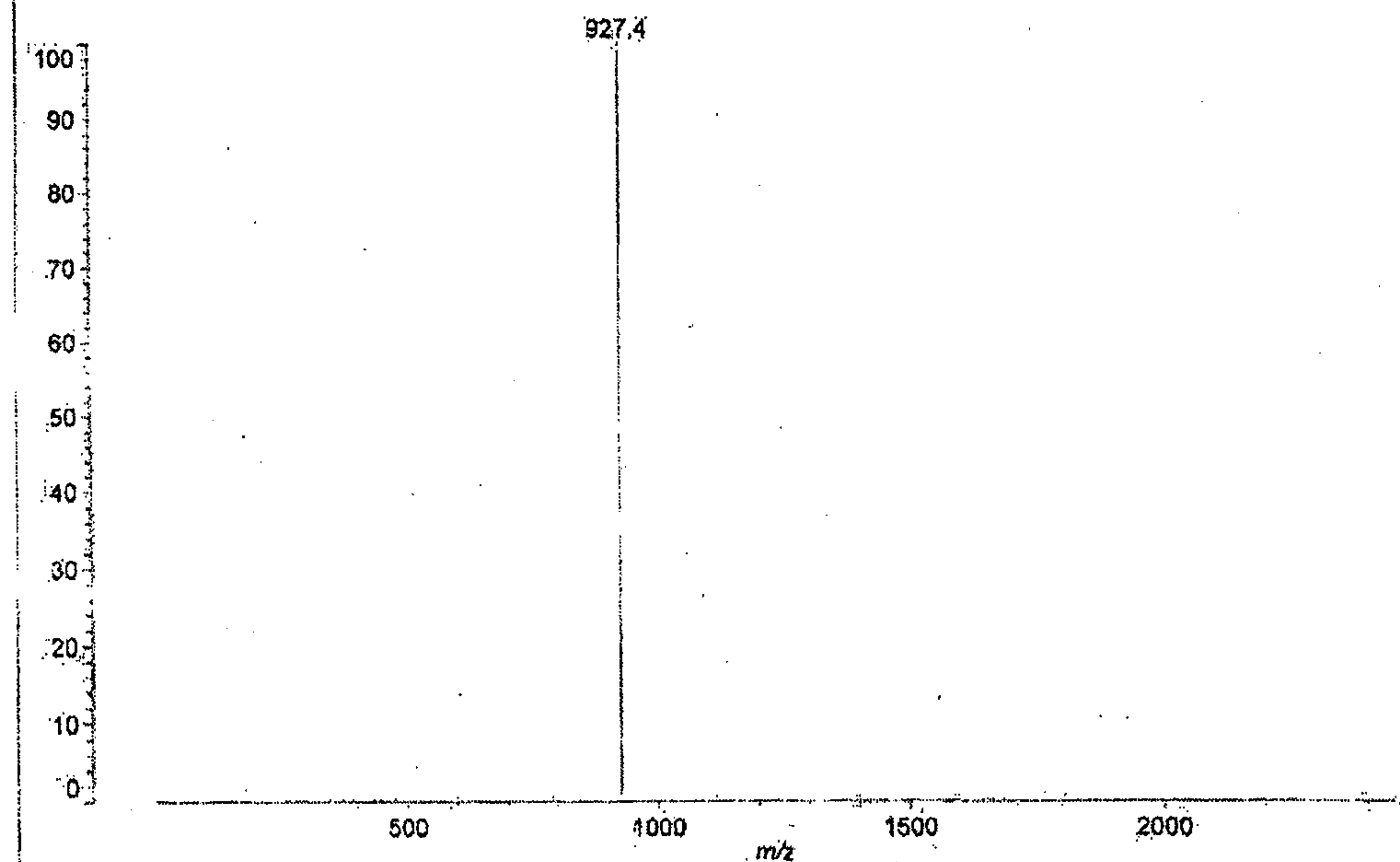


FIG 122

ANYGEN
K171857
Data: <Untitled>.F16[c] 13-Nov-2017 12:45 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int. 254 mV Profiles 1-14; Threshold 25% Centroid [Adaptive]



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FIG 123

ANYGEN
K171858
Data: <Untitled>.G16[c] 13 Nov 2017 12:46 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int. 245 mV Profiles 1-21: Threshold 25% Centroid [Adaptive]

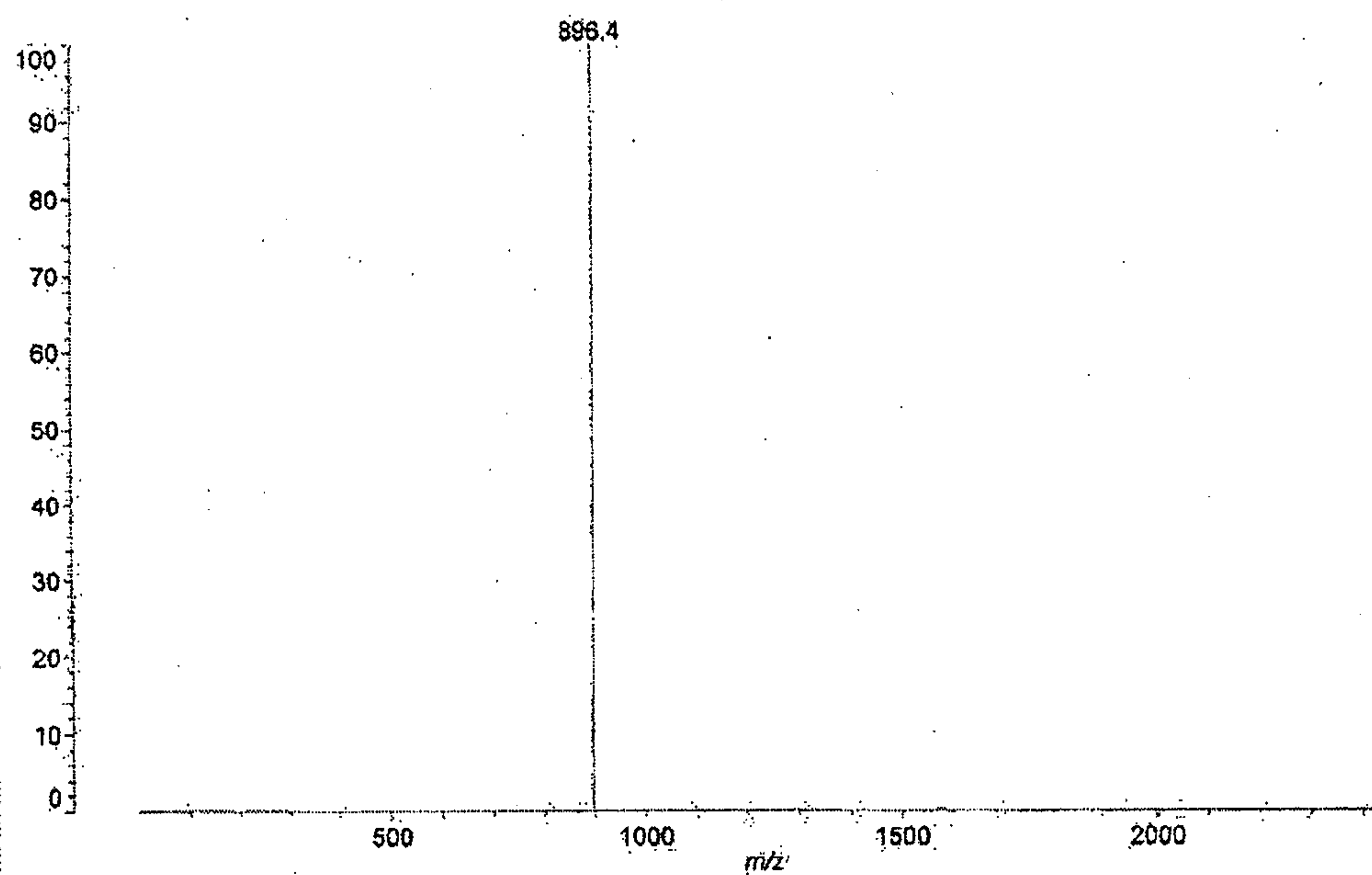
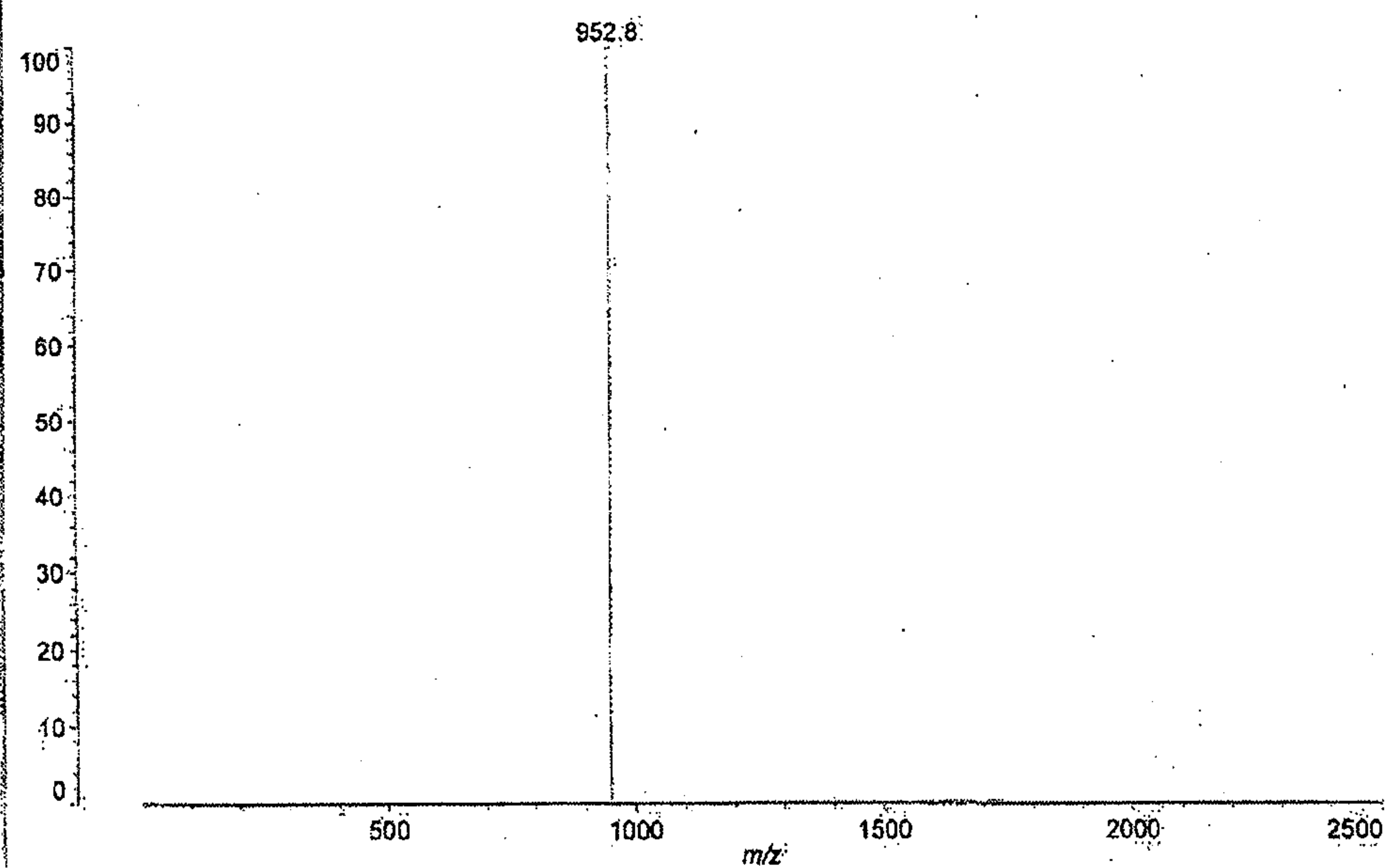


FIG 124

ANYGEN
K171869
Data: <Untitled>.A20[c] 13 Dec 2017 13:34 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int. 91 mV Profiles 1-8: Threshold 25% Centroid [Adaptive]



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FIG 125

ANYGEN
K171870
Data: <Untitled>.D20[c] 20 Dec 2017 12:44 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 24, P.Ext. @ 4000 (bin 90)
%Int. 117 mV Profiles 1-8: Threshold 25% Centroid [Adaptive]

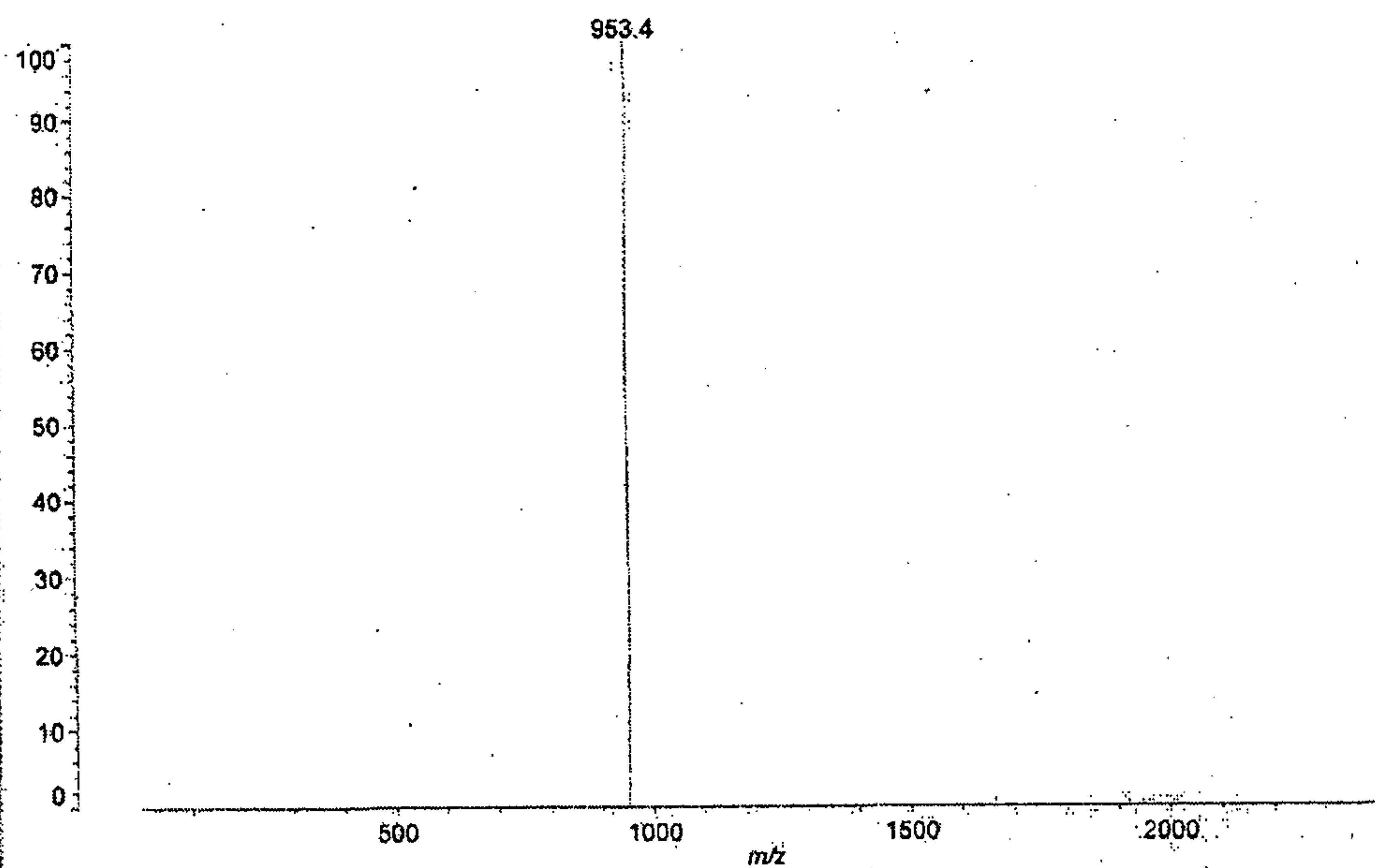
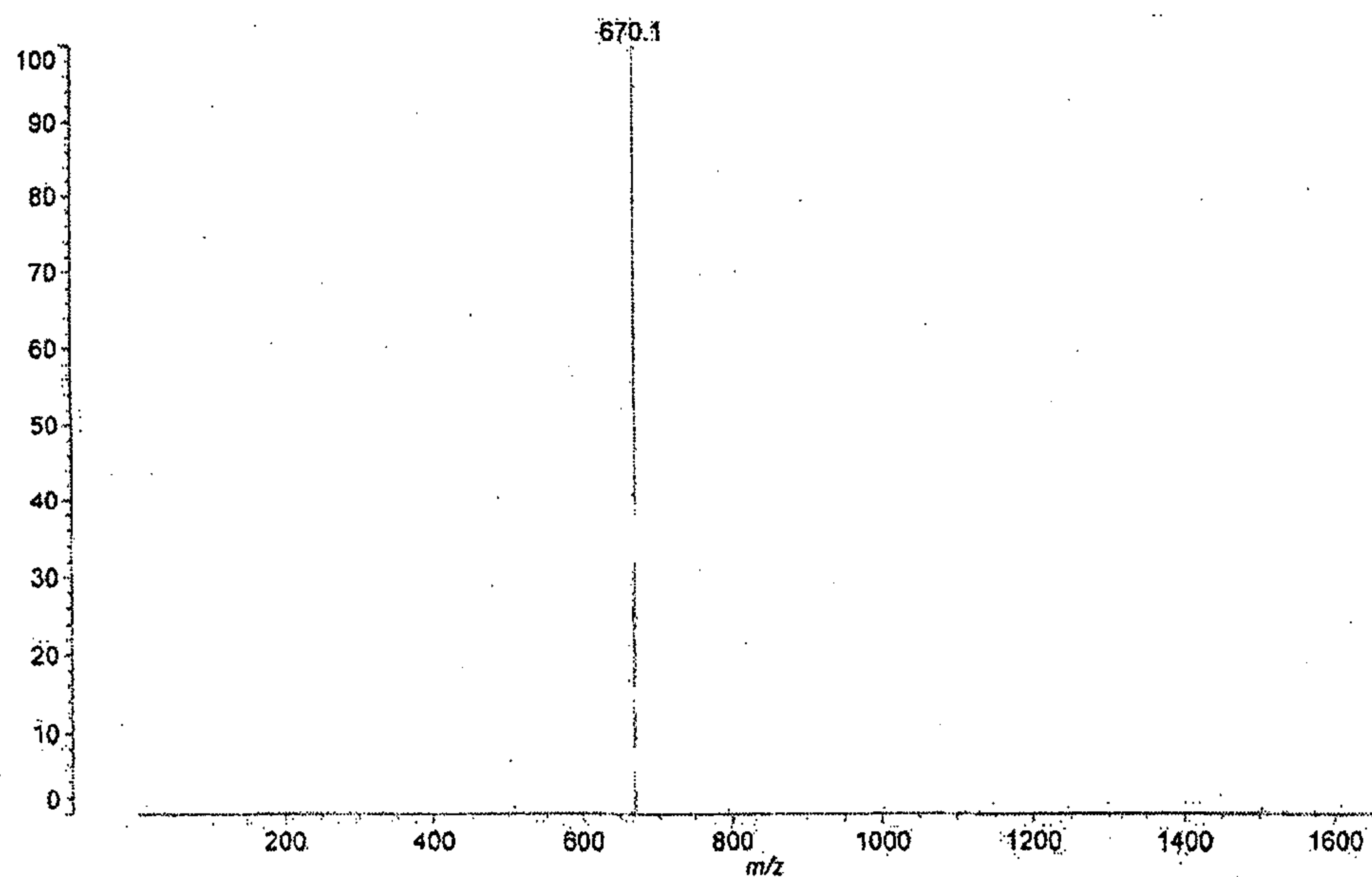


FIG 126

ANYGEN
K171871
Data: <Untitled>.F18[c] 22 Nov 2017 10:55 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 19, P.Ext. @ 4000 (bin 90)
%Int. 3.90 mV Profiles 1-15: Threshold 25% Centroid [Adaptive]



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FIG 127

ANYGEN
K171872
Data: <Untitled>.L20[c] 21 Nov 2017 13:01 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 14, P.Ext. @ 4000 (bin 90)
%Int. 68 mV Profiles 1-18: Threshold 25% Centroid [Adaptive]

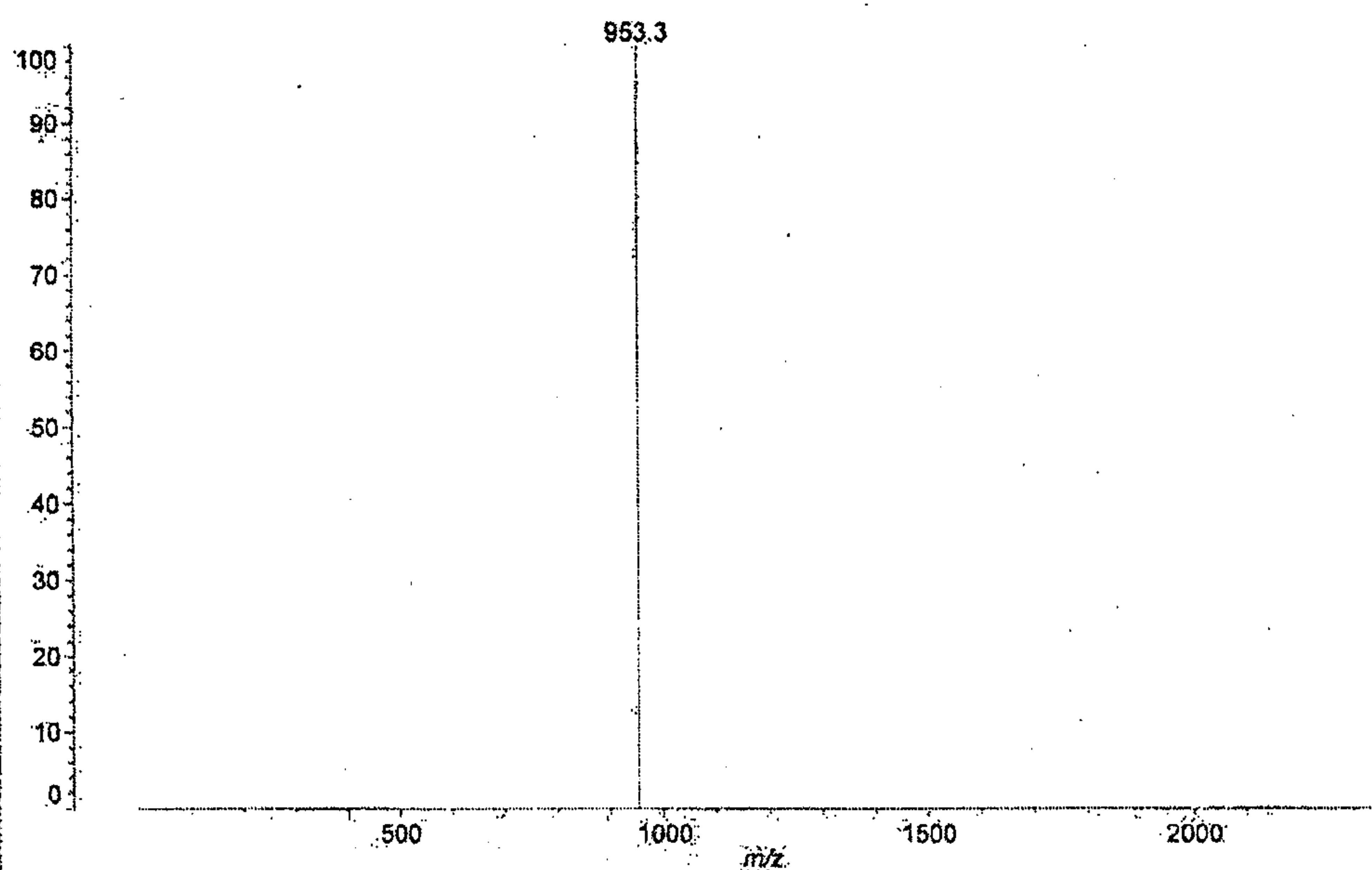
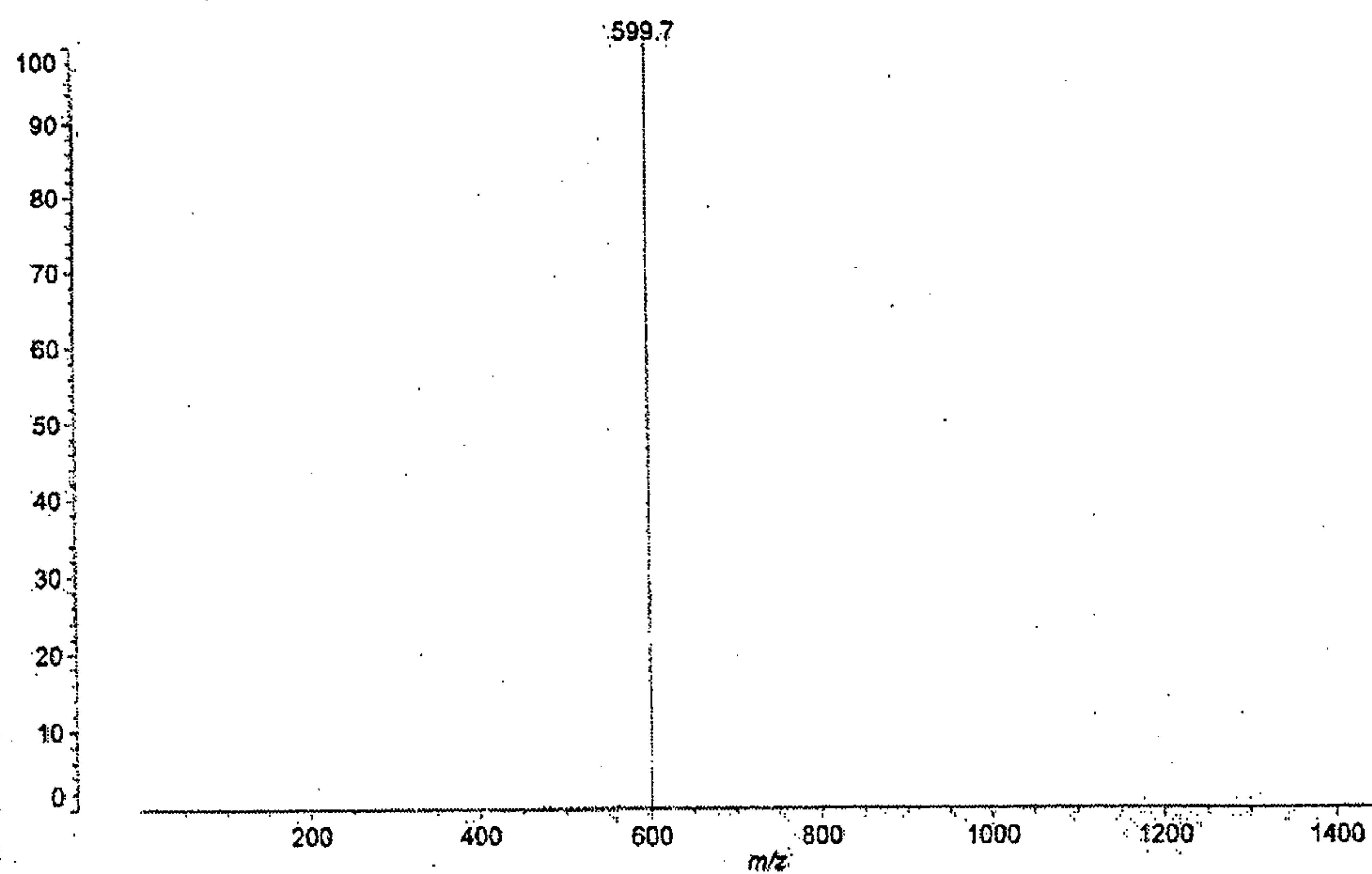


FIG 128

ANYGEN
K171987
Data: <Untitled>.E20[c] 20 Dec 2017 12:45 Cal: 7 Apr 2015 20:50
Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 24, P.Ext. @ 4000 (bin 90)
%Int. 30 mV Profiles 1-10: Threshold 25% Centroid [Adaptive]



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FIG 129

ANYGEN

K171989

Data: <Untitled> J21[c] 4 Dec 2017 12:47 Cal: 7 Apr 2015 20:50

Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 30, P.Ext. @ 4000 (bin 90)

%Int: 54 mV Profiles 1-11: Threshold 25% Centroid [Adaptive]

