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(57) **Abrégé/Abstract:**

The invention provides peptides that are chemically modified by covalent attachment of a water-soluble oligomer. A conjugate of the invention, when administered by any of a number of administration routes, exhibits characteristics that are different from the characteristics of the peptide not attached to the water-soluble oligomer.

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(57) Abstract: The invention provides peptides that are chemically modified by covalent attachment of a water-soluble oligomer. A conjugate of the invention, when administered by any of a number of administration routes, exhibits characteristics that are different from the characteristics of the peptide not attached to the water-soluble oligomer.



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POLYMER CONJUGATES OF THERAPEUTIC PEPTIDES

[0001]

FIELD OF THE INVENTION

[0002] Among other things, the present invention relates to conjugates comprising a therapeutic peptide moiety covalently attached to one or more water-soluble polymers.

BACKGROUND OF THE INVENTION

[0003] In many ways, the chemical and biological properties of peptides make them very attractive candidates for use as therapeutic agents. Peptides are naturally occurring molecules made up of amino acid building blocks, and are involved in countless physiological processes. With 20 naturally occurring amino acids, and any number of non-naturally occurring amino acids, a nearly endless variety of peptides may be generated. Additionally, peptides display a high degree of selectivity and potency, and may not suffer from potential adverse drug-drug interactions or other negative side effects. Moreover, recent advances in peptide synthesis techniques have made the synthesis of peptides practical and economically viable. Thus peptides hold great promise as a highly diverse, highly potent, and highly selective class of therapeutic molecules with low toxicity.

[0004] A number of peptides have been identified as therapeutically promising; however *in vitro* results have often not proven to bear out *in vivo*. Significantly, peptides suffer from a short *in vivo* half life, sometimes mere minutes, making them generally impractical, in their native form, for therapeutic administration. Thus there exists a need in the art for modified therapeutic peptides having an enhanced half-life and/or reduced clearance as well as additional therapeutic advantages as compared to the therapeutic peptides in their unmodified form.

SUMMARY OF THE INVENTION

[0005] Accordingly, the present invention provides conjugates comprising a therapeutic peptide moiety covalently attached to one or more water-soluble polymers. The water-soluble polymer may be stably bound to the therapeutic peptide moiety, or it may be releasably attached to the therapeutic peptide moiety.

[0006] The invention further provides methods of synthesizing such therapeutic peptide polymer conjugates and compositions comprising such conjugates. The invention further provides methods of treating, preventing, or ameliorating a disease, disorder or condition in a mammal comprising administering a therapeutically effective amount of a therapeutic peptide polymer conjugate of the invention.

[0007] Additional embodiments of the present conjugates, compositions, methods, and the like will be apparent from the following description, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention. Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF DRAWINGS

Figure KISS1.1: Cation exchange purification of the PEGylation reaction mixture.

Figure KISS1.2: RP-HPLC analysis of purified [mono]-[mPEG-ButyrALD-30K]-[Kisspeptin-13].

Figure KISS1.3 MALDI-TOF spectrum of purified [mono]-[mPEG-ButyrALD-30K]-[Kisspeptin-13].

Figure KISS2.1. Typical reversed phase purification profile of [mono]-[mPEG-ButyAldehyde-10K]-[Kisspeptin-10].

Figure KISS2.2 Purity analysis of mono-[ButyrAldehyde-10K]-[Kisspeptin-10] by Reversed Phase HPLC.

Figure KISS2.3. MALDI-TOF spectrum of purified mono-[mPEG-butyraldehyde-10k]-[Kisspeptin-10].

Figure KISS3.1. Typical reversed phase purification profile of [mono]-[mPEG-ButyAldehyde-30K]-[Kisspeptin-10].

Figure KISS3.2. Purity analysis of mono-[ButyrAldehyde-30K]-[Kisspeptin-1] by Reversed Phase HPLC.

Figure KISS3.3. MALDI-TOF spectrum of purified mono-[mPEG-Butyraldehyde-30K]-[Kisspeptin-10].

Figure KISS4.1. Typical reversed phase purification profile of mono-[mPEG2-CAC-FMOC-40K]-[Kisspeptin-10].

Figure KISS4.2. Purity analysis of [mono]-[CAC-PEG2-FOMC- 40K]-[Kisspeptin-10] by Reversed Phase HPLC.

Figure KISS4.3. MALDI-TOF spectrum of purified mono-[CAC-PEG2-FMOC-40K]-[Kisspeptin-10].

Figure KISS5.1. Typical reversed phase purification profile of mono-[mPEG-SBC-30K]-[Kisspeptin-10].

Figure KISS5.2. SDS-PAGE, with Coomassie blue staining) of purified mono-[mPEG-SBC-30K]-[Kisspeptin-10].

Figure KISS5.3. Purity analysis of mono-[mPEG-SBC-30K]-[Kisspeptin-10] by Reversed Phase HPLC.

Figure KISS5.4. MALDI-TOF spectrum of purified mono-[mPEG-SBC-30k]-[Kisspeptin-10].

Figure KISS6.1 Typical cation exchange purification profile of mono-[mPEG2-ButyrAldehyde-40K]-[Kisspeptin-54].

Figure KISS6.2. Purity analysis of [mono]-[mPEG2-ButyrAldehyde-40K]-[Kisspeptin-54] conjugate by Reversed Phase HPLC.

Figure KISS6.3. SDS-PAGE with Coomassie staining of purified [mono]-[mPEG2-ButyrAldehyde-40K]-[Kisspeptin-54].

Figure KISS6.4. MALDI-TOF spectrum of purified [mono]-[mPEG2-ButyrAldehyde-40K]-[Kisspeptin-54].

Figure KISS8.1. Agonist activity at GPR54 for stable PEG conjugates of Kisspeptin 10, Kisspeptin 13, and Kisspeptin 54.

Figure KISS8.2. Agonist activity at GPR54 for releasable PEG conjugate of Kisspeptin 10.

Figure KISS8.3. Agonist activity at GPR54 for releasable PEG conjugate of Kisspeptin 10.

Figure ZIC2.1: Cation exchange purification of mono-mPEG-C2-FMOC-20K-ziconotide from the PEGylation reaction mixture.

Figure ZIC2.2: RP-HPLC analysis of purified mono-mPEG-C2-FMOC-20K-ziconotide.

Figure ZIC2.3: MALDI-TOF analysis of purified mono-mPEG-C2-FMOC-20K-ziconotide.

Figure ZIC3.1: Cation exchange purification of mono-mPEG-CAC-FMOC-40K-ziconotide from the PEGylation reaction mixture.

Figure ZIC3.2: RP-HPLC analysis of purified mono-mPEG-CAC-FMOC-40K-ziconotide.

Figure ZIC3.3: MALDI-TOF analysis of purified mono-mPEG-CAC-FMOC-40K-ziconotide.

Figure ZIC4.1: Cation exchange purification of mono-mPEG-SBA-30K-ziconotide from the PEGylation reaction mixture.

Figure ZIC4.2: RP-HPLC analysis of purified mono-mPEG-SBA-30K-ziconotide.

Figure ZIC4.3: MALDI-TOF analysis of purified mono-mPEG-SBA-30K-ziconotide.

Figure ZIC5.1: Cation exchange FPLC chromatography of the PEGylation reaction mixture between ziconotide and mPEG-SBC-30K-NHS.

Figure ZIC6.1. Mean ($\pm$ SEM) percent specific binding of ziconotide conjugates to calcium channel, N-type, in rat cortical membranes.

Figure BIP2.1: (SPA-2K)₂-biphalin purification with CG-71S resin.

Figure BIP2.2: RP-HPLC analysis of reconstituted (SPA-2K)₂-biphalin.

Figure BIP2.3. MALDI TOF MS analysis of reconstituted (SPA-2K)₂-biphalin.

Figure BIP3.1: (C2-20K)₂-biphalin purification with CG-71S resin.

Figure BIP3.2: RP-HPLC analysis of reconstituted (C2-20K)₂-biphalin.

Figure BIP3.3 MALDI-TOF analysis of reconstituted (C2-20K)₂-biphalin.

Figure BIP4.1: (CAC-20K)₂-biphalin purification with CG-71S resin.

Figure BIP4.2: (CAC-20K)₂-biphalin re-purification with CG-71S resin.

Figure BIP4.3: RP-HPLC analysis of reconstituted (CAC-20K)₂-biphalin.

BIP4.4: MALDI-TOF analysis of reconstituted (CAC-20K)₂-biphalin.

Figure BIP5.1: RP-HPLC analysis of SBC-30K and biphalin conjugation reaction mixture.

Figure BIP5.2. The purification of (SBC-30K)₂-biphalin from the reaction mixture.

Figure BIP6.1. Competition binding assay of biphalin and di-CAC-20K-biphalin conjugate at human (A) μ opioid and (B) δ opioid receptors.

Figure BIP6.2. Competition binding assay of biphalin and di-C2-20K-biphalin, di-SBC-30K-biphalin, and di-SPA-2K-biphalin conjugate at human (A) μ opioid and (B) δ opioid receptors.

Fig. BNP2.1. PEGylation rate of BNP-32 with mPEG2-40kDa Butyr-ALD.

Fig. BNP2.2. Typical purification profile for the 40 kDa mPEG2-Butyr-ALD mono-PEG conjugate of BNP-32.

Fig BNP2.3. HPLC analysis of the 40 kDa mPEG2-Butyr-ALD mono-PEG conjugate of BNP-32.

Fig. BNP2.4. MALDI-TOF analysis of the 40 kDa mPEG2-Butyr-ALD mono-PEG conjugate of BNP-32.

Fig. BNP2.5. SDS-PAGE (4-12% Bis-Tris-Nu-PAGE, Invitrogen) analysis of BNP-32 and purified [mono]-[mPEG2-Butyr-ALD-40K]-[BNP-32] conjugate. .

Fig. BNP4.1. Typical cation-exchange purification profile of [mono]-[mPEG-Butyr-ALD-10K]-[BNP-32].

Fig. BNP4.2. SDS-PAGE analysis of BNP-32 and the purified [mono]-[mPEG2-Butyr-ALD-40K]-[BNP-32] conjugate..

Fig BNP4.3. RP-HPLC analysis of the purified [mono]-[mPEG-Butyr-ALD-10K]-[BNP-32] conjugate..

Fig. BNP4.4. MALDI-TOF analysis of the purified [mono]-[mPEG-Butyr-ALD-10K]-[BNP-32] conjugate.

Fig. BNP5.1. Typical first cation-exchange purification profile for [mono]-[mPEG-SBC-30K]-[BNP-32].

Fig. BNP5.2. SDS-PAGE analysis of the purified [mono]-[mPEG-SBC-30K]-[BNP-32] conjugate.

Fig BNP5.3. RP-HPLC analysis of the purified [mono]-[mPEG-SBC-30K]-[BNP-32] conjugate.

Fig. BNP5.4. MALDI-TOF analysis of the purified [mono]-[mPEG-SBC-30K]-[BNP-32] conjugate.

Fig. BNP6.1. Typical first cation-exchange purification profile of [mPEG2-C2-fmoc-NHS-40K].

Fig. BNP6.2. SDS-PAGE analysis of the purified [mPEG2-C2-fmoc-NHS-40K]-[BNP-32] conjugate.

Fig BNP6.3. RP-HPLC analysis of the purified [mPEG2-C2-fmoc-NHS-40K]-[BNP-32] conjugate..

Fig. BNP6.4. MALDI-TOF analysis of the purified [mPEG2-C2-fmoc-NHS-40K]-[BNP-32] conjugate.

Figure BNP7.1 shows the mean plasma concentration-time profiles of for C2-FMOC-PEG2-40K-BNP, its corresponding metabolite and released BNP.

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Figure BNP7.2 shows the non-released PEG-BNP levels after the administration of the two non-releasable PEG constructs (ButyrALD-40K-BNP, ButyrALD-10K-BNP).

Figure PRO2.1. Typical cation exchange purification profile of mono-[mPEG2-CAC-FMOC-40K]-[PG-1].

Figure PRO2.2. SDS-PAGE of purified [mono]-[CAC-PEG2-FOMC-NHS-40K]-[Protegrin-1].

Figure PRO2.3. Purity analysis of [mono]-[CAC-PEG2-FOMC- 40K]-[Protegrin-1] by RP-HPLC.

Figure PRO2.4. MALDI-TOF spectrum of purified mono-[CAC-PEG2-FMOC- 40K]-[Protegrin-1].

Figure PRO3.1 Typical cation exchange purification profile of mono-[mPEG-SBC-30K]-[PG-1].

Figure PRO3.2. SDS-PAGE of purified [mono]-[mPEG-SBC-30K]-[Protegrin-1].

Figure PRO3.3. Purity analysis of [mono]-[mPEG-SBC-30K]-[Protegrin-1] by RP-HPLC.

Figure PRO3.4. MALDI-TOF spectrum of purified [mono]-[mPEG-SBC-30K]-[Protegrin-1].

Figure PRO4.1 Typical reversed phase purification profile of [Protegrin-1]-[PEG-di-ButyrAldehyde-5K]-[Protegrin-1].

Figure PRO4.2. SDS-PAGE of purified [Protegrin-1]-[PEG-di-butyraldehyde-5K]-[Protegrin-1].

Figure PRO4.3. Purity analysis of [Protegrin-1]-[PEG-di-butyraldehyde-5K]-[Protegrin-1] by reversed phase HPLC.

Figure PRO4.4. MALDI-TOF spectrum of [Protegrin-1]-[PEG-di-butyraldehyde-5K]-[Protegrin-1].

Figure PRO5.1. Typical cation-exchange chromatography profile of dextran-butryaldehyde-40K-protegrin-1.

Figure PRO5.2. SDS-PAGE analysis (4-12% gel) of purified dextran-butryaldehyde-40K-protegrin-1.

Figure PRO6.1: PG-1 and (ALD)₂2K conjugates purification with CM Sepharose FF resin.

Figure PRO6.2: RP-HPLC analysis of (PG-1)-(ALD)₂2K-(PG-1).

Figure PRO6.3: MALDI analysis of (PG-1)-(ALD)₂2K-(PG-1).

Figure PRO7.1.1 and 7.1.2: ALD40K-PG-1 purification with SP Sepharose HP resin.

Figure PRO7.2. SDS-PAGE of the purified and concentrated ALD40K-PG-1.

Figure PRO7.3: RP-HPLC analysis of ALD40K-PG-1 (lot # YW-pgALD40K-01).

Figure PRO7.4: MALDI analysis of ALD40K-PG-1 (lot # YW-pgALD40K-01).

Figure PRO8.1: CG40K-PG-1 purification with SP Sepharose HP resin.

Figure PRO8.2: RP-HPLC analysis of purified CG40K-PG-1.

Figure PRO8.3: MALDI-TOF analysis of purified CG40K-PG-1.

Figure PRO9.1. Hemolysis relative to the 100% hemolysis produced by 0.25% Triton X-100.

Figure PRO9.1. Hemolysis by PEG reagent controls.

Figure PRO9.3. Hemolysis at the maximum concentration.

Figure PRO9.4. Hemolytic activities of PG-1
Figure PRO10.1 and PRO10.2 show the mean plasma concentration-time profiles for CG-PEG₂-FMOC-40K-PG-1 and CAC-PEG₂-FMOC-40K-PG-1, their corresponding PEG-metabolite and released Protegrin-1.

Figure PRO10.3 shows the released Protegrin-1 levels after the administration of the two releasable PEG constructs versus the level of Protegrin-1 given as native protein at the same dose (mg/kg).

Figure PRO10.4 shows the mean plasma concentration-time profiles for mPEG₂-PG-1, PG-1[PEG_{2k}-PG-1, PG-1-PEG_{5k}-PG-1.

Figure V2.1. Typical cation-exchange purification profile of [mPEG2-NHS-20K]-[V681(V13AD)].

Figure V2.2. SDS-PAGE analysis of V681(V13AD) PEGylation.

Figure V2.3. Purity analysis of [mono]-[mPEG2-NHS 20K]-[V681(V13AD)] conjugate by reverse phase HPLC.

Figure V2.4. MALDI-TOF spectra for [mono]-[mPEG2-NHS 20K]-[V681(V13AD)].

Figure V3.1. Typical cation-exchange purification profile of [mPEG-SMB-30K]-[V681(V13AD)].

Figure V3.2. SDS-PAGE analysis of V681(V13AD) PEGylation and purification on the SP ion-exchange column.

Figure V3.3. Purity analysis of [mono]-[mPEG-SMB-30K]-[V681(V13AD)] conjugate by reverse phase HPLC.

Figure V3.4. MALDI-TOF spectra for [mono]-[mPEG-SMB 30K]-[V681(V13AD)].

Figure V4.1 shows the mean plasma concentration-time profiles for V681 (V13AD), SMB-30K-V681 (V13AD), and NHS-20K-V681 (V13AD).

Figure V5.1. Hemolysis relative to the 100% hemolysis produced by 0.25% Triton X-100.

Figure C-PEP 2.1. Typical anion-exchange chromatography profile of [[mono]-[mPEG-ru-MAL-30K]-[C-peptide(S20C)].

Figure C-PEP 2.2. Purity analysis of [[mono]-[mPEG-ru-MAL-30K]-[C-peptide(S20C)]] by reversed phase HPLC.

Figure C-PEP2.3. MALDI-TOF spectrum for [mono]-[mPEG-ru-MAL-30K]-[C-peptide(S20C)].

Figure C-PEP3.1. Typical anion-exchange chromatography profile of [[mono]-[mPEG-Butyraldehyde-30K]-[C-peptide(S20C)]].

Figure C-PEP3.2. Purity analysis of [mono]-[mPEG- Butyraldehyde -30K]-[C-peptide(S20C)] by reversed phase HPLC.

Figure C-PEP3.3. MALDI-TOF spectrum for [mono]-[mPEG-Butyraldehyde-30K]-[C-peptide(S20C)] .

Figure C-PEP4.1. Typical anion-exchange chromatography profile of [mono]-[C2-PEG2-FMOC-40K]-[C-peptide(S20C)].

Figure C-PEP4.2. Purity analysis of [[mono]-[C2-PEG2-FMOC-40K]-[C-peptide(S20C)]] by reversed phase HPLC.

Figure C-PEP4.3. MALDI-TOF spectrum for [mono]-[C2-PEG2-FMOC-40K]-[C-peptide(S20C)] .

Figure C-PEP5.1. Typical anion-exchange purification profile of [[mono]-[CAC-PEG2-FMOC-40K]-[C-peptide(S20C)]].

Figure C-PEP5.2. Purity analysis of [mono]-[CAC-PEG2-FMOC-40K]-[C-peptide(S20C)] by reversed phase HPLC.

Figure C-PEP6.1 Typical anion-exchange chromatography profile of dextran-butryaldehyde-40K-C-peptide(S20C).

Figure C-PEP6.2. Concentration of fraction II from the anion-exchange chromatogram shown in Figure c-pep6.1 by a second anion-exchange chromatography run.

Figure C-PEP6.3. Purity analysis of [[mono]-[Dextran-40K]-[C-peptide(S20C)]] by reversed phase HPLC.

Figure C-PEP6.4. MALDI-TOF spectrum for [mono]-[Dextran-40K]-[C-peptide(S20C)].

Figure OGF2.1. Typical CG71S reversed phase purification profile of mono-[mPEG2-CAC-FMOC-40K]-[OGF].

Figure OGF2.2. Purity analysis of [mono]-[CAC-PEG2-FOMC-40K]-[OGF] by reversed phase HPLC.

Figure OGF2.3. MALDI-TOF spectrum of purified mono-[mPEG2-FMOC-CAC-40K]-[OGF].

Figure OGF3.1. Typical CG71S reverse phase purification profile of mono-[mPEG2-C2-FMOC-40K]-[OGF].

Figure OGF3.2. Purity analysis of mono-[mPEG2-FMOC-C2-40K]-[OGF] by reversed phase HPLC.

Figure OGF3.3. MALDI-TOF spectrum of purified mono-[mPEG2-FMOC-C2-40K]-[OGF].

Figure OGF4.1. Typical CG71S reversed phase purification profile of mono-[mPEG-Butyraldehyde-30K]-[OGF].

Figure OGF4.2. Purity analysis of mono-[mPEG-Butyraldehyde-30K]-[OGF] by reversed phase HPLC.

Figure OGF5.1. Typical CG71S reversed phase purification profile of mono-[mPEG-epoxide-5K]-[OGF].

Figure OGF5.2. Purity analysis of mono-[mPEG-epoxide-5K]-[OGF] by reversed phase HPLC.

Figure OGF6.1. Typical CG71S reversed phase purification profile of mono-[mPEG-Butyraldehyde-10K]-[OGF].

Figure OGF6.2. Purity analysis of mono-[mPEG-Butyraldehyde-10K]-[OGF] by reversed phase HPLC.

Figure OGF7.1. Competition binding assay of OGF at human (A) μ opioid and (B) δ opioid receptors: effects of incubation treatment conditions.

Figure OGF7.2. Competition binding assay of OGF and PEG-OGF conjugates (released and unreleased) at human (A) μ opioid and (B) δ opioid receptors.

Figure OGF7.3. Competition binding assay of OGF and free PEGs at human (A) μ opioid and (B) δ opioid receptors.

Fig. INS1.1 Typical anion-exchange chromatography profile of the conjugation reaction mixture with partially acetylated insulin.

Fig. INS1.2 SDS-PAGE analysis of fractions containing dextran-butyrald-40K-insulin collected from anion-exchange chromatography.

Fig. INS1.3 Concentration of purified dextran-butyrald-40K-insulin by anion-exchange chromatography.

Fig. INS1.4. SDS-PAGE analysis of purified dextran-butyrald-40K-insulin.

Fig. INS1.5 Typical anion-exchange chromatography profile of the conjugation reaction mixture with non-acetylated insulin.

In vitro binding of the Insulin-dextran conjugate.

Figure INS3.1. Glucose levels after compound administration (0-8hr).

DETAILED DESCRIPTION

[0008] As used in this specification and the intended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a polymer" includes a single polymer as well as two or more of the same or different polymers; reference to "an optional excipient" or to "a pharmaceutically acceptable excipient" refers to a single optional excipient as well as two or more of the same or different optional excipients, and the like.

[0009] In describing and claiming one or more embodiments of the present invention, the following terminology will be used in accordance with the definitions described below.

[0010] As used herein, the terms "therapeutic peptide" and "therapeutic peptides" mean one or more peptides having demonstrated or potential use in treating, preventing, or ameliorating one or more diseases, disorders, or conditions in a subject in need thereof, as well as related peptides. These terms may be used to refer to therapeutic peptides prior to conjugation to a water-soluble polymer as well as following the conjugation. Therapeutic peptides include, but are not limited to, those disclosed herein, including in Table 1. Therapeutic peptides include peptides found to have use in treating, preventing, or ameliorating one or more diseases, disorders, or conditions after the time of filing of this application. Related peptides include fragments of therapeutic peptides, therapeutic peptide variants, and therapeutic peptide derivatives that retain some or all of the therapeutic activities of the therapeutic peptide. As will be known to one of skill in the art, as a general principle, modifications may be made to peptides that do not alter, or only partially abrogate, the properties and activities of those peptides. In some instances, modifications may be made that result in an increase in therapeutic activities. Thus, in the spirit of the invention, the terms "therapeutic peptide" or "therapeutic peptides" are meant to encompass modifications to the therapeutic peptides defined and/or disclosed herein that do not alter, only partially abrogate, or increase the therapeutic activities of the parent peptide.

[0011] The term "therapeutic activity" as used herein refers to a demonstrated or potential biological activity whose effect is consistent with a desirable therapeutic outcome in humans, or to desired effects in non-human mammals or in other species or organisms. A given therapeutic peptide may have one or more therapeutic activities, however the term

"therapeutic activities" as used herein may refer to a single therapeutic activity or multiple therapeutic activities. "Therapeutic activity" includes the ability to induce a response *in vivo*, and may be measured *in vivo* or *in vitro*. For example, a desirable effect may be assayed in cell culture, or by clinical evaluation, EC₅₀ assays, IC₅₀ assays, or dose response curves. *In vitro* or cell culture assays, for example, are commonly available and known to one of skill in the art for many therapeutic peptides as defined and/or disclosed herein. Therapeutic activity includes treatment, which may be prophylactic or ameliorative, or prevention of a disease, disorder, or condition. Treatment of a disease, disorder or condition can include improvement of a disease, disorder or condition by any amount, including elimination of a disease, disorder or condition.

[0012] As used herein, the terms "peptide," "polypeptide," and "protein," refer to polymers comprised of amino acid monomers linked by amide bonds. Peptides may include the standard 20 α -amino acids that are used in protein synthesis by cells (*i.e.* natural amino acids), as well as non-natural amino acids (non-natural amino acids may be found in nature, but not used in protein synthesis by cells, *e.g.*, ornithine, citrulline, and sarcosine, or may be chemically synthesized), amino acid analogs, and peptidomimetics. Spatola, (1983) in *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*, Weinstein, ed., Marcel Dekker, New York, p. 267. The amino acids may be D- or L-optical isomers. Peptides may be formed by a condensation or coupling reaction between the α -carbon carboxyl group of one amino acid and the amino group of another amino acid. The terminal amino acid at one end of the chain (amino terminal) therefore has a free amino group, while the terminal amino acid at the other end of the chain (carboxy terminal) has a free carboxyl group. Alternatively, the peptides may be non-linear, branched peptides or cyclic peptides. Moreover, the peptides may optionally be modified or protected with a variety of functional groups or protecting groups, including on the amino and/or carboxy terminus.

[0013] Amino acid residues in peptides are abbreviated as follows: Phenylalanine is Phe or F; Leucine is Leu or L; Isoleucine is Ile or I; Methionine is Met or M; Valine is Val or V; Serine is Ser or S; Proline is Pro or P; Threonine is Thr or T; Alanine is Ala or A; Tyrosine is Tyr or Y; Histidine is His or H; Glutamine is Gln or Q; Asparagine is Asn or N; Lysine is Lys or K; Aspartic Acid is Asp or D; Glutamic Acid is Glu or E; Cysteine is Cys or C; Tryptophan is Trp or W; Arginine is Arg or R; and Glycine is Gly or G.

[0014] The terms "therapeutic peptide fragment" or "fragments of therapeutic peptides" refer to a polypeptide that comprises a truncation at the amino-terminus and/or a truncation at the carboxyl-terminus of a therapeutic peptide as defined herein. The terms

"therapeutic peptide fragment" or "fragments of therapeutic peptides" also encompasses amino-terminal and/or carboxyl-terminal truncations of therapeutic peptide variants and therapeutic peptide derivatives. Therapeutic peptide fragments may be produced by synthetic techniques known in the art or may arise from *in vivo* protease activity on longer peptide sequences. It will be understood that therapeutic peptide fragments retain some or all of the therapeutic activities of the therapeutic peptides.

[0015] As used herein, the terms "therapeutic peptide variants" or "variants of therapeutic peptides" refer to therapeutic peptides having one or more amino acid substitutions, including conservative substitutions and non-conservative substitutions, amino acid deletions (either internal deletions and/or C- and/or N- terminal truncations), amino acid additions (either internal additions and/or C- and/or N- terminal additions, *e.g.*, fusion peptides), or any combination thereof. Variants may be naturally occurring (*e.g.* homologs or orthologs), or non-natural in origin. The term "therapeutic peptide variants" may also be used to refer to therapeutic peptides incorporating one or more non-natural amino acids, amino acid analogs, and peptidomimetics. It will be understood that, in accordance with the invention, therapeutic peptide fragments retain some or all of the therapeutic activities of the therapeutic peptides.

[0016] The terms "therapeutic peptide derivatives" or "derivatives of therapeutic peptides" as used herein refer to therapeutic peptides, therapeutic peptide fragments, and therapeutic peptide variants that have been chemically altered other than through covalent attachment of a water-soluble polymer. It will be understood that, in accordance with the invention, therapeutic peptide derivatives retain some or all of the therapeutic activities of the therapeutic peptides.

[0017] As used herein, the terms "amino terminus protecting group" or "N-terminal protecting group," "carboxy terminus protecting group" or "C-terminal protecting group;" or "side chain protecting group" refer to any chemical moiety capable of addition to and optionally removal from a functional group on a peptide (*e.g.*, the N-terminus, the C-terminus, or a functional group associated with the side chain of an amino acid located within the peptide) to allow for chemical manipulation of the peptide.

[0018] "PEG," "polyethylene glycol" and "poly(ethylene glycol)" as used herein, are interchangeable and encompass any nonpeptidic water-soluble poly(ethylene oxide). Typically, PEGs for use in accordance with the invention comprise the following structure $-(OCH_2CH_2)_n-$ where (n) is 2 to 4000. As used herein, PEG also includes

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"-CH₂CH₂-O(CH₂CH₂O)_n-CH₂CH₂-" and "-(OCH₂CH₂)_nO-", depending upon whether or not the terminal oxygens have been displaced. Throughout the specification and claims, it should be remembered that the term "PEG" includes structures having various terminal or "end capping" groups and so forth. The term "PEG" also means a polymer that contains a majority, that is to say, greater than 50%, of -OCH₂CH₂- repeating subunits. With respect to specific forms, the PEG can take any number of a variety of molecular weights, as well as structures or geometries such as "branched," "linear," "forked," "multifunctional," and the like, to be described in greater detail below.

[0019] The terms "end-capped" and "terminally capped" are interchangeably used herein to refer to a terminal or endpoint of a polymer having an end-capping moiety. Typically, although not necessarily, the end-capping moiety comprises a hydroxy or C₁₋₂₀ alkoxy group, more preferably a C₁₋₁₀ alkoxy group, and still more preferably a C₁₋₅ alkoxy group. Thus, examples of end-capping moieties include alkoxy (*e.g.*, methoxy, ethoxy and benzyloxy), as well as aryl, heteroaryl, cyclo, heterocyclo, and the like. It must be remembered that the end-capping moiety may include one or more atoms of the terminal monomer in the polymer [*e.g.*, the end-capping moiety "methoxy" in CH₃O(CH₂CH₂O)_n- and CH₃(OCH₂CH₂)_n]. In addition, saturated, unsaturated, substituted and unsubstituted forms of each of the foregoing are envisioned. Moreover, the end-capping group can also be a silane. The end-capping group can also advantageously comprise a detectable label. When the polymer has an end-capping group comprising a detectable label, the amount or location of the polymer and/or the moiety (*e.g.*, active agent) to which the polymer is coupled can be determined by using a suitable detector. Such labels include, without limitation, fluorescers, chemiluminescers, moieties used in enzyme labeling, colorimetric (*e.g.*, dyes), metal ions, radioactive moieties, gold particles, quantum dots, and the like. Suitable detectors include photometers, films, spectrometers, and the like. The end-capping group can also advantageously comprise a phospholipid. When the polymer has an end-capping group comprising a phospholipid, unique properties are imparted to the polymer and the resulting conjugate. Exemplary phospholipids include, without limitation, those selected from the class of phospholipids called phosphatidylcholines. Specific phospholipids include, without limitation, those selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteoylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine, and lecithin.

[0020] The term "targeting moiety" is used herein to refer to a molecular structure that helps the conjugates of the invention to localize to a targeting area, *e.g.*, help enter a cell,

or bind a receptor. Preferably, the targeting moiety comprises of vitamin, antibody, antigen, receptor, DNA, RNA, sialyl Lewis X antigen, hyaluronic acid, sugars, cell specific lectins, steroid or steroid derivative, RGD peptide, ligand for a cell surface receptor, serum component, or combinatorial molecule directed against various intra- or extracellular receptors. The targeting moiety may also comprise a lipid or a phospholipid. Exemplary phospholipids include, without limitation, phosphatidylcholines, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, and phosphatidylethanolamine. These lipids may be in the form of micelles or liposomes and the like. The targeting moiety may further comprise a detectable label or alternately a detectable label may serve as a targeting moiety. When the conjugate has a targeting group comprising a detectable label, the amount and/or distribution/location of the polymer and/or the moiety (e.g., active agent) to which the polymer is coupled can be determined by using a suitable detector. Such labels include, without limitation, fluorescers, chemiluminescers, moieties used in enzyme labeling, colorimetric (e.g., dyes), metal ions, radioactive moieties, gold particles, quantum dots, and the like.

[0021] "Non-naturally occurring" with respect to a polymer as described herein, means a polymer that in its entirety is not found in nature. A non-naturally occurring polymer of the invention may, however, contain one or more monomers or segments of monomers that are naturally occurring, so long as the overall polymer structure is not found in nature.

[0022] The term "water soluble" as in a "water-soluble polymer" is any polymer that is soluble in water at room temperature. Typically, a water-soluble polymer will transmit at least about 75%, more preferably at least about 95%, of light transmitted by the same solution after filtering. On a weight basis, a water-soluble polymer will preferably be at least about 35% (by weight) soluble in water, more preferably at least about 50% (by weight) soluble in water, still more preferably about 70% (by weight) soluble in water, and still more preferably about 85% (by weight) soluble in water. It is most preferred, however, that the water-soluble polymer is about 95% (by weight) soluble in water or completely soluble in water.

[0023] "Hydrophilic," e.g, in reference to a "hydrophilic polymer," refers to a polymer that is characterized by its solubility in and compatability with water. In non-cross linked form, a hydrophilic polymer is able to dissolve in, or be dispersed in water. Typically, a hydrophilic polymer possesses a polymer backbone composed of carbon and hydrogen, and generally possesses a high percentage of oxygen in either the main polymer backbone or in

pendent groups substituted along the polymer backbone, thereby leading to its "water-loving" nature. The water-soluble polymers of the present invention are typically hydrophilic, *e.g.*, non-naturally occurring hydrophilic.

[0024] Molecular weight in the context of a water-soluble polymer, such as PEG, can be expressed as either a number average molecular weight or a weight average molecular weight. Unless otherwise indicated, all references to molecular weight herein refer to the weight average molecular weight. Both molecular weight determinations, number average and weight average, can be measured using gel permeation chromatography or other liquid chromatography techniques. Other methods for measuring molecular weight values can also be used, such as the use of end-group analysis or the measurement of colligative properties (*e.g.*, freezing-point depression, boiling-point elevation, and osmotic pressure) to determine number average molecular weight, or the use of light scattering techniques, ultracentrifugation or viscometry to determine weight average molecular weight. The polymers of the invention are typically polydisperse (*i.e.*, number average molecular weight and weight average molecular weight of the polymers are not equal), possessing low polydispersity values of preferably less than about 1.2, more preferably less than about 1.15, still more preferably less than about 1.10, yet still more preferably less than about 1.05, and most preferably less than about 1.03.

[0025] The term "active" or "activated" when used in conjunction with a particular functional group refers to a reactive functional group that reacts readily with an electrophile or a nucleophile on another molecule. This is in contrast to those groups that require strong catalysts or highly impractical reaction conditions in order to react (*i.e.*, a "non-reactive" or "inert" group).

[0026] As used herein, the term "functional group" or any synonym thereof is meant to encompass protected forms thereof as well as unprotected forms.

[0027] The terms "spacer moiety," "linkage" and "linker" are used herein to refer to an atom or a collection of atoms optionally used to link interconnecting moieties such as a terminus of a polymer segment and a therapeutic peptide or an electrophile or nucleophile of a therapeutic peptide. The spacer moiety may be hydrolytically stable or may include a physiologically hydrolyzable or enzymatically degradable linkage. Unless the context clearly dictates otherwise, a spacer moiety optionally exists between any two elements of a compound (*e.g.*, the provided conjugates comprising a residue of a therapeutic peptide and a water-soluble polymer that can be attached directly or indirectly through a spacer moiety).

[0028] A "monomer" or "mono-conjugate," in reference to a polymer conjugate of a therapeutic peptide, refers to a therapeutic peptide having only one water-soluble polymer molecule covalently attached thereto, whereas a therapeutic peptide "dimer" or "di-conjugate" is a polymer conjugate of a therapeutic peptide having two water-soluble polymer molecules covalently attached thereto, and so forth.

[0029] "Alkyl" refers to a hydrocarbon, typically ranging from about 1 to 15 atoms in length. Such hydrocarbons are preferably but not necessarily saturated and may be branched or straight chain, although typically straight chain is preferred. Exemplary alkyl groups include methyl, ethyl, propyl, butyl, pentyl, 2-methylbutyl, 2-ethylpropyl, 3-methylpentyl, and the like. As used herein, "alkyl" includes cycloalkyl as well as cycloalkylene-containing alkyl.

[0030] "Lower alkyl" refers to an alkyl group containing from 1 to 6 carbon atoms, and may be straight chain or branched, as exemplified by methyl, ethyl, *n*-butyl, *i*-butyl, and *t*-butyl.

[0031] "Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon chain, including bridged, fused, or spiro cyclic compounds, preferably made up of 3 to about 12 carbon atoms, more preferably 3 to about 8 carbon atoms. "Cycloalkylene" refers to a cycloalkyl group that is inserted into an alkyl chain by bonding of the chain at any two carbons in the cyclic ring system.

[0032] "Alkoxy" refers to an -O-R group, wherein R is alkyl or substituted alkyl, preferably C₁₋₆ alkyl (*e.g.*, methoxy, ethoxy, propyloxy, and so forth).

[0033] The term "substituted" as in, for example, "substituted alkyl," refers to a moiety (*e.g.*, an alkyl group) substituted with one or more noninterfering substituents, such as, but not limited to: alkyl; C₃₋₈ cycloalkyl, *e.g.*, cyclopropyl, cyclobutyl, and the like; halo, *e.g.*, fluoro, chloro, bromo, and iodo; cyano; alkoxy, lower phenyl; substituted phenyl; and the like. "Substituted aryl" is aryl having one or more noninterfering groups as a substituent. For substitutions on a phenyl ring, the substituents may be in any orientation (*i.e.*, ortho, meta, or para).

[0034] "Noninterfering substituents" are those groups that, when present in a molecule, are typically nonreactive with other functional groups contained within the molecule.

[0035] "Aryl" means one or more aromatic rings, each of 5 or 6 core carbon atoms. Aryl includes multiple aryl rings that may be fused, as in naphthyl or unfused, as in biphenyl.

Aryl rings may also be fused or unfused with one or more cyclic hydrocarbon, heteroaryl, or heterocyclic rings. As used herein, "aryl" includes heteroaryl.

[0036] "Heteroaryl" is an aryl group containing from one to four heteroatoms, preferably sulfur, oxygen, or nitrogen, or a combination thereof. Heteroaryl rings may also be fused with one or more cyclic hydrocarbon, heterocyclic, aryl, or heteroaryl rings.

[0037] "Heterocycle" or "heterocyclic" means one or more rings of 5-12 atoms, preferably 5-7 atoms, with or without unsaturation or aromatic character and having at least one ring atom that is not a carbon. Preferred heteroatoms include sulfur, oxygen, and nitrogen.

[0038] "Substituted heteroaryl" is heteroaryl having one or more noninterfering groups as substituents.

[0039] "Substituted heterocycle" is a heterocycle having one or more side chains formed from noninterfering substituents.

[0040] An "organic radical" as used herein shall include alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, and substituted aryl.

[0041] "Electrophile" and "electrophilic group" refer to an ion or atom or collection of atoms, that may be ionic, having an electrophilic center, *i.e.*, a center that is electron seeking, capable of reacting with a nucleophile.

[0042] "Nucleophile" and "nucleophilic group" refers to an ion or atom or collection of atoms that may be ionic having a nucleophilic center, *i.e.*, a center that is seeking an electrophilic center or with an electrophile.

[0043] A "physiologically cleavable" or "hydrolyzable" or "degradable" bond is a bond that reacts with water (*i.e.*, is hydrolyzed) under physiological conditions. The tendency of a bond to hydrolyze in water will depend not only on the general type of linkage connecting two central atoms but also on the substituents attached to these central atoms. Appropriate hydrolytically unstable or weak linkages include but are not limited to carboxylate ester, phosphate ester, anhydrides, acetals, ketals, acyloxyalkyl ether, imines, orthoesters, peptides and oligonucleotides.

[0044] "Releasably attached," *e.g.*, in reference to a therapeutic peptide releasably attached to a water-soluble polymer, refers to a therapeutic peptide that is covalently attached via a linker that includes a degradable linkage as disclosed herein, wherein upon degradation (*e.g.*, hydrolysis), the therapeutic peptide is released. The therapeutic peptide thus released will typically correspond to the unmodified parent or native therapeutic peptide, or may be

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slightly altered, *e.g.*, possessing a short organic tag. Preferably, the unmodified parent therapeutic peptide is released.

[0045] An "enzymatically degradable linkage" means a linkage that is subject to degradation by one or more enzymes.

[0046] A "hydrolytically stable" linkage or bond refers to a chemical bond, typically a covalent bond, that is substantially stable in water, that is to say, does not undergo hydrolysis under physiological conditions to any appreciable extent over an extended period of time. Examples of hydrolytically stable linkages include, but are not limited to, the following: carbon-carbon bonds (*e.g.*, in aliphatic chains), ethers, amides, urethanes, and the like. Generally, a hydrolytically stable linkage is one that exhibits a rate of hydrolysis of less than about 1-2% per day under physiological conditions. Hydrolysis rates of representative chemical bonds can be found in most standard chemistry textbooks. It must be pointed out that some linkages can be hydrolytically stable or hydrolyzable, depending upon (for example) adjacent and neighboring atoms and ambient conditions. One of ordinary skill in the art can determine whether a given linkage or bond is hydrolytically stable or hydrolyzable in a given context by, for example, placing a linkage-containing molecule of interest under conditions of interest and testing for evidence of hydrolysis (*e.g.*, the presence and amount of two molecules resulting from the cleavage of a single molecule). Other approaches known to those of ordinary skill in the art for determining whether a given linkage or bond is hydrolytically stable or hydrolyzable can also be used.

[0047] The terms "pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to an excipient that may optionally be included in the compositions of the invention and that causes no significant adverse toxicological effects to the patient.

[0048] "Pharmacologically effective amount," "physiologically effective amount," and "therapeutically effective amount" are used interchangeably herein to mean the amount of a polymer-(therapeutic peptide) conjugate that is needed to provide a desired level of the conjugate (or corresponding unconjugated therapeutic peptide) in the bloodstream or in the target tissue. The precise amount will depend upon numerous factors, *e.g.*, the particular therapeutic peptide, the components and physical characteristics of the therapeutic composition, intended patient population, individual patient considerations, and the like, and can readily be determined by one skilled in the art, based upon the information provided herein.

[0049] "Multi-functional" means a polymer having three or more functional groups contained therein, where the functional groups may be the same or different. Multi-functional polymeric reagents of the invention will typically contain from about 3-100 functional groups, or from 3-50 functional groups, or from 3-25 functional groups, or from 3-15 functional groups, or from 3 to 10 functional groups, or will contain 3, 4, 5, 6, 7, 8, 9 or 10 functional groups within the polymer backbone. A "difunctional" polymer means a polymer having two functional groups contained therein, either the same (*i.e.*, homodifunctional) or different (*i.e.*, heterodifunctional).

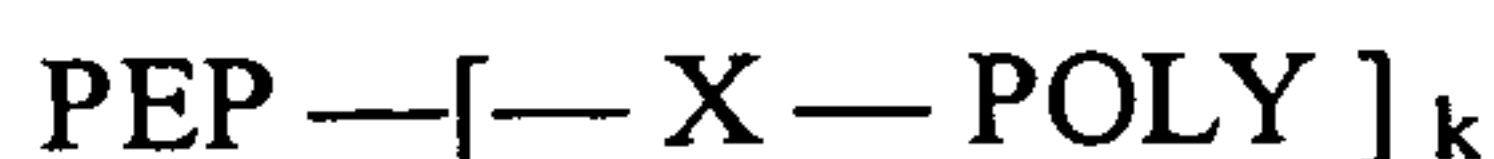
[0050] The terms "subject," "individual," or "patient" are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, murines, rodents, simians, humans, farm animals, sport animals, and pets.

[0051] "Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

[0052] "Substantially" (unless specifically defined for a particular context elsewhere or the context clearly dictates otherwise) means nearly totally or completely, for instance, satisfying one or more of the following: greater than 50%, 51% or greater, 75% or greater, 80% or greater, 90% or greater, and 95% or greater of the condition.

[0053] Unless the context clearly dictates otherwise, when the term "about" precedes a numerical value, the numerical value is understood to mean the stated numerical value and also $\pm 10\%$ of the stated numerical value.

[0054] Turning now to one or more aspects of the invention, conjugates are provided, the conjugates comprising a therapeutic peptide covalently attached (either directly or through a spacer moiety or linker) to a water-soluble polymer. The conjugates generally have the following formula:



wherein PEP is a therapeutic peptide as defined herein, X is a covalent bond or is a spacer moiety or linker, POLY is a water soluble polymer, and k is an integer ranging from 1-10, preferably 1-5, and more preferably 1-3.

Therapeutic Peptides

[0055] As previously stated, the conjugates of the invention comprise a therapeutic peptide as disclosed and/or defined herein. Therapeutic peptides include those currently

known to have demonstrated or potential use in treating, preventing, or ameliorating one or more diseases, disorders, or conditions in a subject in need thereof as well as those discovered after the filing of this application. Therapeutic peptides also include related peptides.

[0056] In some embodiments of the invention, PEP is a therapeutic peptide selected from the group consisting of carperitide; alpha-neoendorphin; 348U87; A-3847; A-4114; A-68552; A-75998; A-84861; AN-1792; AAMP-1; exenatide; AC-625; ACE-inhibitors, Aventis; ACE-inhibitors, SRI; ACTH, Amgen; rupintrivir; AI-102; AI-202; NeuroVax; AI-402; AI-502; AIDS therapeutic vaccine, Repl; AIDS therapy, Inst Pasteur; AIDS vaccine, J&J; AIDS vaccine, Liposome Co; AIDS vaccine, Arana; AIDS vaccine, Peptimmune; AIDS vaccine, Sanofi Past-3; AIDS vaccine, Protherics; AIDS vaccine, SSVI; AIDS vaccine, SWFBR; AIDS vaccine, United-1; AIDS vaccine, United-2; AIDS vaccine-2, Yokohama; AIDS vaccine-3, NIH; AIDS vaccine-4, NIH; AIT-083; teduglutide; Skelite; Allotrap-2702; Alzheimer's imaging agent, Dia; AM-425; AN-238; AnergiX.RA; AnervaX.RA; AS-109; AV-9; AZM-134; addressin, Lilly; allergy vaccine, BioResearch; ambamustine; amylin antagonists, Amylin; anaritide analogues, Bio-Mega; anaritide, Bayer; anaritide, Bristol; anaritide, Aventis-2; anaritide, Astellas; anaritide, GlaxoSmithKline-2; anaritide, Aventis-1; anaritide, Mitsubishi Tanabe; anaritide, Novartis; anaritide, OmniGene; anaritide, Sankyo; anaritide, Scios; angiotensin II antagonists; anti-inflammatories, Affymax; anti-inflammatory peptide, BTG; anti-integrin peptides, Burnha; anti-TCR vaccines; antiallergy peptides, Ajin; antiallergy vaccine, Acambis-1; anticancer matrix, Telios; anticancer peptides, Micrologix; antinflammins; antifungal peptides, BTG; antifungal tripeptides, BTG; antiGnRH immunogen, Apton; Gastrimmune; antirenin vaccine; antirheumatic peptides, Acambis; antithrombin polypeptides; antiviral peptide, Bio-Mega; antiviral peptides, Non-indust; antiviral peptides, Yeda; apolipoprotein, NeuroSearch; apoptosis technology, Receptag; BCH-143; arthritis antigen; atrial natriuretic peptide, Ph; atrial natriuretic peptide, Ra; avorelin; B-956; BCH-2687; BCH-2763; frakefamide; BIM-22015; BIM-26028; BIM-44002; BIO-1006; BIO-1211; Bio-Flow; BPC-15; Britistatin; BST-2001; bivalirudin; bombesin antagonist; brain natriuretic peptide; brain natriuretic peptide, Phar; C-peptide analogues, UCB; C5a antagonist, Abbott; C68-22; Casocidin, Pharis; CBT-101; CCK(27-32), Organon; CD4, Genelabs; CD4-liposome conjugate, Sumito; CEE-04-420; CEP-079; CEP-903; CETP vaccine, Avant; mifamurtide; CGRP analogues, Asahi Chemical; CGRP, CSL; CGRP, Celltech; CGRP, Novartis; CGRP, Asahi Kasei; CGRP, SmithKline Beecham; CGRP, Unigene; rusalatide acetate; CI-782; CKS-17; CMV peptides, City of Hope; CNTF, Fidia; CP-95253; corticorelin acetate; CT-

112, BTG; CT-1508; CTAP-III, Creative; CTP-37; PMD-2850; CVFM; CVT-857; CY-725; CY-726; CYC101; CYC103; CYC102; calcitonin, Peptitrol; calcitonin, Rockefeller; calciseptine; calcitonin analogues, SB; calcitonin, Amgen; calcitonin, Armour; calcitonin, Beaufour; calcitonin, Inhale; calcitonin, Bridgelock; calcitonin, microspheres; calcitonin, Nazdel; calcitonin, Novartis; calcitonin, nasal, Novartis; calcitonin, oral, Mannkind; calcitonin, Panoderm; calcitonin, Pharma Bissendorf; calcitonin, Pharms; calcitonin, Anesiva; calcitonin, Aventis; calcitonin, Teijin; calcitonin, Teikoku; calcitonin, TheraTech; calcitonin, Yissum; calf thymus derived peptides; calpain inhibitors, ResCo; calphobindin I; cancer vaccines, Argonex; cargutocin; casokefamide; cekropin-P; chemokines, Dompe; tasidotin hydrochloride; ceruletide diethylamine; ceruletide, Fukuoka; cetorelix acetate; chimaeric peptides, NIH; cholecystokinin, Ferring; collagenase IV inhibitors; collamers; contraceptive vaccine, Cephalo; contraceptive vaccine, Novarti; corplatin S compounds; corticoliberin, Pharma Bissend; corticoliberin, Salk; corticoliberin, Unigene; corticoliberin, Vanderbilt; D-21775; D-22213; Demegel; DAP inhibitors; DP-640; DP-107; DSIP; DU-728; Dynorphin A; daniplestim; defensins, LSB; desirudin; detirelix; dialytic oligopeptides; disagregin; E-2078; ECE inhibitor, SmithKline; ELS-1; EMD-73495; Enhancins; ecallantide; ES-1005; ES-305; echistatin; efegatran; eglin derivatives; elafin derivatives; elcatonin; eledoisin; encapsulated insulin, INSERM; endorphin, β -, Antigenics; endorphin, pancreatic; endorphin, β -, Mitsubishi; endorphin, β -, Amgen; endothelial cell growth factor; endothelin antagonists, ResCo; eptifibatide; examorelin; Factor VIII fragments, Pharma; FG-002; FG-003; FG-004; FG-005; FR-113680; FTS-Zn; fibrin-binding peptides, ISIS; fibronectin inhibitors, AstraZ; fibronectin-related peptide; follicular regulatory protein; G-4120; GAG-V3-VDP vaccine, Vern; GDL-peptides, Cytogen; EP-51216; GLP-1 + exendin-4, NIH; GLP-1, Amylin; GLP-1, TheraTech; GM-1986; GM-CSF blocker, Hospira; GnRH-associated peptide; GPCR antagonists, NIH; GPIIb/IIIa antags, Selectide; GRF1-44; GRF, Lilly; GT2342; GT2501; GYKI-14451; galanin; gastrin antagonists; gastrin, Novo; glaspimod; glicentin; glucagon antagonists, Synvista; glucagon, Lilly; glucagon, ZymoGenetics; glucagon-121; glycoprotein 1balph fragments; gonadorelin analogues, Syntex; gonadorelin antagonist, Ortho; gonadorelin preparations; gonadorelin, Arana; gonadorelin-MDP vaccine; goralatide; gp120-V3 peptides; growth factor peptides, Biothe; ENMD-0996; H-142, AstraZeneca; Her-2/Neu peptides, GSK; herpes simplex vaccine, Wistar; AIDS vaccine, Cel-Sci; HP-101; vitespen; HSV vaccine, Cel-Sci; HSV-1gD/vaccinia vaccine; heparin binding peptides, NCI; hepatitis-B receptor; hepatitis-B vaccine, Tokyo; hepatitis-B vaccine, Protherics; hepatitis-B vaccine-2, BTG; hirugen; I5B2; iseganan hydrochloride; IgE

peptides; IgG binding factor, Hoechst Ma; netamiftide; Insulin Aspart; Zorcell; icrocaptide; icanibant; immunomodulating peptides, Bio; infertility, E-TRANS; influenza vaccine, GSK-1; influenza vaccine, Yeda; instimulin; insulin analogue, Lilly; insulin analogues, Lilly; insulin analogues, Scios; insulin formulation, Pasteur; insulin glargine; insulin, Nektar, inhaled; insulin molecules, Novo; insulin oral, Inovax; insulin transdermal; insulin, Organon; insulin, ocular; insulin, AERx; insulin, AutoImmune; insulin, BEODAS; insulin, Biobras; insulin, Ferring Pharma; insulin, CJ Corp; insulin, Chiron; insulin, Chong Kun Dang; insulin, Sanofi Pasteur; insulin, Di-Arg, Hoechst Mario; insulin, E-TRANS; insulin, Forest; insulin, Hoechst, semisynth; insulin, Lilly, iodinated; insulin, Genentech, recombi; insulin, Provalis; insulin, Novartis; insulin, nasal; insulin, Ohio; insulin, Nazdel; insulin, Novo, synthetic; insulin, nasal, Novo Nordisk; insulin, oral; insulin, buccal, Generex; insulin, Arana; insulin, Anesiva; insulin, Procter & Gamble; insulin, Qmax; insulin, Innovata; insulin, Roche; insulin, recombinant, Aventis; insulin, Shionogi; insulin, Shire; insulin, Spiros; insulin, SRI; insulin, Structured Biological; insulin, semisynthetic, Biobra; insulin, synthetic, Powerpatch; insulin, Zymo, recombinant; insulin, monocomponent, Novo; IL-1 receptor antagonist, Affym; interleukin-1 β , Sclavo; interleukin-8 antags, Select; J015X; J018X; AG-1776; KNI-549; pralmorelin; KPI-022; katacalcin; ketomethylureas; L-346670; L-364210; L-659837; L-693549; L-709049; L-75; L-761191; L-histidyl peptides; LDV-containing peptides, Antiso; LEAPS-101; LHRH antagonists, Abbott; PD-6735; Lys-Phe; hLF1-11; lagatide; laminin A peptides, NIH; laminin technology, NIH; lanreotide; leuprolide acetate, Atrigel; leuprorelin, Takeda; leuprorelin, Merck Serono; leuprorelin, DUROS; leuprorelin, Powerpatch; lipid-linked anchor technology; lysozyme metabolites, SPA; MCI-826; omiganan pentahydrochloride; MBP, ImmuLogic; MCI-536; MDL-104238; MDL-28050; Metascan; MMP inhibitors, NIH; MN-10006; MOL-376; MR-988; MSH derivatives; MUC-1 vaccine, Pittsburgh; malaria vaccine, Axis; malaria vaccine, Vernalis; malaria vaccine, Cel-Sci; malaria vaccine, Roche; melanoma vaccine, Nobilon; meningitis vaccine, Acambis; mertiatide; metkephamide; metorphamide; monocyte chemotactic factor; montirelin hydrate; motyline; murabutide; muramyl dipeptide derivatives; myelopid; N-acetyl[Leu-28Leu-31]NPY24-36; N-carbobenzoxy peptides; NAGA; tiplimotide; opebecan; insulin detemir; liraglutide; Nona CCK; NP-06; NPC-18545; Nva-FMDP; nacartocin; natural peptide BPC, Pliva; nerve growth factor, Synergen; nesiritide citrate; neuropeptides, Protherics; neuropeptides, Pfizer; neurotensin, Merck; neurotrophic factors, CereMedix; nifalutide; CL22, Innovata; nootropic, Yakult; nociceptin, Euroscreen; Org-2766; Org-30035; OSA peptides, Osteopharm; octreotide; opioid peptides, Unigene; osteogenic growth peptide; osteoporosis

peptides, Telios; oxyntomodulin; P-113, Demegen; PACAP 27; PAPP; PD-83176; PD-122264; PD-132002; PEP-F; Penetratin; Peptigen agents; Phe-X-Gly, ResCo; PL-030; PN1 antagonists, Allelix; POL-443; POL-509; PPA, ResCo; PR-39; Prodaptin-M technology; PSP; tigapotide trifluate; PT-14; PT-5; semparatide; PTL-78968; parathyroid hormone fragments; pancreastatin; papillomavirus vaccine constru; parathyroid antagonist, Merck; enfuvirtide; peptide heterodimers, Cortech; peptide imaging, Diatide; pentapeptide 6A; pentigetide; peptide analogues, ResCo; peptide 6, NY Medical College; peptide G, Arana; peptide inhibitors, ICRT; peptide T analogue, Carl; peptide T analogues; peptide T, Arana; peptide/drug vehicle, BTG; peptides, Sanofi-Aventis; peptides, Scios; peptides, Yeda; peptomers, NIH; pertussis vaccine-1, TRION; ph-914; ph-921; ph-9313; phospholipase inhibitors, Poli; prolactin, Genzyme; pramlintide; pranlukast; proinsulin, Lilly; proinsulin-2, Novartis; progenitor cell inhibitor, RCT; proinsulin fragments, Lilly; proinsulin analogues, Lilly; proinsulin, Genentech; prostate cancer vaccine, United; prostate cancer vaccine, GSK; protirelin; protirelin, Takeda; Pseudomonas elastase inhibitor; QRS-10-001; QRS-5-005; Quilimmune-M; Retropep; RGD peptides; RHAMM targeting peptides, Cange; Ro-25-1553; RP-128; RSV vaccine, Avant; RSV vaccine, Acambis; RWJ-51438; TRH, Ferring; renin inhibitors, Pfizer-2; relaxin, Novartis; renin inhibitors, INSERM; romurtide; rubella vaccine, Protherics; S-17162; S-2441; SC-40476; SC-44900; SDZ-CO-611; SIDR-1204; SK&F-101926; SK&F-110679; SLPI, Synergen; edotreotide; SP-1; SPAAT; SR-41476; SR-42128; SR-42654; SRIF-A; Streptococcus A vaccine, ID; Streptococcus A vaccine, SIGA; calcitonin, PPL; salmon calcitonin, Therapicon; sermorelin, Kabi; saralasin acetate; secretin, Eisai; secretin, Ferring; secretin, Wakunaga; sermorelin, Novartis; sermorelin peptides, Sanofi-Ave; sermorelin, Antigenics; sermorelin, Molecular Genetics; sermorelin acetate, Merck Ser; sermorelin, Sanofi-Aventis; sermorelin, Unigene; sinapultide; sleep inducing peptide, Bissen; small peptides, Centocor; somatoliberin, Takeda; PTR-3173; somatostatin analogue, Shira; somatostatin analogues, Merck; somatostatin analogues, Tulane; somatostatin derivatives; somatostatin, Merck Serono; somatostatin, Ferring; somatostatin, Arana; somatostatin, Sanofi-Synthelabo; somatostatin, BayerScheringPhar; T-205; Streptococcus A vaccine, Active; sulglycotide; syndyphalin; synthetic p16, Dundee; synthetic peptide BPC, Pliva; synthetic peptides, ICRT; T cell receptor peptide vaccin; T-118; T-786; T-cell receptor peptides, Xoma; T22; TA-3712; TASP inhibitors; TCMP-80; Tc-99m P215; Tc-99m P483H; Tc-99m P773; Tc-99m depreotide; Tc-99m-P280; TEI-1345; THF, Pfizer; Theradigm-HBV; Theradigm-HIV; Theratides; Stimuvax; ThGRF 1-29; tesamorelin acetate; ThromboScan; TIMP, Creative BioMolecules; TIMP, Sanofi-Aventis;

TJN-135; TNF inhibitor, Genelabs; TP-9201; TRH analogues, Roche; TRH, Daiichi; TRH, Japan Tobacco; TRH, Medicis; TRH, Arana; TRH-R, Medical Research Council; TT-235; tabilautide; tendamistat; terlipressin; terlipressin, Nordic; teverelix; INKP-2001; thymic peptide; thymoleptic peptides; thymopentin; thymopentin analogues; thymosin alpha-2; thymosin β 4; thymosin fraction 5; tolerizing peptide, Acambis; trefoil peptides, ICRT; triletide; tuftsin, Abic; tuftsin, Sclavo; Type I diabetes vaccine, RCT; tyrosine kinase antags, ICRT; tyrosine-containing dipeptides; UA 1041; UA 1155; UA 1248; Uroguanylin, Pharis; urodilatin; V.F.; VIC, Astellas; VIP analogues, TRION; VIP derivative, Eisai; VIP fusion protein, Kabi; vapreotide, immediate-release; varicella vaccine, ResCo; vitronectin receptor antag; vicalcins; Mycoprex; YIGSR-Stealth; Yisum Project No. 11607; Pharmaprojects No. 1088; Pharmaprojects No. 1113; Pharmaprojects No. 1269; Pharmaprojects No. 1448; Pharmaprojects No. 1507; Pharmaprojects No. 1573; Pharmaprojects No. 1583; Pharmaprojects No. 1626; Pharmaprojects No. 1779; Pharmaprojects No. 1797; Pharmaprojects No. 1843; Pharmaprojects No. 1876; Pharmaprojects No. 1913; Pharmaprojects No. 1939; Pharmaprojects No. 1994; Pharmaprojects No. 2043; Pharmaprojects No. 2044; Pharmaprojects No. 2063; Pharmaprojects No. 2100; Pharmaprojects No. 2122; Pharmaprojects No. 2202; Pharmaprojects No. 2363; Pharmaprojects No. 2388; Pharmaprojects No. 2425; Pharmaprojects No. 2476; Pharmaprojects No. 2527; Pharmaprojects No. 2560; Pharmaprojects No. 2571; Pharmaprojects No. 2825; Pharmaprojects No. 2866; C-type natriuretic peptide, Sun; Pharmaprojects No. 2909; Pharmaprojects No. 2912; Pharmaprojects No. 2913; Pharmaprojects No. 3009; Pharmaprojects No. 3020; Pharmaprojects No. 3051; Pharmaprojects No. 3127; Pharmaprojects No. 3284; Pharmaprojects No. 3341; Pharmaprojects No. 3392; Pharmaprojects No. 3393; Pharmaprojects No. 3400; Pharmaprojects No. 3415; Pharmaprojects No. 3472; Pharmaprojects No. 3503; Pharmaprojects No. 3581; Pharmaprojects No. 3597; Pharmaprojects No. 3654; Pharmaprojects No. 3667; Pharmaprojects No. 3777; Pharmaprojects No. 3862; Pharmaprojects No. 3863; Pharmaprojects No. 3891; Pharmaprojects No. 3903; Pharmaprojects No. 3939; Pharmaprojects No. 3963; Pharmaprojects No. 3989; Pharmaprojects No. 4004; Pharmaprojects No. 4093; Pharmaprojects No. 4098; Pharmaprojects No. 4113; Pharmaprojects No. 4182; Pharmaprojects No. 4209; Pharmaprojects No. 4246; Pharmaprojects No. 4251; Pharmaprojects No. 4300; Pharmaprojects No. 4323; Pharmaprojects No. 4347; Pharmaprojects No. 4367; Pharmaprojects No. 4385; Pharmaprojects No. 4402; Pharmaprojects No. 4445;

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Pharmaprojects No. 4544; Pharmaprojects No. 4625; Pharmaprojects No. 4626; Pharmaprojects No. 4643; Pharmaprojects No. 4705; Pharmaprojects No. 4708; Pharmaprojects No. 4766; GHRP-1, QLT; Pharmaprojects No. 4865; Pharmaprojects No. 491; Pharmaprojects No. 4915; Pharmaprojects No. 4936; Pharmaprojects No. 494; Hematide; Pharmaprojects No. 4975; Pharmaprojects No. 5048; Pharmaprojects No. 5055; Pharmaprojects No. 5076; anti-HER2/neu mimetic, Cyclacel; Pharmaprojects No. 5131; Pharmaprojects No. 5173; Pharmaprojects No. 5181; Pharmaprojects No. 5200; Pharmaprojects No. 5216; Pharmaprojects No. 5292; Pharmaprojects No. 5348; Pharmaprojects No. 5356; Pharmaprojects No. 5412; DMP-444; Pharmaprojects No. 5657; Pharmaprojects No. 5728; Pharmaprojects No. 5839; Pharmaprojects No. 5910; TGF- β antagonists, Inspiraplex; Pharmaprojects No. 5961; Pharmaprojects No. 5991; Pharmaprojects No. 6021; Pharmaprojects No. 6063; Pharmaprojects No. 6083; PI-0824; RIP-3, Rigel; NBI-6024; Pharmaprojects No. 892; Pharmaprojects No. 955; IR-501; A6, Angstrom; leuprolide, ProMaxx; Orolip DP; edratide; 131-I-TM-601; Prosaptide TX14(A), Savient; insulin, Flamel; p1025; NIH; protein kinase R antags, NIH; GLP-1, Daiichi; EMD-249590; secretin, RepliGen; RANTES inhibitor, Milan; Pharmaprojects No. 6236; NY ESO-1/CAG-3 antigen, NIH; BILN-504 SE; NIPs, RCT; insulin, Biphasix; ZRXL peptides, Novartis; BIM-23190; leuprorelin, TheriForm; β -amyloid peptides, CeNeS; oglufanide disodium; amyloid inhibiting peptides, Ax; iprP13; PN-277; differentiation inducers, Topo; immune privilege factor, Proneu; TASP-V; anticancer vaccine, NIH; Pharmaprojects No. 6281; HAV peptide matrix, Adherex; calcitonin, oral, Biocon; analgesic, Nobex; PTH 1-34, Biocon; insulin, oral, Biocon-2; BLS-0597; leuprorelin, Depocore; IDPS; AIDS vaccine, Hollis-Eden; insulin, NovaDel; insulin, Orasome; Pharmaprojects No. 6310; TRP-2. NIH; Pharmaprojects No. 6320; Re-188 P2045; calcitonin, Inovio; golotimod; angiotensin-II, topical, Trine; ETRX-101; antiallergy vaccine, Acambis-2; Tc-99m-P424; Tc-99m-P1666; insulin, Transfersome; Yissum Project No. 11649; SP(V5.2)C; melanoma vaccine, Therion-2; insulin Aspart, biphasic, Novo; Tat peptide analogues, NIH; Pharmaprojects No. 6365; Pharmaprojects No. 6373; Ramot project No. 981; ESP-24218; Pharmaprojects No. 6395; calcitonin, oral, Emisphere; omiganan, topical; AIDS vaccine, United-3; leuprorelin, Archimedes; HPV16 E6 + E7 vaccine, NIH; peptide vaccine, NCI; Chlamydia vaccines, Argonex; delmitide acetate; RSV vaccine, Pierre Fabre-2; F-50040; CPI-1500; AIDS vaccine, BioQuest; insulin, BioSante, inhaled; antiangiogenics, GPC; TNF degradation product, Oncot; insulin, Emisphere; ozarelix; bremelanotide; Pseudomonas vaccine, Millenium; AIDS vaccine, CIBG; AIDS vaccine, Wyeth Vaccines-3; HCV serine protease inhib, BI; insulin, Wockhardt;

cat PAD, Circassia; NOV-002; PPI-3088; insulin 24hr, Altea; AP-811; hNLP, Pharis; ANUP-1, Pharis; serine protease inhbs, Pharis; Pharmaprojects No. 6523; respiratory mucus inhibitor, Em; CLX-0100; AIDS vaccine, Panacos; SPHERE peptide vaccine, Genzyme; P-16 peptide, Transition; EP-51389; insulin, ProMaxx; ET-642; P-50 peptide, Transition Ther; Famoxin; insulin, Alkermes, inhaled; GPCR peptide ligand, Synaptic; DiaPep227; alpha-1-antitrypsin, Cortech; IC-41; tuberculosis vaccine, Intercell; immunosuppressant vaccine, Aixl; malaria vaccine, NYU-2; netupitant; AG-702; insulin, AeroDose; anti-inflammatory, TapImmune; insulin glulisine; GPG-NH2; hepatitis-B therapy, Tripep; Staphylococcus therapy, Tripep; angiogenesis inhibitor, Tripep; bone marrow inhibitor, Tripep; melanoma vaccine, Biovector; lipopeptides, Cubist; ABT-510; parathyroid analogue, Unigene; Adageon-E; A-443654; CJC-1131; FE200 665; insulin, TranXenoGen; Gilatide; TFPI, EntreMed; desmopressin, Unigene; leuprorelin, oral, Unigene; antimicrobials, Isogenica; insulin, oral, Unigene; metastin; TRI-1144; DBI-4022; HM-9239; insulin, Bentley, intranasal; F-992; ZP-10; E1-INT; DEBIO-0513; spinal cord injury vacc, Weizm; DAC:GLP-2; uPAR inhibitors, Message; MBP-8298; PL-14736; anaritide peptides, BTG; SP-1000, Samaritan; leuprorelin, Ardana; melanocyte modulators, IsoTis; HF-1020; leucocyte immobilizing peptide; Dentonin; MET-1000; SGS-111; 5-Helix; HPV vaccine, Ludwig; caries vaccine, Forsyth; talibulin; ATN-161; T05; LY-307161; S pneumoniae vaccine, Milleniu; Alphastatin; anticancer peptides, Wockhardt; PGN-0052; INNO-201; leuprolide, Nektar; insulin, BioSante, oral; ADD-9903; viral vaccines, Bio-Virus; AOD-9604; calcitonin, oral, Pfizer; insulin, INJEX; ETD-XXXX; analgesic, Sigyn; anti-infectives, AM-Pharma; human AMPs, AM-Pharma; INGAP peptide; osteomyelitis peptides, AM-Phar; XOMA-629; XMP-293 derivatives; BlockAide/VP; EradicAide; BlockAide/CR; VAC-12; leuprolide, oral, DOR BioPharm; synthetic erythropoiesis pro; β -amyloid vaccine, Intellect; CEL-1000; sincalide; PankoPep; albiglutide; insulin, Bharat; leuprorelin, Norwood; Reversin 121, Solvo; SB-144; SB-29, STiL; cancer vaccine, Sedac; SDT-021; malaria vaccine, Sedac, ther; malaria vaccine, Seda, prophyl; hepatitis-C cellular ther, Seda; Factor XIIIa inhib, Curacyte; insulin, Micronix; AIDS vaccine, Antigen Express-1; exenatide LAR; AIDS vaccine, Bionor Immuno-1; GV-1002; GV-1001; MSI vaccine, GemVax; PEP-14; PV-267; antibacterials, Provid; hepatitis-B vaccine, Innovata; BA-058; BIM-51077; malaria vaccine, Immunogenics; TM-701; VG-104; AC-162352; antivirals, Genencor; leuprolide acetate, Voyager; calcitonin, nasal, Archimedes; insulin, nasal, West; calcitonin, oral, Unigene; calcitonin, nasal, Unigene; IMX-735; IMX-775; PPI-01; anti-IgE peptide, Allergy Ther; BZK-111; TH-0318; Enkastim; antibiotics, Bayer; Cerebrolysin; colorectal cancer therapy, IDM; wound growth factor,

NephRx; JPD-105; osteoporosis drugs, Ferring; PN-951; CZEN-002; ZP-120; pasireotide; HerVac; CTT; LLG peptide, CTT; Pharmaprojects No. 6779; meptides, Senexis; Q-8008; FX-06; PhG-alpha-1; insulin, oral, Biocon; PP-0102; GTP-010; PAR-2 antagonists, EntreMed; parathyroid analogue, Zelos; K-1020; CTCE-9908; CTCE-0214; urocortin-II, Neurocrine; telomerase vaccine, Dendreon; AKL-0707; PYY3-36, Nastech; prostate cancer vaccine, Pepsca; AEZS-130; LYN-001; CUV-1647; AL-108; AL-309; HNTF-15; BIM-28131; CSF-G agonists, Affymax; IL-5 antagonists, Affymax; TRAIL agonists, Affymax; IgE inhibitors, Affymax; TM-801; TM-901; BN-054; APTA-01; HB-107; AVE cancer vaccine; PxSR; STD peptides, Helix; CF anti-infectives, Helix; HB-50; Homspera; S-0373; PYY3-36, oral, Emisphere; XG-101; XG-201CS; XG-102; insulin, oral, Coremed; Alzheimer's vaccine, Prana; AIDS vaccine, Bionor Immuno; leuprolide acetate, ALZAmer; AUX-202; AR-H044178; PYY3-36, Thiakis; lanreotide SR; malaria vaccine, Pevion; Alzheimer's vaccine, Pevion; melanoma vaccine, Antigen Expr; melanoma vaccine, Pevion; OGP-(10-14)-L; ABS-13; ABS-17; cancer therapeutics, Argolyn; substance P-saporin; diabetes therapeutic, Thera; CGX-1051; OTS-102; Xen-2174; insulin, inhaled, Coremed; WP9QY; osteoporosis treatment, Fulcr; AHNP, Fulcrum; insulin, Technosphere, Mannkind; FX-07; CBP-501; E7 vaccine, Neovacs; LSI-518P; aviptadil, Mondobiotec; anticancer peptide, OrthoLogic; AL-209; OP-145; AT-001; AT-008; CHP-105; AMEP, BioAlliance; cardiovascular ther, Argolyn; TEIPP-03; mental retardation ther, Argol; IMX-002; IMX-942; NLC-001; octreotide, Indevus; DRF-7295; opioid peptide derivatives, Ka; CDX-110; ALT-212; desmopressin, Orexo; IMA-901; obinepitide; TM-30335; HIV therapy, OyaGen-1; calcitonin, oral, ThioMatrix; insulin, oral, ThioMatrix; BRX-00585; Insulin Aspart, biphasic-2, No; CG-55069-11; GLP-1, Emisphere; linacotide acetate; NPT-002; terlipressin, Orphan Therapeut; ZT-153; SciClone; FGLL; Syn-1002; MIP-160; PI-2301; PI-3101; BDM-E; insulin, Medtronic; ST-03; TH-0312; hepatitis-C vaccines, Kochi; cetorelix acetate, once-weekly; RPI-MN; neurodegenerative ther, Recepto; RPI-78M; β -amyloid inhibitor, Alzhyme; DMI-3798; DMI-4983; ruzam; CT-319; EN-122004; glyponectin; EN-122001; EN-122002; KAI-9803; insulin, Advancell; larazotide acetate; calcitonin, oral, Bone Medical; parathyroid hormone, Bone Medi; calcitonin, Merrion; desmopressin, Merrion; acyline, Merrion; IMX-503; AP-214; Streptococcus vaccine, Vaccine; cytomegalovirus vaccine, Vacc; RHS-08; AG-707; antiallergics, Phylogica; PYC-36S; anticancers, Phylogica; Glypromate; NNZ-4945; calcitonin, intranasal, ITI; Peptide T, Advanced Immuni T; APTA-02; CGRP, Akela; TKS-1225; GalR2 peptide agonist, NeuroTa; botulinum vaccine, Emergent; HIV fusion inhibitors, Sequoia; AL-208; APP-018; BKT-RP3; smallpox vaccine, Antigen Expr; CMLVAX-100;

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INNO-105; insulin, Intravail; leptin, Intravail; calcitonin, Intravail; somatropin, Intravail; heparin, Intravail; erythropoietin, Intravail; CT-201; telomerase variants, GemVax; INT, transplantation; INT-3; SPI-1620; BIO-037; anticancers, Bracco; BIO-023; ZT-100; MC-4R agonists, Lilly; LT-1951; PTH (1-34), IGI; CGRP, VasoGenix; BIO-145; BIO-142; stem cell factor, Affymax; VEGFR-2 antagonist, Affymax; KGF receptor agonist, Affymax; YM-216391; AT-007; AT-011; EK2700; EK900-1800; EK900-12; FGLm; ABS-201; Mdbt-12; autoimmune therapy, Antigen; VX-001; IPP-102199; IPP-201101; CTA1-DD; Factor VIIa inhibitor, ProTher; antiangiogenic, ProTherapeutic; IMT-1012; colon cancer vaccine, Immunoto; prohanin, ProTherapeutics; smallpox vaccine, BioDefense; heart failure therapy, ElaCor; PA-401; 802-2; insulin, nasal, Nastech; SEN-304; IMA-920; IMA-940; IMA-910; influenza vaccine, Antigen, H5N1; Primacoll; octreotide, PR Pharmaceuticals; female infertility th, Vyteris; FAR-404; athlete's foot therapy, Helix; leishmaniasis ther, Helix; INNO-305; ALS-02; sNN-0465; NN-5401; TRI-999; Org-214444; Org-33409; IMA-930; YH-APC; PYC-35B; Rev-D4F; insulin, Phosphagenics; coeliac disease ther, Nexpep; coeliac disease therapy, BTG; exendin-4, PC-DAC; exenatide, nasal spray; CAP-232; ACE-011; Cardeva; BL-3020; FM-TP-2000; GGTI-2418; TM-30339; DP-74; DP-68; PPH ther, GeoPharma; MPL-TLB100; AZX-100; Alloferon; S2; S3; S4; PAC-G31P; PAC-745; PAC-525; PAC-113; VEBv; lipopeptide, Combinature; monopeptide-1; monopeptide-2; monopeptide-2+monopeptide-3; monopeptide-4; MLIF; carfilzomib; Affitope AD-01; LT-ZP001; LT-ZMP001; CGX-1204; C3d, Enkam; C5a antagonist, Eucodis; adenocarcinoma vacc, ImmvaRx; insulin, oral, Apollo; renin inhibitors, Servier; Factor VIIa, GTC; ABS-212; NAFB001; NAFB002; insulin, MediVas; ZT-181; anti-inflammatory, Forbes; labour inhibitor, Theratechnolo; glaucoma therapy, Theratechnolo; AG-EM-0040; MS therapy, Aplagen; interleukin-2 mimetic, Aplagen; CNS therapy, Aplagen; Mesd-based peptides, Raptor; parathormone, Sidus; asthma therapy, Synairgen; dekafin-1; anticancer vaccine, Ulm; BT-15; cancer imaging agent, Speci; cardiovascular imaging, Speci; E-75; Prothyx; anticancer, Prothyx, Stealthyx; IL12-NGR; allergy vaccine, China Bio; amylin mimetic, 2nd-gen, Amylin; influenza vaccines, Variation; VLP-0012M; PLT-101; AL-408; anticancers, Aileron; antivirals, Ambrx; hSPN-16; HDL, Cerenis; enterostatin; BSc-2118; SB-006; antimicrobials, Spider Biotech; peptide therapy, Angioblast; octreotide, Ambrilia; GAP-134; Alzheimer's therapy, Il Dong; BL-4020; von Willebrand factor, Baxter; IL-1aQb; POT-4; gamma-secretase inhibitors, BMS; ISCOMATRIX; enfuvirtide, needle-free; connexin modulators, NeuroSol; BT-25; BT-20; AmpTide; HepTide; antimicrobial peptides, Helix; NPY2 agonists, Bayer; ragweed PAD, Circassia; dust mite PAD, Circassia; grass

PAD, Circassia; transplant rejection PAD; insulin, oral, Oramed; cardiac ischaemia therapy, Phy; PYC-18; antidiabetics, Phylogica; PEP-35; ACE-041; ACE-031; ovarian cancer vaccine, Genex; ATX-MS-1467; iATX FVIII; diabetes vaccine, Apitope; allergy vaccine, Apitope; FX-06 analogue; PR-22G; PR-21, Pharmaxon; LT-1945; LT-1942; XG-414; XG-517; AC-163794; MDPTQ; B27PD; AC-2307; sedatives, ProTherapeutics; L-Type Ca channel blocker, Pro; phospholipase A2 inhibitor, Pro; PGL-3001; PGL-1001; influenza vaccine, Variation-2; Homspera nanoparticle, Immune; CVX-096; COR-1; survivin-2B; imMucin; GLP-1, PharmaIN; atherosclerosis vaccine, Affir; adeptide; somatostatin antagonists, Preg; Casimax; CD-NP, Nile; PRX-111; ACT1-C; PRX-102; ACT1-G; AIDS vaccine, ITS; influenza vaccine, ITS; hepatitis-C vaccine, ITS; ALTY-0601; BGLP-40; somatropin, INB; trypanosomal vaccine, INB; RU-COH, Pantarhei; LH-COH, Pantarhei; GLP-1 analogues, Unigene; Polyfensin; VIR-576; Xen-0568; Xen-0495; Xen-0468; LEKTI-6; leukaemia vaccine, MD Anderson; Met receptor agonists, MRCT; insulin HDV, short-acting, Dia; glucagon antagonists, CoGene; GLP-1 agonists, CoGenesys; insulin HDV, oral, Diasome; insulin HDV, long-acting, Dia; glucagon, Particle Therapeutics; GLP-1, Mannkind; insulin, next-generation, Flamel; Ostabolin-C, topical; DAC:HIV; antiviral, HepTide; Insulin Aspart, biphasic-3, No; Innotide; influenza vaccine, Bionor; HPV vaccine, Bionor Immuno; hepatitis-C vaccine, Bionor; Affitope AD-02; Affitope AD-03; RHS-02; RHS-03; insulin, Access; inherbins, Enkam; Dekafin-2; BL-4050; ALS vaccine, Amorfix; cancer vaccine, Canopus; relaxin, Corthera; rhNRG-1; rhErbB3-f; hepatitis-C vacc, Green Cross-3; androgen receptor antag, CRT; GLP-1 analogue CR, OctoPlus; AIDS vaccine, Sanofi Past-12; insulin, Diabetology; Combulin; AIDS vaccine, Sanofi Past-11; AnergiX.MG; AnergiX.MS; insulin, CritiTech; YP-20; NDR/NCE-18; CLT-002; CLT-007; CLT-008, Charlesson; CLT-009; PYC-38; AIM-101; AIM-102; AIM-501; APL-180; metabolic disease therapy, Xen; NP-213; NP-339; antimicrobial peptides, NovaB; lung anti-infectives, NovaBiot; c-peptide analogue, Diabetology; CGEN-855; NN-1250; NN-9535; insulin, rectal, Oramed; insulin, 12hr, Altea; pancreatic cancer vaccine, Onco; SB-101; L-glutamine, Emmaus; glucagon antagonists, Kisspeptin-54; Kisspeptin-14; Kisspeptin-13; Kisspeptin-10; Ziconotide; Biphalin; Nesiritide; Protegrin-1; Protegrin-2; Protegrin-3; Protegrin-4; Protegrin-5; Preprotegrin; V681; V681 (V13A_D); GLP-2; GLP-2 (A2G); GLP-2 (A2G/C34); AOD-9604; Ac-AOD-9604(S8K); Ac-AOD-9604(K17); C-peptide; CR845; and Marcadia.