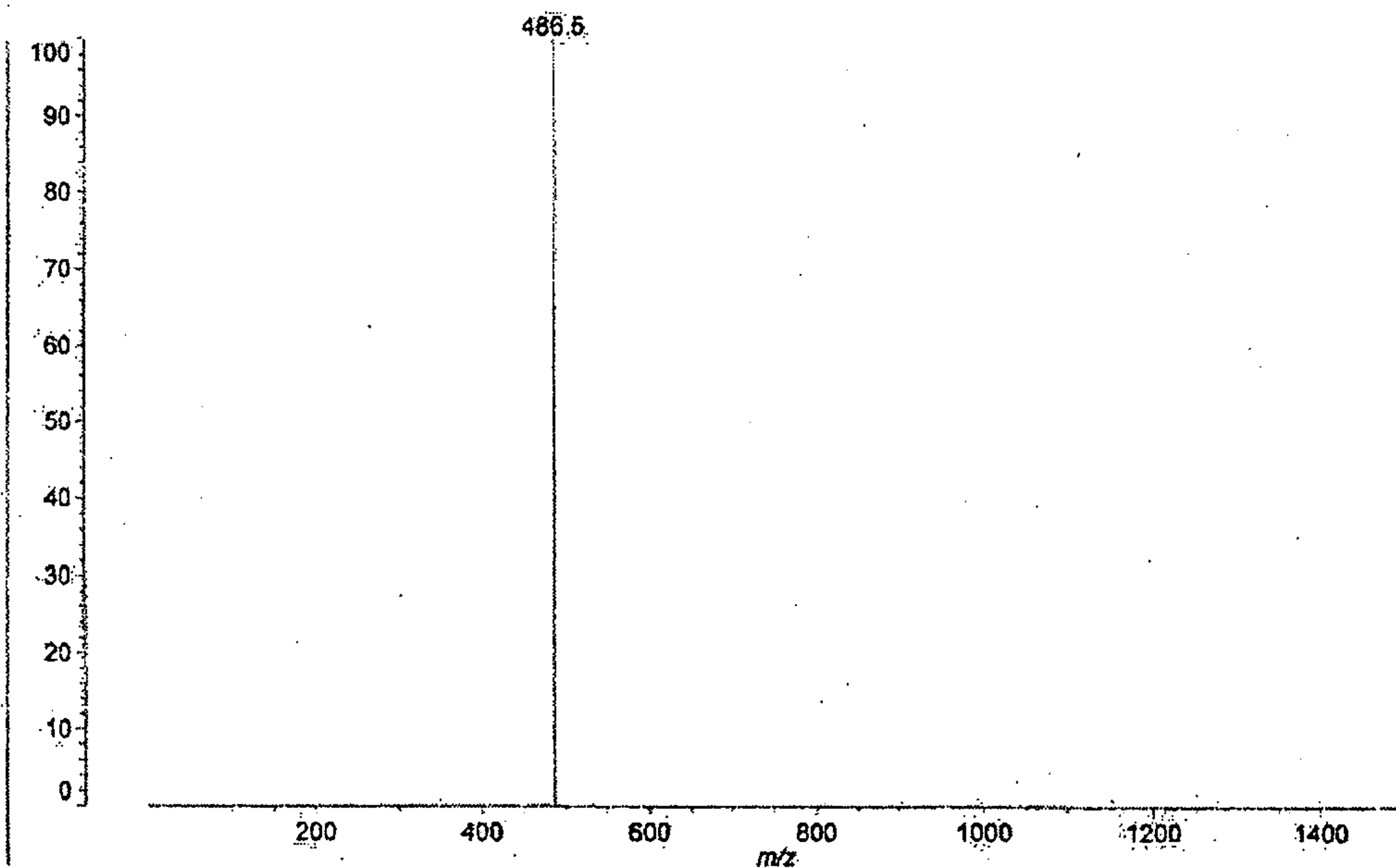


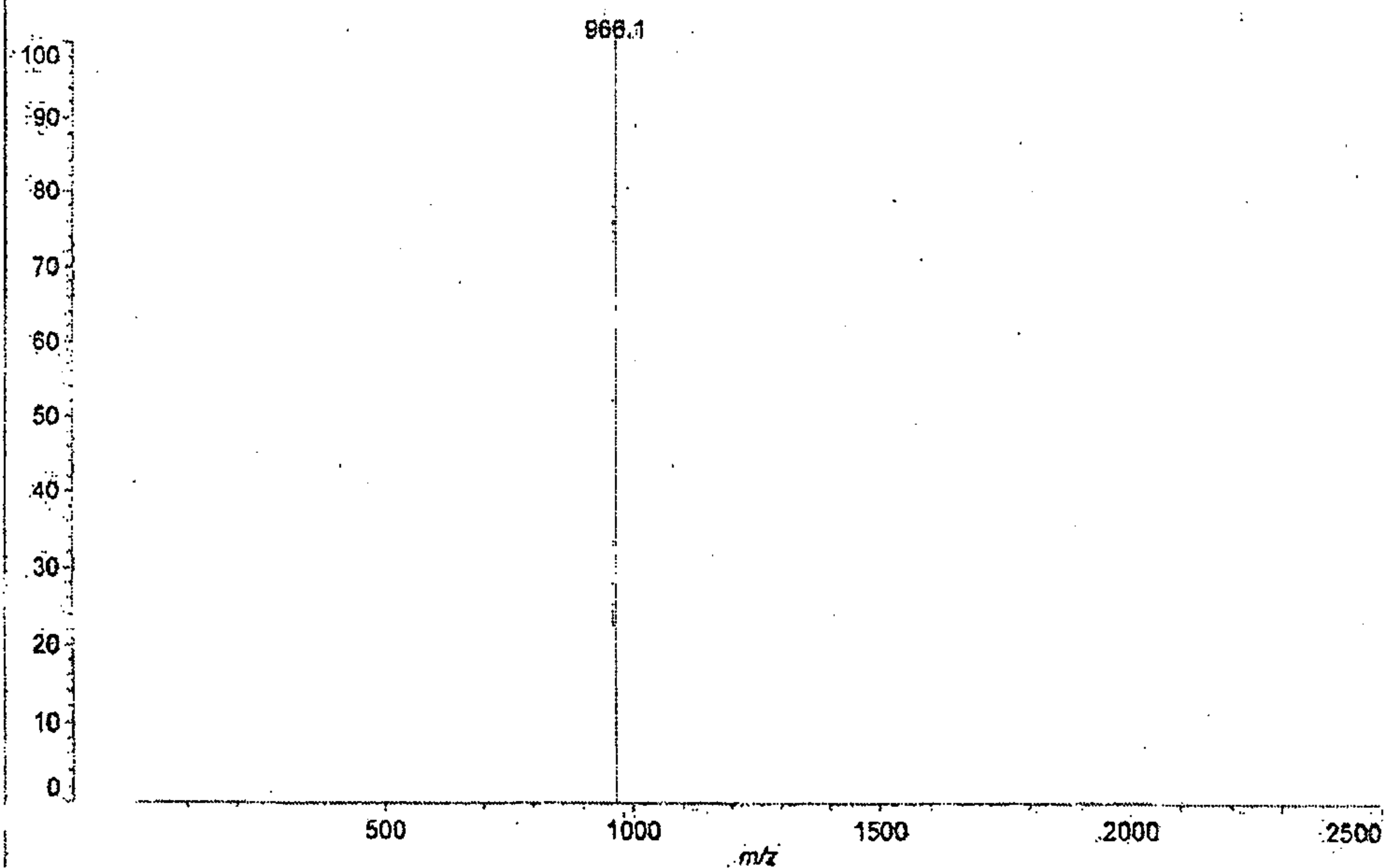
FIG 130

K180115

Data: <Untitled> E1[c] 8 Feb 2018 13:39 Cal: 7 Apr 2015 20:50

Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear_neg, Power: 40, P.Ext. @ 8000 (bin 128)

%Int: 208 mV Profiles 1-14: Threshold 25% Centroid [Adaptive]



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FIG 131

ANYGEN

K180116

Data: <Untitled>.L7[c] 5 Feb 2018 10:30 Cat: 7 Apr 2015 20:50

Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear, Power: 20, P.Ext. @ 3000 (bin 78)

%Int. 305 mV Profiles 1-48: Threshold 25% Centroid [Adaptive]

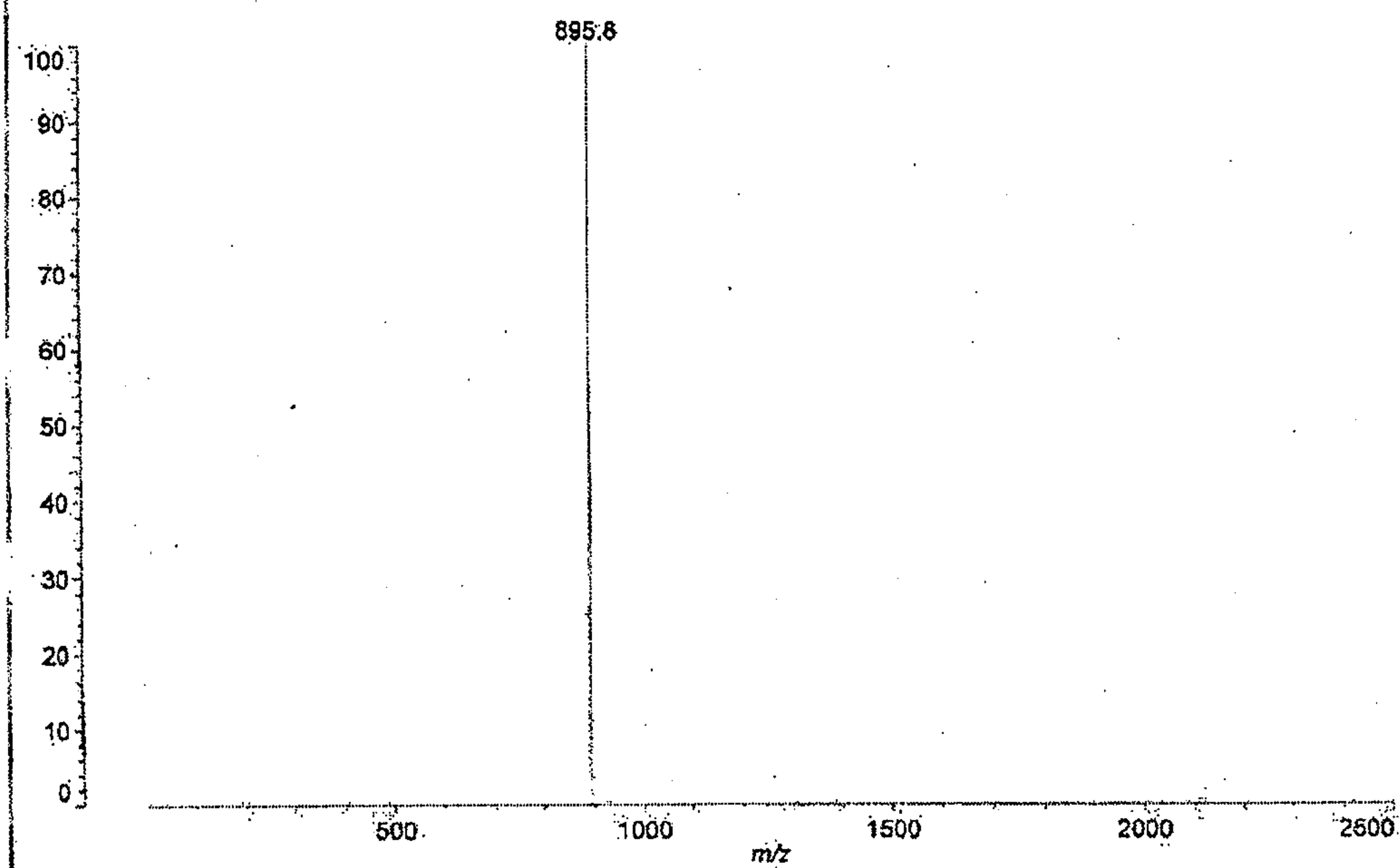


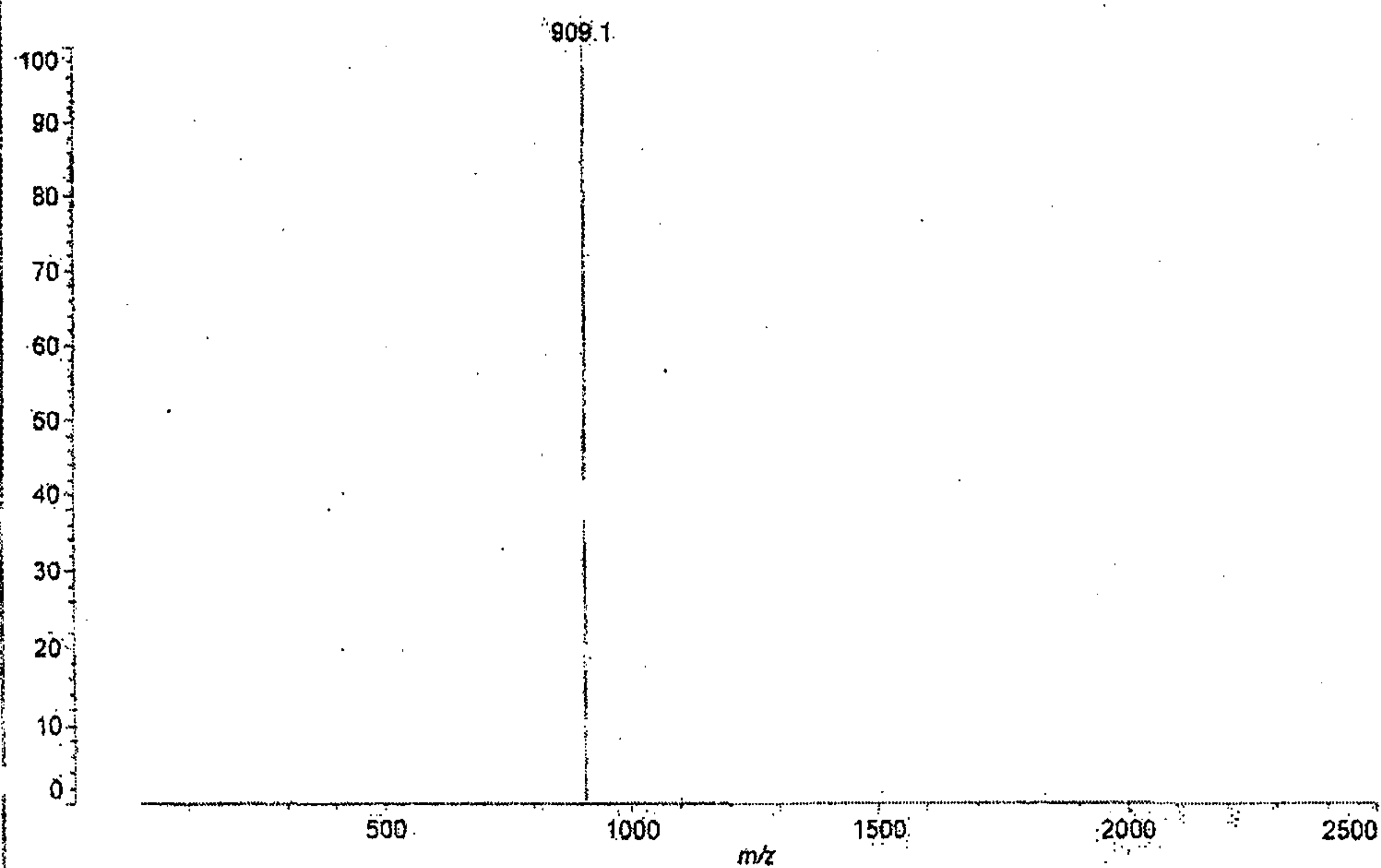
FIG 132

K180117

Data: <Untitled>.F1[c] 8 Feb 2018 13:40 Cat: 7 Apr 2015 20:50

Shimadzu Biotech Axima Assurance 2.9.3.20110624: Mode Linear_neg, Power: 40, P.Ext. @ 8000 (bin 128)

%Int. 186 mV Profiles 1-58: Threshold 25% Centroid [Adaptive]



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FIG 133

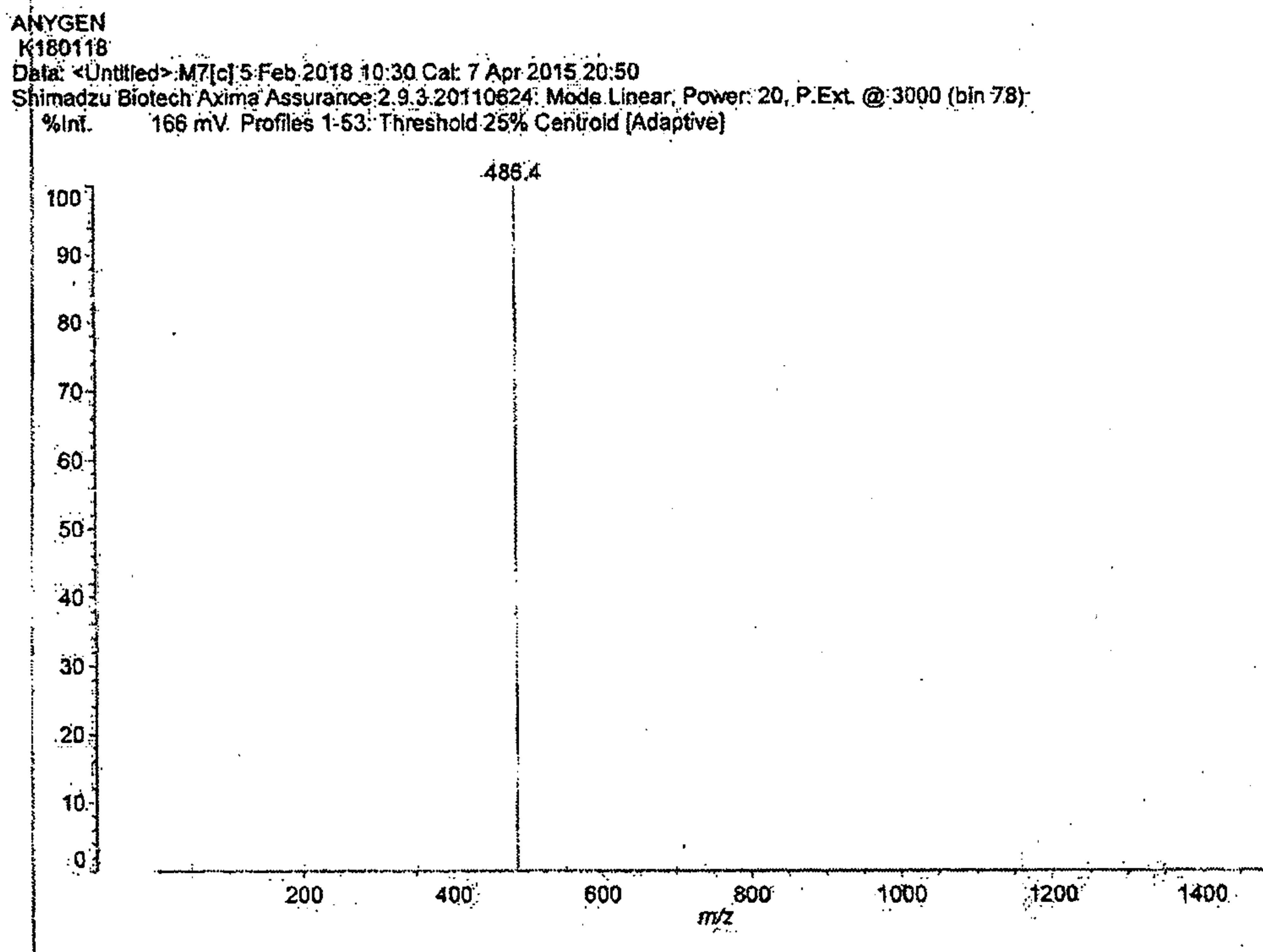
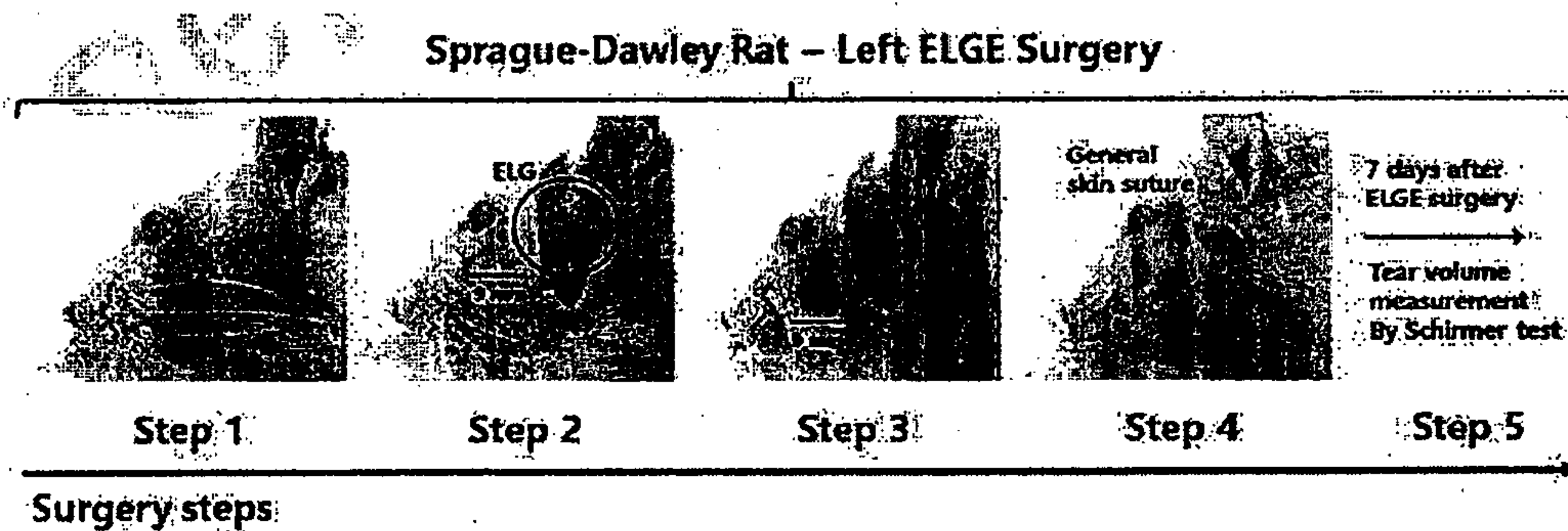


FIG 134



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FIG 135

Groups	Body weights at		Body weight gains	
	Items	ELGE surgery*	First test material topical eye drop [A]	24 hrs after last treatment [B]*
Control				
Sham		213.63±21.04	305.50±33.53	340.50±38.46
ELGE		215.50±16.10	302.63±20.42	339.13±20.01
Reference				
DS		220.50±8.70	304.50±13.11	340.63±10.20
Test materials (0.3% solutions)				
YY-102		211.88±12.89	302.00±20.70	337.75±25.95
YDE-01		212.63±11.30	302.25±24.57	341.00±24.98
YDE-02		210.38±10.89	302.00±15.96	338.00±22.39
YDE-03		212.50±14.84	301.00±20.63	339.38±22.93
YDE-04		217.50±16.25	302.50±19.66	338.50±21.44
YDE-05		212.50±16.75	303.50±17.77	341.50±17.53
YDE-06		212.38±19.00	306.38±25.21	345.13±21.06
YDE-07		219.13±4.73	310.50±9.99	349.88±12.28
YDE-08		213.38±13.99	307.00±13.73	345.63±17.87
YDE-09		215.63±13.69	304.25±18.58	341.38±25.47
YDE-10		216.00±12.99	305.25±13.82	343.63±16.36
YDE-11		219.88±13.42	309.13±20.36	347.00±27.91
YDE-12		222.13±9.98	311.00±15.57	349.88±21.70
YDE-13		217.63±4.69	305.13±7.66	343.25±11.44
YDE-14		216.75±15.53	301.25±20.11	339.75±26.99
YDE-15		214.88±14.74	302.13±16.57	340.00±16.44
YDE-16		213.50±18.31	299.50±16.42	337.38±20.50
YDE-17		214.63±11.81	306.63±17.54	346.25±19.26
YDE-18		213.88±13.24	307.88±13.27	347.38±23.02
YDE-19		218.88±11.29	307.25±12.85	345.38±21.71
YDE-20		217.88±9.61	300.75±16.79	339.25±15.68
YDE-21		216.38±15.31	301.38±20.89	340.13±21.53
YDE-22		219.38±10.85	304.13±14.56	343.50±21.37
YDE-23		219.00±12.54	308.25±15.64	346.00±15.26
YDE-24		212.13±18.41	298.38±25.85	334.00±31.75
YDE-25		213.13±13.39	303.63±21.87	342.50±19.82
YDE-26		213.63±14.71	305.75±23.07	343.25±29.09
YDE-27		214.75±13.73	306.63±25.44	345.38±26.40
YDE-28		212.75±13.36	297.63±21.12	336.38±22.02

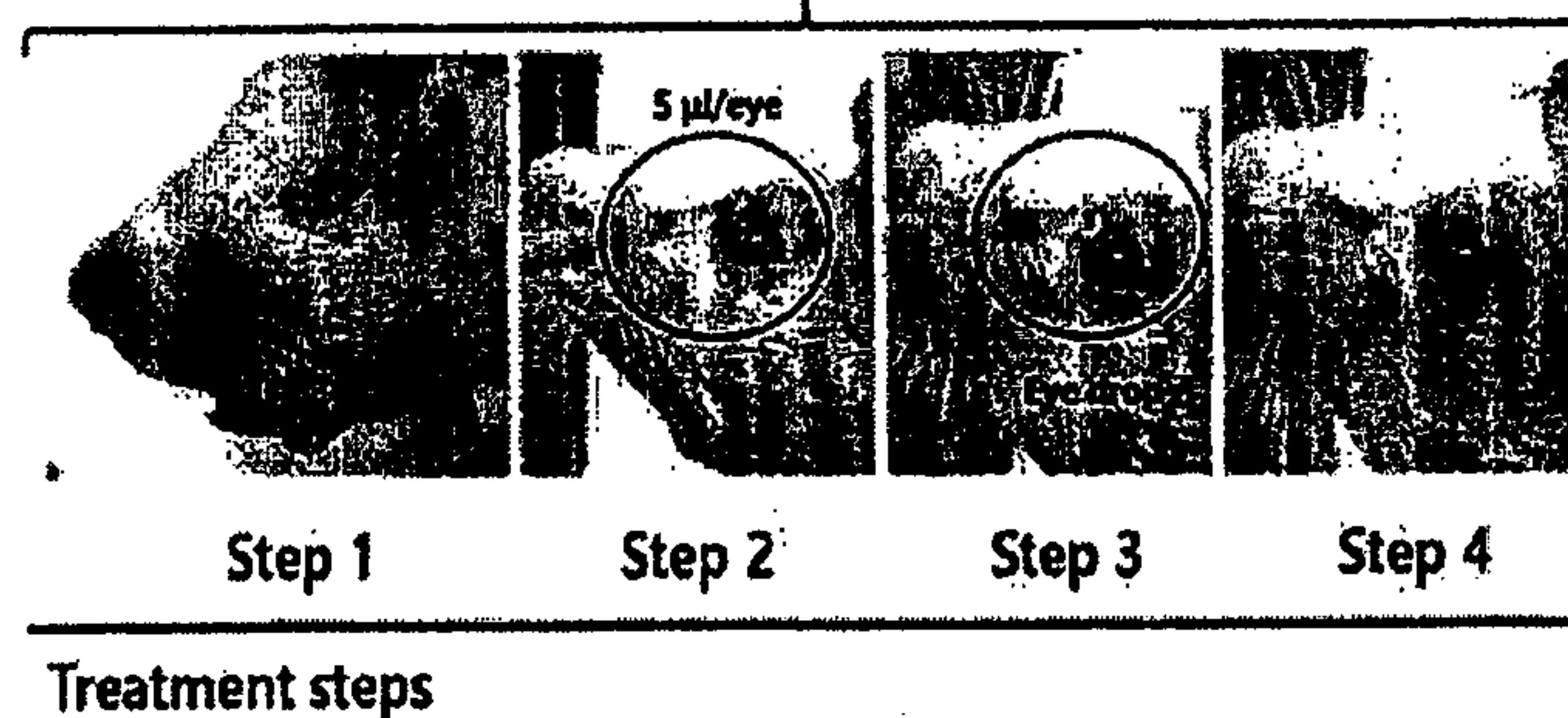
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FIG 136

Groups	Items	Body weights at		24 hrs after last treatment [B]*	Body weight gains [B-A]
		ELGE surgery*	First test material topical eye drop [A]		
Control					
	Sham	242.38±7.73	320.25±9.91	363.38±27.21	43.13±19.71
	ELGE	243.88±3.83	329.25±18.90	367.50±19.89	38.25±11.40
Reference					
	DS	246.63±15.68	330.50±23.33	369.63±37.46	39.13±25.56
	YY-101	241.25±4.37	318.88±10.91	356.25±18.16	37.38±7.82
	YY-102	242.38±11.46	318.75±15.20	361.25±23.56	42.50±9.41
Test materials (0.3% solutions)					
	YDE-029	242.25±16.63	327.38±18.75	373.75±28.50	46.38±12.49
	YDE-030	243.25±10.26	315.88±14.96	355.50±29.68	39.63±16.61
	YDE-031	241.00±15.82	316.75±27.58	359.00±39.87	42.25±14.96
	YDE-032	242.75±9.32	324.25±14.59	365.38±16.16	41.13±10.12
	YDE-033	243.50±11.96	327.50±17.57	377.13±26.59	49.63±16.27
	YDE-034	243.88±8.68	322.63±17.15	361.63±19.08	39.00±4.99
	YDE-035	240.88±11.29	321.00±22.17	358.50±29.18	37.50±20.36
	YDE-036	242.25±14.01	329.38±21.07	378.38±24.20	49.00±10.81
	YDE-037	244.50±10.94	324.88±17.36	369.13±21.43	44.25±8.83
	YDE-039	242.88±7.14	325.25±15.51	363.25±28.35	38.00±15.41
	YDE-040	241.13±13.39	319.25±14.10	357.00±27.93	37.75±19.37
	YDE-041	244.75±14.49	322.88±22.47	366.13±37.43	43.25±16.97
	YDE-042	239.13±8.29	323.38±8.28	372.38±19.46	49.00±13.54
	YDE-043	246.25±7.92	324.00±14.31	361.25±19.20	37.25±13.63

FIG 137

Sprague-Dawley Rat – Left Eye



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FIG 138

Sprague-Dawley Rat – Left Eye

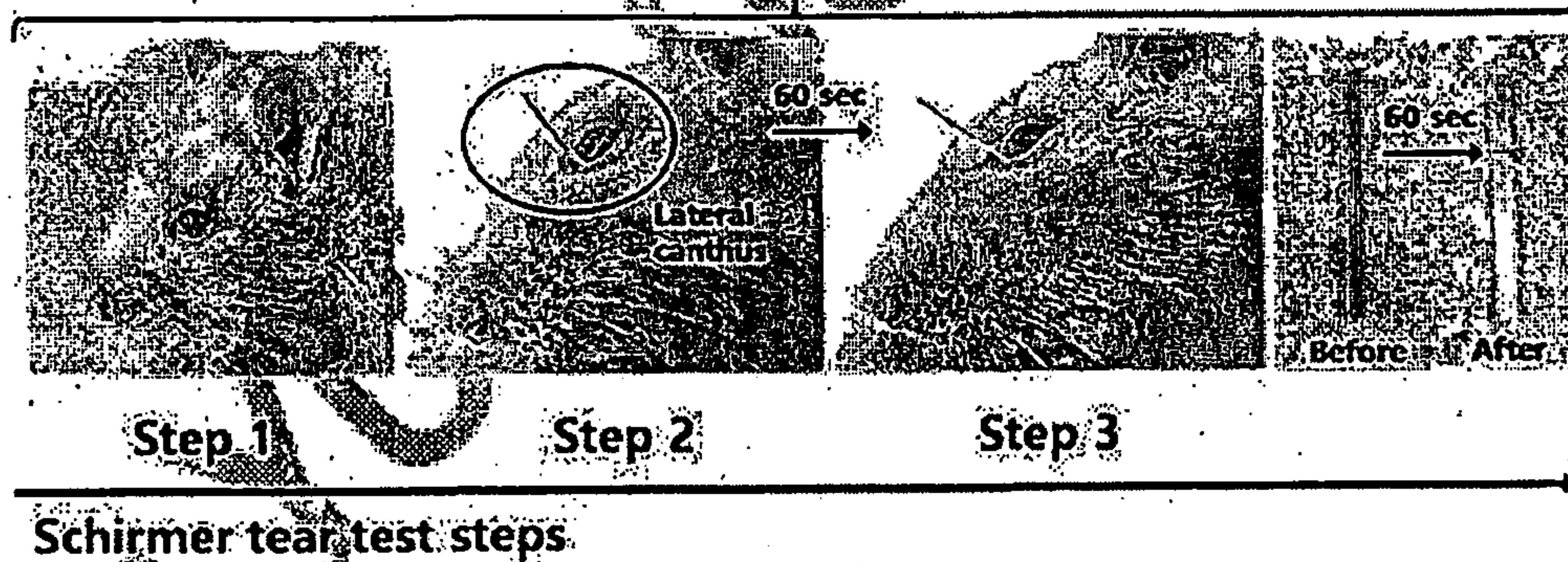
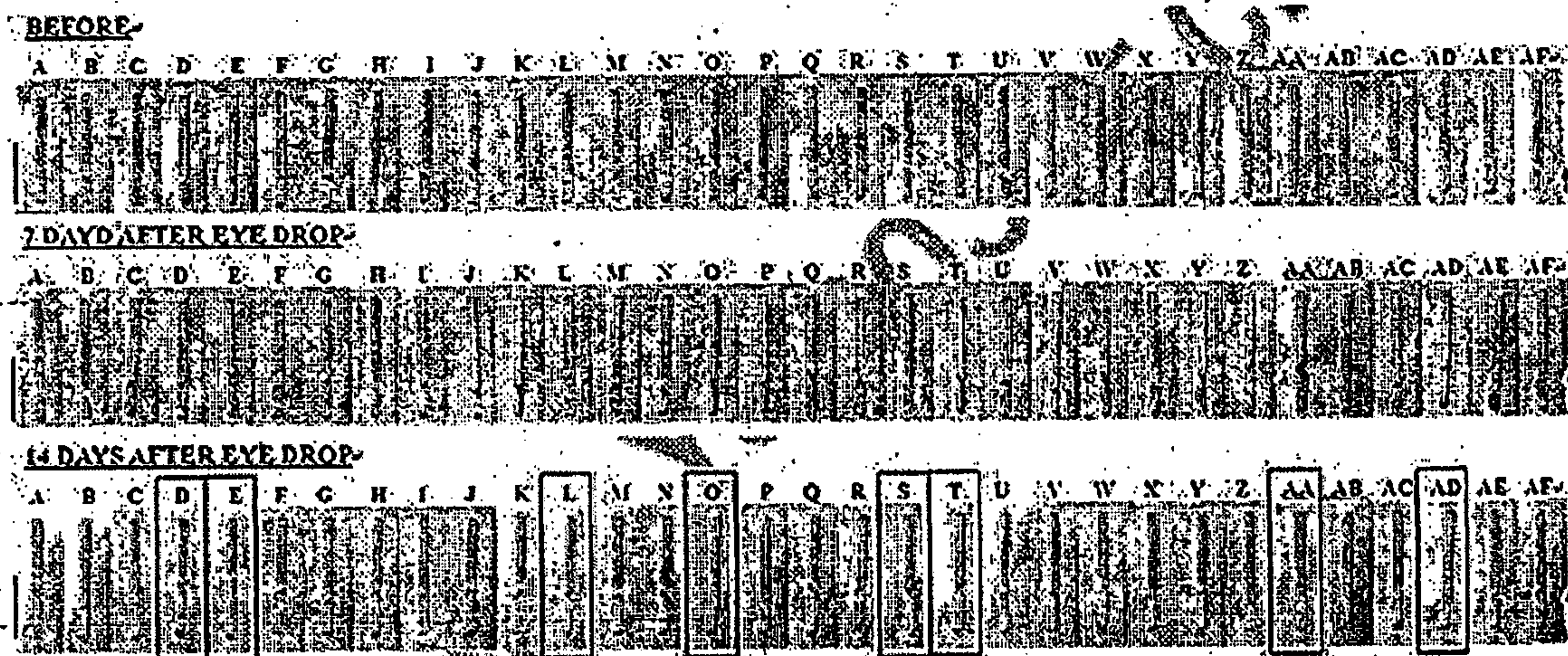


FIG 139



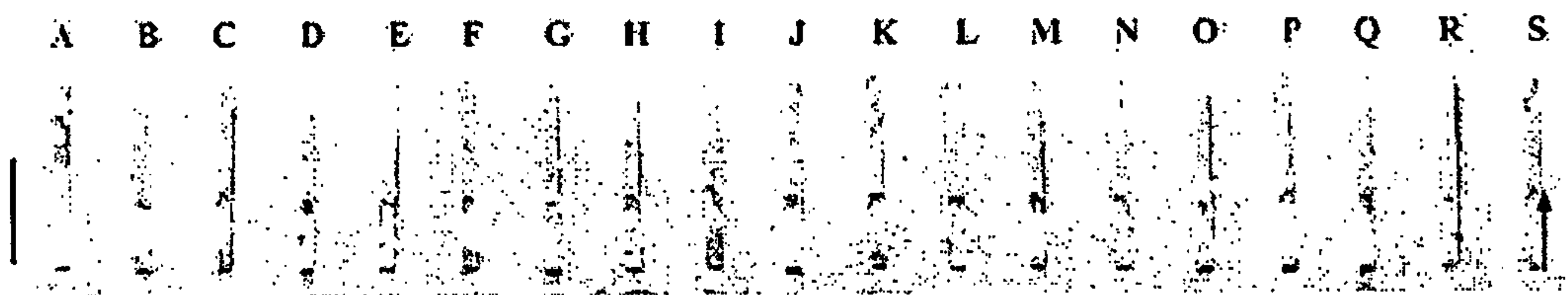
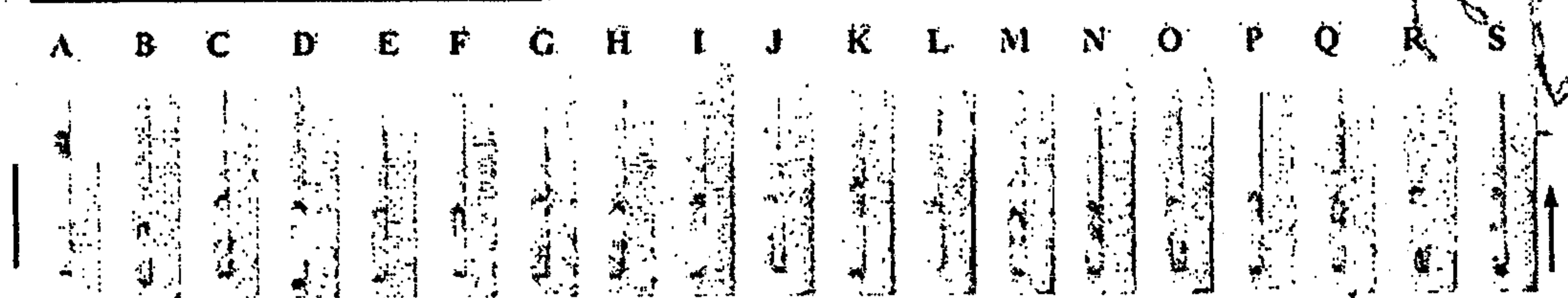
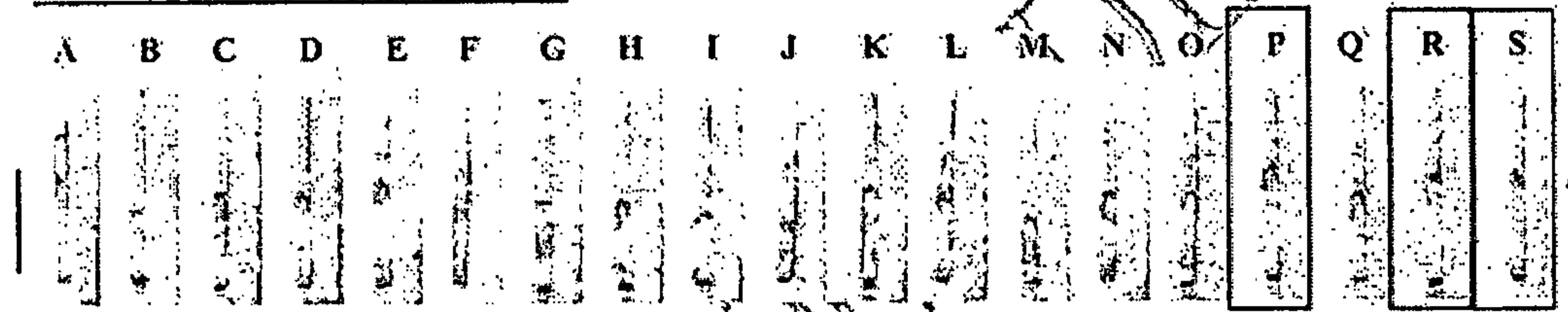
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FIG 140

Items	Tear volumes (mm) after test material topical eye drop		
Groups	-1 day	7 days	14 days
Control			
Sham	8.34±0.73	8.56±0.76	8.63±0.93
ELGE	3.54±0.78 ^a	2.65±0.85 ^a	3.27±1.06 ^a
Reference			
DS	3.53±0.66 ^a	4.10±1.07 ^{ad}	4.80±0.94 ^{ad}
Test materials (0.3% solutions)			
YY-102	3.58±0.93 ^a	4.59±1.43 ^{ac}	5.77±1.99 ^{ac}
YDE-01	3.55±0.93 ^a	4.88±1.62 ^{ac}	5.92±2.19 ^{ac}
YDE-02	3.59±0.75 ^a	3.84±1.16 ^a	5.01±1.67 ^{ad}
YDE-03	3.56±0.74 ^a	4.13±1.76 ^{ad}	4.88±1.57 ^{ad}
YDE-04	3.57±0.55 ^a	3.42±1.06 ^a	5.19±1.84 ^{ad}
YDE-05	3.56±0.86 ^a	3.85±0.93 ^a	5.08±1.91 ^{ad}
YDE-06	3.56±0.65 ^a	3.44±1.69 ^a	5.35±1.68 ^{ad}
YDE-07	3.53±0.68 ^a	3.91±1.28 ^a	5.45±1.26 ^{ad}
YDE-08	3.54±0.82 ^a	4.57±1.25 ^{ac}	6.10±2.36 ^{ac}
YDE-09	3.56±0.78 ^a	3.76±1.21 ^a	4.54±1.11 ^a
YDE-10	3.52±0.61 ^a	3.42±1.31 ^a	4.35±1.36 ^a
YDE-11	3.56±0.88 ^a	4.22±1.45 ^{ac}	6.16±2.16 ^{ac}
YDE-12	3.55±0.71 ^a	3.68±0.99 ^a	5.67±1.86 ^{ac}
YDE-13	3.55±0.49 ^a	5.27±1.50 ^{ac}	5.49±1.92 ^{ac}
YDE-14	3.55±0.60 ^a	3.81±1.21 ^a	5.62±1.85 ^{ac}
YDE-15	3.54±0.73 ^a	4.03±2.19 ^{ad}	6.65±2.13 ^{bc}
YDE-16	3.56±0.93 ^a	4.59±1.13 ^{ac}	5.98±2.27 ^{ac}
YDE-17	3.54±0.91 ^a	4.00±1.22 ^{ad}	4.89±1.50 ^a
YDE-18	3.58±0.68 ^a	3.75±1.54 ^a	4.99±1.60 ^{ad}
YDE-19	3.58±0.63 ^a	4.84±1.39 ^{ac}	4.52±1.07 ^a
YDE-20	3.56±0.86 ^a	3.41±1.47 ^a	4.20±1.35 ^a
YDE-21	3.55±0.72 ^a	4.08±1.33 ^{ad}	4.90±1.13 ^a
YDE-22	3.50±0.75 ^a	3.19±0.67 ^a	4.10±0.95 ^a
YDE-23	3.51±0.72 ^a	5.32±2.30 ^{ac}	5.78±2.23 ^{ac}
YDE-24	3.53±0.63 ^a	3.85±1.30 ^a	5.72±1.36 ^{ac}
YDE-25	3.56±0.75 ^a	3.21±0.72 ^a	4.72±2.19 ^a
YDE-26	3.57±0.57 ^a	4.32±1.47 ^{ad}	6.01±1.83 ^{ac}
YDE-27	3.57±0.64 ^a	2.82±0.86 ^a	3.95±1.52 ^a
YDE-28	3.56±0.91 ^a	4.04±0.99 ^{ad}	4.73±1.18 ^a

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FIG 141

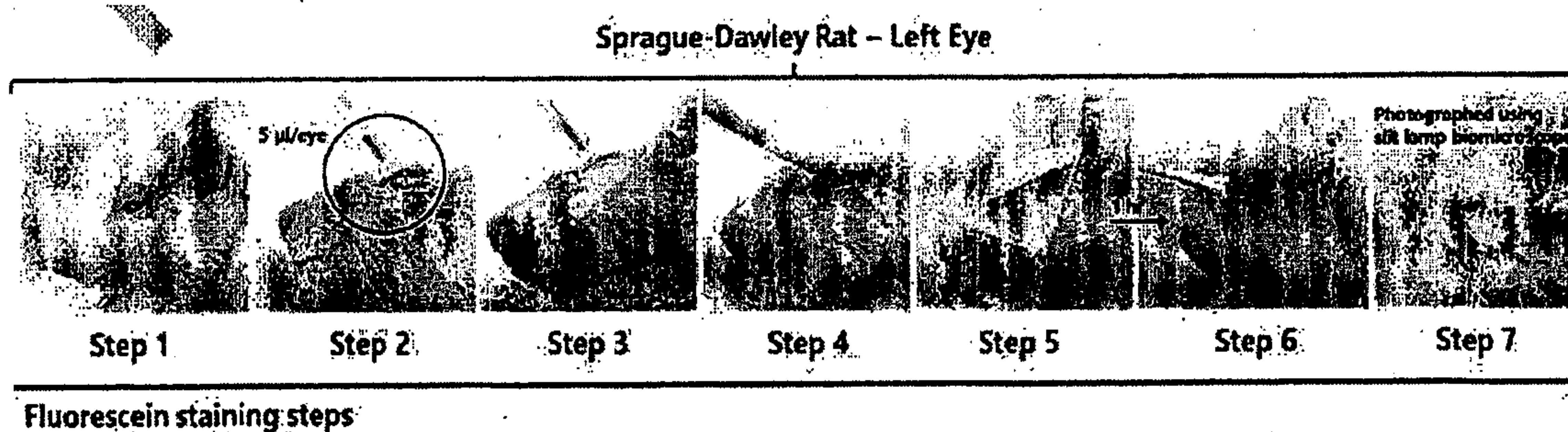
BEFORE**7 DAYD AFTER EYE DROP****14 DAYS AFTER EYE DROP**

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FIG 142

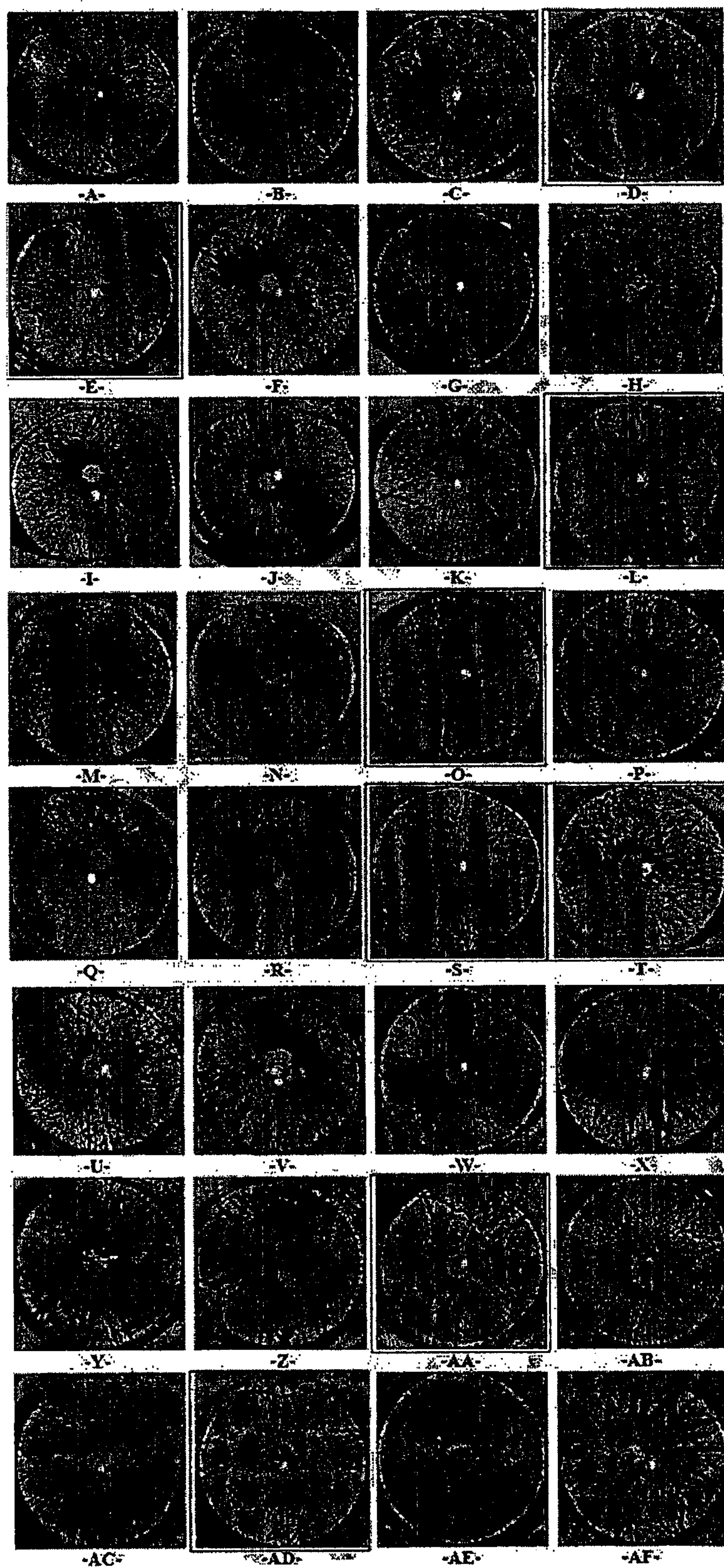
	Items	Tear volumes (mm) after test material topical eye drop		
Groups		-1 day	7 days	14 days
Control				
	Sham	10.90±1.69	10.38±1.08	10.28±0.69
	ELGE	4.81±1.09 ^a	4.37±0.83 ^b	4.70±0.65 ^b
Reference				
	DS	4.74±1.30 ^a	5.72±1.28 ^{be}	6.56±1.15 ^{bd}
	YY-101	4.86±1.08 ^a	5.36±0.68 ^{be}	6.25±0.68 ^{bd}
	YY-102	4.94±0.71 ^a	5.77±1.01 ^{be}	6.60±0.64 ^{bd}
Test materials (0.3% solutions)				
	YDE-029	4.72±1.05 ^a	5.33±1.43 ^b	6.03±1.71 ^b
	YDE-030	4.93±1.15 ^a	5.69±1.79 ^b	6.65±2.17 ^b
	YDE-031	4.70±0.69 ^a	5.63±1.97 ^b	5.91±0.85 ^{be}
	YDE-032	4.94±1.04 ^a	5.58±0.80 ^{be}	5.03±0.93 ^b
	YDE-033	4.77±1.32 ^a	4.99±1.20 ^b	4.54±1.16 ^b
	YDE-034	4.88±1.07 ^a	6.16±1.01 ^{bd}	6.43±1.86 ^b
	YDE-035	4.92±1.18 ^a	4.96±0.96 ^b	6.25±0.79 ^{bd}
	YDE-036	4.83±1.07 ^a	4.95±1.05 ^b	5.13±1.03 ^b
	YDE-037	4.68±0.83 ^a	4.98±0.66 ^b	5.80±0.96 ^{be}
	YDE-039	4.81±1.27 ^a	6.04±1.01 ^{bd}	6.44±1.96 ^{be}
	YDE-040	4.77±0.91 ^a	5.77±1.05 ^{be}	8.63±1.53 ^{cd}
	YDE-041	4.87±1.19 ^a	5.01±1.26 ^b	6.25±2.15 ^b
	YDE-042	4.83±0.84 ^a	6.30±1.08 ^{bd}	7.97±1.48 ^{bd}
	YDE-043	4.86±0.81 ^a	5.90±1.06 ^{bd}	8.16±1.42 ^{bd}

FIG 143



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FIG 144



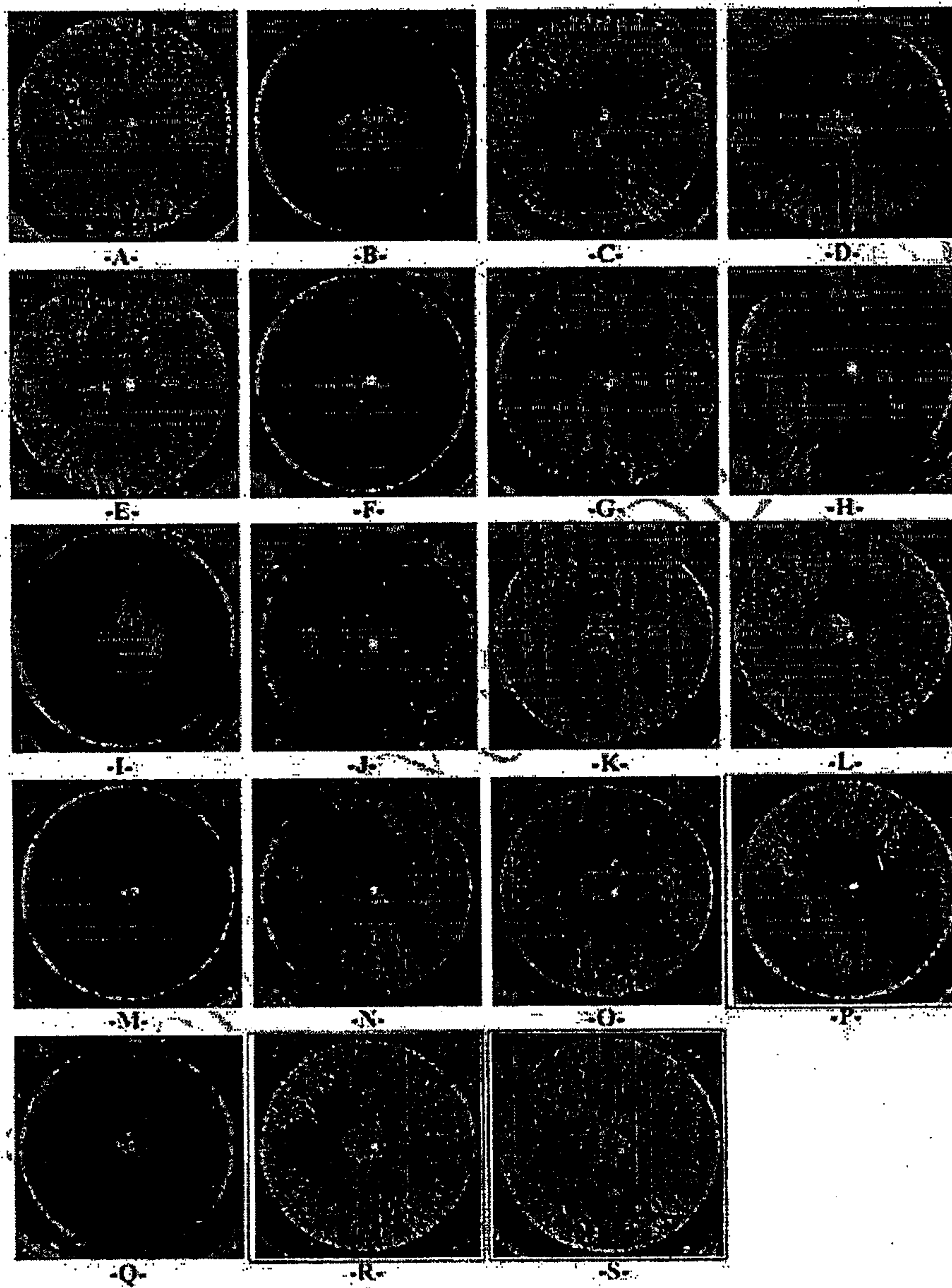
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FIG 145

Groups	Items Fluorescent stained cornea areas (%)
Control	
Sham	2.62±1.71
ELGE	57.34±12.83 ^a
Reference	
DS	35.40±13.32 ^a
Test materials (0.3% solutions)	
YY-102	27.48±14.37 ^c
YDE-01	25.49±11.62 ^c
YDE-02	38.26±11.25 ^c
YDE-03	40.45±6.46 ^c
YDE-04	35.05±11.74 ^c
YDE-05	37.98±11.53 ^c
YDE-06	33.23±13.26 ^c
YDE-07	32.79±10.77 ^c
YDE-08	20.32±11.87 ^c
YDE-09	41.50±7.86 ^c
YDE-10	49.29±12.06 ^a
YDE-11	18.11±11.61 ^{ac}
YDE-12	31.01±11.38 ^c
YDE-13	32.24±7.84 ^c
YDE-14	31.15±10.87 ^c
YDE-15	15.95±6.48 ^{bc}
YDE-16	24.57±10.34 ^c
YDE-17	39.76±7.42 ^c
YDE-18	38.19±10.96 ^c
YDE-19	40.39±12.57 ^c
YDE-20	47.84±13.47 ^a
YDE-21	37.00±10.49 ^c
YDE-22	47.82±10.01 ^a
YDE-23	26.51±8.18 ^c
YDE-24	30.63±10.41 ^c
YDE-25	47.10±11.45 ^a
YDE-26	22.63±11.23 ^c
YDE-27	50.24±11.94 ^a
YDE-28	41.17±10.25 ^c

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FIG 146



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FIG 147

Groups	Items Fluorescent stained cornea areas (%)
Control	
Sham	1.53±0.65
ELGE	66.71±10.02 ^b
Reference	
DS	30.03±10.97 ^{bd}
YY-101	33.80±11.11 ^{bd}
YY-102	27.89±7.10 ^{bd}
Test materials (0.3% solutions)	
YDE-029	63.45±11.57 ^b
YDE-030	30.60±13.61 ^{bd}
YDE-031	33.35±11.01 ^{bd}
YDE-032	58.90±19.81 ^b
YDE-033	60.55±21.22 ^b
YDE-034	32.17±12.94 ^{bd}
YDE-035	27.62±6.51 ^{bd}
YDE-036	57.87±22.91 ^b
YDE-037	36.30±9.75 ^{bd}
YDE-039	29.94±11.40 ^{bd}
YDE-040	18.33±9.41 ^{bd}
YDE-041	46.38±26.65 ^b
YDE-042	20.72±11.37 ^{bd}
YDE-043	19.04±7.36 ^{bd}