[0057] In certain embodiments of the invention, PEP is a therapeutic peptide selected from the therapeutic peptides listed in Table 1.

Table 1

This table lists the SEQ ID NOs., names, sequences, and known or suspected therapeutic activities of various peptides described herein. The SEQ ID NOs. 1-301 describe sequences that are required to be provided with the Sequence Listing and are therefore appended with the instant Specification. In some instances, these peptides contain features that are either inconsistent with or not amenable to inclusion in the Sequence Listing. For example, a sequence with less than four-amino acids; a sequence with a D-amino acid; or certain modification that cannot be described in the Sequence Listing presently, and therefore are not provided in the Sequence Listing. However, for the ease of use and description, a SEQ ID NO. has been provided to these peptides (i.e., SEQ ID NOs: 302-469).

(-NH₂ indicates amidation at the C-terminus; Ac indicates acetylation; other modifications are as described herein and in the specification; SIN indicates Sequence Identification Number)

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
1	carperitide	ANP	SLRRSSCFGGRMDRIGAQSGLGCNSFRY; human alpha-atrial natriuretic peptide; Atriopeptin-28 (human);	Cardio stimulant Respiratory
2	alpha-neoendorphin	Endorphin	H-Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys-OH	Analgesic, other
3	A-3847	Insulin	gi 386828 gb AAA59172.1 insulin [Homo sapiens] MALWMRLPLLLALLALWGPDPAAAFVNQHLCGSHL VEALYLVCGERGFFYTPKTRREAEDLQVGQVELGGG PGAGSLQPLALEGSLQKRGIVEQCCTSI ^{SIN} CSLYQLENYC N	Antidiabetic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
4	A-4114	Insulin	MALWMRLPLLLALLALWGPDPAAAFVNQHLCGSHL VEALYLCGERGFFYTPKTRREAEDLQVGQVELGG	Antidiabetic
5	A-68552		GPGAGSLQPLALEGSLQKRQIVEQCCTICSLYQLENY CN	Anorectic/Antiobesity
302 and 303	A-75998		[Ac-D-2Nal1-D-4CIPhe2-D-3Pal3-NMeTyr5-D-Lys(Nic)6-Lys(Isp)8-D-Ala10]GnRH; N-acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-seryl-N-methyltyrosyl-D-N(epsilon)-nicotinyllysyl-leucyl-N(epsilon)-isopropyllysyl-prolyl-alaninamide acetate	Releasing hormone Reproductive/gonadal, general
6	AN-1792	beta-amyloid peptide	gi 8176533 gb AAB26264.2 beta-amyloid peptide precursor; beta APP [Homo sapiens] GSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFF AEDVGSNKGAIIGLMVGGVVVIAIVIIITLVMLK KQYTSNHHGVVE	Cognition enhancer
7	AAMP-1		MESESESGAAADTPPLETLSFHGDEEIEVVELDPGPPD PDDLAQEMEDVDFEEEEEEGNEEGWVLEPQEGVVG SMEGPDDSEVTFALHSASVFCVSLDPKNTTLAVTGGE DDKAFVWRLSDGELLFECAGHKDSVTCAGFSDSTL VATGDMGSLKLVWQVDTKEEVWSFEAGDLEWMEW	Anticoagulant Anti-inflammatory Immunological Anticancer, other Vulnerary

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			HPRAPVLLAGTADGNTWMWKVPNGDCKTFQGPNC ATCGRVLPDGKRAVVGIEDGTIRIWDLKQGSPIHVLK GTEGHQGPLTCVAANQDGLTLTGSDCCQAKLVSAT GKVVGVFRPETVASQPSLGESESESNSVESLGFCSV MPLAAVGYLDGTLAIYDLATQTLRHQCQHQSGIVQLL WEAGTAVVYTCSLDGIVRLWDARTGRLLTDYRGHTA EILDFALSKDASLVVTTSGDGHKAKVFCVQRPDR	
8	Exenatide	GLP-1	HEGTFTDLSKQMEEAAVRLFIEWLKNGGPSSGAPP PS	Antidiabetic Anorectic/Antiobesity
9	AC-625		Acetyl-ATQRLANELVRLQTYPRTNVGSNTY-NH ₂	Antihypertensive, renin system Symptomatic antidiabetic
10	ACTH		gi 80861463 refNP_001030333.1 proopiomelanocortin preproprotein [Homo sapiens] MPRSCCSRSGALLALLQASMEVRGWCLLESSQCQD LTTESNLLCIRACKPDLSAETPMFPGNGDEQPLTENP RKYVMGHFRWDRFGRRNSSSSGSSGAGQKREDVSAG EDCGPLPEGPEPRSDGAKPGPREGKRYSMEHFRWG KPVGKKRRPVKVYPNGAEDESAAFLFKRELGTQR LREGDGPDPADGAGAQADLEHSLLVAAEKKDEGP	Adrenal and pituitary disorders

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			YRMEHFRWGSPPKDKRYGGFMTSEKSTPLVTLFKN AIIKNAYKKGE	
11	AIDS therapeutic vaccine		gi 288842 emb CAA78890.1 V3 loop [Human immunodeficiency virus type 1] CTRPSNNTRKSIPVGP GKALYATGAIIGNIRQAHC	Therapeutic vaccine
12	AIDS therapy		gi 5081475 gb AAD39400.1 AF128998_1 gag [Human immunodeficiency virus type 1] MGARASVLSGGKLDKWEKIRLRPGGKTTYQLKHIVW ASRELERFVNPGLLETGGGCKQILVQLPSLQTGSEE LKSLYNVAVATLYCVHQGIEVRDTKEALDKIEEEQNKS KKKAQQAADTGNSSQVSQNYPIVQNLQGQMVHQA SPRTLNAWVKVIEEKAFSPEVIPMFSALSEGATPQDLN TMLNTVGGHQAAMQMLKETINEEAAEWDRLHPAHA GPNAPGQMREPRGSDIAGTTSTLQEIGWMTSNPPVP VGEIYKRWIILGLNKIVRMYSVPVILDIRQQGKPEFRDY VDRFYKTLRAEQASQDVKNWMTETLLVQNANPDCK TILKALGPAATLEEMMTACQGVGGPSHKARILAEAMS QVTSPANIMMQRGNFRNQRKTIKCFNCGKEGHLARH CRAPRKKGCWKCGRGEGHQMKDCTERQANFLGKIWP SHKGRPGNFLQSRPEPTAPPEESFRFGEETTPPQKQEP	Antiviral, anti-HIV

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			LPSQKQETIDKDL YPLASLSLFGNDPSLQ	
13 and 14	Allotrap-2702		Allotrap 1258; Allotrap 2702; Allotrap E; Allotrap G; RDP58; peptide Bc-1nl; NLRIALR/RLAIRLN	Immunosuppressant
15 and 16	Alzheimer's imaging agent		H- DAEFRHDSGYEVHHQKL VFFAEDVGSNKGAIIGLMV GGVV-OH; or H- DAEFRHDSGYEVHHQKL VFFAEDVGSNKGAIIGLMV GGVVIA-OH	Imaging agent
17	AM-425		gi 4504991 ref NP_002300.1 leukemia inhibitory factor (cholinergic differentiation factor) [Homo sapiens] MKVLAAGVVPLLLVLHWKHGAGSPLPITPVNATCAIR HPCHNNLMNQIRSQLAQLNGSANALFILYYTAQGEPP PNNLDKLCGPNVTDPPPFHANGTEKAKLVELYRIVVY LGTSLGNITRDQKILNPSALSLHSLKNATADILRGLLSN VLCRLCSKYHVGHVDVTYGPDTSGKDVFKKKLGCQ LLGKYKQIIA VLAQAF	Antiarthritic, immunological
304	AN-238		L-Threoninamide, N-[5-[2-[(2S,4S)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-	Somatostatin Anticancer, hormonal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			3-(2,3-dihydro-1H-pyrrol-1-yl)-alpha-L-lyxo-hexopyranosyl[oxy]-2-naphthacenyl]-2-oxoethoxy]-1,5-dioxopentyl]-D-phenylalanyl-L-cysteiny]-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteiny]-, cyclic (2-7)-disulfide	
305	AV-9		[D-Arg]9-NH ₂	Antiviral, other
8	AZM-134	GLP-1	HGEGTFTSDLSKQMEEAAVRLFIEWLKNGGPSSGAPP PS	Anorectic/Antiobesity Antidiabetic
18	Addressin		gi 109633022 ref NP_570116.2 mucosal vascular addressin cell adhesion molecule 1 isoform a precursor [Homo sapiens] MDFGLALLAGLLGLLGQSLQVKPLQVEPPEPVAV ALGASRQLTCRLACADRGASVQWRGLDTSLGAVQSD TGRSVLTVRNASLSAAGTRVCVGCGRGRTFQHTVQLL VYAFPDQLTVSPAALVPGDPEVACTAHKVTPVDPNAL SFSLLVGGQELEGAAQALGPEVQEEEEEPQGDEEDVLFR VTERWRLPPLGTPVPPALYCQATMRLPGLLSHRQAI PVLHSPTSPEPPDTSPEPDTSPEPDTSPEPDTSPEPDTS PEPPDKTSPEAPQQGSTHTPRSPGSTRTRRPEISQAGP TQGEVIPTGSSKPA GDQLPAALWTSSAVLGLLLALPT	Recombinant, other Anti-inflammatory

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			YHLWKRCRHLAEDDTHPPASLRLLPQVSAWAGLRGT GQVGISPS	
306	ambamustine		L-Methionine, N-[3-[bis(2-chloroethyl)amino]-N-(4-fluoro-L-phenylalanyl)-L-phenylalanyl]-, ethyl ester	Anticancer, alkylating Anticancer, antimetabolite
19	amylin antagonists		DTTVSEPAPSCVTLYQSWRYSQADNGCAETVTVKVV YEDDTEGLCYAVAPGQITTVGDGYIGSHGHARYLAR CL	Antidiabetic
20	anaritide analogues	ANP	gi 178638 gb AAA35529.1 atrial natriuretic peptide MSSFSTTTVSFLLLLAFQLLGQTRANPMYNAVSNADL MDFKNLLDHLEEKMPLEDEVPPQVLSDPNEEAGAA LSPLPEVPPWTGEVSPAQRDGGALGRGPWDSSDRSAL LKSKLRALLTAPRSLRRSSCFGRMDRIGAQSGLGCN SFRY	Antihypertensive, diuretic
21-28	anti-inflammatory peptide		As disclosed in U.S. Patent No. 5,470,831: Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg Val-Lys-Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg. Ser-Gln-Val-Arg-Pro-Arg Val-Arg-Pro-Arg Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg-His-Ile-Thr. Thr-Thr-Ser-Gln-Val	Anti-inflammatory Immunosuppressant Multiple sclerosis treatment Antiarthritic, other Stomatological Dermatological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			Thr-Ser-Gln-Val-Arg	
			Thr-Thr-Ser-Gly-Ile-His-Pro-Lys	
307	antiflammins		L-Leucine, N-[N-[N-[N2-[N2-[N-(N-L-histidyl-L-alpha-aspartyl)-L-methionyl]-L-asparaginy]-L-lysyl]-L-valyl]-L-leucyl]-L-alpha-aspartyl]-	Anti-inflammatory
308	antifungal tripeptides		tripeptides of N3-4-methoxyfumaryl and di- and tripeptides of N3-D-trans 2,3-epoxysuccinamoyl-L-2,3-diaminopropanoic acid	Antifungal
29	Gastrimmune		G17-DT; G17DT (vaccine); Gastrimmune; Glu-Gly-Pro-Trp-Leu-Glu-Glu-Glu -diphtheria toxoid; anti-gastrin 17 immunogen; gastrin 17 vaccine; gastrin-17-diphtheria toxoid conjugate	Anticancer, immunological
30	antithrombin polypeptides		gi 312673 emb CAA51292.1 Hirudin [Hirudinaria manillensis] MFSCLKLFVVFLAVCICVSQAVSYTDCTESGQNYCLCV GGNLCGGGKHCMDGSGNKCVDGEGTPKPKSQT EGDFEEIPDEDILN	Antithrombotic Anticoagulant
31	antiviral peptides		NH ₂ -Tyr-Ala-Gly-Ala-Val-Val-Asn-Asp-Leu-COOH	Antiviral, other
32	apolipoprotein		gi 671882 emb CAA28583.1 apolipoprotein [Homo sapiens]	Hypolipaeic/Antiatherosc

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			MKLLAATVLLLTICSLEGALVRRQAKEPCVESLVSQY FQTVTDYGKDLMEKVKPELQAEAKSYFEKSKE QLTPLIKKAGTELVNFLSYFVELGTHPATQ	lerosis
33	arthritis antigen		gi 46369603 gb AAS89650.1 secreted antigen 85A precursor [Mycobacterium bovis BCG] MQLVDRVRGAVTGMSRRLVVGAVGAALVSGLVGAV GGTATAGAFSRPGLPVEYLQVPSMGRDIKVFQFQSG GANSPALYLLDGLRAQDDFSGWDINTPAFEWYDQSG LSVVMPPVGGQSSFYSDWYQACGKAGCQTYKWETF LTSELPGWLQANRHKPTGSAVVGLSMAASSALTLAI YHPQQFVYAGAMSGLLDPSQAMGPTLIGLAMGDAGG YKASDMWGPKEPAAWQRNDPLLVGKLIANNTRVW VYCGNGKPSDLGGNNLPKFLGEGFVRTSNIKFDAYN AGGGHNGVFDFPDGTHSWEYWGAQLNAMKPDQLQR ALGATPNTGPAPQGA	Recombinant, other Antiartthritic, immunological Immunosuppressant
309	Avorelin		5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-2-methyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide	Releasing hormone Anticancer, hormonal Menstruation disorders
310	B-956		N-[8(R)-Amino-2(S)-benzyl-5(S)-isopropyl-9-sulfanyl-3(Z),6(E)-nonadienoyl]-L-methionine	Anticancer, other

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311	BCH-2687		L-Tyrosyl-D-arginyl-L-phenylalanyl-L-phenylalaninamide	Analgesic, other
34	BCH-2763		L-Leucine, D-phenylalanyl-L-prolyl-5-aminopentanoyl-5-aminopentanoyl-L-alpha-aspartyl-L-phenylalanyl-L-alpha-glutamyl-L-prolyl-L-isoleucyl-L-prolyl- ; BCH-2763; Phe-Pro-(NH(CH ₂) ₄ CO) ₂ -Asp-Phe-Glu-Pro-Ile-Pro-Leu; phenylalanyl-prolyl-(NH(CH ₂) ₄ CO) ₂ -aspartyl-phenylalanyl-glutamyl-prolyl-isoleucyl-prolyl-leucine	Antithrombotic Anticoagulant
312	frakefamide		L-phenylalaninamide, L-tyrosyl-D-alanyl-4-fluoro-L-phenylalanyl-	Analgesic, other
313	BIM-22015		Glycinamide, D-alanyl-L-glutaminy-L-tyrosyl-L-phenylalanyl-L-arginyl-L-tryptophyl-	ACTH Neurological
35	BIM-26028		Pyroglutamyl-glutaminy-arginyl-leucyl-glycyl-asparaginy-glutaminy-tryptyl-alanyl-valyl-glycyl-histidiny-leucyl-leucyl-NH ₂	Releasing hormone Respiratory Anorectic/Antiobesity Anticancer, hormonal
314	BIM-44002		L-Tyrosinamide, L-phenylalanyl-L-norleucyl-L-histidyl-L-asparaginy-L-leucyl-D-tryptophyl-L-lysyl-L-histidyl-L-leucyl-L-seryl-L-seryl-L-norleucyl-L-alpha-glutamyl-L-arginyl-L-valyl-L-.alpha.-glutamyl-L-tryptophyl-L-leucyl-L-arginyl-L-lysyl-L-lysyl-L-leucyl-L-glutaminy-L-alpha-	Hormone Osteoporosis treatment

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			aspartyl-L-valyl-L-histidyl-L-asparaginy-	
36	BIO-1211		L-Proline, N-((4-(((2-methylphenyl)aminocarbonyl)amino)phenyl)acetyl)-L-leucyl-L-alpha-aspartyl-L-valyl- ; BIO-1211; N-((4-(((2-methylphenyl)amino)carbonyl)amino)phenyl)acetyl)-leucyl-aspartyl-valyl-proline	Antiasthma GI inflammatory/bowel disorders Multiple sclerosis treatment
37	BPC-15		BPC 15; BPC-15; BPC-157; booly protection compound 15; L-Valine, glycyl-L-alpha-glutamyl-L-prolyl-L-prolyl-L-prolylglycyl-L-lysyl-L-prolyl-L-alanyl-L-alpha-aspartyl-L-alpha-aspartyl-L-alanylglycyl-L-leucyl-	Anti-inflammatory
315	bivalirudin		L-Leucine, D-phenylalanyl-L-prolyl-L-arginyl-L-prolylglycylglycylglycyl-L-asparaginyglycyl-L-alpha-aspartyl-L-phenylalanyl-L-alpha-glutamyl-L-alpha-glutamyl-L-isoleucyl-L-prolyl-L-alpha-glutamyl-L-tyrosyl- ; D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycylglycylglycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate	Anticoagulant Antianginal
38	bombesin antagonist		5-oxoPro-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-MetNH ₂ [CAS], Bombesin 14; Bombesin	Anticancer, other

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			Dihydrochloride; Dihydrochloride, Bombesin	
39	brain natriuretic peptide	BNP	SPKMVQSGCFCGRKMDRISSSSGLGCKVLRHH	COPD treatment, cardiac
41	C-peptide analogues	C-peptide	Glu-Ala-Glu-Asp-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln	Symptomatic antidiabetic Ophthalmological Neurological
316	C5a antagonist		Me-Phe-Lys-Pro-D-Cha-L-Cha-D-Phe	Anti-inflammatory
42	CBT-101		L-Cysteinamide, L-asparaginy-L-leucylglycyl-L-valyl-S-[(acetylamino)methyl]-, monoacetate	Antiglaucoma
43	CCK(27-32)		Tyr(SO ₃)-Met-Gly-Trip-Met-Asp; CBZ-CCK (27-32)-NH ₂ ; cholecystokinin (27-32) amide, benzoyloxycarbonyl-, D-Trip	Analgesic, obesity, other
44	CD4		CD4 (81-92), D-Ile; CD4 (81-92), D-Tyr; CD4 (81-92), D-Tyr,D-Cys,D-Glu(5); CD4(81-92); TYICEVEDQKEE; Thr-Tyr-Ile-Cys-Glu-Val-Glu-Asp-Gln-Lys-Glu-Glu; threonyl-tyrosyl-isoleucyl-cysteiny-glutamyl-valyl-glutamyl-aspartyl-glutaminy-lysyl-glutamyl-glutamic acid	Antiviral, anti-HIV
317	CEE-04-420		Lys-D-Pro-Thr and Lys-D-Pro-Val	Analgesic, other
45	CEP-079		gi 108796063 ref NP_001007140.2 insulin-like growth factor 2 isoform 1 precursor [Homo sapiens] MGIPMGKSMVLVLLTFLAFASCCIAAYRPSETLCGGEL	Ophthalmological

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			VDTLQFVCGDRGFYFSRPAASRVSRRSRGIVEEC CFRSCDLALLETYCATPAKSERDVSTPPTVLPDNFPRY PVGKFFQYDTWKQSTQRLRRGLPALLRARRGH VLAKELEAFREAKRHRPLIALPTQDPAHGGAPPEMAS NRK	
318	mifamurtide		L-Alaninamide, N-(N-acetylmuramoyl)-L-alanyl-D-alpha-glutaminy-1-N-[4-hydroxy-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacos-1-yl]-, P-oxide, monosodium salt, (R)-	Anticancer, immunological
46	CGRP analogues	CGRP	ACDTATCVTHRLAGLLSRSGGVKNNFVPTNVGSKA F-NH₂	Hormone Cardiovascular
47	rusalatlade acetate		gi 4503635 ref NP_000497.1 coagulation factor II preproprotein [Homo sapiens] MAHVRGLQLPGCLALAAALCSLVHSQHVFAPQARS LLQRRRANTFLEEVRKGNLERECVEETCSYEEAFEA LESSTATDVFWAKYTACETARTPRDKLAACLEGNCA EGLGTNYRGHVNITRSGIECQLWRSRYPHKPEINSTTH PGADLQENFCRNPDSSTTGPWCYTDTDPTVRRQECIPV CGQDQVTVAMTPRSEGSSVNLSPPLEQCVDRGQQY QGRLA VTTHGLPCLAWASQAQAKALSKHQDFNSAVQL	Musculoskeletal Vulnerary Symptomatic antidiabetic Cardiovascular Anti-infective, other Ophthalmological

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			VENFCRNPDGDEGVWCYVAGKPGDFGYCDLNYCE EAVEEETGDGDESDRAIEGRTATSEYQTFFNPRTFG SGEADCGLRPLFEKKSLKEDKTERELLESYIDGRIVEGS DAEIGMSPWQVMLFRKSPQELLCGASLISDRWVLTAA HCLLYPPWDKNFTENDLLVRIGKHSRTRYERNIEKISM LEKIYIHPRYNWRENDRDIALMKLKKPVAFSDYIHP VCLPDRETAASLLQAGYKGRVTGWGNLKETWTANV GKGQPSVLQVNLPIVERPVCKDSTRITDNMFCAG YKPDEGKRGDACEGDSGGPFVMSPFNNRWYQMGI VSWGEGCDRDGKYGFYTHVFRLKKWKVIDQFGE	
48	CKS-17		L-Leucine, L-leucyl-L-glutaminy-L-asparaginy-L-arginyl-L-arginylglycyl-L-leucyl-L-alpha-aspartyl-L-leucyl-L-leucyl-L-phenylalanyl-L-leucyl-L-lysyl-L-alpha-glutamylglycylglycyl- ; CKS-17; CKS-17 peptide	Immunosuppressant Anticancer, immunological
10	corticotropin acetate	corticotropin	gi 80861463 ref NP_001030333.1 proopiomelanocortin preproprotein [Homo sapiens] MPRSCCSRSGALLALLQASMEVRGWCLSSQCQD LTTESNLLLECIRACKPDLSAETPMFPGNGDEQPLTENP RKYYVMGHFRWDRFGRNRSSSSGSSGAGQKREDVSAG EDCGPLPEGPEPRSDGAKPGREGKRYSMEHFRWG	Neuroprotective Antiasthma Anti-inflammatory

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			KPVGKKRRPVKVYPNGAEDESAEAFPLEFKRELTGQR LREGDGPDPADGAGAQADLEHSLLVAAEKKDEGP YRMEHFRWGSPPKDKRYGGFMTSEKSTPLVTLEKN AIIKNAYKKGE	
49	CT-112		L-Arginine, L-threonyl-L-threonyl-L-seryl-L-glutaminy-L-valyl-L-arginyl-L-prolyl- ; 5-(3-ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione	Antiarthritic, immunological
50	CTAP-III		phenylalanyl--cysteiny--tyrosyl-tryptophyl-arginyl-threonyl-penicillaminy-threoninamide; rCTAP-III-Leu-21 (des 1-15); somatostatin analog CTAP	Vulnerary Antiarthritic, other Musculoskeletal Recombinant, other
51	CVFM		Cys-Val-Phe-Met	Anticancer, other
52 and 53	calcitonin	calcitonin	CGNLSTCMLGTYTQDFNKFHTFPQT AIGVGAP (human) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH ₂ (salmon)	Formulation, oral, other Hormone Osteoporosis treatment
54	calciseptine		sp P22947 TXCAS_DENPO Calciseptin OS=Dendroaspis polylepis polylepis PE=1 SV=1 RICYIHKASLPRA TKTCVENTCYKMFIRTQREYISERG	Antihypertensive, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			CGCPTAMWPYQTECCKGDRCNK	
52 and 53	calcitonin analogues	calcitonin	CGNLSTCMLGTYTQDFNKFHTFPQTAIGVGAP (human) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH ₂ (salmon)	Hormone Osteoporosis treatment
55	calphobindin I		gi 186680508 ref NM_001154.3 Homo sapiens annexin A5 (ANXA5), MAQVLRGTVTDPPGFDERADAETLRKAMKGLGTDEE SILTLLTSRSNAQRQEISAFKTLFGRDLLDLKSELTG KFEKLIVALMKPSRLYDAYELKHALKGAGTNEKVLT EIIASRTPEELRAIKQVYEEYGSSEDDVVGDTSGYY QRMLVLLQANRDPDAGIDEAQVEQDAQALFQAGEL KWGTDEEKFITIFGTRSVSHLRKVFDKYM TISGFQIEE TIDRETSGNLEQLLLAVVKSIRSIPAYLAETLYYAMKG AGTDDHTLIRVMVSRSEIDLFNIRKEFRKNFATSLYSM IKGDTSGDYKKALLLCGEDD	Ophthalmological, Vulnerary
319	cargutocin		1,6-Dicarbaoxytocin, 1-butanoic acid-7-glycine-	Labour inducer
320	casokefamide		L-Tyrosinamide, L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl-	Antidiarrhoeal

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56	cekropin-P		sp P14661 CECP1_PIG Cecropin-P1 OS=Sus scrofa PE=1 SV=1 SWLSKTAKKLENSAKKRISSEGIAIAIQGGPR	Antibacterial, other
57	tasidotin hydrochloride		N,N-Dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-propyl-L-proline-tert-butylamide	Anticancer, other
58	ceruletide diethylamine		Pyr-Gln-Asp-Tyr(SO ₃ H)-Thr-Gly-Trp-Met-Asp-Phe-C(O)-NH ₂	Analgesic, other Gastroprokinetic
321	cetrorelix acetate		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N ⁵ -(aminocarbonyl)-D-ol-L-leucyl-L-arginyl-L-prolyl-	Fertility enhancer Prostate disorders Menstruation disorders Anticancer, hormonal
59	corticoliberin	corticoliberin	SQEPPISLDLTFHLLREVLEMTKADQLAQQAHNRKL LDIA	Releasing hormone
322	D-22213		L-Histidinamide, N ² -[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-L-glutaminy-L-tryptophyl-L-alanyl-L-valylglycyl-N-[1-[[[1-(aminocarbonyl)-3-methylbutyl]amino]methyl]-3-methylbutyl]-, [1(R),6[S-(R*,R*)]]]-, monoacetate	Anticancer, other
323	DAP inhibitors		L-AP-L-Ala and L-Ala-L-Ala-DL-AP;	Antibacterial, other
60	DP-640	insulin	L-Tyrosinamide, β-alanyl-L-arginylglycyl-L-phenylalanyl-	Insulin

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			L-phenylalanyl-, diacetate (salt)	Antidiabetic
61	DP-107		L-Leucine, L-methionyl-L-threonyl-L-leucyl-L-threonyl-L-valyl-L-glutaminy-L-alanyl-L-arginyl-L-glutaminy-L-leucyl-L-leucyl-L-seryl-L-glutaminy-L-isoleucyl-L-valyl-L-glutaminy-L-glutaminy-L-glutaminy-L-asparaginy-L-asparaginy-L-leucyl-L-leucyl-L-arginyl-L-alanyl-L-isoleucyl-L-.alpha.-glutamyl-L-alanyl-L-glutaminy-L-glutaminy-L-histidyl-L-leucyl-L-leucyl-L-glutaminy-L-leucyl-L-threonyl-L-valyl-L-tryptophylglycyl-L-isoleucyl-L-lysyl-L-glutaminy-L-	Antiviral, anti-HIV
62	DU-728		Arg-Gly-Asp-Ser	Antithrombotic
63	Dynorphin A		H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln-OH	Analgesic, other Neuroprotective Dependence treatment
64	defensins		gi 181535 gb AA52304.1 defensin precursor MRTLAILAAILLVALQAQAEPLQARADEVAAPEQIA ADIPEVVVSLAWDESLAPKHPGSRKNMDCYCRIPACI AGERRYGTCTIYQGRLWAFCC	Antibiotic, other Antifungal Vulnerary
324	detirelix		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-tyrosyl-N6-	Releasing hormone Abortifacient

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			[bis(ethylamino)methylene]-D-lysyl-L-leucyl-L-arginyl-L-prolyl-	Male contraceptive
65	disagregin		gi 545738 gb AAB30092.1 disagregin=fibrinogen receptor antagonist [Ornithodoros moubata=tick, salivary gland, Peptide, 60 aa] SDDKCCQGRPMYGCREDDDSVFGWTYDSNHGQCWKG SYCKHRRQPSNYFASQQECRNTCGA	Antithrombotic Cardiovascular
66 and 65	E-2078		D-Leucinamide, N-methyl-L-tyrosylglycylglycyl-L-phenylalanyl-L-leucyl-L-arginyl-N2-methyl-L-arginyl-N-ethyl- SDDKCCQGRPMYGCREDDDSVFGWTYDSNHGQCWKG SYCKHRRQPSNYFASQQECRNTCGA	Analgesic, other
	ELS-1		Arg-Lys-Glu	Immunostimulant, other
67	ecallantide		Glu-Ala-Met-His-Ser-Phe-Cys-Ala-Phe-Lys-Ala-Asp-Asp-Gly-Pro-Cys-Arg-Ala-Ala-His-Pro-Arg-Trp-Phe-Phe-Asn-Ile-Phe-Thr-Arg-Gln-Cys-Glu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Gln-Asn-Arg-Phe-Glu-Ser-Leu-Glu-Glu-Cys-Lys-Lys-Met-Cys-Thr-Arg-Asp	Angioedema, Anti-inflammatory, Haemostatic, Antiarthritic, other
325	ES-1005		bis-(1-naphthyl)methylacetyl-His-Sta-Leu-E-Lys diHCl	Antihypertensive, renin system

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326	efegatran		L-prolinamide, N-methyl-D-phenylalanyl-n-(4-((aminoiminomethyl)amino)-1-formylbutyl), (S)-	Antithrombotic Antianginal
68 and 69	elafin derivatives		gi 999146 gb AAB34627.1 elafin [Homo sapiens] MRASSFLIVVFLIAGTLVLE H-Ala-Gln-Glu-Pro-Val-Lys-Gly-Pro-Val-Ser-Thr-Lys-Pro-Gly-Ser-Cys-Pro-Ile-Ile-Leu-Ile-Arg-Cys-Ala-Met-Leu-Asn-Pro-Pro-Asn-Arg-Cys-Leu-Lys-Asp-Thr-Asp-Cys-Pro-Gly-Ile-Lys-Lys-Cys-Cys-Glu-Gly-Ser-Cys-Gly-Met-Ala-Cys-Phe-Val-Pro-Gln-OH (Disulfide bonds between Cys16-Cys45, Cys23-Cys49, Cys32-Cys44, Cys38-Cys53)	Respiratory COPD treatment Antiarthritic, other
70 and 52	elcatonin	calcitonin	Ser-Asn-Leu-Ser-Thr-Asn-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Val-Gly-Ala-Gly-Thr-Pro-NH ₂ CGNLSTCMLGTYTQDFNKFHTFPQT AIGVGAP (human)	Hormone Osteoporosis treatment Analgesic, other
71	eledoisin		5-oxo-L-Pro-L-Pro-L-Ser-L-Lys-L-Asp-L-Ala-L-Phe-L-Ala-L-isoleucylglycyl-L-Leu-L-methionin-amide	Ophthalmological
3	encapsulated insulin	insulin	gi 386828 gb AAA59172.1 insulin [Homo sapiens] MALWMRLPLLLALLALWGPDPAAAFVNQHLCGSHL V EALYLVCGERGFFYTPKTRREAEDLQVGQVELGGGPG	Formulation, optimized, nanoparticles Insulin

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			AGSLQPLALEGSLQKRQIVEQCCTICSLSYQLENYCN	Antidiabetic
72	endorphin, β -		YGGFMTSEKSTPLVTLFKNAIKNAYKKGE	Analgesic, other
72	endorphin, pancreatic		YGGFMTSEKSTPLVTLFKNAIKNAYKKGE	Analgesic, other
73	endothelial cell growth factor		gi 189701 gb AA60043.1 endothelial cell growth factor MAALMTPGTGAPPAPGDFSGEGSQGLPDPSPEPKQLP ELIRMKRDGGRLEADIRGFVAAVNGSAQGAQIGA MLMAIRLRGMDLEETSVLTQALAQSGQQLEWPEAWR QQLVDDKHSTGGVDKVSLLAPALACGCKVPMISG RGLGHTGGTLDKLEIPGFNVISPEQMQLLDQAGC CIVGQSEQLVPADGILYAARDVTATVDSLPLITASILSK KLVEGLSALVVDVKFGGAAVFPNQEARELAKTLVG VGASLGLRVAALTAAMDKPLGRVCVGHAEVEEALLC MDGAGPPDLRDLVTTLGGALLWLSGHAGTQAQGAA RVAAALDDGSALGRFERMLAAQGVDPGLARALCSGS PAERRQLPRAREQEELLAPADGTVELVRALPLALVL HELGAGRSRAGEPLRLGVGAELLVDVGQRLRRGTPW LRVHRDGPALSGPQSRALQEALVLSDRAPFAAPSPFA ELVLPPQQ	Cardiovascular
74	eptifibatide		MAP-HAR-GLY-ASP-TRP-PRO-CYS-NH ₂	Antianginal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				Cardiovascular
327	examorelin	GHRP	L-Lysinamide, L-histidyl-2-methyl-D-tryptophyl-L-alanyl-L-tryptophyl-D-phenylalanyl-	Releasing hormone Vulnerary Cardiovascular
75	FG-005		SMR1-QHNPR	Male sexual dysfunction
328	FR-113680		L-Phenylalaninamide, N-acetyl-L-threonyl-1-formyl-D-tryptophyl-N-methyl-N-(phenylmethyl)-	Antiasthma
76	fibronectin-related peptide		Gly-Arg-Gly-Asp-Ser	Anticancer, other
329	G-4120		L-Cysteine, N-(mercaptoacetyl)-D-tyrosyl-L-arginylglycyl-L-alpha-aspartyl-, cyclic (1-5)-sulfide, S-oxide	Antithrombotic
330	EP-51216		2S)-6-amino-2-[[[(2S)-2-[[[(2R)-2-[(4-aminobutanoylamino)-3-(2-methyl-1H-indol-3-yl)propanoyl]amino]-3-(2-methyl-1H-indol-3-yl)propanoyl]amino]-3-(2-methyl-1H-indol-3-yl)propanoyl]amino]hexanamide	GH Releasing hormone Vulnerary, endocrine
8	GLP-1 + exendin-4	GLP-1	HGEGTFTSDLKQMEEAAVRLFIEWLKNGGPSSGAPP PS	Antidiabetic
77	GM-1986		YYWIGIR	Anti-inflammatory
78	GnRH-	GnRH	gi 133908612 refNP_001076580.1 gonadotropin-releasing	Antiprolactin

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	associated peptide		hormone 1 precursor [Homo sapiens] MKPIQKLLAGLILLTWCVEGCSSQHWYGLRPGGKR DAENLIDSFQEIVKEVGQLAETQRFECTTHQPRSPLRD LKGALESLEEETGQKKI	Menstruation disorders Fertility enhancer
79	GRF1-44		gi 11034841 ref NP_066567.1 growth hormone releasing hormone preproprotein [Homo sapiens] MPLWVFFVILTLNSSHCSPPPPLTLRMRRYADAIFT NSYRKV	Musculoskeletal
80	GRF	GHRF	gi 337133 gb AA52609.1 growth hormone releasing factor MPLWVFFVILTLNSSHCSPPPPLTLRMRRYADAIFT NSYRKVLGQLSARKLLQDIMSRQQGESNQERGARAR LGRQVDSMWAEQKQMELESILVALLQKHRNSQG	Idiopathic growth hormone deficiency; cachexia
331	GYKI-14451		L-Prolinamide, N-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]-, (S)-	Antithrombotic
81	galanin		gi 1247490 emb CAA01907.1 galanin [Homo sapiens] MARGSALLLASLLAAALSASAGLWSPAKEKRGWTL NSAGYLLGPHAVGNHRFSFDKNGLTSKRELRPEDDM KPGSFDRSIPENNIMRTIEFLSFLHLKEAGALDRLLDL PAAASSEDIERS	Releasing hormone

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
82	gastrin antagonists		(benzyloxycarbonyl)-L-Glu-L-Ala-L-Tyr-Gly-L-Tyr-L-Met-L-aspartic acid amide	Antiulcer
332	glaspimod		N2,N2'-[2,7-Bis(pyroglutamyl-glutamyl-aspartylamino)-octanediolyl]bis(lysine)	Immunomodulator, anti-infective Immunostimulant, other Radio/chemoprotective
83	glicentin		gi 125987831 sp P01275.3 GLUC_HUMAN Glucagon precursor [Contains: Glicentin; Glicentin-related polypeptide (GRPP); Oxyntomodulin (OXY) (OXM); Glucagon; Glucagon-like peptide 1 (GLP-1); Glucagon-like peptide 1(7-37) (GLP-1(7-37)); Glucagon-like peptide 1(7-36) (GLP-1(7-36)); Glucagon-like peptide 2 (GLP-2)] MKSIYFVAGLFVMLVQGSWQRSLQDTEEKSRFSASQ ADPLSDPDQMNEKRRHSQGTFSTDSYSKYLSRRRAQD FVQWLMNTKRRNRNNIAKRHDEFERHAEGTFTSDVSS YLEGQAKEFIAWLVKGRGRDRDFPEEVAIVEELGRRH ADGSFSDENMTILDNLAARDFINWLIQKITDRK	Insulin Antiulcer Antidiabetic
84	glucagon		H ₂ N-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COOH	hypoglycemia Diagnostic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
84	glucagon	glucagon	His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr	Hypoglycemia
85	gonadorelin analogues	gonadorelin	gi 121522 sp P01148.1 GON1_HUMAN Progonadoliberin-1 precursor (Progonadoliberin I) [Contains: Gonadoliberin-1 (Gonadoliberin I) (Luteinizing hormone-releasing hormone I) (LH-RH I) (Gonadotropin-releasing hormone I) (GnRH-I) (Luliberin I) (Gonadorelin); GnRH-associated peptide 1 (GnRH-associated peptide I)] MKPIQKLLAGLILLTWCVEGCSSQHWSYGLRPGGKR DAENLIDSFQEIVKEVGQLAETQRFECTTHQPRSPRLRD LKGALESLEEETGQKKI	Female contraceptive; enometiosis, uterine leiomyoma, precocious puberty, prostate and breast cancer
333	gonadorelin antagonist		[Ac-DNAL1(2),4FDPhe2,D-Trp3,D-Arg6]-LHRH	Female contraceptive; enometiosis, uterine leiomyoma, precocious puberty, prostate and breast cancer
86	gonadorelin	gonadorelin	5-oxo-L-His-L-Trp-L-Ser-L-Tyr-Gly-L-Leu-L-Arg-L-Pro-glycinamide	Female contraceptive; enometiosis, uterine leiomyoma, precocious

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				puberty, prostate and breast cancer
334	goralatide		L-Proline, 1-[N2-[N-(N-acetyl-L-seryl)-L- α -aspartyl]-L-lysyl]-	Haematological Immunological Radio/chemoprotective
335	H-142		L-Lysine, N2-[N-[N-[4-methyl-2-[[N-[N-[1-(N-L-prolyl-L-histidyl)-L-prolyl]-L-phenylalanyl]-L-histidyl]amino]pentyl]-L-valyl]-L-isoleucyl]-L-histidyl]-, (S)-	Antihypertensive, renin system
336	I5B2		L-Tyrosinamide, N-methyl-L-valyl-N-[2-(4-hydroxyphenyl)-1-phosphonoethyl]-	Antihypertensive, renin system
87	iseganan hydrochloride		L-Argininamide, L-arginylglycylglycyl-L-leucyl-L-cysteinyl-L-tyrosyl-L-cysteinyl-L-arginylglycyl-L-arginyl-L-phenylalanyl-L-cysteinyl-L-valyl-L-cysteinyl-L-valylglycyl-, cyclic (5-14),(7-12)-bis(disulfide) hydrochloride	Antibacterial, other Antifungal Antiviral, other
88	netamifide		L-Tryptophanamide, 4-fluoro-L-phenylalanyl-(4R)-4-hydroxy-L-prolyl-L-arginylglycyl-, bis(trifluoroacetate) (salt)	Antidepressant Anxiolytic
337	icrocaptide		L-Arginine, glycyl-N2-ethyl-L-lysyl-L-prolyl-	Cardiovascular Septic shock treatment

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
338	icatibant		L-Arginine, D-arginyl-L-arginyl-L-prolyl-trans-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2 α ,3 α ,7 α)-octahydro-1H-indole-2-carbonyl-	Cardiovascular Hepatoprotective Vulnerary
339	AG-1776		3-[2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl]-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide	Antiviral, anti-HIV
340	pralmorelin		L-Lysinamide, D-alanyl-3-(2-naphthalenyl)-D-alanyl-L-alanyl-L-tryptophyl-D-phenylalanyl-	Diagnostic Releasing hormone
89	katacalcin	calcitonin	gi 115478 sp P01258.1 CALC_HUMAN Calcitonin precursor [Contains: Calcitonin; Katacalcin (Calcitonin carboxyl-terminal peptide) (CCP) (PDN-21)] MGFQKFSPFLALSILVLLQAGSLHAAPFRSALESSPAD PATLSEDEARLLAALVQDYVQMKASELEQEEREQS SLDSPRSKRCGNLSTCMLGTYTQDFNKFHTFPQTAIG VGAPGKKRDMSSDLERDHRPHVSMPPQAN	Osteoporosis treatment Hormone Recombinant, other
341	ketomethylurea s		N-[N-[3-benzoylamino-4-phenyl-2-oxobutyl]-N-methylaminocarbonyl]proline	Antihypertensive, renin system
90	L-346670		N-L-arginyl-8-L-methionine-21a-L-phenylalanine-21b-L-arginine-21c-L-tyrosine-	Antihypertensive, diuretic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
91	L-364210		N-isovaleryl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-(3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid)-L-leucyl-L-phenylalanylamide	Antihypertensive, renin system
342	L-659837		L-Phenylalanine, N-[2-(3-amino-2-oxo-1-pyrrolidinyl)-4-methyl-1-oxopentyl]-L-methionyl-L-glutaminy-L-tryptophyl-, cyclic (4-1)-peptide, [S-(R*,S*)]-	Analgesic, other
343	L-693549		5(S)-(tert-butoxycarbonylamino)-4(S)-hydroxy-N-[2(R)-hydroxyindan-1(S)-yl]-2(R)-[4-(3-hydroxypropyl)benzyl]-6-phenylhexamide	Antiviral, anti-HIV
344	L-709049		L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-(2-carboxy-1-formylethyl)-, (S)-	Anti-inflammatory
92	LDV-containing peptides		4-((N'-2-methylphenyl)ureido)phenylalanyl-leucyl-alpha-aspartyl-valyl-prolyl-alanyl-alanyl-lysine	Anticancer, other
	Lys-Phe		L-Phenylalanine, N-L-lysyl-	Haematological Antisickling
93	lagatide		D-Alaninamide, L-prolyl-L-valyl-L-threonyl-L-lysyl-L-prolyl-L-glutaminy-	Antidiarrhoeal
94	laminin A peptide		seryl-isoleucyl-lysyl-valyl-alanyl-valinamide	Anticancer, other Neurological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
95	laminin		tyrosyl-isoleucyl-glycyl-serylarginine	Anticancer, other
345	lanreotide	somatostatin	L-Threoninamide, 3-(2-naphthalenyl)-D-alanyl-L-cysteinyll-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyll-, cyclic (2-7)-disulfide ; L-Threoninamide, 3-(1-naphthalenyl)-D-alanyl-L-cysteinyll-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyll-, cyclic (2-7)-disulfide	Acromegaly Anticancer, hormonal Cardiovascular Antidiarrhoeal
346	leuprolide acetate		Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Formulation, implant Anticancer, hormonal Menstruation disorders
347	MCI-826		Butanoic acid, 2,2-diethyl-4-[[3-[2-[4-(1-methylethyl)-2-thiazolyl]ethenyl]phenyl]amino]-4-oxo-, (E)-	Antiasthma
96	omiganan pentahydrochloride		L-lysineamide, L-isoleucyl-L-leucyl-L-arginyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-tryptophyl-L-tryptophyl-L-arginyl, pentahydrochloride	Peptide antibiotic
97-100	MBP		gi 68509940 ref NP_001020272.1 Golli-mbp isoform 1 [Homo sapiens] MGNHAGKRELNAEKASTNSETNRGESEKKNLGEELS RTTSEDNEVFGEADANQNNGTSSQDTAVTDSKRTAD PKNAWQDAHPADPGSRPHLIRLFSDAPGREDNTFKD RPSEDELQTIQEDSAATSESLDVMASQKRPSQRHGSK	Multiple sclerosis treatment Immunosuppressant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			YLATASTMDHARHGFLPRHRDTGILD SIGRFFGGDRG APKRGSGKDSHHPARTAHYGSLPQKSHGRTQDENPV VHFFKNIVTPRTPPPSQKGKGRGLSLSRFSWGAEGRPG FGYGGRASDYKSAHKGFGKVDAQGTLSKIFKLGGRD SRSGSPMARR gi 68509938 ref NP_001020271.1 Golli-mbp isoform 2 [Homo sapiens] MGNHAGKRELNAEKASTNSETNRGESEKKRNLGELS RTTSEDNEVFGEADANQNNGTSSQDTAVTDSKRTAD PKNAWQDAHPADPGSRPHILIRLFSRDAPGREDNTFKD RPSEDELQTIQEDSAATSESLDVMA SQKRP SQRHGSK YLATASTMDHARHGFLPRHRDTGILD SIGRFFGGDRG APKRGSGKVSSEE gi 68509930 ref NP_001020252.1 myelin basic protein isoform 1 [Homo sapiens] MASQKRPSQRHGSKYLATASTMDHARHGFLPRHRDT GILD SIGRFFGGDRGAPKRGSGKVPWLKPGRSPLPSHA RSQPGLCNMYKDSHHPARTAHYGSLPQKSHGRTQDE NPVVHFFKNIVTPRTPPPSQKGKGRGLSLSRFSWGAEQQ RPGFGYGGRASDYKSAHKGFGKVDAQGTLSKIFKLG	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			GRDSRSGSPMARR gi 4505123 ref NP_002376.1 myelin basic protein isoform 2 [Homo sapiens] MASQKRPSQRHGSKYLATATM	
348	MDL-104238		N-[4-(4-morpholinylcarbonyl)benzoyl]-L-valyl-N'-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-2-azetamide	Anti-inflammatory
349	MDL-28050		D-Glutamic acid, N-[N-[N-[N-[1-[N-[1-[N-(3-carboxy-1-oxopropyl)-L-tyrosyl]-L-alpha-glutamyl]-L-prolyl]-L-isoleucyl]-L-prolyl]-L-alpha-glutamyl]-L-alpha-glutamyl]-L-alanyl]-3-cyclohexyl-L-alanyl]-	Antithrombotic Anticoagulant
101	MMP inhibitors		FN 439; FN-439; H2N-C6H4-CO-Gly-Pro-Leu-Ala-NHOH; MMP-inhibitor I; p-NH ₂ -Bz-Gly-Pro-D-Leu-D-Ala-NHOH	Antiarthritic, Anticancer, Anti-inflammatory
350	MR-988		N-pivaloyl-leucyl-gamma-aminobutyric acid	Antiepileptic
351	mertiatide		Glycine, N-[N-[N-(mercaptoacetyl)glycyl]glycyl]-	Diagnostic
352	metkephamide		L-Methioninamide, L-tyrosyl-D-alanyl-glycyl-L-phenylalanyl-N2-methyl-, monoacetate (salt)	Analgesic, other
353	murabutide		D-Glutamine, N2-[N-(N-acetylmuramoyl)-L-alanyl]-, butyl ester	Immunomodulator, anti-infective Anticancer, immunological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				Immunostimulant, other
354	muramyl dipeptide derivatives		D-alpha-Glutamine, N2-[N-(N-acetylmuramoyl)-L-alanyl]-	Immunomodulator, anti-infective Anticancer, immunological Immunostimulant, other
355	NPY24-36		N-acetyl[Leu-28Leu-31]NPY24-36	Antihypotensive
102	NAGA		Asn-Ala-Gly-Ala	Analgesic, other
356	tiplimotide		L-Proline, D-alanyl-L-lysyl-L-prolyl-L-valyl-L-valyl-L-histidyl-L-leucyl-L-phenylalanyl-L-alanyl-L-asparaginyll-L-isoleucyl-L-valyl-L-threonyl-L-prolyl-L-arginyl-L-threonyl-	Multiple sclerosis treatment
103	opebecan		gi 157276599 ref NP_001716.2 bactericidal/permeability-increasing protein precursor [Homo sapiens] MRENMARGPCNAPRWASLMVLVAIGTAVTAAVNPG VVVRISQKGLDYASQQGTALQKELKRIKIPDYSDFS KIKHLGKGHYSFYSMDIREFQLPSSQISMVNPVGLKFS ISNANIKISGKWKAQKRFLKMSGNFDSLIEGMSISADL KLGSNPTSGKPTITCSCSSHINSVHVHISKSKVGWLIQ LFHKKIESALRNKMNSQVCEKVTNSVSSELQPYFQTL PVMTKIDSVAGINYGLVAPPATTAETLDVQMKGEFYS ENHHNPPPFAPPVMEFFAAHDRMVYGLGLSDYFFNTA	Recombinant, other Antibacterial, other GI inflammatory/bowel disorders Vulnerary Anti-inflammatory Symptomatic antidiabetic Ophthalmological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			GLVYQEAGVLKMTLRDDMIPKESKFRLLTTKFFGTFLP EVAKKFPNMKIQIHVSASTPPHLSVQPTGLTFYPVDV QAFVLPNSSLASLFLIGMHTTGSMESVSAESNRLVGE LKLDRLLELKHSNIGPPVELLDIMNYIVPILVLPV NEKLQKGFPLTPARVQLYNVVLQPHQNFLFLFGADV VYK	
104 and 105	liraglutide	GLP-1	Glycine, L-histidyl-L-alanyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-alpha-glutamylglycyl-L-glutaminy-L-alanyl-L-alanyl-N6-[N-(1-oxohexadecyl)-L-gamma-glutamyl]-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-	Antidiabetic Anorectic/Antiobesity
			SFKIKHLGKGHYSFYSM DIREFQLPSSQISMV PNVGLK FSISNANIKISGKWKAQKRFLKMSGNFDLSIE	
106	Nona CCK		GMSISADLKLGSNPTSGKPTITCSSSSHINSVHVHISK SKVGWLIQLFHKKIESALRNKMNSQVCEKVT	Diagnostic Neuroleptic Anorectic/Antiobesity Antidepressant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
107 and 108	NP-06		Cysteinyl-leucyl-glycyl-valyl-glycyl-seryl-cysteiny-l-asparaginy-l-phenylalanyl-alanyl-glycyl-cysteiny-l-glycyl-tyrosyl-alanyl-isoleucyl-valyl-cysteiny-l-phenylalanyl-tryptophan S-3.1-S-3.13:S-3.7-S-3.19-bis(disulfide)N-2.1-C-4.9-lactam NSVSSELQPYFQTLPVMTKIDSVAGINYGLVAPPATTA ETLDVQMKGEFYSENHHNPPPFAPPVMEFPAA	Antiviral, anti-HIV
109	NPC-18545		Bradykinin, N2-D-arginyl-3-(trans-4-hydroxy-L-proline)-7-(D-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid)-8-[L-(2alpha,3aß,7a.beta.)-octahydro-1H-indole-2-carboxylic acid]- HDRMVYGLSDYFFNTAGLVYQEAGVLKMTLRDDM IPKESKFRLTTKFFGTFLPEVAKKFPNMKIQIHVS	Anti-inflammatory
110	Nva-FMDP		Nva-N3-4-methoxyfumaroyl-L-2,3-diaminopropanoic acid ASTPPHLSVQPTGLTFYPAVDVQAFVLPNSSLASLFL IGMHTTGSMEVSAESNRLVGELKLDRLLELK	Antifungal
111	nacartocin		6-Carbaoxytocin, 1-(3-mercaptopropanoic acid)-2-(4-ethyl-L-phenylalanine)- HSNIGPFPVELLQDIMNYIVPILVLPRVNEKLQKGFPLP	Hormone Labour inducer Antihypertensive, diuretic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			TPARVQLYNVVLQPHQNFLFLFGADVVK	
112	natural peptide		U.S. Patent No. 5,288,708 Partial N terminal sequence: H ₂ N-Gly-Glu-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-... --COOH	Antiulcer Hepatoprotective Vulnerary Anti-inflammatory Antiparkinsonian Urological
39	nesiritide citrate	BNP	SPKMVQSGGCFGRKMDRISSSSGLGCKVLRH	Cardiostimulant Vasodilator, coronary
113-141	neurotrophic factors		U.S. Patent No. 5,545,719: AspLeuGlnValPheVal; GlyGluLysLysAsp; AlaThrHisGluSer; CysLeuProValSerGly;LeuProValSerGlySer; ProCysHisAlaProPro; GlyGlyHisAspLeuGluSerGly; AspAspLeuGlnValPhe 15 ProLeuThrSerGly 15 LeulleHisPheGluGluGlyVal 15 (2) INFORMATION FOR SEQ ID NO:11: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE	Cognition enhancer Neuroprotective

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			DESCRIPTION: SEQ ID NO:11: GlyGluPheSerTyrAspSer 15 (2) INFORMATION FOR SEQ ID NO:12: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12: HisAlaProProLeuThrSer 15 (2) INFORMATION FOR SEQ ID NO:13: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14: GlyGluPheSerValCysAspSer 15 (2) INFORMATION FOR SEQ ID NO:15: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 10 amino acids (B) TYPE: amino acid (D)	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15: LysLysGlyGluPheSerValAlaAspSer 1510 (2) INFORMATION FOR SEQ ID NO:16: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 9 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16: LysLysGlyGluPheTyrCysSerArg 15 (2) INFORMATION FOR SEQ ID NO:17: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 13 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17: GlyLeuArgValArgValTrpAsnGlyLysPheProLys 1510 (2) INFORMATION FOR SEQ ID NO:18: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE:	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18: GlyValAlaPheGluGluAlaProAspAspHisSerPhePheLeuPhe 151015 (2) INFORMATION FOR SEQ ID NO:19: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19: GlyGlyHisAspLeuSerGly 15 (2) INFORMATION FOR SEQ ID NO:20: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20: GlyGlyHisAspLeuGluSerGly 15 (2) INFORMATION FOR SEQ ID NO:21: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21: GlyGlyHisAspLeuGluSerGlyGluPheSerTyrAspSer 1510 (2)	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			INFORMATION FOR SEQ ID NO:22: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22: GlyGlySerAspLeuSerGlyGluPheSerValCysAspSer 1510 (2) INFORMATION FOR SEQ ID NO:23: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23: GlyGlySerAspLeuSerGlyGlyGluPheSerValCysAspSer 151015 (2) INFORMATION FOR SEQ ID NO:24: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: GlyGlySerAspLeuSerGlyGlyGluPheSerValAlaAspSer 151015 (2) INFORMATION FOR SEQ ID NO:25: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25: GlyGlySerAspLeuSerGlyGluPheSerValAlaAspSer 1510 (2) INFORMATION FOR SEQ ID NO:26: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 6 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26: GluThrLeuGlnPheArg 15 (2) INFORMATION FOR SEQ ID NO:27: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27: LysLysGluThrLeuGlnPheArg 15 (2) INFORMATION FOR SEQ ID NO:28: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			DESCRIPTION: SEQ ID NO:28: GluThrLeuGlnPheArgLysLys 15 (2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 9 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: LysAlaSerThrThrThrAsnTyrThr 15	
357	nifalotide		L-Prolinamide, L-tyrosyl-4-(methylsulfinyl)-D-2-aminobutanoylglycyl-4-nitro-L-phenylalanyl-	Antidiarrhoeal Analgesic, other
358	Org-2766		L-Phenylalanine, 4-(methylsulfonyl)-L-2-aminobutanoyl-L-alpha-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-	ACTH Symptomatic antidiabetic Radio/chemoprotective Neurological
359	Org-30035		L-Phenylalanine, glycylglycyl-L-phenylalanyl-4-(methylsulfonyl)-L-2-aminobutanoyl-D-lysyl-	Neuroleptic Anxiolytic
360	octreotide	somatostatin	L-Cysteinamide, D-phenylalanyl-L-cysteinyll-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]- ; L-Cysteinamide, D-phenylalanyl-L-cysteinyll-	Acromegaly Antidiarrhoeal Anticancer, hormonal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-(2-hydroxy-1-(hydroxymethyl)propyl)-, cyclic (2-7)-disulfide, (R-(R*,R*))-	
142	osteogenic growth peptide		Glycine, L-alanyl-L-leucyl-L-lysyl-L-arginyl-L-glutamylglycyl-L-arginyl-L-threonyl-L-leucyl-L-tyrosylglycyl-L-phenylalanylglycyl-	Osteoporosis treatment
143	P-113		Angiotensin II, 1-(N-methylglycine)-5-L-valine-8-L-alanine-[CAS]; (Sar(1),Ala(8))ANGII; (Sar1,Val5,Ala8)Angiotensin II; 1 Sar 8 Ala Angiotensin II; 1 Sarcosine 8 Alanine Angiotensin II; 1-Sar-8-Ala Angiotensin II; 1-Sar-8-Ala-angiotensin II; 1-Sarcosine-8-Alanine Angiotensin II; Acetate, Hydrated Saralasin; Angiotensin II, 1-Sar-8-Ala; Angiotensin II, 1-Sarcosine-8-Alanine; Anhydrous Saralasin Acetate; Hydrated Saralasin Acetate; P-113; P-113 Acetate; Sar Arg Val Tyr Val His Pro Ala; Sar-Arg-Val-Tyr-Val-His-Pro-Ala; Saralasin Acetate; Saralasin Acetate, Anhydrous; Saralasin Acetate, Hydrated; angiotensin II, Sar(1)-Ala(8)-; angiotensin II, sarcosyl(1)-alanine(8)-	Stomatological Antibacterial, other Antifungal
361	PACAP 27		Pituitary adenylate cyclase-activating peptide-27	Antiviral, anti-HIV
362	PAPP		N-(dibenzoyloxyposphophonyl)-L-alanyl-L-prolyl-L-	Antihypertensive, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			proline	
363	PD-83176		CBZ-his-tyr(OBn)-ser(OBn)-trp-D-ala-NH ₂	Anticancer, other
364	PD-122264		N-[(1,1-dimethylethoxy)carbonyl]-alpha-methyltryptophyl-L-phenylalaninamide	Anorectic/Antiobesity Analgesic, other
365	PD-132002		DL-Serinamide, N-(4-morpholinsulfonyl)-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]-O-methyl-3-oxo-, [1S-(1R*,2S*,3R*)]-	Antihypertensive, renin system
144	Penetratin		U.S. Patent Nos. 5,888,762 and 6,080,762; PCT Pub. Nos. WO/2000/29427 and WO/2000/01417: NH2-Arg Lys Arg Gly Arg Gln Thr Tyr Thr Arg Tyr Gln Thr Leu Glu Leu Glu Lys Glu Phe His Phe Asn Arg Tyr Leu Thr Arg Arg Arg Arg Ile Glu Ile Ala His Ala Leu Cys Leu Thr Glu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys Glu Asn-COOH.	Formulation technology
366	PL-030		Glycinamide, L-tyrosyl-L-prolyl-N-methyl-L-phenylalanyl-D-prolyl-	Analgesic, other
367	POL-443		Z-prolyl-leucyl-tryptophan	Antihypertensive, renin system
368	POL-509		L-Tryptophan, N-[N-(5-oxo-L-prolyl)-L-leucyl]-, methyl ester-	Immunostimulant, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
369	PPA		D-phenylalanine-L-proline-L-arginylchloromethane	Anticoagulant Diagnostic Antithrombotic
145	PR-39		L-Prolinamide, L-arginyl-L-arginyl-L-arginyl-L-prolyl-L-arginyl-L-prolyl-L-prolyl-L-tyrosyl-L-leucyl-L-prolyl-L-arginyl-L-prolyl-L-arginyl-L-phenylalanyl-L-prolyl-L-phenylalanyl-L-prolyl-L-arginyl-L-leucyl-L-prolyl-L-arginyl-L-isoleucyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-prolyl-L-arginyl-L-phenylalanyl-L-prolyl-L-phenylalanyl-L-phenylalanyl-	Antibacterial, other
146	tigapotide triflutate		L-Threonine, L-alpha-glutamyl-L-tryptophyl-L-glutaminyll-threonyl-L-alpha-aspartyl-L-asparaginyll-S-[(acetylamino)methyl]-L-cysteinyl-L-alpha-glutamyl-L-threonyl-S-[(acetylamino)methyl]-L-cysteinyl-L-threonyl-S-[(acetylamino)methyl]-L-cysteinyl-L-tyrosyl-L-alpha-glutamyl-, mono(trifluoroacetate)	Anticancer, other
370	PT-14		L-Lysinamide, N-acetyl-L-norleucyl-L-alpha-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-, cyclic (2-7)-peptide	Male sexual dysfunction Female sexual dysfunction
147	PT-5	somatostatin	gi 21619156 gb AAH32625.1 Somatostatin [Homo sapiens]	Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQFLQK SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLLELQRSANSNPAMAPRERKAGCKNFF WKTFTSC	
148	semparatide	PTHrP	gi 131542 sp P12272.1 PTHR_HUMAN Parathyroid hormone-related protein precursor (PTH-rP) (PTHrP) [Contains: PTHrP[1-36]; PTHrP[38-94]; Osteostatin (PTHrP[107-139])] MQRRLVQQWSVAVFLLSYAVPSCGRSVEGLSRRLKR AVSEHQLLDKKGKSIQDLRRRFFLHHLIAEIHAEIRA TSEVSPNSKPSNTKNHPVFGSDDEGRYLTQETNKVE TYKEQPLKTPGKKKKKGKPGKRKEQKKRRTRSAWL DSGVTGSGLEGDHLSDTSTTSLELDSRRH	Hormone Osteoporosis treatment
149	parathyroid hormone fragments	PTH	SVSEIQLMHNLGKHLNSMERVEWLKKLQDVHNF	Osteoporosis treatment
150	enfuvirtide		L-Phenylalaninamide, N-acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histidyl-L-seryl-L-leucyl-L-isoleucyl-L-alpha-glutamyl-L-alpha-glutamyl-L-seryl-L-glutamyl-L-asparaginy-L-glutaminy-L-glutaminy-L-	Antiviral, anti-HIV

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			alpha-glutamyl-L-lysyl-L-asparaginyL-L-alpha-glutamyl-L-glutaminyL-L-alpha-glutamyl-L-leucyl-L-leucyl-L-alpha-glutamyl-L-leucyl-L-alpha-aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-asparaginyL-L-tryptophyl-	
151	pentapeptide 6A		Ala-Arg-Pro-Ala-Lys	Vasodilator, coronary
371	pentigetide		L-Arginine, N2-[1-[N-(N-L-alpha-aspartyl-L-seryl)-L-alpha-aspartyl]-L-prolyl]-	Antiallergic, non-asthma Ophthalmological Antiasthma
372	peptide analogues		N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-N1-methylisophthalamide	Ophthalmological Antiarthritic, other Antiulcer Antihypertensive, other Multiple sclerosis treatment COPD treatment
373	peptide G		[Arg(6),D-Trp(7,9),MePhe(8)]substance P	Anticancer, other
374	peptide T analogue		D-Ala1-peptide T	Antiviral, anti-HIV

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
375	peptide T		L-Threonine, N-[N-[N2-[N-[N-[N-(N-L-alanyl-L-seryl)-L-threonyl]-L-threonyl]-L-threonyl]-L-asparaginy]]-L-tyrosyl]-	Analgesic, other Antiviral, other Antiarthritic, other GI inflammatory/bowel disorders Anti-inflammatory
152	pramlintide		1,2-Dithia-5,8,11,14,17-pentaazacycloeicosane, cyclic peptide derivative U.S. Patent No. 5,998,367 gi 10066209 gb AAE39671.1 Sequence 1 from patent US 5998367 KCNTATCATQRLANFLVHSSNFGAILSSTNVGSNTY;	Antidiabetic Anorectic/Antiobesity
376	pranlukast		Benzamide, N-[4-oxo-2-(1H-tetrazol-5-yl)-4H-1-benzopyran-8-yl]-4-(4-phenylbutoxy)- ; 8-(4 (4-phenylbutoxy)benzoyl)amino-2-(tetrazol-5'-yl)-4-oxo-4H-1-benzopyran	Antiasthma Antiallergic, non-asthma
3	proinsulin	proinsulin	gi 59036749 gb AAW83741.1 proinsulin [Homo sapiens] MALWMRLLPLLALLALWGPDPAAAFVNQHLCGSHL VEALYLVCGERGFFYTPKTRREAEDLQVGVQLGGG PGAGSLQPLALEGSLQKRGIVEQCCTSIKSLYQLENYC	Antidiabetic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			N	
377	protirelin	TRH	L-Prolinamide, 5-oxo-L-prolyl-L-histidyl- ; 2-Nle-3-Prot-protirelin; TRH, Nle(2)-Prot(3)-; pyroglutamyl-norleucyl-proline thioamide	Releasing hormone Diagnostic
378	protirelin	TRH	prolinamide, 5-oxo-L-prolyl-L-histidyl-	Releasing hormone Cognition enhancer
153	Ro-25-1553		L-Threoninamide, N-acetyl-L-histidyl-L-seryl-L-alpha-aspartyl-L-alanyl-L-valyl-L-phenylalanyl-L-threonyl-L-alpha-glutamyl-L-asparaginy-L-tyrosyl-L-threonyl-L-lysyl-L-leucyl-L-arginyl-L-lysyl-L-glutaminy-L-norleucyl-L-alanyl-L-alanyl-L-lysyl-L-lysyl-L-tyrosyl-L-leucyl-L-asparaginy-L-alpha-aspartyl-L-leucyl-L-lysyl-L-lysylglycylglycyl-, (25-21)-lactam	Antiasthma Anti-inflammatory
379	RWJ-51438		N-methylphenylalanyl-N-(4-((aminoiminomethyl)amino)-1-(((6-carboxy-2-benzothiazolyl)carbonyl)butyl)prolinamide	Antithrombotic
380	TRH	TRH	L-Prolinamide, 5-oxo-L-prolyl-L-histidyl-3,3-dimethyl- ; pyroGlu-His-Pro-NH ₂ (or 5-oxo-L-prolyl-L-histidyl-L-prolinamide)	Diagnostic Thyroid hormone Releasing hormone
154	renin inhibitors		Boc-Leu-Lys-Arg-Met-Pro-OMe	Antihypertensive,
381	romurtide		L-Lysine, N2-[N2-[N-(N-acetyl-muramoyl)-L-alanyl]-D-	Radio/chemoprotective