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FIG 148

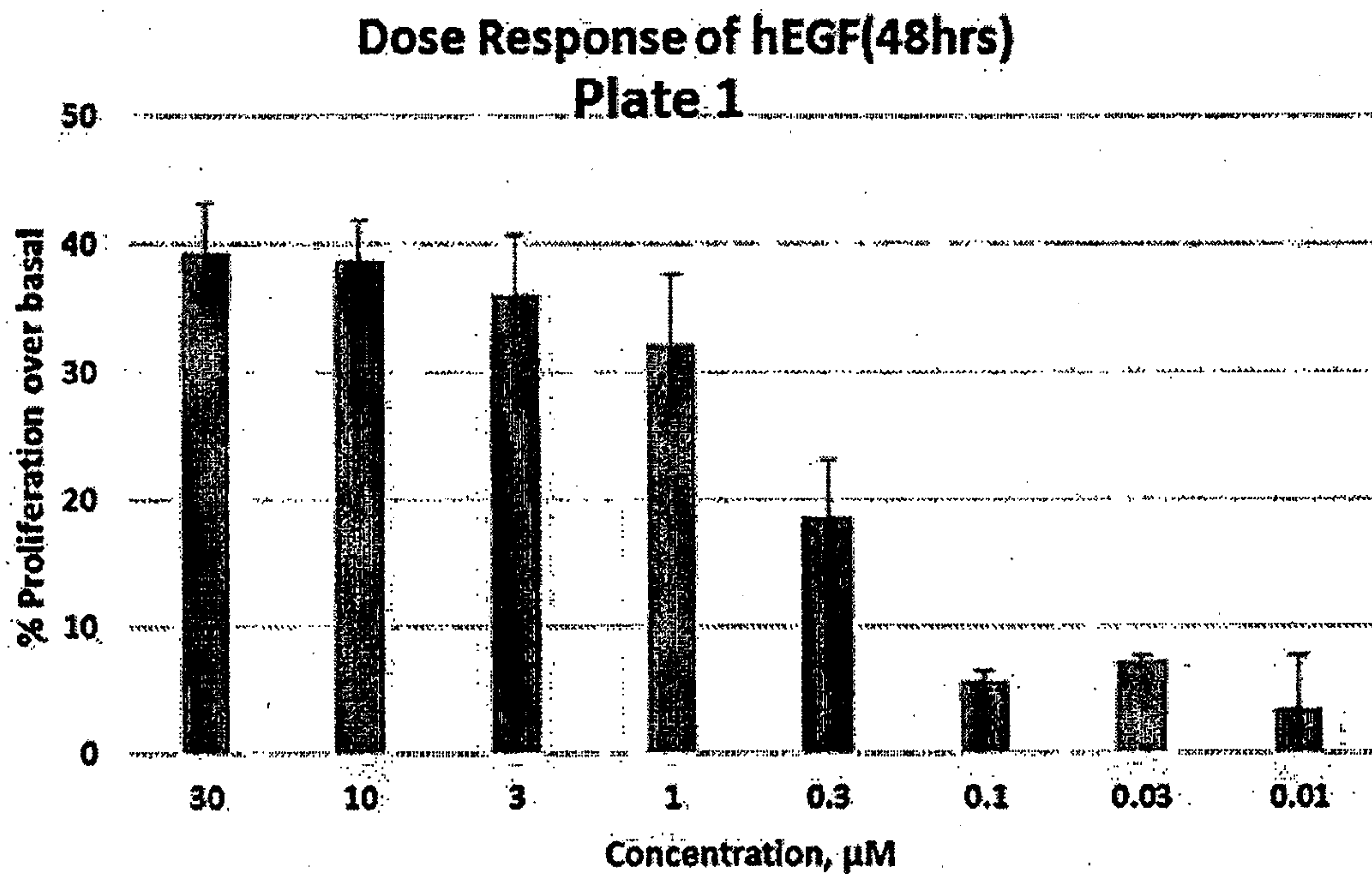
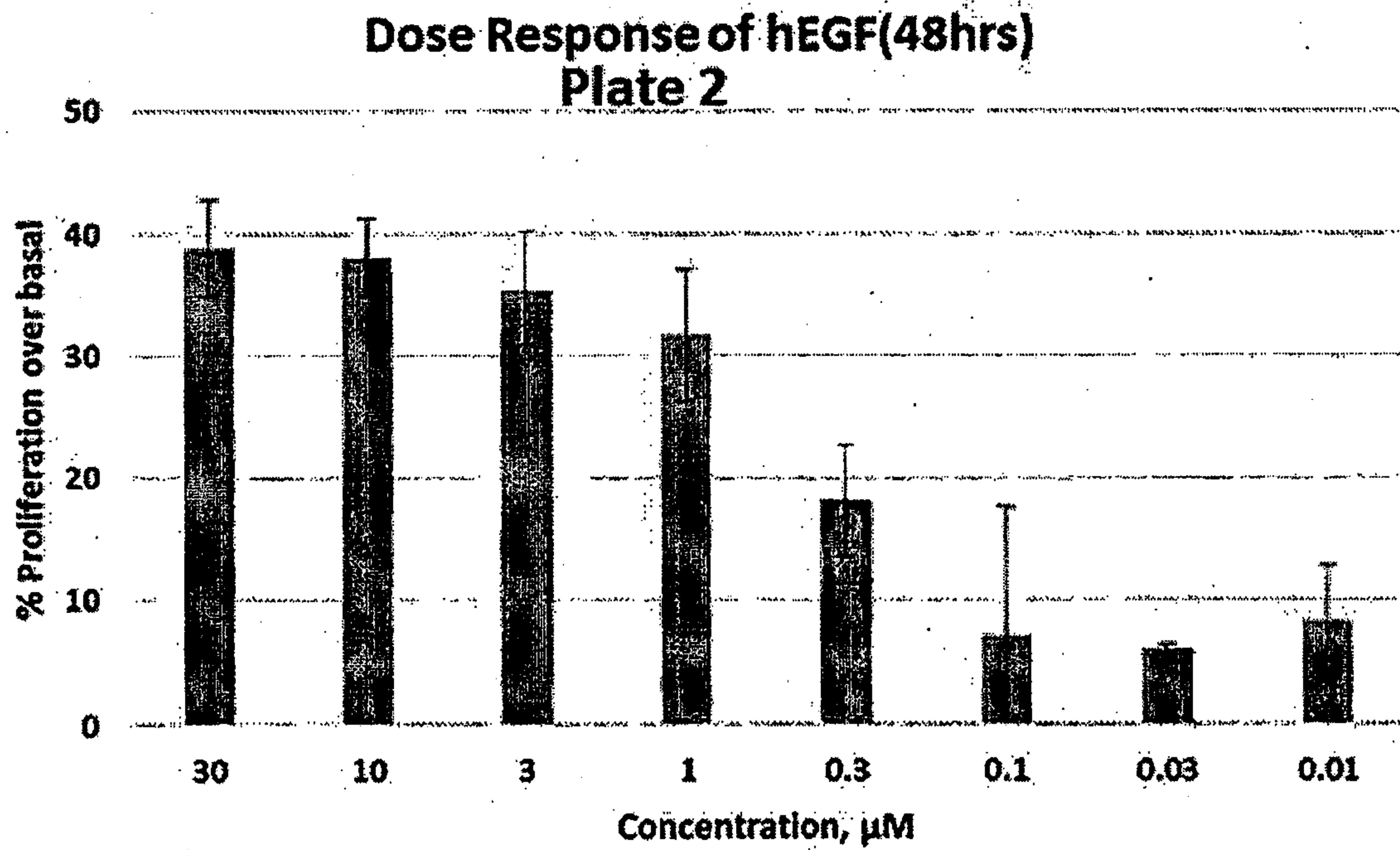


FIG 149



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FIG 150

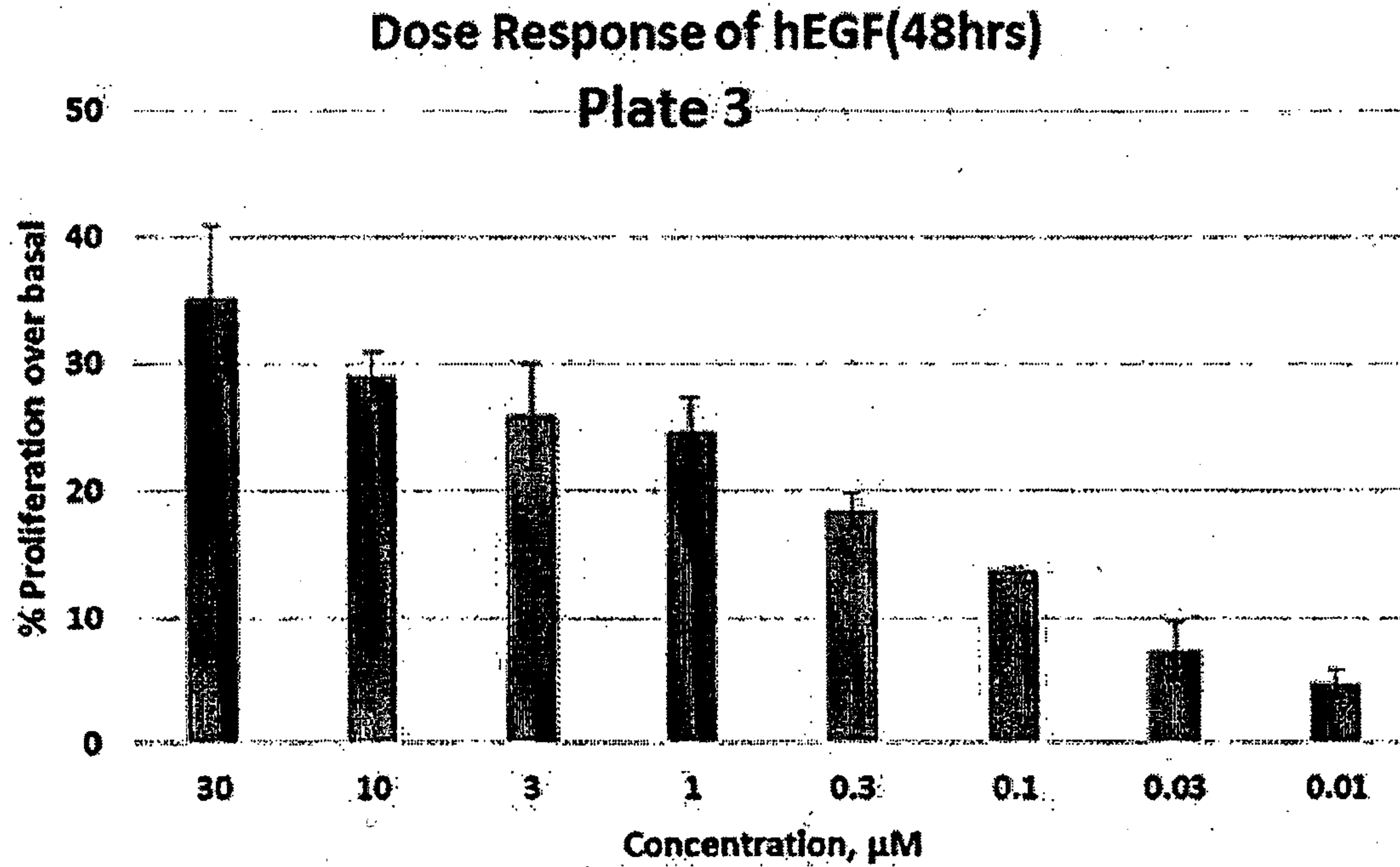
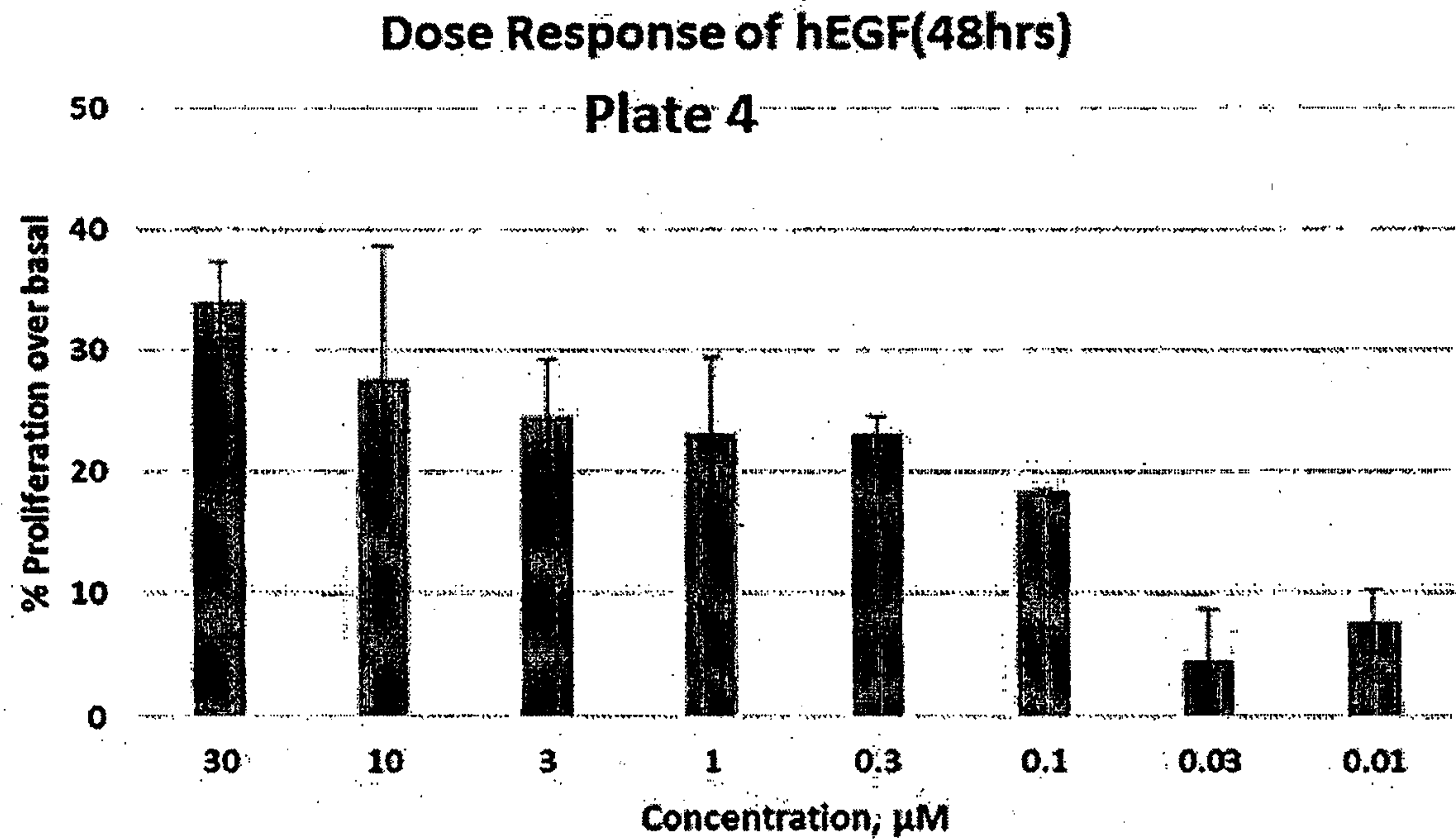


FIG 151



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FIG 152

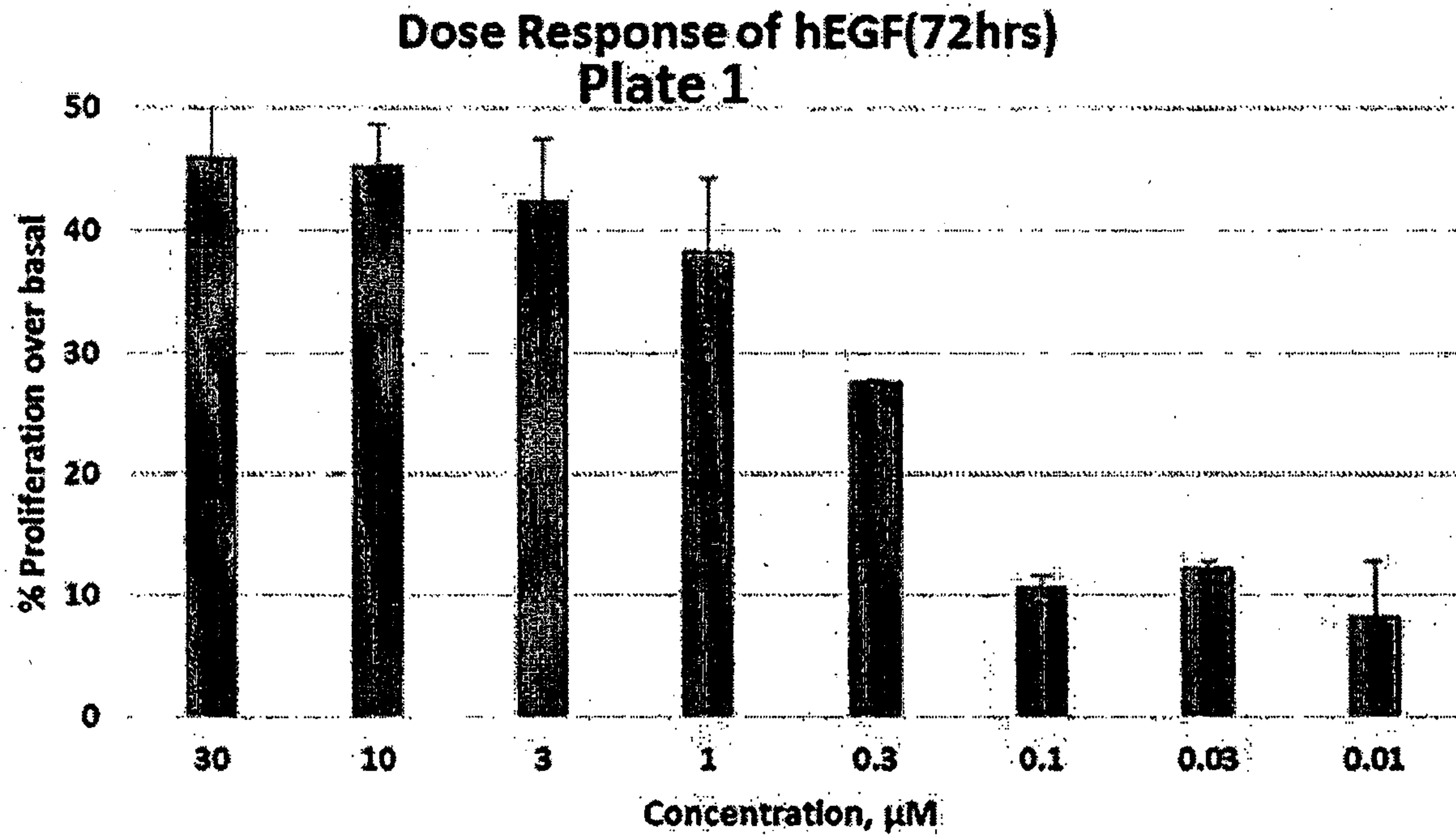
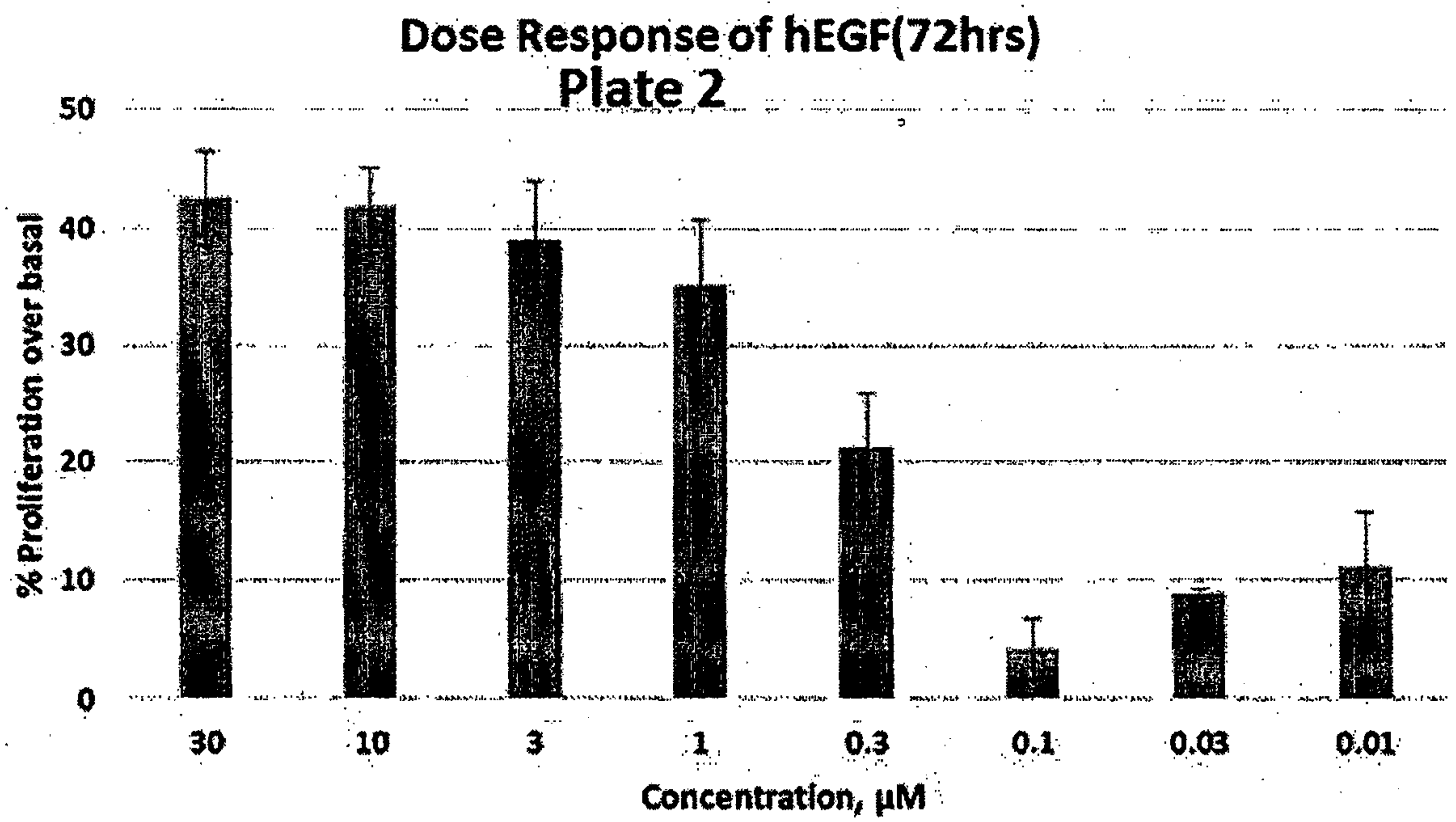


FIG 153



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FIG 154

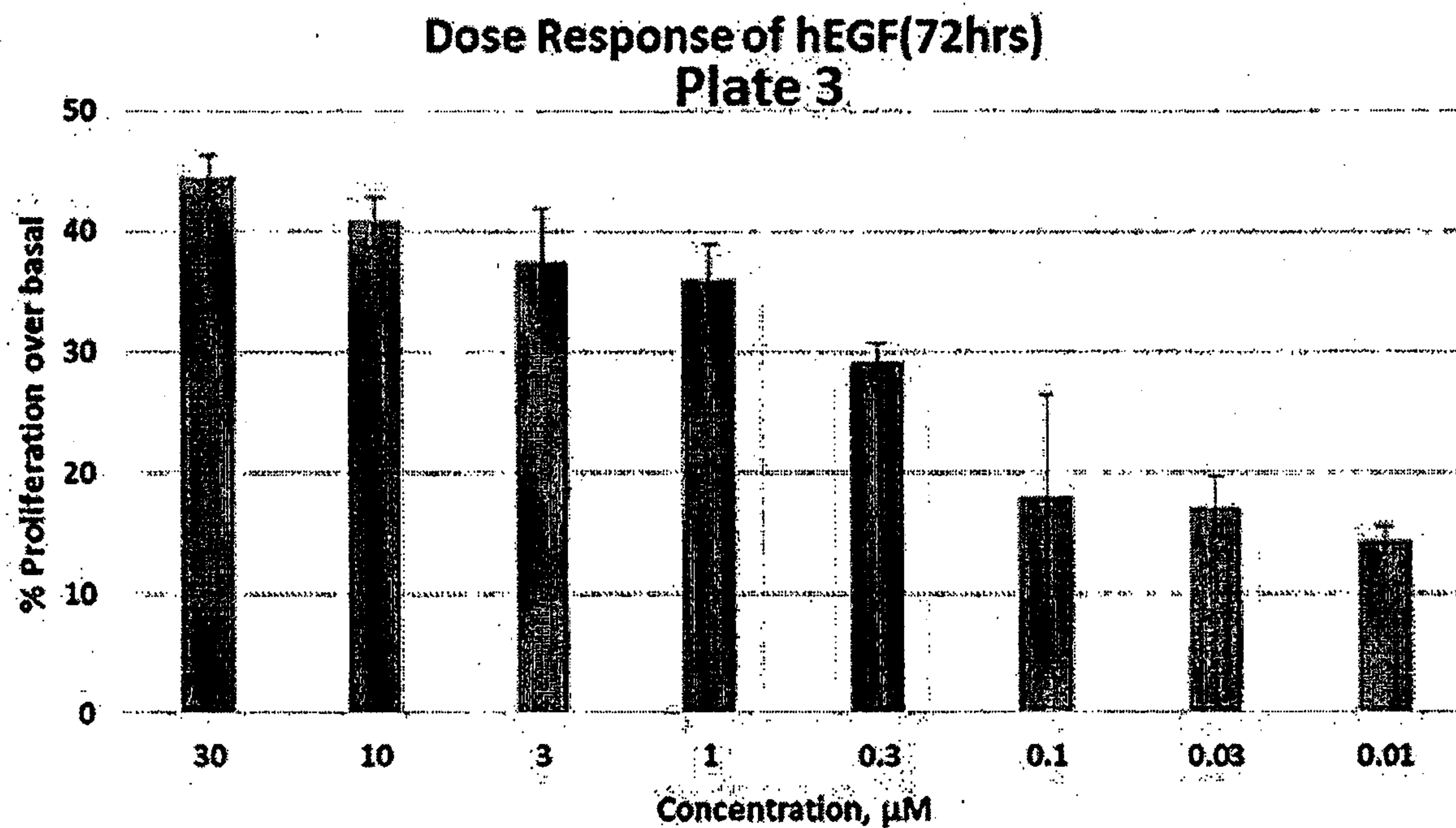
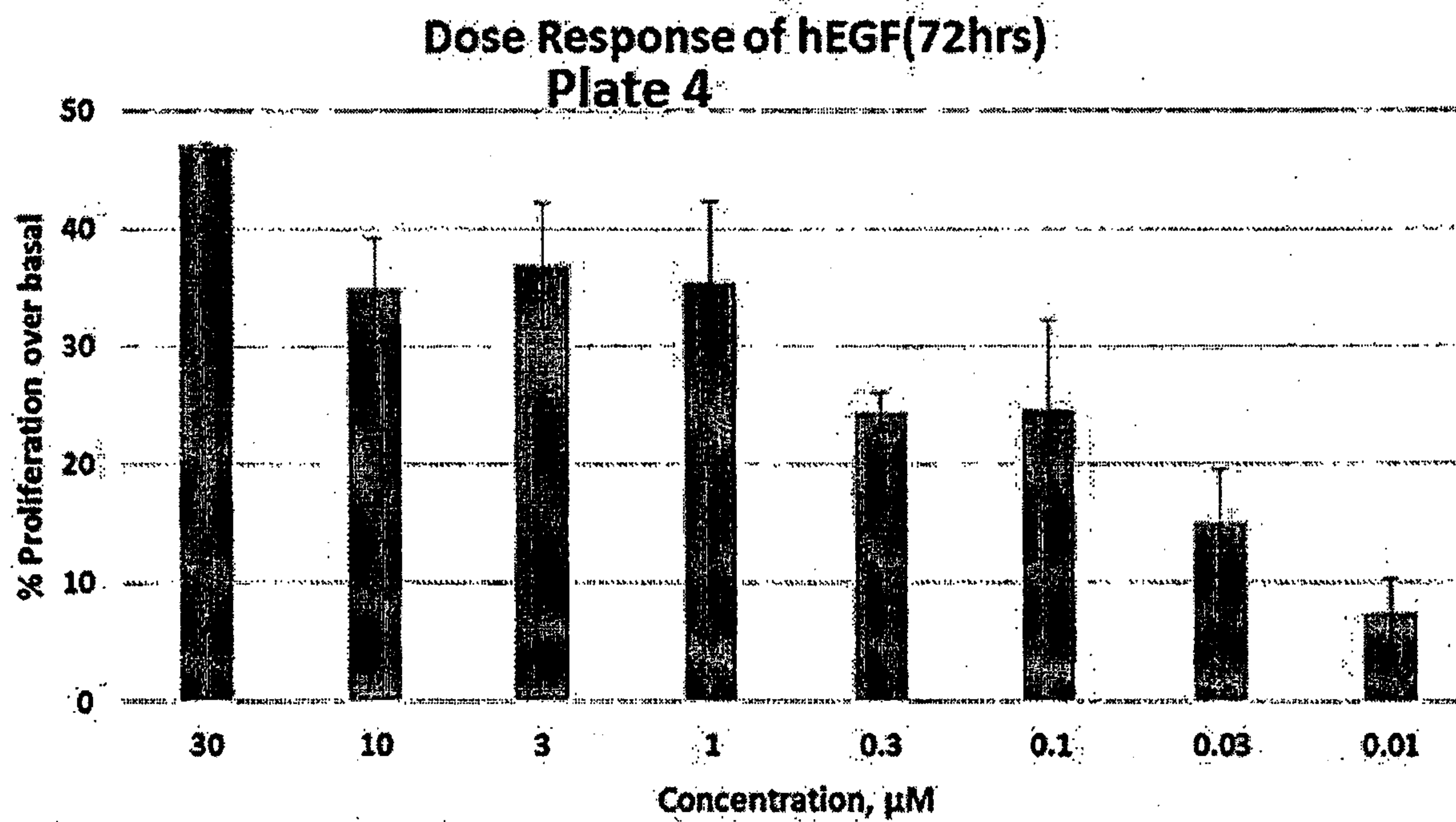
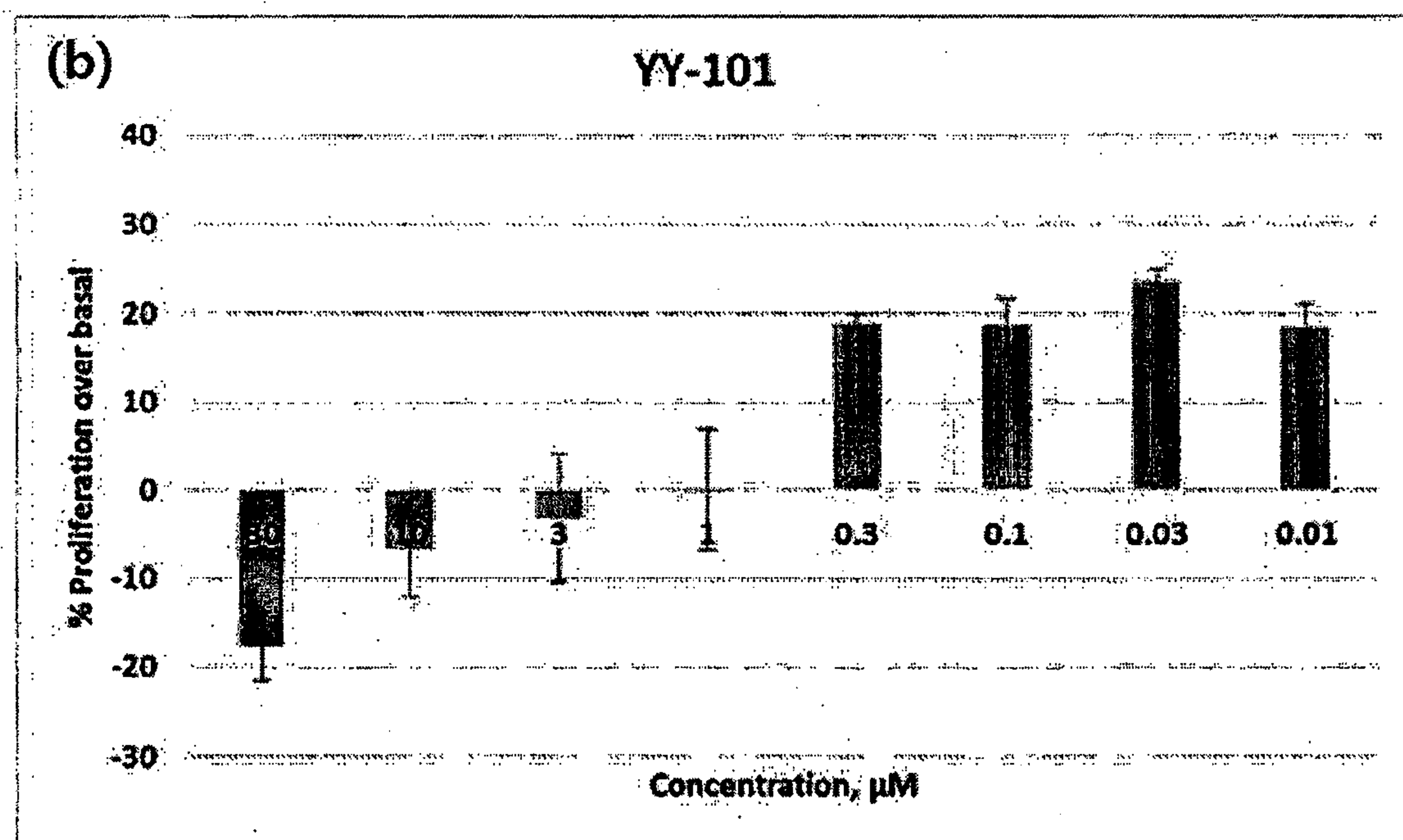
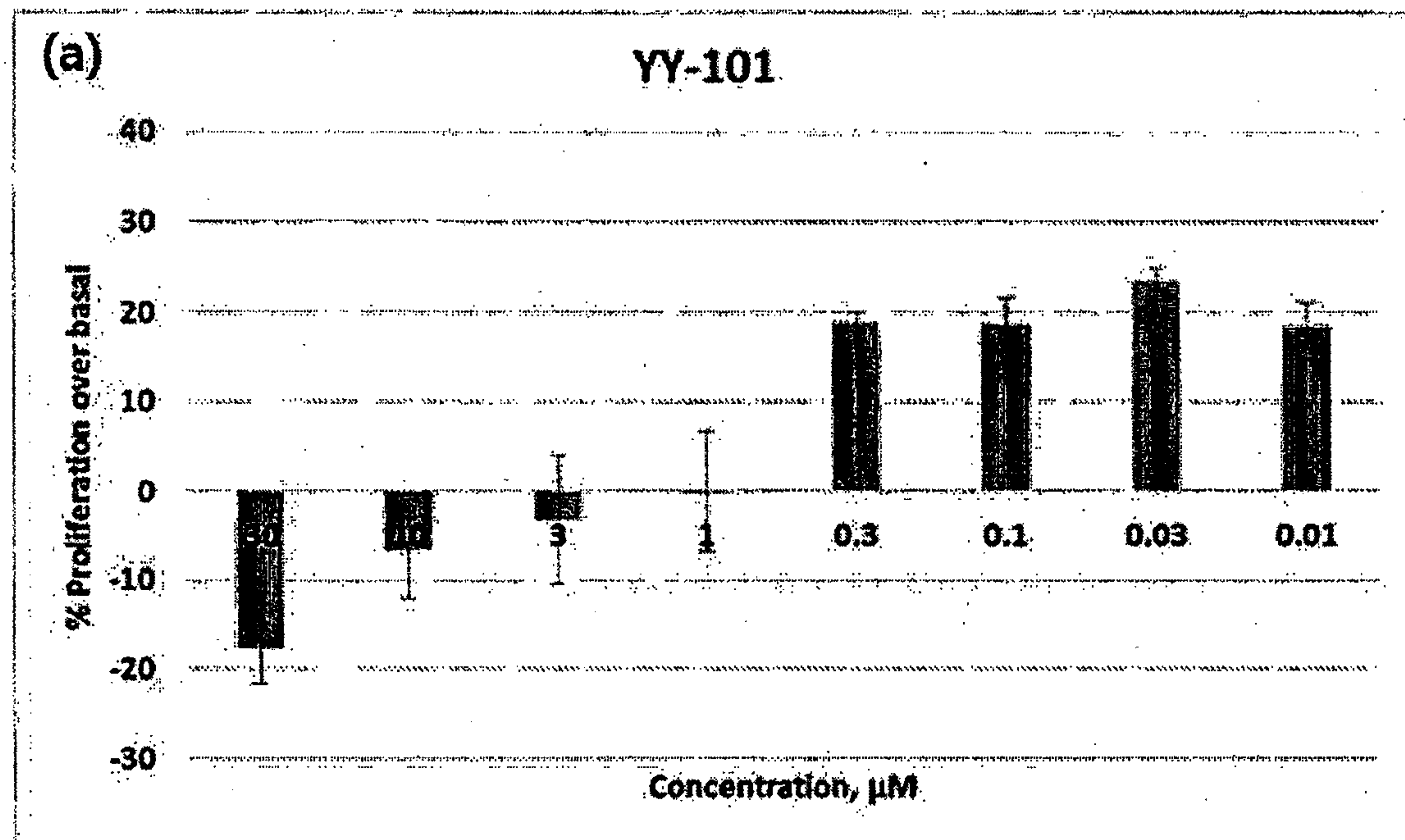


FIG 155



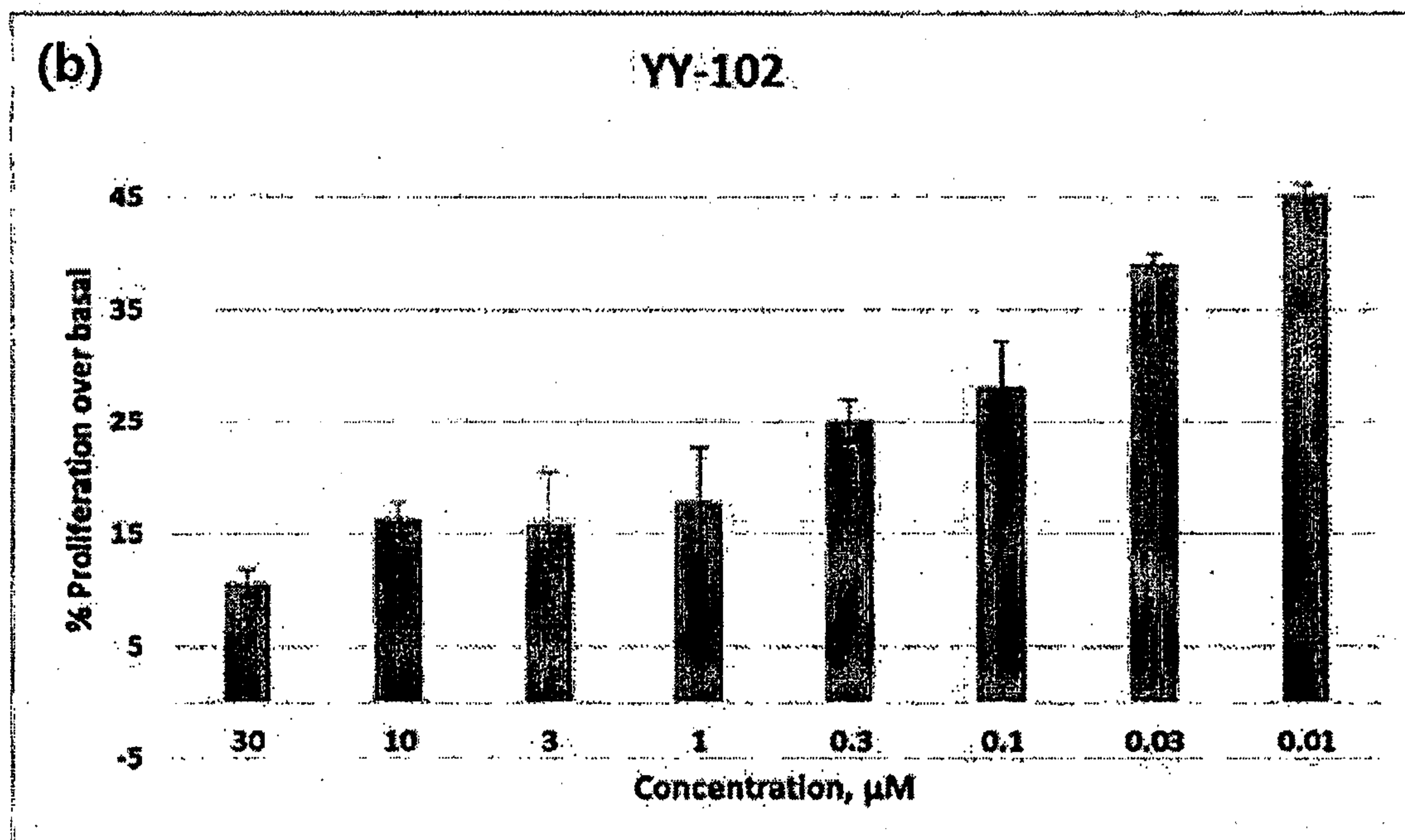
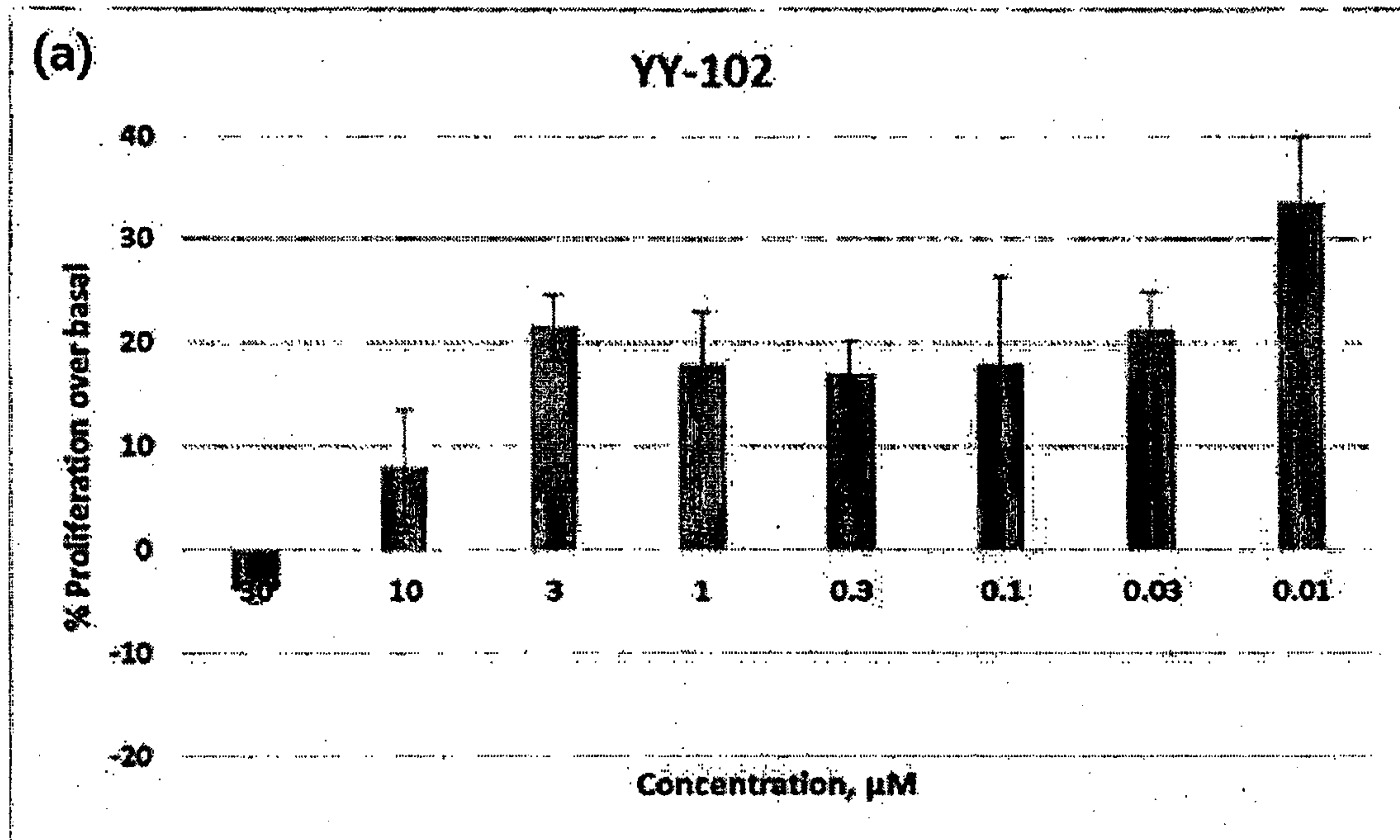
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FIG 156



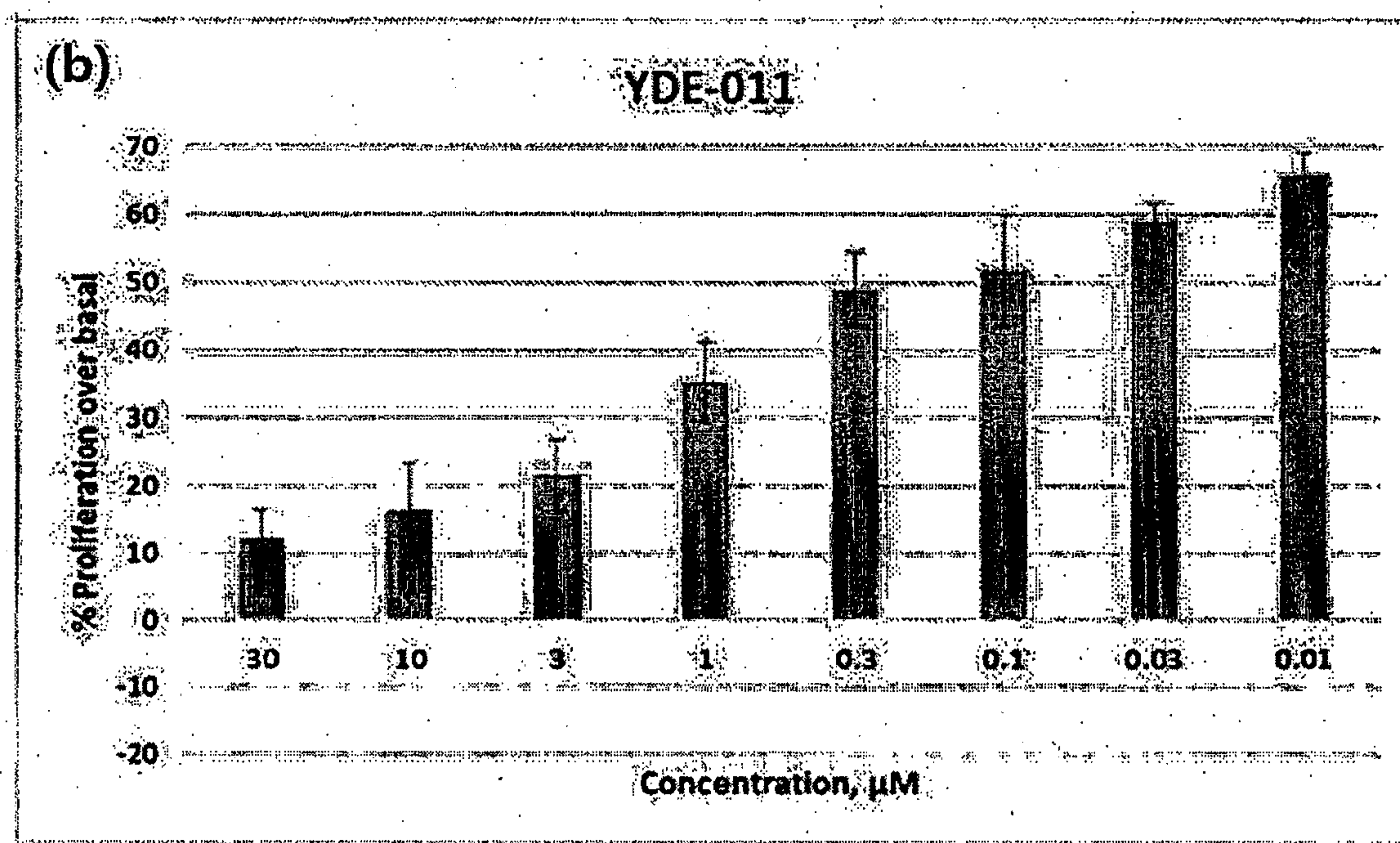
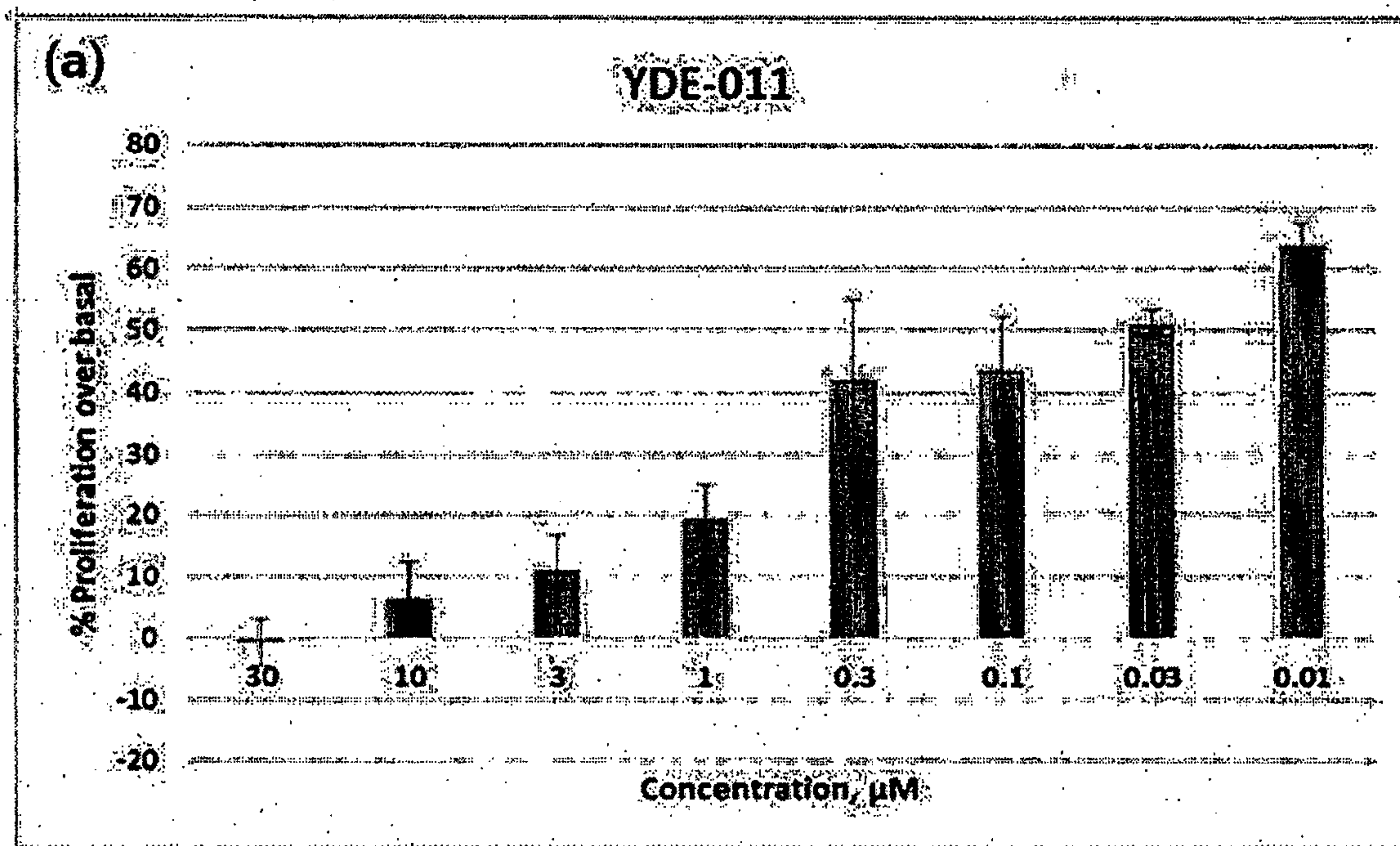
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FIG 157



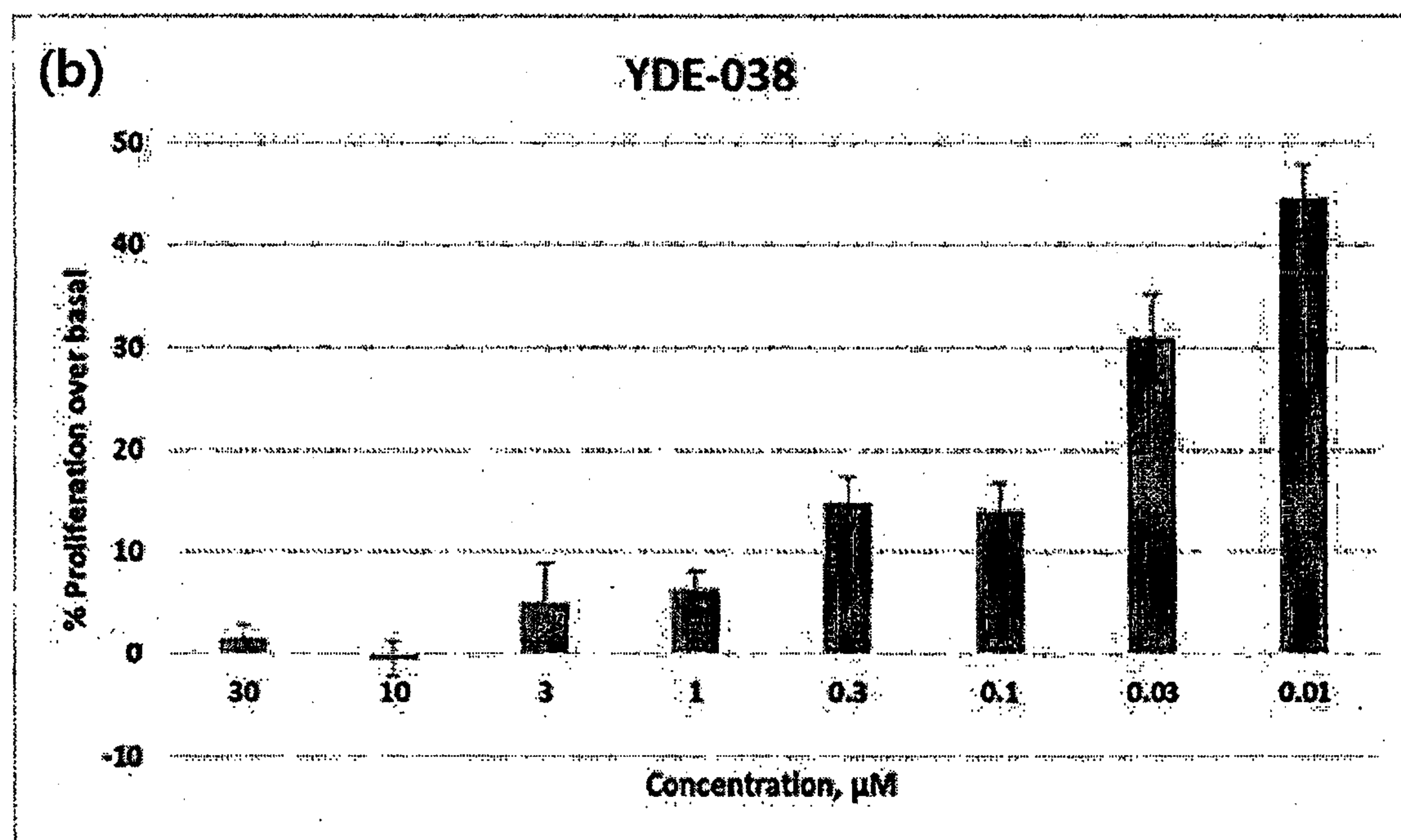
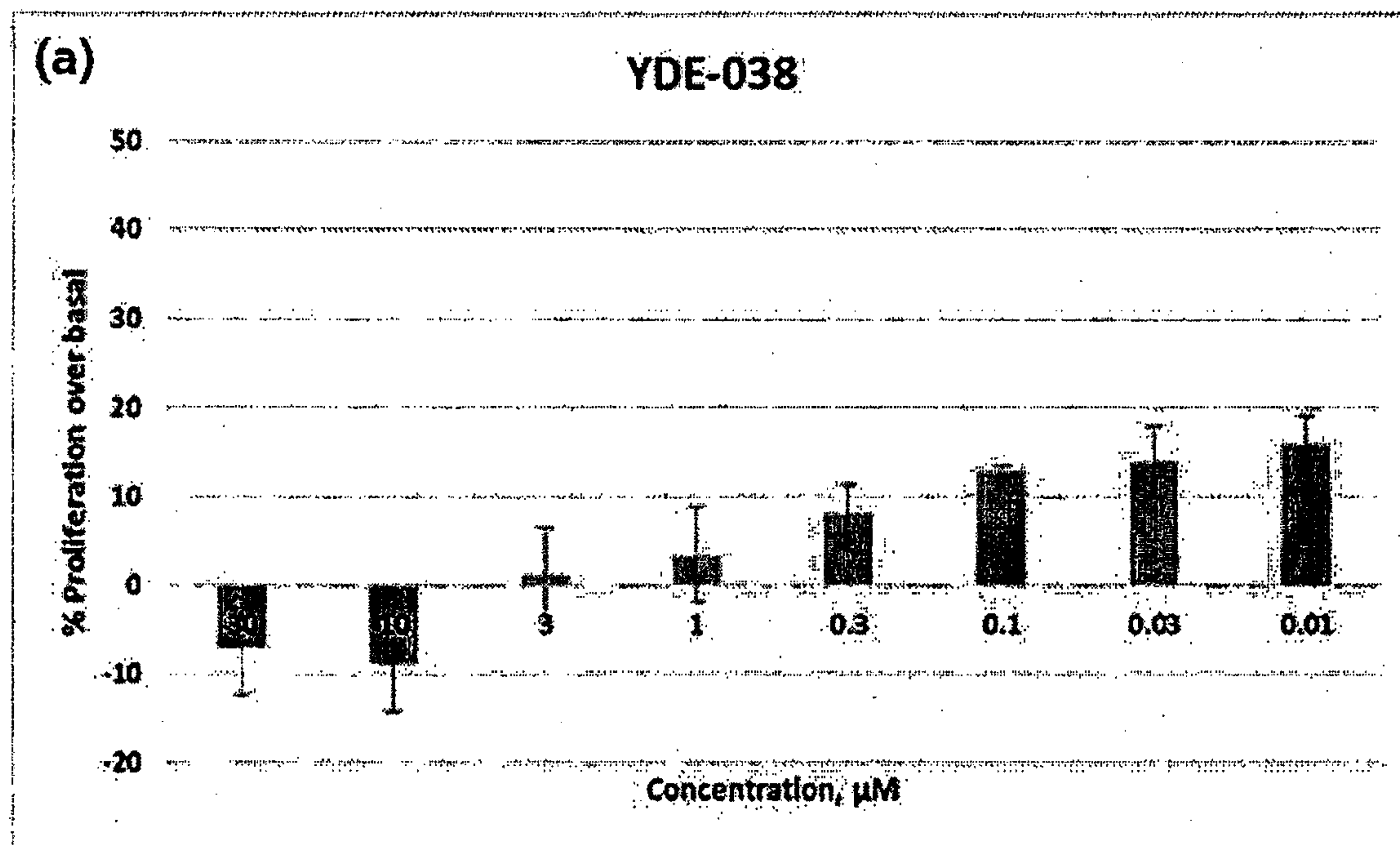
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FIG 158