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			alpha-glutaminy]-N6-(1-oxooctadecyl)- ; L-Lysine, N2-(N2-(N-(N-acetylmuramoyl)-L-alanyl)-D-alpha-glutaminy)-N6-(1-oxooctadecyl)-	Immunostimulant, other
382	S-17162		L-Tryptophan, N-[(2,3-dihydroxypropoxy)hydroxyphosphiny]-L-leucyl-, disodium salt	Urological
383	S-2441		L-Argininamide, D-prolyl-L-phenylalanyl-N-heptyl-	Antimigraine Antigout Septic shock treatment
384	SDZ-CO-611	somatostatin	L-Cysteinamide, N-(1-deoxy-4-O-.alpha.-D-glucopyranosyl-D-fructopyranos-1-yl)-D-phenylalanyl-L-cysteiny]-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2.fwdarw.7)-disulfide, [R-(R*,R*)]-	Somatostatin
385	SK&F-101926		L-Argininamide, O-ethyl-N-[(1-mercaptocyclohexyl)acetyl]-D-tyrosyl-L-phenylalanyl-L-valyl-L-asparaginy]-L-cysteinyl-L-prolyl-, cyclic (1-5)-disulfide	Antihypertensive, diuretic
386	SK&F-110679		His-D-Trp-Ala-Trp-D-Phe-LysNH ₂	Releasing hormone Vulnerary
387	edotreotide		[N-[2-[4,7-Bis[(carboxy-kappaO)methyl]-10-	Anticancer, hormonal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl-kappaN1,kappaN4,kappaN10[acetyl]-D-phenylalanyl-L-cysteiny-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteiny-L-threoninol cyclic (2-7)-disulfidato(3-)]yttrium	
155	SP-1		pGlu-Glu-Asp-Cys-Lys	Anticancer, other
156	SPAAT		L-Lysine, L-methionyl-L-phenylalanyl-L-leucyl-L-alpha-glutamyl-L-alanyl-L-isoleucyl-L-prolyl-L-methionyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-alpha-glutamyl-L-valyl-L-lysyl-L-phenylalanyl-L-asparaginy-L-lysyl-L-prolyl-L-phenylalanyl-L-valyl-L-phenylalanyl-L-leucyl-L-methionyl-L-isoleucyl-L-alpha-glutamyl-L-glutaminy-L-asparaginy-L-threonyl-L-lysyl-L-seryl-L-prolyl-L-leucyl-L-phenylalanyl-L-methionylglycyl-L-lysyl-L-valyl-L-valyl-L-asparaginy-L-prolyl-L-threonyl-L-glutaminy-L-	COPD treatment
388	SR-41476		Z-Tyr-Val-Sta-Ala-Sta-OMe	Antiviral, anti-HIV
389	SR-42128		1-[N-(3-methyl-1-oxobutyl)-L-phenylalanine]-2-L-norleucine-	Antihypertensive, renin system
157	SR-42654		isoval-phe-norleu-sta-ala-sta-lys	Antihypertensive, renin system
147	SRIF-A	somatostatin	gi 21619156 gb AAH32625.1 Somatostatin [Homo sapiens]	Somatostatin

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			MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQFLQK SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLQLQRSANSNPAMAPRERKAGCKNFF WKTFTSC 8-D-tryptophan-14-D-cysteinesomatostatin (sheep)	Haemostatic Alimentary/Metabolic, other
158	calcitonin	calcitonin	CSNLSTCVLGKLSQELHKLQTYPRNTGSGTP	Osteoporosis treatment
390	salmon calcitonin	calcitonin	11,18-Arg-14-Lys-salmon calcitonin; 11,18-arginyl-14-lysine-salmon calcitonin; Arg-Lys-Arg-CT; calcitonin, salmon, arginyl(11,18)-lysine(14)-	Osteoporosis treatment
159	sermorelin		Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH ₂	Idiopathic growth hormone deficiency Imaging agent
391	saralasin acetate		1-Sar-8-Ala-angiotensin; Angiotensin II, 1-(N-methylglycine)-5-L-valine-8-L-alanine-	Antihypertensive, renin system
160	secretin		His-Ser-Asp-Gly-Thr-Phe-OMe; histidyl-seryl-aspartyl-glycyl-threonyl-phenylalanine-O-methyl-	Haemostatic; pancreatic dysfunction (diagnostic), asthma, COPD, others
159	sermorelin acetate		Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-	Releasing hormone Diagnostic

[illegible]

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
165	somatostatin analogue	somatostatin	des-(Ala1,Gly2)-(D-Trp8,D-Asu(3,14))-somatostatin, ARARLGRQVDSMWAEQKQMELESILVALLQKHSRNS QG	Acromegaly Antidiabetic Diagnostic
392	somatostatin analogues	somatostatin	cyclo-(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe)-somatostatin	Acromegaly Antidiabetic
393	somatostatin	somatostatin	3,14-Dicarbasonatostatin, 1-de-L-alanine-2-deglycine-3-butanoic acid-11-L-tyrosine-	Acromegaly
394	somatostatin	somatostatin	3,14-Dicarbasonatostatin, 1-de-L-alanine-2-deglycine-3-butanoic acid-11-L-tyrosine-	Acromegaly
395	syndyphalin		Glycinamide, L-tyrosyl-4-(methylsulfinyl)-D-2-aminobutanoyl-N-methyl-N-(2-phenylethyl)-	Analgesic, other
166	synthetic peptide BPC		gi 109948285 refNP_001035971.1 poly(A) binding protein, cytoplasmic 1-like 2B [Homo sapiens] MASLYVGDLHPEVTEAMLYEKFSPAGPILSIRICRDKI TRRSLGYAYVNYQQPVDAKRALETNLNFDVIKG RPVRIMWSQRDPSLRKSGVGNVFIKNLTKIDNKALY NIFS AFGNILSCKVACDEKGPKGYGVFHFQKQE SAERAIDVMNGMFLNYRKIFVGRFKSHKERE AERGA WARQSTSADV KDFEEDTDEEATLR	Antiulcer Hepatoprotective Vulnerary Anti-inflammatory Antiparkinsonian Musculoskeletal
167	T22		L-Argininamide, L-arginyl-L-arginyl-L-tryptophyl-L-	Antiviral, anti-HIV

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-L-cysteiny-L-tyrosyl-L-lysylglycyl-L-tyrosyl-L-cysteiny-L-tyrosyl-L-arginyl-L-lysyl-L-cysteiny-, cyclic (4-17),(8-13)-bis(disulfide)	
396	Tc-99m depreotide		Technetium-99Tc, (cyclo(L-homocysteinyl-N-methyl-L-phenylalanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl) (1-1')-thioether with 3-((mercaptoacetyl)amino)-L-alanyl-L-lysyl-L-cysteiny-L-lysynamidato(3-))oxo-, (SP-5-24)-	Imaging agent
397	Tc-99m-P280		13, 13'-[Oxybis[methylene(2,5-dioxo-1,3-pyrrolidinediy)]][bis[N-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinyglycyl-L-alpha-aspartyl-L-cisteinyglycylglycyl-S-[(acetylamino)mehtyl]-L-cysteinyglycyl-S-[(acetylamino)methyl-L-cysteinyglycylglycyl-L-cysteinamide], cyclic (1 --> 5), (1' --> 5'), -bis(sulfide)	Imaging agent Antithrombotic
398	TEI-1345		(7E)-8-(2-naphthyl)-5,6-trans-5,6-methano-7-octenyl 3-(3,4-dimethoxyphenyl)-2-propenoate	Anti-inflammatory
168	THF		Leu-Glu-Asp-Gly-Pro-Lys-Phe-Leu;leucyl-glutamyl-aspartyl-glycyl-prolyl-lysyl-phenylalanyl-leucine	Immunomodulator, anti-infective, Immunostimulant, anti-AIDS

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
169	Theradigm-HBV		Dipalmitoyl-Lys-Ser-Ser-Gln-Tyr-Ile-Lys-Ala-Asn-Ser-Lys-Phe-Ile-Gly-Ile-Thr-Glu-Ala-Ala-Phe-Leu-Pro-Ser-Asp-Phe-Phe-Pro-Ser-Val-OH	Immunomodulator, anti-infective Immunostimulant
80	tesamorelin acetate	GHRF	gi 337133 gb AA52609.1 growth hormone releasing factor MPLWVFFVFVILTLNSSHCSPPPPLTLRMRRYADAIFT NSYRKVLGQLSARKLLQDIMSRQQGESNQERGARAR LGRQVDSMWAEQKQMELESILVALLQKHRNSQG (3E)-Hex-3-enoylsomatoliberin (human) acetate (salt)	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
170	TP-9201		L-Cysteinamide, N-acetyl-L-cysteinyll-L-asparaginyll-L-prolyl-L-arginylglycyl-L-alpha-aspartyl-O-methyl-L-tyrosyl-L-arginyl-, cyclic (1-9)-disulfide	Neuroprotective, Antithrombotic, Antianginal, Cardiovascular
399	TRH analogues	TRH	pyroGlu-His-Pro-NH ₂ (or 5-oxo-L-prolyl-L-histidyl-L-prolinamide)	Cognition enhancer
400	TT-235		[β,β-(3-Thiapentamethylene)-β-sulfanylpropionic acid, D-Trp2, Pen6, Arg8]-oxytocin acetate	Labour inhibitor
401	tabilautide		L-Lysinamide, 6-carboxy-N6-[N-[N-(1-oxododecyl)-L-alanyl]-D-gamma-glutamyl]-, (S)-	Immunomodulator, anti-infective Radio/chemoprotective

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				Immunostimulant, other
171 and 172	terlipressin		N-[N-(N-glycylglycyl)glycyl]-8-L-lysine- ; Gly-Gly-Gly-8-Lys-vasopressin; N-(alpha)-glycyl-glycyl-glycyl-8-lysine vasopressin; Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH ₂ ; N-(N-(N-glycylglycyl)glycyl)-8-L-lysine vasopressin	Haemostatic; GI bleeding
171 and 172	terlipressin		N-[N-(N-glycylglycyl)glycyl]-8-L-lysine- ; Gly-Gly-Gly-8-Lys-vasopressin; N-(alpha)-glycyl-glycyl-glycyl-8-lysine vasopressin; Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH ₂	Haemostatic; GI bleeding
402	teverelix		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N6-(aminocarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-	Anticancer, hormonal Prostate disorders Menstruation disorders Fertility enhancer Male contraceptive
403	thymopentin		L-Tyrosine, N-[N-[N-(N2-L-arginyl-L-lysyl)-L-alpha-aspartyl]-L-valyl]- ; L-Tyrosine, N-(N-(N2-L-arginyl-L-lysyl)-L-alpha-aspartyl)-L-valyl)-	Immunostimulant, other Immunomodulator, anti-infective
404	triletide		L-Histidine, N-[N-(N-acetyl-L-phenylalanyl)-L-phenylalanyl]-, methylester	Antiulcer

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
405	tuftsin		L-Arginine, N2-[1-(N2-L-threonyl-L-lysyl)-L-prolyl]-	Anticancer, immunological Immunostimulant, other
173	Uroguanylin		Guanylin (rat reduced), 1-L-glutamine-2-L-glutamic acid-3-L-aspartic acid-6-L-leucine-8-L-isoleucine-9-L-asparagine-10-L-valine-	Alimentary/Metabolic, other Antidiarrhoeal Diagnostic
174	VIC		gi 6681267 ref NP_031929.1 endothelin 3 [Mus musculus] MEPGLWLLGLTVTSAAGLVPCPQSGDSGRASVSQGP PEAGSERGCEETVAGPGERIVSPTVALPAQPESAGQER APGRSGKQEDKGLPAHHRPRRRCCTCFTYKDKECVYYC HLDIIWINTPEQTVPYGLSNYRESLRGKRSLGPVPESQ PSPWTRLRCTCMGADDKACAHFCARTRDVTSYSGRA ERPAAEEMRETGGPRQRRLMSRTDKAHRP	Gastroprokinetic
175	VIP derivative		gi 5803023 ref NP_006807.1 lectin, mannose-binding 2 [Homo sapiens] MAAEGWIWRWGWGRRCLGRPGLLGP GPPTTPLFLL LLLSVTADITDGNSEHLKREHSLIKPYQGVGSSSMPL WDFQGSTMLTSQYVRLTPDERSKEGSIWNHQP CFLKD WEMHVHFKVHGTGKKNLHGDGIALWYTRDRLVP GP VFGSKDNFHLAIFLDTPNDETTTERVFPYISVMVNN	Antiasthma Vasodilator, peripheral

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			GSLSYDHSKDGRWTELAGCTADFRNRDHDFTFLAVRY SRGRLTVMTDLEDKNEWKNCIDITGVRLPTGYFFGAS AGTGDLSDNHDISMKLFQLMVEHTPDEESIDWTKIEP SVNFLKSPKDNVDDPTGNFRSGPLTGWRVFLLLCAL LGIVVCAVVGA VVFQKRQERNKRFY	
147	vapreotide, immediate- release	somatostatin	gi 21619156 gb AAH32625.1 Somatostatin [Homo sapiens] MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQLQK SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLQLQRSANSNPAMAPRERKAGCKNFF WKTFTSC L-Tryptophanamide, D-phenylalanyl-L-cysteiny-L-tyrosyl- D-tryptophyl-L-lysyl-L-valyl-L-cysteiny-L-, cyclic (2-7)- disulfide-	Formulation, modified- release, immediate Somatostatin Haemostatic Anticancer, hormonal Antidiarrhoeal GI inflammatory/bowel disorders
406	Pharmaprojects No. 1269		L-Proline, 1-[N-[N-[1-[4-(4-hydroxyphenyl)-1-oxobutyl]-L-prolyl]-.alpha.-methyl-DL-phenylalanyl]glycyl]-	Vasodilator, renal
407	Pharmaprojects No. 1583		N(alpha)-((3S)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-histidyl-L-prol inamide	Neuroleptic Antiparkinsonian
408	Pharmaprojects No. 1626		D-2-phenylglycyl-D-2-phenylglycine	Anticancer, immunological Immunostimulant, other
409	Pharmaprojects		N-acyl-D-glutamyl-l-meso-diaminopimelyl-l-lysine	Immunomodulator, anti-

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	No. 1779		tripeptide derivatives	infective Immunostimulant, other
176	Pharmaprojects No. 1876		Thr-Asp-Ser-Phe-Val-Gly-Leu-Methionylamide	Antihypertensive, other
410	Pharmaprojects No. 1913		L-leucyl-D-methionyl-glucyl-N-(2-adamantyl)-L-phenylalanylamide	Antihypertensive, renin system
177	Pharmaprojects No. 1939		Lys-Pro-Gly-Glu-Pro-Gly-Pro-Lys	Anticoagulant
178-182, 178, 183-185 and 178	Pharmaprojects No. 2063		U.S. Patent No. 4,461,724 and European Patent No. EP0078228: GSHK; ASHK; A _D SHK; LSHK; TSHK; YSHK; GSHKCH ₃ COOH.H ₂ O; SAR-SHK; PSHK; (PYR)ESHK; WSHK; GSHK.2TosOH	Antiulcer Antithrombotic
411	Pharmaprojects No. 2363		N-methyl-D-Phe-Pro-Arg-H	Antithrombotic
186	Pharmaprojects No. 2388		N-3-(4-hydroxyphenyl)propionyl-Pro-Hyp-Gly-Ala-Gly	Antiarrhythmic
412	Pharmaprojects No. 2425		Glp-lys-NH ₂ -L-mandelate	Anticancer, immunological Immunostimulant, other
413	Pharmaprojects No. 3341		D-1-Tiq-Pro-Arg-H-sulfate	Antithrombotic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
414	Pharmaprojects No. 3415		(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide	Antiviral, anti-HIV
415	Pharmaprojects No. 4004		Piv-1-Ser-Leu-GABA, and Piv-Ser-Leu-GABA	Neurological
416	Pharmaprojects No. 4323		(1R,4aR,8aR)-1,2,3,4,5,6,7,8-perhydroisoquinolin-1-carbonyl-(L)-prolinyl-(L)-arinine aldehyde	Antithrombotic Anticoagulant
187, and 417	Pharmaprojects No. 491		H-Trp-Ala-Ser-Gly-L-Asn-OH & H-Trp-D-Ala-Ser-Gly-Asp(OH) ₂	Hypnotic/Sedative Antidepressant Neuroprotective
188	Pharmaprojects No. 4975		H ₂ N-Asp-Ala-Asp-Pro-Arg-Gln-Tyr-Ala-COOH	Anti-inflammatory
418	Pharmaprojects No. 5200		2-Amino-N-{1-(R)-benzyloxymethyl-2-[4-(morpholine-4-carbonyl)-4-phenyl-piperidin-1-yl]-2-oxo-ethyl}-isobutyramide	Osteoporosis treatment
419	Pharmaprojects No. 5356		4-chloro-phenylcarbonyl-thienylalanyl-leucyl-phenylalanine	Anti-inflammatory Anti-infective, other
420	DMP-444		synthetic cyclic pentapeptide (cyclo(D-Val-NMeArg-Gly-Asp-Mamb))with a tethered hydrazinonicotinyl (HYNIC) chelator for radiolabelling with 99mTc	Imaging agent

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189	RIP-3		MSCVKLWPSGAPAPLVSIIELENQELVGKGGFTVFR AQHRKWGYDVAVKIVNSKAISREVKAMASLDNEFVL RLEGVIEKVNWDQDPKPALVTKFMENGSLGSLQSQ CPRPWPLLCRLLKEVVGLGMFYLHDQNPVLLHRDLKPS NVLLDPELVKLAADFGLSTFQGGSGSGTSGGEGGTL GYLAPELFVNVRKASTASDVYSFGILMWA VLAGRE VELPTEPSLVYEAVCNQRNRP SLAELPQAGPETPGLEG LKELMQLCWSSEPKDRPSFQECLPKTDEVFQMVENN MNAAVSTVKDFLSQLRSSNR RFSIPESGQGGTEMDFG RRTIENQHSRNDVMVSEWLNKLNLEPPSSVPKKCPS LTKRSRAQEEQVPQAWTAGTSSDSMAQPPQTPETSTF RNQMPSPTSTGTSPGPRGNQGAERQGMNWSCRTPEP NPVTGRPLVNIYNCSGVQVGDNNYLTMQQTALPTW GLAPSGKGRGLQHPPPVGSQEGPKDPEAWSRPQGWY NHSGK	Anticancer, other
421	Pharmaprojects No. 955		N-(N-acetyl-L-isoleucyl-L-tyrosyl)-(-)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid	Antihypertensive, other
422	leuprolide		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Formulation, modified-release, Anticancer
190	edratide		L-glycyl-L-tyrosyl-L-tyrosyl- L-tryptophyl-L-seryl-L-	Immunosuppressant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			tryptophyl-L-isoleucyl-L-arginyl-L-glutamyl-L-prolyl-L-prolyl-L-glycyl-L-lysyl-L-glycyl-L-glutamyl-L-glutamyl-L-tryptophyl-L-isoleucyl-L-glycine	
423	Prosaptide TX14(A)		H-Thr-D-Ala-Leu-Ile-Asp-Asn-Asn-Ala-Thr-Glu-Glu-Ile-Leu-Tyr-OH	Symptomatic antidiabetic Neurological Analgesic, other
8	GLP-1	GLP-1	HGEGTFTSDLSKQMEEAAVRLFIEWLKNGGPSSGAPP PS	Antidiabetic
160	secretin		His-Ser-Asp-Gly-Thr-Phe-OMe; histidyl-seryl-aspartyl-glycyl-threonyl-phenylalanine-O-methyl-	Hormone, Diagnostic, GI inflammatory/bowel disorders, Neurological, Neuroleptic
147	BIM-23190	somatostatin	gi 21619156 gb AAH32625.1 Somatostatin [Homo sapiens] MLSCRLQCALAAALSIVLALGCVTGAPSDPRLRQFLQK SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLLELQRSANSNPAMAPRERKAGCKNFF WKTFTSC L-Threoninamide, N-[[4-(2-hydroxyethyl)-1-piperazinyl]acetyl]-D-phenylalanyl-L-cysteiny-L-tyrosyl-D-tryptophyl-L-lysyl-(2S)-2-aminobutanoyl-L-cysteinyL-	Acromegaly Antidiabetic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			cyclic (2-7)-disulfide	
424	leuprorelin		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Formulation, Anticancer
191	β -amyloid peptides	beta-amyloid peptide	gi 8176533 gb AAB26264.2 beta-amyloid peptide precursor; beta APP [Homo sapiens] GSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFF AEDVGSNKGAIIGLMVGGVVIATVIIIITLVMLK KQYTSNHHGVVE	Cognition enhancer
425	oglufanide disodium		L-tryptophan, L-alpha-glutamyl-, disodium salt	Immunomodulator, anti-infective Anticancer, immunological
192	HAV peptide matrix		leucyl-arginyl-alanyl-histidyl-alanyl-valyl-aspartyl-valyl-asparaginy-glycinamide	Neurological
149	PTH 1-34	PTH	SVSEIQLMHNLGKHLNSMERVEWLKKLQDVHNF	Hormone
	leuprorelin		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Anticancer
193	TRP-2		H-Leu-Leu-Pro-Gly-Gly-Arg-Pro-Tyr-Arg-OH	Anticancer, immunological
426	golotimod		(2R)-2-amino-5-[[[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino]-5-oxopentanoic acid	Immunostimulant, other Immunomodulator, anti-infective Anticancer, immunological Stomatological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
194	angiotensin-II	Angiotensin II	gi 28710 emb CAA77513.1 angiotensin II [Homo sapiens] MILNSTEDGIKRIQDDCPKAGRHNIFVMIPTLYSIIF VVGIFGNSLVVIVIFYFYMKLKTVASVFLNLALADLCF LLTLPLWAVYTAMEYRWPFGNLYCKIASASVSFNLY ASVFLLTCLSIDRYLAIVHPMKSRLLRRTMLVAKVTCIII WLLAGLASLP AIIHRNVFFIENTNITVCAFHYESQNSTL PIGLGLTKNILGFLFPFLIILTSYTLIWKALKKAYEIQKN KPRNDDIFKIIMAIVLFFFFSWIPHQIFTFLDVLIQLGIIR DCRIADIVDTAMPITICLAYFNNCNLNPLFYGFLGKKFKR YFLQLLKYYPPKAKSHSNLSTKMSTLSYRPSDNVSSST KKPAPCFEVE	Vulnerary Symptomatic antidiabetic
195	omiganan		L-lysineamide, L-isoleucyl-L-leucyl-L-arginyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-tryptophyl-L-tryptophyl-L-arginyl-L-arginyl, pentahydrochloride	Formulation, dermal, topical Peptide antibiotic Antiacne
427	leuprorelin		6-D-leucine-9-(N-ethyl-L-prolineamide)-10-deglycinamide-	Transmucosal, nasal, Menstruation disorders, Anticancer, hormonal, Fertility enhancer
428	delmitide		D-Tyrosinamide, D-arginyl-D-norleucyl-D-norleucyl-D-	GI inflammatory/bowel

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	acetate		norleucyl-D-arginyl-D-norleucyl-D-norleucyl-D-norleucylglycyl-,monoacetate	disorders, Radio/chemoprotective, Antipsoriasis, Antipruritic/inflamm, allergic, Multiple sclerosis treatment, Alimentary /Metabolic, other, Antiviral, anti-HIV, Antiasthma, COPD treatment, Respiratory Stomatological
196	cat PAD		MRGALLVLALLVTQALGVKMAETCPIFYDVFFAVAN GNELLDLSLTKVNATEPERTAMKKIQDCYVENGLIS RVLDGLVMTTISSSKDCMGEAVQNTVEDLKLNTLGR	Antiasthma Antiallergic, non-asthma
429	NOV-002		bis-(gamma-L-glutamyl)-L-cysteiny-l-bis-glycin disodium salt	Anticancer, immunological Radio/chemosensitizer Antidote
430	GPG-NH2		glycyl-prolyl-glycine amide	Antiviral, anti-HIV
431	ABT-510		NAc-Sar-Gly-ValDallolThrNValleArgProNHE	Anticancer, other
8	CJC-1131	GLP-1	HGEGTFTSDLSKQMEEEA VRLFIEWLKNGGPSSGAPP	Antidiabetic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			PS	
432	desmopressin		Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine-	Formulation, oral, Hormone, Antidiabetic, Urological
197	metastin		MNSLVSWQLLFLCATHFGEPEKVASVGNRPTGQQ LESLGLLAPGEQSLPCTERKPAATARLSRRGTSLSPPE SSGSPQQPGLSAPHSRQIPAPQGAVLVQREKDLPNYN WNSFGLRFGKREAAPGNHGRSAGRG	Anticancer, other
433	leuprorelin		5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)	Anticancer
434	SGS-111		N-phenylacetylprolylglycine ethyl ester	Cognition enhancer Neuroprotective
435	taltobulin		(4S)-4-[[[(2S)-3,3-dimethyl-2-[[[(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanoyl]methylamino]-2,5-dimethylhex-2-enoic acid	Anticancer, other
436	leuprolide		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	inhalable, systemic, Anticancer , Menstruation disorders

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
103	XOMA-629		gi 157276599 ref NP_001716.2 bactericidal/permeability-increasing protein precursor [Homo sapiens] MRENMARGPCNAPRWASLMVLVAIGTAVTAAVNPG VVVRISQGLDYASQQGTAALQKELKRIKIPDYSDFS KIKHLGKGHYFYSMDIREFQLPSSQISMVPNVGLKFS ISNANIKISGKWKAQKRFLKMSGNFDLSIEGMSISADL KLGSNPTSGKPTITCSCSSHINSVHVHISKSKVGWLIQ LFHKKIESALRNKMNSQVCEKVTNSVSSELQPYFQTL PVMTKIDSVAGINYGLVAPPATTAETLDVQMKGEFYS ENHHNPPPFAPPVMEFFAAHDRMVYLGSDYFFNTA GLVYQEAGVLKMTLRDDMIPKESKRLTTKFFGTFLP EVAKKFPNMKIQIHVSASTPPHLSVQPTGLTFYPADV QAFVLPNSSLASFLIGMHTTGSMESAEVNRLVGE LKLDRLLELKHSNIGPPVELLQDIMNYIVPILVLPV NEKLQKGFPLTPARVQLYNVVLQPHQNFLFLFGADV VYK	Antiacne Anti-infective, other
198	synthetic erythropoiesis pro		gi 8393713 ref NP_058651.1 Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase isoform 1 [Homo sapiens] MSTSYGCFWRRFIHGIGRSGDISAVQPKAAGSSLNKI	Antianaemic Radio/chemoprotective

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			TNSLVLDIIKLAGVHTVANCVVPMATGMSLTLCFLT LRHKRPKAKYIIWPRIDQKSCFKSMITAGFEPVVIENV LEGDELRTDLKAVEAKVQELGPDCLCIHSTTSCFAPR VPDRLEELAVICANYDIPHIVNNA YGVQSSKCMHLIQ QGARVGRIDAFVQSLDKNFMPVPGGAIAGFNDSEFIQE ISKMYPGRASAPSLDVLITLLSLGNGYKKLLKERKE MFSYLSNQIKKLSEAYNERLLHTPHNPISLAMTLKTLD EHRDKAVTQLGSMFLTKQVSGARVVPLGSMQTVSGY TFRGFMSHTNNYP CAYLNAASAIGMKMQDVDLFNR LDRCLKAVRERSKESDDNYDKTEDVDIEEMALKLD NVLLDTYQDA SS	
191	β -amyloid vaccine	beta-amyloid peptide	gi 8176533 gb AAB26264.2 beta-amyloid peptide precursor; beta APP [Homo sapiens] GSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFF AEDVGSNKGAIIGLMVGGVVIA TVIIITLVMLKKQYTS NHHGVVE	Cognition enhancer
437	sincalide		1-De-(5-oxo-L-proline)-2-de-L-glutamine-5-L-methioninecaerulein	Imaging agent Alimentary/Metabolic
438	albiglutide		([8-glycine]human glucagon-like peptide 1-(7-36)-	Antidiabetic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			peptidyl)([8-glycine]human glucagon-like peptide 1-(7-36)-peptidyl)(human serum albumin (585 residues))	Anorectic/Antiobesity
199	SB-144		gi 13899257 refNP_113622.1 transmembrane and ubiquitin-like domain containing 1 [Homo sapiens] MTLIEGVGDEVTVLFSVLACLLVLALAWVSTHTAEG GDPLPQPSGTPTSPQPSAAMAATDSMRGEAPGAETPS LRHRGQAAQPEPSTGFTATPPAPDSPQEPLVLRLKFLN DSEQVARAWPHDTIGSLKRTQFPGREQQVRLIYQGQL LGDDTQTLGSLHLPPNCVLHCHVSTRVGPPNPPCPPGS EPGSGLEIGSLLPLLLLLLLWYCQIQYRPFPLTA TLGLAGFTLLLSLLAFAMYRP	Anticancer, other Radio/chemosensitizer
200	exenatide LAR		L-histidylglycyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutaminy-L-methionyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-asparaginyglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-serinamide	Antidiabetic
201	BA-058	PTHrP	gi 131542 sp P12272.1 PTHr_HUMAN Parathyroid	Osteoporosis treatment

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			hormone-related protein precursor (PTH-rP) (PTHrP) [Contains: PTHrP[1-36]; PTHrP[38-94]; Osteostatin (PTHrP[107-139])] MQRRLVQQWSVAVFLLSYAVPSCGRSVEGLSRRLKR AVSEHQLLHDKGKSIQDLRRRFFLHHLIAEHTAEIRA TSEVSPNSKSPNTKNHPVRFGSDDEGRYLTQETNKV ETTYKEQPLKTPGKKKKKGKPGKRKEQKKRRTRSAW LDSGVTGSGLEGDHLSDTSTTSLELDSRRH	
8	BIM-51077	GLP-1	HGEGTFTSDLSKQMEEEA VRLFIEWLKNGGPSSGAPP PS [(aminoisobutyric acid) 8,35]hGLP- 1(1-36)NH 2, has the same amino acid sequence as human GLP-1(7-36 amide) except for the replacement of amino acids 8 and 35 with α - aminoisobutyric acid (Aib) to reduce protease susceptibility.	Antidiabetic
202	TM-701		H-Met-Cys-Met-Pro-Cys-Phe-Thr-Thr-Asp-His-Gln-Met- Ala-Arg-Lys-Cys-Asp-Asp-Cys-Cys-Gly-Gly-Lys-Gly-Arg- Gly-Lys-Cys-Tyr-Gly-Pro-Gln-Cys-Leu-Cys-Arg-NH ₂ (Disulfide bridge: 2-19, 5-28, 16-33, 20-35)	Anticancer, other Radio/chemosensitizer
439	CZEN-002		[dNal(2')-7,Phe-12]- α -MSH 6-13	Antifungal, Antibacterial, other, Antiviral, anti-HIV,

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				Immunosuppressant, Metabolic and enzyme disorders, Anti-inflammatory, Antiarthritic, otherGI inflammatory/bowel disorders
203	ZP-120		Ac-RYYRWKKKKKKK-NH ₂	Cardiostimulant
204	CTT		H-Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys-OH	Formulation technology
205	PYY3-36		gi 71361686 refNP_004151.2 peptide YY [Homo sapiens] MVFVRRPWPALTTVLLALLVCLGALVDAYPEAPR EDASPEELNRYASYLRHYLNLVTRQRYGKRDPDTLL SKTFFPDGEDRPVRSRSEGPLDW	Anorectic/Antiobesity
	AEZS-130		EP1572 UMV1843 [Aib-DTrp-DgTrp-CHO]	Growth hormone Anabolic Musculoskeletal
206	AL-108		H-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-OH	Neuroprotective Cognition enhancer Antiparkinsonian Ophthalmological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
202	TM-801		H-Met-Cys-Met-Pro-Cys-Phe-Thr-Thr-Asp-His-Gln-Met-Ala-Arg-Lys-Cys-Asp-Cys-Gly-Gly-Lys-Gly-Arg-Gly-Lys-Cys-Tyr-Gly-Pro-Gln-Cys-Leu-Cys-Arg-NH ₂ (Disulfide bridge: 2-19, 5-28, 16-33, 20-35)	Imaging agent
202	TM-901		H-Met-Cys-Met-Pro-Cys-Phe-Thr-Thr-Asp-His-Gln-Met-Ala-Arg-Lys-Cys-Asp-Cys-Gly-Gly-Lys-Gly-Arg-Gly-Lys-Cys-Tyr-Gly-Pro-Gln-Cys-Leu-Cys-Arg-NH ₂ (Disulfide bridge: 2-19, 5-28, 16-33, 20-35)	Anticancer, other Imaging agent
440	S-0373	TRH	pyroGlu-His-Pro-NH ₂ (or 5-oxo-L-prolyl-L-histidyl-L-prolinamide)	Neurological Psychostimulant Antiparkinsonian
205	PYY3-36		gi 71361686 ref NP_004151.2 peptide YY [Homo sapiens] MVFVRRPWPALTTVLLALLVCLGALVDA YPIKPEAPR EDASPEELNRY YASLRHYLNLVTRQRYGKRDPDPTLL SKTFFPDGEDRPVRSRSEGPLW	Formulation, oral, other Anorectic/Antiobesity
207	XG-101		gi 4885433 ref NP_005447.1 mitogen-activated protein kinase 8 interacting protein 1 [Homo sapiens] MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLLTHD ISLEEFEDLSEITDECISLQCKDTLSLRPPRAGLLSA GGGAGSRLQAEMLQMDLIDATGDTPGAEDDEEDDD	Immunological Cardiovascular Neuroprotective Immunosuppressant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			EERARRPGAGPPKAESGQEPASRGQGQSQSQGPG SGDTYRPKRPTTLNLFQVPRSQDTLNNNSLGKKHSW QDRVSRSSPLKTGEQTPPHEHICLSDELPPQSGPAPT DRGTSTDSPCRRSTATQMAPPGGPPAAPPGGRGHSR DRIHYQADVRLEATEEILTPVQRPPDAAEPTSAFLPP TESRMSVSSDPDPAAYPSTAGRPHPSISEEEEEGFDCSS PERAEPGGGWRGSLGEP PPPRASLSSDTSALSYSV KYTLVVDEHAQLELVSLRPCFGDYSDSDSATVYDNC ASVSSPYESAIGEEYEEAPRPQPACLSDESTPDEPDVH FSKKFLNVFMGRSRSSSAESFGLFSCIINGEEQEQTHR AIFRFVPRHEDELELEVDDPLLVELQAEDYWYEAYN MRTGARGVFPAYYAIEVTKEPEHMAALAKNSDWVD QFRVKFLGSVQVPYHKGNDVLCAMQKIATTRRLTV HFNPPSSCVLEISVRGVKIGVKADDSQEAAGNKCSEHFF QLKNISFCGYHPKNNKYFGFITKHPADHRFACHVFVS EDSTKALAESVGRAQQFYKQFVEYTCPTEDIYLE	
208	XG-102		gi 4885433 ref NP_005447.1 mitogen-activated protein kinase 8 interacting protein 1 [Homo sapiens] MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLTHD ISLEEFEDLSEITDECGISLQCKDTLSLRPPRAGLLSA	Neuroprotective Cardiovascular Otolological Ophthalmological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			GGGAGSRLQAEMLQMDLIDATGDTGPAEDDEEDDD EERAARRPGAGPPKAESGQEPASRGQGSQGSQGP SGDTYRPKRPTTLNLFQVPRSQDTLNNNSLGKKHSW QDRVSRSSPLKTGEQTPPEHICLSDELPPQSGPAPT DRGTSTDSPCRRSTATQMAPPGGPPAAPGGGRGHSR DRIHYQADVRLEATEEILTPVQRPPDAAEPTSAFLPP TESRMSVSSDPDPAAYPSTAGRPHPSISEEEEGFDCCLSS PERAEPGGGWRGSLGEP PPPRASLSSDTSALSYSV KYTLVVDEHAQLELVSLRPCFGDYSDSDSATVYDNC ASVSSPYESAIGEEYEEAPRPQPPACLSEDSTPDEPDVH FSKKFLNVFMGRSRSSAESFGLFSCIINGEEQEQT AIFRFVPRHEDELELEVDDPLLVELQAEDYWYEAYN MRTGARGVFPAYYAIEVTKEPEHMAALAKNSDWVD QFRVKFLGSVQVPYHKGNDVLC AAMQKIATTRRLTV HFNPPSSCVLEISVRGVKGVKADDSQEA KGNKCSHFF QLKNISFCGYHPKNNKYFGFITKHPADHRFACHVFS EDSTKALAESVGRAQQFYKQFVEYTCPTEDIYLE	Antiparkinsonian Immunosuppressant
441	lanreotide SR		L-Threonamide,3-(2-naphthalenyl)-D-alanyl-L-cysteiny l-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteiny l-, cyclic (2-7)-disulfide	Formulation, modified- release, other Somatostatin

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				Antihypertensive, other
209	OGP-(10-14)-L		H-Tyrosine-Glycine-Phenylalanine-Glycine-Glycine-OH	Haematological Musculoskeletal
210	WP9QY		cyclo(Tyr-Cys-Trp-Ser-Gln-Tyr-Leu-Cys-Tyr); cyclo(tyrosyl-cysteiny1-tryptophyl-seryl-glutaminy1-tyrosyl-leucyl-cysteiny1-tyrosyl)	Antiarthritic, other Anti-inflammatory
211	aviptadil		His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn	Antihypertensive, other Respiratory Immunosuppressant
212	AL-209		Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala	Neuroprotective Cognition enhancer Ophthalmological
442	octreotide		L-Cysteinamide, D-phenylalanyl-L-cysteiny1-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threony1-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	Formulation, implant Formulation, modified-release, >24hr Somatostatin
213	CDX-110		Leu-Glu-Glu-Lys-Lys-Gly-Asn-Tyr-Val-Val-Thr-Asp-His-Cys-KLH	Recombinant vaccine Anticancer, immunological
444	desmopressin		Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine-	Hormone, Urological, Reproductive/gonadal,

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				general
445	obinepitide		[34-L-glutamine]pancreatic hormone (human)	Anorectic/Antiobesity
	Insulin		Insulin (ox), 8A-L-threonine-10A-L-isoleucine-30B-L-threonine-	solubility-enhanced Insulin
171	terlipressin		N-(N-(N-glycylglycyl)glycyl)-8-L-lysinevasopressin [CAS]; Gly-Gly-Gly-8-Lys-vasopressin; N-(alpha)-glycyl-glycyl-glycyl-8-lysine vasopressin; Remestyp; TGLVP; glipressin; glycylpressin; glypressin; terlypressin; triglycyl lysine vasopressin; triglycyl-(8-lysine)vasopressin; triglycylvasopressin; vasopressin, tri-Gly-8-Lys-	Hepatoprotective, Urological, Gi bleeding
214	ZT-153		Asn-Phe-Gly-Ala-Ile-Leu; NFGAIL; asparagyl-phenylalanyl-glycyl-alanyl-isoleucyl-leucine; islet amyloid polypeptide (22-27)	Antidiabetic
215, 215 and 216	FGLL		gi 42544189 ref NP_004458.3 fibrinogen-like 1 precursor [Homo sapiens] MAKVFSFILVTTALTMGREISALEDCAQEQMRLRAQV RLLETRVKQQVKIKQLQENEVQFLDKGDENTVIDL GSKRQYADCSEIFNDGYKLSGFYKIKPLQSPAEFVYC DMSDGGGWTVIQRRSDGSENFNRGWKDYENGFGNF VQKHGEYWLGNKNLHFLTQTQEDYTLKIDLADFEKNS	Cognition enhancer Neurological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			RYAQYKNFKVGDEKNFYELNIGEYSGTAGDSLGNF HPEVQWWASHQRMKFSTWDRDHDNYEGNCAEEDQS GWWFNRCHSANLNGVYYSGPYTAKTDNGIVWYTW WH GWWYSLKSVMKIRPNDFIPNVI gi 42544200 ref NP_963846.1 fibrinogen-like 1 precursor [Homo sapiens] MAKVFSFILVTTALTMGREISALEDCAQEQMRLRAQV RLLETRVKQQVKIKQLQENEVQFLDKGDENTVIDL GSKRQYADCSEIFNDGYKLSGFYKIKPLQSPAEFVYC DMSDGGGWTVIQRRSDGSENFNRGWKDYENGFGNF VQKHGEYWLGNKNLHFLTQEDYTLKIDLADFEKNS RYAQYKNFKVGDEKNFYELNIGEYSGTAGDSLGNF HPEVQWWASHQRMKFSTWDRDHDNYEGNCAEEDQS GWWFNRCHSANLNGVYYSGPYTAKTDNGIVWYTW WH GWWYSLKSVMKIRPNDFIPNVI gi 42544198 ref NP_671736.2 fibrinogen-like 1 precursor [Homo sapiens] MAKVFSFILVTTALTMGREISALEDCAQEQMRLRAQV	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			RLLETRVKQQQVKIKQLQENEVQFLD	
217	ST-03		gi 386634 gb AAB27460.1 01-ST-3=heat-stable enterotoxin [Vibrio cholerae, 01, Peptide, 19 aa] NLIDCCEICCNPAFCGLN	Recombinant growth factor Musculoskeletal Osteoporosis treatment
446	cetrorelax acetate		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)-D-ol-L-leucyl-L-arginyl-L-prolyl-	Formulation, modified-release, >24hr Menstruation disorders
218	neurodegenerative		alpha toxin, Naja; cobra alpha toxin; cobra toxin alpha; toxin alpha, cobra; gi 64054 emb CAA26373.1 unnamed protein product [Laticauda semifasciata] MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTC SPGESSCYNKQWSDFRGTIIERGCGCPTVKPGIKLSCC ESEVCNN gi 4519816 dbj BAA75752.1 short chain neurotoxin [Laticauda semifasciata] MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTC	Cognition enhancer

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			SPGESSCYNKQWSDFRGTIIERGCGCPTVKPGIKLSCC ESEVCNN	
			gi 32140561 dbj BAC78199.1 erabutoxin a [Laticauda semifasciata]	
			MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTKTC	
			SPGESSCYNKQWSDFRGTIIERGCGCPTVKPGIKLSCC ESEVCNN	
219	CT-319		gi 32140563 dbj BAC78200.1 erabutoxin a [Laticauda semifasciata]	Antiviral, anti-HIV
			MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTKTC	
			SPGESSCYNKQWSDFRGTIIERGCGCPTVKPGIKLSCC	
			ESEVCNN	
447	Peptide T		MSNKKIHKIQLQIPGGKANPAPPIGPALGAAGVNIMGF	Antipsoriasis
			CKEFNAATQDRPGDLLPVVIT	
			VYSDKTFSEVMKQSPVSSLKKALGLESKIPNRNKV	
			GKLTRAQITVIAEQKMKDMDVV LLESAERMVEGTARSMGVDVE	
			L-Threonine, N-(N-(N2-(N-(N-(N-(N-D-alanyl-L-seryl)-L-	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			threonyl)-L-threonyl)-L-threonyl)-L-asparaginy)-L-tyrosyl)-[CAS]; HIV Peptide T; Peptide T, HIV	Multiple sclerosis treatment Cognition enhancer Musculoskeletal
220 and 221	APP-018		pallidin [Mus musculus] gi 9790039 ref NP_062762.1 [9790039] MSVPEPPPPDGVLTGPSDSLEAGEPTPGLSDTSPDEGLI EDFPVDDRAVEHLVGGLLSHY LPDLQSKRALQELTONQVVLDTLEQEISKFECHS MLDINALFTEAKHYHAKLVIRK EMLLHEKTSKLLKRALKLQKQRQREELEREQREK EFEREKQLTAKPAKRT envelope glycoprotein [Human immunodeficiency virus type 1] gi 4205319 gb AAD11044.1 [4205319] KLTPLCVTLNCTDLRLNTNTTTEERGEMKNCSFN ITTNIRDYQKEYALFYKLDVIP IKEDNTSDNTSYRLISCNSTSVITQACPKIS	Hypolipemic/Antiatherosclerosis
222	somatropin		gi 60651145 gb AAX31661.1 somatotropin [Bubalus	Formulation, transmucosal,

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			bubalis] AFPAMSSLFANAVLRAQHLHQLAADTFKEFERTYI PEGQRYSIQNTQVAFCFSETIPA PTGKNEAQQKSDLELLRISLLLIQSWLGPLQLSRVFT NSLVFGTSDRVYEKLKDLLEEGI LALMRELEDGTPRAGQILKRTYDKFDTNMRSDDALL KNYGLLSCFRKDLHKTETYLRLVMKCRRFGEASCAF	nasal Growth hormone Anabolic Reproductive/gonadal, general
448	heparin		6-[5-acetamido-4,6-dihydroxy-2-(sulfooxymethyl)oxan-3-yl]oxy-3-[5-(6-carboxy-4,5-dihydroxy-3-sulfooxoyoxan-2-yl)oxy-6-(hydroxymethyl)-3-(sulfoamino)-4-sulfooxoyoxan-2-yl]oxy-4-hydroxy-5-sulfooxoyoxane-2-carboxylic acid	Formulation, transmucosal, nasal Anticoagulant
46	CGRP	CGRP	ACDTATCVTHRLAGLLSRSGGVKNNFVPTNVGSKA F-NH₂	Cardiovascular Cardiostimulant
449	YM-216391		A concise total synthesis of the unusual oxazole-based cyclopeptide structure YM-216391, which also establishes the stereochemistry of the natural product i.e. 1, is described. The unusual polyoxazole-thiazole-based cyclopeptide 1, designated YM-216391, was recently isolated from	Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			Streptomyces nobilis.1 It shares both a structural and biological homology with the potent telomerase inhibitor telomestatin 2 which is showing promise in cancer chemotherapy.2 The structure of YM-216391 comprises a continuum of five azoles which have their origins in serine, cysteine and phenylalanine, linked via a glycine- valine- isoleucine tripeptide tether. The complete stereochemical assignment of YM-216391 has not been established. In this communication we describe a concise total synthesis of the cyclopeptide, which not only confirms its unique structure but also allows the assignment of its stereochemistry, shown in formula 1. Thus, the 2,4-disubstituted oxazoles 3 and 4 and the trisubstituted oxazole 5 were first elaborated	
223	FGLm		LSENDEWTQDRAKP	Cognition enhancer Neurological
224	prohanin		NPFPTWRKRPG	Analgesic, other
225	heart failure therapy	NP	gi 189079 gb AA36355.1 natriuretic peptide MDPQTAPSRALLLLFLHLAFLGGRSHPLGSPGSASDL ETSGLQEQRNHLQGKLSELQVEQTSLEPLQES	Cardiostimulant

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			PRPTGVWKSREVATEGIRGHRKMVLYTLRAPRSPKM VQSGGCFGRKMDRISSSSGLGCKVLR RH	
450	SEN-304		D-[(chG)Y-(chG)(chG)(MeL)]-NH ₂ , where chG is R-cyclohexylglycine	Cognition enhancer Anti-inflammatory
451	Primacoll		Synthetic growth factor	Musculoskeletal
452	Octreotide		L-Cysteinamide, D-phenylalanyl-L-cysteiny l-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	Formulation, modified-release, >24hr Symptomatic antidiabetic Ophthalmological Somatostatin
453	ALS-02		Glycine, N-(aminoiminomethyl)-N-methyl-	Neuroprotective
200	exendin-4, PC-DAC	GLP-1	L-histidylglycyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutaminy l-L-methionyl-L-glutamyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-asparaginy lglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide	Antidiabetic
226	Exenatide		gi 1916067 gb AAB51130.1 exendin 4 [Heloderma	Formulation, transmucosal,

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			suspectum] MKIILWLCVGLFLATLFPISWQMPVESGLSSEDSASS ESFASKIKRHGEGTFTSDLSKQMEEEAVRLFIEWLKN GPSSGAPPPSG	nasal Antidiabetic
225	Cardeva	BNP	gi 113836 sp P16860.1 ANFB_HUMAN Natriuretic peptides B precursor [Contains: Gamma-brain natriuretic peptide; Brain natriuretic peptide 32 (BNP-32)] MDPQTAPSRALLLLFLHLAFLGGRSHPLGSPGSASDL ETSGLQEQRNHLQGLSELQVEQTSLEPLQES PRPTGVWKSREVAATEGIRGHRKRMVLYTLRAPRSPKM VQSGGCFGRKMDRISSSSGLGCKVLRRH	Cardiostimulant
227	Alloferon		H-His-Gly-Val-Ser-Gly-His-Gly-Gln-His-Gly-Val-His-Gly- OH	Immunomodulator, anti-infective
454	PAC-G31P		AMCF-I; Alveolar Macrophage Chemotactic Factor I; Alveolar Macrophage Chemotactic Factor-I; Anionic Neutrophil Activating Peptide; Anionic Neutrophil- Activating Peptide; CXCL8 Chemokine; CXCL8 Chemokines; CXCL8, Chemokine; Chemokine CXCL8; Chemokine, CXCL8; Chemokines, CXCL8; Chemotactic Factor, Macrophage Derived; Chemotactic Factor,	Recombinant interleukin Respiratory Asthma COPD treatment

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			Macrophage-Derived; Chemotactic Factor, Neutrophil; Chemotactic Factor, Neutrophil, Monocyte-Derived; Chemotactic Peptide-Interleukin-8, Granulocyte; Granulocyte Chemotactic Peptide Interleukin 8; Granulocyte Chemotactic Peptide-Interleukin-8; IL-8; Interleukin 8; Lymphocyte-Derived Neutrophil-Activating Peptide; Macrophage-Derived Chemotactic Factor; Monocyte-Derived Neutrophil Chemotactic Factor; Monocyte-Derived Neutrophil-Activating Peptide; Neutrophil Activating Peptide, Lymphocyte Derived; Neutrophil Activating Peptide, Monocyte Derived; Neutrophil Activation Factor; Neutrophil Chemotactic Factor; Neutrophil-Activating Peptide, Anionic; Neutrophil-Activating Peptide	
228	PAC-525		Ac-KWRRWVRWI-NH ₂	Antibacterial, other
229, 229 and 230	PAC-113		Lys-Phe-His-Glu-Lys-His-His-Ser-His-Arg-Gly-Tyr histatin 10, human; histatin 11, human; histatin 12, human; histatin 3, human; histatin 4, human; histatin 5, human; histatin 6, human; histatin 7, human; histatin 8, human; histatin 9, human; histatin-3 (1-24), human; histatin-3 (1-25),	Antifungal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			human; histatin-3 (12-24), human; histatin-3 (12-25), human; histatin-3 (12-32), human; histatin-3 (13-25), human; histatin-3 (5-11), human; histatin-3 (5-12), human; lysyl-phenylalanyl-histidyl-glutamyl-lysyl-histidyl-histidyl-seryl-histidyl-arginyl-glycyl-tyrosine gi 4557653 ref NP_000191.1 histatin 3 [Homo sapiens] MKFFVFALILALMLSMGTGADSHAKRHHGYKRFHEK HHSHRGYRSNYLYDN	
231	MLIF		Met-Gln-Cys-Asn-Ser U.S. Patent No. 6,524,591	Anti-inflammatory
454	carfilzomib		L-Phenylalaninamide, (alphaS)-alpha-[(4-morpholinylacetyl)amino]benzenebutanoyl-L-leucyl-N-[[(1S)-3-methyl-1-[[[(2R)-2-methyloxiranyl]carbonyl]butyl]-	Anticancer, other
232	NAFB001		gi 63025222 ref NP_000651.3 transforming growth factor, beta 1 [Homo sapiens] MPPSGLRLLPLLPLLWLLVLTGPRPAAGLSTCKTIDM ELVKKRIEAIKRGILSKRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESAEPEPEADYYAKE VTRVLMVETHNEIYDKFKQSTHSIYMFFNTSEL	Ophthalmological Hepatoprotective

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			REAVPEPVLLSRAELRLRLKLKVEQHVELYQKYSNN SWRYLSNRL LAPSDPEWLSFDVTGVVRQWLSR GGEIEGFRLSAHCSDSRDNTLQVDINGFTTGRRGDL ATIHGMNRPFLLLMATPLERAQHLQSSRHRRAL DTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKG YHANFCLGPCYIWSLDTQYSKVLALYNQHNPGA SAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSC KCS [PIR]	
233	IL12-NGR		H-Cys-Asn-Gly-Arg-Cys-Gly-OH (Disulfide bridge: 1-5)	Recombinant, other Cytokine Anticancer, immunological
234 and 235	enterostatin		Val-Pro-Val-Asp; Val-Pro-Asp-Pro-Arg	Anorectic/Antiobesity
455	octreotide		L-Cysteinamide, D-phenylalanyl-L-cysteiny-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	Formulation, modified-release, >24hr Somatostatin
150	enfuvirtide		L-Phenylalaninamide, N-acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histidyl-L-seryl-L-leucyl-L-isoleucyl-L-alpha-glutamyl-L-alpha-glutamyl-L-seryl-L-	Formulation, parenteral, needle-free Antiviral, anti-HIV

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			glutaminyl-L-asparaginyL-L-glutaminyL-L-glutaminyL-L-alpha-glutamyl-L-lysyl-L-asparaginyL-L-alpha-glutamyl-L-glutaminyL-L-alpha-glutamyl-L-leucyl-L-leucyl-L-alpha-glutamyl-L-leucyl-L-alpha-aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-asparaginyL-L-tryptophyl-	
236	PR-21		gi 2213924 gb AAB61615.1 neural cell adhesion molecule [Homo sapiens] MLQTKDLIWTLFFLGTAVSLQVDIVPSQGEISVGESKF FLCQVAGDAKDKDISWFSNGEKLTPNQQRIS VWVNDSSSTLTINYANIDDAgiYKCVVTGEDGSESE ATVNVKIFQKLMFKNAPTPQEFREGEDAVIVCD VVSSLPPTIIWKHKGRDVILKKDVRFIFLSNNYLPIPI KKTDEGTYRCEGRILARGEINFNDIQVIVNV PPTIQRQNIVNATANLGQSVTLVCDAEGFPGPTMSW TKDGEQIEQEEHDEKYLFSDDSSHLTIKKVDKN HEAENICIAENKVGEDQATIHLLKVFAPKQITYVEDQTA MELAEQVILTVEASGDHIPYITWWTSTWQI	Neurological Cognition enhancer
237	AC-163794	GIP	gi 183221 gb AAA53192.1 gastric inhibitory polypeptide precursor	Antidiabetic

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			MVATKTFALLLSLFLAVGLGEKKEGHFSALPSLPVG SHAKVSSPQPRGPRYAEGTFISDYSIAMDKIHQ QDFVNWLLAQKGKKNDWKHNITQREARALELASQA NRKEEEAVEPQSSPAKNPSDEDLRLDLIQELLAC LLDQTNLCRLRSR;	
456	glucagon		Glucagon (1-29); Glukagon; HG Factor; HG-Factor; Hyperglycemic Glycogenolytic Factor; Hyperglycemic- Glycogenolytic Factor; Proglucagon (33-61)	Formulation, transdermal, systemic hypoglycemia
457	Insulin		Insulin (ox), 8A-L-threonine-10A-L-isoleucine-30B-L- threonine-	Formulation, oral, other Formulation, optimized, nanoparticles Antidiabetic
458	Dekafin-2		DNA Synthesis Factor; Fibroblast Growth Factor; Fibroblast Growth Regulatory Factor; Growth Factor, Fibroblast; Growth Factors, Fibroblast	Anticancer, other
238 and 239	relaxin		(1) Glu-Leu-Tyr-Ser-Ala-Leu-Ala-Asn-Lys-Cys-Cys-His- Val-Gly-Cys-Thr-Lys-Arg-Ser-Leu-Ala-Arg-Phe-Cys (2) H-Asp-Ser-Trp-Met-Glu-Glu-Val-Ile-Lys-Leu-Cys-Gly- Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Cys-Gly-Met-	Recombinant hormone Hormone Labour inducer Antihypertensive, other

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			Ser-Thr-Ser Cys 11 of each chain form disulfide bond; cys 24 of the first chain forms disulfide bond with cys 23 of chain 2	
459	rhNRG-1		Differentiation Factor, neu; GGF Protein; Glial Growth Factor; Heregulin; NDF Protein; NRG1 Protein; Neuregulin 1; neu Differentiation Factor	Recombinant, other Cardiostimulant
240	c-peptide analogue	C-peptide	Glu-Ala-Glu-Asp-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln	Symptomatic antidiabetic
241	SB-101		gi 30353933 gb AAH52287.1 CD44 protein [Homo sapiens] MDKFWWHAAWGLCLVPLSLAQIDLNITCRFAGVFHV EKNGRYSISRTEAADLCKAFNSTLPTMAQMEKAL SIGFETCSST	Recombinant, other Anticancer, other
242	Britistatin		gi 66270695 gb AAAY43681.1 disintegrin isoform D-1 [Bitis arietans] SPPVCGNKILEQGEDCDCGSPANCQDRCCNAATCKLT PGSQCNYPECCDQCRFKKAGTVCRIARGDWNDDYCT GKSSDCPWNH	Antithrombotic
243	echistatin		gi 208338 gb AAA72777.1 echistatin MECESGPCCRNCKFLKEGTICKRARGDDLDDYCNGK	Antithrombotic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			TCDCPRNPHKGPAT	
244	gastrin		gi 4503923:20-101 gastrin preproprotein [Homo sapiens] EASWKPRSQQPDAPLGTGANRDLELPWLEQQGPASH HRRQLGPQGPPHLVADPSKKQGPWLEEEEEAYGWM DFGRRSAEDEN	diabetes
245	herpes simplex vaccine		gi 9629447:1-23 envelope glycoprotein D [Human herpesvirus 1] MGGAAARLGAVILFVVIVGLHGV	Prophylactic vaccine
246	neurotensin		gi 5453816:152-163 neurotensin/neuromedin N preproprotein [Homo sapiens] LYENKPRRPYIL	Analgesic, other
247	nociceptin		gi 5453922 ref NP_006219.1 prepronociceptin [Homo sapiens] MKVLLCDLLLLSLFSSVFSSCQRDCLTCQEKLHPALDS FDLEVCILECEEKVFPSPWTPCTKVMARSSWQLSPA APEHVAAALYQPRASEMQHLRRMPRVRSLFQEQUEEP EPGMEEAGEMEQLKQKRFGGFTGARKSARKLANQ KRFSEFMRQYLVLMSMQSSQRRRTLHQNGNV	Neurological Cognition enhancer Analgesic, other
248	oxynotomodulin		sp P01275.3 GLUC_HUMAN:53-89 Glucagon precursor [Contains: Glicentin; Glicentin-related polypeptide (GRPP);	Obesity; Antiulcer

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			Oxyntomodulin (OXY) (OXM)] HSQGTFTSDYSKYLDSRRAQDFVQWLMNTRNRNNI A	
249	pancreastatin		gi 164417:256-304 chromogranin A precursor GWPQAPAMDGAGKTGAEEAQPPEGKGAREHSRQEEE EETAGAPQGLFRG	Antidiabetic
250	relaxin	Relaxin	gi 5902052 ref NP_008842.1 relaxin 1 preproprotein [Homo sapiens] MPRLFLHLLLEFCLLNQFSRAVAKWKDDVIKLCGR ELVRAQIAICGMSTWSKRSLSQEDAPQTTPRPVAEIVPS FINKDTETIIIMLEFIANLPPELKAALSERQPSLPQLQQY VPALKDSNLSFEEFKKLI RNRQSEAADSNPSELKYLGL DTHSQKKRRPYVALFEKCCCLIGCTKRSLAKYC	Recombinant hormone Hormone Labour inducer
251	secretin		gi 11345450:28-54 secretin preproprotein [Homo sapiens] HSDGTFTSELSRLREGARLQRLQLGLV	Haemostatic; diagnostic of pancreatic dysfunction, asthma, COPD, others
252	TIMP		MAPFEPLASGILLLLWLIAPSRACVCVPPHPQTAF CNS DLVIRAKFVGTPENVNQTTL YQRYEIKMTKMYKGFQA LGDAADIRFVYTPAMESVCGYFHRSHNRSEEF LIAGK LQDGLLHITCSFVAPWNSLSLAQRRGFTKTYTVGCE	Recombinant, other Vulnerary Antiarthritic, other Stomatological

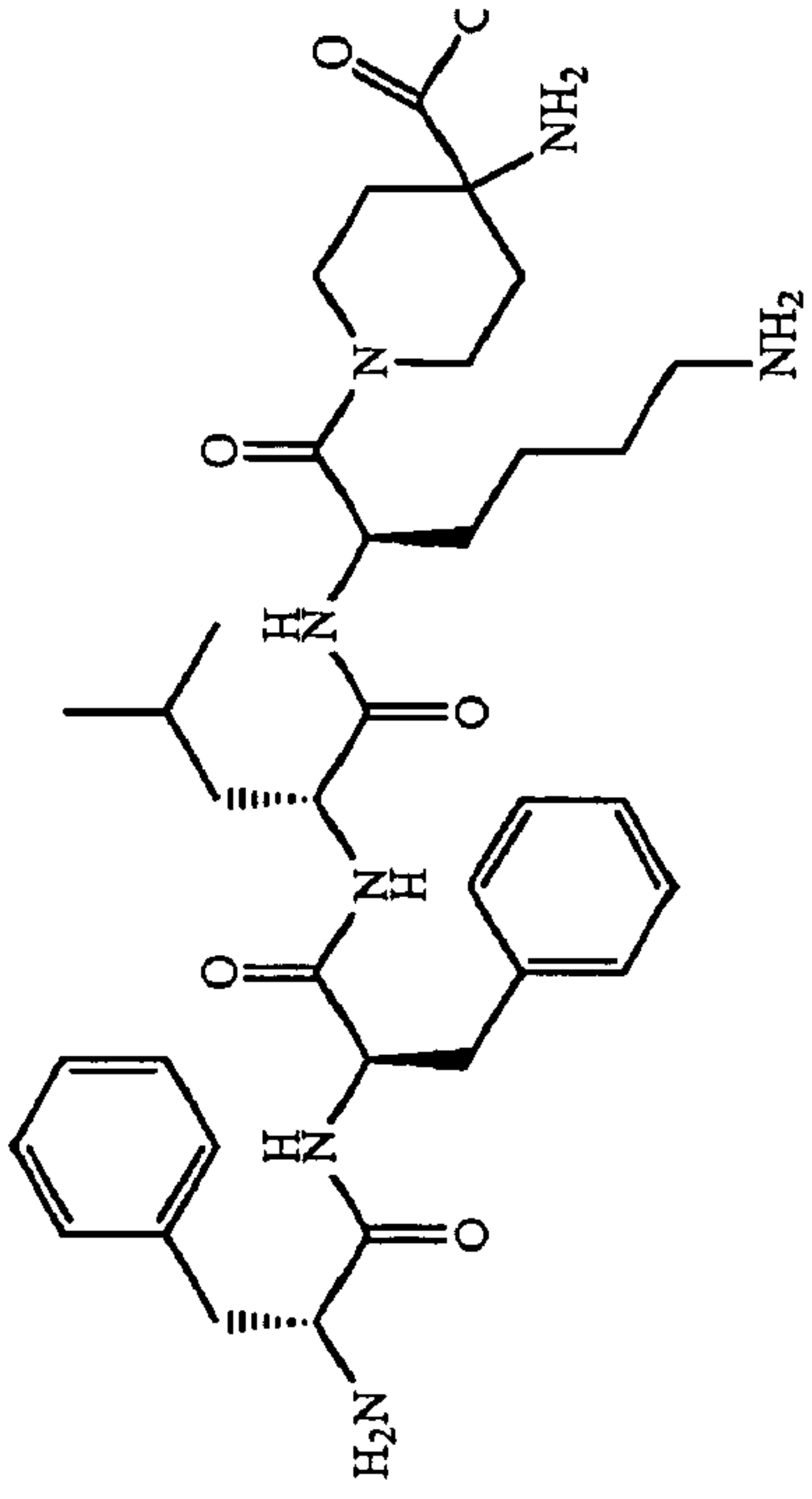
SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			ECTVFPCLSIPCKLQSGTHCLWTDQLLQGSEKGFQSRH LACLPREGLCTWQSLRSQIA	
252	TIMP		MAPFEPLASGILLLLWLIAPSRACCTCVPPHPQTAF CNS DLVIRAKFVGTPEVNQTTL YQRYEIKMTKMYKGFQA LGDAADIRFVYTPAMESVCGYFHRSHNRSEEF LIAGK LQDGLLHITTCSFVAPWNSLSLAQRRGFTKTYTVGCE ECTVFPCLSIPCKLQSGTHCLWTDQLLQGSEKGFQSRH LACLPREGLCTWQSLRSQIA	Recombinant, other Antiarthritic, other Stomatological
253	tendamistat		Asp-Thr-Thr-Val-Ser-Glu-Pro-Ala-Pro-Ser-Cys-Val-Thr- Leu-Tyr-Gln-Ser-Trp-Arg-Tyr-Ser-Gln-Ala-Asp-Asn-Gly- Cys-Ala-Gln-Thr-Val-Thr-Val-Lys-Val-Val-Tyr-Glu-Asp- Asp-Thr-Glu-Gly-Leu-Cys-Tyr-Ala-Val-Ala-Pro-Gly-Gln- Ile-Thr-Thr-Val-Gly-Asp-Gly-Tyr-Ile-Gly-Ser-His-Gly-His- Ala-Arg-Tyr-Leu-Ala-Arg-Cys-Leu	Antidiabetic
254	thymosin β 4		gi 11056061 ref NP_066932.1 thymosin, beta 4 [Homo sapiens] MSDKPDMAEIEKFDKSKLKKTTETQEKNPLPSKETIEQE KQAGES	Vulnerary Ophthalmological Symptomatic antidiabetic Dermatological Cardiovascular Septic shock treatment

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				Antiasthma
255	urodilatin		Thr-Ala-Pro-Arg-Ser-Leu-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr	Cardiostimulant Urological Antiasthma
256	Pharmaprojects No. 6236		Gly-Ser-Arg-Ala-His-Ser-Ser-His-Leu-Lys	Anticancer, other Antiarrhythmic Antiparkinsonian Cognition enhancer Neuroprotective
257	ANUP-1		Glu-Leu-Lys-Cys-Tyr-Thr-Cys-Lys-Glu-Pro-Met-Thr-Ser-Ala-Ala-Cys	Anticancer, other
258	DMI-4983		Asp-Ala-His-Lys	Cardiovascular
460	Glypromate		Gly-Pro-Glu	Neuroprotective
259	CD-NP		Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Ile Ser Ser Ser Gly Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro Asn Ala Pro Ser Thr Ser Ala	Cardiostimulant
260	Kisspeptin-54		GTSLSPPESSGSPQQPGLSAPHSRQIPAPQGAVLVQRE KDLPNYNWN SFGLRF-NH2	Cancer metastasis, angiogenesis

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
261	Kisspeptin-14		DLPNYNWN SFGLRF-NH ₂	Cancer metastasis, angiogenesis
262	Kisspeptin-13		LPNYNWN SFGLRF-NH ₂	Cancer metastasis, angiogenesis
263	Kisspeptin-10		YNWN SFGLRF-NH ₂	Cancer metastasis, angiogenesis
264	Ziconotide		CKGKGAKCSRLMYDCCTGSCRSKGC	
461	Biphalin		Tyr-D-Ala-Gly-Phe-NH-NH-Phe-Gly-D-Ala-Tyr	
39	Nesiritide	Brain Natriuretic peptide (BNP)	SPKMVQSGGCFGRKMDRISSSSGLGCKVLRH	
40	CD-NP		GLSKGCFGLKLDRIGSM SGLGCP SLRDP RP NAP TSA	
265	Protegrin-1	Cytolytic	RGGRLCYCRRRFCVCVGR-NH ₂	antibiotic
266	V681		Ac-KWKSFLKTFKSAVKTVLHTALKAISS-NH ₂	
462	V681 (V13A _D)		Ac-KWKSFLKTFKSA(AD)KTVLHTALKAISS-NH ₂	'(AD)' discloses the D-

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
				configuration of Alanine
267	V681 des A12		KWKSFLKTFKSVKTVLHTALKAISS	
268	V681 V13K		KWKSFLKTFKSAKKTVLHTALKAISS	
269	V681 V13K, T15K		KWKSFLKTFKSAKKKVLHTALKAISS	
270	GLP-2	GLP	HADGSFSDNMTILDNLAARDFINWLIQTKITD	
271	GLP-2 (A2G)	GLP	HGDGSFSDNMTILDNLAARDFINWLIQTKITD	
272	GLP-2 (A2G/C34)	GLP	HGDGSFSDNMTILDNLAARDFINWLIQTKITDC	
273	AOD-9604	Human Growth Hormone	LRIVQCASVEGSCGFY	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
274	Ac-AOD- 9604(S8K)	Human Growth	Ac-LRIVQCAKVEGSCGFY	Musculoskeletal, COPD, Hypnotic/Sedative,

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
		Hormone		Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
275	Ac-AOD- 9604(K17)	Human Growth Hormone	Ac-LRIVQCASVEGSCGFYK	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
276	C-peptide	Insulin	EAEDLQVGQVELGGPGAGSLQPLALEGSLQ	
463	CR845	Opioids	peripherally-selective kappa opioid receptor agonists	acute and chronic pain of visceral, inflammatory and neuropathic origin, and for the treatment of pruritis (itch)

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			 D-Phe-D-Phe-D-Leu-D-Lys-[ω(4-aminopiperidine-4-carboxylic acid)]-OH	
277	Protegrin-2	Cytolytic	RGRLCYCRRRFCICV	antibiotic
278	Protegrin-3	Cytolytic	RGGLCYCRRFCVCVGRG	antibiotic
279	Protegrin-4	Cytolytic	RGRLCYCRGWICFCVGRG	antibiotic
280	Protegrin-5	Cytolytic	RGRLCYCRPRFCVCVGRG	antibiotic
281	Preprotegrin	Cytolytic	METQRASLCLGRWSLWLLLLGLVVPASAQAQALSYRE AVLRAVDRLNEQSSEANLYRLLELDQPPKADEDPGT PKPVSFVKETVCPRPRTQPPELCDFKENGVRVKQCV GTVTLDQIKDPLDITCNEVQGVGRGLCYCRPRFCV	antibiotic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			CVGRG	
248	Oxyntomodulin		HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRRNNI A	
276	C-peptide		EAEDLQVGQVELGGGPGAGSLQPLALEGSLQ	
282	C-peptide mutant		EGSLC	
283	Human Opioid Growth Factor	Enkephalin	Tyr-Gly-Gly-Phe-Met	
284	cholecystokinin		RDY(SO3-)TGW(Nle)DF	
285	Dynorphin A (1-13)		YGGFLRRIRPKLK	
464	Pralmorelin (GHRFA)		D-Ala-D-2-Nal-Ala-Trp-D-Phe-Lys-NH ₂	
286	Aniritide		RSSCFGGRMDRIGAQSGLGCNSFRY	
287	Vessel dilator proANP31-67		EVVPPQVLSDPNEEAGAAALSPLEVPVPPWTGEVSPAQR	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
465	Peptide G		Arg-Pro-Lys-Pro-Gln-Arg-D-Trp-MePhe-D-Trp-Leu-Met	
466	Tiplimotide		D - Ala - lys - pro - val - val - his - leu - phe - ala - asp - ile - val - thr - pro - arg - thr - pro	
288	Desirudin (63-desulfohirudin)		VVYTDCTESGQNLCCEGSNVCGQGKNKCILGSDGEK NQCVTGEGTPKPQSHNDGDFEEIPEEYLQ	
467	Examorelin		His-DTrp(2-Me)-Ala-Trp-DPhe-Lys-NH ₂	
172	Terlipressin	Vesopressin	Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH ₂	
289	Osteogenic Growth Factor (WT)		ALKRQGR ₁ TLYGFGG	
290	Osteogenic Growth Factor (10-14)		YGFGG	
291	Myelin Basic Protein peptide		Ac-ASQKRPSQRHG	
292	Myelin Basic Protein peptide		Ac-ASQYRPSQRHG	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	Ac1-11[4Y]			
293	Gonadorelin (24-33)		pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly CONH2	
468	Bremelanotide	Alpha-MSH	Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-OH	
294	Islet Neogenesis associated peptide (INGAP)		GLHDPSHGTLPNGSG	Diabetes
295	Urocortin II		IVLSLDVPIGLLQILLEQARARAAREQATTNARILARV GHC	
296	A6 (anti-angiogenic peptide)		CH3CO-NH2-KPSSPPEE-CONH2	
297	Obestatin		H-Phe-Asn-Ala-Pro-Phe-Asp-Val-Gly-Ile-Lys-Leu-Ser-Gly-Val-Gln-Tyr-Gln-Gln-His-Ser-Gln-Ala-Leu-NH2	
298	ITF-1697		Gly-Lys(Et)-Pro-Arg	
299	CNP (C-type)		GLSKGCFGLKLDRI GSMGLGC	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	netriuretic peptide			
300	Osteocalcin		YLYQWLGAPVPYPDPLEPRREVCELNPDCDELADHIG FQEAYRRFYGPV	Diabetes
301			EAEDLQVGQVELGGPGAGCLQPLALEGSLQ	
469	D4F-APO1 mimetic peptide		Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH ₂	

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[0058] In other embodiments, the therapeutic peptides are selected from the group consisting of peptide G, OTS-102, Angiocol (antiangiogenic peptide group), ABT-510 (antiangiogenic peptide group), A6 (antiangiogenic peptide group), islet neogenesis gene associated protein (INGAP), tendamistat, recombinant human carperitide (alpha-atrial natriuretic peptide) (natriuretic peptide group), urodilatin (natriuretic peptide group), desirudin, Obestatin, ITF-1697, oxyntomodulin, cholecystokinin, bactericidal permeability increasing (BPI) protein, C-peptide, Prosaptide TX14(A), sermorelin acetate (GHRFA group), pralmorelin (GHRFA group), growth hormone releasing factor (GHRFA group), examorelin (GHRFA group), gonadorelin (LH-related peptide group), corticoliberin, atrial natriuretic peptide (natriuretic peptide group), anergix, somatostatin (GHRFA group), 29-amino-acid peptide growth hormone releasing hormone (GHRH) analogue (GHRFA group), bremelanotide (melanocortin agonist group), melanocortin peptidomimetic compound (melanocortin agonist group), antiprogestogens - GnRH antagonists (LH-related peptide group), recombinant LH (luteinizing hormone) (LH-related peptide group), terlipressin, Ecallantide - 60-amino-acid recombinant peptide kallikrein inhibitor, calphobindin I, tiplimotide, osteogenic growth peptide, myelin basic protein, dynorphin A, anaritide (natriuretic peptide group), secretin, GLP-2, and gastrin.

[0059] The therapeutic peptides of the invention may comprise any of the 20 natural amino acids, and/or non-natural amino acids, amino acid analogs, and peptidomimetics, in any combination. The peptides may be composed of D- amino acids or L-amino acids, or a combination of both in any proportion. In addition to natural amino acids, the therapeutic peptides may contain, or may be modified to include, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, or more non-natural amino acids. Exemplary non-natural amino acids and amino acid analogs that can be use with the invention include, but are not limited to, 2-aminobutyric acid, 2-aminoisobutyric acid, 3-(1-naphthyl)alanine, 3-(2-naphthyl)alanine, 3-methylhistidine, 3-pyridylalanine, 4-chlorophenylalanine, 4-fluorophenylalanine, 4-hydroxyproline, 5-hydroxylysine, alloisoleucine, citrulline, dehydroalanine, homoarginine, homocysteine, homoserine, hydroxyproline, N-acetylserine, N-formylmethionine, N-methylglycine, N-methylisoleucine, norleucine, N- α -methylarginine, O-phosphoserine, ornithine, phenylglycine, pipercolinic acid, piperazic acid, pyroglutamine, sarcosine, valanine, β -alanine, and β -cyclohexylalanine.

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[0060] The therapeutic peptides may be, or may be modified to be, linear, branched, or cyclic, with or without branching.