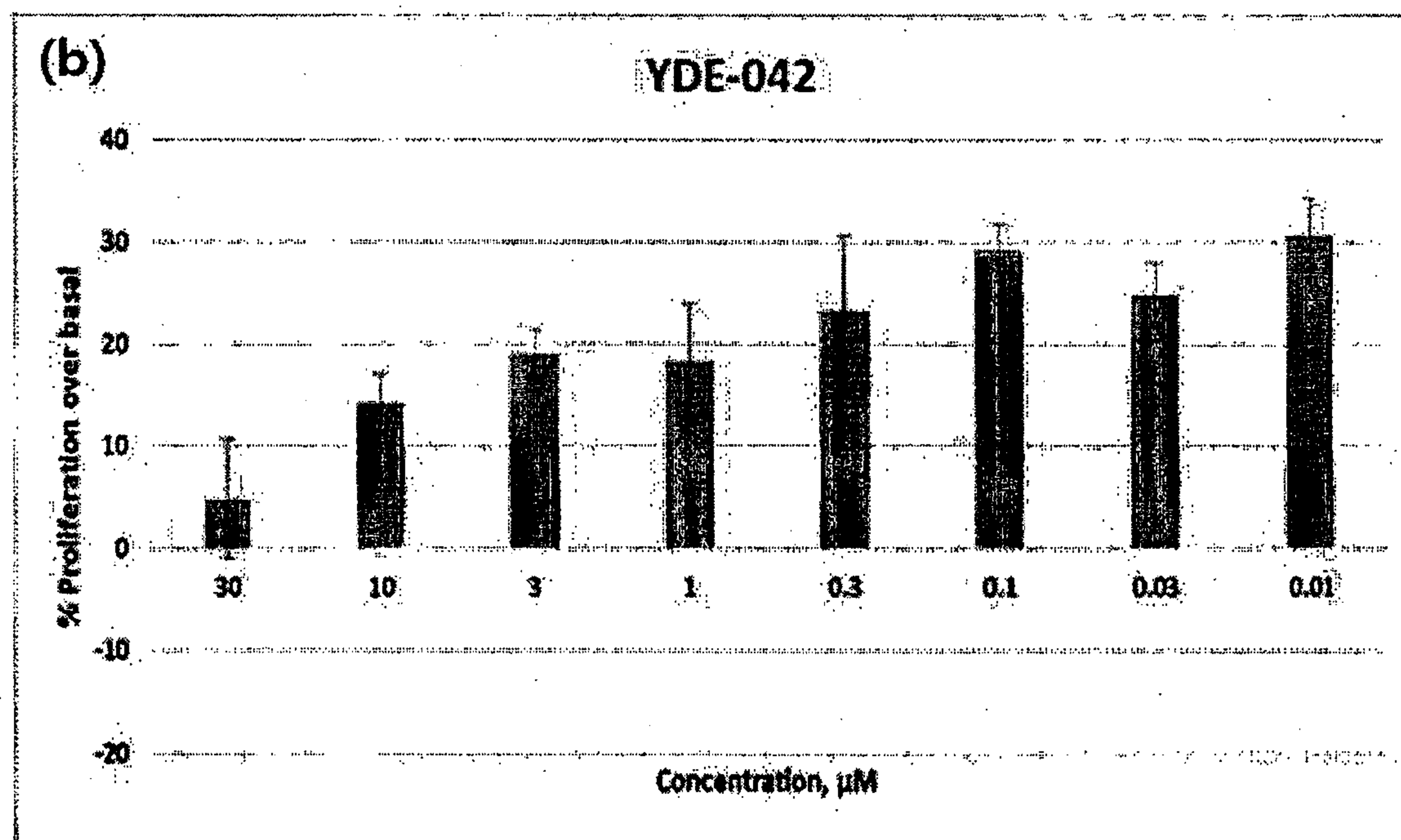
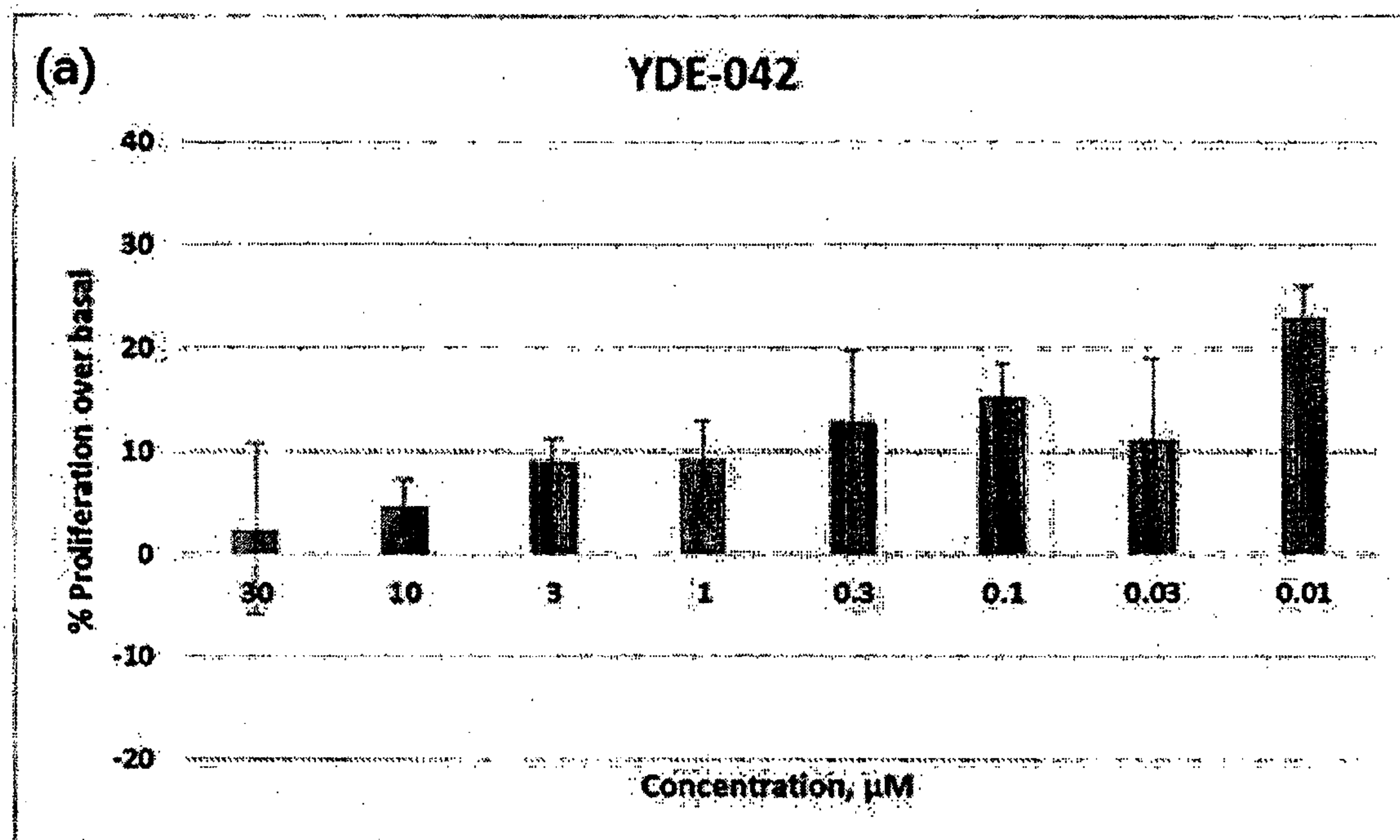
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FIG 159



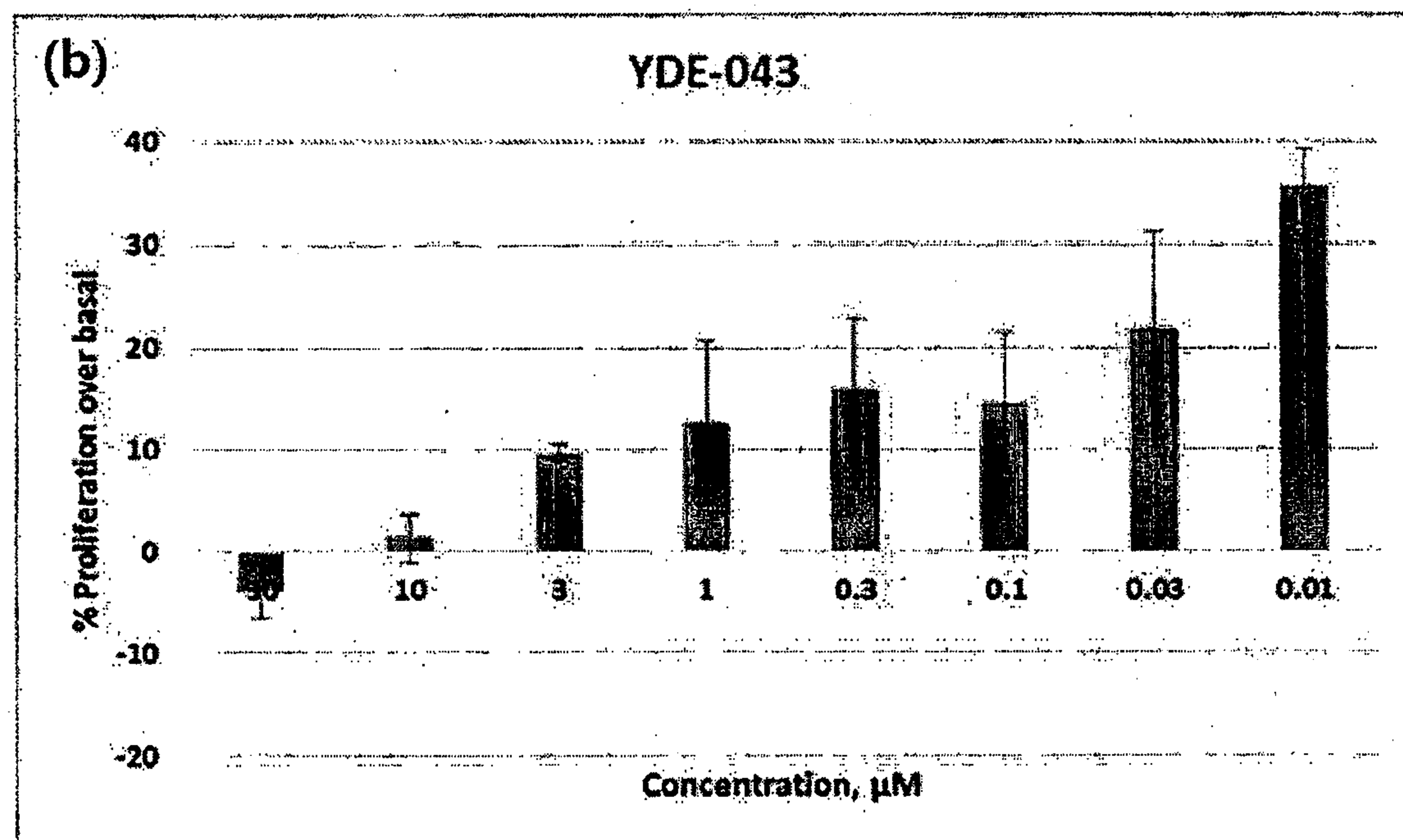
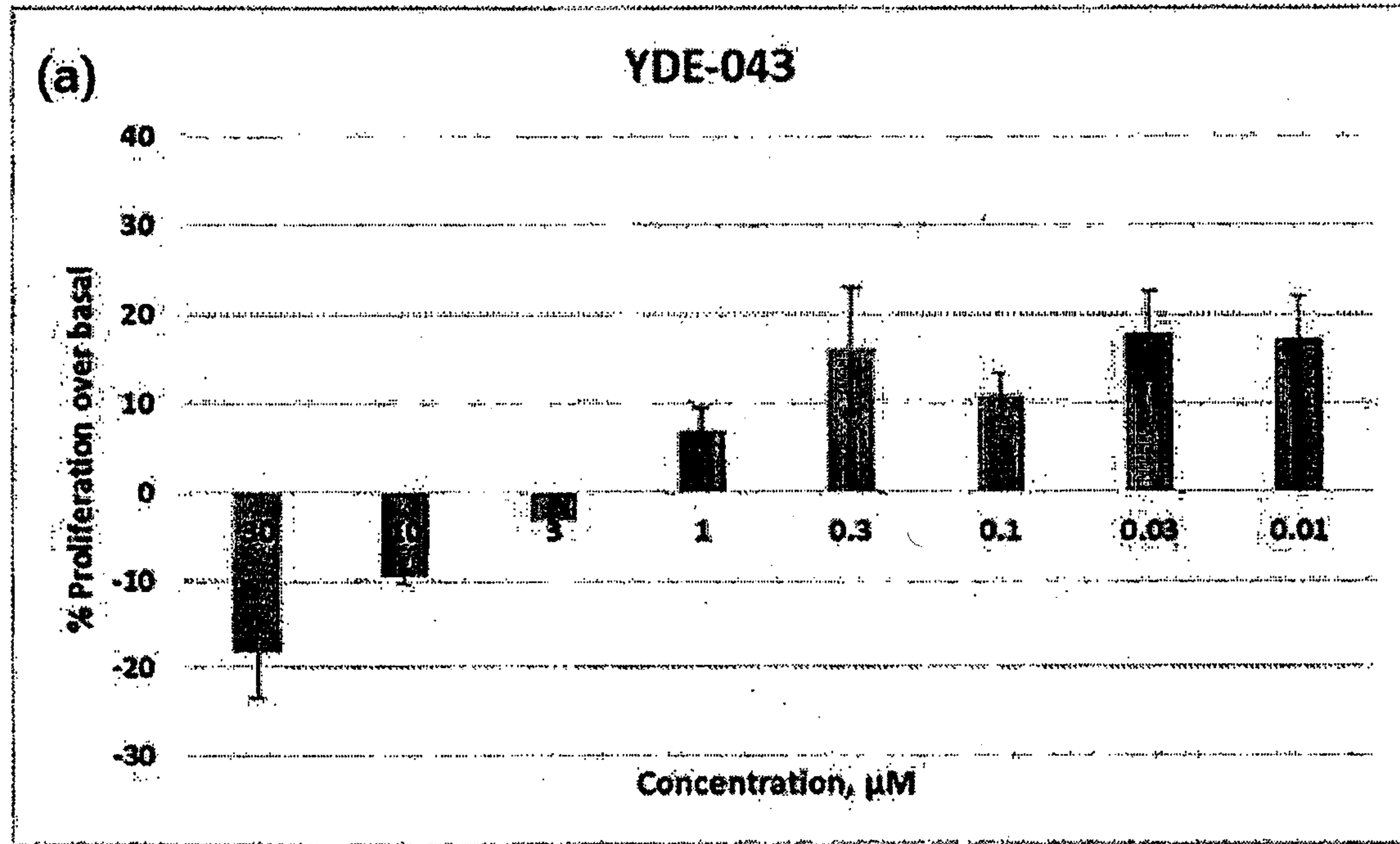
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FIG 160



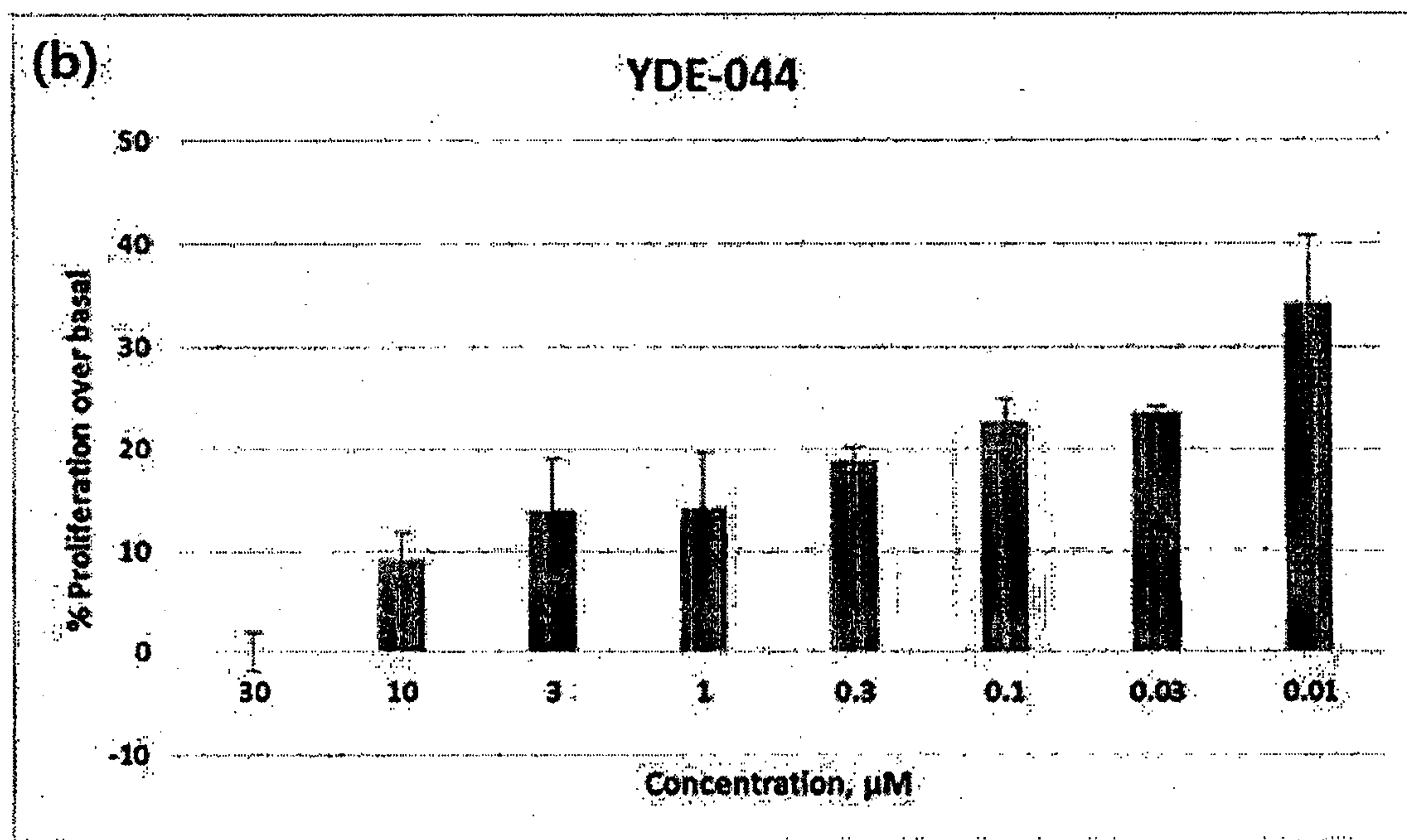
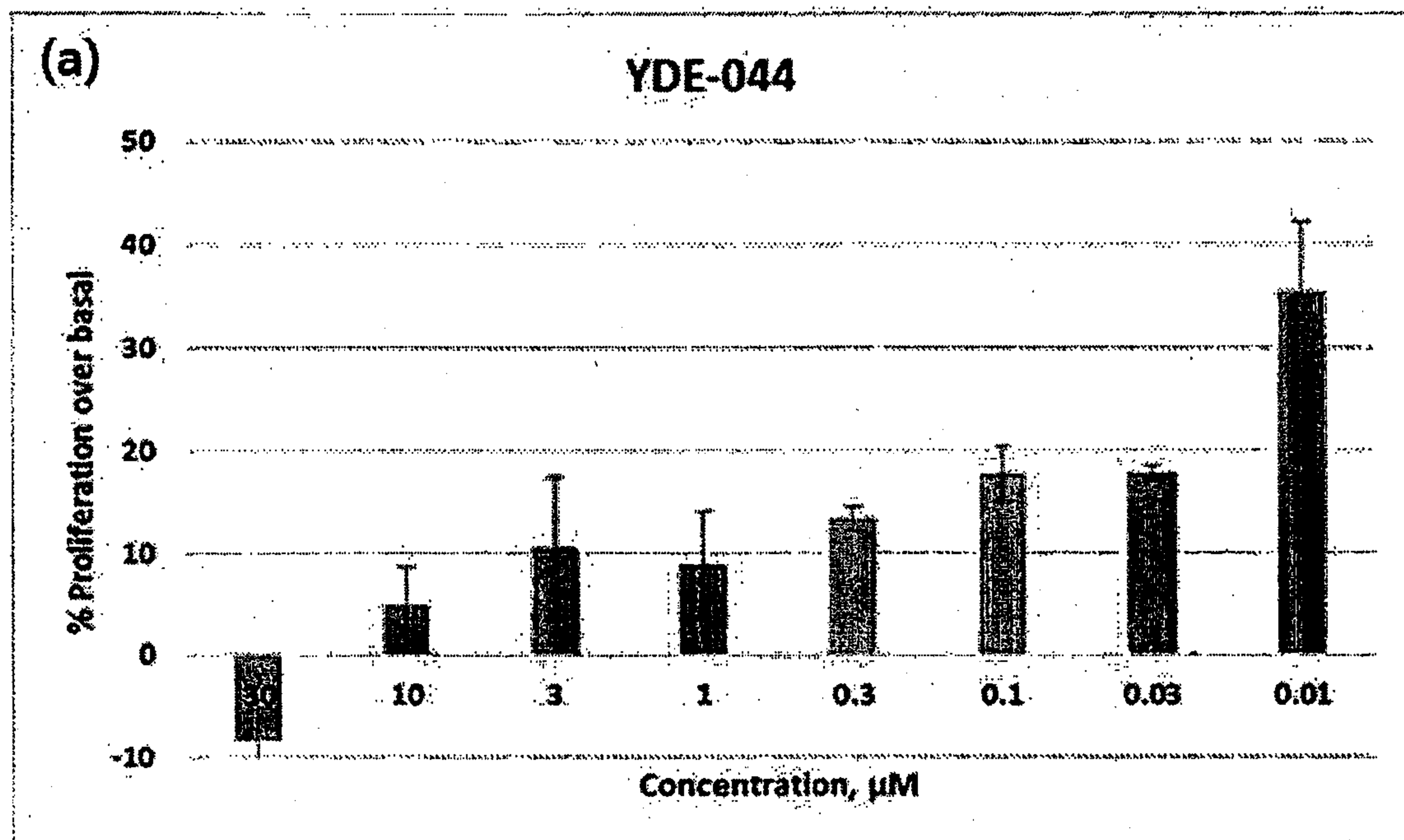
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FIG 161



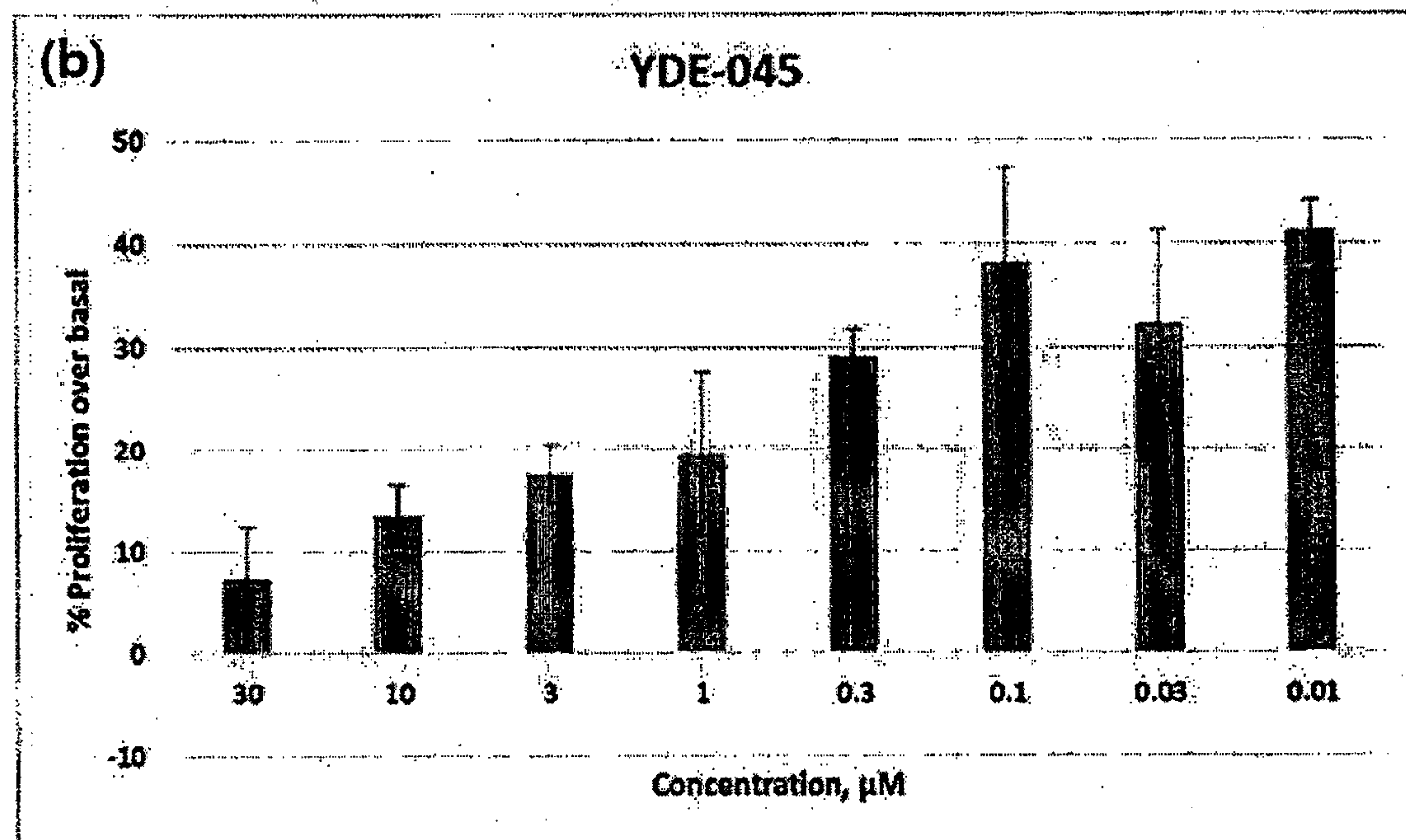
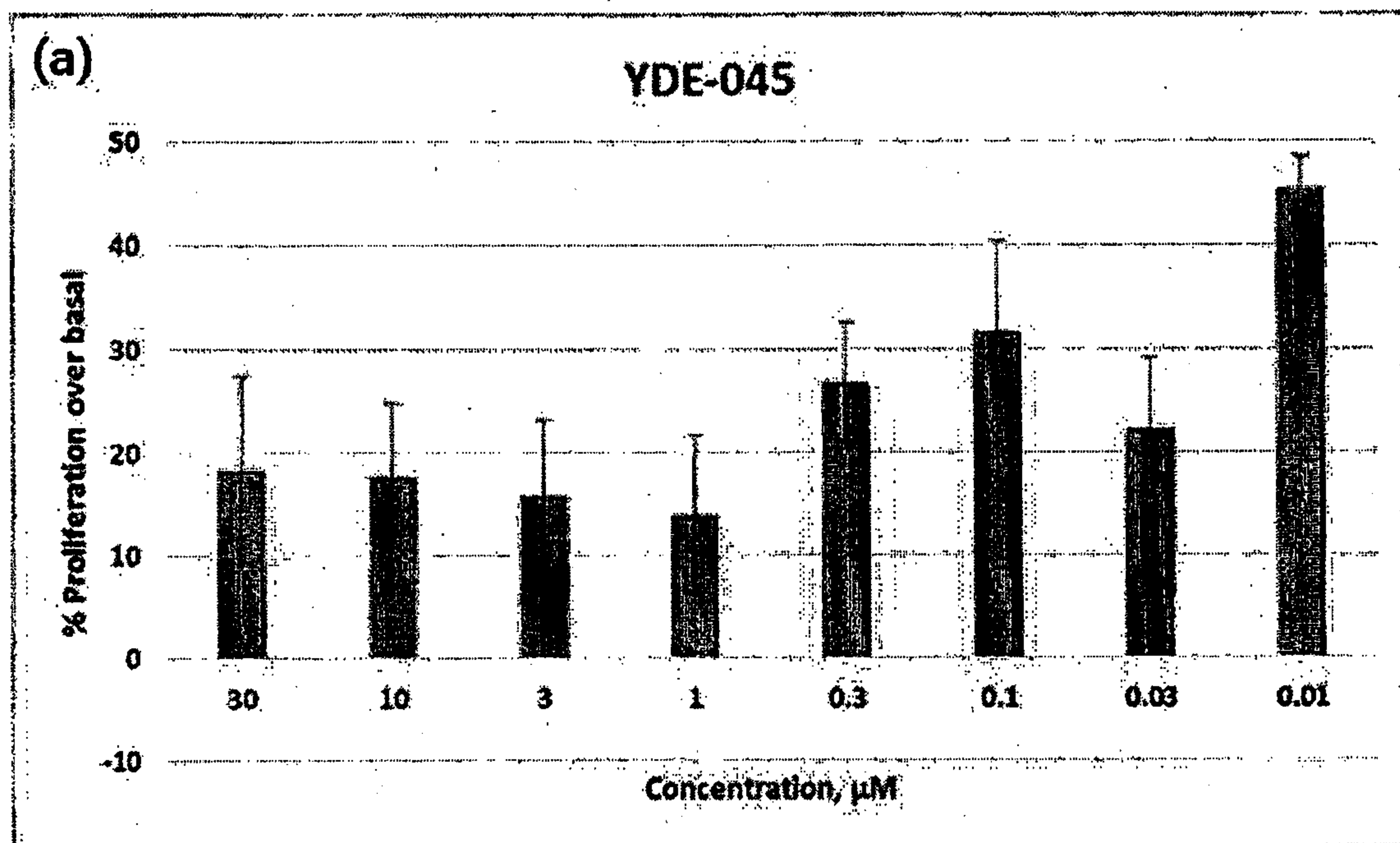
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FIG 162



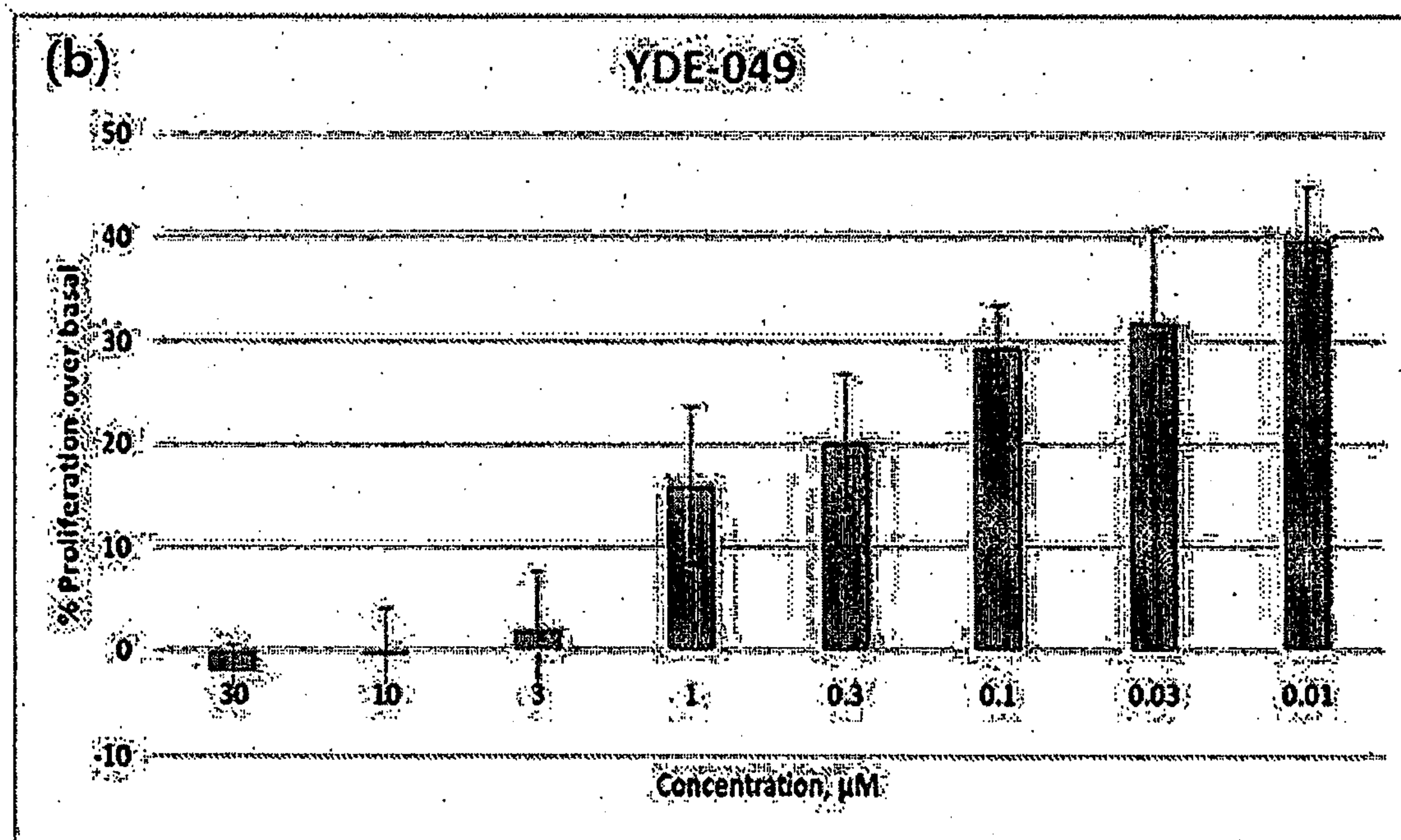
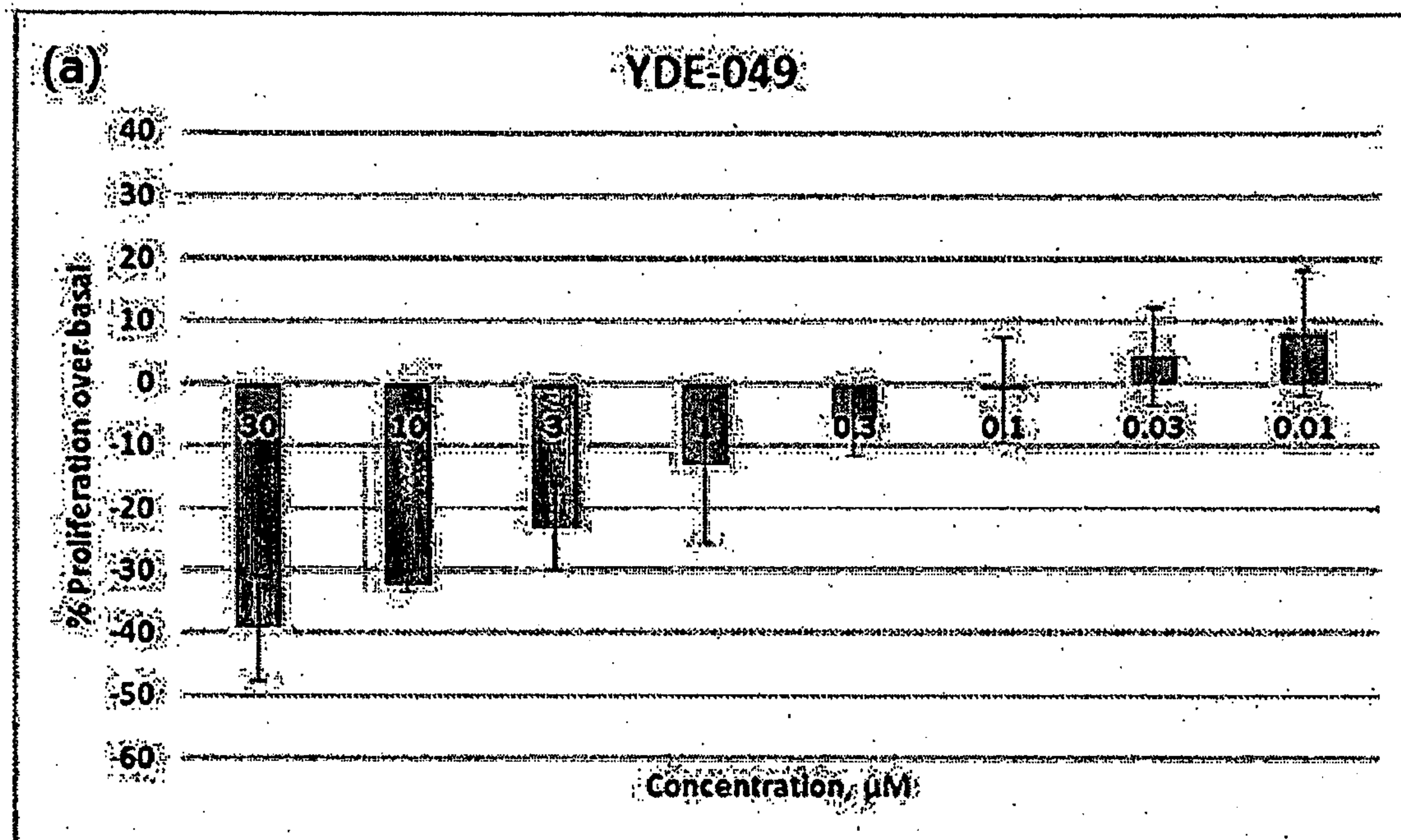
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FIG 163