[0061] Additionally, the therapeutic peptides may optionally be modified or protected with a variety of functional groups or protecting groups, including amino terminus protecting groups and/or carboxy terminus protecting groups. Protecting groups, and the manner in which they are introduced and removed are described, for example, in "Protective Groups in Organic Chemistry," Plenum Press, London, N.Y. 1973; and. Greene *et al.*, "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS" 3rd Edition, John Wiley and Sons, Inc., New York, 1999. Numerous protecting groups are known in the art. An illustrative, non-limiting list of protecting groups includes methyl, formyl, ethyl, acetyl, t-butyl, anisyl, benzyl, trifluoroacetyl, N-hydroxysuccinimide, t-butoxycarbonyl, benzoyl, 4-methylbenzyl, thioanisyl, thiocresyl, benzyloxymethyl, 4-nitrophenyl, benzyloxycarbonyl, 2-nitrobenzoyl, 2-nitrophenylsulphenyl, 4-toluenesulphonyl, pentafluorophenyl, diphenylmethyl, 2-chlorobenzyloxycarbonyl, 2,4,5-trichlorophenyl, 2-bromobenzyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, triphenylmethyl, and 2,2,5,7,8-pentamethyl-chroman-6-sulphonyl. For discussions of various different types of amino- and carboxy-protecting groups, see, for example, U.S. Pat. No. 5,221,736 (issued Jun. 22, 1993); U.S. Pat. No. 5,256,549 (issued Oct. 26, 1993); U.S. Pat. No. 5,049,656 (issued Sep. 17, 1991); and U.S. Pat. No. 5,521,184 (issued May 28, 1996).

[0062] The therapeutic peptides contain, or may be modified to contain, functional groups to which a water-soluble polymer may be attached, either directly or through a spacer moiety or linker. Functional groups include, but are not limited to, the N-terminus of the therapeutic peptide, the C-terminus of the therapeutic peptide, and any functional groups on the side chain of an amino acid, *e.g.* lysine, cysteine, histidine, aspartic acid, glutamic acid, tyrosine, arginine, serine, methionine, and threonine, present in the therapeutic peptide.

[0063] The therapeutic peptides can be prepared by any means known in the art, including non-recombinant and recombinant methods, or they may, in some instances, be commercially available. Chemical or non-recombinant methods include, but are not limited to, solid phase peptide synthesis (SPPS), solution phase peptide synthesis, native chemical ligation, intein-mediated protein ligation, and chemical ligation, or a combination thereof. In a preferred embodiment, the therapeutic peptides are synthesized using standard SPPS, either manually or by using commercially available automated SPPS synthesizers.

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[0064] SPPS has been known in the art since the early 1960's (Merrifield, R. B., *J. Am. Chem. Soc.*, 85:2149-2154 (1963)), and is widely employed. (See also, Bodanszky, Principles of Peptide Synthesis, Springer-Verlag, Heidelberg (1984)). There are several known variations on the general approach. (See, for example, "Peptide Synthesis, Structures, and Applications" © 1995 by Academic Press, Chapter 3 and White (2003) *Fmoc Solid Phase Peptide Synthesis, A practical Approach*, Oxford University Press, Oxford). Very briefly, in solid phase peptide synthesis, the desired C-terminal amino acid residue is coupled to a solid support. The subsequent amino acid to be added to the peptide chain is protected on its amino terminus with Boc, Fmoc, or other suitable protecting group, and its carboxy terminus is activated with a standard coupling reagent. The free amino terminus of the support-bound amino acid is allowed to react with the carboxy-terminus of the subsequent amino acid, coupling the two amino acids. The amino terminus of the growing peptide chain is deprotected, and the process is repeated until the desired polypeptide is completed. Side chain protecting groups may be utilized as needed.

[0065] Alternatively, the therapeutic peptides may be prepared recombinantly. Exemplary recombinant methods used to prepare therapeutic peptides include the following, among others, as will be apparent to one skilled in the art. Typically, a therapeutic peptide as defined and/or described herein is prepared by constructing the nucleic acid encoding the desired peptide or fragment, cloning the nucleic acid into an expression vector, transforming a host cell (e.g., plant, bacteria such as *Escherichia coli*, yeast such as *Saccharomyces cerevisiae*, or mammalian cell such as Chinese hamster ovary cell or baby hamster kidney cell), and expressing the nucleic acid to produce the desired peptide or fragment. The expression can occur via exogenous expression or via endogenous expression (when the host cell naturally contains the desired genetic coding). Methods for producing and expressing recombinant polypeptides *in vitro* and in prokaryotic and eukaryotic host cells are known to those of ordinary skill in the art. See, for example, U.S. Patent No. 4,868,122, and Sambrook et al., *Molecular Cloning--A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1989)..

[0066] To facilitate identification and purification of the recombinant peptide, nucleic acid sequences that encode an epitope tag or other affinity binding sequence can be inserted or added in-frame with the coding sequence, thereby producing a fusion peptide comprised of the desired therapeutic peptide and a peptide suited for binding. Fusion peptides can be identified and purified by first running a mixture containing the fusion peptide through an affinity column

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bearing binding moieties (*e.g.*, antibodies) directed against the epitope tag or other binding sequence in the fusion peptide, thereby binding the fusion peptide within the column. Thereafter, the fusion peptide can be recovered by washing the column with the appropriate solution (*e.g.*, acid) to release the bound fusion peptide. Optionally, the tag may subsequently be removed by techniques known in the art. The recombinant peptide can also be identified and purified by lysing the host cells, separating the peptide, *e.g.*, by size exclusion chromatography, and collecting the peptide. These and other methods for identifying and purifying recombinant peptides are known to those of ordinary skill in the art.

Related Peptides

[0067] It will be appreciated and understood by one of skill in the art that certain modifications can be made to the therapeutic peptides defined and/or disclosed herein that do not alter, or only partially abrogate, the properties and activities of these therapeutic peptides. In some instances, modifications may be made that result in an increase in therapeutic activities. Additionally, modifications may be made that increase certain biological and chemical properties of the therapeutic peptides in a beneficial way, *e.g.* increased *in vivo* half life, increased stability, decreased susceptibility to proteolytic cleavage, etc. Thus, in the spirit and scope of the invention, the term "therapeutic peptide" is used herein in a manner to include not only the therapeutic peptides defined and/or disclosed herein, but also related peptides, *i.e.* peptides that contain one or more modifications relative to the therapeutic peptides defined and/or disclosed herein, wherein the modification(s) do not alter, only partially abrogate, or increase the therapeutic activities as compared to the parent peptide.

[0068] Related peptides include, but are not limited to, fragments of therapeutic peptides, therapeutic peptide variants, and therapeutic peptide derivatives. Related peptides also include any and all combinations of these modifications. In a non-limiting example, a related peptide may be a fragment of a therapeutic peptide as disclosed herein having one or more amino acid substitutions. Thus it will be understood that any reference to a particular type of related peptide is not limited to a therapeutic peptide having only that particular modification, but rather encompasses a therapeutic peptide having that particular modification and optionally any other modification.

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[0069] Related peptides may be prepared by action on a parent peptide or a parent protein (*e.g.* proteolytic digestion to generate fragments) or through *de novo* preparation (*e.g.* solid phase synthesis of a peptide having a conservative amino acid substitution relative to the parent peptide). Related peptides may arise by natural processes (*e.g.* processing and other post-translational modifications) or may be made by chemical modification techniques. Such modifications are well-known to those of skill in the art.

[0070] A related peptide may have a single alteration or multiple alterations relative to the parent peptide. Where multiple alterations are present, the alterations may be of the same type or a given related peptide may contain different types of modifications. Furthermore, modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains, and the *N*- or *C*- termini.

[0071] As previously noted, related peptides include fragments of the therapeutic peptides defined and/or disclosed herein, wherein the fragment retains some of or all of at least one therapeutic activity of the parent peptide. The fragment may also exhibit an increase in at least one therapeutic activity of the parent peptide. In certain embodiments of the invention, therapeutic peptides include related peptides having at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, or 100 contiguous amino acid residues, or more than 125 contiguous amino acid residues, of any of the therapeutic peptides disclosed, herein, including in Table 1. In other embodiments of the invention, therapeutic peptides include related peptides having 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acid residues deleted from the *N*-terminus and/or having 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acid residues deleted from the *C*-terminus of any of the therapeutic peptides disclosed herein, including in Table 1.

[0072] Related peptides also include variants of the therapeutic peptides defined and/or disclosed herein, wherein the variant retains some of or all of at least one therapeutic activity of the parent peptide. The variant may also exhibit an increase in at least one therapeutic activity of the parent peptide. In certain embodiments of the invention, therapeutic peptides include variants having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 conservative and/or non-conservative amino acid substitutions relative to the therapeutic peptides disclosed herein, including in Table 1. Desired amino acid substitutions, whether conservative or non-conservative, can be determined by those skilled in the art.

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[0073] In certain embodiments of the invention, therapeutic peptides include variants having conservative amino substitutions; these substitutions will produce a therapeutic peptide having functional and chemical characteristics similar to those of the parent peptide. In other embodiments, therapeutic peptides include variants having non-conservative amino substitutions; these substitutions will produce a therapeutic peptide having functional and chemical characteristics that may differ substantially from those of the parent peptide. In certain embodiments of the invention, therapeutic peptide variants have both conservative and non-conservative amino acid substitutions. In other embodiments, each amino acid residue may be substituted with alanine.

[0074] Natural amino acids may be divided into classes based on common side chain properties: nonpolar (Gly, Ala, Val, Leu, Ile, Met); polar neutral (Cys, Ser, Thr, Pro, Asn, Gln); acidic (Asp, Glu); basic (His, Lys, Arg); and aromatic (Trp, Tyr, Phe). By way of example, non-conservative amino acid substitutions may involve the substitution of an amino acid of one class for that of another, and may be introduced in regions of the peptide not critical for therapeutic activity.

[0075] Preferably, amino acid substitutions are conservative. Conservative amino acid substitutions may involve the substitution of an amino acid of one class for that of the same class. Conservative amino acid substitutions may also encompass non-natural amino acid residues, including peptidomimetics and other atypical forms of amino acid moieties, and may be incorporated through chemical peptide synthesis,

[0076] Amino acid substitutions may be made with consideration to the hydropathic index of amino acids. The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is generally understood in the art (Kyte *et al.*, 1982, *J. Mol. Biol.* 157:105-31). Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. The hydropathic indices are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

[0077] It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In

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making changes based upon the hydropathic index, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

[0078] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its biological properties. According to U.S. Patent No. 4,554,101, the following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 $\pm$ 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

[0079] In certain embodiments of the invention, therapeutic peptides include variants having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acid deletions relative to the therapeutic peptides disclosed herein, including in Table 1. The deleted amino acid(s) may be at the *N*- or *C*- terminus of the peptide, at both termini, at an internal location or locations within the peptide, or both internally and at one or both termini. Where the variant has more than one amino acid deletion, the deletions may be of contiguous amino acids or of amino acids at different locations within the primary amino acid sequence of the parent peptide.

[0080] In other embodiments of the invention, therapeutic peptides include variants having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acid additions relative to the therapeutic peptides disclosed herein, including in Table 1. The added amino acid(s) may be at the *N*- or *C*- terminus of the peptide, at both termini, at an internal location or locations within the peptide, or both internally and at one or both termini. Where the variant has more than one amino acid addition, the amino acids may be added contiguously, or the amino acids may be added at different locations within the primary amino acid sequence of the parent peptide.

[0081] Addition variants also include fusion peptides. Fusions can be made either at the *N*-terminus or at the *C*-terminus of the therapeutic peptides disclosed herein, including in Table

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1. In certain embodiments, the fusion peptides have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acid additions relative to the therapeutic peptides disclosed herein, including in Table 1. Fusions may be attached directly to the therapeutic peptide with no connector molecule or may be through a connector molecule. As used in this context, a connector molecule may be an atom or a collection of atoms optionally used to link a therapeutic peptide to another peptide. Alternatively, the connector may be an amino acid sequence designed for cleavage by a protease to allow for the separation of the fused peptides.

[0082] The therapeutic peptides of the invention may be fused to peptides designed to improve certain qualities of the therapeutic peptide, such as therapeutic activity, circulation time, or reduced aggregation. Therapeutic peptides may be fused to an immunologically active domain, *e.g.* an antibody epitope, to facilitate purification of the peptide, or to increase the *in vivo* half life of the peptide. Additionally, therapeutic peptides may be fused to known functional domains, cellular localization sequences, or peptide permeant motifs known to improve membrane transfer properties.

[0083] In certain embodiments of the invention, therapeutic peptides also include variants incorporating one or more non-natural amino acids, amino acid analogs, and peptidomimetics. Thus the present invention encompasses compounds structurally similar to the therapeutic peptides defined and/or disclosed herein, which are formulated to mimic the key portions of the therapeutic peptides of the present invention. Such compounds may be used in the same manner as the therapeutic peptides of the invention. Certain mimetics that mimic elements of protein secondary and tertiary structure have been previously described. Johnson *et al.*, Biotechnology and Pharmacy, Pezzuto *et al.* (Eds.), Chapman and Hall, NY, 1993. The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions. A peptide mimetic is thus designed to permit molecular interactions similar to the parent peptide. Mimetics can be constructed to achieve a similar spatial orientation of the essential elements of the amino acid side chains. Methods for generating specific structures have been disclosed in the art. For example, U.S. Patent Nos. 5,446,128, 5,710,245, 5,840,833, 5,859,184, 5,440,013; 5,618,914, 5,670,155, 5,475,085, 5,929,237, 5,672,681 and 5,674,976,

all disclose peptidomimetics structures

that may have improved properties over the parent peptide, for example they may be

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conformationally restricted, be more thermally stable, exhibit increased resistance to degradation, etc.

[0084] In another embodiment, related peptides comprise or consist of a peptide sequence that is at least 70% identical to any of the therapeutic peptides disclosed herein, including in Table 1. In additional embodiments, related peptides are at least 75% identical, at least 80% identical, at least 85% identical, 90% identical, at least 91% identical, at least 92% identical, 93% identical, at least 94% identical, at least 95% identical, 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to any of the therapeutic peptides disclosed herein, including in Table 1.

[0085] Sequence identity (also known as % homology) of related polypeptides can be readily calculated by known methods. Such methods include, but are not limited to those described in *Computational Molecular Biology* (A.M. Lesk, ed., Oxford University Press 1988); *Biocomputing: Informatics and Genome Projects* (D.W. Smith, ed., Academic Press 1993); *Computer Analysis of Sequence Data* (Part 1, A.M. Griffin and H.G. Griffin, eds., Humana Press 1994); G. von Heinle, *Sequence Analysis in Molecular Biology* (Academic Press 1987); *Sequence Analysis Primer* (M. Gribskov and J. Devereux, eds., M. Stockton Press 1991); and Carillo *et al.*, 1988, *SIAM J. Applied Math.*, 48:1073.

[0086] Preferred methods to determine sequence identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine sequence identity are described in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, the GCG program package, including GAP (Devereux *et al.*, 1984, *Nucleic Acids Res.* 12:387; Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, and FASTA (Altschul *et al.*, 1990, *J. Mol. Biol.* 215:403-10). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (Altschul *et al.*, *BLAST Manual* (NCB NLM NIH, Bethesda, MD); Altschul *et al.*, 1990, *supra*). The well-known Smith Waterman algorithm may also be used to determine identity.

[0087] For example, using the computer algorithm GAP (Genetics Computer Group, University of Wisconsin, Madison, WI), two polypeptides for which the percent sequence identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span," as determined by the algorithm). A gap opening penalty (which is calculated as

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3X the average diagonal; the “average diagonal” is the average of the diagonal of the comparison matrix being used; the “diagonal” is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 0.1X the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. A standard comparison matrix is also used by the algorithm (*see Dayhoff et al., 5 Atlas of Protein Sequence and Structure* (Supp. 3 1978)(PAM250 comparison matrix); Henikoff et al., 1992, *Proc. Natl. Acad. Sci USA* 89:10915-19 (BLOSUM 62 comparison matrix)). The particular choices to be made with regard to algorithms, gap opening penalties, gap extension penalties, comparison matrices, and thresholds of similarity will be readily apparent to those of skill in the art and will depend on the specific comparison to be made.

[0088] Related peptides also include derivatives of the therapeutic peptides defined and/or disclosed herein, wherein the variant retains some of or all of at least one therapeutic activity of the parent peptide. The derivative may also exhibit an increase in at least one therapeutic activity of the parent peptide. Chemical alterations of therapeutic peptide derivatives include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, T. E. Creighton, *Proteins, Structure and Molecular Properties*, 2nd ed., W.H. Freeman and Company, New York (1993); *Posttranslational Covalent Modification of Proteins*, B. C. Johnson, ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., *Meth. Enzymol* 182:626-46 (1990); Rattan et al., *Ann. N.Y. Acad. Sci.* 663:48-62, 1992).

[0089] Therapeutic peptide derivatives also include molecules formed by the deletion of one or more chemical groups from the parent peptide. Methods for preparing chemically

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modified derivatives of the therapeutic peptides defined and/or disclosed herein are known to one of skill in the art.

[0090] In some embodiments of the invention, the therapeutic peptides may be modified with one or more methyl or other lower alkyl groups at one or more positions of the therapeutic peptide sequence. Examples of such groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, etc. In certain preferred embodiments, arginine, lysine, and histidine residues of the therapeutic peptides are modified with methyl or other lower alkyl groups.

[0091] In other embodiments of the invention, the therapeutic peptides may be modified with one or more glycoside moieties relative to the parent peptide. Although any glycoside can be used, in certain preferred embodiments the therapeutic peptide is modified by introduction of a monosaccharide, a disaccharide, or a trisaccharide or it may contain a glycosylation sequence found in natural peptides or proteins in any mammal. The saccharide may be introduced at any position, and more than one glycoside may be introduced. Glycosylation may occur on a naturally occurring amino acid residue in the therapeutic peptide, or alternatively, an amino acid may be substituted with another for modification with the saccharide.

[0092] Glycosylated therapeutic peptides may be prepared using conventional Fmoc chemistry and solid phase peptide synthesis techniques, *e.g.*, on resin, where the desired protected glycoamino acids are prepared prior to peptide synthesis and then introduced into the peptide chain at the desired position during peptide synthesis. Thus, the therapeutic peptide polymer conjugates may be conjugated *in vitro*. The glycosylation may occur before deprotection. Preparation of aminoacid glycosides is described in U.S. Patent No. 5,767,254, WO 2005/097158, and Doores, K., *et al.*, *Chem. Commun.*, 1401-1403, 2006.

For example, alpha and beta selective glycosylations of serine and threonine residues are carried out using the Koenigs-Knorr reaction and Lemieux's *in situ* anomerization methodology with Schiff base intermediates. Deprotection of the Schiff base glycoside is then carried out using mildly acidic conditions or hydrogenolysis. A composition, comprising a glycosylated therapeutic peptide conjugate made by stepwise solid phase peptide synthesis involving contacting a growing peptide chain with protected amino acids in a stepwise manner, wherein at least one of the protected amino acids is glycosylated, followed by water-soluble polymer conjugation, may have a purity of at least 95%, such as at least 97%, or at least 98%, of a single species of the glycosylated and conjugated therapeutic peptide.

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[0093] Monosaccharides that may be used for introduction at one or more amino acid residues of the therapeutic peptides defined and/or disclosed herein include glucose (dextrose), fructose, galactose, and ribose. Additional monosaccharides suitable for use include glyceraldehydes, dihydroxyacetone, erythrose, threose, erythrulose, arabinose, lyxose, xylose, ribulose, xylulose, allose, altrose, mannose, N-Acetylneuraminic acid, fucose, N-Acetylgalactosamine, and N-Acetylglucosamine, as well as others. Glycosides, such as mono-, di-, and trisaccharides for use in modifying a therapeutic peptide, may be naturally occurring or may be synthetic. Disaccharides that may be used for introduction at one or more amino acid residues of the therapeutic peptides defined and/or disclosed herein include sucrose, lactose, maltose, trehalose, melibiose, and cellobiose, among others. Trisaccharides include acarbose, raffinose, and melezitose.

[0094] In further embodiments of the invention, the therapeutic peptides defined and/or disclosed herein may be chemically coupled to biotin. The biotin/therapeutic peptide molecules can then bind to avidin.

[0095] As previously noted, modifications may be made to the therapeutic peptides defined and/or disclosed herein that do not alter, or only partially abrogate, the properties and activities of these therapeutic peptides. In some instances, modifications may be made that result in an increase in therapeutic activity. Thus, included in the scope of the invention are modifications to the therapeutic peptides disclosed herein, including in Table 1, that retain at least 1%, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, and any range derivable therein, such as, for example, at least 70% to at least 80%, and more preferably at least 81% to at least 90%; or even more preferably, between at least 91% and at least 99% of the therapeutic activity relative to the unmodified therapeutic peptide. Also included in the scope of the invention are modifications to the therapeutic peptides disclosed herein, including in Table 1, that have greater than 100%, greater than 110%, greater than 125%, greater than 150%, greater than 200%, or greater than 300%, or greater than 10-fold or greater than 100-fold, and any range derivable therein, of the therapeutic activity relative to the unmodified therapeutic peptide.

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[0096] The level of therapeutic activity of a given therapeutic peptide, or a modified therapeutic peptide, may be determined by any suitable *in vivo* or *in vitro* assay. For example, therapeutic activity may be assayed in cell culture, or by clinical evaluation, EC₅₀ assays, IC₅₀ assays, or dose response curves. *In vitro* or cell culture assays, for example, are commonly available and known to one of skill in the art for many therapeutic peptides as disclosed herein, including in Table 1. It will be understood by one of skill in the art that the percent activity of a modified therapeutic peptide relative to its unmodified parent can be readily ascertained through a comparison of the activity of each as determined through the assays disclosed herein or as known to one of skill in the art.

[0097] One of skill in the art will be able to determine appropriate modifications to the therapeutic peptides defined and/or disclosed herein, including those disclosed herein, including in Table 1. For identifying suitable areas of the therapeutic peptides that may be changed without abrogating their therapeutic activities, one of skill in the art may target areas not believed to be essential for activity. For example, when similar peptides with comparable activities exist from the same species or across other species, one of skill in the art may compare those amino acid sequences to identify residues that are conserved among similar peptides. It will be understood that changes in areas of a therapeutic peptide that are not conserved relative to similar peptides would be less likely to adversely affect the therapeutic activity. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids while retaining therapeutic activity. Therefore, even areas that may be important for biological activity and/or for structure may be subject to amino acid substitutions without destroying the therapeutic activity or without adversely affecting the peptide structure.

[0098] Additionally, as appropriate, one of skill in the art can review structure-function studies identifying residues in similar peptides that are important for activity or structure. In view of such a comparison, one can predict the importance of an amino acid residue in a therapeutic peptide that corresponds to an amino acid residue that is important for activity or structure in similar peptides. One of skill in the art may opt for amino acid substitutions within the same class of amino acids for such predicted important amino acid residues of the therapeutic peptides.

[0099] Also, as appropriate, one of skill in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar peptides. In view of

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such information, one of skill in the art may predict the alignment of amino acid residues of a therapeutic peptide with respect to its three dimensional structure. One of skill in the art may choose not to make significant changes to amino acid residues predicted to be on the surface of the peptide, since such residues may be involved in important interactions with other molecules. Moreover, one of skill in the art may generate variants containing a single amino acid substitution at each amino acid residue for test purposes. The variants could be screened using therapeutic activity assays known to those with skill in the art. Such variants could be used to gather information about suitable modifications. For example, where a change to a particular amino acid residue resulted in abrogated, undesirably reduced, or unsuitable activity, variants with such a modification would be avoided. In other words, based on information gathered from routine experimentation, one of skill in the art can readily determine the amino acids where further modifications should be avoided either alone or in combination with other modifications.

[00100] One of skill in the art may also select suitable modifications based on secondary structure predication. A number of scientific publications have been devoted to the prediction of secondary structure. See Moulton, 1996, *Curr. Opin. Biotechnol.* 7:422-27; Chou *et al.*, 1974, *Biochemistry* 13:222-45; Chou *et al.*, 1974, *Biochemistry* 113:211-22; Chou *et al.*, 1978, *Adv. Enzymol. Relat. Areas Mol. Biol.* 47:45-48; Chou *et al.*, 1978, *Ann. Rev. Biochem.* 47:251-276; and Chou *et al.*, 1979, *Biophys. J.* 26:367-84. Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two peptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40%, often have similar structural topologies. Recent growth of the protein structural database (PDB, <http://www.rcsb.org/pdb/home/home.do>) has provided enhanced predictability of secondary, tertiary, and quaternary structure, including the potential number of folds within the structure of a peptide or protein. See Holm *et al.*, 1999, *Nucleic Acids Res.* 27:244-47. It has been suggested that there are a limited number of folds in a given peptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate (Brenner *et al.*, 1997, *Curr. Opin. Struct. Biol.* 7:369-76).

[00101] Additional methods of predicting secondary structure include "threading" (Jones, 1997, *Curr. Opin. Struct. Biol.* 7:377-87; Sippl *et al.*, 1996, *Structure* 4:15-19), "profile analysis" (Bowie *et al.*, 1991, *Science*, 253:164-70; Gribskov *et al.*, 1990, *Methods Enzymol.* 183:146-59;

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Gribskov *et al.*, 1987, *Proc. Nat. Acad. Sci. U.S.A.* 84:4355-58), and “evolutionary linkage” (See Holm *et al.*, *supra*, and Brenner *et al.*, *supra*).

Therapeutic Peptide Conjugates

[00102] As described above, a conjugate of the invention comprises a water-soluble polymer covalently attached (either directly or through a spacer moiety or linker) to a therapeutic peptide. Typically, for any given conjugate, there will be about one to five water-soluble polymers covalently attached to a therapeutic peptide (wherein for each water-soluble polymer, the water-soluble polymer can be attached either directly to the therapeutic peptide or through a spacer moiety).

[00103] To elaborate, a therapeutic peptide conjugate of the invention typically has about 1, 2, 3, or 4 water-soluble polymers individually attached to a therapeutic peptide. That is to say, in certain embodiments, a conjugate of the invention will possess about 4 water-soluble polymers individually attached to a therapeutic peptide, or about 3 water-soluble polymers individually attached to a therapeutic peptide, or about 2 water-soluble polymers individually attached to a therapeutic peptide, or about 1 water-soluble polymer attached to a therapeutic peptide. The structure of each of the water-soluble polymers attached to the therapeutic peptide may be the same or different. One therapeutic peptide conjugate in accordance with the invention is one having a water-soluble polymer releasably attached to the therapeutic peptide, particularly at the *N*-terminus of the therapeutic peptide. Another therapeutic peptide conjugate in accordance with the invention is one having a water-soluble polymer stably attached to the therapeutic peptide, particularly at the *N*-terminus of the therapeutic peptide. Another therapeutic peptide conjugate is one having a water-soluble polymer releasably attached to the therapeutic peptide, particularly at the *C*-terminus of the therapeutic peptide. Another therapeutic peptide conjugate in accordance with the invention is one having a water-soluble polymer stably attached to the therapeutic peptide, particularly at the *C*-terminus of the therapeutic peptide. Other therapeutic peptide conjugates in accordance with the invention are those having a water-soluble polymer releasably or stably attached to an amino acid within the therapeutic peptide. Additional water-soluble polymers may be releasably or stably attached to other sites on the therapeutic peptide, *e.g.*, such as one or more additional sites. For example, a therapeutic peptide conjugate having a water-soluble polymer releasably attached to the *N*-terminus may additionally possess a water-soluble polymer stably attached to a lysine residue. In one embodiment, one or more amino

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acids may be inserted, at the *N*- or *C*-terminus, or within the peptide to releasably or stably attach a water soluble polymer. One preferred embodiment of the present invention is a mono-therapeutic peptide polymer conjugate, *i.e.*, a therapeutic peptide having one water-soluble polymer covalently attached thereto. In an even more preferred embodiment, the water-soluble polymer is one that is attached to the therapeutic peptide at its *N*-terminus.

[00104] Preferably, a therapeutic peptide polymer conjugate of the invention is absent a metal ion, *i.e.*, the therapeutic peptide is not chelated to a metal ion.

[00105] For the therapeutic peptide polymer conjugates described herein, the therapeutic peptide may optionally possess one or more *N*-methyl substituents. Alternatively, for the therapeutic peptide polymer conjugates described herein, the therapeutic peptide may be glycosylated, *e.g.*, having a mono- or disaccharide, or naturally-occurring amino acid glycosylation covalently attached to one or more sites thereof.

[00106] As discussed herein, the compounds of the present invention may be made by various methods and techniques known and available to those skilled in the art.

The Water-Soluble Polymer

[00107] A conjugate of the invention comprises a therapeutic peptide attached, stably or releasably, to a water-soluble polymer. The water-soluble polymer is typically hydrophilic, nonpeptidic, and biocompatible. A substance is considered biocompatible if the beneficial effects associated with use of the substance alone or with another substance (*e.g.*, an active agent such a therapeutic peptide) in connection with living tissues (*e.g.*, administration to a patient) outweighs any deleterious effects as evaluated by a clinician, *e.g.*, a physician. A substance is considered nonimmunogenic if the intended use of the substance *in vivo* does not produce an undesired immune response (*e.g.*, the formation of antibodies) or, if an immune response is produced, that such a response is not deemed clinically significant or important as evaluated by a clinician. Typically, the water-soluble polymer is hydrophilic, biocompatible and nonimmunogenic.

[00108] Further the water-soluble polymer is typically characterized as having from 2 to about 300 termini, preferably from 2 to 100 termini, and more preferably from about 2 to 50 termini. Examples of such polymers include, but are not limited to, poly(alkylene glycols) such as polyethylene glycol (PEG), poly(propylene glycol) ("PPG"), copolymers of ethylene glycol

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and propylene glycol and the like, poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α -hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N-acryloylmorpholine), and combinations of any of the foregoing, including copolymers and terpolymers thereof.

[00109] The water-soluble polymer is not limited to a particular structure and may possess a linear architecture (*e.g.*, alkoxy PEG or bifunctional PEG), or a non-linear architecture, such as branched, forked, multi-armed (*e.g.*, PEGs attached to a polyol core), or dendritic (*i.e.* having a densely branched structure with numerous end groups). Moreover, the polymer subunits can be organized in any number of different patterns and can be selected, *e.g.*, from homopolymer, alternating copolymer, random copolymer, block copolymer, alternating tripolymer, random tripolymer, and block tripolymer.

[00110] One particularly preferred type of water-soluble polymer is a polyalkylene oxide, and in particular, polyethylene glycol (or PEG). Generally, a PEG used to prepare a therapeutic peptide polymer conjugate of the invention is "activated" or reactive. That is to say, the activated PEG (and other activated water-soluble polymers collectively referred to herein as "polymeric reagents") used to form a therapeutic peptide conjugate comprises an activated functional group suitable for coupling to a desired site or sites on the therapeutic peptide. Thus, a polymeric reagent for use in preparing a therapeutic peptide conjugate includes a functional group for reaction with the therapeutic peptide.

[00111] Representative polymeric reagents and methods for conjugating such polymers to an active moiety are known in the art, and are, *e.g.*, described in Harris, J.M. and Zalipsky, S., eds, *Poly(ethylene glycol), Chemistry and Biological Applications*, ACS, Washington, 1997; Veronese, F., and J.M Harris, eds., *Peptide and Protein PEGylation*, Advanced Drug Delivery Reviews, 54(4); 453-609 (2002); Zalipsky, S., *et al.*, "Use of Functionalized Poly(Ethylene Glycols) for Modification of Polypeptides" in *Polyethylene Glycol Chemistry: Biotechnical and Biomedical Applications*, J. M. Harris, ed., Plenus Press, New York (1992); Zalipsky (1995) *Advanced Drug Reviews* 16:157-182, and in Roberts, *et al.*, *Adv. Drug Delivery Reviews*, 54, 459-476 (2002).

[00112] Additional PEG reagents suitable for use in forming a conjugate of the invention, and methods of conjugation are described in the Pasut, G., *et al.*, *Expert Opin. Ther. Patents*

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(2004), 14(5). PEG reagents suitable for use in the present invention also include those available from NOF Corporation, as described generally on the NOF website.

Additional PEGs for use in forming a therapeutic peptide conjugate of the invention include those available from Polypure (Norway) and from QuantaBioDesign LTD (Ohio).

In addition, water soluble polymer reagents useful for preparing peptide conjugates of the invention can be prepared synthetically. Descriptions of the water soluble polymer reagent synthesis can be found in, for example, U.S. Patent Nos. 5,252,714, 5,650,234, 5,739,208, 5,932,462, 5,629,384, 5,672,662, 5,990,237, 6,448,369, 6,362,254, 6,495,659, 6,413,507, 6,376,604, 6,348,558, 6,602,498, and 7,026,440.

[00113] Typically, the weight-average molecular weight of the water-soluble polymer in the conjugate is from about 100 Daltons to about 150,000 Daltons. Exemplary ranges include weight-average molecular weights in the range of from about 250 Daltons to about 80,000 Daltons, from 500 Daltons to about 80,000 Daltons, from about 500 Daltons to about 65,000 Daltons, from about 500 Daltons to about 40,000 Daltons, from about 750 Daltons to about 40,000 Daltons, from about 1000 Daltons to about 30,000 Daltons. In a preferred embodiment, the weight average molecular weight of the water-soluble polymer in the conjugate ranges from about 1000 Daltons to about 10,000 Daltons. In certain other preferred embodiments, the range is from about 1000 Daltons to about 5000 Daltons, from about 5000 Daltons to about 10,000 Daltons, from about 2500 Daltons to about 7500 Daltons, from about 1000 Daltons to about 3000 Daltons, from about 3000 Daltons to about 7000 Daltons, or from about 7000 Daltons to about 10,000 Daltons. In a further preferred embodiment, the weight average molecular weight of the water-soluble polymer in the conjugate ranges from about 20,000 Daltons to about 40,000 Daltons. In other preferred embodiments, the range is from about 20,000 Daltons to about 30,000 Daltons, from about 30,000 Daltons to about 40,000 Daltons, from about 25,000 Daltons to about 35,000 Daltons, from about 20,000 Daltons to about 26,000 Daltons, from about 26,000 Daltons to about 34,000 Daltons, or from about 34,000 Daltons to about 40,000 Daltons.

[00114] For any given water-soluble polymer, a molecular weight in one or more of these ranges is typical. Generally, a therapeutic peptide conjugate in accordance with the invention, when intended for subcutaneous or intravenous administration, will comprise a PEG or other

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suitable water-soluble polymer having a weight average molecular weight of about 20,000 Daltons or greater, while a therapeutic peptide conjugate intended for pulmonary administration will generally, although not necessarily, comprise a PEG polymer having a weight average molecular weight of about 20,000 Daltons or less.

[00115] Exemplary weight-average molecular weights for the water-soluble polymer include about 100 Daltons, about 200 Daltons, about 300 Daltons, about 400 Daltons, about 500 Daltons, about 600 Daltons, about 700 Daltons, about 750 Daltons, about 800 Daltons, about 900 Daltons, about 1,000 Daltons, about 1,500 Daltons, about 2,000 Daltons, about 2,200 Daltons, about 2,500 Daltons, about 3,000 Daltons, about 4,000 Daltons, about 4,400 Daltons, about 4,500 Daltons, about 5,000 Daltons, about 5,500 Daltons, about 6,000 Daltons, about 7,000 Daltons, about 7,500 Daltons, about 8,000 Daltons, about 9,000 Daltons, about 10,000 Daltons, about 11,000 Daltons, about 12,000 Daltons, about 13,000 Daltons, about 14,000 Daltons, about 15,000 Daltons, about 20,000 Daltons, about 22,500 Daltons, about 25,000 Daltons, about 30,000 Daltons, about 35,000 Daltons, about 40,000 Daltons, about 45,000 Daltons, about 50,000 Daltons, about 55,000 Daltons, about 60,000 Daltons, about 65,000 Daltons, about 70,000 Daltons, and about 75,000 Daltons.

[00116] Branched versions of the water-soluble polymer (*e.g.*, a branched 40,000 Dalton water-soluble polymer comprised of two 20,000 Dalton polymers or the like) having a total molecular weight of any of the foregoing can also be used. In one or more particular embodiments, depending upon the other features of the subject therapeutic peptide polymer conjugate, the conjugate is one that does not have one or more attached PEG moieties having a weight-average molecular weight of less than about 6,000 Daltons.

[00117] In instances in which the water-soluble polymer is a PEG, the PEG will typically comprise a number of (OCH₂CH₂) monomers. As used herein, the number of repeat units is typically identified by the subscript "*n*" in, for example, "(OCH₂CH₂)_{*n*}." Thus, the value of (*n*) typically falls within one or more of the following ranges: from 2 to about 3400, from about 100 to about 2300, from about 100 to about 2270, from about 136 to about 2050, from about 225 to about 1930, from about 450 to about 1930, from about 1200 to about 1930, from about 568 to about 2727, from about 660 to about 2730, from about 795 to about 2730, from about 795 to about 2730, from about 909 to about 2730, and from about 1,200 to about 1,900. Preferred ranges of *n* include from about 10 to about 700, and from about 10 to about 1800. For any given

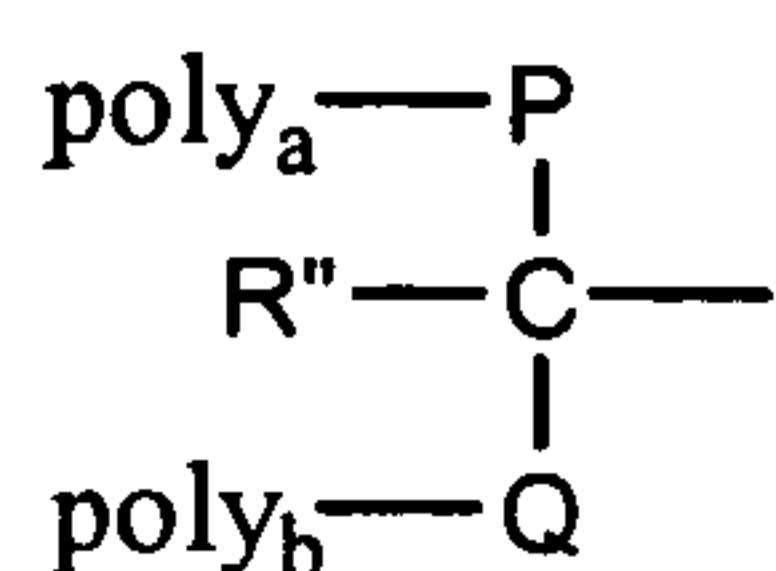
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polymer in which the molecular weight is known, it is possible to determine the number of repeating units (i.e., "n") by dividing the total weight-average molecular weight of the polymer by the molecular weight of the repeating monomer.

[00118] With regard to the molecular weight of the water-soluble polymer, in one or more embodiments of the invention, depending upon the other features of the particular therapeutic peptide conjugate, the conjugate comprises a therapeutic peptide covalently attached to a water-soluble polymer having a molecular weight greater than about 2,000 Daltons.

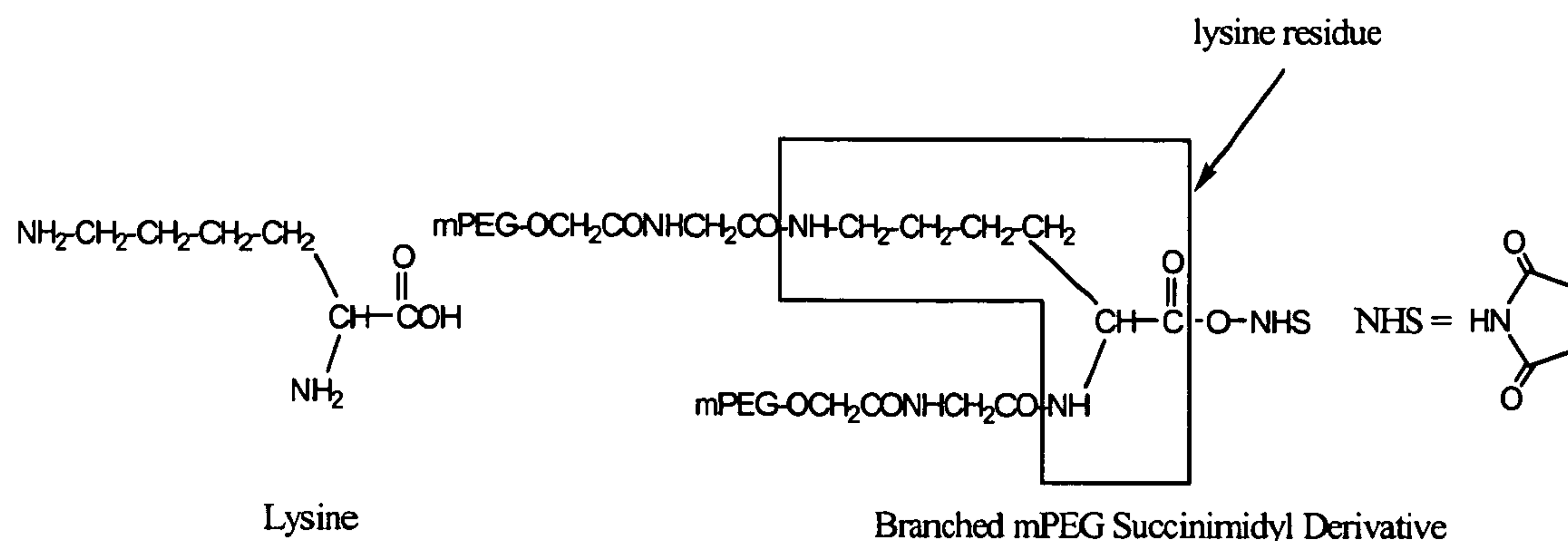
[00119] A polymer for use in the invention may be end-capped, that is, a polymer having at least one terminus capped with a relatively inert group, such as a lower alkoxy group (i.e., a C₁₋₆ alkoxy group) or a hydroxyl group. One frequently employed end-capped polymer is methoxy-PEG (commonly referred to as mPEG), wherein one terminus of the polymer is a methoxy (-OCH₃) group. The -PEG- symbol used in the foregoing generally represents the following structural unit: -CH₂CH₂O-(CH₂CH₂O)_n-CH₂CH₂-, where (n) generally ranges from about zero to about 4,000.

[00120] Multi-armed or branched PEG molecules, such as those described in U.S. Patent No. 5,932,462, are also suitable for use in the present invention. For example, the PEG may be described generally according to the structure:



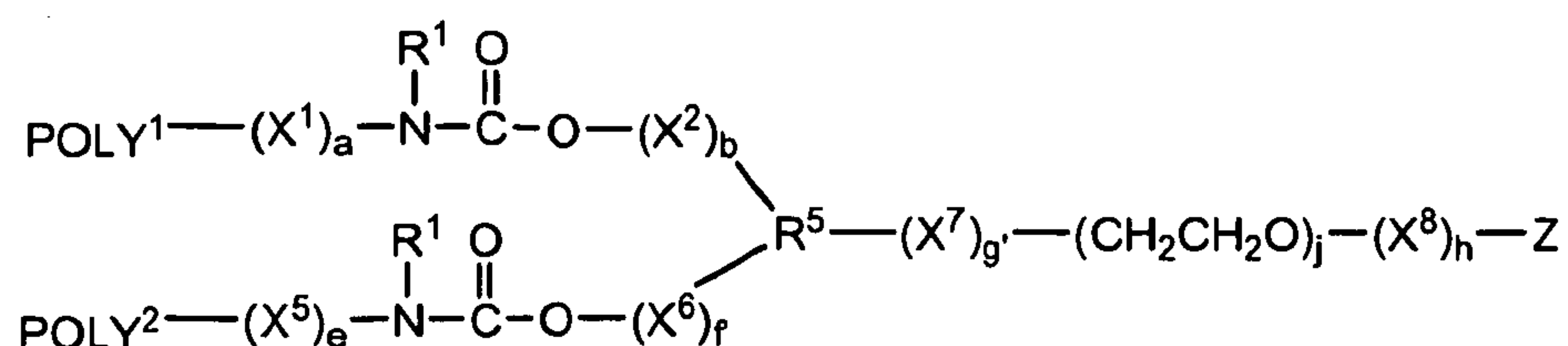
where poly_a and poly_b are PEG backbones (either the same or different), such as methoxy poly(ethylene glycol); R'' is a non-reactive moiety, such as H, methyl or a PEG backbone; and P and Q are non-reactive linkages. In one embodiment, the branched PEG molecule is one that includes a lysine residue, such as the following reactive PEG suitable for use in forming a therapeutic peptide conjugate. Although the branched PEG below is shown with a reactive succinimidyl group, this represents only one of a myriad of reactive functional groups suitable for reacting with a therapeutic peptide.

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[00121] In some instances, the polymeric reagent (as well as the corresponding conjugate prepared from the polymeric reagent) may lack a lysine residue in which the polymeric portions are connected to amine groups of the lysine via a "-OCH₂CONHCH₂CO-" group. In still other instances, the polymeric reagent (as well as the corresponding conjugate prepared from the polymeric reagent) may lack a branched water-soluble polymer that includes a lysine residue (wherein the lysine residue is used to effect branching).

[00122] Additional branched-PEGs for use in forming a therapeutic peptide conjugate of the present invention include those described in co-owned U.S. Patent Application Publication No. 2005/0009988. Representative branched polymers described therein include those having the following generalized structure:



where POLY¹ is a water-soluble polymer; POLY² is a water-soluble polymer; (a) is 0, 1, 2 or 3; (b) is 0, 1, 2 or 3; (c) is 0, 1, 2 or 3; (d) is 0, 1, 2 or 3; (e) is 0, 1, 2 or 3; (f') is 0, 1, 2 or 3; (g') is 0, 1, 2 or 3; (h) is 0, 1, 2 or 3; (j) is 0 to 20; each R¹ is independently H or an organic radical selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl and substituted aryl; X¹, when present, is a spacer moiety; X², when present, is a spacer moiety; X⁵, when present, is a spacer

[00124] Branched polymers suitable for preparing a conjugate of the invention also include those represented more generally by the formula $R(\text{POLY})_y$, where R is a central or core molecule from which extends 2 or more POLY arms such as PEG. The variable y represents the number of POLY arms, where each of the polymer arms can independently be end-capped or alternatively, possess a reactive functional group at its terminus. A more explicit structure in accordance with this embodiment of the invention possesses the structure, $R(\text{POLY-Z})_y$, where each Z is independently an end-capping group or a reactive group, *e.g.*, suitable for reaction with a therapeutic peptide. In yet a further embodiment when Z is a reactive group, upon reaction with a therapeutic peptide, the resulting linkage can be hydrolytically stable, or alternatively, may be degradable, *i.e.*, hydrolyzable. Typically, at least one polymer arm possesses a terminal functional group suitable for reaction with, *e.g.*, a therapeutic peptide. Branched PEGs such as those represented generally by the formula, $R(\text{PEG})_y$ above possess 2 polymer arms to about 300 polymer arms (*i.e.*, n ranges from 2 to about 300). Preferably, such branched PEGs typically possess from 2 to about 25 polymer arms, such as from 2 to about 20 polymer arms, from 2 to

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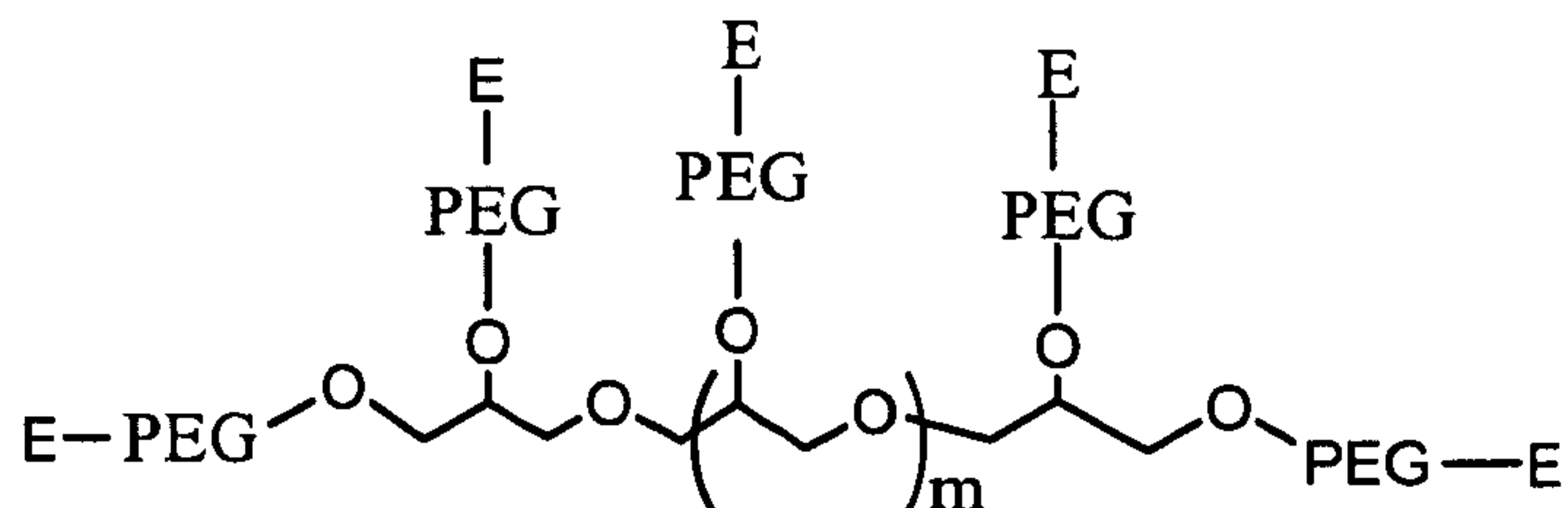
about 15 polymer arms, or from 3 to about 15 polymer arms. Multi-armed polymers include those having 3, 4, 5, 6, 7 or 8 arms.

[00125] Core molecules in branched PEGs as described above include polyols, which are then further functionalized. Such polyols include aliphatic polyols having from 1 to 10 carbon atoms and from 1 to 10 hydroxyl groups, including ethylene glycol, alkane diols, alkyl glycols, alkylidene alkyl diols, alkyl cycloalkane diols, 1,5-decalindiol, 4,8-bis(hydroxymethyl)tricyclodecane, cycloalkylidene diols, dihydroxyalkanes, trihydroxyalkanes, and the like. Cycloaliphatic polyols may also be employed, including straight chained or closed-ring sugars and sugar alcohols, such as mannitol, sorbitol, inositol, xylitol, quebrachitol, threitol, arabitol, erythritol, adonitol, ducitol, facose, ribose, arabinose, xylose, lyxose, rhamnose, galactose, glucose, fructose, sorbose, mannose, pyranose, altrose, talose, tagitose, pyranosides, sucrose, lactose, maltose, and the like. Additional aliphatic polyols include derivatives of glyceraldehyde, glucose, ribose, mannose, galactose, and related stereoisomers. Other core polyols that may be used include crown ether, cyclodextrins, dextrans and other carbohydrates such as starches and amylose. Typical polyols include glycerol, pentaerythritol, sorbitol, and trimethylolpropane.

[00126] As will be described in more detail in the linker section below, although any of a number of linkages can be used to covalently attach a polymer to a therapeutic peptide, in certain instances, the linkage is degradable, designated herein as L_D , that is to say, contains at least one bond or moiety that hydrolyzes under physiological conditions, e.g., an ester, hydrolyzable carbamate, carbonate, or other such group. In other instances, the linkage is hydrolytically stable.

[00127] Illustrative multi-armed PEGs having 3 arms, 4 arms, and 8 arms are known and are available commercially and/or can be prepared following techniques known to those skilled in the art. Multi-armed activated polymers for use in the method of the invention include those corresponding to the following structure, where E represents a reactive group suitable for reaction with a reactive group on the therapeutic peptide. In one or more embodiments, E is an -OH (for reaction with a therapeutic peptide carboxy group or equivalent), a carboxylic acid or equivalent (such as an active ester), a carbonic acid (for reaction with therapeutic peptide -OH groups), or an amino group.

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[00128] In the structure above, PEG is $-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-$, and m is selected from 3, 4, 5, 6, 7, and 8. In certain embodiments, typical linkages are ester, carboxyl and hydrolyzable carbamate, such that the polymer-portion of the conjugate is hydrolyzed *in vivo* to release the therapeutic peptide from the intact polymer conjugate. In such instances, the linker L is designated as L_D .

[00129] Alternatively, the polymer may possess an overall forked structure as described in U.S. Patent No. 6,362,254. This type of polymer segment is useful for reaction with two therapeutic peptide moieties, where the two therapeutic peptide moieties are positioned a precise or predetermined distance apart.

[00130] In any of the representative structures provided herein, one or more degradable linkages may additionally be contained in the polymer segment, POLY, to allow generation *in vivo* of a conjugate having a smaller PEG chain than in the initially administered conjugate. Appropriate physiologically cleavable (*i.e.*, releasable) linkages include but are not limited to ester, carbonate ester, carbamate, sulfate, phosphate, acyloxyalkyl ether, acetal, and ketal. Such linkages when contained in a given polymer segment will often be stable upon storage and upon initial administration.

[00131] The PEG polymer used to prepare a therapeutic peptide polymer conjugate may comprise a pendant PEG molecule having reactive groups, such as carboxyl or amino, covalently attached along the length of the PEG rather than at the end of the PEG chain(s). The pendant reactive groups can be attached to the PEG directly or through a spacer moiety, such as an alkylene group.

[00132] In certain embodiments, a therapeutic peptide polymer conjugate according to one aspect of the invention is one comprising a therapeutic peptide releasably attached, preferably at its N-terminus, to a water-soluble polymer. Hydrolytically degradable linkages, useful not only as a degradable linkage within a polymer backbone, but also, in the case of certain embodiments

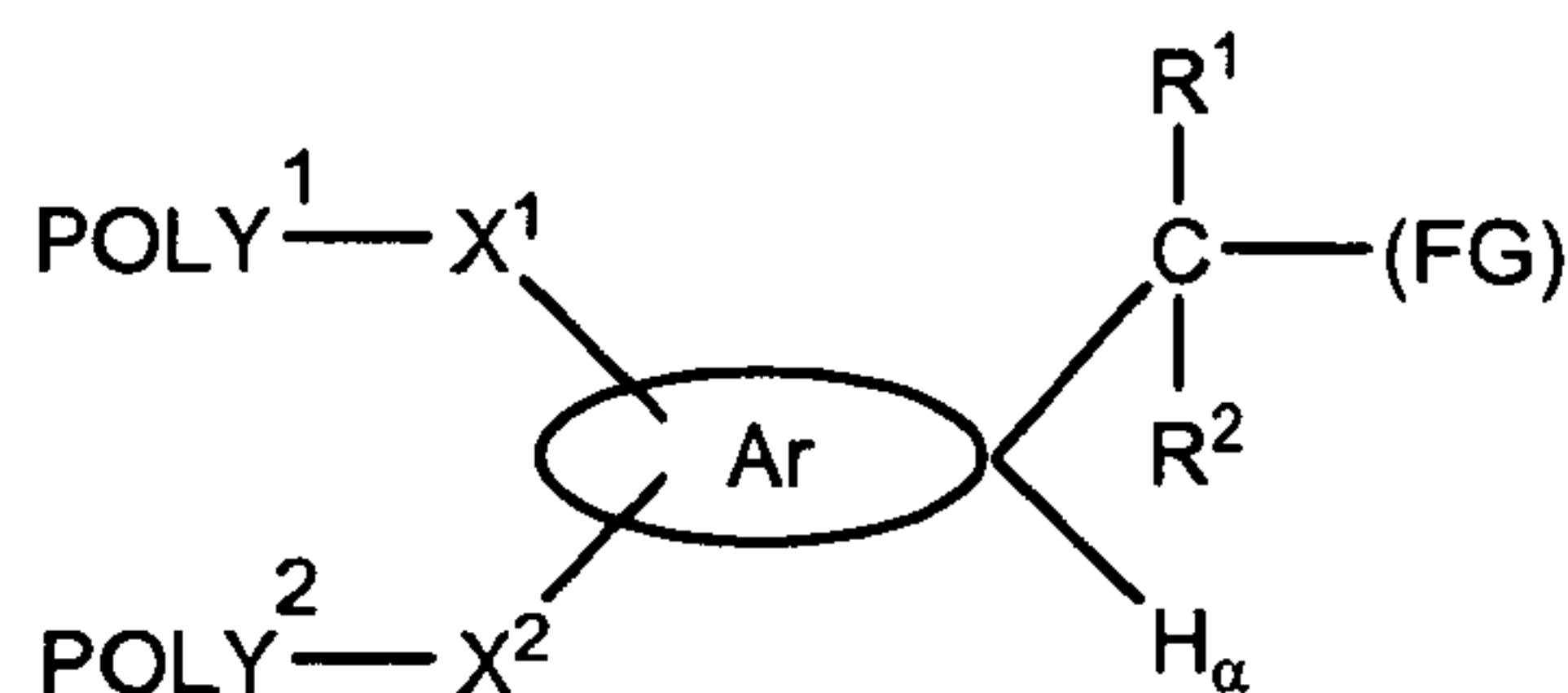
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of the invention, for covalently attaching a water-soluble polymer to a therapeutic peptide, include: carbonate; imine resulting, for example, from reaction of an amine and an aldehyde (see, *e.g.*, Ouchi *et al.* (1997) *Polymer Preprints* 38(1):582-3); phosphate ester, formed, for example, by reacting an alcohol with a phosphate group; hydrazone, *e.g.*, formed by reaction of a hydrazide and an aldehyde; acetal, *e.g.*, formed by reaction of an aldehyde and an alcohol; orthoester, formed, for example, by reaction between a formate and an alcohol; and esters, and certain urethane (carbamate) linkages.

[00133] Illustrative PEG reagents for use in preparing a releasable therapeutic peptide conjugate in accordance with the invention are described in U.S. Patent Nos. 6,348,558, 5,612,460, 5,840,900, 5,880,131, and 6,376,470.

[00134] Additional PEG reagents for use in the invention include hydrolyzable and/or releasable PEGs and linkers such as those described in U.S. Patent Application Publication No. 2006-0293499. In the resulting conjugate, the therapeutic peptide and the polymer are each covalently attached to different positions of the aromatic scaffold, *e.g.*, Fmoc or FMS, structure, and are releasable under physiological conditions. Generalized structures corresponding to the polymers described therein are provided below.

[00135] For example, one such polymeric reagent comprises the following structure:



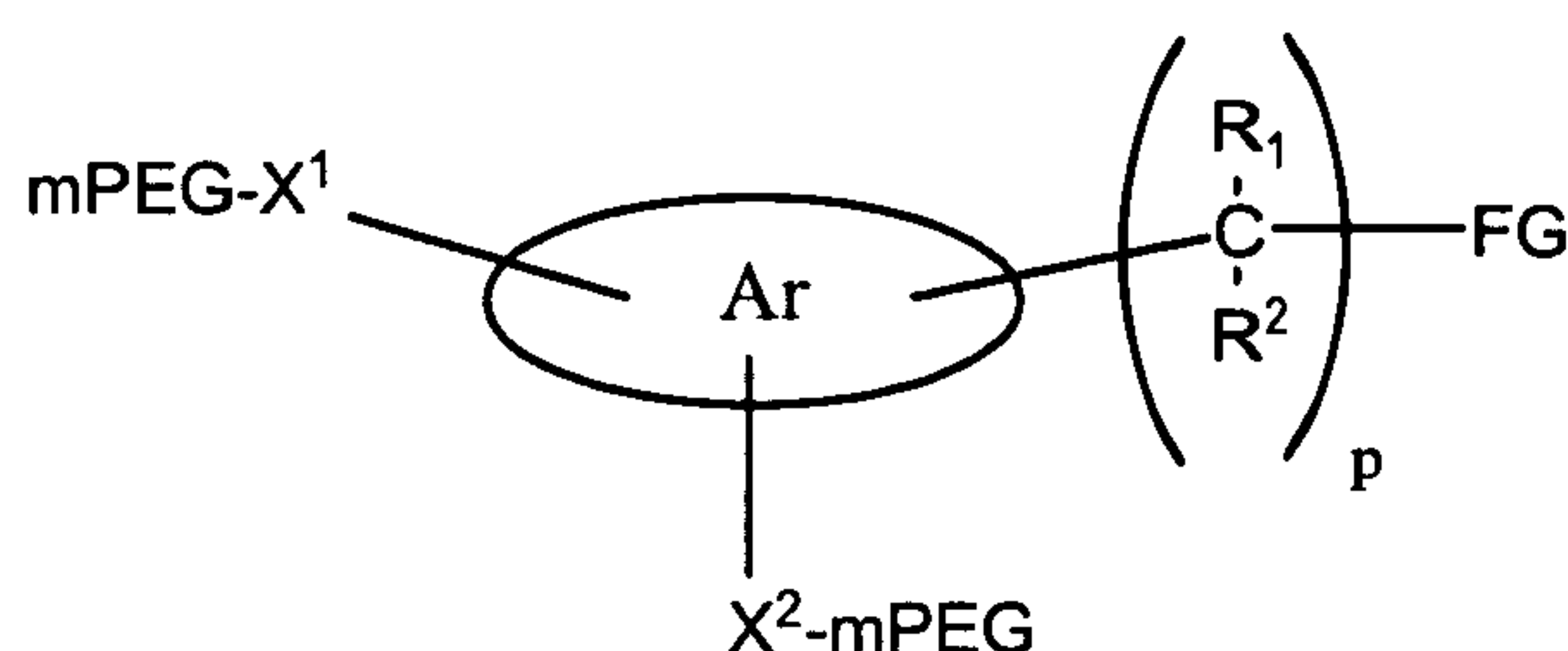
where POLY¹ is a first water-soluble polymer; POLY² is a second water-soluble polymer; X¹ is a first spacer moiety; X² is a second spacer moiety;  H_α is an aromatic-containing moiety bearing an ionizable hydrogen atom, H_α; R¹ is H or an organic radical; R² is H or an organic radical; and (FG) is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage, such as a carbamate linkage (such as N-succinimidyloxy, 1-benzotriazolyloxy, oxycarbonylimidazole, -O-C(O)-Cl, O-C(O)-Br, unsubstituted aromatic carbonate radicals and substituted aromatic carbonate radicals). The polymeric reagent can

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include one, two, three, four or more electron altering groups attached to the aromatic-containing moiety.

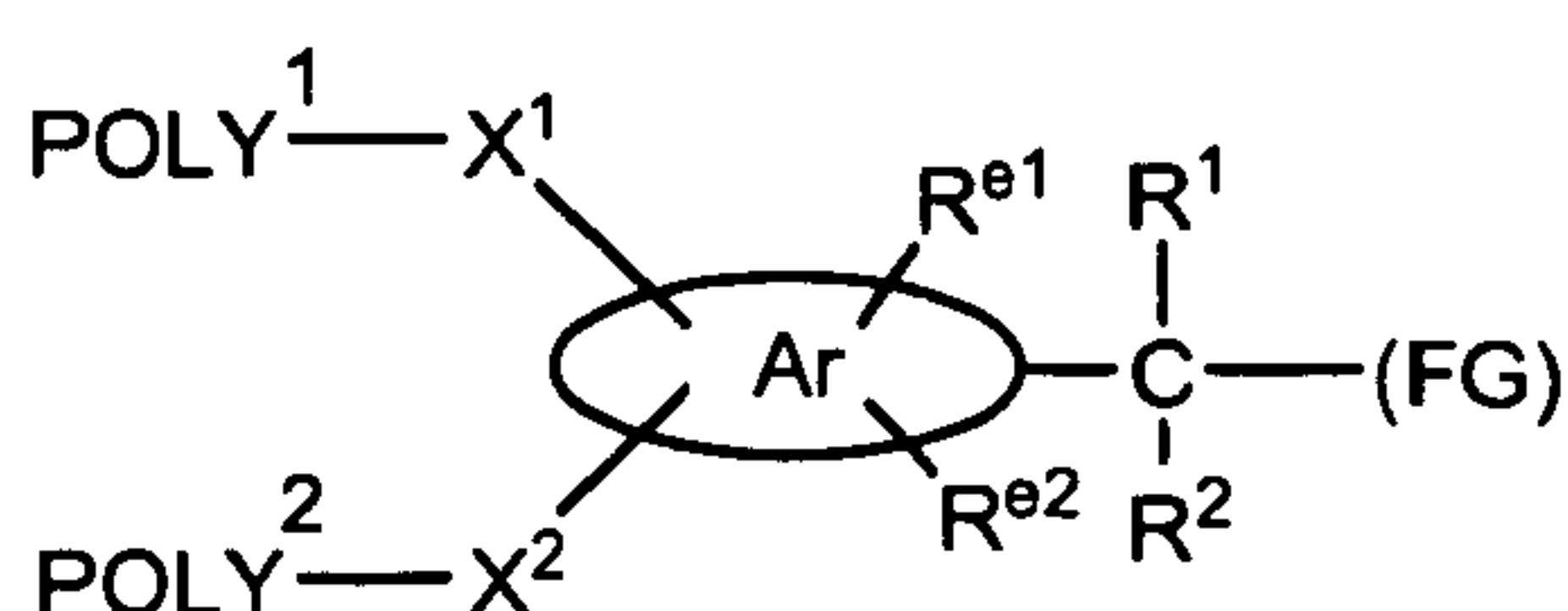
[00136] Preferred aromatic-containing moieties are bicyclic and tricyclic aromatic hydrocarbons. Fused bicyclic and tricyclic aromatics include pentalene, indene, naphthalene, azulene, heptalene, biphenylene, as-indacene, s-indacene, acenaphthylene, fluorene, phenalene, phenanthrene, anthracene, and fluoranthene.

[00137] A preferred polymer reagent possesses the following structure,



where mPEG corresponds to $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-$, X^1 and X^2 are each independently a spacer moiety having an atom length of from about 1 to about 18 atoms, n ranges from 10 to 1800, p is an integer ranging from 1 to 8, R^1 is H or lower alkyl, R^2 is H or lower alkyl, and Ar is an aromatic hydrocarbon, preferably a bicyclic or tricyclic aromatic hydrocarbon. FG is as defined above. Preferably, FG corresponds to an activated carbonate ester suitable for reaction with an amino group on therapeutic peptide. Preferred spacer moieties, X^1 and X^2 , include $-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{O}-$, $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_q-\text{O}-$, $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_q-\text{C}(\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_q-$, and $-\text{C}(\text{O})-\text{NH}-$, where q is selected from 2, 3, 4, and 5. Preferably, although not necessarily, the nitrogen in the preceding spacers is proximal to the PEG rather than to the aromatic moiety.

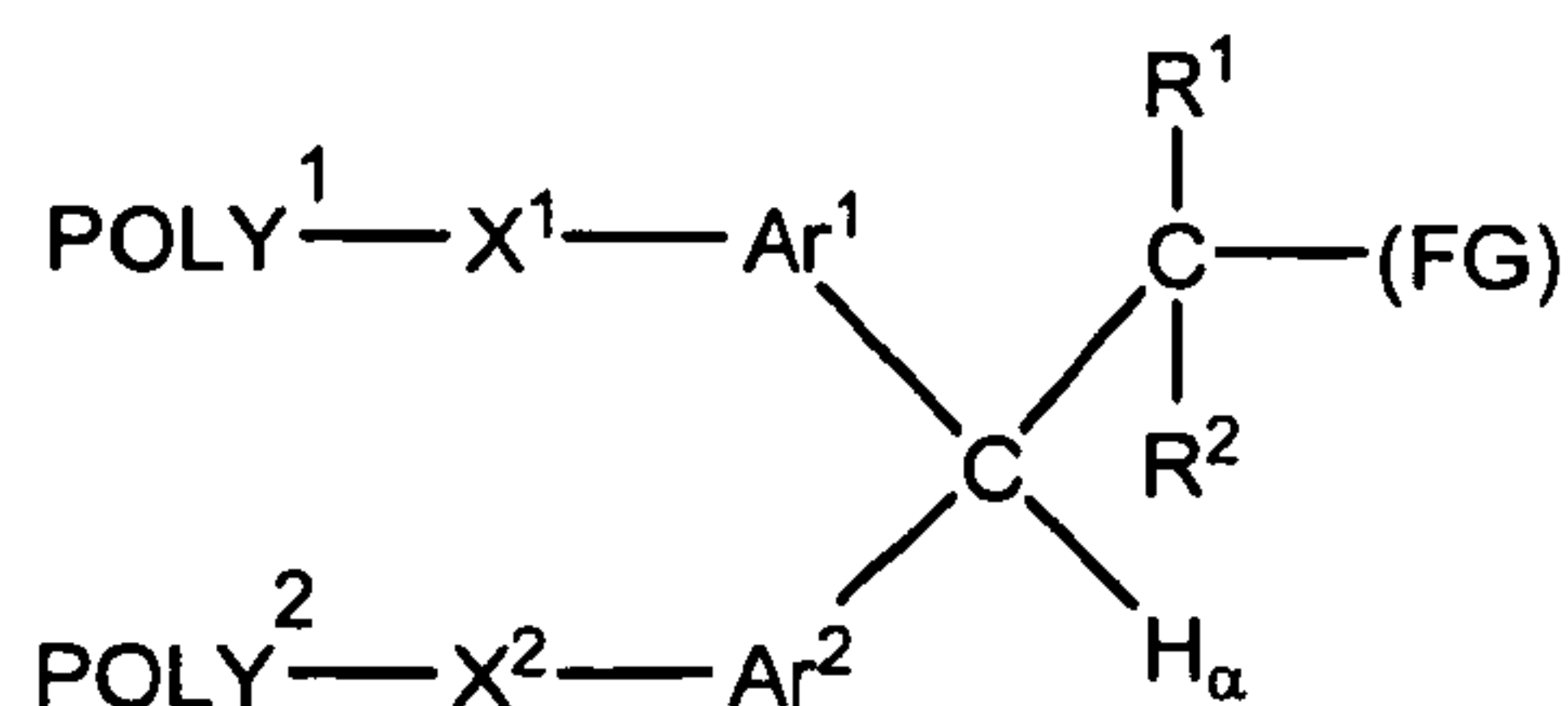
[00138] Another such branched (2-armed) polymeric reagent comprised of two electron altering groups comprises the following structure:



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wherein each of POLY¹, POLY², X¹, X², R¹, R², , and (FG) is as defined immediately above, and R^{e1} is a first electron altering group; and R^{e2} is a second electron altering group. An electron altering group is a group that is either electron donating (and therefore referred to as an "electron donating group"), or electron withdrawing (and therefore referred to as an "electron withdrawing group"). When attached to the aromatic-containing moiety bearing an ionizable hydrogen atom, an electron donating group is a group having the ability to position electrons away from itself and closer to or within the aromatic-containing moiety. When attached to the aromatic-containing moiety bearing an ionizable hydrogen atom, an electron withdrawing group is a group having the ability to position electrons toward itself and away from the aromatic-containing moiety. Hydrogen is used as the standard for comparison in the determination of whether a given group positions electrons away or toward itself. Preferred electron altering groups include, but are not limited to, -CF₃, -CH₂CF₃, -CH₂C₆F₅, -CN, -NO₂, -S(O)R, -S(O)Aryl, -S(O₂)R, -S(O₂)Aryl, -S(O₂)OR, -S(O₂)OAryl, , -S(O₂)NHR, -S(O₂)NHAryl, -C(O)R, -C(O)Aryl, -C(O)OR, -C(O)NHR, and the like, wherein R is H or an organic radical.

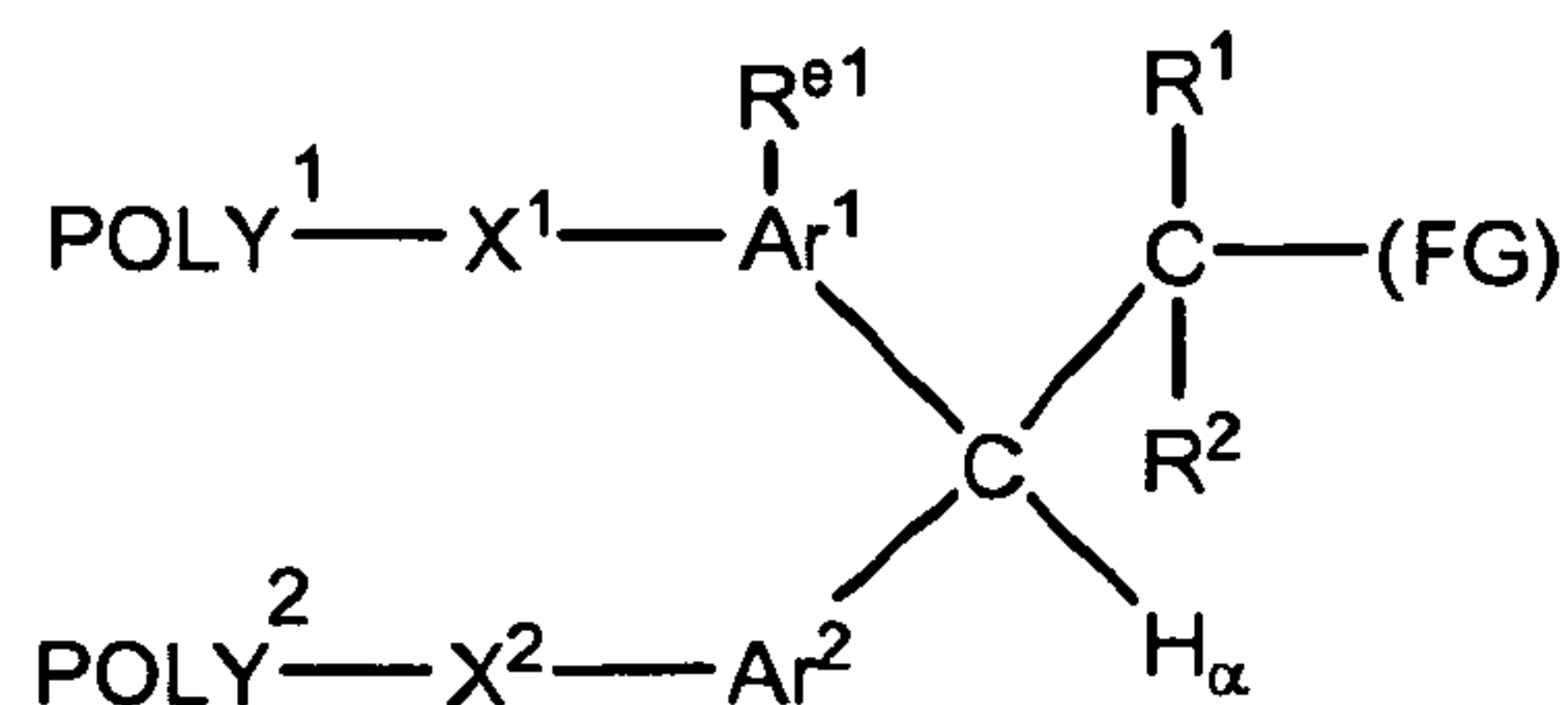
[00139] An additional branched polymeric reagent suitable for use in the present invention comprises the following structure:



where POLY¹ is a first water-soluble polymer; POLY² is a second water-soluble polymer; X¹ is a first spacer moiety; X² is a second spacer moiety; Ar¹ is a first aromatic moiety; Ar² is a second aromatic moiety; H_α is an ionizable hydrogen atom; R¹ is H or an organic radical; R² is H or an organic radical; and (FG) is a functional group capable of reacting with an amino group of therapeutic peptide to form a releasable linkage, such as carbamate linkage.

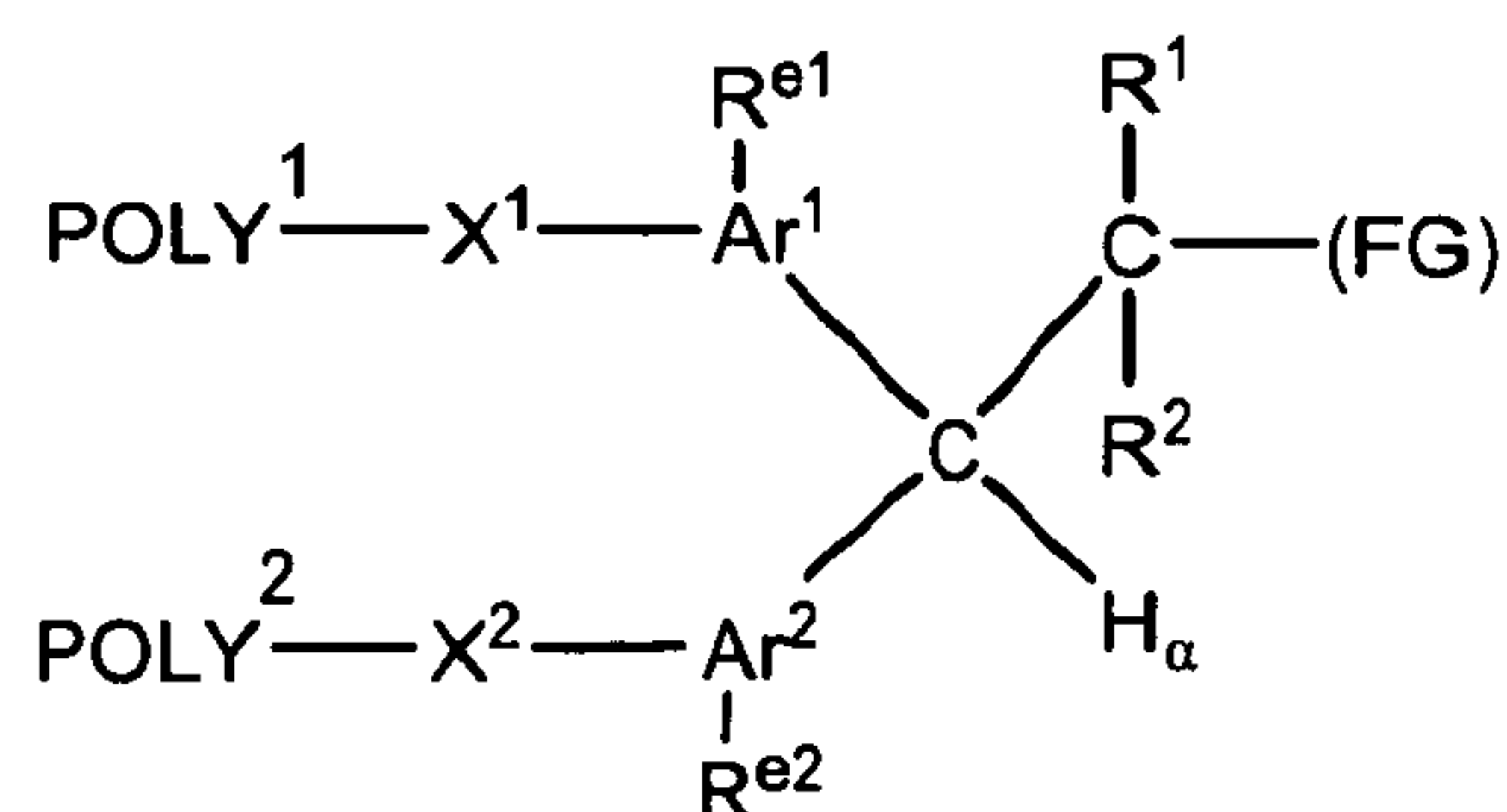
[00140] Another exemplary polymeric reagent comprises the following structure:

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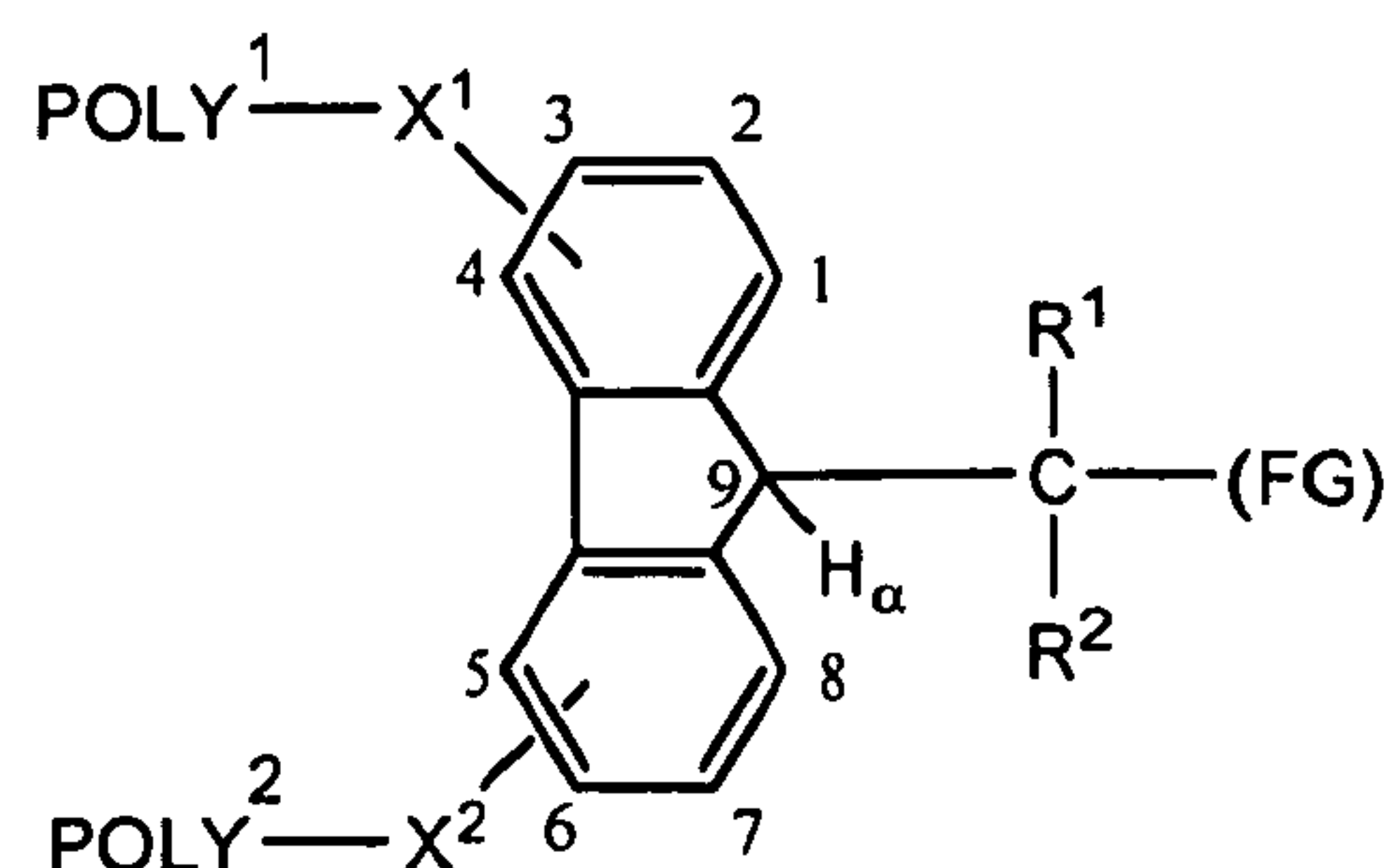
wherein each of POLY¹, POLY², X¹, X², Ar¹, Ar², H_α, R¹, R², and (FG) is as previously defined, and R^{e1} is a first electron altering group. While stereochemistry is not specifically shown in any structure provided herein, the provided structures contemplate both enantiomers, as well as compositions comprising mixtures of each enantiomer in equal amounts (*i.e.*, a racemic mixture) and unequal amounts.

[00141] Yet an additional polymeric reagent for use in preparing a therapeutic peptide conjugate possesses the following structure:



wherein each of POLY¹, POLY², X¹, X², Ar¹, Ar², H_α, R¹, R², and (FG) is as previously defined, and R^{e1} is a first electron altering group; and R^{e2} is a second electron altering group.

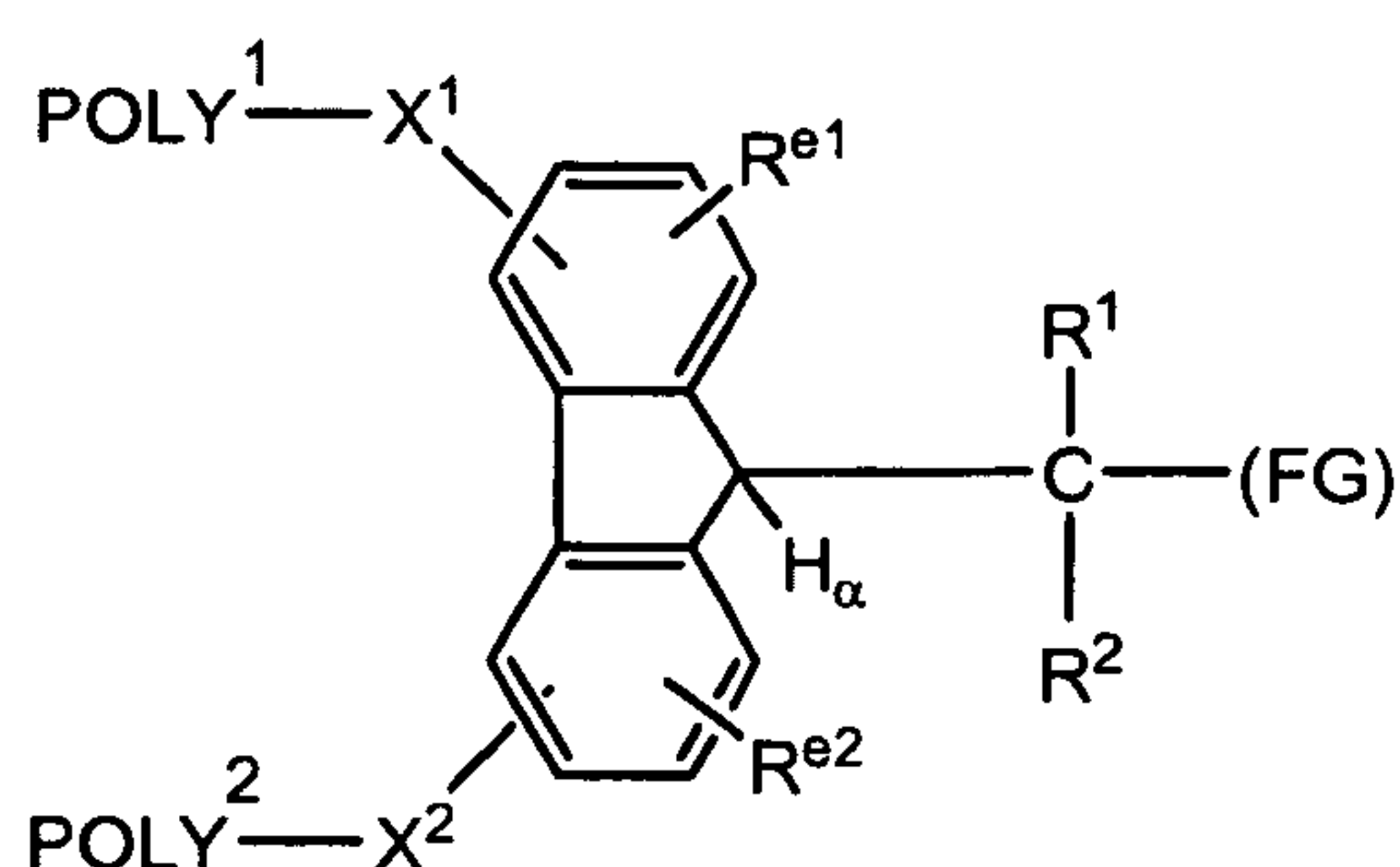
[00142] A preferred polymeric reagent comprises the following structure:



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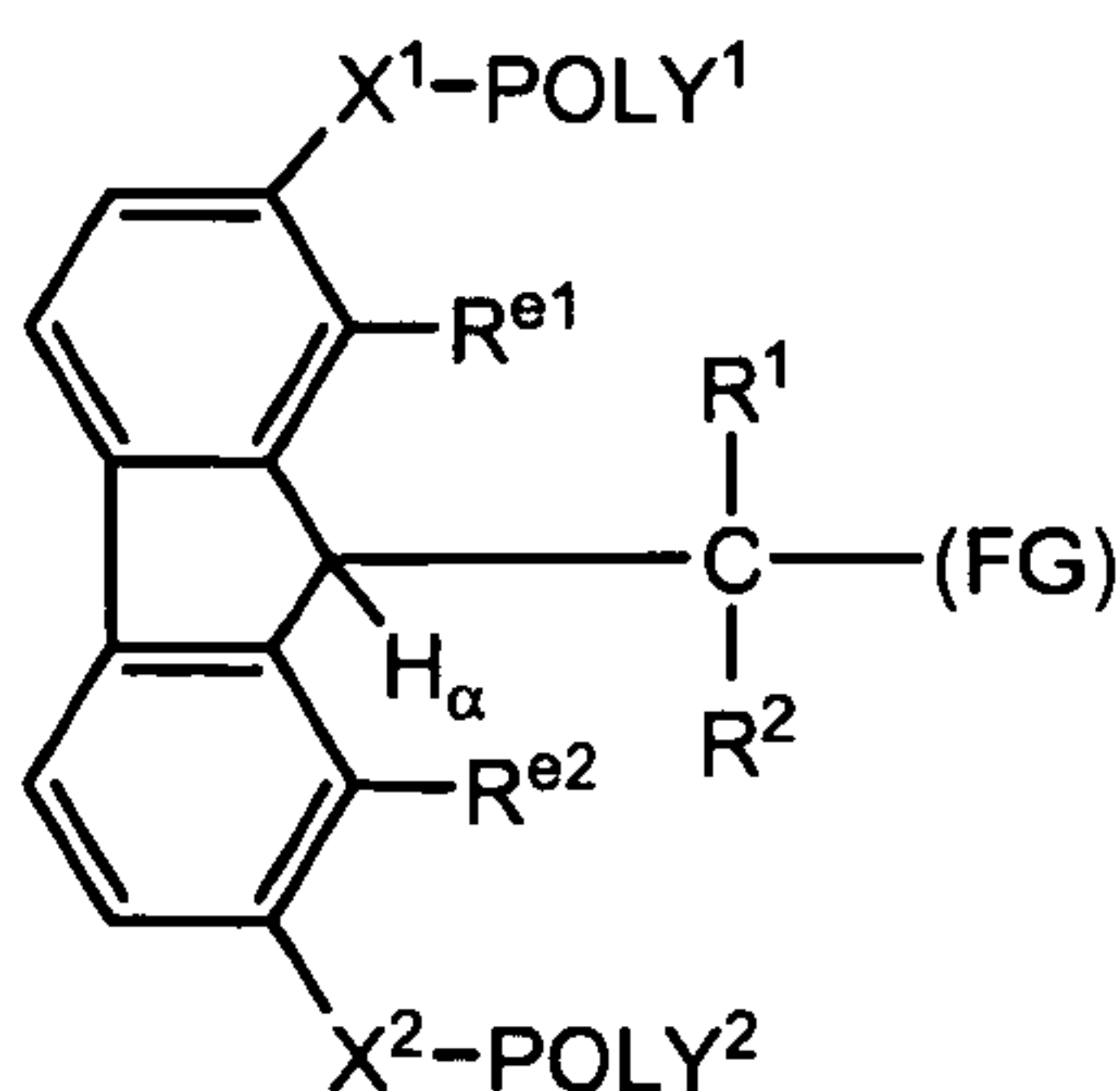
wherein each of POLY^1 , POLY^2 , X^1 , X^2 , R^1 , R^2 , H_α and (FG) is as previously defined, and, as can be seen from the structure above, the aromatic moiety is a fluorene. The POLY arms substituted on the fluorene can be in any position in each of their respective phenyl rings, *i.e.*, $\text{POLY}^1\text{-X}^1$ can be positioned at any one of carbons 1, 2, 3, and 4, and $\text{POLY}^2\text{-X}^2$ can be in any one of positions 5, 6, 7, and 8.

[00143] Yet another preferred fluorene-based polymeric reagent comprises the following structure:



wherein each of POLY^1 , POLY^2 , X^1 , X^2 , R^1 , R^2 , H_α and (FG) is as previously defined, and $\text{R}^{\text{e}1}$ is a first electron altering group; and $\text{R}^{\text{e}2}$ is a second electron altering group as described above.

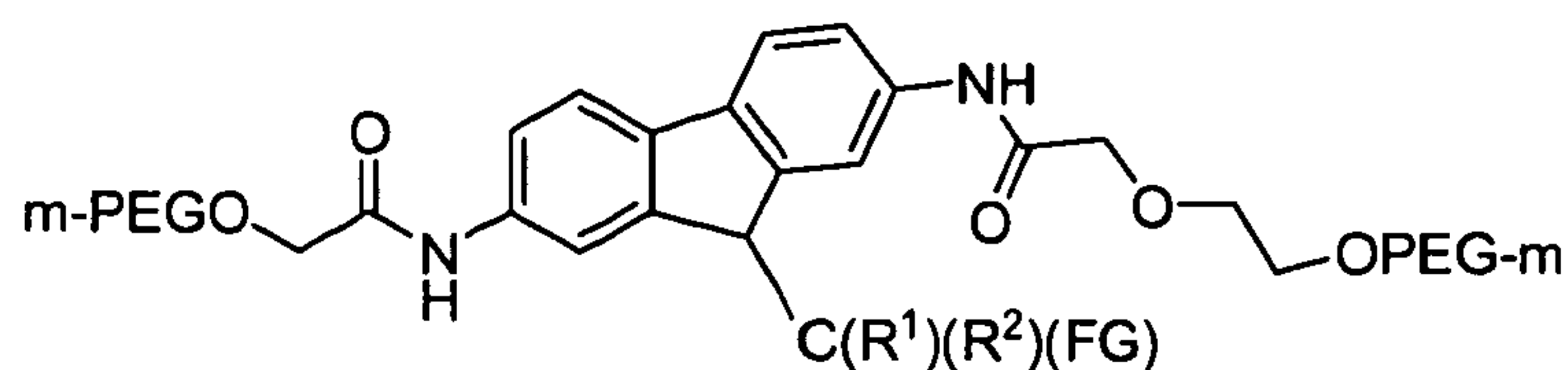
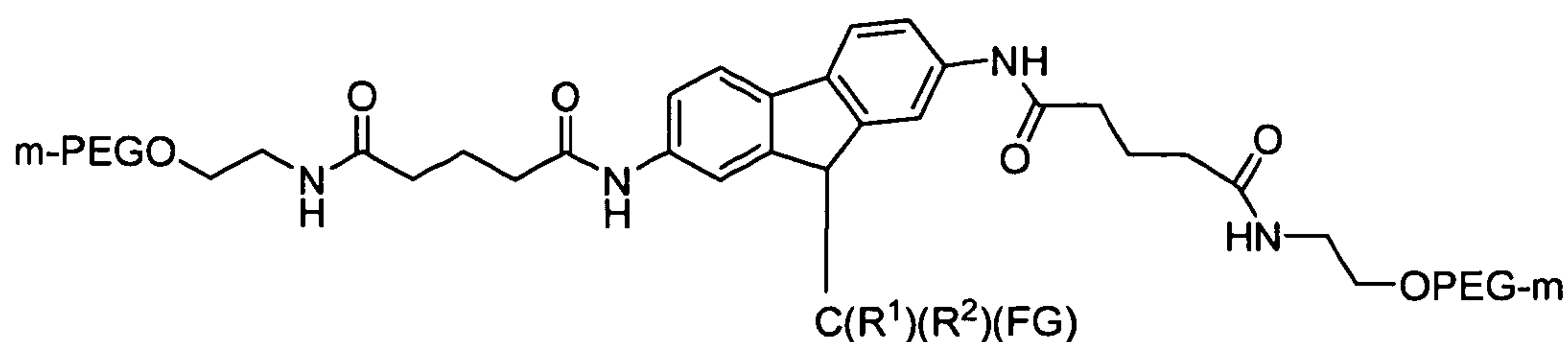
[00144] Yet another exemplary polymeric reagent for conjugating to a therapeutic peptide comprises the following fluorene-based structure:



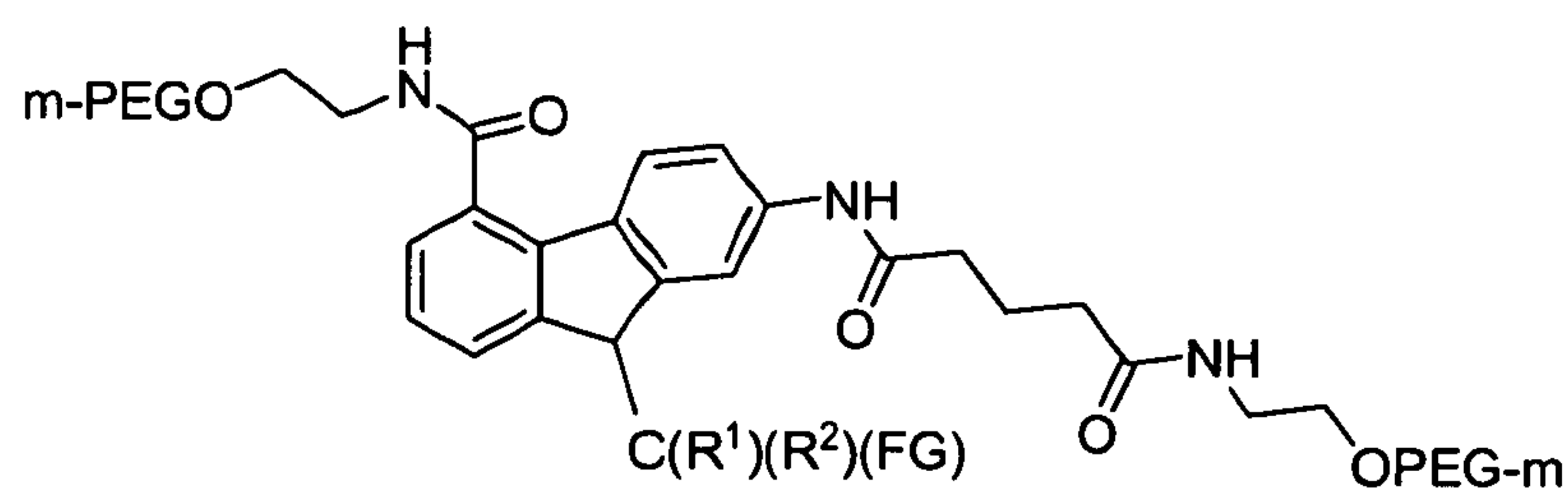
wherein each of POLY^1 , POLY^2 , X^1 , X^2 , R^1 , R^2 , H_α and (FG) is as previously defined, and $\text{R}^{\text{e}1}$ is a first electron altering group; and $\text{R}^{\text{e}2}$ is a second electron altering group.

[00145] Particular fluorene-based polymeric reagents for forming a releasable therapeutic peptide polymer conjugate in accordance with the invention include the following:

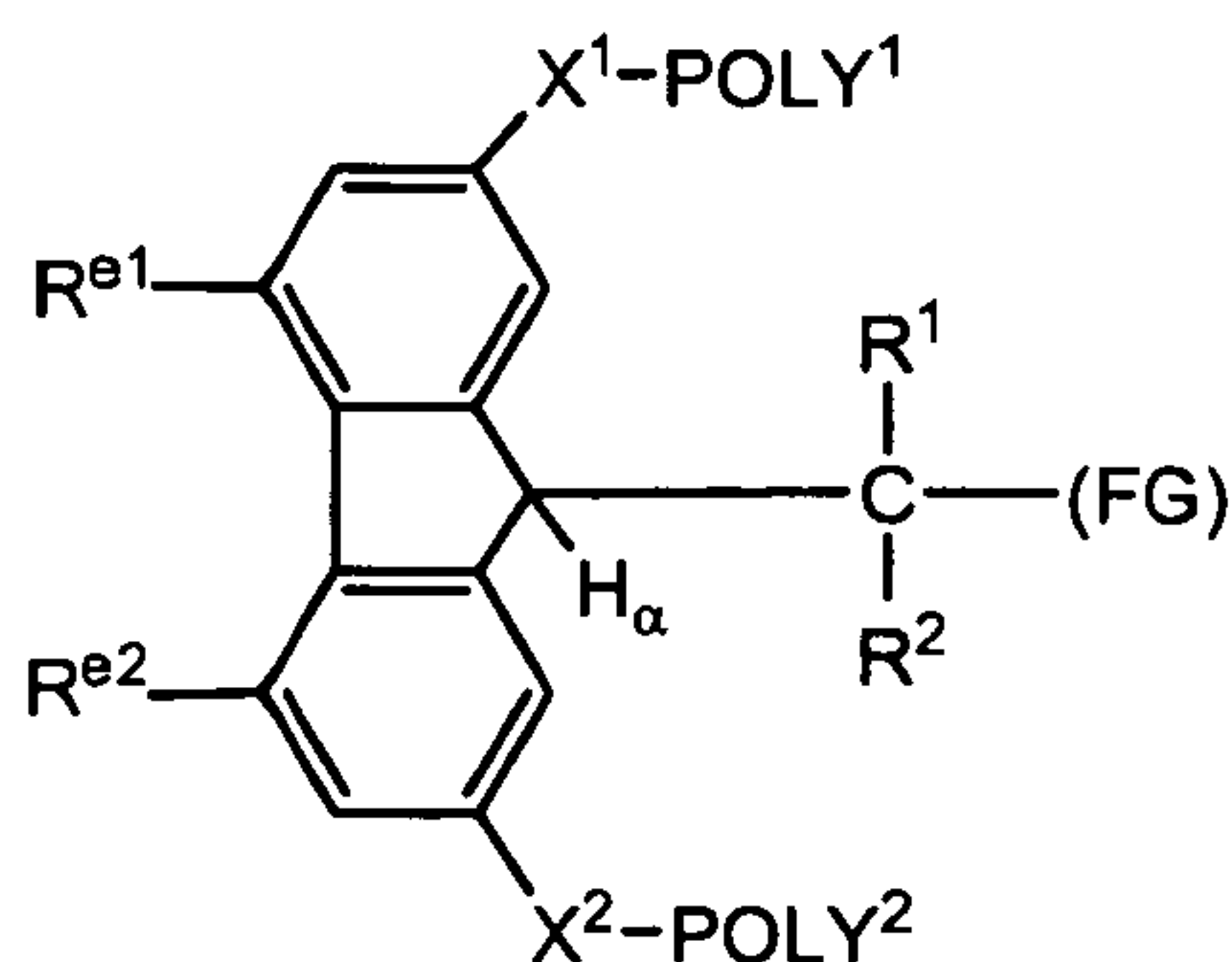
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and



[00146] Still another exemplary polymeric reagent comprises the following structure:



wherein each of POLY¹, POLY², X¹, X², R¹, R², H_α and (FG) is as previously defined, and R^{e1} is a first electron altering group; and R^{e2} is a second electron altering group. Branched reagents suitable for preparing a releasable therapeutic peptide conjugate include N-{di(mPEG(20,000)oxymethylcarbonylamino)fluoren-9-ylmethoxycarbonyloxy}succinimide, N-[2,7-di(4mPEG(10,000)aminocarbonylbutyrylamino)fluoren-9-ylmethoxycarbonyloxy]-

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succinimide ("G2PEG2Fmoc_{20k}-NHS"), and PEG2-CAC-Fmoc_{4k}-BTC. Of course, PEGs of any molecular weight as set forth herein may be employed in the above structures, and the particular activating groups described above are not meant to be limiting in any respect, and may be substituted by any other suitable activating group suitable for reaction with a reactive group present on the therapeutic peptide.

[00147] Those of ordinary skill in the art will recognize that the foregoing discussion describing water-soluble polymers for use in forming a therapeutic peptide conjugate is by no means exhaustive and is merely illustrative, and that all polymeric materials having the qualities described above are contemplated. As used herein, the term "polymeric reagent" generally refers to an entire molecule, which can comprise a water-soluble polymer segment, as well as additional spacers and functional groups.

The Linkage

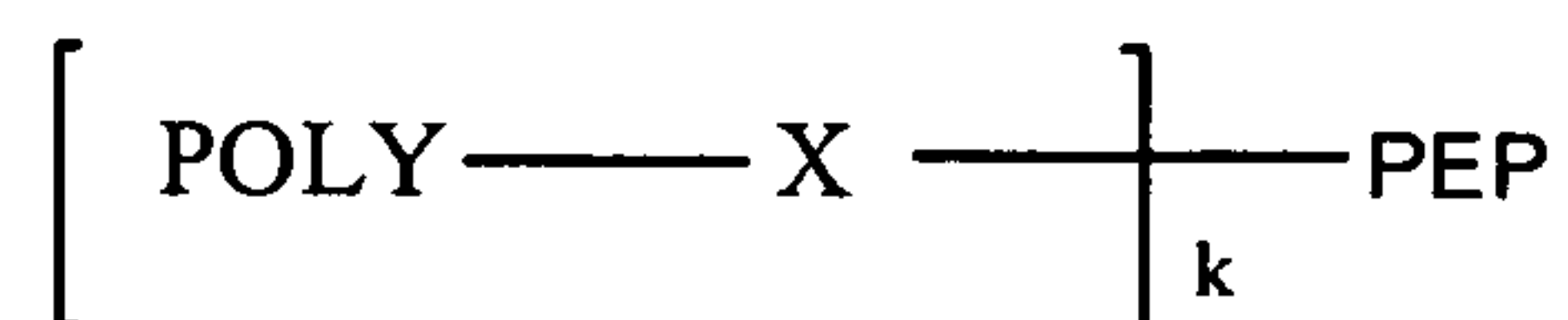
[00148] The particular linkage between the therapeutic peptide and the water-soluble polymer depends on a number of factors. Such factors include, for example, the particular linkage chemistry employed, the particular spacer moieties utilized, if any, the particular therapeutic peptide, the available functional groups within the therapeutic peptide (either for attachment to a polymer or conversion to a suitable attachment site), and the possible presence of additional reactive functional groups or absence of functional groups within the therapeutic peptide due to modifications made to the peptide such as methylation and/or glycosylation, and the like.

[00149] In one or more embodiments of the invention, the linkage between the therapeutic peptide and the water-soluble polymer is a releasable linkage. That is, the water-soluble polymer is cleaved (either through hydrolysis, an enzymatic processes, or otherwise), thereby resulting in an unconjugated therapeutic peptide. Preferably, the releasable linkage is a hydrolytically degradable linkage, where upon hydrolysis, the therapeutic peptide, or a slightly modified version thereof, is released. The releasable linkage may result in the water-soluble polymer (and any spacer moiety) detaching from the therapeutic peptide *in vivo* (and *in vitro*) without leaving any fragment of the water-soluble polymer (and/or any spacer moiety or linker) attached to the therapeutic peptide. Exemplary releasable linkages include carbonate, carboxylate ester,

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phosphate ester, thiolester, anhydrides, acetals, ketals, acyloxyalkyl ether, imines, carbamates, and orthoesters. Such linkages can be readily formed by reaction of the therapeutic peptide and/or the polymeric reagent using coupling methods commonly employed in the art. Hydrolyzable linkages are often readily formed by reaction of a suitably activated polymer with a non-modified functional group contained within the therapeutic peptide. Preferred positions for covalent attachment of a water-soluble polymer include the N-terminal, the C-terminal, as well as the internal lysines. Preferred releasable linkages include carbamate and ester.

[00150] Generally speaking, a preferred therapeutic peptide conjugate of the invention will possess the following generalized structure:



where POLY is a water-soluble polymer such as any of the illustrative polymeric reagents provided in Tables 2-4 herein, X is a linker, and in some embodiments a hydrolyzable linkage (L_D), and k is an integer selected from 1, 2, and 3, and in some instances 4, 5, 6, 7, 8, 9 and 10. In the generalized structure above, where X is L_D , L_D refers to the hydrolyzable linkage per se (e.g., a carbamate or an ester linkage), while "POLY" is meant to include the polymer repeat units, e.g., $\text{CH}_3(\text{OCH}_2\text{CH}_2)_n$, -. In a preferred embodiment of the invention, at least one of the water-soluble polymer molecules is covalently attached to the N-terminus of therapeutic peptide. In one embodiment of the invention, k equals 1 and X is $-\text{O}-\text{C}(\text{O})-\text{NH}-$, where the $-\text{NH}-$ is part of the therapeutic peptide residue and represents an amino group thereof.

[00151] Although releasable linkages are exemplary, the linkage between the therapeutic peptide and the water-soluble polymer (or the linker moiety that is attached to the polymer) may be a hydrolytically stable linkage, such as an amide, a urethane (also known as carbamate), amine, thioether (also known as sulfide), or urea (also known as carbamide). One such embodiment of the invention comprises a therapeutic peptide having a water-soluble polymer such as PEG covalently attached at the N-terminus of therapeutic peptide. In such instances, alkylation of the N-terminal residue permits retention of the charge on the N-terminal nitrogen.

[00152] With regard to linkages, in one or more embodiments of the invention, a conjugate is provided that comprises a therapeutic peptide covalently attached at an amino acid

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residue, either directly or through a linker comprised of one or more atoms, to a water-soluble polymer.

[00153] The conjugates (as opposed to an unconjugated therapeutic peptide) may or may not possess a measurable degree of therapeutic peptide activity. That is to say, a conjugate in accordance with the invention will typically possess anywhere from about 0% to about 100% or more of the therapeutic activity of the unmodified parent therapeutic peptide. Typically, compounds possessing little or no therapeutic activity contain a releasable linkage connecting the polymer to the therapeutic peptide, so that regardless of the lack of therapeutic activity in the conjugate, the active parent molecule (or a derivative thereof having therapeutic activity) is released by cleavage of the linkage (*e.g.*, hydrolysis upon aqueous-induced cleavage of the linkage). Such activity may be determined using a suitable *in vivo* or *in vitro* model, depending upon the known activity of the particular moiety having therapeutic peptide activity employed.

[00154] Optimally, cleavage of a linkage is facilitated through the use of hydrolytically cleavable and/or enzymatically cleavable linkages such as urethane, amide, certain carbamate, carbonate or ester-containing linkages. In this way, clearance of the conjugate via cleavage of individual water-soluble polymer(s) can be modulated by selecting the polymer molecular size and the type of functional group for providing the desired clearance properties. In certain instances, a mixture of polymer conjugates is employed where the polymers possess structural or other differences effective to alter the release (*e.g.*, hydrolysis rate) of the therapeutic peptide, such that one can achieve a desired sustained delivery profile.

[00155] One of ordinary skill in the art can determine the proper molecular size of the polymer as well as the cleavable functional group, depending upon several factors including the mode of administration. For example, one of ordinary skill in the art, using routine experimentation, can determine a proper molecular size and cleavable functional group by first preparing a variety of polymer-(therapeutic peptide) conjugates with different weight-average molecular weights, degradable functional groups, and chemical structures, and then obtaining the clearance profile for each conjugate by administering the conjugate to a patient and taking periodic blood and/or urine samples. Once a series of clearance profiles has been obtained for each tested conjugate, a conjugate or mixture of conjugates having the desired clearance profile(s) can be determined.

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[00156] For conjugates possessing a hydrolytically stable linkage that couples the therapeutic peptide to the water-soluble polymer, the conjugate will typically possess a measurable degree of therapeutic activity. For instance, such conjugates are typically characterized as having a therapeutic activity satisfying one or more of the following percentages relative to that of the unconjugated therapeutic peptide: at least 2%, at least 5%, at least 10%, at least 15%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 100%, more than 105%, more than 10-fold, or more than 100-fold (when measured in a suitable model, such as those presented here and/or known in the art). Often, conjugates having a hydrolytically stable linkage (*e.g.*, an amide linkage) will possess at least some degree of the therapeutic activity of the unmodified parent therapeutic peptide.

[00157] Exemplary conjugates in accordance with the invention will now be described. Amino groups on a therapeutic peptide provide a point of attachment between the therapeutic peptide and the water-soluble polymer. For example, a therapeutic peptide may comprise one or more lysine residues, each lysine residue containing an ϵ -amino group that may be available for conjugation, as well as one amino terminus.

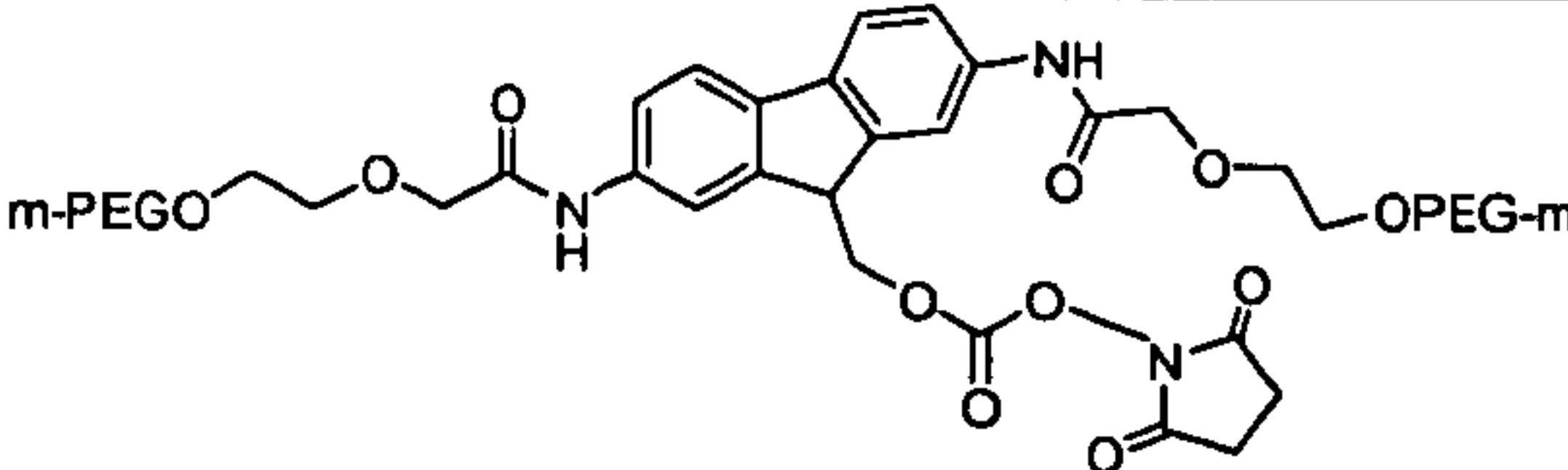
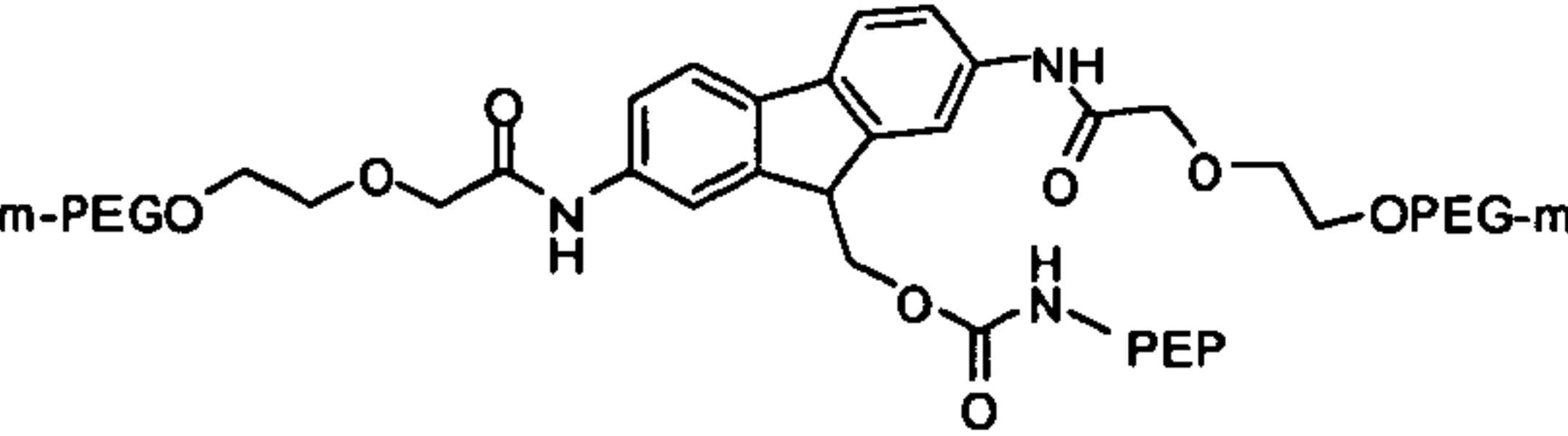
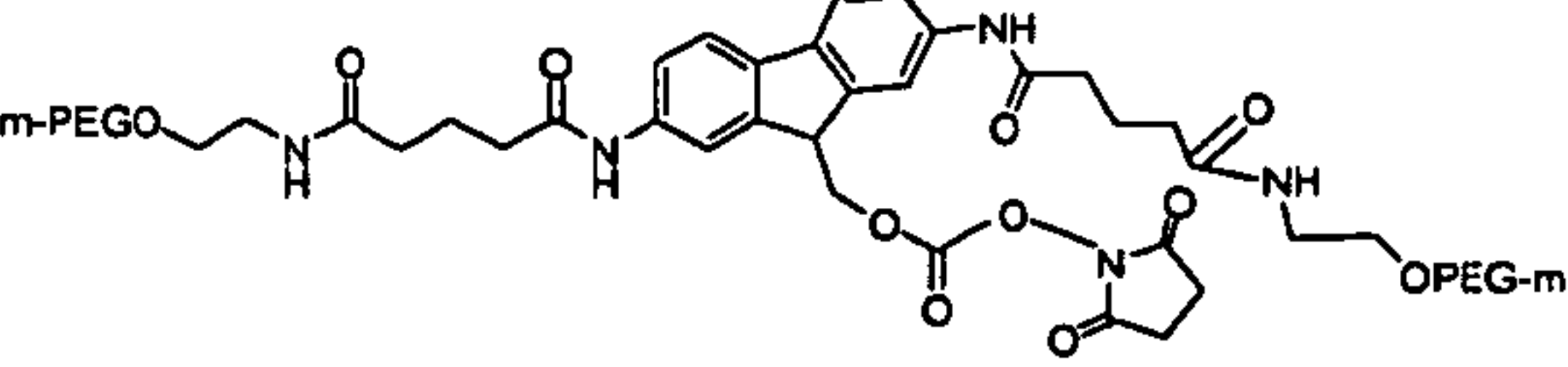
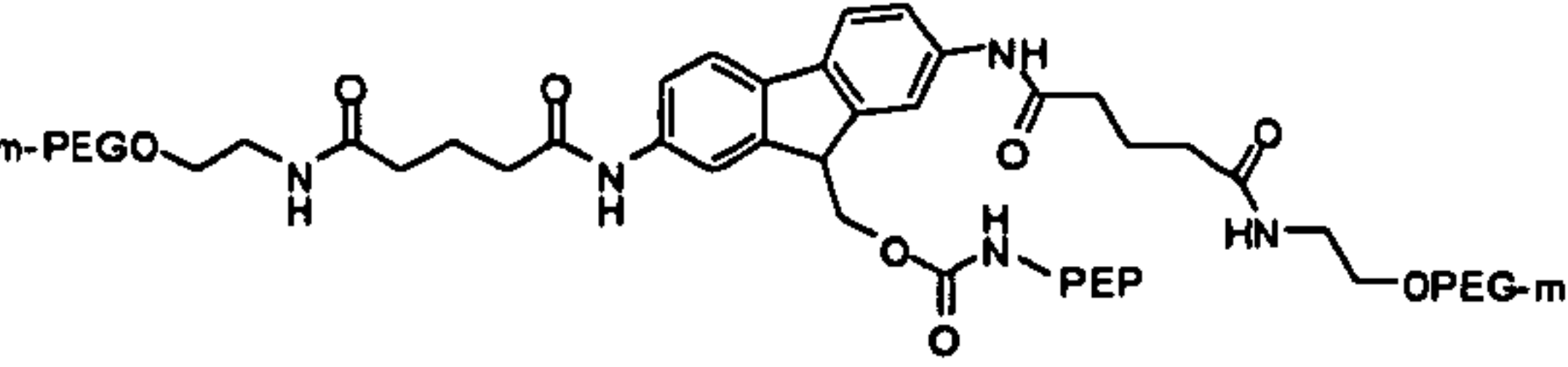
[00158] There are a number of examples of suitable water-soluble polymeric reagents useful for forming covalent linkages with available amines of a therapeutic peptide. Certain specific examples, along with the corresponding conjugates, are provided in Table 2 below. In the table, the variable (n) represents the number of repeating monomeric units and "PEP" represents a therapeutic peptide following conjugation to the water-soluble polymer. While each polymeric portion [*e.g.*, $(\text{OCH}_2\text{CH}_2)_n$ or $(\text{CH}_2\text{CH}_2\text{O})_n$] presented in Table 2 terminates in a "CH₃" group, other groups (such as H and benzyl) can be substituted therefore.

[00159] As will be clearly understood by one skilled in the art, for conjugates such as those set forth below resulting from reaction with a therapeutic peptide amino group, the amino group extending from the therapeutic peptide designation "~NH-PEP" represents the residue of the therapeutic peptide itself in which the ~NH- is an amino group of the therapeutic peptide. One preferred site of attachment for the polymeric reagents shown below is the *N*-terminus. Further, although the conjugates in Tables 2-4 herein illustrate a single water-soluble polymer covalently attached to a therapeutic peptide, it will be understood that the conjugate structures on the right are meant to also encompass conjugates having more than one of such water-soluble

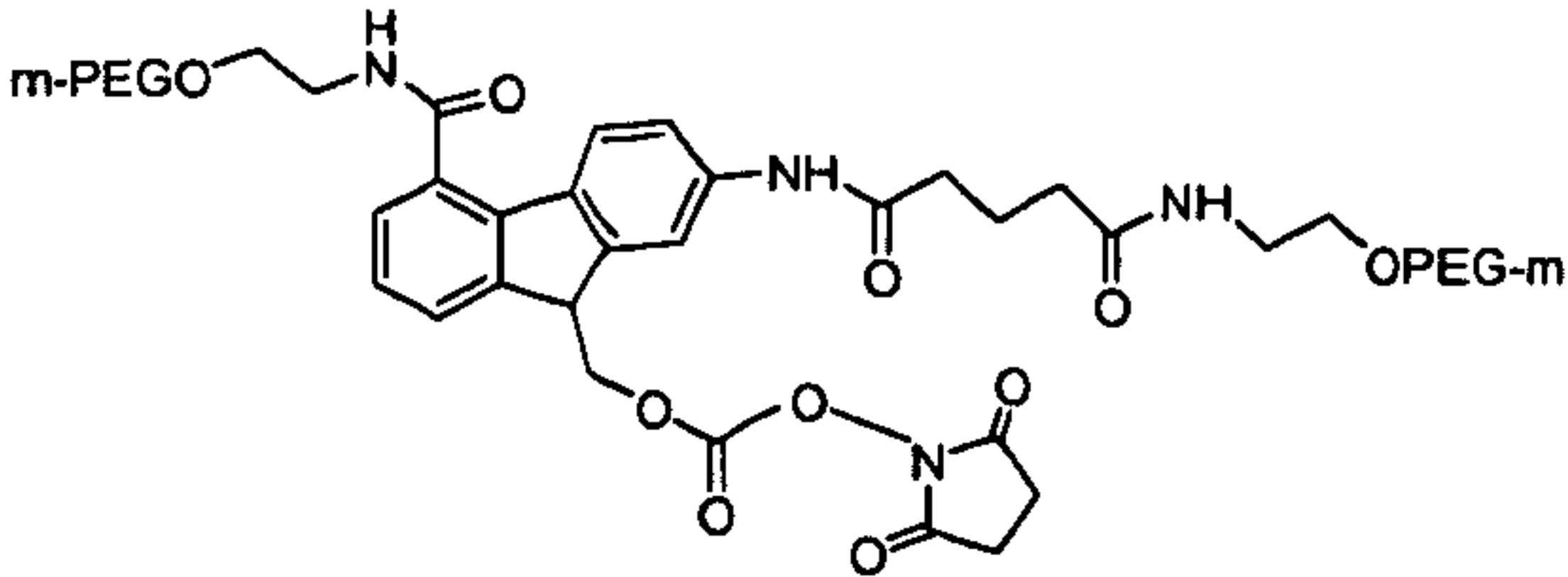
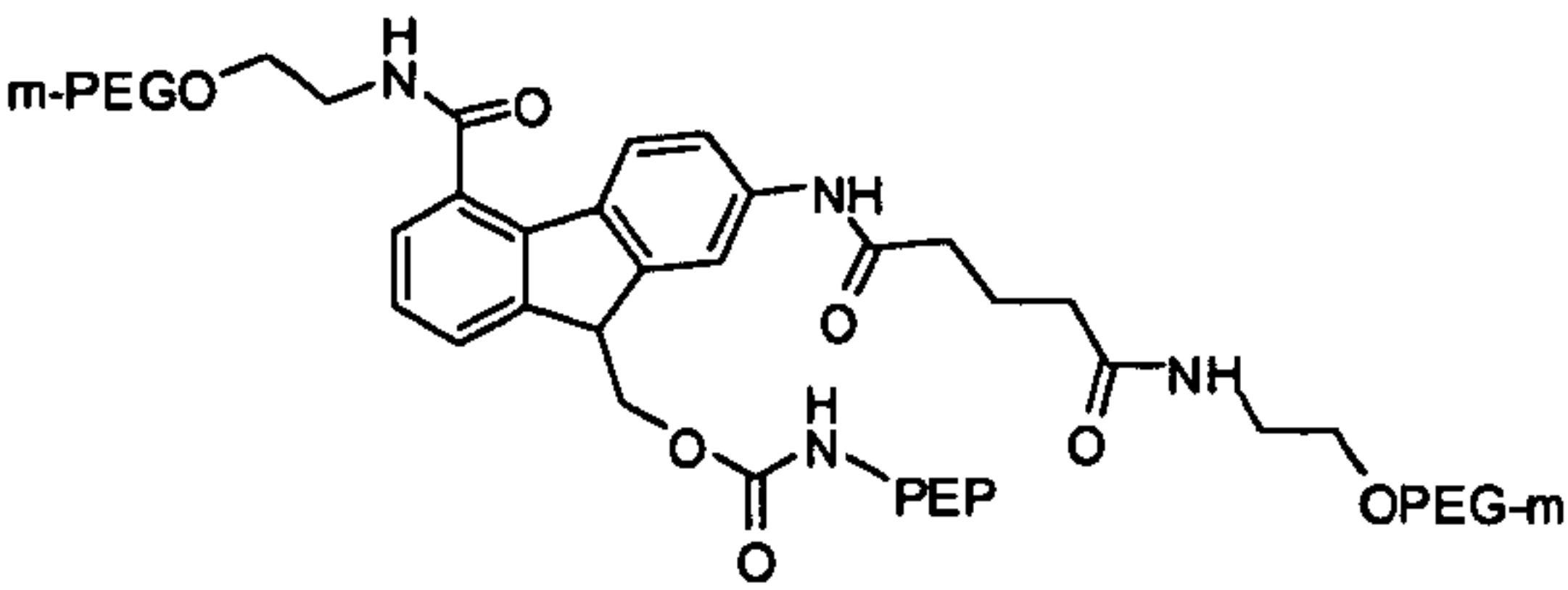
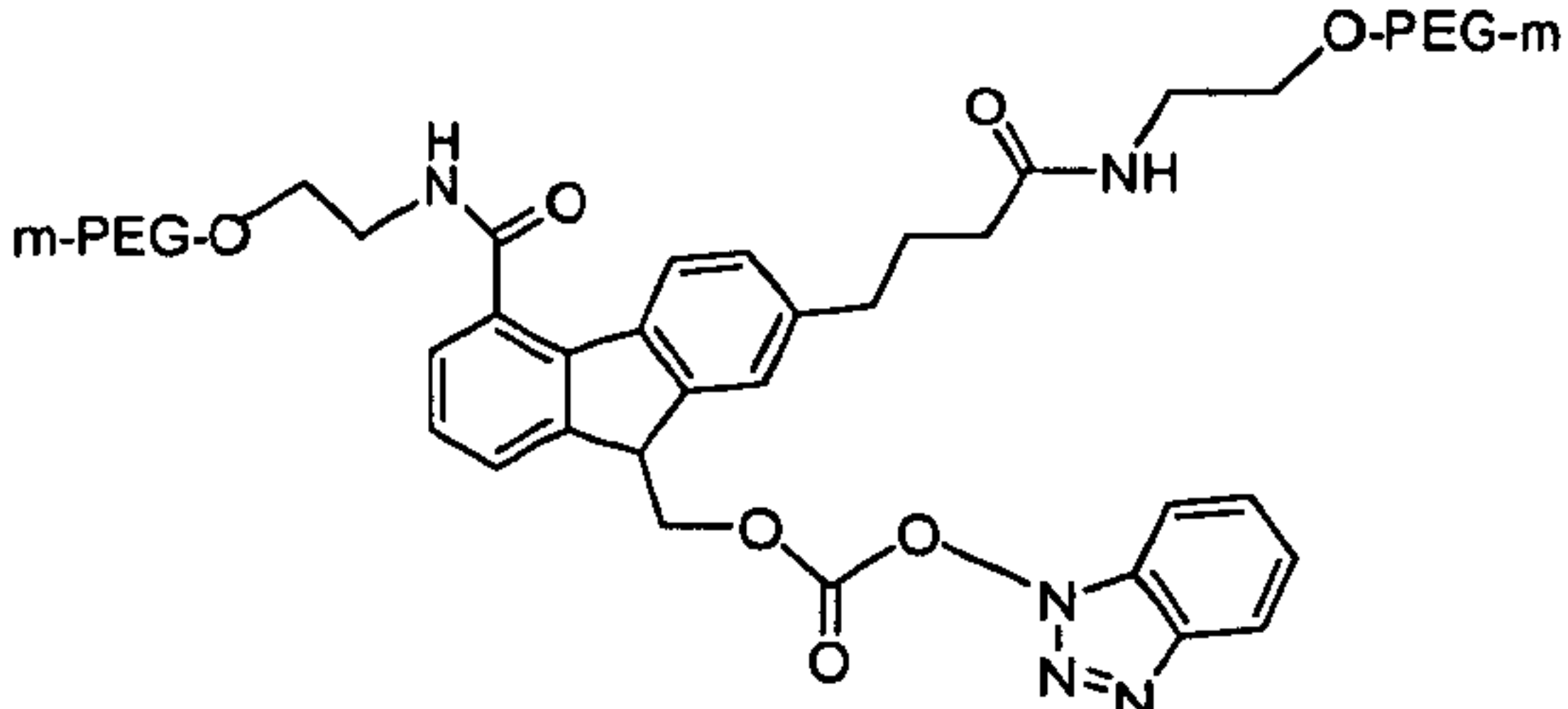
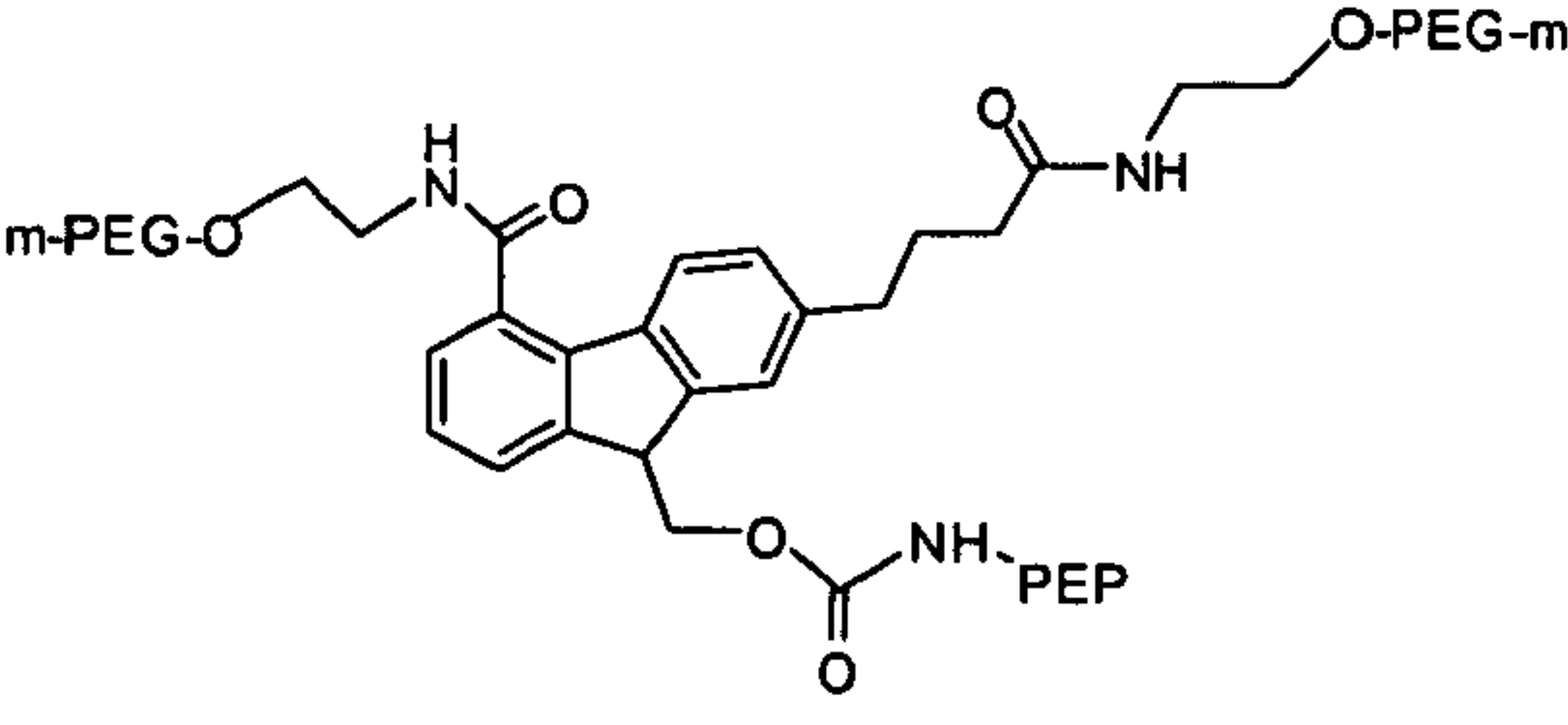
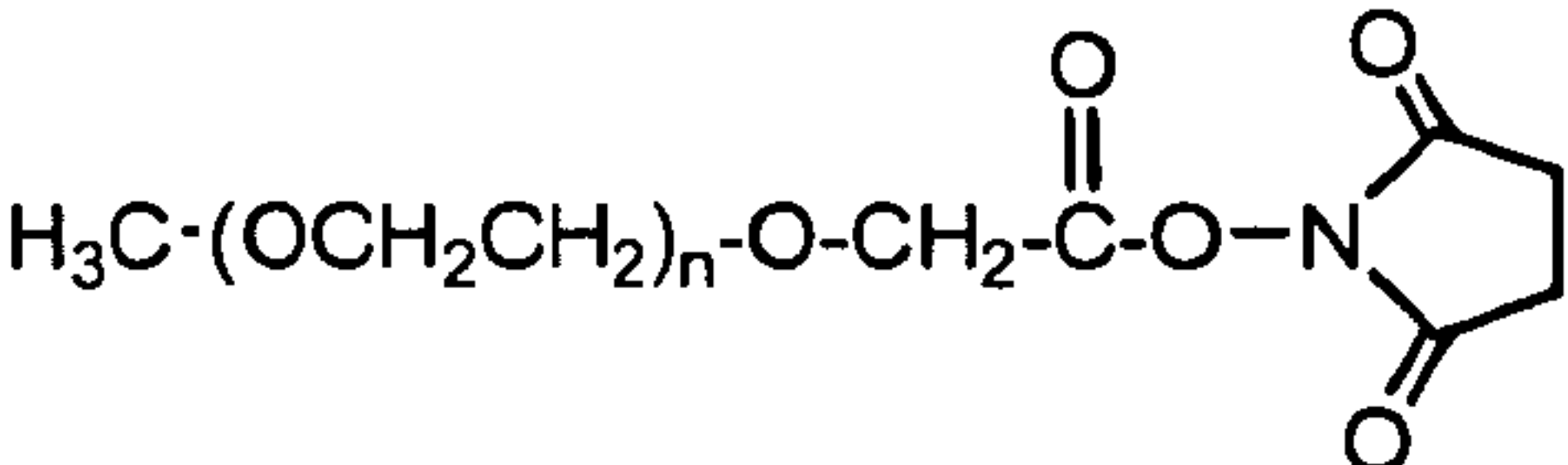
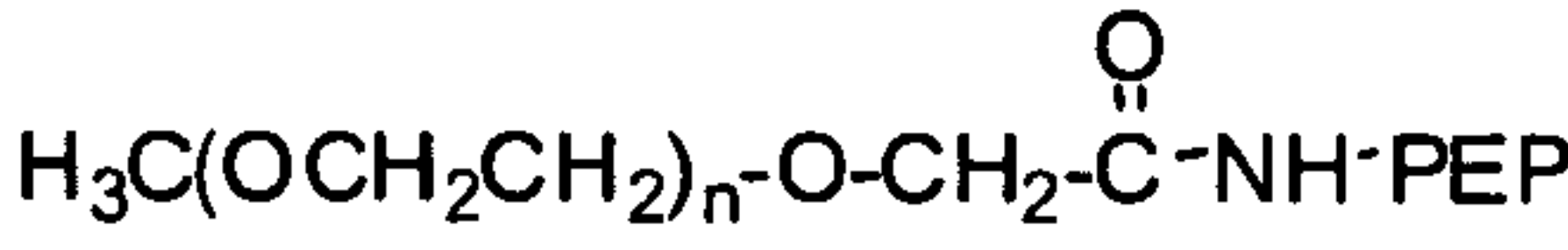
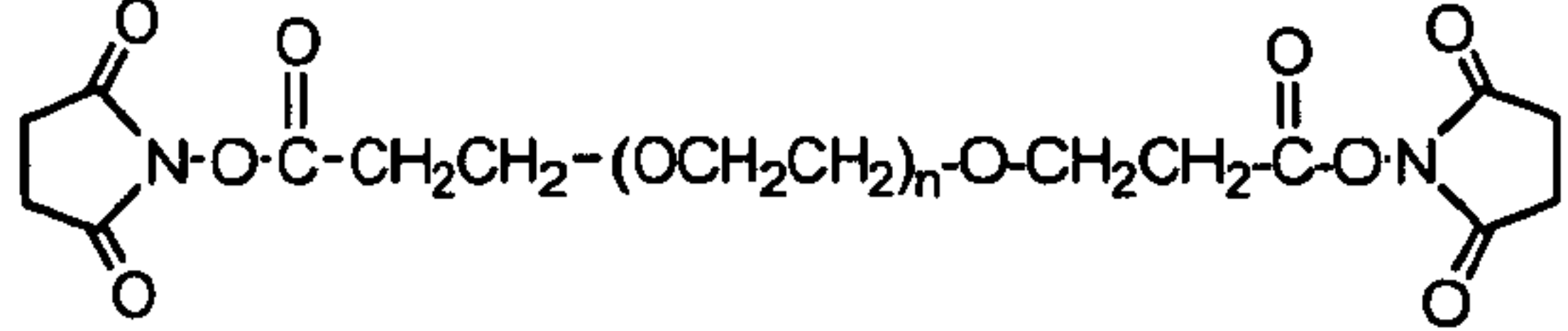
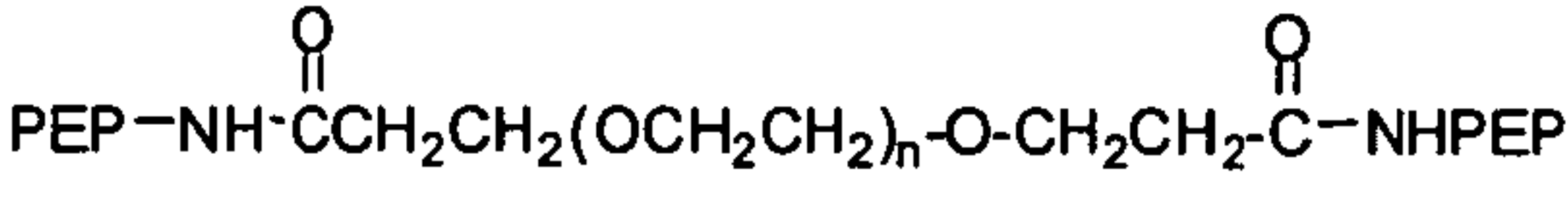
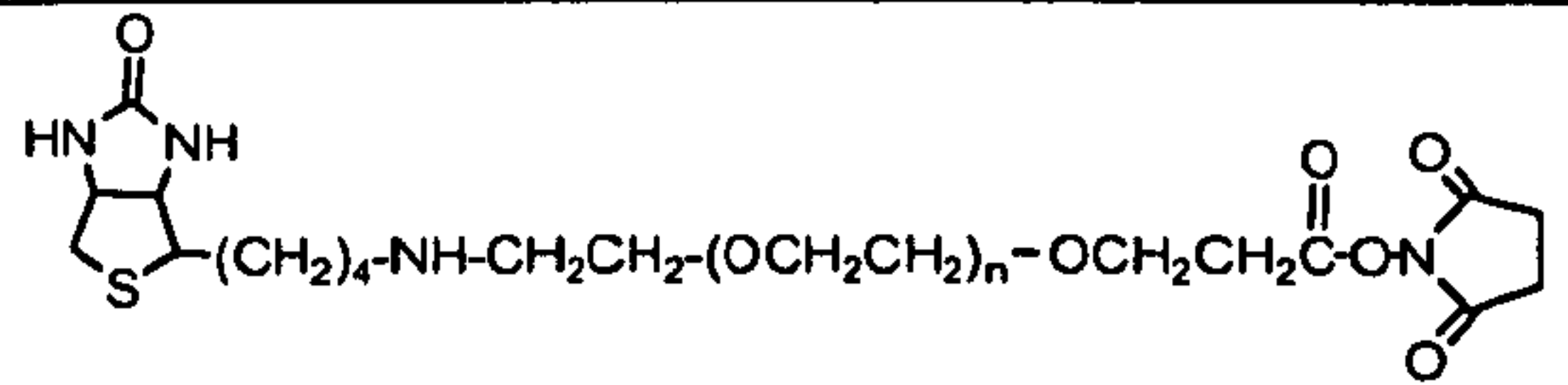
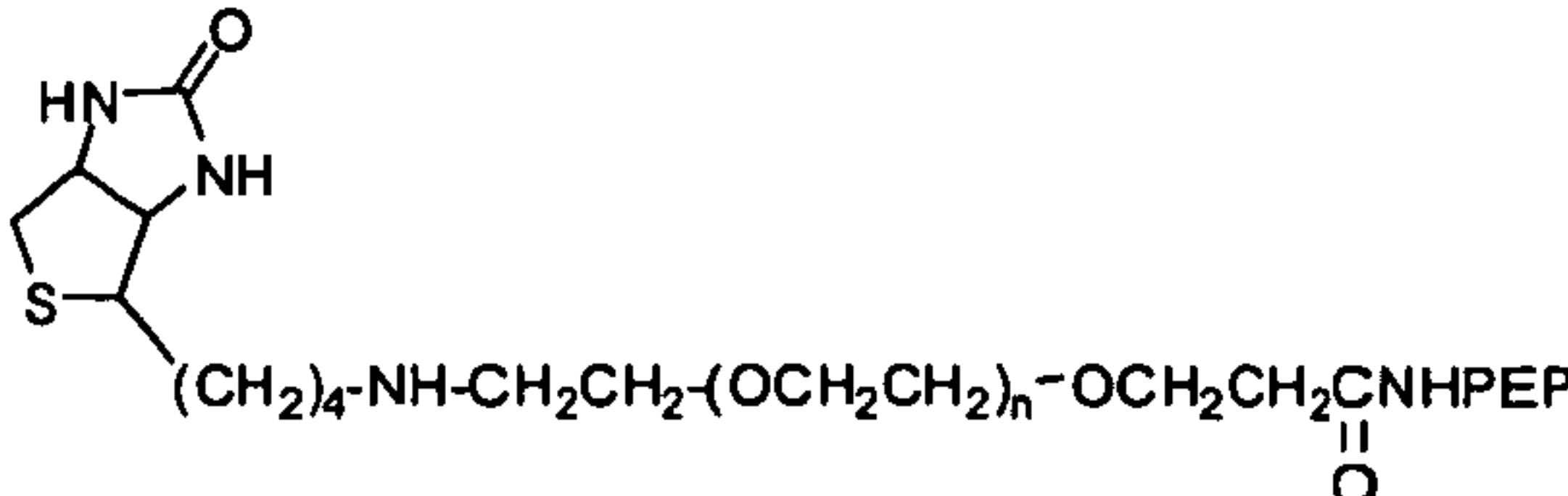
polymer molecules covalently attached to therapeutic peptide, *e.g.*, 2, 3, or 4 water-soluble polymer molecules.