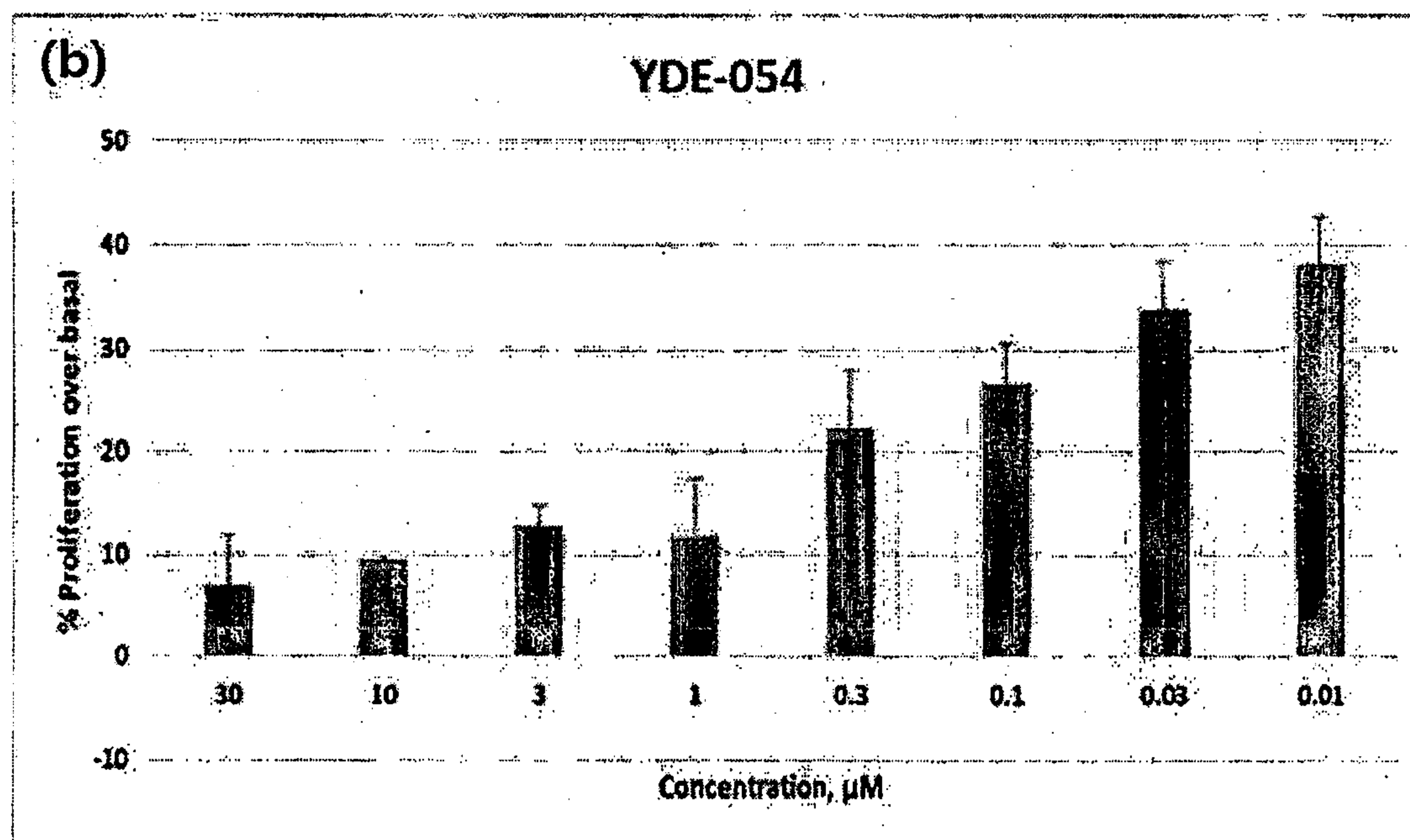
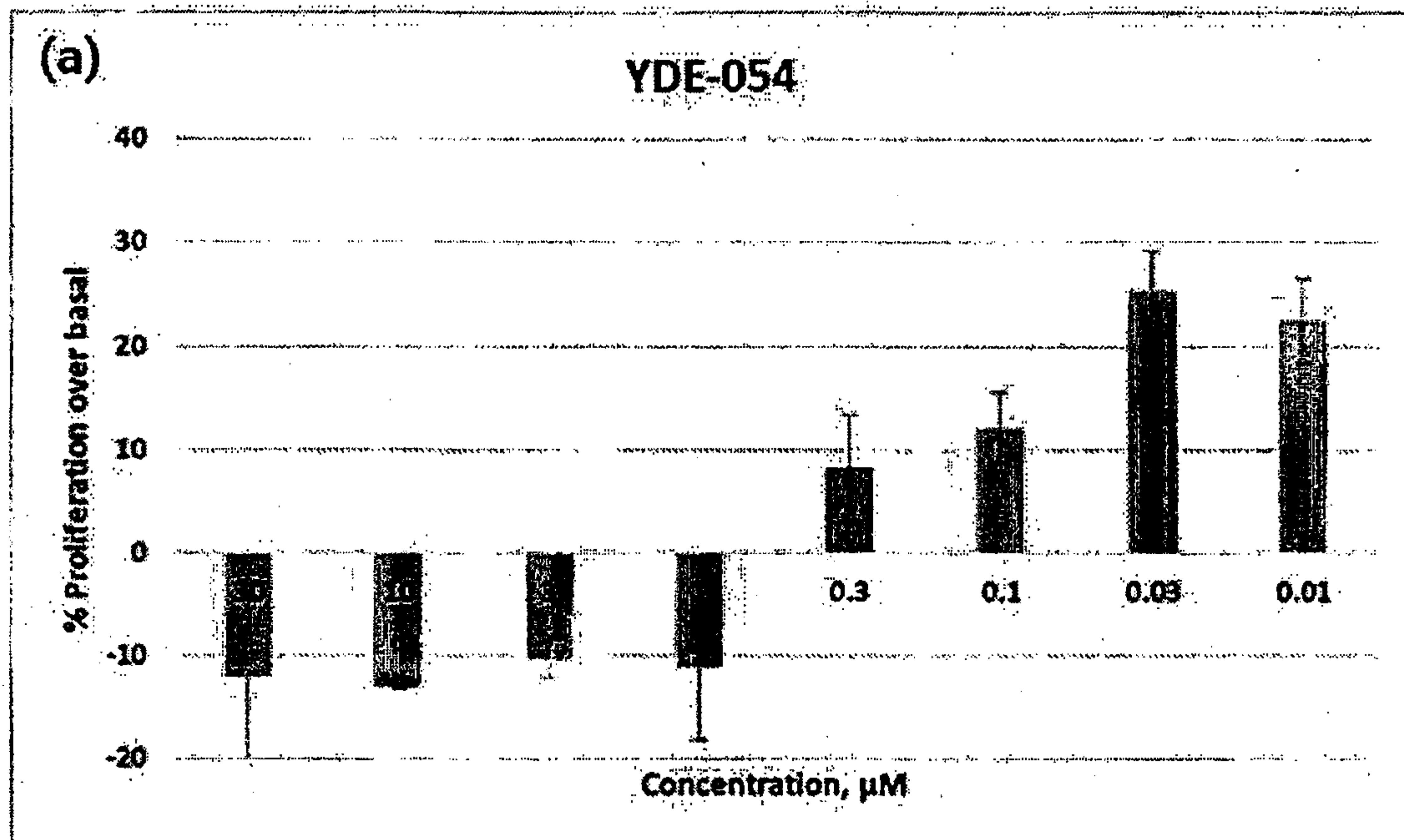
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FIG 164



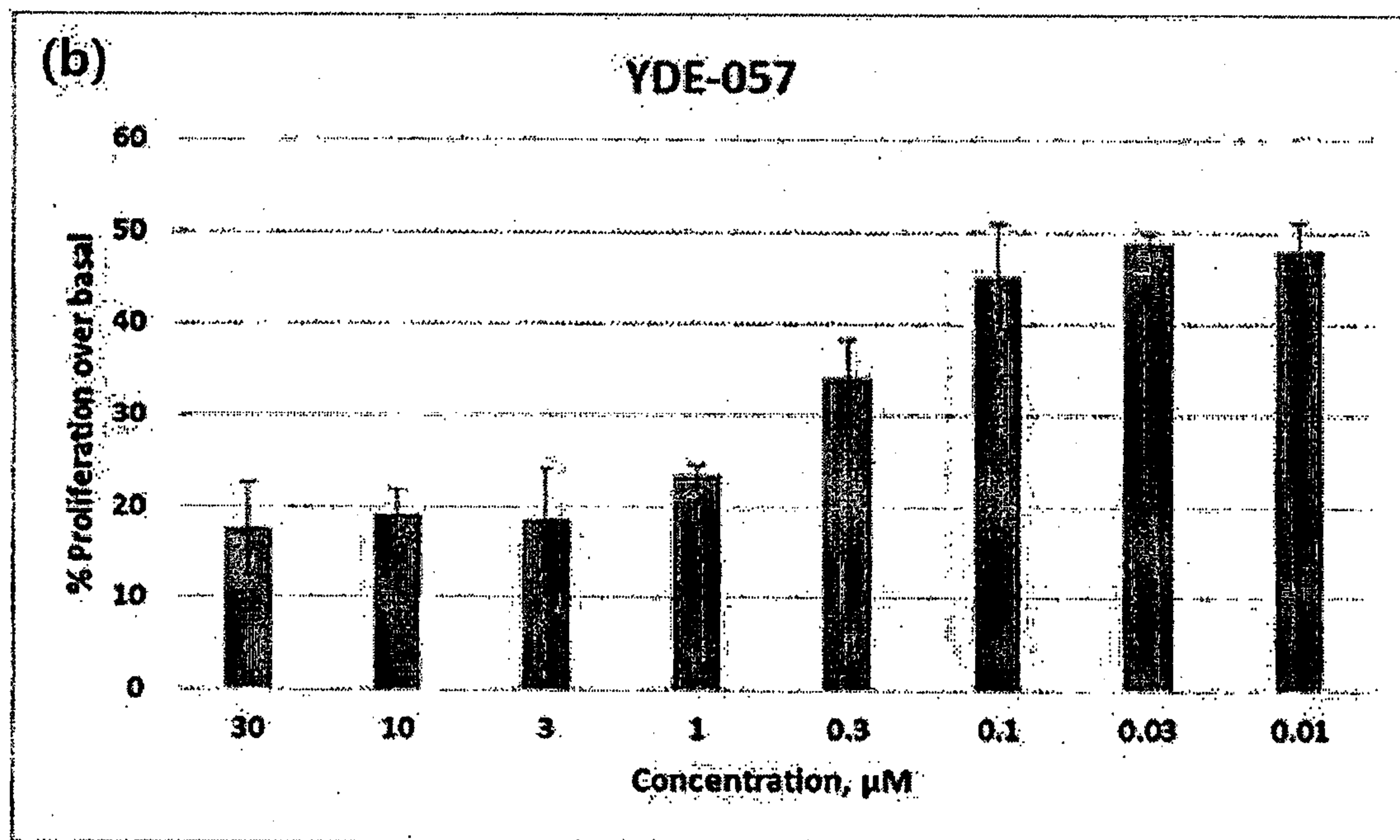
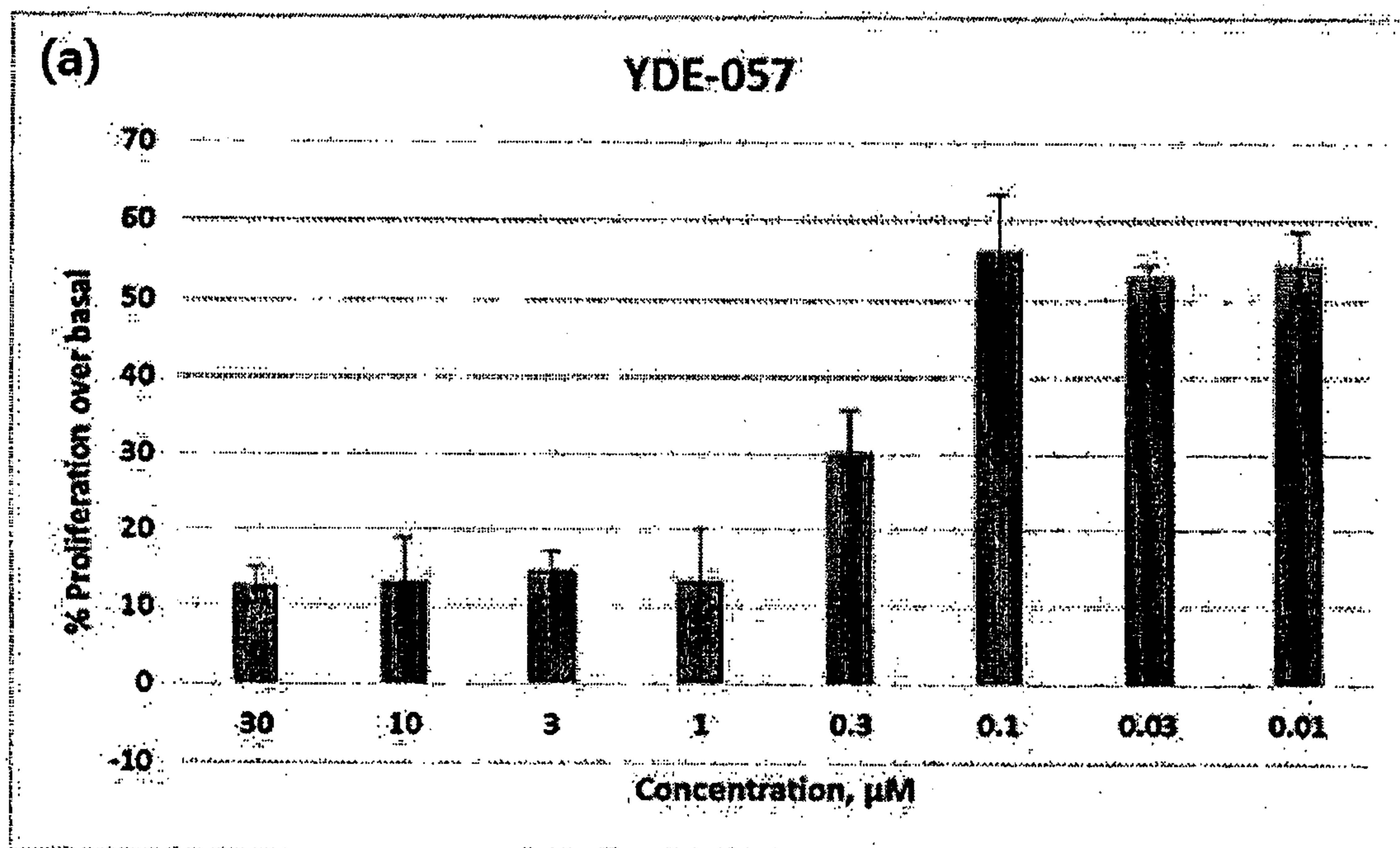
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FIG 165



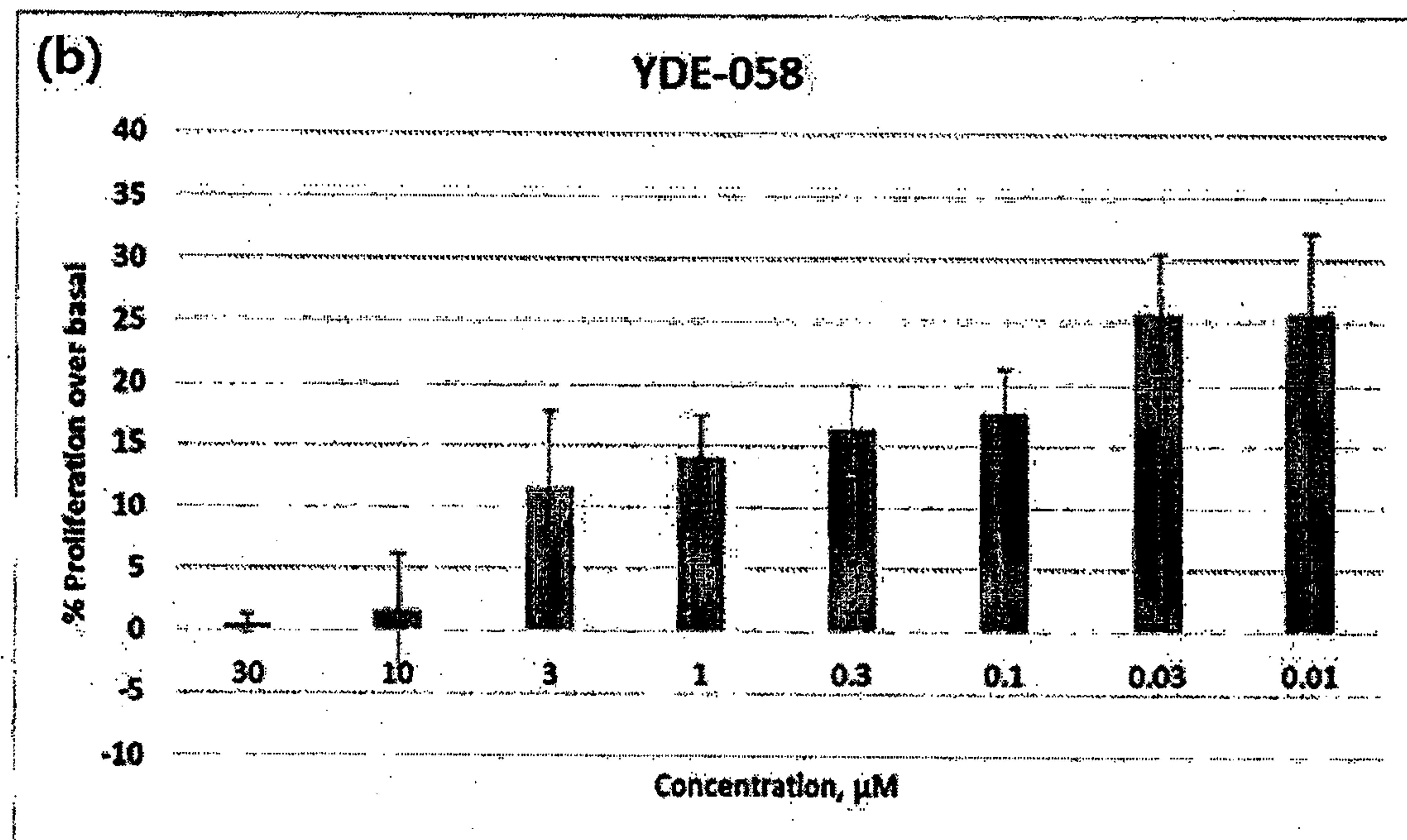
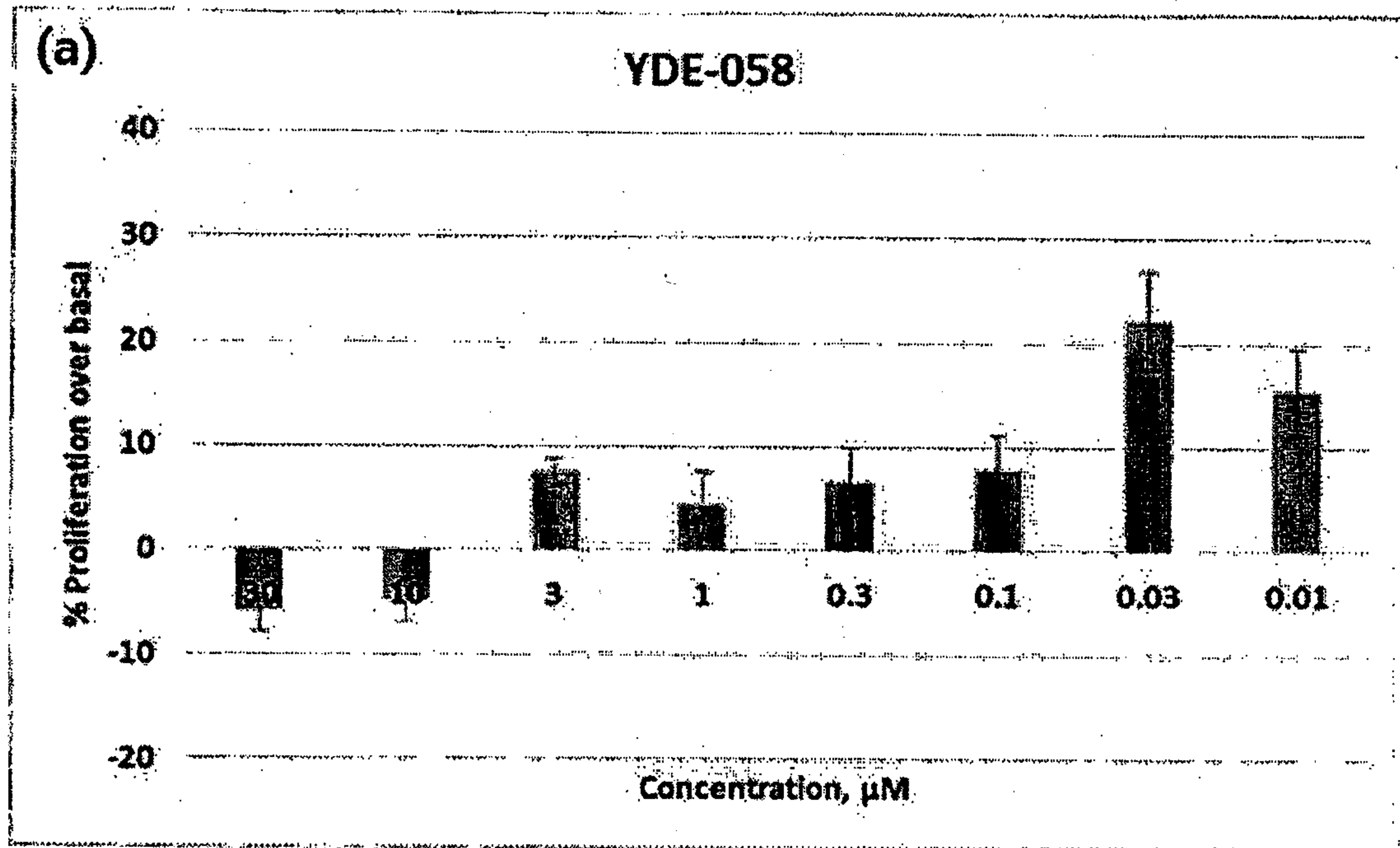
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FIG 166



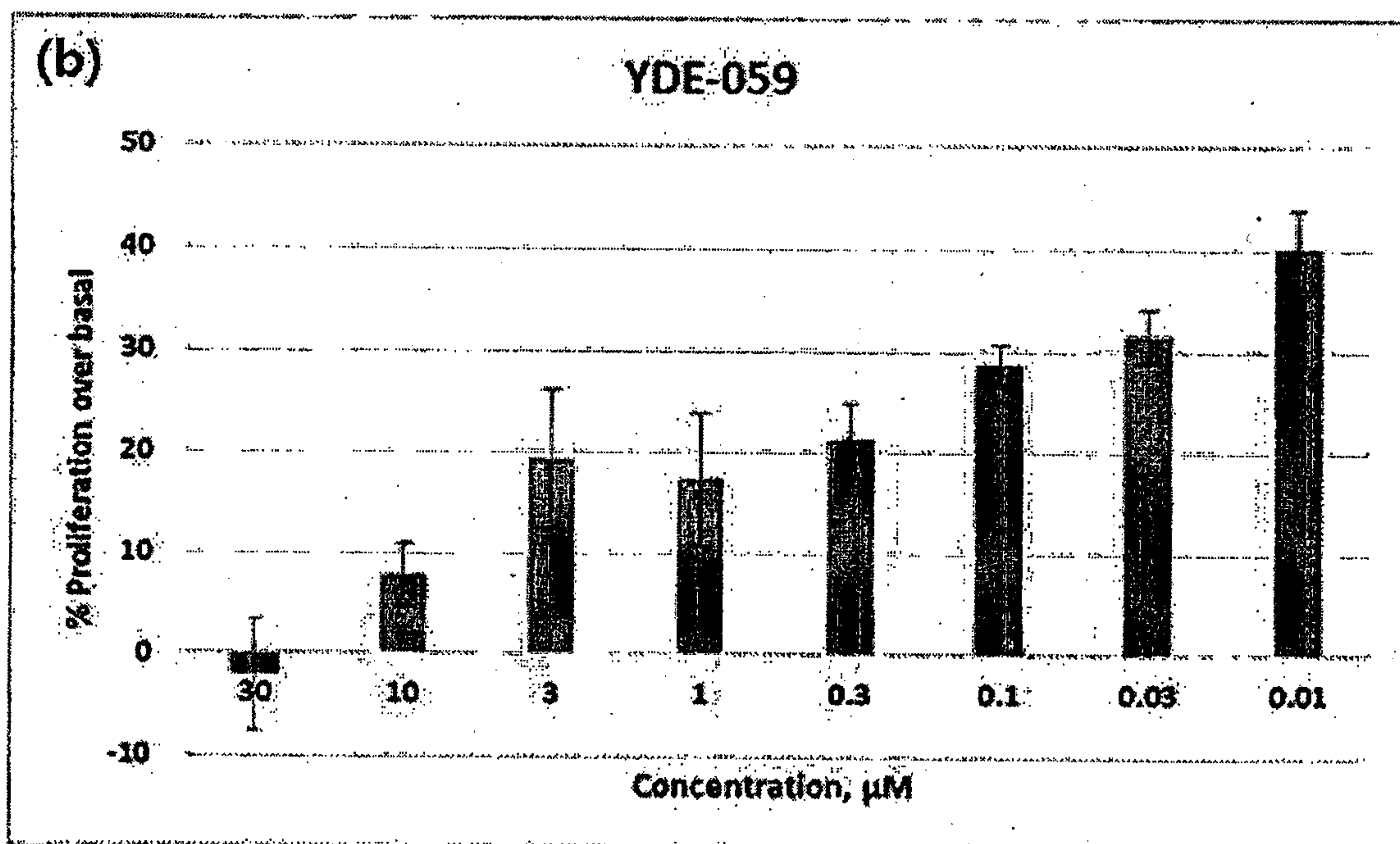
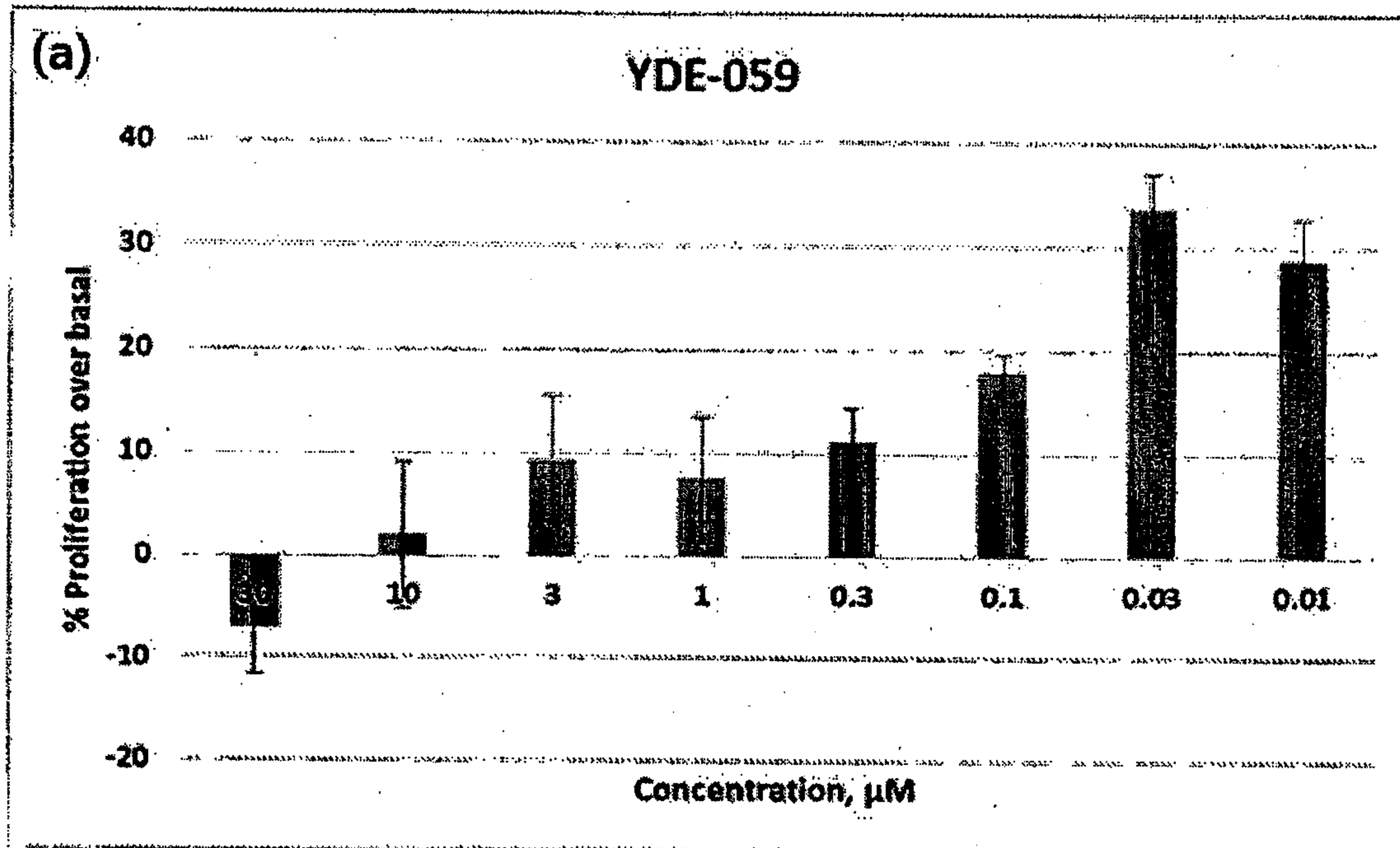
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FIG 167