Table 2

Amine-Specific Polymeric Reagents and the Therapeutic Peptide Conjugates Formed Therefrom

Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{N} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array}$ mPEG-Oxycarbonylimidazole Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Carbamate Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{O}-\text{C}_6\text{H}_4-\text{NO}_2$ mPEG Nitrophenyl Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Carbamate Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{O}-\text{C}_6\text{H}_2(\text{Cl})_3$ mPEG-Trichlorophenyl Carbonate Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Carbamate Linkage
 Fmoc-NHS Reagent	 Carbamate Linkage
 Fmoc-NHS Reagent	 Carbamate Linkage

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Polymeric Reagent	Corresponding Conjugate
 Fmoc-NHS Reagent	 Carbamate Linkage
 Fmoc-BTC Reagent	 Carbamate Linkage
 mPEG-Succinimidyl Reagent	 Amide Linkage
 Homobifunctional PEG-Succinimidyl Reagent	 Amide Linkages
 Heterobifunctional PEG-Succinimidyl Reagent	 Amide Linkage

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Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{O} \cdot \text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_4\text{H}_4\text{O}_2$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{C}(\text{OCH}_2\text{CH}_2)_n \cdot \text{O} \cdot \text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Amide Linkage
$\text{H}_3\text{CO} \cdot (\text{CH}_2\text{CH}_2\text{O})_n \cdot \text{CH}_2\text{CH}_2\text{NH} \cdot \text{C}(=\text{O}) \cdot \text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_4\text{H}_4\text{O}_2$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{CO} \cdot (\text{CH}_2\text{CH}_2\text{O})_n \cdot \text{CH}_2\text{CH}_2\text{NH} \cdot \text{C}(=\text{O}) \cdot \text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Amide Linkage
$\text{H}_3\text{CO} \cdot (\text{CH}_2\text{CH}_2\text{O})_n \cdot \text{CH}_2\text{CH}_2\text{SH} \cdot \text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_4\text{H}_4\text{O}_2$ mPEG Succinimidyl Reagent	$\text{H}_3\text{CO} \cdot (\text{CH}_2\text{CH}_2\text{O})_n \cdot \text{CH}_2\text{CH}_2\text{SH} \cdot \text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Amide Linkage
$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{O} \cdot \text{CH}_2\text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_4\text{H}_4\text{O}_2$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{O} \cdot \text{CH}_2\text{CH}_2\text{CH}_2 \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Amide Linkage
$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{O} \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_6\text{H}_4\text{N}_2$ mPEG-Benzotriazole Carbonate Reagent	$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{O} \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Carbamate Linkage
$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{NH} \cdot \text{C}(=\text{O}) \cdot \text{C}_6\text{H}_4 \cdot \text{O} \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_4\text{H}_4\text{O}_2$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{C} \cdot (\text{OCH}_2\text{CH}_2)_n \cdot \text{NH} \cdot \text{C}(=\text{O}) \cdot \text{C}_6\text{H}_4 \cdot \text{O} \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Carbamate Linkage
$\text{H}_3\text{CO} \cdot (\text{CH}_2\text{CH}_2\text{O})_n \cdot \text{C}_6\text{H}_4 \cdot \text{O} \cdot \text{C}(=\text{O}) \cdot \text{O} \cdot \text{N} \cdot \text{C}_4\text{H}_4\text{O}_2$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{CO} \cdot (\text{CH}_2\text{CH}_2\text{O})_n \cdot \text{C}_6\text{H}_4 \cdot \text{O} \cdot \text{C}(=\text{O}) \cdot \text{NH} \cdot \text{PEP}$ Amide Linkage

Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})\cdot\text{O}-\text{N}$ mPEG Succinimidyl Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})\cdot\text{O}-\text{NH}-\text{PEP}$ Amide Linkage
Branched mPEG2-N-Hydroxysuccinimide Reagent	Amide Linkage
Branched mPEG2-Aldehyde Reagent	Secondary Amine Linkage
$\text{H}_3\text{C}\cdot(\text{OCH}_2\text{CH}_2)_n\cdot\text{O}-\text{CH}_2-\text{C}(=\text{O})-\text{O}-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-\text{C}(=\text{O})\cdot\text{O}-\text{N}$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{C}\cdot(\text{OCH}_2\text{CH}_2)_n\cdot\text{O}-\text{CH}_2-\text{C}(=\text{O})-\text{O}-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Amide Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})\cdot\text{O}-\text{N}$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Amide Linkage
Homobifunctional PEG-Succinimidyl Reagent	Amide Linkages

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Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{C}(=\text{O})-\text{O}-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{C}_4\text{H}_4$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Amide Linkage
$\begin{array}{c} \text{O} \\ \parallel \\ \text{N}-\text{O}-\text{C}-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}-\text{C}(=\text{O})-\text{O}-\text{N} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{O} \qquad \qquad \qquad \text{O} \end{array} \text{C}_4\text{H}_4$ Homobifunctional PEG-Succinimidyl Propionate Reagent	$\begin{array}{c} \text{O} \qquad \qquad \qquad \text{O} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{NH}-\text{C}-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\underset{\text{CH}_3}{\text{CH}}-\text{C}-\text{NH} \\ \qquad \qquad \qquad \\ \text{PEP} \qquad \qquad \text{PEP} \end{array}$ Amide Linkages
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{C}(=\text{O})-\text{O}-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{C}_4\text{H}_4$ mPEG-Succinimidyl Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Amide Linkage
$\begin{array}{c} \text{O} \qquad \qquad \qquad \text{O} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \\ \qquad \qquad \qquad \\ \text{HC}-\text{OCH}_2\text{CH}_2\text{CH}-\text{C}(=\text{O})-\text{O}-\text{N} \\ \qquad \qquad \qquad \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \qquad \text{CH}_3 \end{array} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{C}_4\text{H}_4$ Branched mPEG2-N-Hydroxysuccinimide Reagent	$\begin{array}{c} \text{O} \qquad \qquad \qquad \text{O} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \\ \qquad \qquad \qquad \\ \text{HC}-\text{OCH}_2\text{CH}_2\text{CH}-\text{C}(=\text{O})-\text{NH}-\text{PEP} \\ \qquad \qquad \qquad \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \qquad \text{CH}_3 \end{array}$ Amide Linkage
$\begin{array}{c} \text{O} \qquad \qquad \qquad \text{O} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \\ \qquad \qquad \qquad \\ \text{HC}-\text{OCH}_2\text{CH}_2\text{CH}_2-\text{C}-\text{O}-\text{N} \\ \qquad \qquad \qquad \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \end{array} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{C}_4\text{H}_4$ Branched mPEG2-N-Hydroxysuccinimide Reagent	$\begin{array}{c} \text{O} \qquad \qquad \qquad \text{O} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \\ \qquad \qquad \qquad \\ \text{HC}-\text{OCH}_2\text{CH}_2\text{CH}_2-\text{C}-\text{NH}-\text{PEP} \\ \qquad \qquad \qquad \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\text{C}-\text{O}-\text{CH}_2 \end{array}$ Amide Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{S}-\text{C}_5\text{H}_4\text{N}$ mPEG-Thioester Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{PEP}$ Amide Linkage
$\text{O} \qquad \qquad \qquad \text{O} \\ \parallel \qquad \qquad \qquad \parallel \\ \text{HC}-\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{CH}$ Homobifunctional PEG Propionaldehyde Reagent	$\begin{array}{c} \text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH} \\ \qquad \qquad \qquad \\ \text{PEP} \qquad \qquad \text{PEP} \end{array}$ Secondary Amine Linkages

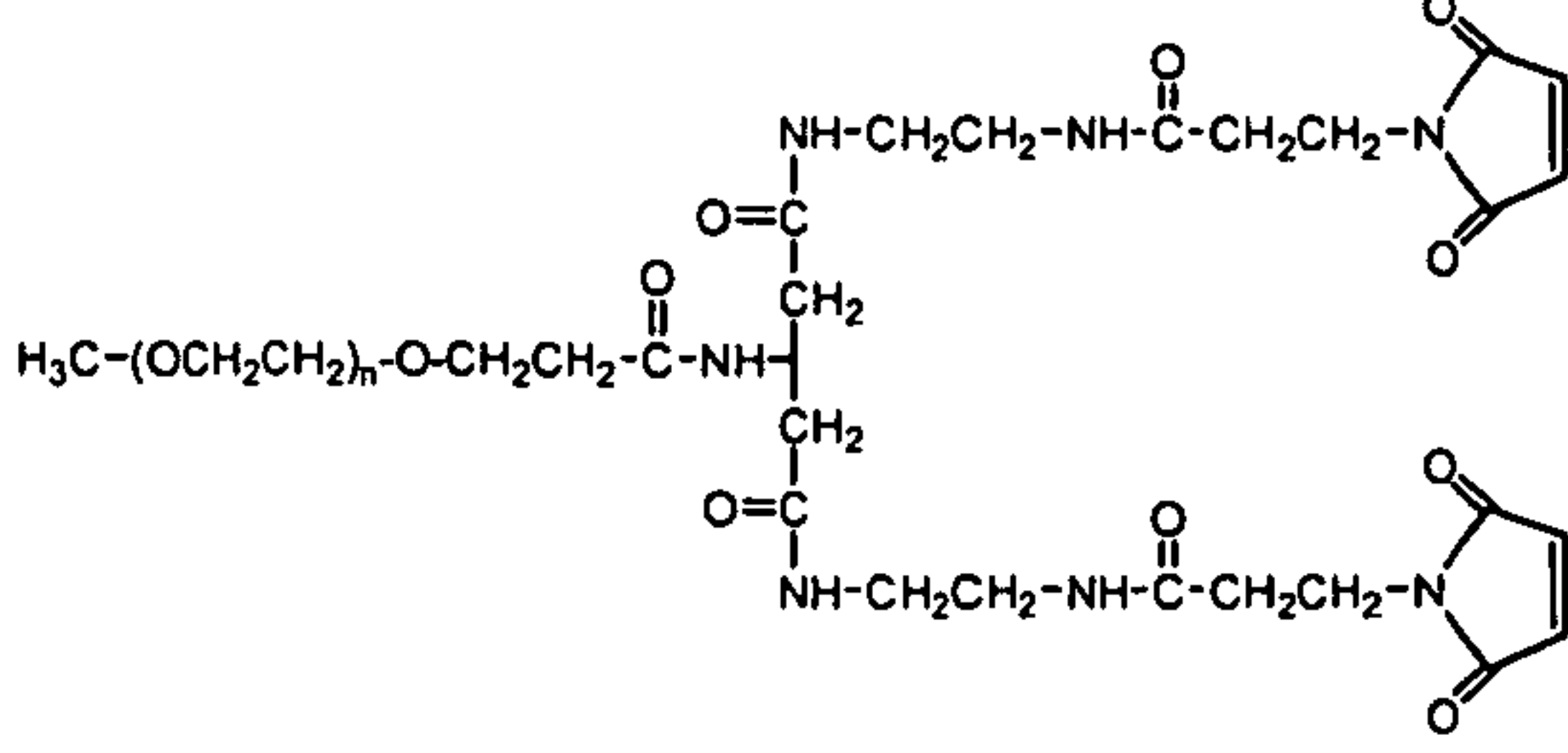
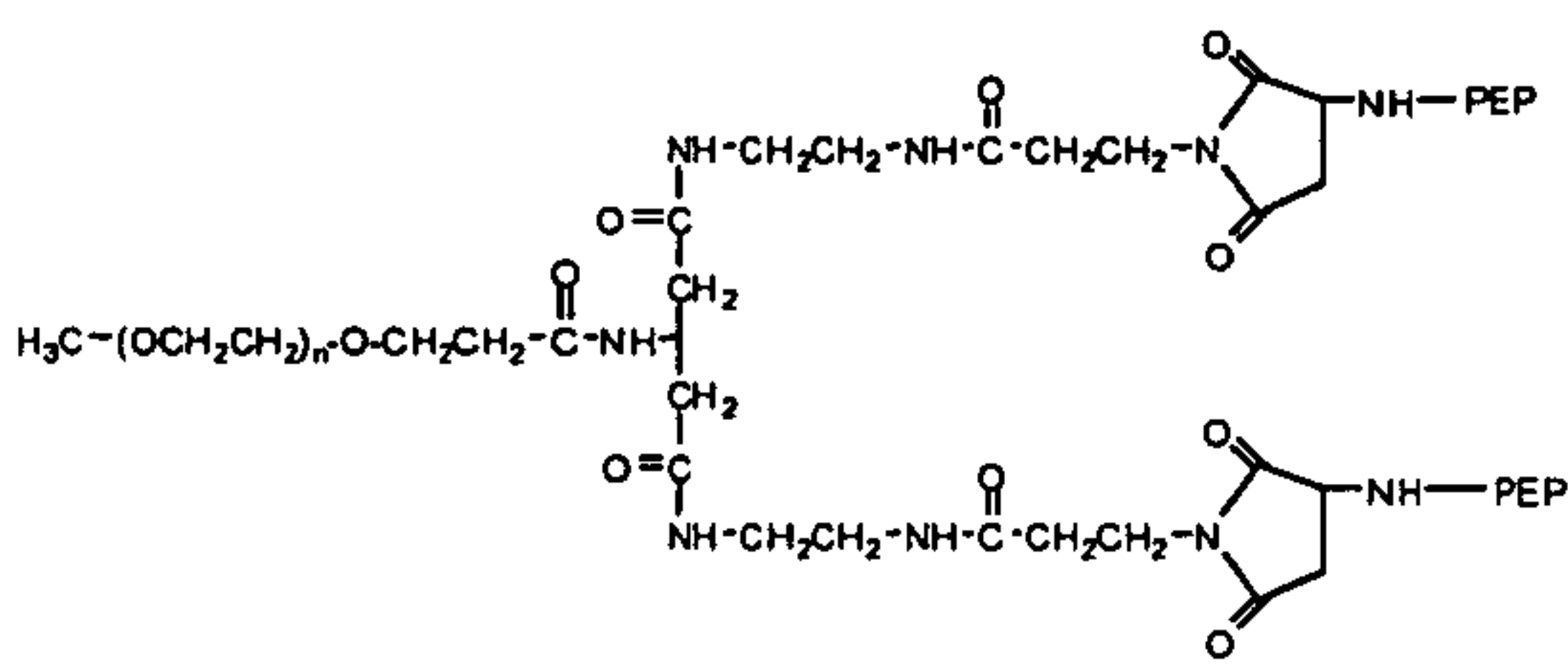
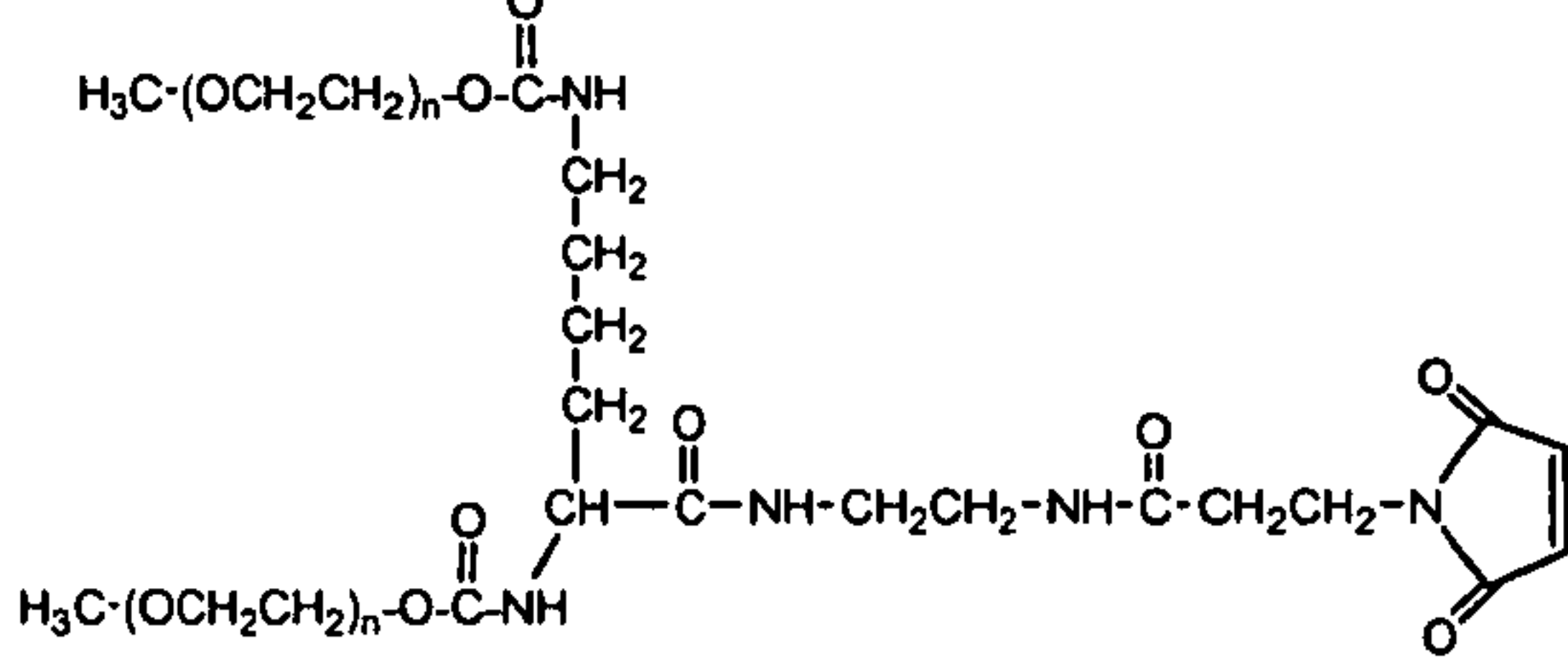
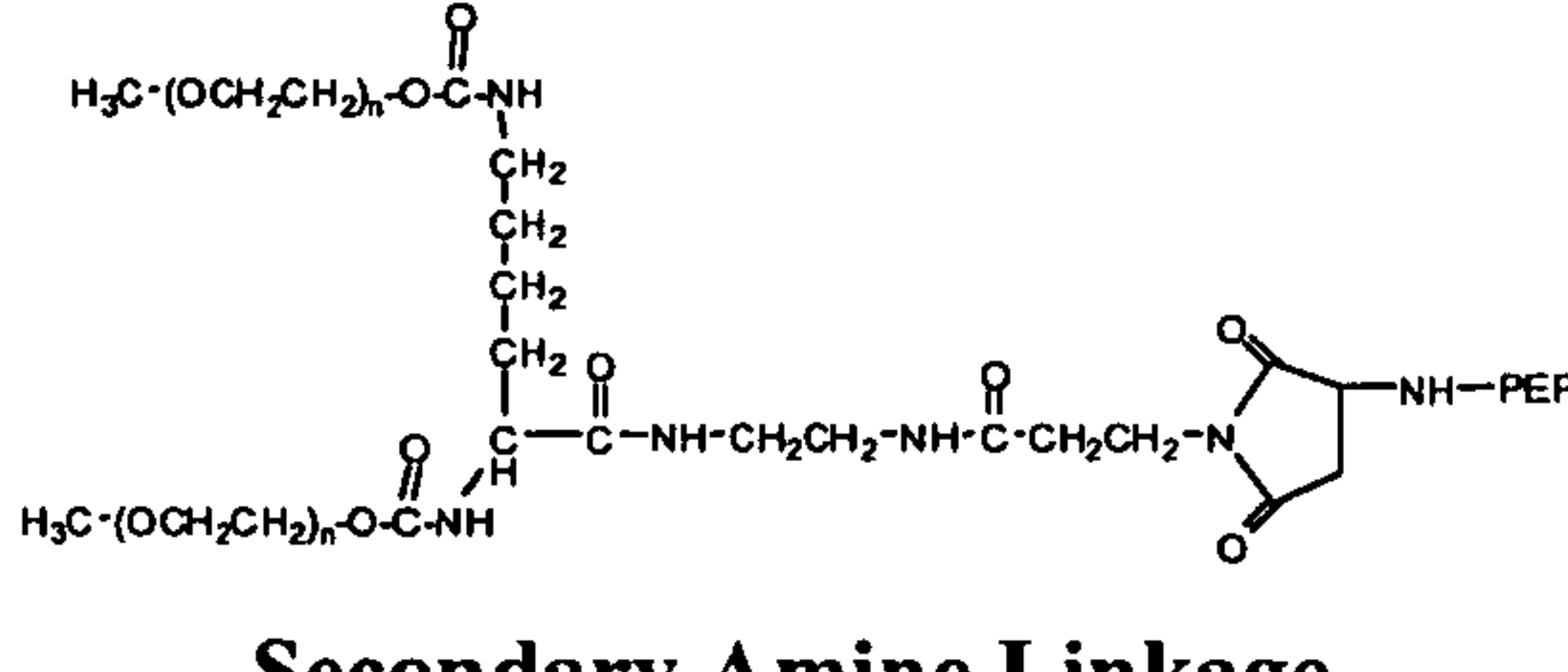
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Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH}$ mPEG Propionaldehyde Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP}$ Secondary Amine Linkage
$\overset{\text{O}}{\parallel}\text{HCCH}_2\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH}$ Homobifunctional PEG Butyraldehyde Reagent	$\begin{array}{c} \text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH} \\ \qquad \qquad \qquad \\ \text{PEP} \qquad \qquad \qquad \text{PEP} \end{array}$ Secondary Amine Linkages
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH}$ mPEG Butyraldehyde Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP}$ Secondary Amine Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH}$ mPEG Butyraldehyde Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP}$ Secondary Amine Linkage
$\begin{array}{c} \overset{\text{O}}{\parallel}\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH} \\ \\ \text{HN}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH} \end{array}$ Homobifunctional PEG Butyraldehyde Reagent	$\begin{array}{c} \overset{\text{O}}{\parallel}\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP} \\ \\ \text{HN}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP} \end{array}$ Secondary Amine Linkages
$\begin{array}{c} \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH} \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH} \end{array}$ Branched mPEG2 Butyraldehyde Reagent	$\begin{array}{c} \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH} \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP} \end{array}$ Secondary Amine Linkage
$\begin{array}{c} \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{CH}_2 \\ \\ \text{HC}-\text{OCH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{CH} \\ \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{CH}_2 \end{array}$ Branched mPEG2 Butyraldehyde Reagent	$\begin{array}{c} \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{CH}_2 \\ \\ \text{HC}-\text{OCH}_2\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-\text{NH}-\text{PEP} \\ \\ \text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{CH}_2 \end{array}$ Secondary Amine Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2-\overset{\text{OCH}_2\text{CH}_3}{\underset{ }{\text{CH}}}-\text{OCH}_2\text{CH}_3$ mPEG Acetal Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{NH}-\text{PEP}$ Secondary Amine Linkage

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Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{N}\text{---}\text{C}_4\text{H}_8\text{---}\overset{\text{O}}{\parallel}\text{C}$ mPEG Piperidone Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{N}\text{---}\text{C}_4\text{H}_8\text{---}\text{NH---PEP}$ Secondary Amine Linkage (to a secondary carbon)
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-(\text{CH}_2)_{2-5}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_3$ mPEG Methylketone Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-(\text{CH}_2)_{2-5}-\overset{\text{NH---PEP}}{\underset{ }{\text{CH}}}-\text{CH}_3$ secondary amine linkage (to a secondary carbon)
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\overset{\text{O}}{\parallel}\text{S}-\text{CH}_2-\text{CF}_3$ mPEG Tresylate Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{NH---PEP}$ Secondary Amine Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{N}\text{---}\text{C}_4\text{H}_3\text{O}_2$ mPEG Maleimide Reagent (under certain reaction conditions such as pH > 8)	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{N}\text{---}\text{C}_4\text{H}_3\text{O}_2\text{---}\text{NH---PEP}$ Secondary Amine Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N}\text{---}\text{C}_4\text{H}_3\text{O}_2$ mPEG Maleimide Reagent (under certain reaction conditions such as pH > 8)	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N}\text{---}\text{C}_4\text{H}_3\text{O}_2\text{---}\text{NH---PEP}$ Secondary Amine Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N}\text{---}\text{C}_4\text{H}_3\text{O}_2$ mPEG Maleimide Reagent (under certain reaction conditions such as pH > 8)	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N}\text{---}\text{C}_4\text{H}_3\text{O}_2\text{---}\text{NH---PEP}$ Secondary Amine Linkage

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Polymeric Reagent	Corresponding Conjugate
 mPEG Forked Maleimide Reagent (under certain reaction conditions such as pH > 8)	 Secondary Amine Linkages
 Branched mPEG2 Maleimide Reagent (under certain reaction conditions such as pH > 8)	 Secondary Amine Linkage

Amine Conjugation and Resulting Conjugates

[00160] Conjugation of a polymeric reagent to an amine group of a therapeutic peptide can be accomplished by a variety of techniques. In one approach, a therapeutic peptide is conjugated to a polymeric reagent functionalized with an active ester such as a succinimidyl derivative (*e.g.*, an N-hydroxysuccinimide ester). In this approach, the polymeric reagent bearing the reactive ester is reacted with the therapeutic peptide in aqueous media under appropriate pH conditions, *e.g.*, from pHs ranging from about 3 to about 8, about 3 to about 7, or about 4 to about 6.5. Most polymer active esters can couple to a target peptide such as therapeutic peptide at physiological pH, *e.g.*, at 7.0. However, less reactive derivatives may require a different pH. Typically, activated PEGs can be attached to a peptide such as therapeutic peptide at pHs from about 7.0 to about 10.0 for covalent attachment to an internal lysine. Typically, lower pHs are used, *e.g.*, 4 to about 5.75, for preferential covalent attachment to the N-terminus. Thus, different reaction conditions (*e.g.*, different pHs or different

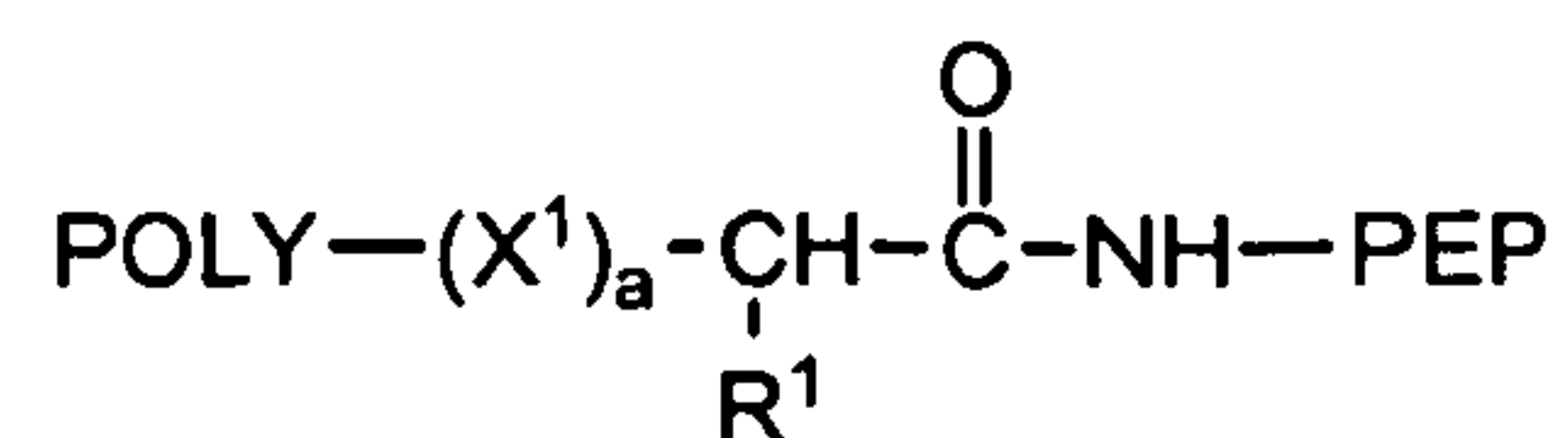
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temperatures) can result in the attachment of a water-soluble polymer such as PEG to different locations on the therapeutic peptide (*e.g.*, internal lysines versus the N-terminus). Coupling reactions can often be carried out at room temperature, although lower temperatures may be required for particularly labile therapeutic peptide moieties. Reaction times are typically on the order of minutes, *e.g.*, 30 minutes, to hours, *e.g.*, from about 1 to about 36 hours), depending upon the pH and temperature of the reaction. N-terminal PEGylation, *e.g.*, with a PEG reagent bearing an aldehyde group, is typically conducted under mild conditions, pHs from about 5-10, for about 6 to 36 hours. Varying ratios of polymeric reagent to therapeutic peptide may be employed, *e.g.*, from an equimolar ratio up to a 10-fold molar excess of polymer reagent. Typically, up to a 5-fold molar excess of polymer reagent will suffice.

[00161] In certain instances, it may be preferable to protect certain amino acids from reaction with a particular polymeric reagent if site specific or site selective covalent attachment is desired using commonly employed protection/deprotection methodologies such as those well known in the art.

[00162] In an alternative approach to direct coupling reactions, the PEG reagent may be incorporated at a desired position of the therapeutic peptide during peptide synthesis. In this way, site-selective introduction of one or more PEGs can be achieved. See, *e.g.*, International Patent Publication No. WO 95/00162, which describes the site selective synthesis of conjugated peptides.

[00163] Exemplary conjugates that can be prepared using, for example, polymeric reagents containing a reactive ester for coupling to an amino group of therapeutic peptide, comprise the following alpha-branched structure:



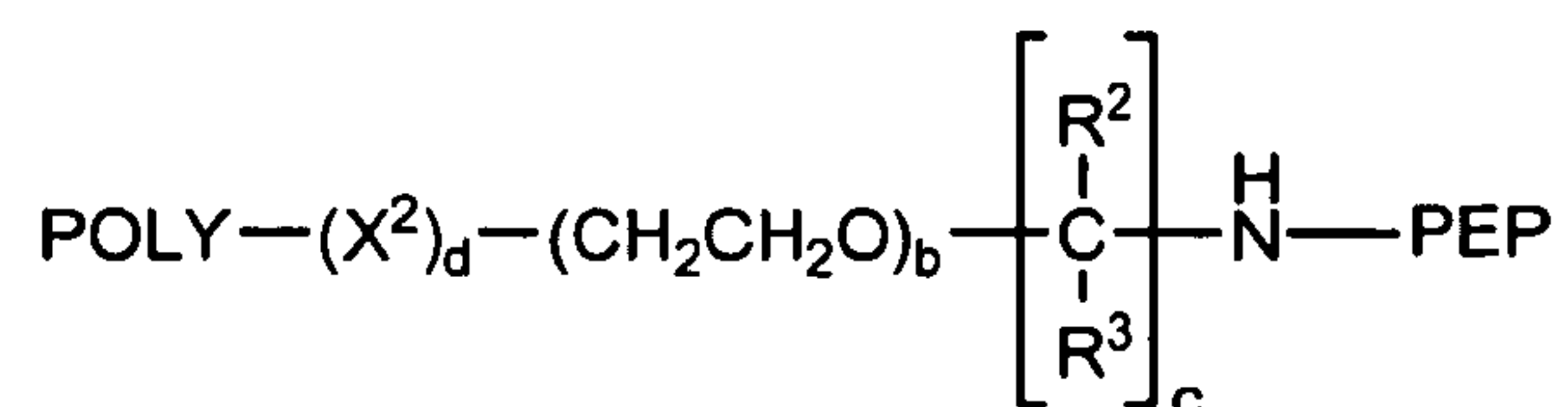
where POLY is a water-soluble polymer, (a) is either zero or one; X¹, when present, is a spacer moiety comprised of one or more atoms; R¹ is hydrogen an organic radical; and “~NH-PEP” represents a residue of a therapeutic peptide, where the underlined amino group represents an amino group of the therapeutic peptide.

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[00164] With respect to the structure corresponding to that referred to in the immediately preceding paragraph, any of the water-soluble polymers provided herein can be defined as POLY, any of the spacer moieties provided herein can be defined as X^1 (when present), any of the organic radicals provided herein can be defined as R^1 (in instances where R^1 is not hydrogen), and any of the therapeutic peptides provided herein can be employed. In one or more embodiments corresponding to the structure referred to in the immediately preceding paragraph, POLY is a poly(ethylene glycol) such as $H_3CO(CH_2CH_2O)_n-$, wherein (n) is an integer having a value of from 3 to 4000, more preferably from 10 to about 1800; (a) is one; X^1 is a C_{1-6} alkylene, such as one selected from methylene (*i.e.*, $-CH_2-$), ethylene (*i.e.*, $-CH_2-CH_2-$) and propylene (*i.e.*, $-CH_2-CH_2-CH_2-$); R^1 is H or lower alkyl such as methyl or ethyl; and PEP corresponds to any therapeutic peptide disclosed herein, including in Table 1.

[00165] Typical of another approach for conjugating a therapeutic peptide to a polymeric reagent is reductive amination. Typically, reductive amination is employed to conjugate a primary amine of a therapeutic peptide with a polymeric reagent functionalized with a ketone, aldehyde or a hydrated form thereof (*e.g.*, ketone hydrate and aldehyde hydrate). In this approach, the primary amine from the therapeutic peptide (*e.g.*, the N-terminus) reacts with the carbonyl group of the aldehyde or ketone (or the corresponding hydroxy-containing group of a hydrated aldehyde or ketone), thereby forming a Schiff base. The Schiff base, in turn, is then reductively converted to a stable conjugate through use of a reducing agent such as sodium borohydride or any other suitable reducing agent. Selective reactions (*e.g.*, at the N-terminus) are possible, particularly with a polymer functionalized with a ketone or an alpha-methyl branched aldehyde and/or under specific reaction conditions (*e.g.*, reduced pH).

[00166] Exemplary conjugates that can be prepared using, for example, polymeric reagents containing an aldehyde (or aldehyde hydrate) or ketone or (ketone hydrate) possess the following structure:

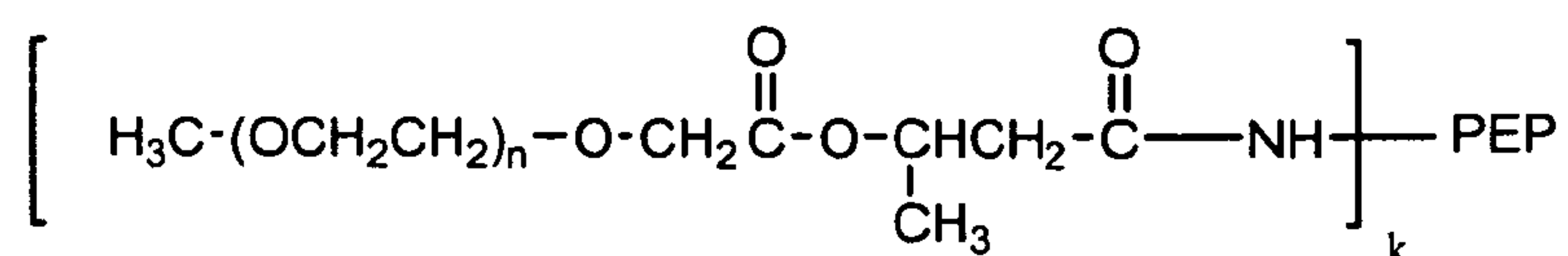


where POLY is a water-soluble polymer; (d) is either zero or one; X^2 , when present, is a spacer moiety comprised of one or more atoms; (b) is an integer having a value of one through ten; (c)

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is an integer having a value of one through ten; R^2 , in each occurrence, is independently H or an organic radical; R^3 , in each occurrence, is independently H or an organic radical; and “~NH-PEP” represents a residue of a therapeutic peptide, where the underlined amino group represents an amino group of the therapeutic peptide.

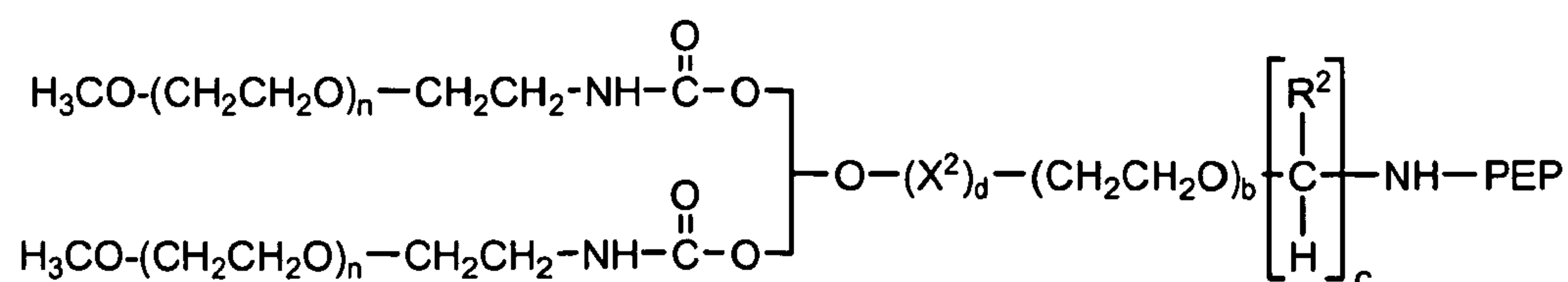
[00167] Yet another illustrative conjugate of the invention possesses the structure:



where k ranges from 1 to 3, and n ranges from 10 to about 1800.

[00168] With respect to the structure corresponding to that referred to in immediately preceding paragraph, any of the water-soluble polymers provided herein can be defined as POLY, any of the spacer moieties provided herein can be defined as X^2 (when present), any of the organic radicals provided herein can be independently defined as R^2 and R^3 (in instances where R^2 and R^3 are independently not hydrogen), and any of the PEP moieties provided herein can be defined as a therapeutic peptide. In one or more embodiments of the structure referred to in the immediately preceding paragraph, POLY is a poly(ethylene glycol) such as $\text{H}_3\text{CO}(\text{CH}_2\text{CH}_2\text{O})_n-$, wherein (n) is an integer having a value of from 3 to 4000, more preferably from 10 to about 1800; (d) is one; X^1 is amide [*e.g.*, $-\text{C}(\text{O})\text{NH}-$]; (b) is 2 through 6, such as 4; (c) is 2 through 6, such as 4; each of R^2 and R^3 are independently H or lower alkyl, such as methyl when lower alkyl; and PEP is therapeutic peptide.

[00169] Another example of a therapeutic peptide conjugate in accordance with the invention has the following structure:

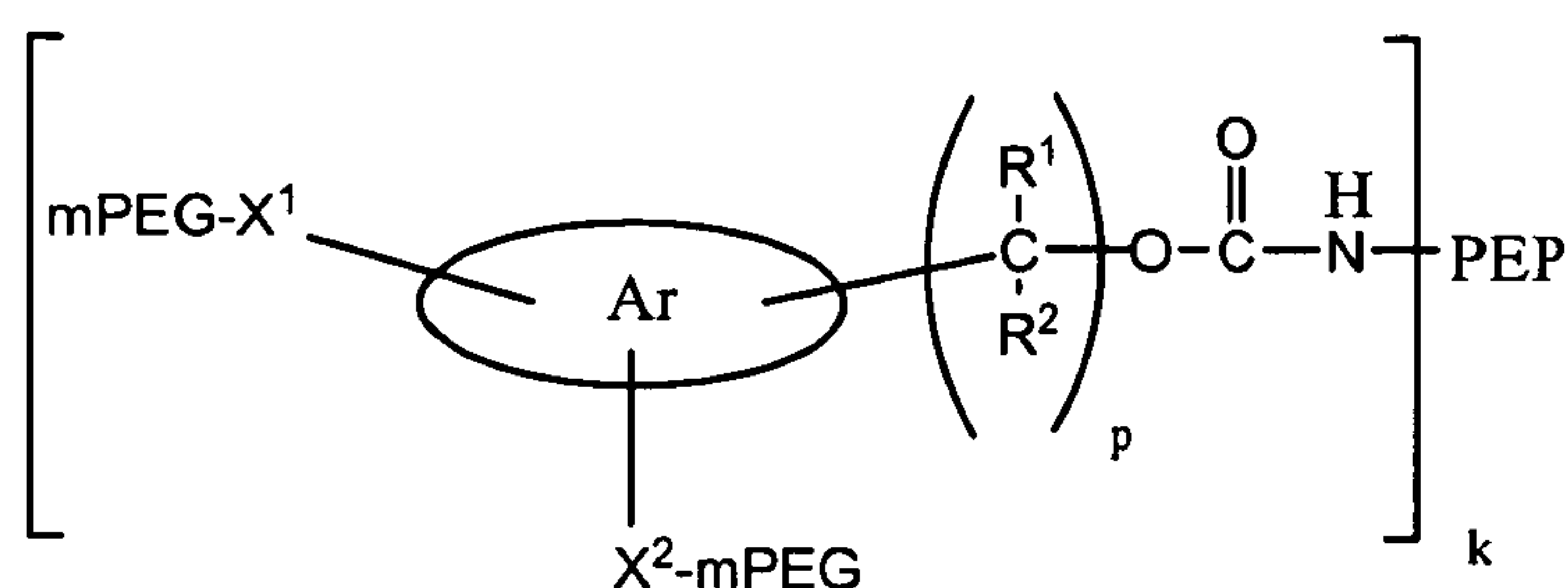


wherein each (n) is independently an integer having a value of from 3 to 4000, preferably from 10 to 1800; X^2 is as previously defined; (b) is 2 through 6; (c) is 2 through 6; R^2 , in each

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occurrence, is independently H or lower alkyl; and “~NH-PEP” represents a residue of a therapeutic peptide, where the underlined amino group represents an amino group of the therapeutic peptide.

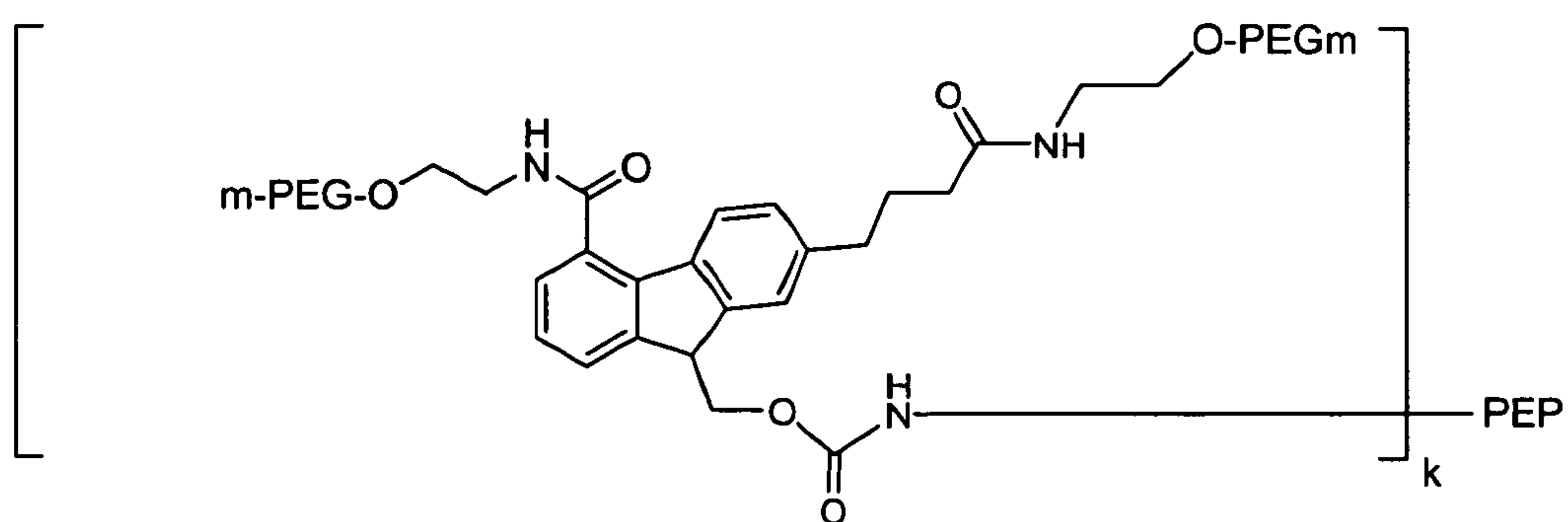
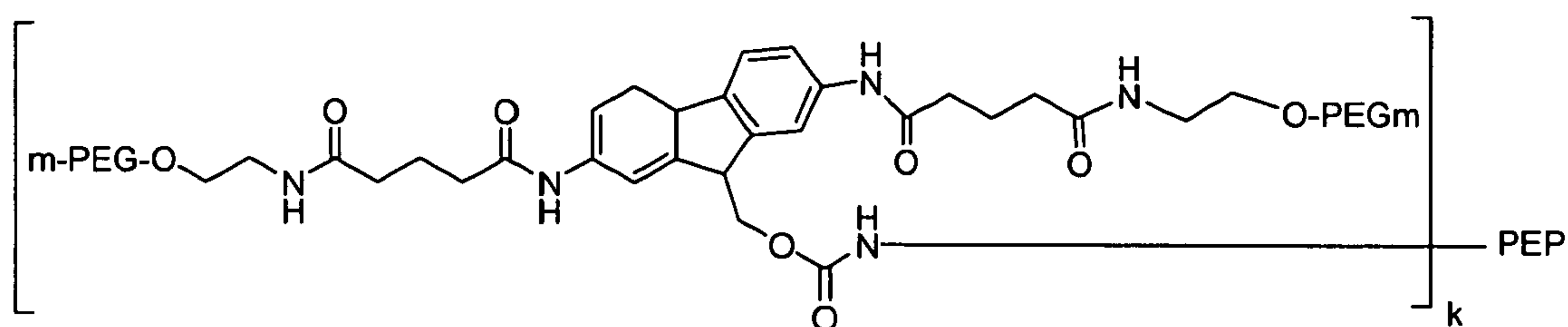
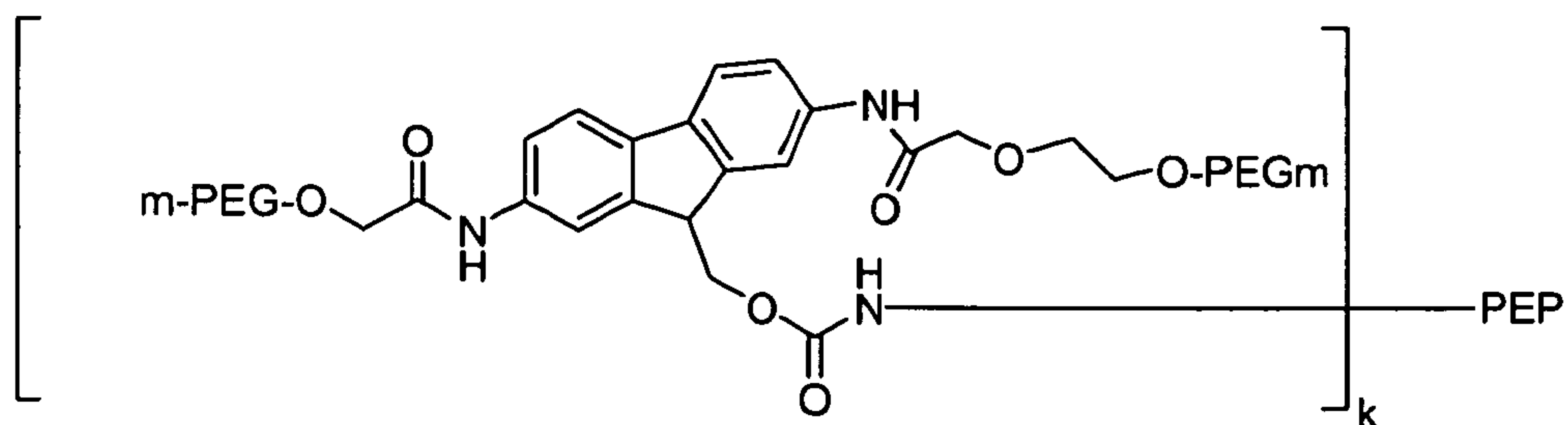
[00170] Additional therapeutic peptide polymer conjugates resulting from reaction of a water-soluble polymer with an amino group of therapeutic peptide are provided below. The following conjugate structures are releasable. One such structure corresponds to:



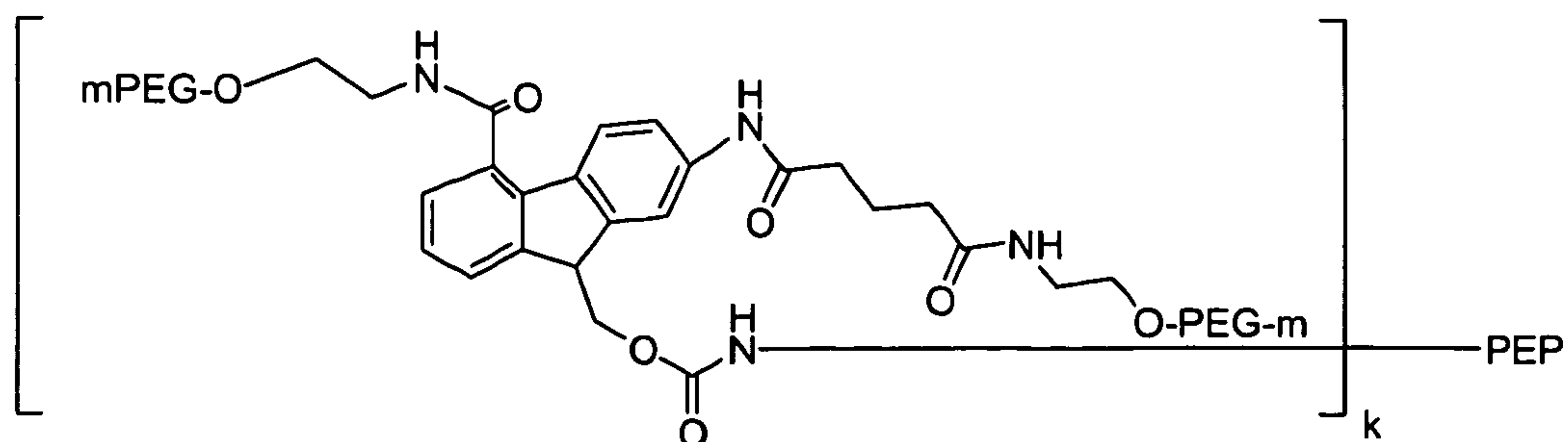
where mPEG is $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-$, n ranges from 10 to 1800, p is an integer ranging from 1 to 8, R^1 is H or lower alkyl, R^2 is H or lower alkyl, Ar is an aromatic hydrocarbon, such as a fused bicyclic or tricyclic aromatic hydrocarbon, X^1 and X^2 are each independently a spacer moiety having an atom length of from about 1 to about 18 atoms, ~NH-PEP is as previously described, and k is an integer selected from 1, 2, and 3. The value of k indicates the number of water-soluble polymer molecules attached to different sites on the therapeutic peptide. In a preferred embodiment, R^1 and R^2 are both H. The spacer moieties, X^1 and X^2 , preferably each contain one amide bond. In a preferred embodiment, X^1 and X^2 are the same. Preferred spacers, *i.e.*, X^1 and X^2 , include $-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{O}-$, $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_q-\text{O}-$, $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_q-\text{C}(\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_q-$, and $-\text{C}(\text{O})-\text{NH}-$, where q is selected from 2, 3, 4, and 5. Although the spacers can be in either orientation, preferably, the nitrogen is proximal to the PEG rather than to the aromatic moiety. Illustrative aromatic moieties include pentalene, indene, naphthalene, indacene, acenaphthylene, and fluorene.

[00171] Particularly preferred conjugates of this type are provided below.

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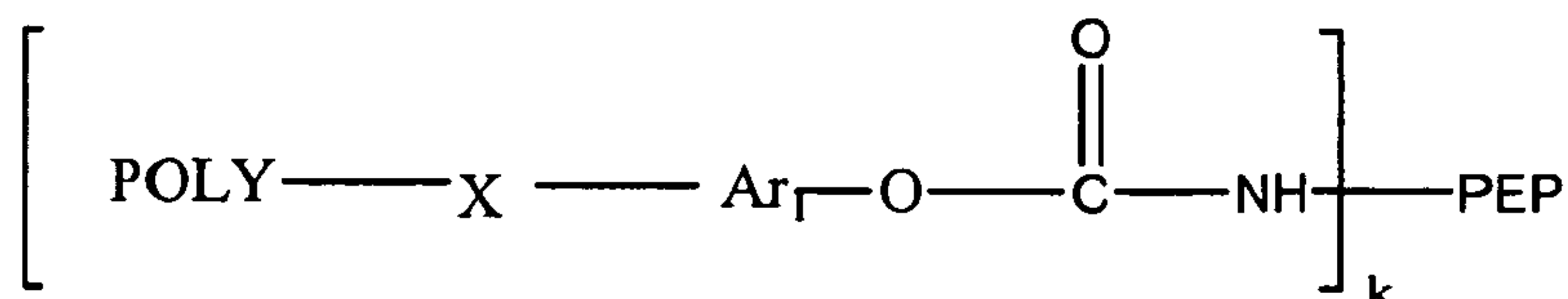


and

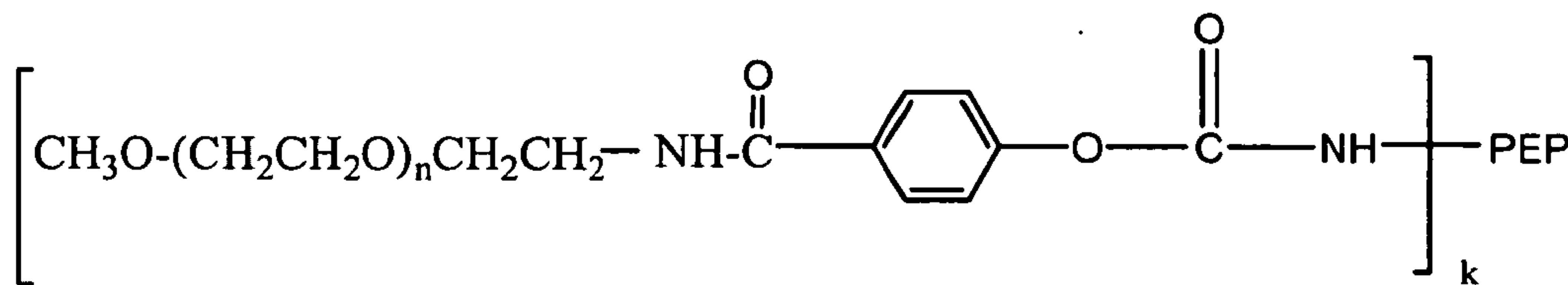
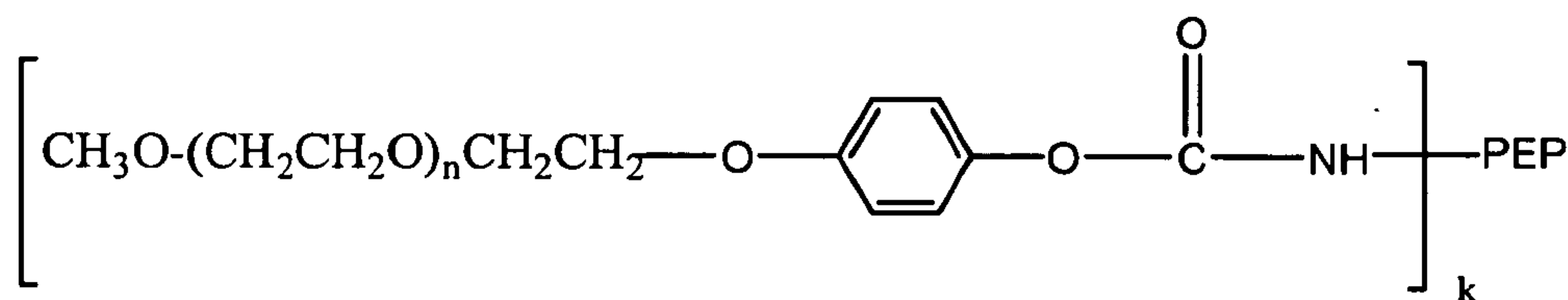


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[00172] Additional therapeutic peptide conjugates resulting from covalent attachment to amino groups of therapeutic peptide that are also releasable include the following:

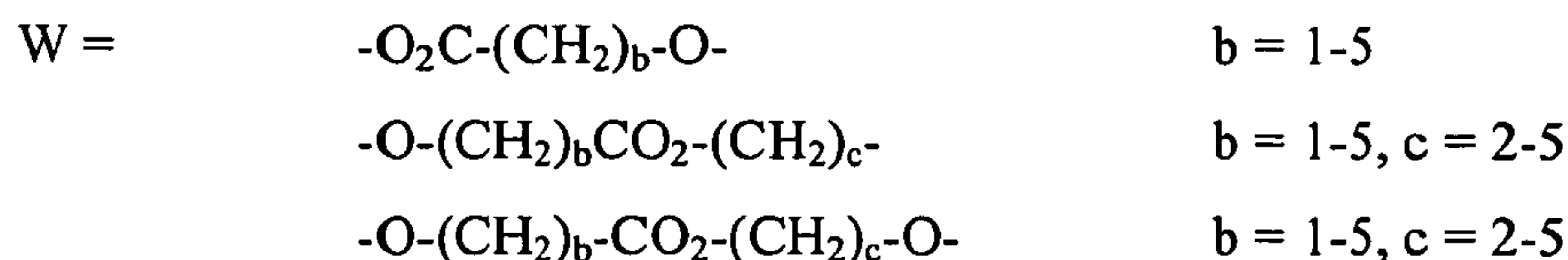


where X is either $-\text{O}-$ or $-\text{NH}-\text{C}(\text{O})-$, Ar_1 is an aromatic group, *e.g.*, *ortho*, *meta*, or *para*-substituted phenyl, and k is an integer selected from 1, 2, and 3. Particular conjugates of this type include:



where n ranges from about 10 to about 1800.

[00173] Additional releasable conjugates in accordance with the invention are prepared using water-soluble polymer reagents such as those described in U.S. Patent No. 6,214,966. Such water-soluble polymers result in a releasable linkage following conjugation, and possess at least one releasable ester linkage close to the covalent attachment to the active agent. The polymers generally possess the following structure, PEG-W-CO₂-NHS or an equivalent activated ester, where



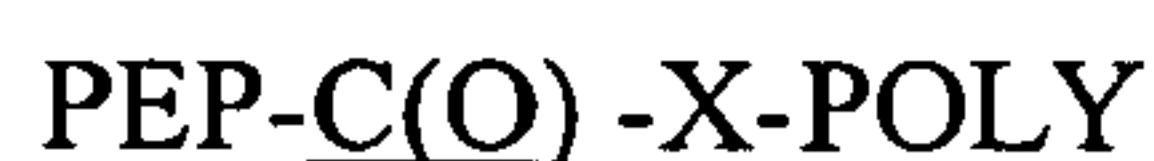
and NHS is N-hydroxysuccinimidyl. Upon hydrolysis, the resulting released active agent, *e.g.*, therapeutic peptide, will possess a short tag resulting from hydrolysis of the ester functionality of the polymer reagent. Illustrative releasable conjugates of this type include: mPEG-O-(CH₂)_b-

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COOCH₂C(O)-NH-therapeutic peptide, and mPEG-O-(CH₂)_b-COO-CH(CH₃)-CH₂-C(O)-NH-therapeutic peptide, where the number of water-soluble polymers attached to therapeutic peptide can be anywhere from 1 to 4, or more preferably, from 1 to 3.

Carboxyl Coupling and Resulting Conjugates

[00174] Carboxyl groups represent another functional group that can serve as a point of attachment to the therapeutic peptide. The conjugate will have the following structure:



where PEP-C(O) ~ corresponds to a residue of a therapeutic peptide where the carbonyl is a carbonyl (derived from the carboxy group) of the therapeutic peptide, X is a spacer moiety, such as a heteroatom selected from O, N(H), and S, and POLY is a water-soluble polymer such as PEG, optionally terminating in an end-capping moiety.

[00175] The C(O)-X linkage results from the reaction between a polymeric derivative bearing a terminal functional group and a carboxyl-containing therapeutic peptide. As discussed above, the specific linkage will depend on the type of functional group utilized. If the polymer is end-functionalized or "activated" with a hydroxyl group, the resulting linkage will be a carboxylic acid ester and X will be O. If the polymer backbone is functionalized with a thiol group, the resulting linkage will be a thioester and X will be S. When certain multi-arm, branched or forked polymers are employed, the C(O)X moiety, and in particular the X moiety, may be relatively more complex and may include a longer linker structure.

[00176] Polymeric reagents containing a hydrazide moiety are also suitable for conjugation at a carbonyl. To the extent that the therapeutic peptide does not contain a carbonyl moiety, a carbonyl moiety can be introduced by reducing any carboxylic acid functionality (*e.g.*, the C-terminal carboxylic acid). Specific examples of polymeric reagents comprising a hydrazide moiety, along with the corresponding conjugates, are provided in Table 3, below. In addition, any polymeric reagent comprising an activated ester (*e.g.*, a succinimidyl group) can be converted to contain a hydrazide moiety by reacting the polymer activated ester with hydrazine (NH₂-NH₂) or tert-butyl carbamate [NH₂NHCO₂C(CH₃)₃]. In the table, the variable (n) represents the number of repeating monomeric units and "=C-(PEP)" represents a residue of a therapeutic peptide following conjugation to the polymeric reagent where the underlined C is part

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of the therapeutic peptide. Optionally, the hydrazone linkage can be reduced using a suitable reducing agent. While each polymeric portion [e.g., $(\text{OCH}_2\text{CH}_2)_n$ or $(\text{CH}_2\text{CH}_2\text{O})_n$] presented in Table 3 terminates in a "CH₃" group, other groups (such as H and benzyl) can be substituted therefor.

Table 3

Carboxyl-Specific Polymeric Reagents and the GM-Therapeutic Peptide Conjugates Formed Therefrom

Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\overset{\text{H}}{\underset{\text{H}}{\text{N}}}-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{S}}{\parallel}\text{C}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{S}}{\parallel}\text{C}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage

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Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\text{NH}-\overset{\text{S}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\overset{\text{H}}{\underset{\parallel}{\text{N}}}-\text{NH}-\overset{\text{S}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{NH}_2$ mPEG-Hydrazine Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{N}=\text{C}-\text{PEP}$ Hydrazone Linkage

Thiol Coupling and Resulting Conjugates

[00177] Thiol groups contained within the therapeutic peptide can serve as effective sites of attachment for the water-soluble polymer. The thiol groups contained in cysteine residues of the therapeutic peptide can be reacted with an activated PEG that is specific for reaction with thiol groups, *e.g.*, an N-maleimidyl polymer or other derivative, as described in, for example, U.S. Patent No. 5,739,208, WO 01/62827, and in Table 4 below. In certain embodiments, cysteine residues may be introduced in the therapeutic peptide and may be used to attach a water-soluble polymer.

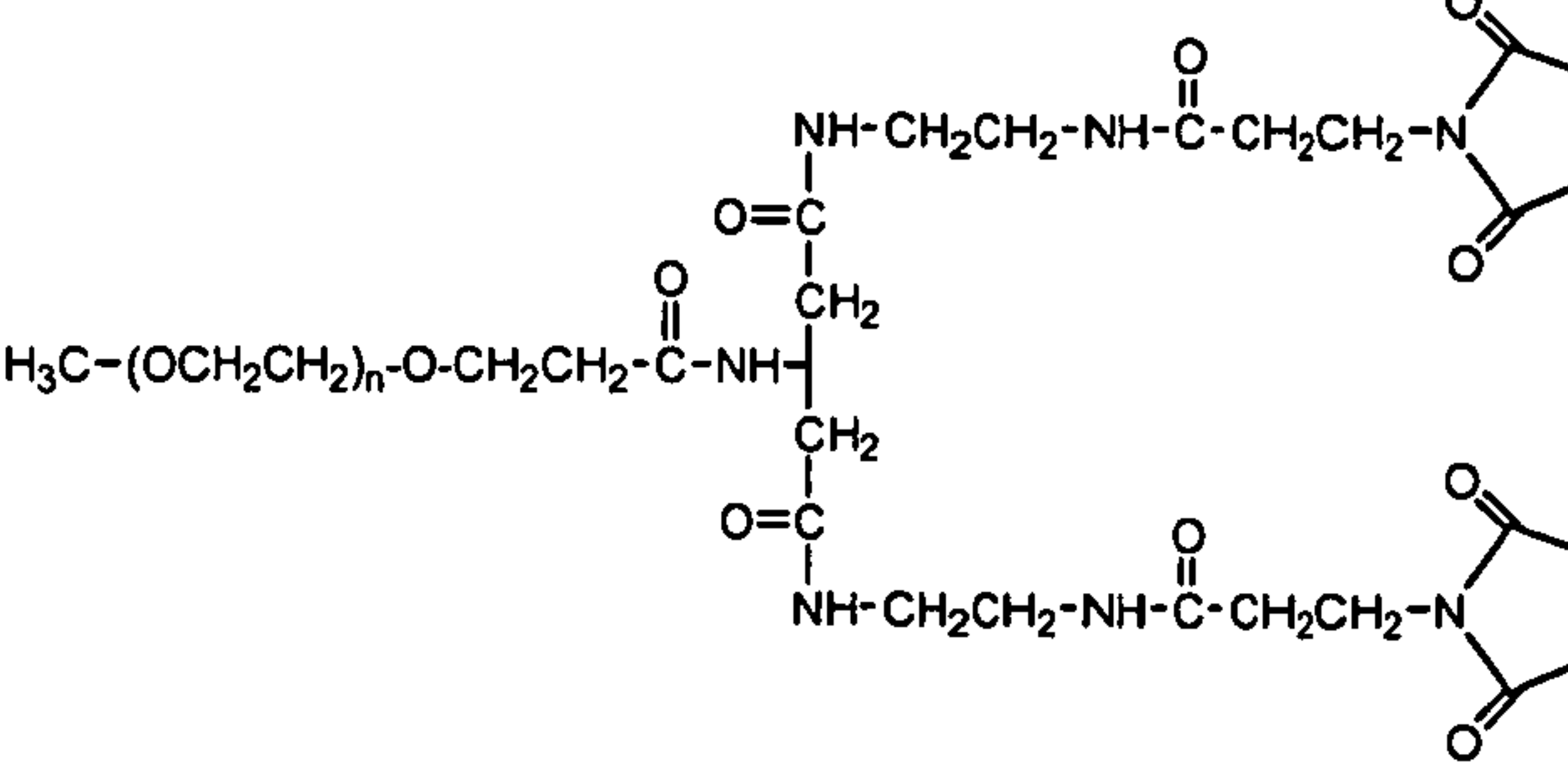
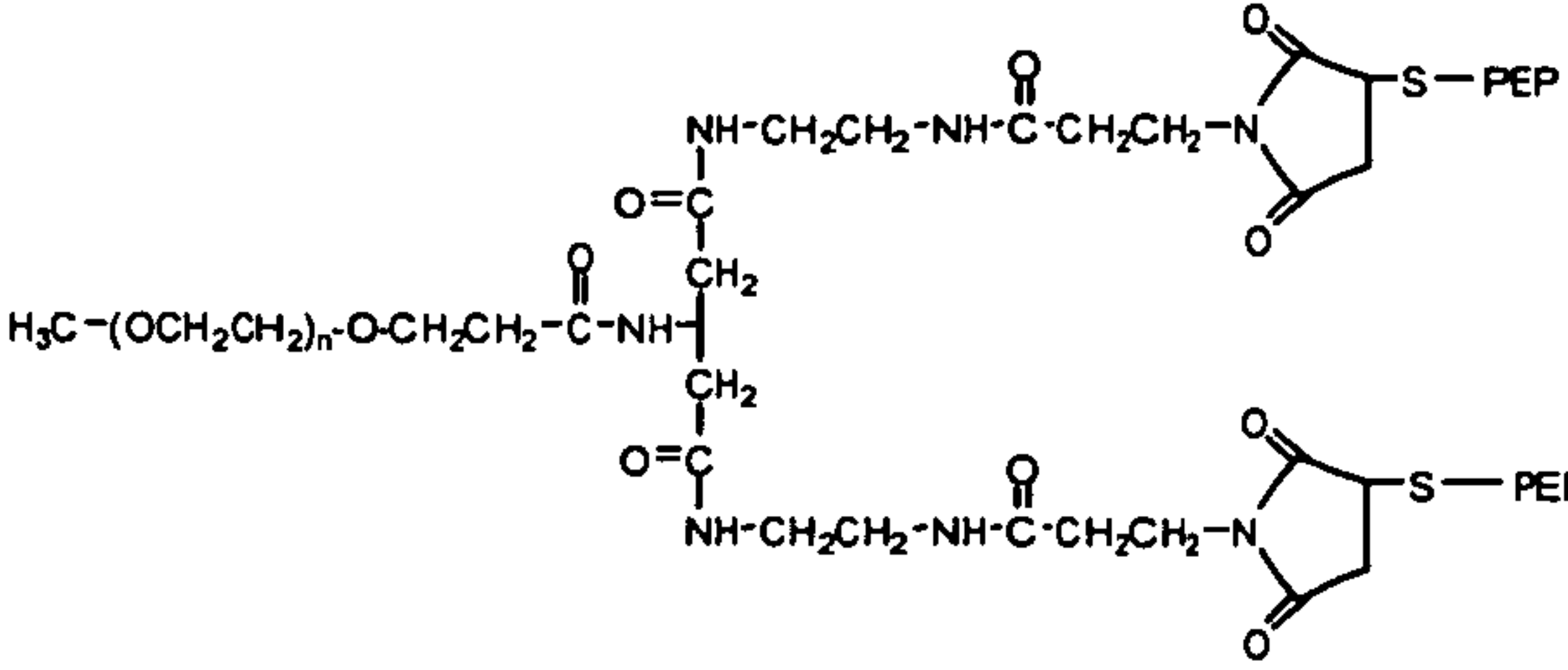
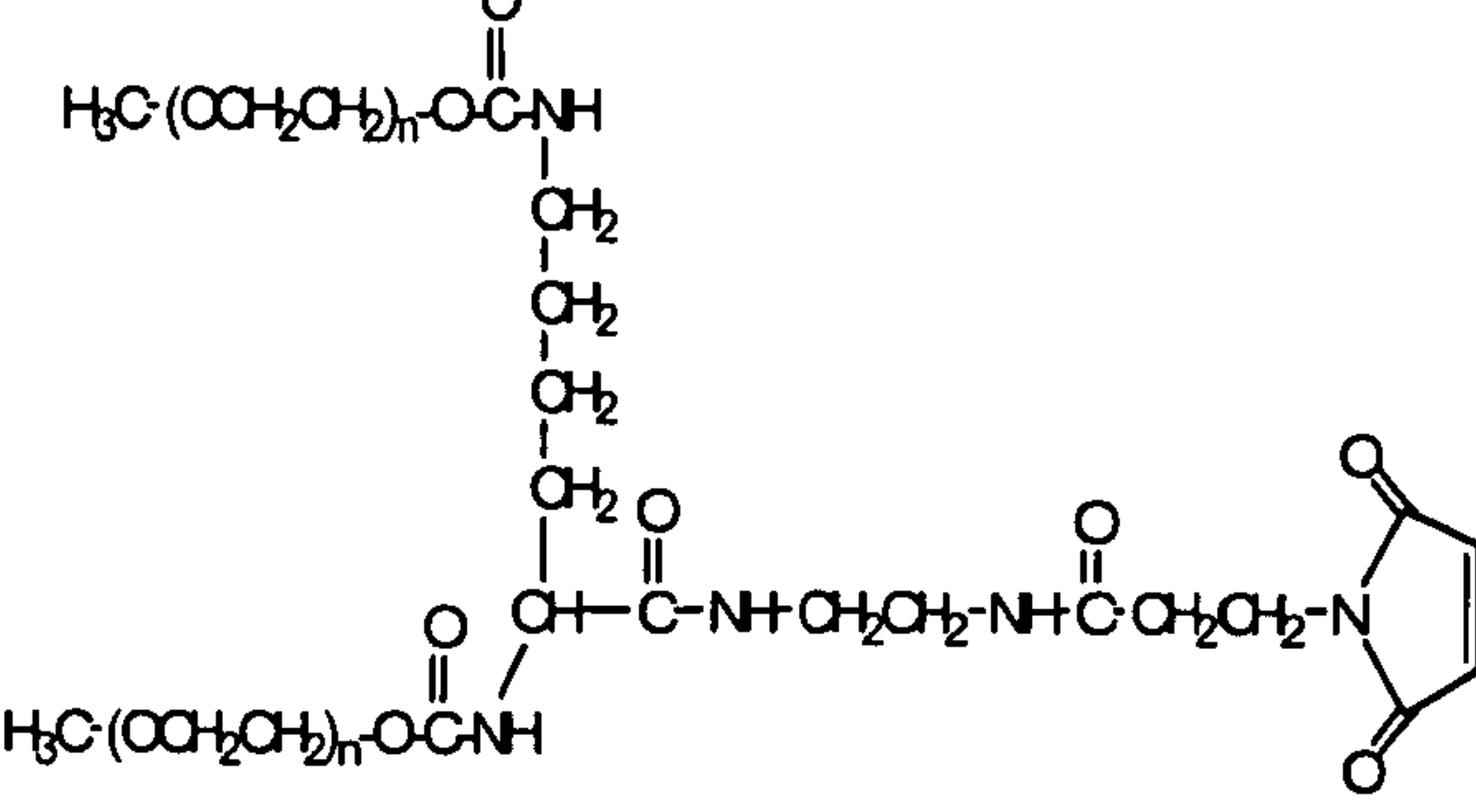
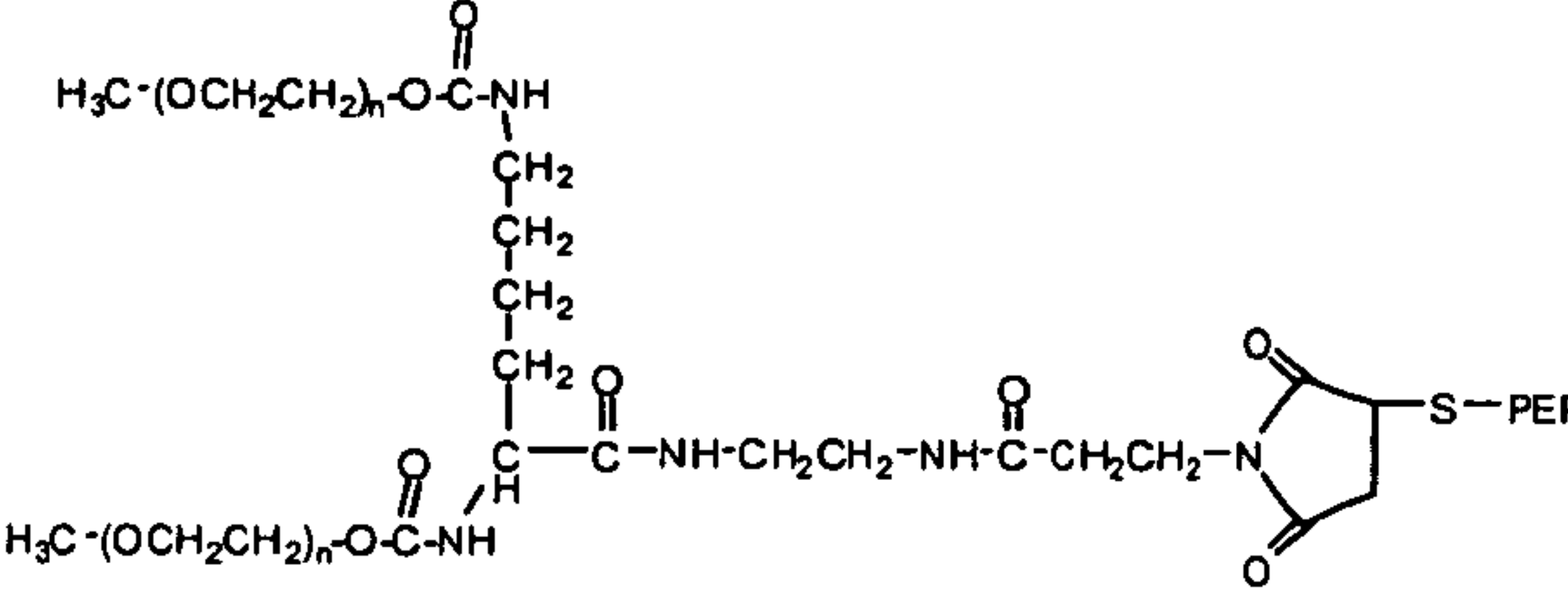
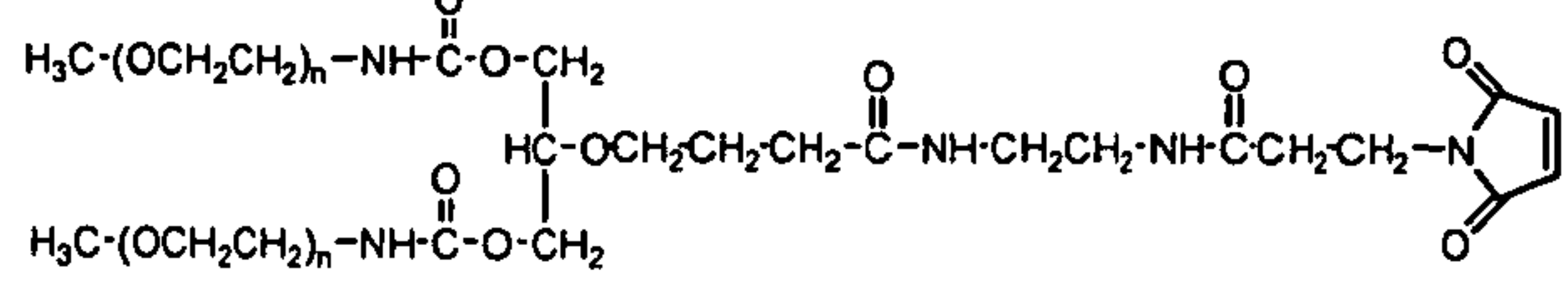
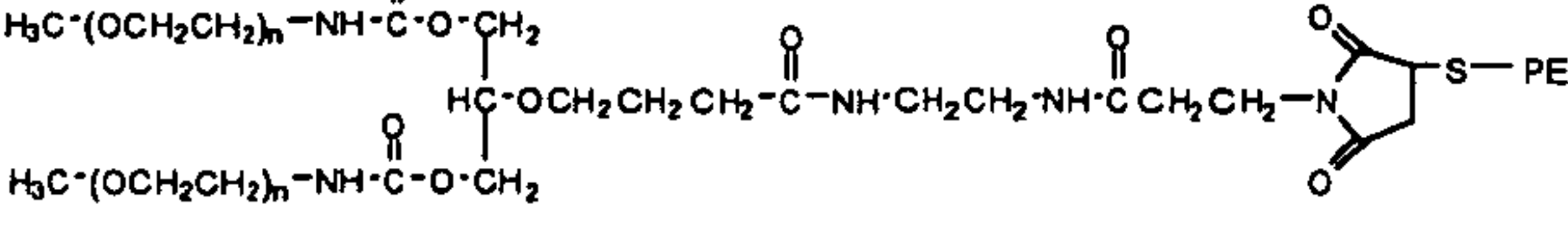
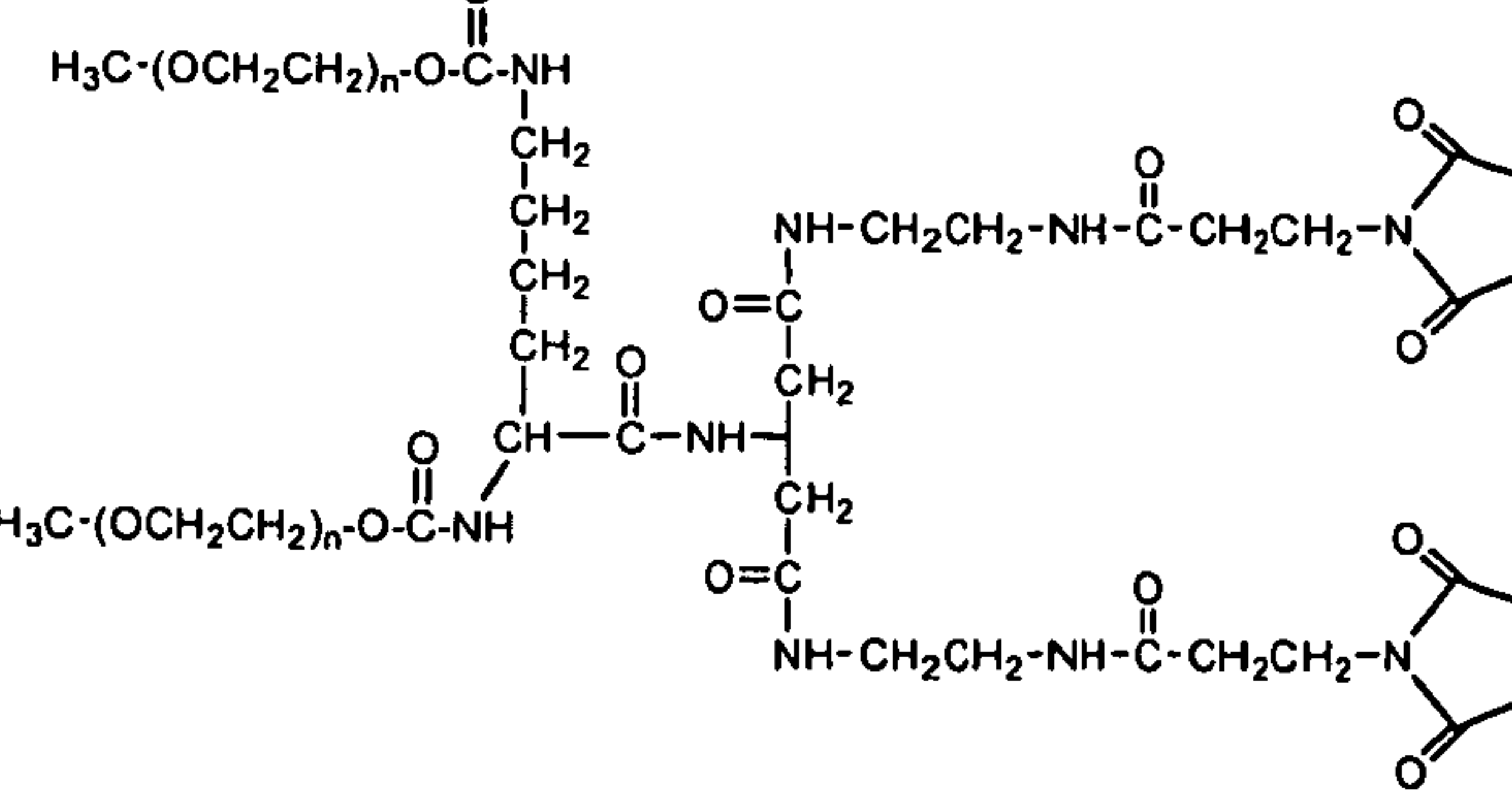
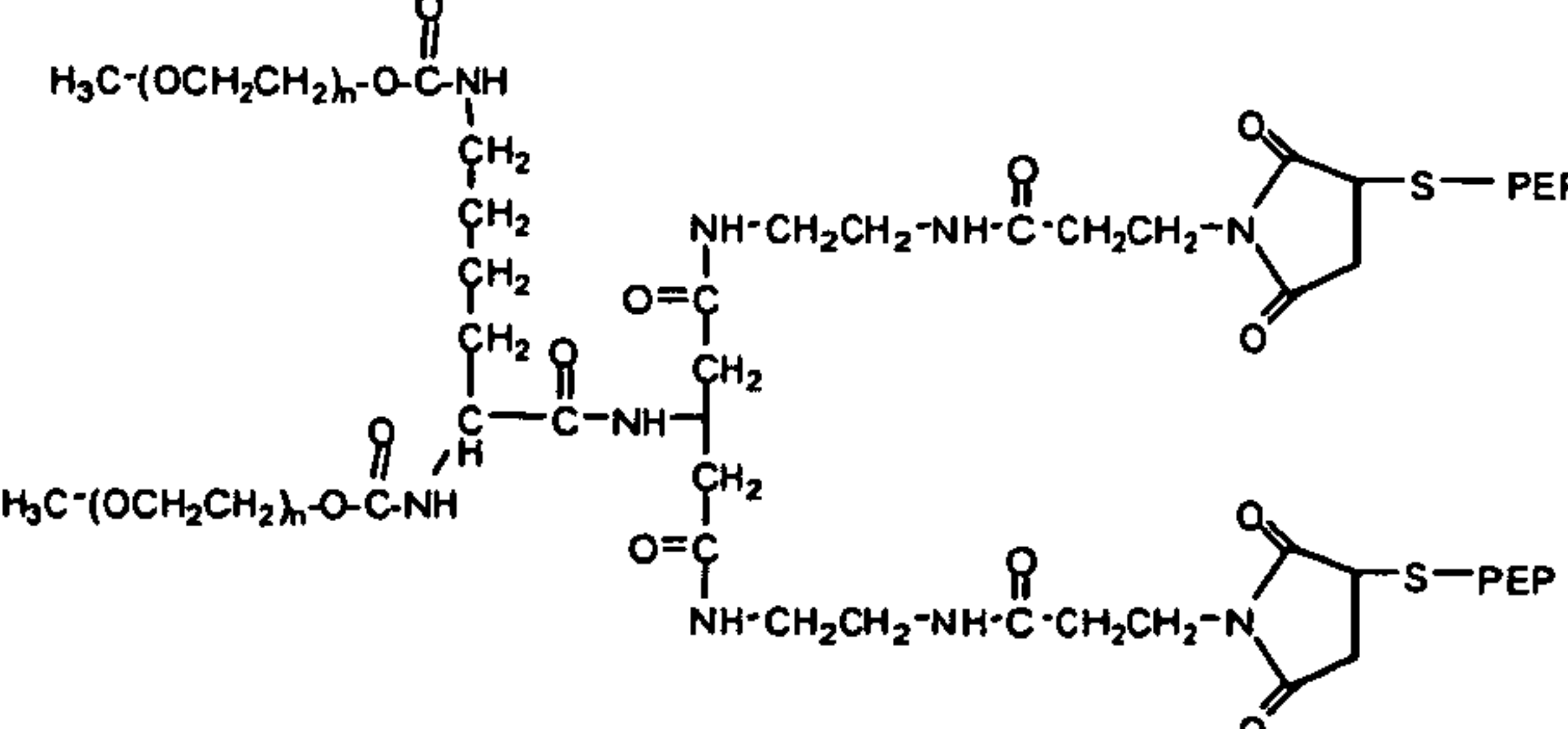
[00178] Specific examples of the reagents themselves, along with the corresponding conjugates, are provided in Table 4 below. In the table, the variable (n) represents the number of repeating monomeric units and "-S-(PEP)" represents a residue of a therapeutic peptide following conjugation to the water-soluble polymer, where the S represents the residue of a therapeutic peptide thiol group. While each polymeric portion [*e.g.*, (OCH₂CH₂)_n or (CH₂CH₂O)_n] presented in Table 4 terminates in a "CH₃" group, other end-capping groups (such as H and benzyl) or reactive groups may be used as well.

Table 4

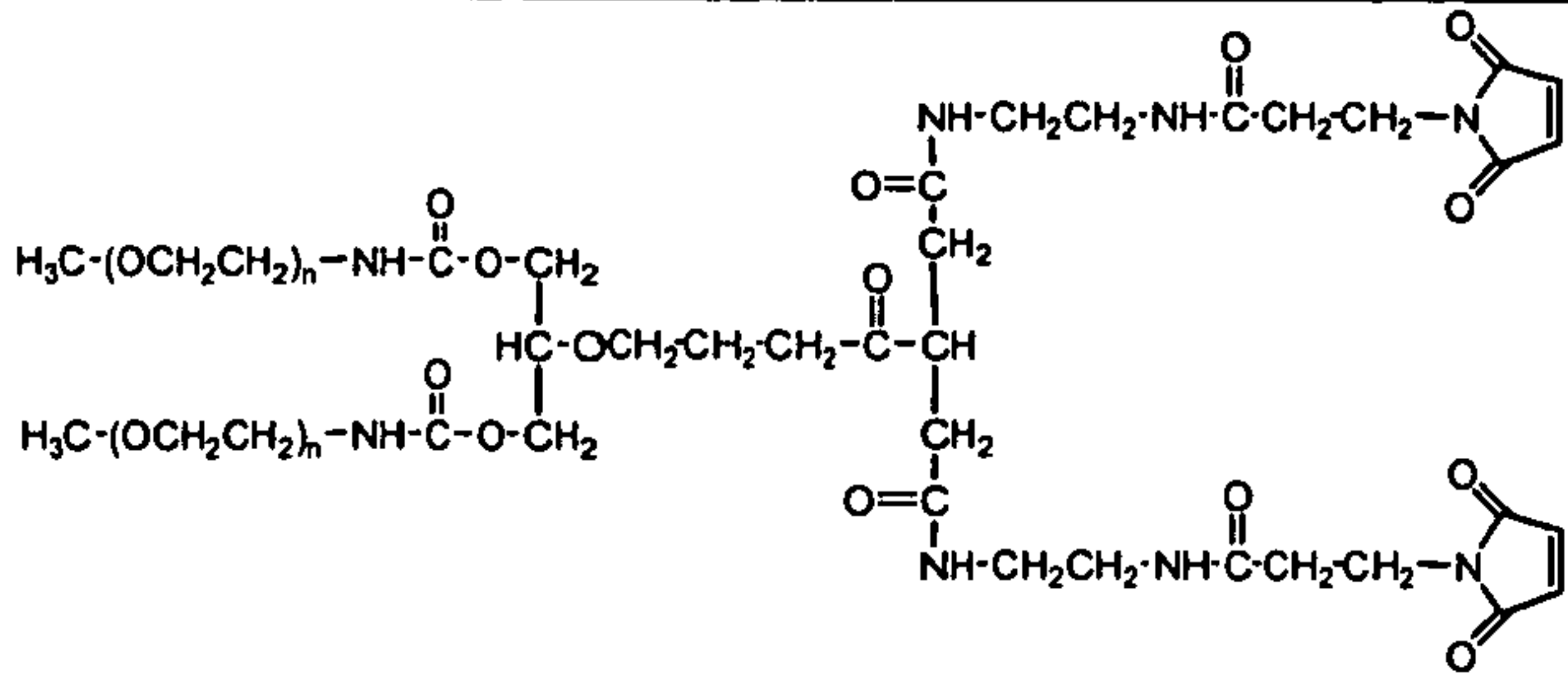
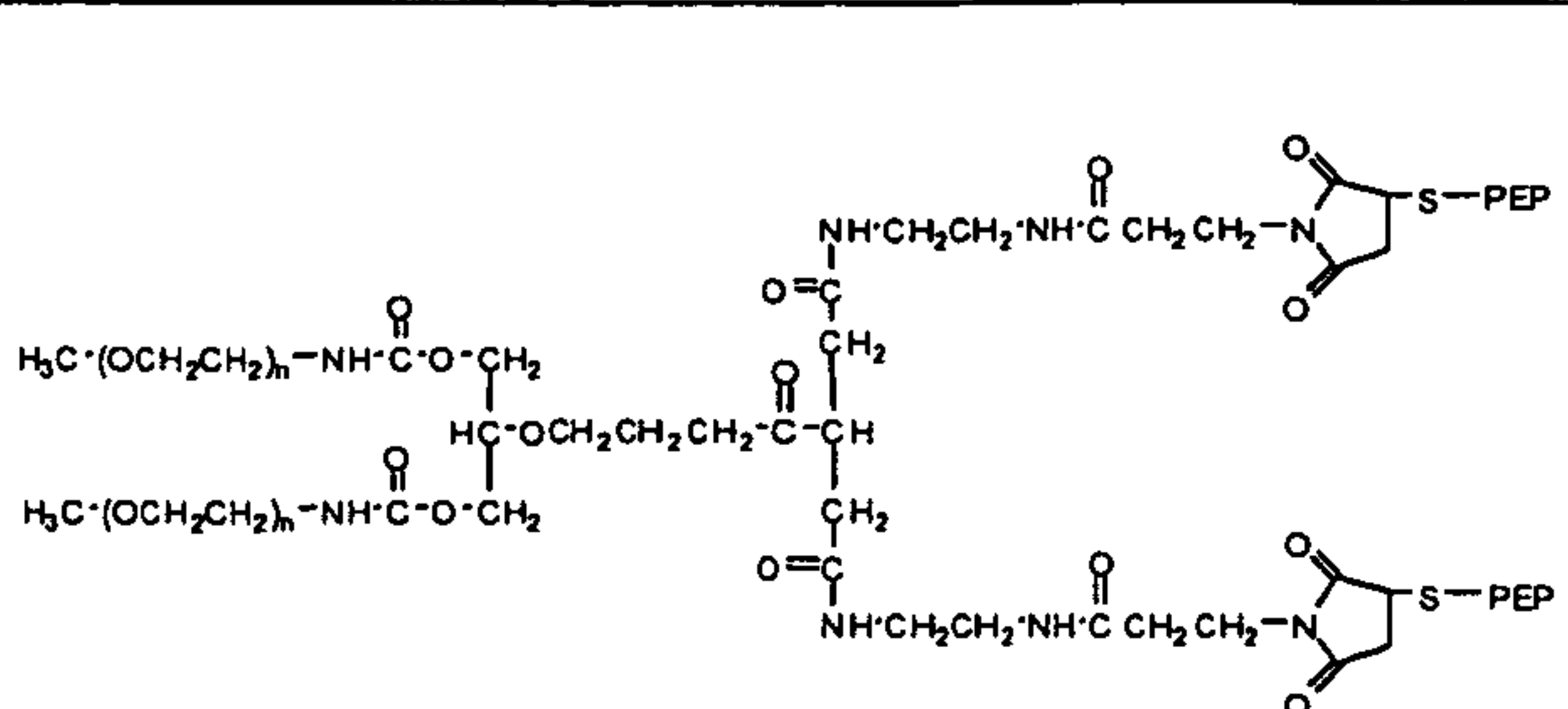
Thiol-Specific Polymeric Reagents and the Therapeutic peptide Conjugates Formed Therefrom

Polymeric Reagent	Corresponding Conjugate
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ mPEG Maleimide Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{S}-\text{PEP}$ Thioether Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ mPEG Maleimide Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{S}-\text{PEP}$ Thioether Linkage
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ mPEG Maleimide Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{S}-\text{PEP}$ Thioether Linkage
$\begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{N}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ Homobifunctional mPEG Maleimide Reagent	$\text{PEP}-\text{S} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{N}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{S}-\text{PEP}$ Thioether Linkages
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ mPEG Maleimide Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{S}-\text{PEP}$ Thioether Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ mPEG Maleimide Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \text{S}-\text{PEP}$ Thioether Linkage

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Polymeric Reagent	Corresponding Conjugate
 mPEG Forked Maleimide Reagent	 Thioether Linkage
 Branched mPEG2 Maleimide Reagent	 Thioether Linkage
 Branched mPEG2 Maleimide Reagent	 Thioether Linkage
 Branched mPEG2 Forked Maleimide Reagent	 Thioether Linkages

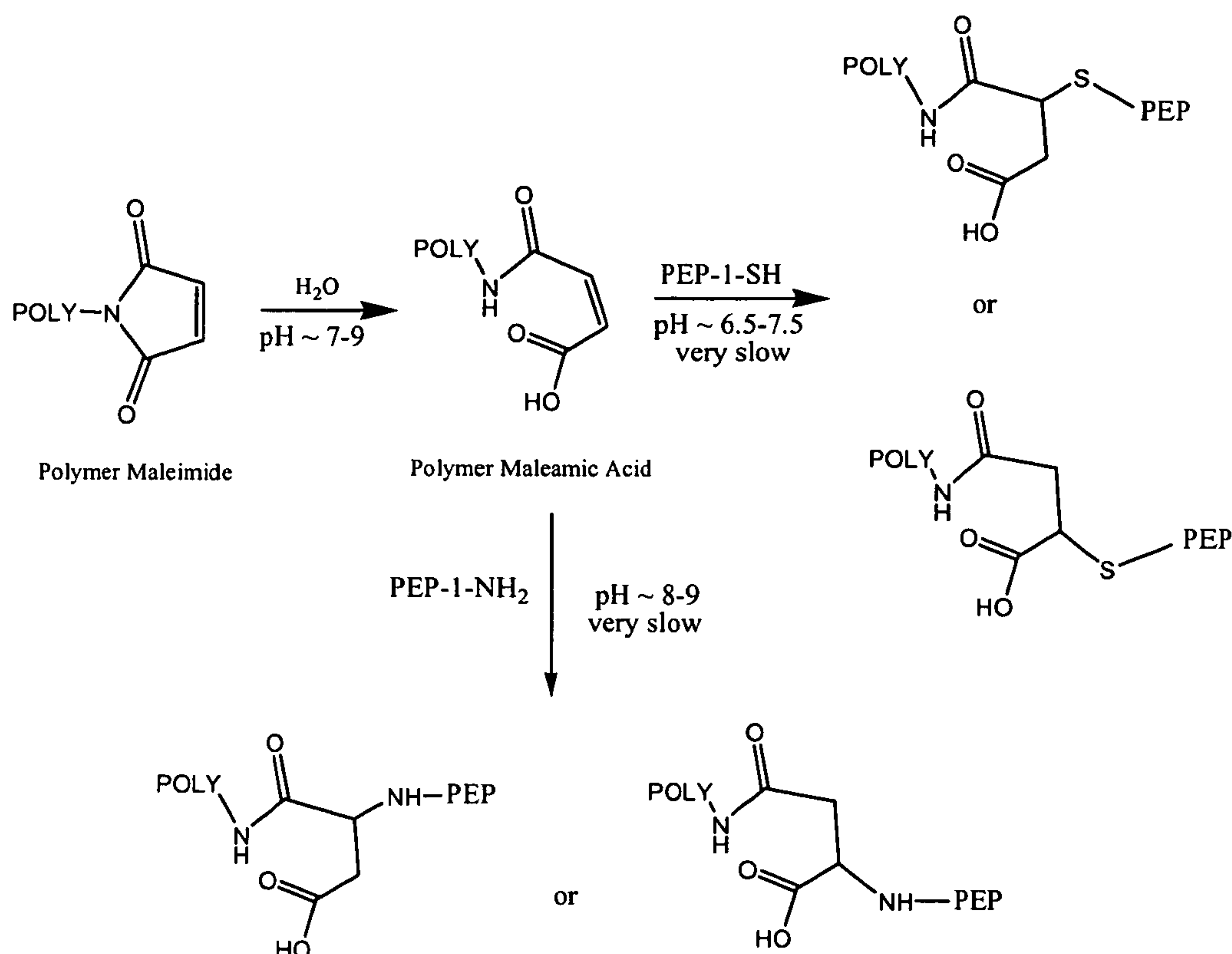
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Polymeric Reagent	Corresponding Conjugate
 Branched mPEG2 Forked Maleimide Reagent	 Thioether Linkages
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{S}(=\text{O})_2-\text{CH}=\text{CH}_2$ mPEG Vinyl Sulfone Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{S}(=\text{O})_2-\text{CH}_2-\text{CH}_2-\text{S}-\text{PEP}$ Thioether Linkage
$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-\text{CH}_2-\text{SH}$ mPEG Thiol Reagent	$\text{H}_3\text{C}-(\text{OCH}_2\text{CH}_2)_n-\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-\text{CH}_2-\text{S}-\text{S}-\text{PEP}$ Disulfide Linkage
$\text{HS}-\text{CH}_2\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2-\text{SH}$ Homobifunctional PEG Thiol Reagent	$\text{PEP}-\text{S}-\text{S}-\text{CH}_2\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_n-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2-\text{S}-\text{S}-\text{PEP}$ Disulfide Linkages
$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-\text{S}-\text{C}_5\text{H}_4\text{N}$ mPEG Disulfide Reagent	$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-\text{S}-\text{PEP}$ Disulfide Linkage
$\text{C}_5\text{H}_4\text{N}-\text{S}-\text{S}-\text{CH}_2\text{CH}_2-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-\text{S}-\text{C}_5\text{H}_4\text{N}$ Homobifunctional PEG Disulfide Reagent	$\text{PEP}-\text{S}-\text{S}-\text{CH}_2\text{CH}_2-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-\text{S}-\text{PEP}$ Disulfide Linkages

[00179] With respect to conjugates formed from water-soluble polymers bearing one or more maleimide functional groups (regardless of whether the maleimide reacts with an amine or thiol group on the therapeutic peptide), the corresponding maleamic acid form(s) of the water-soluble polymer can also react with the therapeutic peptide. Under certain conditions (e.g., a pH of about 7-9 and in the presence of water), the maleimide ring will "open" to form the corresponding maleamic acid. The maleamic acid, in turn, can react with an amine or thiol group of a therapeutic peptide. Exemplary maleamic acid-based reactions are schematically

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shown below. POLY represents the water-soluble polymer, and ~S-PEP represents a residue of a therapeutic peptide, where the S is derived from a thiol group of the therapeutic peptide.



[00180] Thiol PEGylation is specific for free thiol groups on the therapeutic peptide. Typically, a polymer maleimide is conjugated to a sulfhydryl-containing therapeutic peptide at pHs ranging from about 6-9 (*e.g.*, at 6, 6.5, 7, 7.5, 8, 8.5, or 9), more preferably at pHs from about 7-9, and even more preferably at pHs from about 7 to 8. Generally, a slight molar excess of polymer maleimide is employed, for example, a 1.5 to 15-fold molar excess, preferably a 2-fold to 10 fold molar excess. Reaction times generally range from about 15 minutes to several hours, *e.g.*, 8 or more hours, at room temperature. For sterically hindered sulfhydryl groups, required reaction times may be significantly longer. Thiol-selective conjugation is preferably conducted at pHs around 7. Temperatures for conjugation reactions are typically, although not necessarily, in the range of from about 0 °C to about 40 °C; conjugation is often carried out at room temperature or less. Conjugation reactions are often carried out in a buffer such as a phosphate or acetate buffer or similar system.

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[00181] With respect to reagent concentration, an excess of the polymeric reagent is typically combined with the therapeutic peptide. The conjugation reaction is allowed to proceed until substantially no further conjugation occurs, which can generally be determined by monitoring the progress of the reaction over time.

[00182] Progress of the reaction can be monitored by withdrawing aliquots from the reaction mixture at various time points and analyzing the reaction mixture by SDS-PAGE or MALDI-TOF mass spectrometry or any other suitable analytical method. Once a plateau is reached with respect to the amount of conjugate formed or the amount of unconjugated polymer remaining, the reaction is assumed to be complete. Typically, the conjugation reaction takes anywhere from minutes to several hours (*e.g.*, from 5 minutes to 24 hours or more). The resulting product mixture is preferably, but not necessarily purified, to separate out excess reagents, unconjugated reactants (*e.g.*, therapeutic peptide) undesired multi-conjugated species, and free or unreacted polymer. The resulting conjugates can then be further characterized using analytical methods such as MALDI, capillary electrophoresis, gel electrophoresis, and/or chromatography.

[00183] An illustrative therapeutic peptide conjugate formed by reaction with one or more therapeutic peptide thiol groups may possess the following structure:



where POLY is a water-soluble polymer, X is an optional linker, Z is a heteroatom selected from the group consisting of O, NH, and S, and Y is selected from the group consisting of C₂₋₁₀ alkyl, C₂₋₁₀ substituted alkyl, aryl, and substituted aryl, and -S-PEP is a residue of a therapeutic peptide, where the S represents the residue of a therapeutic peptide thiol group. Such polymeric reagents suitable for reaction with a therapeutic peptide to result in this type of conjugate are described in U.S. Patent Application Publication No. 2005/0014903.

[00184] With respect to polymeric reagents suitable for reacting with a therapeutic peptide thiol group, those described here and elsewhere can be obtained from commercial sources. In addition, methods for preparing polymeric reagents are described in the literature.

Additional Conjugates and Features Thereof

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[00185] As is the case for any therapeutic peptide polymer conjugate of the invention, the attachment between the therapeutic peptide and water-soluble polymer can be direct, wherein no intervening atoms are located between the therapeutic peptide and the polymer, or indirect, wherein one or more atoms are located between the therapeutic peptide and polymer. With respect to the indirect attachment, a "spacer moiety or linker" serves as a link between the therapeutic peptide and the water-soluble polymer. The one or more atoms making up the spacer moiety can include one or more of carbon atoms, nitrogen atoms, sulfur atoms, oxygen atoms, and combinations thereof. The spacer moiety can comprise an amide, secondary amine, carbamate, thioether, and/or disulfide group. Nonlimiting examples of specific spacer moieties (including "X", X^1 , X^2 , and X^3) include those selected from the group consisting of -O-, -S-, -S-S-, -C(O)-, -C(O)O-, -OC(O)-, -CH₂-C(O)O-, -CH₂-OC(O)-, -C(O)O-CH₂-, -OC(O)-CH₂-, -C(O)-NH-, -NH-C(O)-NH-, -O-C(O)-NH-, -C(S)-, -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -O-CH₂-, -CH₂-O-, -O-CH₂-CH₂-, -CH₂-O-CH₂-, -CH₂-CH₂-O-, -O-CH₂-CH₂-CH₂-, -CH₂-O-CH₂-CH₂-, -CH₂-CH₂-O-CH₂-, -CH₂-CH₂-CH₂-O-, -O-CH₂-CH₂-CH₂-CH₂-, -CH₂-O-CH₂-CH₂-CH₂-, -CH₂-CH₂-O-CH₂-CH₂-, -CH₂-CH₂-CH₂-O-CH₂-, -CH₂-CH₂-CH₂-CH₂-O-, -C(O)-NH-CH₂-, -C(O)-NH-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-, -CH₂-CH₂-C(O)-NH-, -C(O)-NH-CH₂-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-CH₂-C(O)-NH-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-, -C(O)-NH-CH₂-CH₂-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-CH₂-CH₂-, -CH₂-CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-C(O)-NH-, -C(O)-O-CH₂-, -CH₂-C(O)-O-CH₂-, -CH₂-CH₂-C(O)-O-CH₂-, -C(O)-O-CH₂-CH₂-, -NH-C(O)-CH₂-, -CH₂-NH-C(O)-CH₂-, -CH₂-CH₂-NH-C(O)-CH₂-, -NH-C(O)-CH₂-CH₂-, -CH₂-NH-C(O)-CH₂-CH₂-, -CH₂-CH₂-NH-C(O)-CH₂-CH₂-, -C(O)-NH-CH₂-, -C(O)-NH-CH₂-CH₂-, -O-C(O)-NH-CH₂-, -O-C(O)-NH-CH₂-CH₂-, -NH-CH₂-, -NH-CH₂-CH₂-, -CH₂-NH-CH₂-, -CH₂-CH₂-NH-CH₂-, -C(O)-CH₂-, -C(O)-CH₂-CH₂-, -CH₂-C(O)-CH₂-, -CH₂-CH₂-C(O)-CH₂-, -CH₂-CH₂-C(O)-CH₂-CH₂-, -CH₂-CH₂-C(O)-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-C(O)-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-C(O)-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-C(O)-CH₂-CH₂-, -O-C(O)-NH-[CH₂]_h-(OCH₂CH₂)_j-, bivalent cycloalkyl group, -O-, -S-, an amino acid, -N(R⁶)-, and combinations of two or more of

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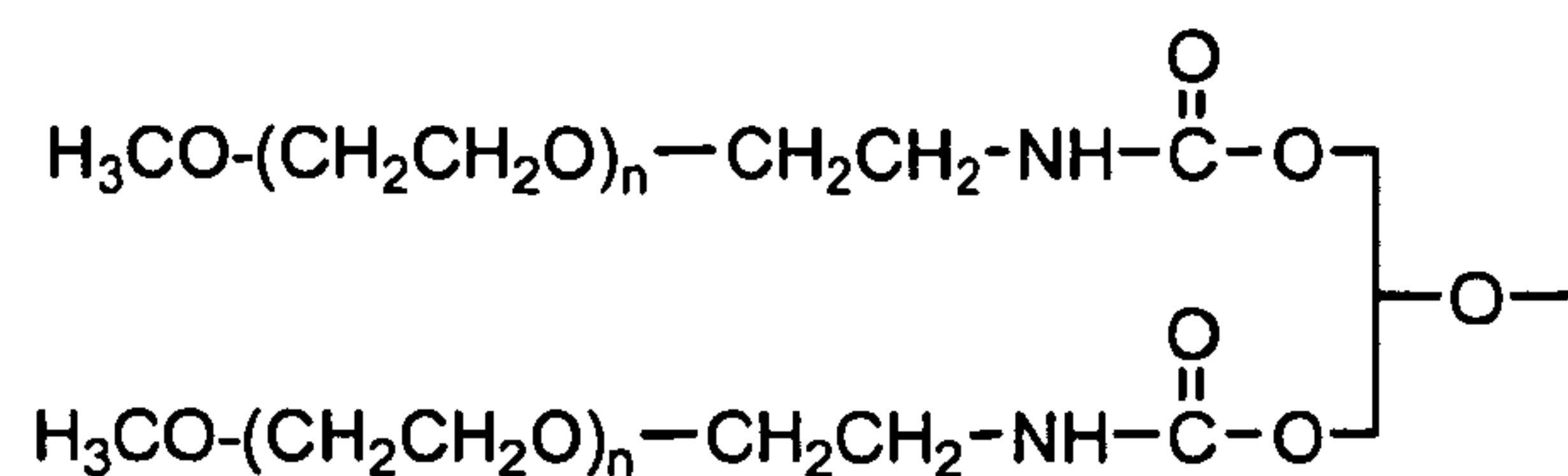
any of the foregoing, wherein R^6 is H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl and substituted aryl, (h) is zero to six, and (j) is zero to 20. Other specific spacer moieties have the following structures: $-C(O)-NH-(CH_2)_{1-6}-NH-C(O)-$, $-NH-C(O)-NH-(CH_2)_{1-6}-NH-C(O)-$, and $-O-C(O)-NH-(CH_2)_{1-6}-NH-C(O)-$, wherein the subscript values following each methylene indicate the number of methylenes contained in the structure, e.g., $(CH_2)_{1-6}$ means that the structure can contain 1, 2, 3, 4, 5 or 6 methylenes. Additionally, any of the above spacer moieties may further include an ethylene oxide oligomer chain comprising 1 to 20 ethylene oxide monomer units [*i.e.*, $-(CH_2CH_2O)_{1-20}$]. That is, the ethylene oxide oligomer chain can occur before or after the spacer moiety, and optionally in between any two atoms of a spacer moiety comprised of two or more atoms. Also, the oligomer chain would not be considered part of the spacer moiety if the oligomer is adjacent to a polymer segment and merely represent an extension of the polymer segment.

[00186] As indicated above, in some instances the water-soluble polymer-(PEP) conjugate will include a non-linear water-soluble polymer. Such a non-linear water-soluble polymer encompasses a branched water-soluble polymer (although other non linear water-soluble polymers are also contemplated). Thus, in one or more embodiments of the invention, the conjugate comprises a therapeutic peptide covalently attached, either directly or through a spacer moiety comprised of one or more atoms, to a branched water-soluble polymer, at in a non-limiting example, an internal or *N*-terminal amine. As used herein, an internal amine is an amine that is not part of the *N*-terminal amino acid (meaning not only the *N*-terminal amine, but any amine on the side chain of the *N*-terminal amino acid).

[00187] Although such conjugates include a branched water-soluble polymer attached (either directly or through a spacer moiety) to a therapeutic peptide at an internal amino acid of the therapeutic peptide, additional branched water-soluble polymers can also be attached to the same therapeutic peptide at other locations as well. Thus, for example, a conjugate including a branched water-soluble polymer attached (either directly or through a spacer moiety) to a therapeutic peptide at an internal amino acid of the therapeutic peptide, can further include an additional branched water-soluble polymer covalently attached, either directly or through a spacer moiety comprised of one or more atoms, to the *N*-terminal amino acid residue, such as at the *N*-terminal amine.

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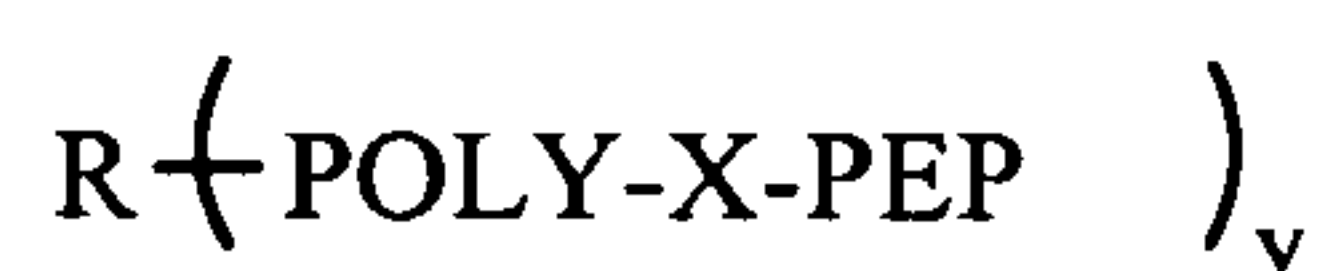
[00188] One preferred branched water-soluble polymer comprises the following structure:



wherein each (n) is independently an integer having a value of from 3 to 4000, or more preferably, from about 10 to 1800.

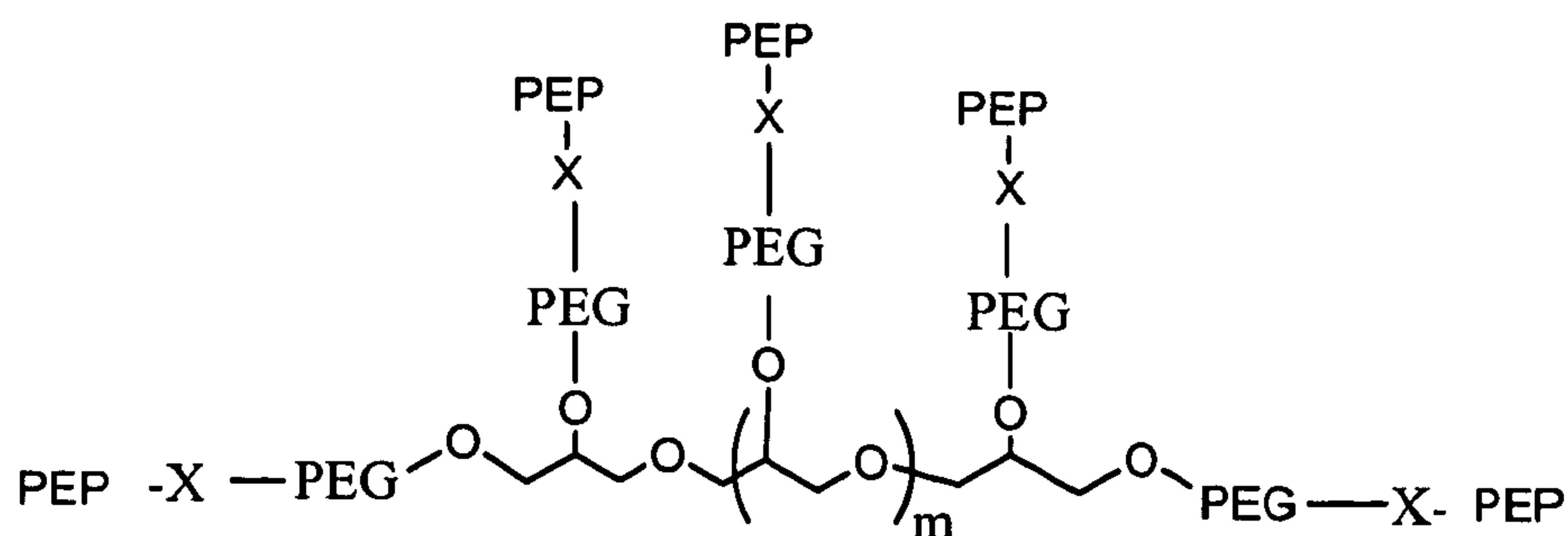
[00189] Also forming part of the invention are multi-armed polymer conjugates comprising a polymer scaffold having 3 or more polymer arms each suitable for capable of covalent attachment of a therapeutic peptide.

Exemplary conjugates in accordance with this embodiment of the invention will generally comprise the following structure:



wherein R is a core molecule as previously described, POLY is a water-soluble polymer, X is a cleavable, *e.g.*, hydrolyzable linkage, and y ranges from about 3 to 15.

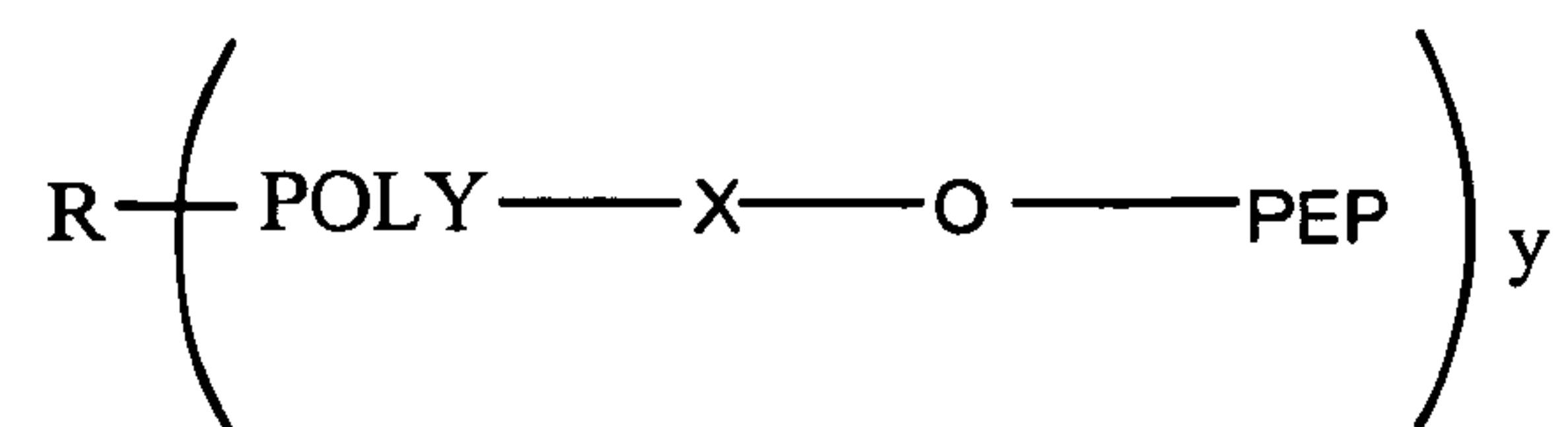
[00190] More particularly, such a conjugate may comprise the structure:



where m is selected from 3, 4, 5, 6, 7, and 8.

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[00191] In yet a related embodiment, the therapeutic peptide conjugate may correspond to the structure:



where R is a core molecule as previously described, X is -NH-P-Z-C(O) P is a spacer, Z is -O-, -NH-, or -CH₂-, -O-PEP is a hydroxyl residue of a therapeutic peptide, and y is 3 to 15. Preferably, X is a residue of an amino acid.

Purification

[00192] The therapeutic peptide polymer conjugates described herein can be purified to obtain/isolate different conjugate species. Specifically, a product mixture can be purified to obtain an average of anywhere from one, two, or three or even more PEGs per therapeutic peptide. In one embodiment of the invention, preferred therapeutic peptide conjugates are mono-conjugates. The strategy for purification of the final conjugate reaction mixture will depend upon a number of factors, including, for example, the molecular weight of the polymeric reagent employed, the therapeutic peptide, and the desired characteristics of the product – *e.g.*, monomer, dimer, particular positional isomers, etc.

[00193] If desired, conjugates having different molecular weights can be isolated using gel filtration chromatography and/or ion exchange chromatography. Gel filtration chromatography may be used to fractionate different therapeutic peptide conjugates (*e.g.*, 1-mer, 2-mer, 3-mer, and so forth, wherein "1-mer" indicates one polymer molecule per therapeutic peptide, "2-mer" indicates two polymers attached to therapeutic peptide, and so on) on the basis of their differing molecular weights (where the difference corresponds essentially to the average molecular weight of the water-soluble polymer). While this approach can be used to separate PEG and other therapeutic peptide polymer conjugates having different molecular weights, this approach is generally ineffective for separating positional isomers having different polymer attachment sites within the therapeutic peptide. For example, gel filtration chromatography can be used to

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separate from each other mixtures of PEG 1-mers, 2-mers, 3-mers, and so forth, although each of the recovered PEG-mer compositions may contain PEGs attached to different reactive amino groups (*e.g.*, lysine residues) or other functional groups of the therapeutic peptide.

[00194] Gel filtration columns suitable for carrying out this type of separation include Superdex™ and Sephadex™ columns available from Amersham Biosciences (Piscataway, NJ). Selection of a particular column will depend upon the desired fractionation range desired. Elution is generally carried out using a suitable buffer, such as phosphate, acetate, or the like. The collected fractions may be analyzed by a number of different methods, for example, (i) optical density (OD) at 280 nm for protein content, (ii) bovine serum albumin (BSA) protein analysis, (iii) iodine testing for PEG content (Sims *et al.* (1980) *Anal. Biochem.*, 107:60-63), and (iv) sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE), followed by staining with barium iodide.

[00195] Separation of positional isomers is typically carried out by reverse phase chromatography using a reverse phase-high performance liquid chromatography (RP-HPLC) C18 column (Amersham Biosciences or Vydac) or by ion exchange chromatography using an ion exchange column, *e.g.*, a DEAE- or CM-Sepharose™ ion exchange column available from Amersham Biosciences. Either approach can be used to separate polymer-therapeutic peptide isomers having the same molecular weight (positional isomers).

[00196] The resulting purified compositions are preferably substantially free of the non-conjugated therapeutic peptide. In addition, the compositions preferably are substantially free of all other non-covalently attached water-soluble polymers.

Compositions

Compositions of conjugate isomers

[00197] Also provided herein are compositions comprising any one or more of the therapeutic peptide polymer conjugates described herein. In certain instances, the composition will comprise a plurality of therapeutic peptide polymer conjugates. For instance, such a composition may comprise a mixture of therapeutic peptide polymer conjugates having one, two, three and/or even four water-soluble polymer molecules covalently attached to sites on the therapeutic peptide. That is to say, a composition of the invention may comprise a mixture of

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monomer, dimer, and possibly even trimer or 4-mer. Alternatively, the composition may possess only mono-conjugates, or only di-conjugates, etc. A mono-conjugate therapeutic peptide composition will typically comprise therapeutic peptide moieties having only a single polymer covalently attached thereto, e.g., preferably releasably attached. A mono-conjugate composition may comprise only a single positional isomer, or may comprise a mixture of different positional isomers having polymer covalently attached to different sites within the therapeutic peptide.

[00198] In yet another embodiment, a therapeutic peptide conjugate may possess multiple therapeutic peptides covalently attached to a single multi-armed polymer having 3 or more polymer arms. Typically, the therapeutic peptide moieties are each attached at the same therapeutic peptide amino acid site, e.g., the N-terminus.

[00199] With respect to the conjugates in the composition, the composition will typically satisfy one or more of the following characteristics: at least about 85% of the conjugates in the composition will have from one to four polymers attached to the therapeutic peptide; at least about 85% of the conjugates in the composition will have from one to three polymers attached to the therapeutic peptide; at least about 85% of the conjugates in the composition will have from one to two polymers attached to the therapeutic peptide; or at least about 85% of the conjugates in the composition will have one polymer attached to the therapeutic peptide (e.g., be monoPEGylated); at least about 95% of the conjugates in the composition will have from one to four polymers attached to the therapeutic peptide; at least about 95% of the conjugates in the composition will have from one to three polymers attached to the therapeutic peptide; at least about 95% of the conjugates in the composition will have from one to two polymers attached to the therapeutic peptide; at least about 95% of the conjugates in the composition will have one polymers attached to the therapeutic peptide; at least about 99% of the conjugates in the composition will have from one to four polymers attached to the therapeutic peptide; at least about 99% of the conjugates in the composition will have from one to three polymers attached to the therapeutic peptide; at least about 99% of the conjugates in the composition will have from one to two polymers attached to the therapeutic peptide; and at least about 99% of the conjugates in the composition will have one polymer attached to the therapeutic peptide (e.g., be monoPEGylated).

[00200] In one or more embodiments, the conjugate-containing composition is free or substantially free of albumin.

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[00201] In one or more embodiments of the invention, a pharmaceutical composition is provided comprising a conjugate comprising a therapeutic peptide covalently attached, *e.g.*, releasably, to a water-soluble polymer, wherein the water-soluble polymer has a weight-average molecular weight of greater than about 2,000 Daltons; and a pharmaceutically acceptable excipient.

[00202] Control of the desired number of polymers for covalent attachment to therapeutic peptide is achieved by selecting the proper polymeric reagent, the ratio of polymeric reagent to the Therapeutic peptide, temperature, pH conditions, and other aspects of the conjugation reaction. In addition, reduction or elimination of the undesired conjugates (*e.g.*, those conjugates having four or more attached polymers) can be achieved through purification mean as previously described.

[00203] For example, the water-soluble polymer-(therapeutic peptide) conjugates can be purified to obtain/isolate different conjugated species. Specifically, the product mixture can be purified to obtain an average of anywhere from one, two, three, or four PEGs per therapeutic peptide, typically one, two or three PEGs per therapeutic peptide. In one or more embodiments, the product comprises one PEG per therapeutic peptide, where PEG is releasably (via hydrolysis) attached to PEG polymer, *e.g.*, a branched or straight chain PEG polymer.

Pharmaceutical Compositions

[00204] Optionally, a therapeutic peptide conjugate composition of the invention will comprise, in addition to the therapeutic peptide conjugate, a pharmaceutically acceptable excipient. More specifically, the composition may further comprise excipients, solvents, stabilizers, membrane penetration enhancers, etc., depending upon the particular mode of administration and dosage form.

[00205] Pharmaceutical compositions of the invention encompass all types of formulations and in particular those that are suited for injection, *e.g.*, powders or lyophilates that can be reconstituted as well as liquids, as well as for inhalation. Examples of suitable diluents for reconstituting solid compositions prior to injection include bacteriostatic endotoxin-free water for injection, dextrose 5% in water, phosphate-buffered saline, Ringer's solution, saline, sterile water, deionized water, and combinations thereof. With respect to liquid pharmaceutical compositions, solutions and suspensions are envisioned.

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[00206] Exemplary pharmaceutically acceptable excipients include, without limitation, carbohydrates, inorganic salts, antimicrobial agents, antioxidants, surfactants, buffers, acids, bases, and combinations thereof.

[00207] Representative carbohydrates for use in the compositions of the present invention include sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers. Exemplary carbohydrate excipients suitable for use in the present invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like. Preferred, in particular for formulations intended for inhalation, are non-reducing sugars, sugars that can form a substantially dry amorphous or glassy phase when combined with the composition of the present invention, and sugars possessing relatively high glass transition temperatures, or Tgs (*e.g.*, Tgs greater than 40°C, or greater than 50°C, or greater than 60°C, or greater than 70°C, or having Tgs of 80°C and above). Such excipients may be considered glass-forming excipients.

[00208] Additional excipients include amino acids, peptides and particularly oligomers comprising 2-9 amino acids, or 2-5 mers, and polypeptides, all of which may be homo or hetero species.

[00209] Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. The compositions may also include a buffer or a pH-adjusting agent, typically but not necessarily a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid. Other suitable buffers include Tris, tromethamine hydrochloride, borate, glycerol phosphate, and phosphate. Amino acids such as glycine are also suitable.

[00210] The compositions of the present invention may also include one or more additional polymeric excipients/additives, *e.g.*, polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, FICOLLs (a polymeric sugar), hydroxyethylstarch (HES), dextrates (*e.g.*, cyclodextrins, such as

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2-hydroxypropyl- β -cyclodextrin and sulfobutylether- β -cyclodextrin), polyethylene glycols, and pectin.

[00211] The compositions may further include flavoring agents, taste-masking agents, inorganic salts (*e.g.*, sodium chloride), antimicrobial agents (*e.g.*, benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (*e.g.*, polysorbates such as "TWEEN 20" and "TWEEN 80," and pluronics such as F68 and F88, available from BASF), sorbitan esters, lipids (*e.g.*, phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines, although preferably not in liposomal form), fatty acids and fatty esters, steroids (*e.g.*, cholesterol), and chelating agents (*e.g.*, zinc and other such suitable cations). The use of certain di-substituted phosphatidylcholines for producing perforated microstructures (*i.e.*, hollow, porous microspheres) may also be employed.

[00212] Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the present invention are listed in "Remington: The Science & Practice of Pharmacy," 21st ed., Williams & Williams, (2005), and in the "Physician's Desk Reference," 60th ed., Medical Economics, Montvale, N.J. (2006).

[00213] The amount of the therapeutic peptide conjugate (*i.e.*, the conjugate formed between the active agent and the polymeric reagent) in the composition will vary depending on a number of factors, but will optimally be a therapeutically effective amount when the composition is stored in a unit dose container (*e.g.*, a vial). In addition, a pharmaceutical preparation, if in solution form, can be housed in a syringe. A therapeutically effective amount can be determined experimentally by repeated administration of increasing amounts of the conjugate in order to determine which amount produces a clinically desired endpoint.

[00214] The amount of any individual excipient in the composition will vary depending on the activity of the excipient and particular needs of the composition. Typically, the optimal amount of any individual excipient is determined through routine experimentation, *i.e.*, by preparing compositions containing varying amounts of the excipient (ranging from low to high), examining the stability and other parameters, and then determining the range at which optimal performance is attained with no significant adverse effects.

[00215] Generally, however, the excipient or excipients will be present in the composition in an amount of about 1% to about 99% by weight, from about 5% to about 98% by weight, from about 15 to about 95% by weight of the excipient, or with concentrations less than 30% by

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weight. In general, a high concentration of the therapeutic peptide is desired in the final pharmaceutical formulation.

Combination of Actives

[00216] A composition of the invention may also comprise a mixture of water-soluble polymer-(therapeutic peptide) conjugates and unconjugated therapeutic peptide, to thereby provide a mixture of fast-acting and long-acting therapeutic peptide.

[00217] Additional pharmaceutical compositions in accordance with the invention include those comprising, in addition to an extended-action therapeutic peptide water-soluble polymer conjugate as described herein, a rapid acting therapeutic peptide polymer conjugate where the water-soluble polymer is releasably attached to a suitable location on the therapeutic peptide.

Administration

[00218] The therapeutic peptide conjugates of the invention can be administered by any of a number of routes including without limitation, oral, rectal, nasal, topical (including transdermal, aerosol, buccal and sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous and intradermal), intrathecal, and pulmonary. Preferred forms of administration include parenteral and pulmonary. Suitable formulation types for parenteral administration include ready-for-injection solutions, dry powders for combination with a solvent prior to use, suspensions ready for injection, dry insoluble compositions for combination with a vehicle prior to use, and emulsions and liquid concentrates for dilution prior to administration, among others.

[00219] In some embodiments of the invention, the compositions comprising the peptide-polymer conjugates may further be incorporated into a suitable delivery vehicle. Such delivery vehicles may provide controlled and/or continuous release of the conjugates and may also serve as a targeting moiety. Non-limiting examples of delivery vehicles include, adjuvants, synthetic adjuvants, microcapsules, microparticles, liposomes, and yeast cell wall particles. Yeast cells walls may be variously processed to selectively remove protein component, glucan, or mannan layers, and are referred to as whole glucan particles (WGP), yeast beta-glucan mannan particles (YGMP), yeast glucan particles (YGP), \Rhodotorula yeast cell particles (YCP). Yeast cells

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such as *S.cerevisiae* and *Rhodotorula* sp. are preferred; however, any yeast cell may be used. These yeast cells exhibit different properties in terms of hydrodynamic volume and also differ in the target organ where they may release their contents. The methods of manufacture and characterization of these particles are described in US Patent Nos. 5,741,495; 4,810,646; 4,992,540; 5,028,703; 5,607,677, and US Patent Applications Nos. 2005/0281781, and 2008/0044438.

[00220] In one or more embodiments of the invention, a method is provided, the method comprising delivering a conjugate to a patient, the method comprising the step of administering to the patient a pharmaceutical composition comprising a therapeutic peptide polymer conjugate as provided herein. Administration can be effected by any of the routes herein described. The method may be used to treat a patient suffering from a condition that is responsive to treatment with therapeutic peptide by administering a therapeutically effective amount of the pharmaceutical composition.

[00221] As previously stated, the method of delivering a therapeutic peptide polymer conjugate as provided herein may be used to treat a patient having a condition that can be remedied or prevented by administration of therapeutic peptide.

[00222] Certain conjugates of the invention, *e.g.*, releasable conjugates, include those effective to release the therapeutic peptide, *e.g.*, by hydrolysis, over a period of several hours or even days (*e.g.*, 2-7 days, 2-6 days, 3-6 days, 3-4 days) when evaluated in a suitable *in-vivo* model.

[00223] The actual dose of the therapeutic peptide conjugate to be administered will vary depending upon the age, weight, and general condition of the subject as well as the severity of the condition being treated, the judgment of the health care professional, and conjugate being administered. Therapeutically effective amounts are known to those skilled in the art and/or are described in the pertinent reference texts and literature. Generally, a conjugate of the invention will be delivered such that plasma levels of a therapeutic peptide are within a range of about 0.5 picomoles/liter to about 500 picomoles/liter. In certain embodiments the conjugate of the invention will be delivered such that plasma levels of a therapeutic peptide are within a range of about 1 picomoles/liter to about 400 picomoles/liter, a range of about 2.5 picomoles/liter to about 250 picomoles/liter, a range of about 5 picomoles/liter to about 200 picomoles/liter, or a range of about 10 picomoles/liter to about 100 picomoles/liter.

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[00224] On a weight basis, a therapeutically effective dosage amount of a therapeutic peptide conjugate as described herein will range from about 0.01 mg per day to about 1000 mg per day for an adult. For example, dosages may range from about 0.1 mg per day to about 100 mg per day, or from about 1.0 mg per day to about 10 mg/day. On an activity basis, corresponding doses based on international units of activity can be calculated by one of ordinary skill in the art.

[00225] The unit dosage of any given conjugate (again, such as provided as part of a pharmaceutical composition) can be administered in a variety of dosing schedules depending on the judgment of the clinician, needs of the patient, and so forth. The specific dosing schedule will be known by those of ordinary skill in the art or can be determined experimentally using routine methods. Exemplary dosing schedules include, without limitation, administration five times a day, four times a day, three times a day, twice daily, once daily, three times weekly, twice weekly, once weekly, twice monthly, once monthly, and any combination thereof. Once the clinical endpoint has been achieved, dosing of the composition is halted.

[00226] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, the foregoing description as well as the examples that follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

[00227]

EXPERIMENTAL

[00228] The practice of the invention will employ, unless otherwise indicated, conventional techniques of organic synthesis and the like, which are within the skill of the art. Such techniques are fully explained in the literature. Reagents and materials are commercially available unless specifically stated to the contrary. See, for example, J. March, *Advanced Organic Chemistry: Reactions Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience, 1992), *supra*.

[00229] In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.) but some experimental error and

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deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C and pressure is at or near atmospheric pressure at sea level.

[00230] Although other abbreviations known by one having ordinary skill in the art will be referenced, other reagents and materials will be used, and other methods known by one having ordinary skill in the art will be used, the following list and methods description is provided for the sake of convenience.

Abbreviations

mPEG-SPA	mPEG-succinimidyl propionate
mPEG-SBA	mPEG-succinimidyl butanoate
mPEG-SPC	mPEG-succinimidyl phenyl carbonate
mPEG-OPSS	mPEG-orthopyridyl-disulfide
mPEG-MAL	mPEG-maleimide, $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{MAL}$
mPEG-SMB	mPEG-succinimidyl α -methylbutanoate, $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{CH}(\text{CH}_3)-\text{C}(\text{O})-\text{O}-\text{succinimide}$
mPEG-ButyrALD	$\text{H}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_4-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{H}$
mPEG-PIP	$\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{C}(\text{O})-\text{piperidin-4-one}$
mPEG-CM	$\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{OH}$
anh.	Anhydrous
CV	column volume
Fmoc	9-fluorenylmethoxycarbonyl
NaCNBH_3	sodium cyanoborohydride
HCl	hydrochloric acid
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
NMR	nuclear magnetic resonance
DCC	1,3-dicyclohexylcarbodiimide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DI	deionized
MW	molecular weight
K or kDa	kilodaltons

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SEC	Size exclusion chromatography
HPLC	high performance liquid chromatography
FPLC	fast protein liquid chromatography
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
MALDI-TOF	Matrix Assisted Laser Desorption Ionization Time-of-Flight
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran

Materials

[00231] All PEG reagents referred to in the appended examples are commercially available unless otherwise indicated.

mPEG reagent preparation

[00232] Typically, a water-soluble polymer reagent is used in the preparation of peptide conjugates of the invention. For purposes of the present invention, a water-soluble polymer reagent is a water-soluble polymer-containing compound having at least one functional group that can react with a functional group on a peptide (*e.g.*, the *N*-terminus, the *C*-terminus, a functional group associated with the side chain of an amino acid located within the peptide) to create a covalent bond. Taking into account the known reactivity of the functional group(s) associated with the water-soluble polymer reagent, it is possible for one of ordinary skill in the art to determine whether a given water-soluble polymer reagent will form a covalent bond with the functional group(s) of a peptide.

[00233] Representative polymeric reagents and methods for conjugating such polymers to an active moiety are known in the art, and are, *e.g.*, described in Harris, J.M. and Zalipsky, S., eds, *Poly(ethylene glycol), Chemistry and Biological Applications*, ACS, Washington, 1997; Veronese, F., and J.M Harris, eds., *Peptide and Protein PEGylation*, Advanced Drug Delivery Reviews, 54(4); 453-609 (2002); Zalipsky, S., *et al.*, "Use of Functionalized Poly(Ethylene Glycols) for Modification of Polypeptides" in *Polyethylene Glycol Chemistry: Biotechnical and Biomedical Applications*, J. M. Harris, ed., Plenus Press, New York (1992); Zalipsky (1995) *Advanced Drug Reviews* 16:157-182, and in Roberts, *et al.*, *Adv. Drug Delivery Reviews*, 54, 459-476 (2002).

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[00234] Additional PEG reagents suitable for use in forming a conjugate of the invention, and methods of conjugation are described in Shearwater Corporation, Catalog 2001; Shearwater Polymers, Inc., Catalogs, 2000 and 1997-1998, and in Pasut. G., et al., *Expert Opin. Ther. Patents* (2004), 14(5). PEG reagents suitable for use in the present invention also include those available from NOF Corporation (Tokyo, Japan), as described generally on the NOF website (2006) under Products, High Purity PEGs and Activated PEGs.

Additional PEGs for use in forming a GLP-1 conjugate of the invention include those available from Polypure (Norway) and from QuantaBioDesign LTD (Powell, Ohio).

[00235] In addition, water-soluble polymer reagents useful for preparing peptide conjugates of the invention is prepared synthetically. Descriptions of the water-soluble polymer reagent synthesis can be found in, for example, U.S. Patent Nos. 5,252,714, 5,650,234, 5,739,208, 5,932,462, 5,629,384, 5,672,662, 5,990,237, 6,448,369, 6,362,254, 6,495,659, 6,413,507, 6,376,604, 6,348,558, 6,602,498, and 7,026,440.

Example 1

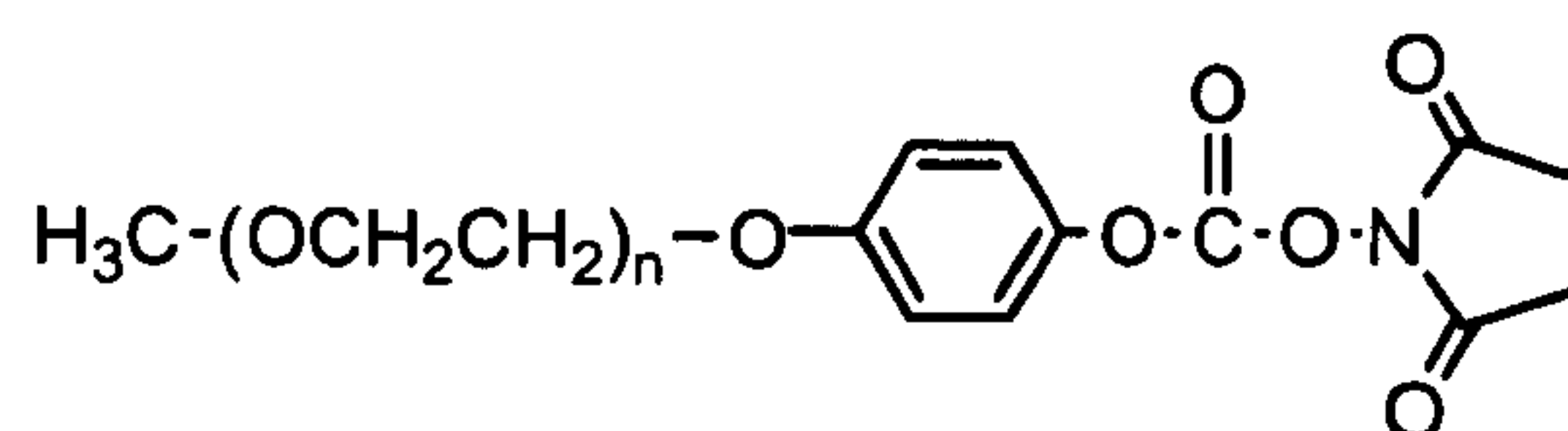
Peptide G-mPEG conjugates

[00236] Peptide G is an amino acid synthetic peptide containing residues 161-189 of the 40 kDa laminin binding domain of 67LR, which has been found to inhibit laminin-coated melanoma cells from attaching to endothelial cells that express the 67 kDa laminin receptor (Gastronovo *et al.*, *J. Biol. Chem.* **1991**, 266, 20440-6. The 20 amino acid sequence is Ile-Pro-Cys-Asn-Asn-Lys-Gly-Ala-His-Ser-Val-Gly-Leu-Met-Trp-Trp-Met-Leu-Ala-Arg, has been proposed as potential new antimetastatic agent. (Gastronovo *et al.*, *Cancer Res.* **1991**, 51, 5672-8).

a) mPEG-N^{ter}-Peptide G via mPEG-SPC

[00237] Peptide G is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent,

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'SPC' polymer reagent

is covalently attached to the N-terminus of Peptide G, to provide a N^{ter} -conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20°C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Peptide G prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG- N^{ter} -Peptide G conjugate formation.

[00238] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Peptide G - C^{ter} -mPEG

[00239] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Peptide G, to provide a C^{ter} -conjugate form of the peptide. For coupling to the C-terminus, a protected Peptide G (Prot-Peptide G, *e.g.*, Fmoc-Ile-Pro-Cys(tBu)-Asn-Asn-Lys(Fmoc)-Gly-Ala-His-Ser(Dmab)-Val-Gly-Leu-Met-Trp-Trp-Met-Leu-Ala-Arg(Tos)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20°C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-Peptide G is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced

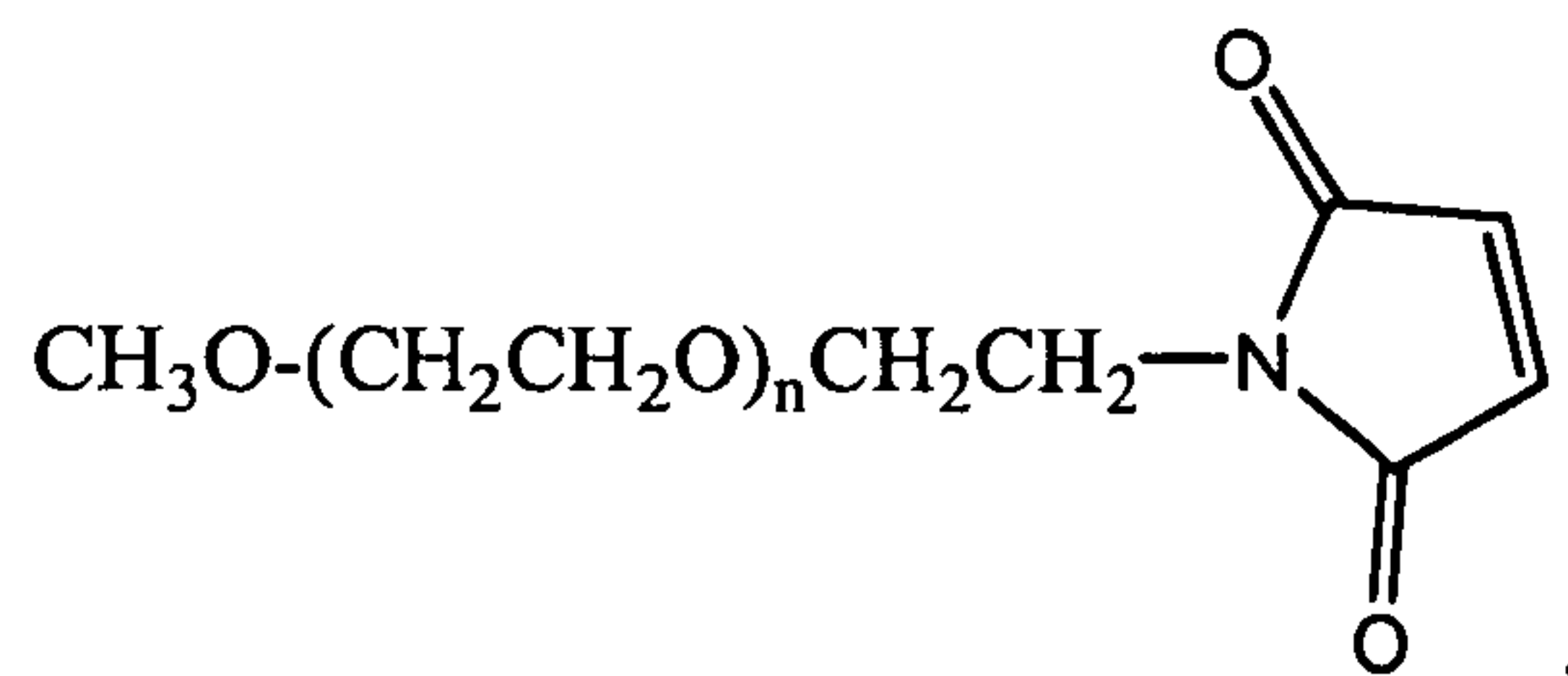
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and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-Peptide G- C^{ter} -*mPEG* conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Peptide G- C^{ter} -*mPEG* conjugate.

[00240] Using this same approach, other conjugates are prepared using *mPEG* derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Peptide G-*Cys*(*S-mPEG*)

[00241] *mPEG*-Maleimide is obtained having a molecular weight of 5 kDa and having the basic structure shown below:



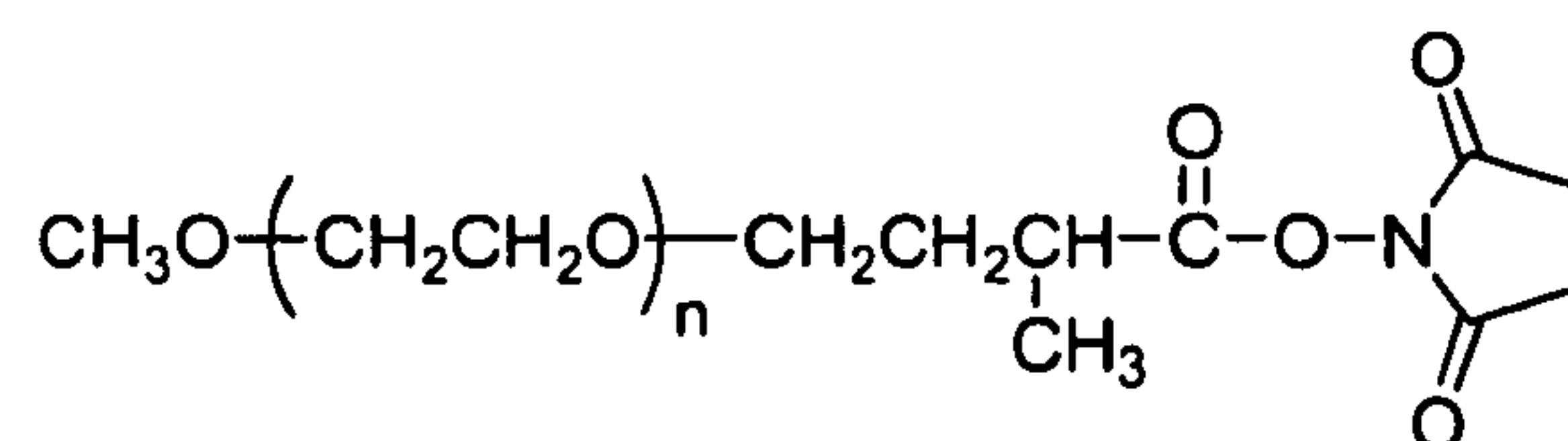
mPEG-MAL, 5kDa

[00242] Peptide G, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of *mPEG*-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00243] Using this same approach, other conjugates are prepared using *mPEG*-MAL having other weight average molecular weights.

d) *mPEG-N^{ter}*-Peptide G via *mPEG-SMB*

[00244] An *mPEG*-N-Hydroxysuccinimide is obtained having a molecular weight of 5 kDa and having the basic structure shown below:



(*mPEG*-Succinimidyl α -Methylbutanoate Derivative, 5kDa ("*mPEG*-SMB"))

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[00245] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Peptide G solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00246] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 2

OTS102-mPEG conjugates

[00247] OTS-102 is an angiogenesis inhibitor for cancer treatment consisting of KDR169, the nine amino acid sequence starting at residue 169 of VEGFR2. KDR169 activates CD8-positive CTL's in an HLA-A2402 dependent manner. Augmented CTL exerts cytotoxicity to tumor-associated neovascular endothelial cells expressing KDR (VEGF receptor), and shows anti-tumor activity (*see*, U.S. Patent Application No. 2006/216301 A1 and OncoTherapy Sciences, Inc web site. KDR169 has the sequence, Arg-Phe-Val-Pro-Asp-Gly-Asn-Arg-Ile (RFVPDGNRI) (*see*, Seq. No. 8, in US2006/216301A1).

a) mPEG-N^{ter}-OTS102 via mPEG-SPC

[00248] The 9-aa KDR169 peptide is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of KDR169, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of KDR169 prepared in phosphate buffered saline, PBS, pH 7.4 is added and the

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mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-*N*^{ter}-OTS102 conjugate formation.

[00249] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) OTS102-C^{ter}-mPEG

[00250] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of KDR169, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected KDR169 (Prot-KDR169, *e.g.*, Fmoc-Arg(Tos)-Phe-Val-Pro-Asp(OBz)-Gly-Asn-Arg(Tos)-Ile-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-KDR169 is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-KDR169-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the OTS102-C^{ter}-mPEG conjugate.

[00251] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) OTS102-Asp(O-mPEG)

[00252] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Asp residue of KDR169, to provide a Asp-conjugate form of the peptide. For coupling to the

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Asp residue, a protected KDR169 (Prot2-KDR169, *e.g.*, Fmoc-Arg(Tos)-Phe-Val-Pro-Asp(OBz)-Gly-Asn-Arg(Tos)-Ile-O(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Asp(OBz) residue (H_2/Pd) yields the free-Asp carboxylate for subsequent coupling (Prot3-KDR169, *e.g.*, Fmoc-Arg(Tos)-Phe-Val-Pro-Asp(OH)-Gly-Asn-Arg(Tos)-Ile-O(tBu)). mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-KDR169 is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-KDR169-(Asp-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the *OTS102-Asp(O-mPEG)* conjugate.

[00253] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

d) mPEG-N^{ter}-OTS102 via mPEG-SMB

[00254] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock OTS102 solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00255] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

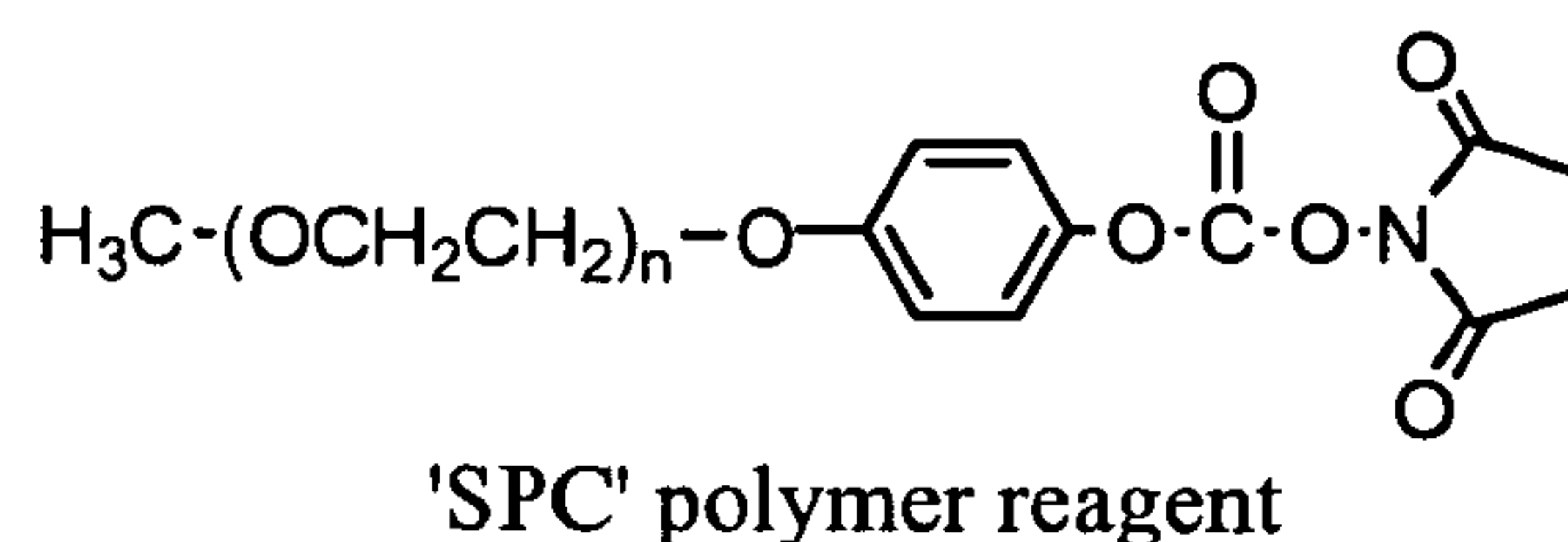
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Example 3*AngiocolTM-mPEG conjugates*

[00256] *AngiocolTM* is a recombinant protein derived from the non-collagenous domain (alpha-2) of type IV collagen, which has been shown in preclinical studies to inhibit macrovascular endothelial cell proliferation (new blood vessel growth), as well as tumour growth, in *in vitro* and *in vivo* models by targeting the assembly and organization of the vascular basal lamina. *AngiocolTM* has been proposed for the treatment of retinal neovascularization (Coleman *et al.*, *Microcirculation* **2004**, *11*, 530).

a) mPEG-N^{ter}-Angiocol via mPEG-SPC

[00257] *AngiocolTM* is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent,



is covalently attached to the N-terminus of *AngiocolTM*, to provide a *N^{ter}*-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of *AngiocolTM* prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-*N^{ter}*- *Angiocol* conjugate formation.