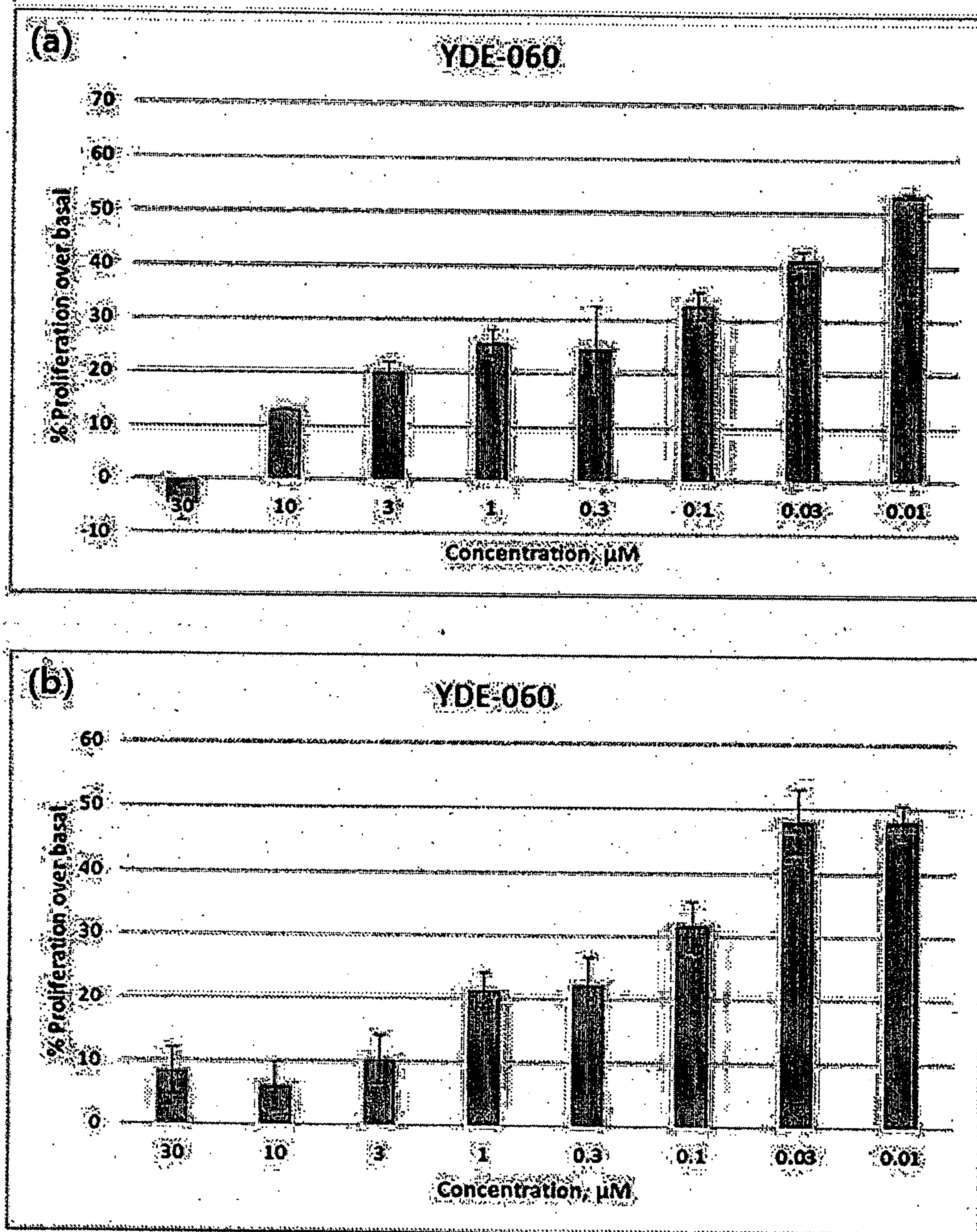
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FIG 168



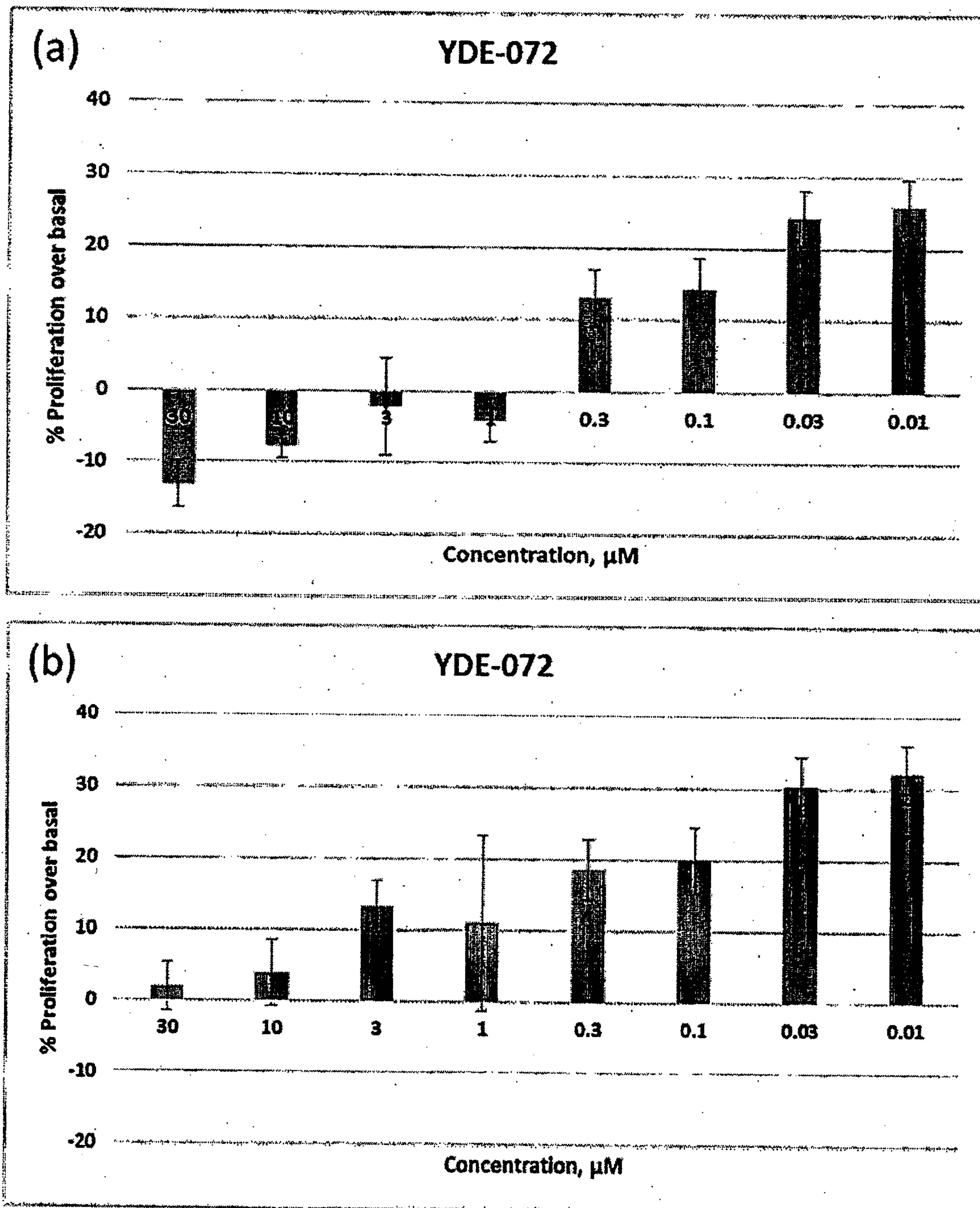
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FIG 169



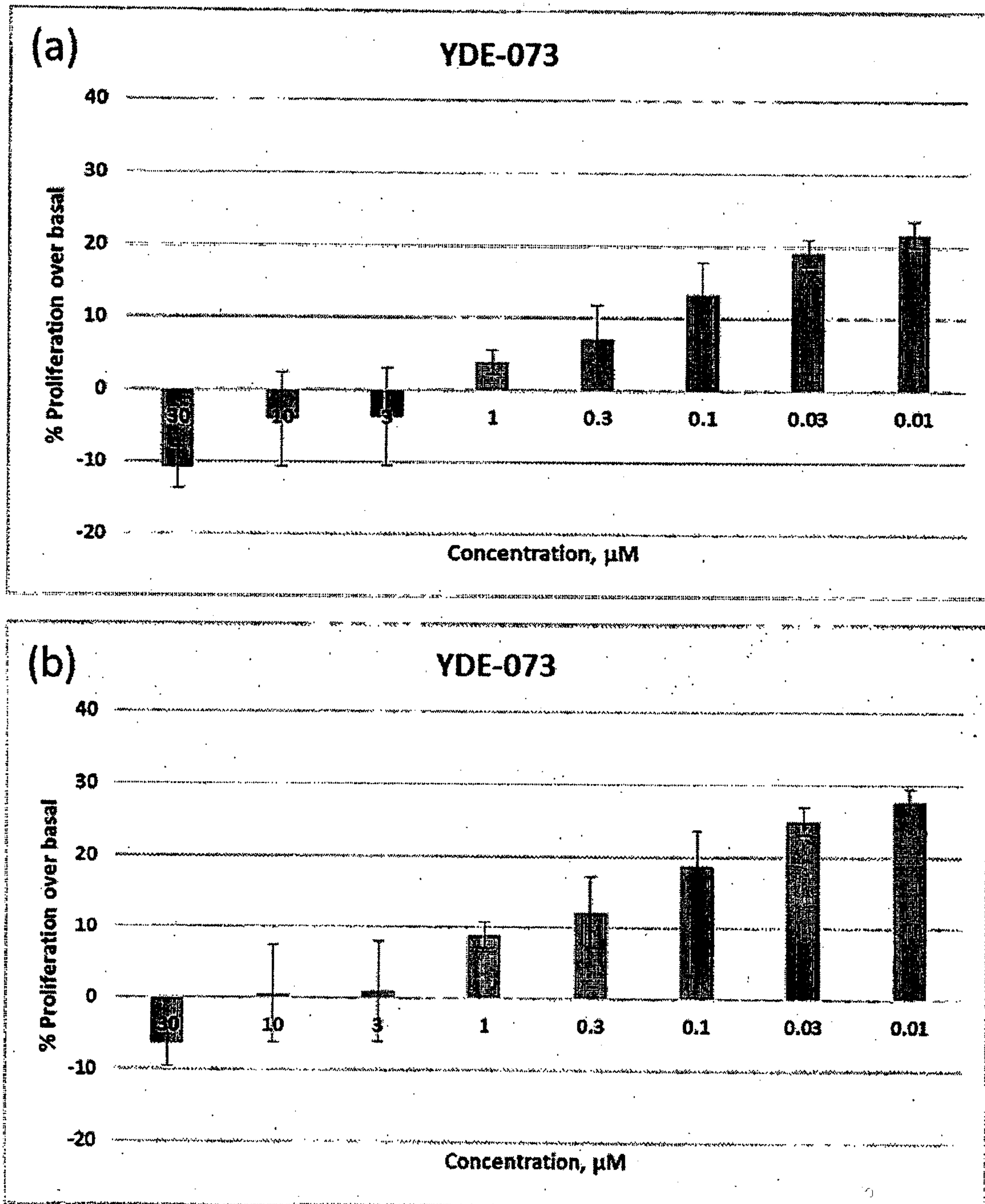
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FIG 170



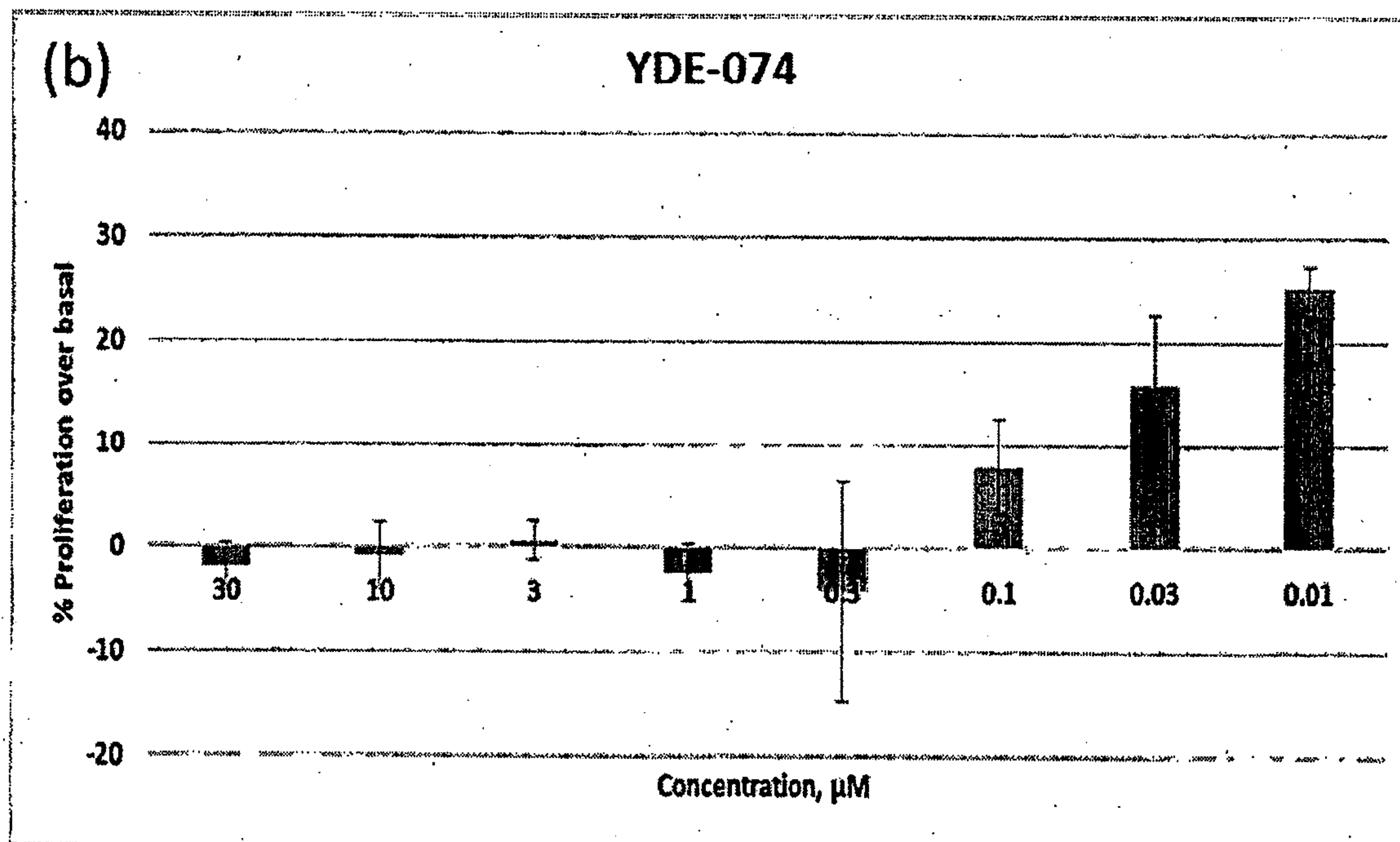
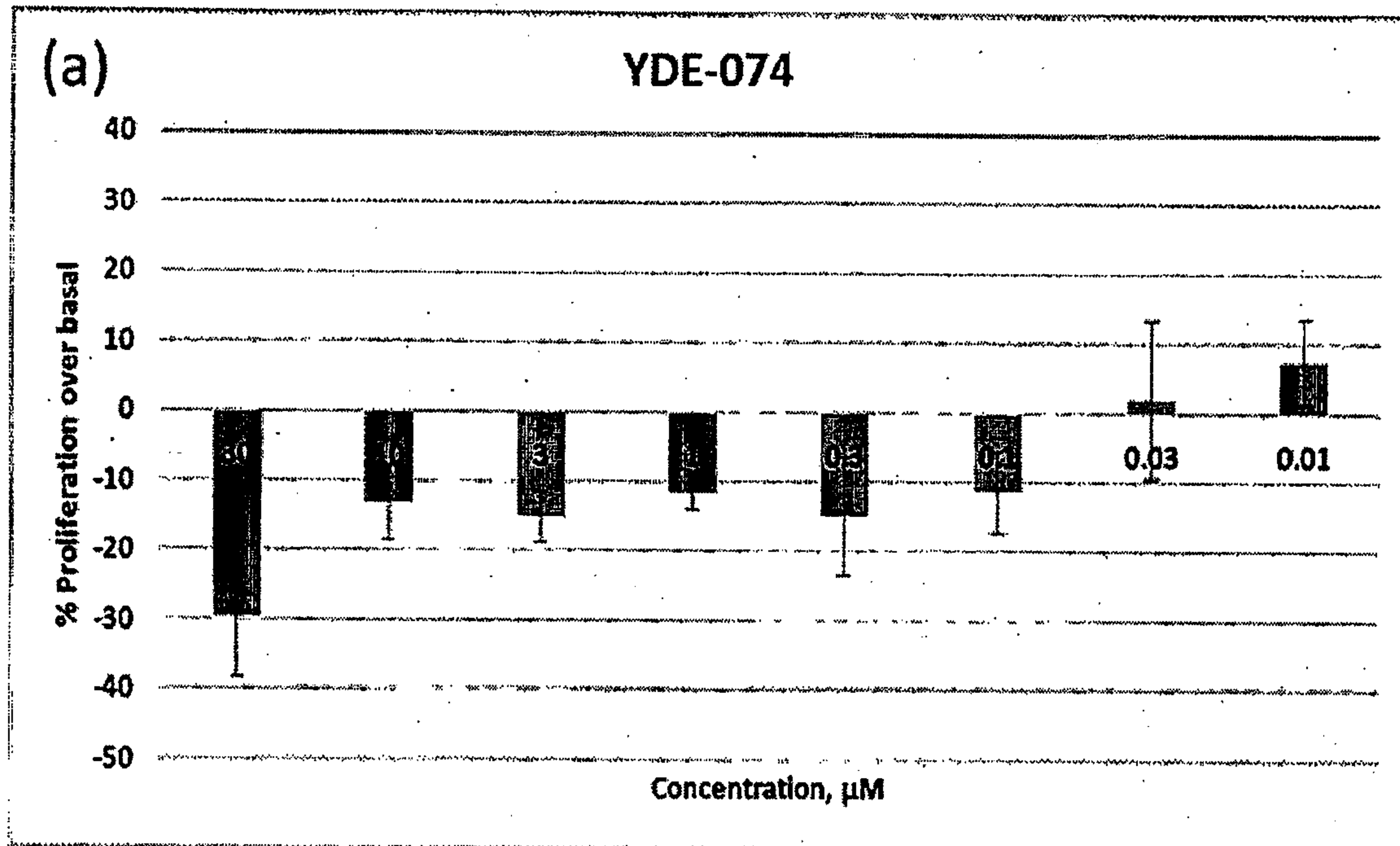
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FIG 171



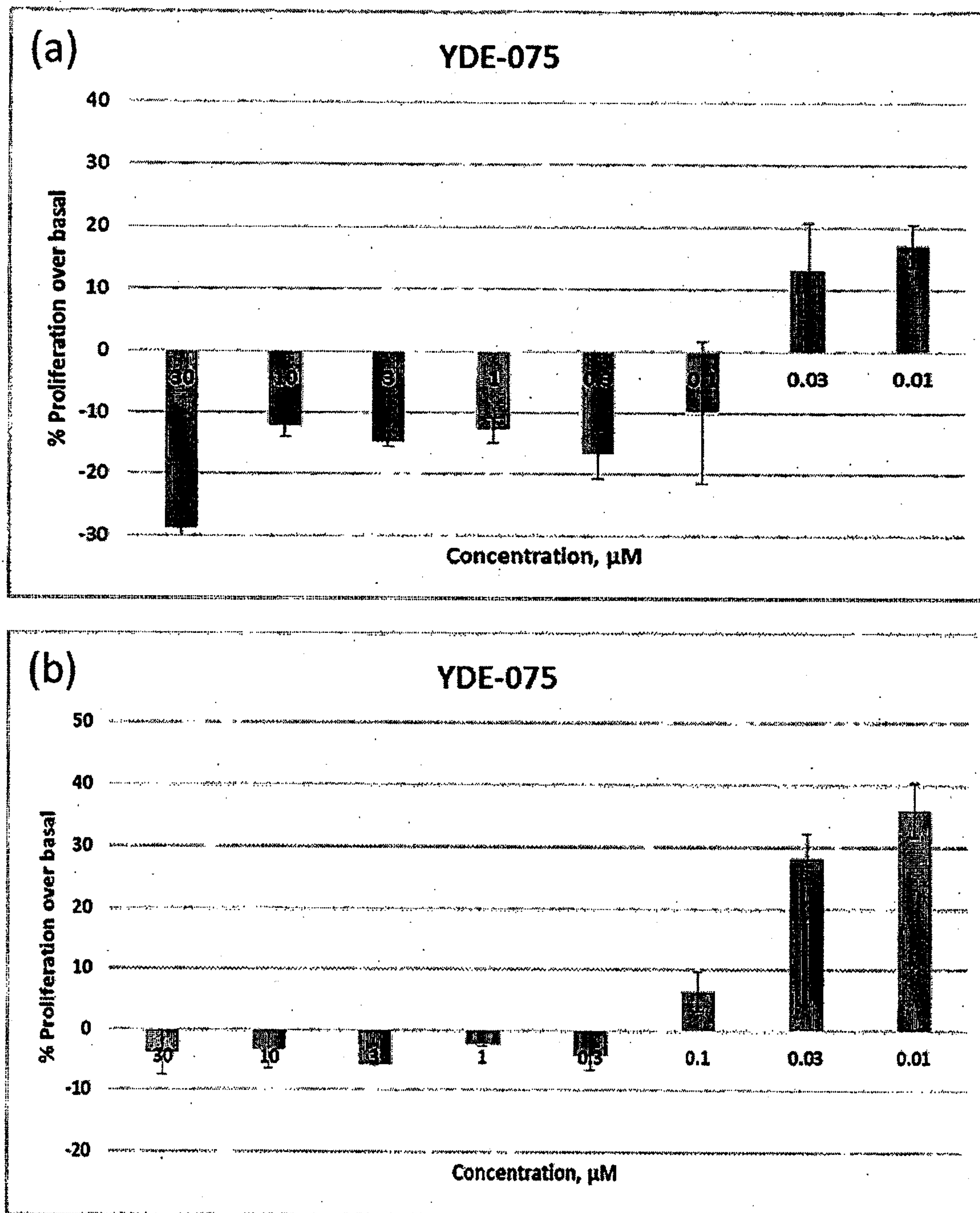
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FIG 172



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FIG 173



No.	Lot Number	Peptide Name	Sequence	M.W.	Purity (%)	Amount (mg)	Solubility (0.5mg/ml)
1	K161389	YDE-001	GG OGQEGLAGPK (O : Hydroxyproline)	969.1	>99.7%	5.0mg 10.0mg	Water
2	K161390	YDE-002	HH OGQNGLAGPK (O : Hydroxyproline)	954.0	>99.7%	5.0mg 10.0mg	Water
3	K161391	YDE-003	II OGQQGLAGPK (O : Hydroxyproline)	968.1	>99.7%	5.0mg 10.0mg	Water
4	K161392	YDE-004	JJ OGQHGLAGPK (O : Hydroxyproline)	977.1	>99.7%	5.0mg 10.0mg	Water
5	K161393	YDE-005	KK OGQKGLAGPK (O : Hydroxyproline)	968.1	>99.5%	5.0mg 10.0mg	Water
6	K161394	YDE-006	LL OGQSGLAGPK (O : Hydroxyproline)	927.0	>98.9%	5.0mg 10.0mg	Water
7	K161395	YDE-007	MM OGQTGLAGPK (O : Hydroxyproline)	941.0	>98.6%	5.0mg 10.0mg	Water
8	K161396	YDE-008	NN OGQAGLAGPK (O : Hydroxyproline)	911.0	>98.8%	5.0mg 10.0mg	Water
9	K161397	YDE-009	OO OGQVGLAGPK (O : Hydroxyproline)	939.1	>98.1%	5.0mg 10.0mg	Water
10	K161398	YDE-010	PP OGQIGLAGPK (O : Hydroxyproline)	953.1	>99.0%	5.0mg 10.0mg	Water
11	K161399	YDE-011	QQ OGQLGLAGPK (O : Hydroxyproline)	953.1	>98.3%	5.0mg 10.0mg	Water
12	K161400	YDE-012	RR OGQFGLAGPK (O : Hydroxyproline)	987.1	>98.9%	5.0mg 10.0mg	Water
13	K161401	YDE-013	SS OGQYGLAGPK (O : Hydroxyproline)	1003.1	>98.7%	5.0mg 10.0mg	Water
14	K161402	YDE-014	TT OGQWGLAGPK (O : Hydroxyproline)	1026.2	>98.5%	5.0mg 10.0mg	Water
15	K161403	YDE-015	UU OGQDVLAGPK (O : Hydroxyproline)	997.1	>99.1%	5.0mg 10.0mg	Water
16	K161404	YDE-016	VV OGQDILAGPK (O : Hydroxyproline)	1011.1	>99.4%	5.0mg 10.0mg	Water
17	K161405	YDE-017	WW OGQDLLAGPK (O : Hydroxyproline)	1011.1	>98.0%	5.0mg 10.0mg	Water
18	K161406	YDE-018	XX OGQDALAGPK (O : Hydroxyproline)	969.1	>99.6%	5.0mg 10.0mg	Water
19	K161407	YDE-019	YY OGQDFLAGPK (O : Hydroxyproline)	1045.2	>99.6%	5.0mg 10.0mg	Water
20	K161408	YDE-020	ZZ OGQDYLAGPK (O : Hydroxyproline)	1061.2	>99.2%	5.0mg 10.0mg	Water
21	K161409	YDE-021	AAA OGQDWLAGPK (O : Hydroxyproline)	1084.2	>98.1%	5.0mg 10.0mg	Water
22	K161410	YDE-022	BBB OGQDHLAGPK (O : Hydroxyproline)	1035.1	>98.3%	5.0mg 10.0mg	Water
23	K161411	YDE-023	CCC OGQDSLAGPK (O : Hydroxyproline)	985.1	>96.1%	5.0mg 10.0mg	Water
24	K161412	YDE-024	DDD OGQDTLAGPK (O : Hydroxyproline)	999.1	>98.9%	5.0mg 10.0mg	Water
25	K161413	YDE-025	EEE OGQD-Sar-LAGPK (Sar : me-Gly) (O : Hydroxyproline)	969.1	>95%	5.0mg 10.0mg	Water
26	K161414	YDE-026	FFF OGQS*GLAGPK (S* : homo-Ser) (O : Hydroxyproline)	941.1	>95%	5.0mg 10.0mg	Water
27	K161415	YDE-027	GGG OGQD*GLAGPK (D* : D(OMe)) (O : Hydroxyproline)	969.1	>95%	5.0mg 10.0mg	Water
28	K161416	YDE-028	HHH OGQN*GLAGPK (N* : N(NMe)) (O : Hydroxyproline)	968.1	>95%	5.0mg 10.0mg	Water

III

III ... Water