[00258] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

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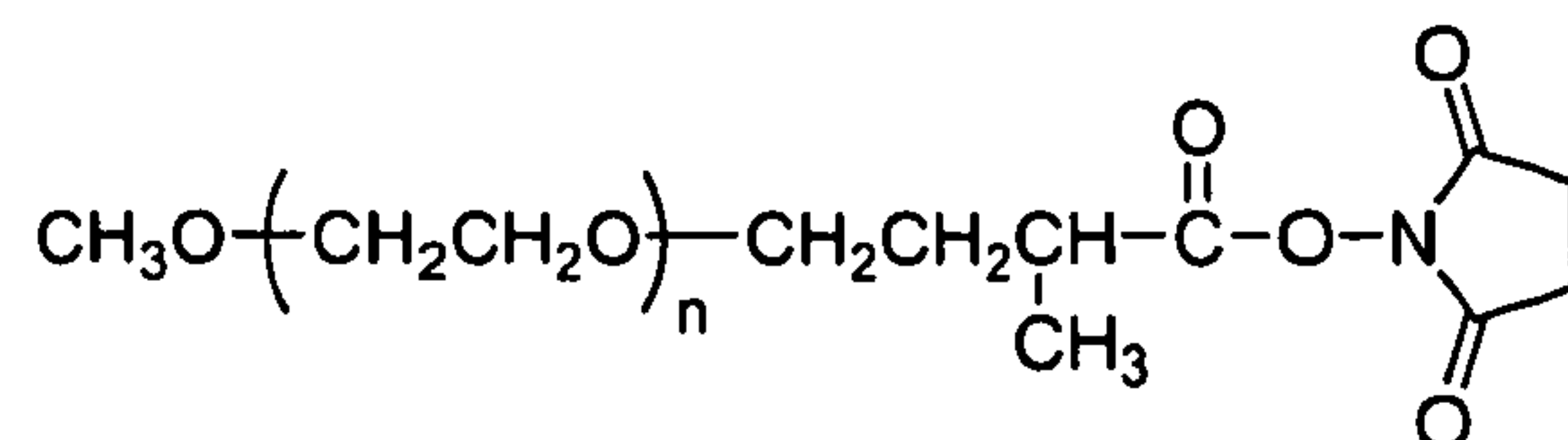
b) Angiocol -C^{ter}-mPEG

[00259] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of AngiocolTM, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected AngiocolTM (Prot- AngiocolTM) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot- AngiocolTM is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot- Angiocol-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Angiocol-C^{ter}-mPEG conjugate.

[00260] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) mPEG-N^{ter}- AngiocolTM via mPEG-SMB

[00261] An mPEG-N-Hydroxysuccinimide is obtained having a molecular weight of 5 kDa and having the basic structure shown below:



(mPEG-Succinimidyl α-Methylbutanoate Derivative, 5kDa ("mPEG-SMB"))

[00262] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock AngiocolTM solution and mixed well. After the addition

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of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00263] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 4

ABT-510 (antiangiogenic peptide group) -mPEG conjugates

[00264] ABT-510 is nonapeptide analogue that mimics the anti-angiogenic activity of the endogenous protein thrombospondin-1 (TSP-1) which is in development for treatment of advanced malignancies. ABT-510 blocks the actions of multiple pro-angiogenic growth factors known to play a role in cancer related blood vessel growth, such as VEGF, bFGF, HGF, and IL-8 (Haviv *et al.*, *J. Med. Chem.* **2005**, 48, 2838; Baker *et al.*, *J. Clin. Oncol.* **2005**, 23, 9013). In human studies, ABT-510 was found to be safe and have efficacy in phase I trials in combination regimens (Gietema *et al.*, *Ann. Oncol.* **2006**, 17, 1320-7). NAc-Sar-Gly-Val-(d-allo-Ile)-Thr-Nva-Ile-Arg-ProNEt (PubChem Substance ID: 12015488)

a) mPEG-N^{ter}-ABT-510 via mPEG-SPC

[00265] ABT-510 is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art, without the N-terminal acetyl group (NH₂-ABT-510). An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of NH₂-ABT-510, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of NH₂-ABT-510 prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured

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and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG- N^{ter} -ABT-510 conjugate formation.

[00266] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) ABT-510- C^{ter} -mPEG

[00267] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of ABT-510, to provide a C^{ter} -conjugate form of the peptide. For coupling to the C-terminus, a protected ABT-510, lacking the C-terminal ethyl amide (Prot-ABT-510, e.g., NAc-Sar(tBu)-Gly-Val-(d-allo-Ile)-Thr(tBu)-Nva-Ile-Arg(Tos)-Pro-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-ABT-510 is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-ABT-510- C^{ter} -mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the ABT-510- C^{ter} -mPEG conjugate.

[00268] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) mPEG- N^{ter} -ABT-510 via mPEG-SMB

[00269] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock NH₂-ABT-510 (as in Example 4a) solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and

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adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00270] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 5

A6-mPEG conjugates

[00271] A6 is a urokinase-derived eight amino-acid peptide, NAc-Lys-Pro-Ser-Ser-Pro-Pro-Glu-Glu-NH₂, with anti-angiogenic properties which has been shown to suppress metastases and prolong the life span of prostate tumor-bearing mice (Boyd *et al.*, *Am. J. Pathology* **2003**, 162. 619).

a) mPEG-N^{ter}-A6 via mPEG-SPC

[00272] A6 is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art, without the N-terminal acetyl group (NH₂-A6). An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of NH₂-A6, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of NH₂-A6 prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter}-A6 conjugate formation.

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[00273] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) A6-C^{ter}-mPEG

[00274] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of A6, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected A6, lacking the C-terminal amide (Prot-A6, *e.g.*, NAc-Lys(Fmoc)-Pro-Ser(tBu)-Ser(tBu)-Pro-Pro-Glu(tBu)-Glu(tBu)-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-A6 is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-A6-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the ABT-510-C^{ter}-mPEG conjugate.

[00275] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) mPEG-N^{ter}-A6 via mPEG-SMB

[00276] An mPEG-N-Hydroxysuccinimide is obtained having a molecular weight of 5 kDa and having the basic structure shown below: mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock NH₂-A6 (as in Example 4a) solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several

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hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00277] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

d) A6-Glu(O-mPEG)

[00278] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Glu residue of A6, to provide a Glu-conjugate form of the peptide. For coupling to the Glu residue, a protected A6 (Prot2-A6, *e.g.*, NAc-Lys(Fmoc)-Pro-Ser(tBu)-Ser(tBu)-Pro-Pro-Glu(OBz)-Glu(tBu)-O(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Glu(OBz) residue (H₂/Pd) yields the free-Glu carboxylate for subsequent coupling (Prot3-A6, *e.g.*, NAc-Lys(Fmoc)-Pro-Ser(tBu)-Ser(tBu)-Pro-Pro-Glu-Glu(tBu)-O(tBu)) mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-A6 is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-A6-(Glu-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the *A6-Glu(O-mPEG)* conjugate.

[00279] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

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Example 6*Islet neogenesis gene associated protein (INGAP) -mPEG conjugates*

[00280] Islet Neogenesis-Associated Protein (INGAP) is a member of the Reg family of proteins implicated in various settings of endogenous pancreatic regeneration. The expression of INGAP and other RegIII proteins has also been linked with the induction of islet neogenesis in animal models of disease and regeneration. Administration of a peptide fragment of INGAP (INGAP peptide) has been demonstrated to reverse chemically induced diabetes as well as improve glycemic control and survival in an animal model of type 1 diabetes. (Lipsett *et al.*, *Cell Biochem. Biophys.* **2007**, 48, 127). INGAP peptide (INGAPP) is a 15 amino acid sequence contained within the 175 amino acid INGAP (*see*, amino acids 103-117 of SEQ ID. NO: 2 of U.S. Pat. No. 5,834,590): Ile-Gly-Leu-His-Asp-Pro-Ser-His-Gly-Thr-Leu-Pro-Asn-Gly-Ser.

a) mPEG-N^{ter}-INGAPP via mPEG-SPC

[00281] INGAPP is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of INGAPP, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of INGAPP prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter}-INGAPP conjugate formation.

[00282] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

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b) INGAPP-C^{ter}-mPEG

[00283] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of INGAPP, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected INGAPP (Prot-INGAPP, *e.g.* Fmoc-Ile-Gly-Leu-His-Asp(tBu)-Pro-Ser(tBu)-His-Gly-Thr(tBu)-Leu-Pro-Asn-Gly-Ser(tBu)-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-INGAPP is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-INGAPP-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the *INGAPP-C^{ter}-mPEG* conjugate.

[00284] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) mPEG-N^{ter}-INGAPP via mPEG-SMB

[00285] An mPEG-N-Hydroxysuccinimide is obtained having a molecular weight of 5,000 Daltons and having the basic structure shown below: mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock INGAPP solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a

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conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00286] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

d) INGAPP-Asp(O-mPEG)

[00287] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Asp residue of INGAPP, to provide a Asp-conjugate form of the peptide. For coupling to the Asp residue, a protected *INGAPP* (Prot2-INGAPP, *e.g.*, Fmoc-Ile-Gly-Leu-His-Asp(OBz)-Pro-Ser(tBu)-His-Gly-Thr(tBu)-Leu-Pro-Asn-Gly-Ser(tBu)-O(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Asp(OBz) residue (H₂/Pd) yields the free-Asp carboxylate for subsequent coupling (Prot3-INGAPP, *e.g.*, Fmoc-Ile-Gly-Leu-His-Asp(OBz)-Pro-Ser(tBu)-His-Gly-Thr(tBu)-Leu-Pro-Asn-Gly-Ser(tBu)-O(tBu)). mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-INGAPP is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-*INGAPP*-(Asp-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the *INGAPP-Asp(O-mPEG)* conjugate.

[00288] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

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Example 7*Tendamistat-mPEG conjugates*

[00289] Tendamistat (HOE 467) is 74 residue alpha-amylase inactivator which effectively attenuates starch digestion (Meyer *et al.*, *S. Afr. Med. J.* 1984, 66, 222), having the sequence, Asp-Thr-Thr-Val-Ser-Glu-Pro-Ala-Pro-Ser-Cys-Val-Thr-Leu-Tyr-Gln-Ser-Trp-Arg-Tyr-Ser-Gln-Ala-Asp-Asp-Gly-Cys-Ala-Glu-Thr-Val-Thr-Val-Lys-Val-Val-Tyr-Glu-Asp-Asp-Thr-Glu-Gly-Leu-Cys-Tyr-Ala-Val-Ala-Pro-Gly-Gln-Ile-Thr-Thr-Val-Gly-Asp-Gly-Tyr-Ile-Gly-Ser-His-Gly-His-Ala-Arg-Tyr-Leu-Ala-Arg-Cys-Leu (DTTVSEPPAPS CVTLYQSWRY SQADNGCAET VTVKVVYEDD TEGLCYAVAP GQITTVGDGY IGSHGHARYL ARCL) (PubChem Protein Accession No. CAA00655)

a) mPEG-N^{ter}-Tendamistat- via mPEG-SPC

[00290] Tendamistat is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of Tendamistat, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Tendamistat prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter}- Tendamistat conjugate formation.

[00291] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Tendamistat-C^{ter}-mPEG

[00292] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Tendamistat, to provide a C^{ter}-conjugate form of the peptide. For coupling to

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the C-terminus, a protected Tendamistat (Prot-Tendamistat, *e.g.*, Fmoc-Asp(tBu)-Thr(tBu)-Thr(tBu)-Val-Ser(tBu)-Glu(tBu)-Pro-Ala-Pro-Ser(tBu)-Cys(tBu)-Val-Thr(tBu)-Leu-Tyr(tBu)-Gln-Ser(tBu)-Trp-Arg(Tos)-Tyr-Ser(tBu)-Gln-Ala-Asp(tBu)-Asp(tBu)-Gly-Cys(tBu)-Ala-Glu(tBu)-Thr(tBu)-Val-Thr(tBu)-Val-Lys(Fmoc)-Val-Val-Tyr(tBu)-Glu(tBu)-Asp(tBu)-Asp(tBu)-Thr(tBu)-Glu(tBu)-Gly-Leu-Cys(tBu)-Tyr(tBu)-Ala-Val-Ala-Pro-Gly-Gln-Ile-Thr(tBu)-Thr(tBu)-Val-Gly-Asp(tBu)-Gly-Tyr(tBu)-Ile-Gly-Ser(tBu)-His-Gly-His-Ala-Arg(Tos)-Tyr(tBu)-Leu-Ala-Arg(Tos)-Cys(tBu)-Leu) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-Tendamistat is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-Tendamistat-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Tendamistat-C^{ter}-mPEG conjugate.

[00293] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Tendamistat-Cys(S-mPEG)

[00294] Tendamistat, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00295] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

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d) mPEG-N^{ter}-Tendamistat via mPEG-SMB

[00296] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Tendamistat solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00297] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

e) Tendamistat-Glu(O-mPEG)

[00298] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Glu residue of Tendamistat, to provide a Glu-conjugate form of the peptide. For coupling to the Glu residue, a protected Tendamistat (Prot2-Tendamistat, *e.g.*, Fmoc-Asp(tBu)-Thr(tBu)-Thr(tBu)-Val-Ser(tBu)-Glu(OBz)-Pro-Ala-Pro-Ser(tBu)-Cys(tBu)-Val-Thr(tBu)-Leu-Tyr(tBu)-Gln-Ser(tBu)-Trp-Arg(Tos)-Tyr-Ser(tBu)-Gln-Ala-Asp(tBu)-Asp(tBu)-Gly-Cys(tBu)-Ala-Glu(tBu)-Thr(tBu)-Val-Thr(tBu)-Val-Lys(Fmoc)-Val-Val-Tyr(tBu)-Glu(tBu)-Asp(tBu)-Asp(tBu)-Thr(tBu)-Glu(tBu)-Gly-Leu-Cys(tBu)-Tyr(tBu)-Ala-Val-Ala-Pro-Gly-Gln-Ile-Thr(tBu)-Thr(tBu)-Val-Gly-Asp(tBu)-Gly-Tyr(tBu)-Ile-Gly-Ser(tBu)-His-Gly-His-Ala-Arg(Tos)-Tyr(tBu)-Leu-Ala-Arg(Tos)-Cys(tBu)-Leu(OtBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Glu(OBz) residue (H₂/Pd) yields the free-Glu carboxylate for subsequent coupling (Prot3-Tendamistat, *e.g.*, Fmoc-Asp(tBu)-Thr(tBu)-Thr(tBu)-Val-Ser(tBu)-Glu-Pro-Ala-Pro-Ser(tBu)-Cys(tBu)-Val-Thr(tBu)-Leu-Tyr(tBu)-Gln-Ser(tBu)-Trp-Arg(Tos)-Tyr-Ser(tBu)-Gln-Ala-Asp(tBu)-Asp(tBu)-Gly-Cys(tBu)-Ala-Glu(tBu)-Thr(tBu)-Val-Thr(tBu)-Val-Lys(Fmoc)-Val-Val-Tyr(tBu)-Glu(tBu)-Asp(tBu)-Asp(tBu)-Thr(tBu)-Glu(tBu)-Gly-Leu-Cys(tBu)-Tyr(tBu)-Ala-Val-Ala-Pro-Gly-Gln-Ile-Thr(tBu)-Thr(tBu)-Val-Gly-Asp(tBu)-Gly-Tyr(tBu)-Ile-Gly-Ser(tBu)-His-Gly-His-Ala-Arg(Tos)-Tyr(tBu)-Leu-Ala-Arg(Tos)-Cys(tBu)-Leu(OtBu)) mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient

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temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-Tendamistat is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-Tendamistat-(Glu-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Tendamistat-Glu(O-mPEG) conjugate.

[00299] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

Example 8

recombinant human Carperitide-mPEG conjugates

[00300] Carperitide (α -atriopeptin) is secreted by the heart, is a member of the natriuretic peptide family which is comprised of peptides secreted by various organs. Carperitide is has been proposed for the treatment of acute heart failure and shown therapeutic potential to treat peripheral arterial diseases refractory to conventional therapies (Park *et al.*, *Endocrinology* 2008, 149, 483). Carperitide has the amino acid sequence Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr (SLRRSSCFGGRMDRIGAQSGLGCNSFRY).

a) mPEG-N^{ter}-Carperitide - via mPEG-SPC

[00301] Carperitide can be prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of Carperitide, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used, based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of

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Carperitide prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is rapidly stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-*N*^{ter}- Carperitide conjugate formation.

[00302] Using this same approach, other conjugates can be prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Carperitide-C^{ter}-mPEG

[00303] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Carperitide, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected Carperitide (Prot-Carperitide, *e.g.*, Fmoc-Ser(tBu)-Leu-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ser(tBu)-Cys(tBu)-Phe-Gly-Gly-Arg(Tos)-Met-Asp(tBu)-Arg(Tos)-Ile-Gly-Ala-Gln-Ser(tBu)-Gly-Leu-Gly-Cys(tBu)-Asn-Ser(tBu)-Phe-Arg(Tos)-Tyr(tBu)-OH) can be prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot- Carperitide is prepared in N,N-dimethylformamide is added and the mixture is rapidly stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot- Carperitide -C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Carperitide -C^{ter}-mPEG conjugate.

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[00304] Using this same approach, other conjugates can be prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Carperitide-Cys(S-mPEG)

[00305] Carperitide, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00306] Using this same approach, other conjugates can be prepared using mPEG-MAL having other weight average molecular weights.

d) mPEG-N^{ter}-Carperitide via mPEG-SMB

[00307] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Carperitide solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00308] Using this same approach, other conjugates can be prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

e) Carperitide-Asp(O-mPEG)

[00309] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Asp residue of Carperitide, to provide a Asp-conjugate form of the peptide. For coupling to the Asp residue, a protected Carperitide (Prot2-Carperitide, *e.g.*, Fmoc-Ser(tBu)-Leu-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ser(tBu)-Cys(tBu)-Phe-Gly-Gly-Arg(Tos)-Met-Asp(OBz)-Arg(Tos)-Ile-Gly-Ala-Gln-Ser(tBu)-Gly-Leu-Gly-Cys(tBu)-Asn-Ser(tBu)-Phe-Arg(Tos)-Tyr(tBu)-O(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Asp(OBz) residue (H₂/Pd) yields the free-Asp carboxylate for subsequent coupling (Prot3-Carperitide, *e.g.*, Fmoc-Ser(tBu)-Leu-Arg(Tos)-

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Arg(Tos)-Ser(tBu)-Ser(tBu)-Cys(tBu)-Phe-Gly-Gly-Arg(Tos)-Met-Asp-Arg(Tos)-Ile-Gly-Ala-Gln-Ser(tBu)-Gly-Leu-Gly-Cys(tBu)-Asn-Ser(tBu)-Phe-Arg(Tos)-Tyr(tBu)-O(tBu)). mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-Carperitide is prepared in N,N-dimethylformamide is added and the mixture is rapidly stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-Carperitide-(Asp-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Carperitide-*Asp(O-mPEG)* conjugate.

[00310] Using this same approach, other conjugates is prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

Example 9

Urodilatin-mPEG conjugates

[00311] Urodilatin is a member of the natriuretic peptide family which is comprised of peptides secreted by various organs, has been studied for use in treating various conditions, including renal failure or congestive heart failure (see, *e.g.*, U.S. Pat. Nos. 5,571,789 and 6,831,064; Kentsch *et al.*, *Eur. J. Clin. Invest.* **1992**, 22, 662; Kentsch *et al.*, *Eur. J. Clin. Invest.* **1995**, 25, 281; Elsner *et al.*, *Am. Heart J.* **1995**, 129, 766; Forssmann *et al.*, *Clinical Pharmacology and Therapeutics* **1998**, 64, 322; and US Patent Application Publication No. 2006/0264376A1). Urodilatin has the amino acid sequence set forth in GenBank Accession No. 1506430A; Thr-Ala-Pro-Arg-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr (TAPRSLRRSS CFGGRMDRIG AQSGGLGCNSF RY). Urodilatin is also the 95-126 fragment [ANP(95-126)] of atrial natriuretic peptide (ANP).

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a) mPEG-N^{ter}-Urodilatin - via mPEG-SPC

[00312] Urodilatin is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of Urodilatin, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Urodilatin prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter}- Urodilatin conjugate formation.

[00313] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Urodilatin-C^{ter}-mPEG

[00314] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Urodilatin, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected Urodilatin (Prot-Urodilatin, *e.g.*, Fmoc-Thr(tBu) -Ala-Pro-Arg(Tos)-Ser(tBu)-Leu-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ser(tBu)-Cys(tBu)-Phe-Gly-Gly-Arg(Tos)-Met-Asp(tBu)-Arg(Tos)-Ile-Gly-Ala-Gln-Ser(tBu)-Gly-Leu-Gly-Cys(tBu)-Asn-Ser(tBu)-Phe-Arg(Tos)-Tyr(tBu)-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-Urodilatin is prepared in *N, N*-

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dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-Urodilatin-*C^{ter}*-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Urodilatin -*C^{ter}*-mPEG conjugate.

[00315] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Urodilatin-Cys(S-mPEG)

[00316] Urodilatin, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00317] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

d) mPEG-N^{ter}-Urodilatin via mPEG-SMB

[00318] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Urodilatin solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00319] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

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e) Urodilatin-Asp(O-mPEG)

[00320] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Asp residue of Urodilatin, to provide a Asp-conjugate form of the peptide. For coupling to the Asp residue, a protected Urodilatin (Prot2-Urodilatin, *e.g.*, Fmoc-Thr(tBu)-Ala-Pro-Arg(Tos)-Ser(tBu)-Leu-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ser(tBu)-Cys(tBu)-Phe-Gly-Gly-Arg(Tos)-Met-Asp(OBz)-Arg(Tos)-Ile-Gly-Ala-Gln-Ser(tBu)-Gly-Leu-Gly-Cys(tBu)-Asn-Ser(tBu)-Phe-Arg(Tos)-Tyr(tBu)-NH₂) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Asp(OBz) residue (H₂/Pd) yields the free-Asp carboxylate for subsequent coupling (Prot3-Urodilatin, *e.g.* Fmoc-Thr(tBu)-Ala-Pro-Arg(Tos)-Ser(tBu)-Leu-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ser(tBu)-Cys(tBu)-Phe-Gly-Gly-Arg(Tos)-Met-Asp-Arg(Tos)-Ile-Gly-Ala-Gln-Ser(tBu)-Gly-Leu-Gly-Cys(tBu)-Asn-Ser(tBu)-Phe-Arg(Tos)-Tyr(tBu)-NH₂). mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-Urodilatin is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-Urodilatin-(Asp-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Urodilatin-Asp(O-mPEG) conjugate.

[00321] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

Example 10*Desirudin-mPEG conjugates*

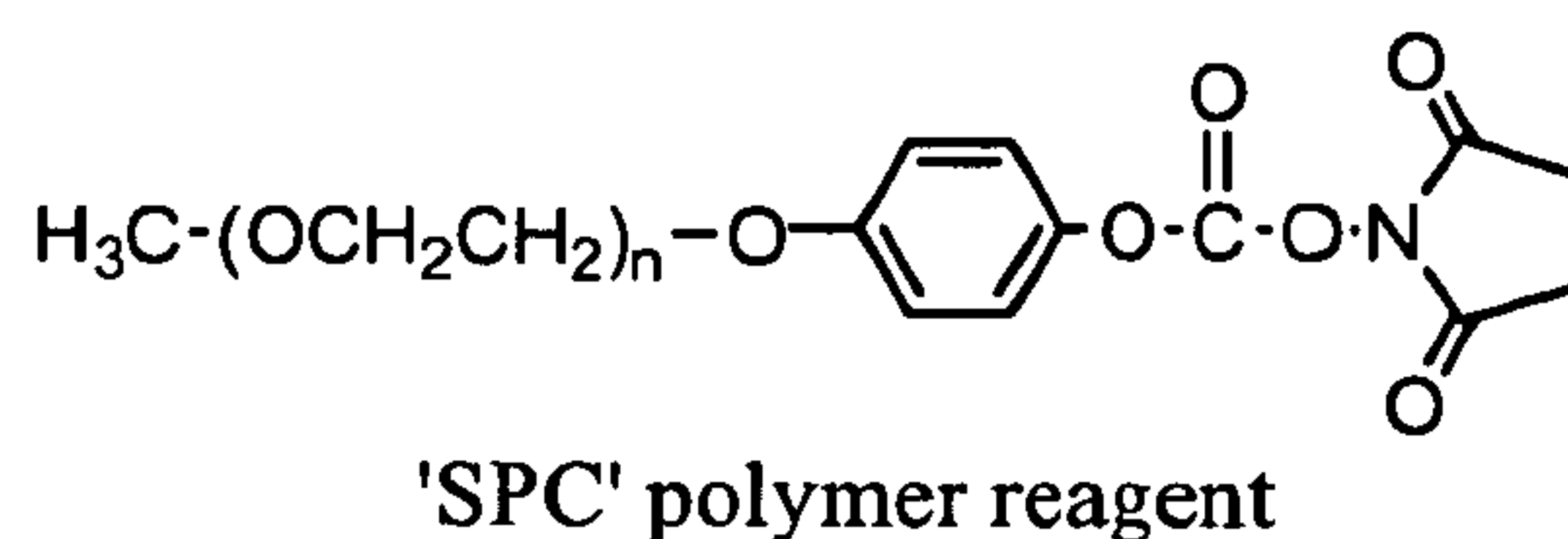
[00322] Desirudin, a recombinant hirudin, is a member of a class of anticoagulants that act by directly inhibiting thrombin. Desirudin acts via a bivalent binding arrangement with both the

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active site and fibrinogen-binding site (exosite 1) of thrombin, and has been shown to be useful in the prevention and management of thromboembolic disease, reducing the incidence of deep vein thrombosis (DVT) in patients undergoing elective hip replacement, preventing restenosis after coronary angioplasty for unstable angina, and in the treatment of acute coronary syndromes for patients in whom heparin therapy is not a viable option (Matheson and Goa, *Drugs* **2000**, *60*, 679). Desirudin has the primary sequence Val-Val-Tyr-Thr-Asp-Cys-Thr-Glu-Ser-Gly-Gln-Asn-Leu-Cys-Leu-Cys-Glu-Gly-Ser-Asn-Val-Cys-Gly-Gln-Gly-Asn-Lys-Cys-Ile-Leu-Gly-Ser-Asp-Gly-Glu-Lys-Asn-Gln-Cys-Val-Thr-Gly-Glu-Gly-Thr-Pro-Lys-Pro-Gln-Ser-His-Asn-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln.

a) mPEG-N^{ter} - Desirudin via mPEG-SPC

[00323] Desirudin is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent,



is covalently attached to the N-terminus of Desirudin, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Desirudin prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter} - Desirudin conjugate formation.

[00324] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

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b) Desirudin -C^{ter}-mPEG

[00325] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Desirudin, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected Desirudin (Prot-Val-Val-Tyr(tBu)-Thr(tBu)-Asp(tBu)-Cys(tBu)-Thr(tBu)-Glu(tBu)-Ser(tBu)-Gly-Gln-Asn-Leu-Cys(tBu)-Leu-Cys-Glu(tBu)-Gly-Ser(tBu)-Asn-Val-Cys(tBu)-Gly-Gln-Gly-Asn-Lys(Fmoc)-Cys(tBu)-Ile-Leu-Gly-Ser(tBu)-Asp(tBu)-Gly-Glu(tBu)-Lys(Fmoc)-Asn-Gln-Cys(tBu)-Val-Thr(tBu)-Gly-Glu(tBu)-Gly-Thr(tBu)-Pro-Lys(Fmoc)-Pro-Gln-Ser(tBu)-His-Asn-Asp(tBu)-Gly-Asp(tBu)-Phe-Glu(tBu)-Glu(tBu)-Ile-Pro-Glu(tBu)-Glu(tBu)-Tyr(tBu)-Leu-Gln-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot- Desirudin is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot- Desirudin -C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Desirudin -C^{ter}-mPEG conjugate.

[00326] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Desirudin-Cys(S-mPEG)

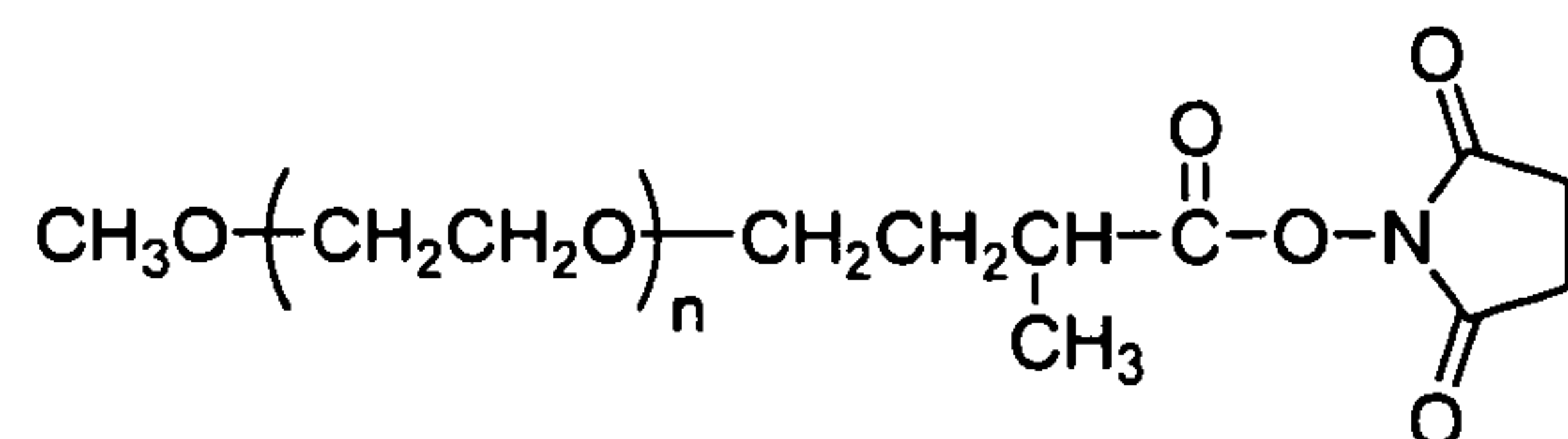
[00327] Desirudin, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00328] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

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d) *mPEG-N^{ter}* - Desirudin via *mPEG-SMB*

[00329] An *mPEG-N-Hydroxysuccinimide* is obtained having a molecular weight of 5 kDa and having the basic structure shown below:



(*mPEG-Succinimidyl α-Methylbutanoate Derivative*, 5kDa ("*mPEG-SMB*"))

[00330] *mPEG-SMB*, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed *mPEG-SMB* is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Desirudin solution and mixed well. After the addition of the *mPEG-SMB*, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the *mPEG-SMB* to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00331] Using this same approach, other conjugates are prepared using *mPEG* derivatives having other weight-average molecular weights that also bear an *N-hydroxysuccinimide* moiety.

e) Desirudin-Asp(*O-mPEG*)

[00332] An illustrative polymeric reagent, *mPEG-NH₂* reagent is covalently attached to the Asp residue of Desirudin, to provide a Asp-conjugate form of the peptide. For coupling to the Asp residue, a protected Desirudin (Prot2-Desirudin, *e.g.* Fmoc-Val-Val-Tyr(*tBu*)-Thr(*tBu*)-Asp(OBz)-Cys(*tBu*)-Thr(*tBu*)-Glu(*tBu*)-Ser(*tBu*)-Gly-Gln-Asn-Leu-Cys(*tBu*)-Leu-Cys-Glu(*tBu*)-Gly-Ser(*tBu*)-Asn-Val-Cys(*tBu*)-Gly-Gln-Gly-Asn-Lys(Fmoc)-Cys(*tBu*)-Ile-Leu-Gly-Ser(*tBu*)-Asp(*tBu*)-Gly-Glu(*tBu*)-Lys(Fmoc)-Asn-Gln-Cys(*tBu*)-Val-Thr(*tBu*)-Gly-Glu(*tBu*)-Gly-Thr(*tBu*)-Pro-Lys(Fmoc)-Pro-Gln-Ser(*tBu*)-His-Asn-Asp(*tBu*)-Gly-Asp(*tBu*)-Phe-Glu(*tBu*)-Glu(*tBu*)-Ile-Pro-Glu(*tBu*)-Glu(*tBu*)-Tyr(*tBu*)-Leu-Gln-NH₂) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Asp(OBz) residue (H₂/Pd) yields the free-Asp carboxylate for subsequent coupling (Prot3-Desirudin, *e.g.* Fmoc-Val-Val-Tyr(*tBu*)-Thr(*tBu*)-Asp-Cys(*tBu*)-Thr(*tBu*)-

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Glu(tBu)-Ser(tBu)-Gly-Gln-Asn-Leu-Cys(tBu)-Leu-Cys-Glu(tBu)-Gly-Ser(tBu)-Asn-Val-Cys(tBu)-Gly-Gln-Gly-Asn-Lys(Fmoc)-Cys(tBu)-Ile-Leu-Gly-Ser(tBu)-Asp(tBu)-Gly-Glu(tBu)-Lys(Fmoc)-Asn-Gln-Cys(tBu)-Val-Thr(tBu)-Gly-Glu(tBu)-Gly-Thr(tBu)-Pro-Lys(Fmoc)-Pro-Gln-Ser(tBu)-His-Asn-Asp(tBu)-Gly-Asp(tBu)-Phe-Glu(tBu)-Glu(tBu)-Ile-Pro-Glu(tBu)-Glu(tBu)-Tyr(tBu)-Leu-Gln-NH₂). mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3- Desirudin is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3- Desirudin-(Asp-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Desirudin - Asp(O-mPEG) conjugate.

Example 11

Obestatin-mPEG conjugates

[00333] Obestatin is 28-amino acid, acylated, orexigenic peptide that is a ligand for growth hormone secretagogue receptors and is encoded by the same gene that also encodes ghrelin, a peptide hormone that increases appetite. Treatment of rats with obestatin suppressed food intake, inhibited jejunal contraction, and decreased body-weight gain (Zhang *et al.*, *Science* 2005, 310, 996). Synthetic human obestatin is available from California Peptide Research, Inc (Napa, CA), having the sequence, Phe-Asn-Ala-Pro-Phe-Asp-Val-Gly-Ile-Lys-Leu-Ser-Gly-Val-Gln-Tyr-Gln-Gln-His-Ser-Gln-Ala-Leu-NH₂ (PubChem Substance ID: 47205412).

a) mPEG-N^{ter}-Obestatin via mPEG-SPC

[00334] An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of Obestatin, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is

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used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Obestatin prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-*N*^{ter}-Obestatin conjugate formation.

[00335] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Obestatin-C^{ter}-mPEG

[00336] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Obestatin, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected Obestatin lacking the C-terminus amide (Prot-Obestatin, *e.g.*, Fmoc-Phe-Asn-Ala-Pro-Phe-Asp(tBu)-Val-Gly-Ile-Lys(Fmoc)-Leu-Ser(tBu)-Gly-Val-Gln-Tyr(tBu)-Gln-Gln-His-Ser(tBu)-Gln-Ala-Leu-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-Obestatin is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-Obestatin-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Obestatin-C^{ter}-mPEG conjugate.

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[00337] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Obestatin -Cys(S-mPEG)

[00338] Obestatin, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00339] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

d) mPEG-N^{ter}-Obestatin via mPEG-SMB

[00340] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Obestatin solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00341] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

e) Obestatin-Lys-mPEG

[00342] PEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock protected Obestatin (*e.g.*, Fmoc-Phe-Asn-Ala-Pro-Phe-Asp(tBu)-Val-Gly-Ile-Lys-Leu-Ser(tBu)-Gly-Val-Gln-Tyr(tBu)-Gln-Gln-His-Ser(tBu)-Gln-Ala-Leu-NH₂) solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred

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for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer. The remaining protecting groups are removed under standard deprotection conditions to yield the Obestatin-Lys(O-*m*PEG) conjugate.

[00343] Using this same approach, other conjugates are prepared using *m*PEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 12

ITF-1697(Icrocapide)-mPEG conjugates

[00344] ITF-1697 is a tetrapeptide, Gly-(N-Et)Lys-Pro-Arg (PubChem Compound ID: 216295), which reduces mortality and tissue damage in lipopolysaccharide (LPS)-induced systemic endotoxemia and coronary ischemia and ischemia/reperfusion (see, *International Patent Application Publication WO 1995/10531*). A randomized, double-blind study in patients with acute myocardial infarction undergoing coronary revascularisation demonstrated reduce infarct size by radionuclide imaging (Syeda *et al.*, *Drugs R & D* 2004, 5, 141).

a) mPEG-N^{ter}-ITF-1697 - via mPEG-SPC

[00345] ITF-1697 is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, *m*PEG-SPC reagent, is covalently attached to the N-terminus of ITF-1697, to provide a *N^{ter}*-conjugate form of the peptide. *m*PEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of *m*PEG-SPC 20 kDa reagent is used based upon absolute peptide content. The *m*PEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of ITF-1697 prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the *m*PEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of *m*PEG-*N^{ter}*-ITF-1697 conjugate formation.

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[00346] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) ITF-1697-C^{ter}-mPEG

[00347] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of ITF-1697, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected ITF-1697 (Prot-ITF-1697, *e.g.*, Fmoc-Gly-(N-Et)Lys(Fmoc)-Pro-Arg(Tos)-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-ITF-1697 is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-ITF-1697-C^{ter}-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the ITF-1697 - C^{ter}-mPEG conjugate.

[00348] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) mPEG-N^{ter}-ITF-1697 via mPEG-SMB

[00349] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock ITF-1697 solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the

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dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00350] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

d) ITF-1697-Lys-mPEG

[00351] PEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock protected ITF-1697 (*e.g.*, Fmoc-Gly-(N-Et)Lys-Pro-Arg(Tos)-O(tBu)) solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer. The remaining protecting groups are removed under standard deprotection conditions to yield the ITF-1697-Lys(O-mPEG) conjugate.

[00352] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 13

Oxyntomodulin-mPEG conjugates

[00353] Oxyntomodulin (Amylin) is a 37-amino acid peptide derived from proglucagon found in the colon, produced by the oxyntic (fundic) cells of the oxyntic mucosa and is known to bind both the Glucagon-like peptide-1 (GLP-1) and the glucagon receptors. A randomized, double-blind, placebo-controlled, cross-over study in humans has shown Oxyntomodulin suppresses appetite and food intake (Cohen *et al.*, J. Clin. Endocrin. Met. 2003, 88, 4696). Oxyntomodulin is commercially available from GenScript Corporation (Piscataway, NJ; Cat. No. RP11278) with the sequence, Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-

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Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Ala-Ile-Leu-Ser-Ser-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH₂ (KCNTATCATQ RLANFLVHSS NNFGAILSST NVGSNTY-NH₂).

a) mPEG-N^{ter}-Oxyntomodulin - via mPEG-SPC

[00354] An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of Oxyntomodulin, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Oxyntomodulin prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter}-Oxyntomodulin conjugate formation.

[00355] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Oxyntomodulin-C^{ter}-mPEG

[00356] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Oxyntomodulin, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected Oxyntomodulin lacking the C-terminus amide (Prot-Oxyntomodulin, e.g., Fmoc-Lys(Fmoc)-Cys(tBu)-Asn-Thr(tBu)-Ala-Thr(tBu)-Cys(tBu)-Ala-Thr(tBu)-Gln-Arg(Tos)-Leu-Ala-Asn-Phe-Leu-Val-His-Ser(tBu)-Ser(tBu)-Asn-Asn-Phe-Gly-Ala-Ile-Leu-Ser(tBu)-Ser(tBu)-Thr(tBu)-Asn-Val-Gly-Ser(tBu)-Asn-Thr(tBu)-Tyr(tBu)-OH) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-

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NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-Oxyntomodulin is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-Oxyntomodulin-*C^{ter}*-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Oxyntomodulin-*C^{ter}*-mPEG conjugate.

[00357] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Oxyntomodulin-*Cys(S-mPEG)*

[00358] Oxyntomodulin, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00359] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

d) mPEG-*N^{ter}* - Oxyntomodulin via mPEG-SMB

[00360] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Oxyntomodulin solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00361] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

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e) Oxyntomodulin-Lys-mPEG

[00362] PEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock protected Oxyntomodulin (*e.g.*, Fmoc-Lys-Cys(tBu)-Asn-Thr(tBu)-Ala-Thr(tBu)-Cys(tBu)-Ala-Thr(tBu)-Gln-Arg(Tos)-Leu-Ala-Asn-Phe-Leu-Val-His-Ser(tBu)-Ser(tBu)-Asn-Asn-Phe-Gly-Ala-Ile-Leu-Ser(tBu)-Ser(tBu)-Thr(tBu)-Asn-Val-Gly-Ser(tBu)-Asn-Thr(tBu)-Tyr(tBu)-O(tBu)) solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer. The remaining protecting groups are removed under standard deprotection conditions to yield the Oxyntomodulin-Lys(O-mPEG) conjugate.

[00363] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 14*Cholecystokinin-mPEG conjugates*

[00364] Cholecystokinin is a peptide hormone secreted by the upper intestinal mucosa which increases gallbladder contraction, release of pancreatic exocrine (or digestive) enzymes, and is responsible for stimulating the digestion of fat and proteins. Cholecystokinin has also been shown to be a physiologic regulator of gastric emptying in humans (Liddle *et al.*, *J. Clin. Invest.* **1986**, 77, 992). Cholecystokinin has the sequence, Met-Asn-Ser-Gly-Val-Cys-Leu-Cys-Val-Leu-Met-Ala-Val-Leu-Ala-Ala-Gly-Ala-Leu-Thr-Gln-Pro-Val-Pro-Pro-Ala-Asp-Pro-Ala-Gly-Ser-Gly-Leu-Gln-Arg-Ala-Glu-Glu-Ala-Pro-Arg-Arg-Gln-Leu-Arg-Val-Ser-Gln-Arg-Thr-Asp-Gly-Glu-Ser-Arg-Ala-His-Leu-Gly-Ala-Leu-Leu-Ala-Arg-Tyr-Ile-Gln-Gln-Ala-Arg-Lys-Ala-Pro-Ser-Gly-Arg-Met-Ser-Ile-Val-Lys-Asn-Leu-Gln-Asn-Leu-Asp-Pro-Ser-His-Arg-Ile-Ser-Asp-Arg-Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-Gly-Arg-Arg-Ser-Ala-Glu-Glu-Tyr-Glu-Tyr-Pro-Ser (MNSGVCLCVL MAVLAAGALT QPVPPADPAG SGLQRAEEAP RRQLRVSQRT

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DGESRAHLGA LLARYIQQAR KAPSGRMSIV KNLQNLDPSH RISDRDYMGW
MDFGRRSAEE YEYPS; PubChem Protein Accession No. AAA53094; Takahashi *et al.*, *Gene*,
1986, 50, 353).

a) mPEG-N^{ter}-Cholecystokinin - via mPEG-SPC

[00365] Cholecystokinin is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of Cholecystokinin, to provide a N^{ter}-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of Cholecystokinin prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-N^{ter}- Cholecystokinin conjugate formation.

[00366] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) Cholecystokinin-C^{ter}-mPEG

[00367] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of Cholecystokinin, to provide a C^{ter}-conjugate form of the peptide. For coupling to the C-terminus, a protected Cholecystokinin (Prot-Cholecystokinin, *e.g.*, Fmoc-Met-Asn-Ser(tBu)-Gly-Val-Cys(tBu)-Leu-Cys(tBu)-Val-Leu-Met-Ala-Val-Leu-Ala-Ala-Gly-Ala-Leu-Thr(tBu)-Gln-Pro-Val-Pro-Pro-Ala-Asp(tBu)-Pro-Ala-Gly-Ser(tBu)-Gly-Leu-Gln-Arg(Tos)-Ala-Glu(tBu)-Glu(tBu)-Ala-Pro-Arg(Tos)-Arg(Tos)-Gln-Leu-Arg(Tos)-Val-Ser(tBu)-Gln-Arg(Tos)-Thr(tBu)-Asp(tBu)-Gly-Glu(tBu)-Ser(tBu)-Arg(Tos)-Ala-His-Leu-Gly-Ala-Leu-Leu-Ala-Arg(Tos)-Tyr(tBu)-Ile-Gln-Gln-Ala-Arg(Tos)-Lys(Fmoc)-Ala-Pro-Ser(tBu)-Gly-Arg(Tos)-Met-

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Ser(tBu)-Ile-Val-Lys(Fmoc)-Asn-Leu-Gln-Asn-Leu-Asp(tBu)-Pro-Ser(tBu)-His-Arg(Tos)-Ile-Ser(tBu)-Asp(tBu)-Arg(Tos)-Asp(tBu)-Tyr(tBu)-Met-Gly-Trp-Met-Asp(tBu)-Phe-Gly-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ala-Glu(tBu)-Glu(tBu)-Tyr(tBu)-Glu(tBu)-Tyr(tBu)-Pro-Ser(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-Cholecystokinin is prepared in *N,N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-Cholecystokinin-*C^{ter}*-mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Cholecystokinin-*C^{ter}*-mPEG conjugate.

[00368] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) Cholecystokinin-Cys(S-mPEG)

[00369] Cholecystokinin, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00370] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

d) mPEG-N^{ter}-Cholecystokinin via mPEG-SMB

[00371] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock Cholecystokinin solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to

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6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00372] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

e) Cholecystokinin-Glu(O-mPEG)

[00373] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Glu residue of Cholecystokinin, to provide a Glu-conjugate form of the peptide. For coupling to the Glu residue, a protected Cholecystokinin (Prot2-Cholecystokinin, *e.g.*, Fmoc-Met-Asn-Ser(tBu)-Gly-Val-Cys(tBu)-Leu-Cys(tBu)-Val-Leu-Met-Ala-Val-Leu-Ala-Ala-Gly-Ala-Leu-Thr(tBu)-Gln-Pro-Val-Pro-Pro-Ala-Asp(tBu)-Pro-Ala-Gly-Ser(tBu)-Gly-Leu-Gln-Arg(Tos)-Ala-Glu(OBz)-Glu(tBu)-Ala-Pro-Arg(Tos)-Arg(Tos)-Gln-Leu-Arg(Tos)-Val-Ser(tBu)-Gln-Arg(Tos)-Thr(tBu)-Asp(tBu)-Gly-Glu(tBu)-Ser(tBu)-Arg(Tos)-Ala-His-Leu-Gly-Ala-Leu-Leu-Ala-Arg(Tos)-Tyr(tBu)-Ile-Gln-Gln-Ala-Arg(Tos)-Lys(Fmoc)-Ala-Pro-Ser(tBu)-Gly-Arg(Tos)-Met-Ser(tBu)-Ile-Val-Lys(Fmoc)-Asn-Leu-Gln-Asn-Leu-Asp(tBu)-Pro-Ser(tBu)-His-Arg(Tos)-Ile-Ser(tBu)-Asp(tBu)-Arg(Tos)-Asp(tBu)-Tyr(tBu)-Met-Gly-Trp-Met-Asp(tBu)-Phe-Gly-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ala-Glu(tBu)-Glu(tBu)-Tyr(tBu)-Glu(tBu)-Tyr(tBu)-Pro-Ser(tBu)-O(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Glu(OBz) residue (H₂/Pd) yields the free-Glu carboxylate for subsequent coupling (Prot3-Cholecystokinin, *e.g.*, Fmoc-Met-Asn-Ser(tBu)-Gly-Val-Cys(tBu)-Leu-Cys(tBu)-Val-Leu-Met-Ala-Val-Leu-Ala-Ala-Gly-Ala-Leu-Thr(tBu)-Gln-Pro-Val-Pro-Pro-Ala-Asp(tBu)-Pro-Ala-Gly-Ser(tBu)-Gly-Leu-Gln-Arg(Tos)-Ala-Glu-Glu(tBu)-Ala-Pro-Arg(Tos)-Arg(Tos)-Gln-Leu-Arg(Tos)-Val-Ser(tBu)-Gln-Arg(Tos)-Thr(tBu)-Asp(tBu)-Gly-Glu(tBu)-Ser(tBu)-Arg(Tos)-Ala-His-Leu-Gly-Ala-Leu-Leu-Ala-Arg(Tos)-Tyr(tBu)-Ile-Gln-Gln-Ala-Arg(Tos)-Lys(Fmoc)-Ala-Pro-Ser(tBu)-Gly-Arg(Tos)-Met-Ser(tBu)-Ile-Val-Lys(Fmoc)-Asn-Leu-Gln-Asn-Leu-Asp(tBu)-Pro-Ser(tBu)-His-Arg(Tos)-Ile-Ser(tBu)-Asp(tBu)-Arg(Tos)-Asp(tBu)-Tyr(tBu)-Met-Gly-Trp-Met-Asp(tBu)-Phe-Gly-Arg(Tos)-Arg(Tos)-Ser(tBu)-Ala-Glu(tBu)-Glu(tBu)-Tyr(tBu)-Glu(tBu)-Tyr(tBu)-Pro-Ser(tBu)-O(tBu)) mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature.

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The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-Cholecystokinin is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-Cholecystokinin -(Glu-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the Cholecystokinin-Glu(O-mPEG) conjugate.

[00374] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

Example 15

Bactericidal permeability increasing (BPI) protein-mPEG conjugates

[00375] Bactericidal permeability increasing protein (BPI) is a 487 residue (~50kDa) protein which is part of the innate immune system and which displays selective cytotoxicity toward gram-negative bacteria through binding to lipopolysaccharides produced by the bacteria. BPI has the sequence, MRENMARGPC NAPRWVSLMV LVAIGTAVTA AVNPGVVVRI SQKGLDYASQ QGTAALQKEL KRIKIPDYSD SFKIKHLGKG HYSFYSDIR EFQLPSSQIS MVPNVGLKFS ISNANIKISG KWKAQKRFLK MSGNFDLSIE GMSISADLKL GSNPTSGKPT ITCSSCSSHI NSVHVHISKS KVGWLIQLFH KKIESALRNK MNSQVCEKVT NSVSSKLQPY FQTLPVMTKI DSVAGINYGL VAPPATTAET LDVQMKGEFY SENHHNPPPF APPVMEFPAA HDRMVYLGLS DYFFNTAGLV YQEAGVLKMT LRDDMIPKES KFRLTTKFFG TFLPEVAKKF PNMKIQIHVS ASTPPHLSVQ PTGLTFYPAV DVQAFAVLPN SSLASLFLIG MHTTGSMEVS AESNRLVGEL KLDRLLELK HSNIGPFPVE LLQDIMNYIV PILVLPRVNE KLQKGFPLPT PARVQLYNVV LQPHQNFLLF GADVYK (PubChem Protein Accession No. AAA51841; Gray *et al.*, *J. Biol. Chem.* **1989**, 264, 9505).

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a) *mPEG-N^{ter}-BPI- via mPEG-SPC*

[00376] BPI is prepared and purified according to standard recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, mPEG-SPC reagent, is covalently attached to the N-terminus of BPI, to provide a *N^{ter}*-conjugate form of the peptide. mPEG-SPC 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-SPC 20 kDa reagent is used based upon absolute peptide content. The mPEG-SPC reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of BPI prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the mPEG-SPC is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG-*N^{ter}*- BPI conjugate formation.

[00377] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) *BPI-C^{ter}-mPEG*

[00378] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of BPI, to provide a *C^{ter}*-conjugate form of the peptide. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of BPI is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of BPI-*C^{ter}*-mPEG conjugate formation. The *C^{ter}* conjugate is isolated and purified according the the general procedure outlined above.

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[00379] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) BPI -Cys(S-mPEG)

[00380] BPI, which has a thiol-containing cysteine residue, is dissolved in buffer. To this peptide solution is added a 3-5 fold molar excess of mPEG-MAL, 5 kDa. The mixture is stirred at room temperature under an inert atmosphere for several hours. Analysis of the reaction mixture reveals successful conjugation of this peptide.

[00381] Using this same approach, other conjugates are prepared using mPEG-MAL having other weight average molecular weights.

d) mPEG-N^{ter}-BPI via mPEG-SMB

[00382] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock BPI solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer. The N^{ter} conjugate is isolated and purified according the the general procedure outlined above.

[00383] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

e) BPI-Lys-mPEG

[00384] PEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock BPI solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the

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dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer. The Lys conjugate is isolated and purified according to the general procedure outlined above to yield the BPI-Lys-*mPEG* conjugate.

[00385] Using this same approach, other conjugates are prepared using *mPEG* derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

Example 16

C-peptide-mPEG conjugates

[00386] C-peptide is a product of the cleavage of proinsulin, consisting of the B and A chains of insulin linked together via a connecting C-peptide, produced when proinsulin is released into the blood stream in response to a rise in serum glucose. C-peptide has the sequence, Glu-Ala-Glu-Asp-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln (US Pat. No. 6,610,649). C-peptide alone has been proposed for the treatment of diabetes (EP 132 769); insulin in combination with C-peptide can be administered for the prevention of diabetic complications (SE 460334).

a) mPEG-N^{ter}-C-peptide - via mPEG-SPC

[00387] C-peptide is prepared and purified according to standard automated peptide synthesis or recombinant techniques known to those skilled in the art. An illustrative polymeric reagent, *mPEG-SPC* reagent, is covalently attached to the N-terminus of C-peptide, to provide a *N^{ter}*-conjugate form of the peptide. *mPEG-SPC* 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of *mPEG-SPC* 20 kDa reagent is used based upon absolute peptide content. The *mPEG-SPC* reagent is weighed into a glass vial containing a magnetic stirrer bar. A solution of C-peptide prepared in phosphate buffered saline, PBS, pH 7.4 is added and the mixture is stirred using a magnetic stirrer until the *mPEG-SPC* is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The reaction is optionally quenched to terminate the reaction. The pH of the conjugate solution at the end of the reaction is measured and further acidified by addition of 0.1M HCl, if necessary, to bring the pH

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of the final solution to about 5.5. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of mPEG- N^{ter} -C-peptide conjugate formation.

[00388] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

b) C-peptide- C^{ter} -mPEG

[00389] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the C-terminus of C-peptide, to provide a C^{ter} -conjugate form of the peptide. For coupling to the C-terminus, a protected C-peptide (Prot-C-peptide, *e.g.*, Fmoc-Glu(tBu)-Ala-Glu(tBu)-Asp(tBu)-Leu-Gln-Val-Gly-Gln-Val-Glu(tBu)-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser(tBu)-Leu-Gln-Pro-Leu-Ala-Leu-Glu(tBu)-Gly-Ser(tBu)-Leu-Gln) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. About 3-5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot-C-peptide is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot-C-peptide- C^{ter} -mPEG conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the C-peptide- C^{ter} -mPEG conjugate.

[00390] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

c) mPEG- N^{ter} -C-peptide via mPEG-SMB

[00391] mPEG-SMB, 5kDa, stored at -20 °C under argon, is warmed to ambient temperature. A five-fold excess (relative to the amount of the peptide) of the warmed mPEG-SMB is dissolved in buffer to form a 10% reagent solution. The 10% reagent solution is quickly added to the aliquot of a stock C-peptide solution and mixed well. After the addition of the mPEG-SMB, the pH of the reaction mixture is determined and adjusted to 6.7 to 6.8 using

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conventional techniques. To allow for coupling of the mPEG-SMB to the peptide via an amide linkage, the reaction solution is stirred for several hours (*e.g.*, 5 hours) at room temperature in the dark or stirred overnight at 3-8 °C in a cold room, thereby resulting in a conjugate solution. The reaction is quenched with a 20-fold molar excess (with respect to the peptide) of Tris buffer.

[00392] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an N-hydroxysuccinimide moiety.

d) C-peptide-Glu(O-mPEG)

[00393] An illustrative polymeric reagent, mPEG-NH₂ reagent is covalently attached to the Glu residue of C-peptide, to provide a Glu-conjugate form of the peptide. For coupling to the Glu residue, a protected C-peptide (Prot2 C-peptide, *e.g.*, Fmoc-Glu(tBu)-Ala-Glu(tBu)-Asp(tBu)-Leu-Gln-Val-Gly-Gln-Val-Glu(OBz)-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser(tBu)-Leu-Gln-Pro-Leu-Ala-Leu-Glu(tBu)-Gly-Ser(tBu)-Leu-Gln)-O(tBu)) is prepared and purified according to standard automated peptide synthesis techniques known to those skilled in the art. Deprotection of the Glu(OBz) residue (H₂/Pd) yields the free-Glu carboxylate for subsequent coupling (Prot3-C-peptide, *e.g.*, Fmoc-Glu(tBu)-Ala-Glu(tBu)-Asp(tBu)-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser(tBu)-Leu-Gln-Pro-Leu-Ala-Leu-Glu(tBu)-Gly-Ser(tBu)-Leu-Gln)-O(tBu)) mPEG-NH₂ 20 kDa, stored at -20 °C under argon, is warmed to ambient temperature. The reaction is performed at room temperature. A 5-fold molar excess of mPEG-NH₂, PyBOP (benzotriazol-1-yloxy)tripyrrolidinonophosphonium hexafluorophosphate), and 1-hydroxybenzotriazole (HOBt) are used, based upon absolute peptide content. The mPEG-NH₂, PyBOP, HOBt are weighed into a glass vial containing a magnetic stirrer bar. A solution of Prot3-C-peptide is prepared in *N, N*-dimethylformamide is added and the mixture is stirred using a magnetic stirrer until the mPEG-NH₂ is fully dissolved. The stirring speed is reduced and the reaction is allowed to proceed to formation of conjugate product. The conjugate solution is then analyzed by SDS-PAGE and RP-HPLC (C18) to determine the extent of Prot3-C-peptide-(Glu-O-mPEG) conjugate formation. The remaining protecting groups are removed under standard deprotection conditions to yield the C-peptide-Glu(O-mPEG) conjugate.

[00394] Using this same approach, other conjugates are prepared using mPEG derivatives having other weight-average molecular weights that also bear an amino moiety.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

Claims:

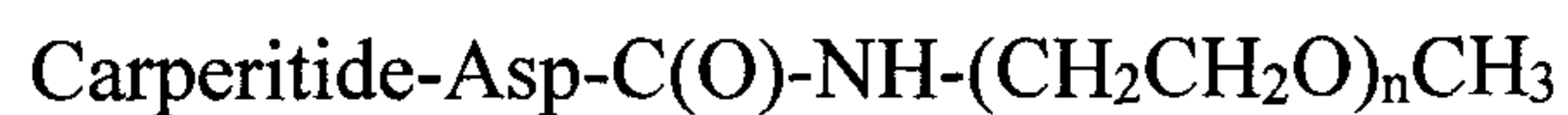
1. A conjugate comprising a residue of a carperitide moiety as set forth in SEQ ID NO:1 covalently attached at the carboxyl group of the aspartic acid to a poly(ethylene glycol) moiety via an amide linkage.
2. A conjugate of claim 1, wherein the poly(ethylene glycol) moiety is linear.
3. A conjugate of claim 1, wherein the poly(ethylene glycol) moiety is branched.
4. The conjugate of any one of claims 1, 2 and 3, wherein the carperitide moiety is recombinantly prepared.
5. The conjugate of any one of claims 1, 2 and 3, wherein the carperitide moiety is prepared by chemical synthesis.
6. The conjugate of any of claims 1-5, wherein the poly(ethylene glycol) is terminally capped with an end-capping moiety selected from the group consisting of hydroxy, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, alkynoxy, substituted alkynoxy, aryloxy and substituted aryloxy.
7. The conjugate of any of claims 1-5, wherein the poly(ethylene glycol) has a weight-average molecular weight in a range of from about 500 Daltons to about 100,000 Daltons.
8. The conjugate of claim 10, wherein the poly(ethylene glycol) has a weight-average molecular weight in a range of from about 2000 Daltons to about 50,000 Daltons.

9. The conjugate of claim 11, wherein the poly(ethylene glycol) has a weight-average molecular weight in a range of from about 5000 Daltons to about 40,000 Daltons.

10. A pharmaceutical composition comprising a conjugate of any one of claims 1-9 and a pharmaceutically acceptable excipient.

11. The conjugate of any of claims 1-9 for use in the treatment of heart failure.

12. The conjugate of claim 1, having the structure:



wherein:

-Asp-C(O)- is a carboxyl residue from the aspartic acid of carperitide; and

n is an integer from 2 to 3,400.

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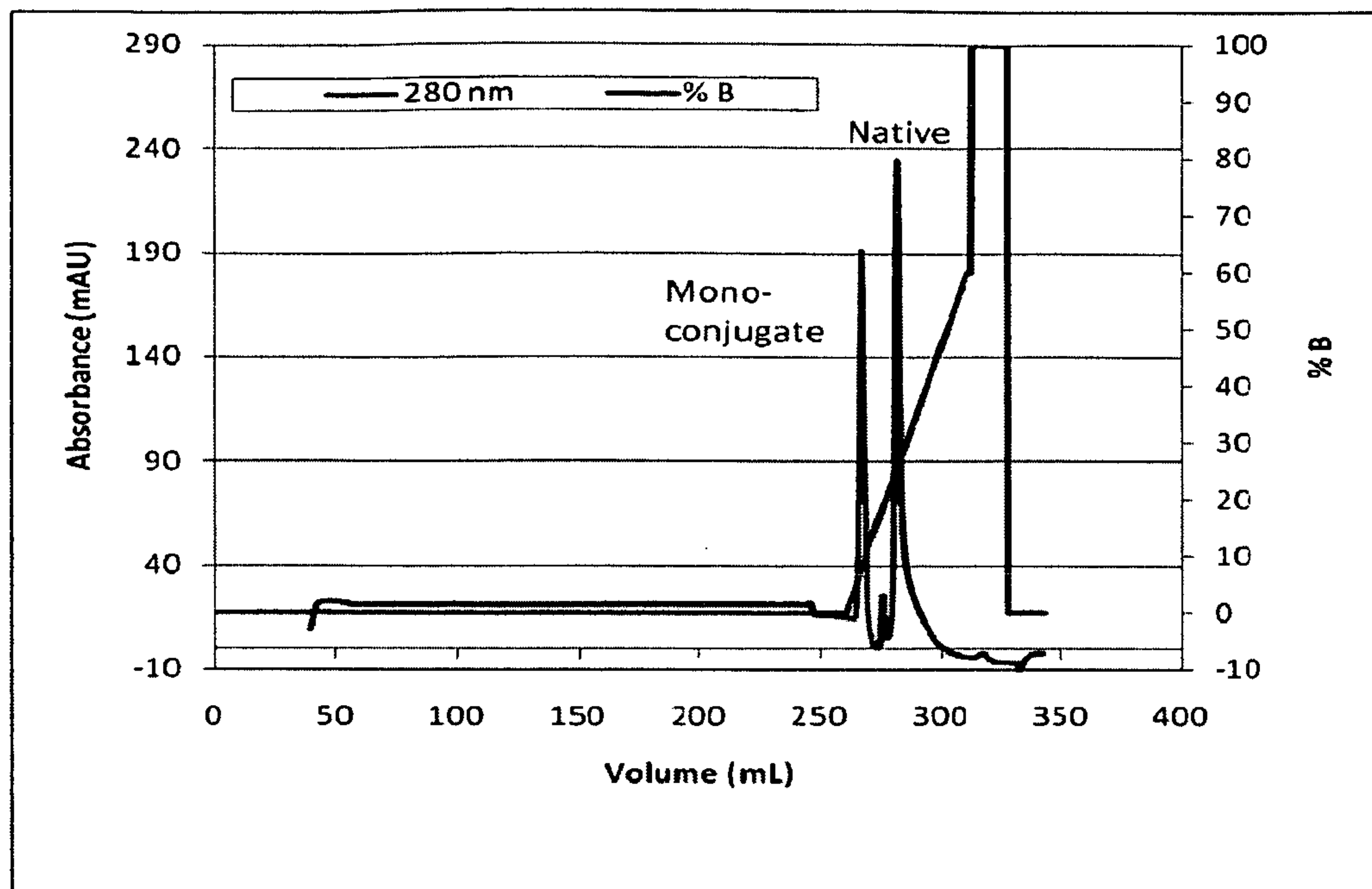


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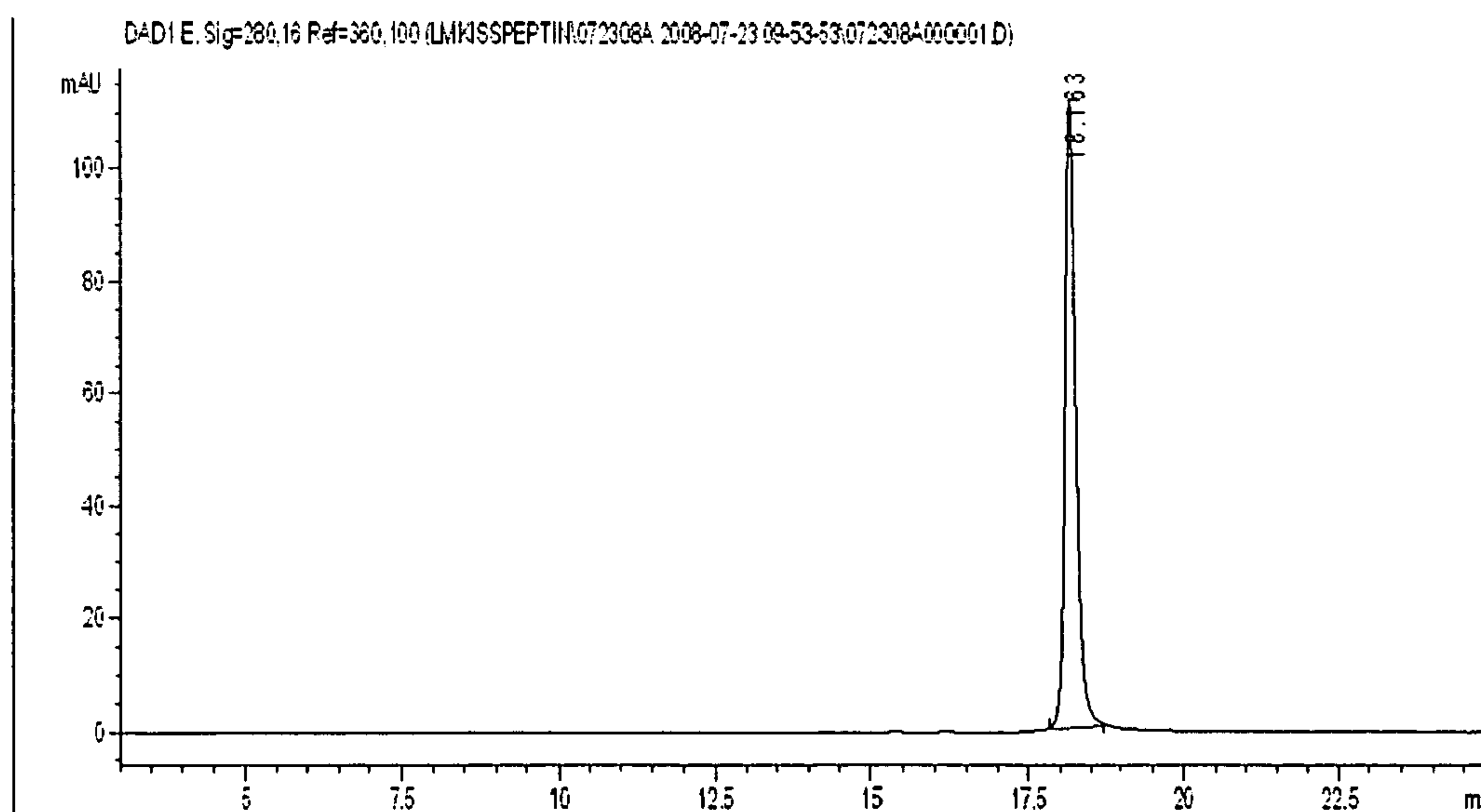


Figure KISS1.2

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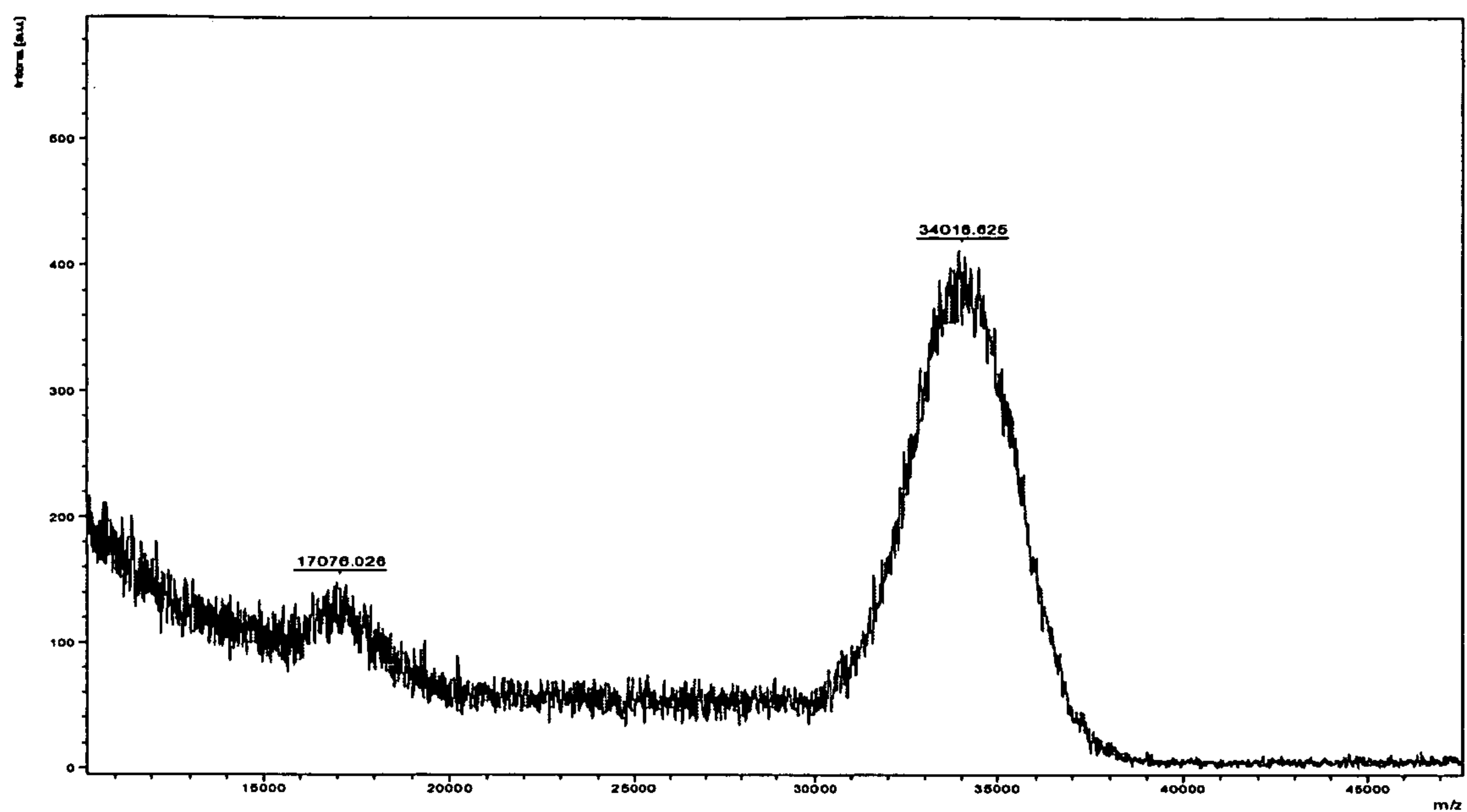


Figure KISS1.3

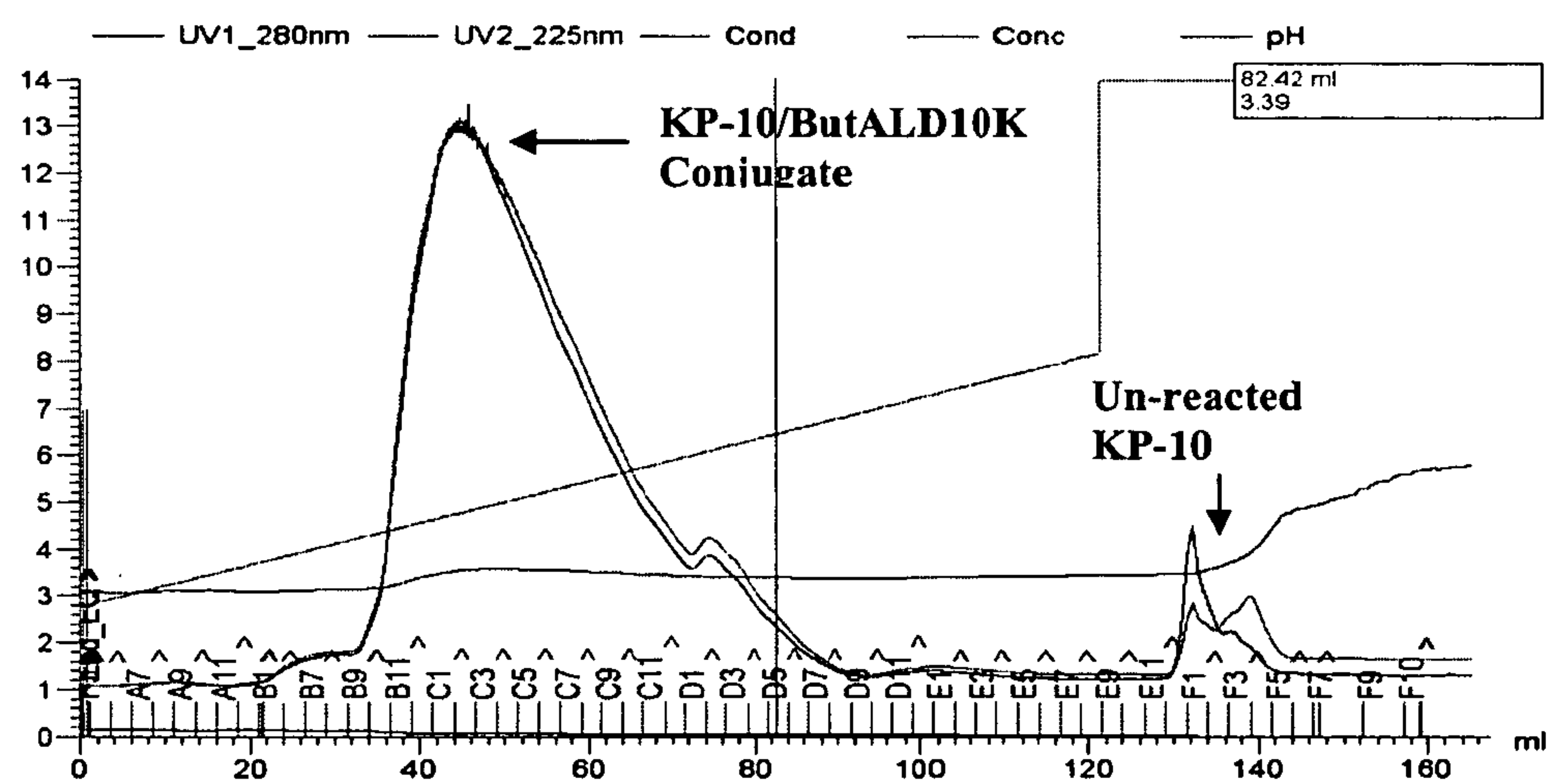


Figure KISS2.1

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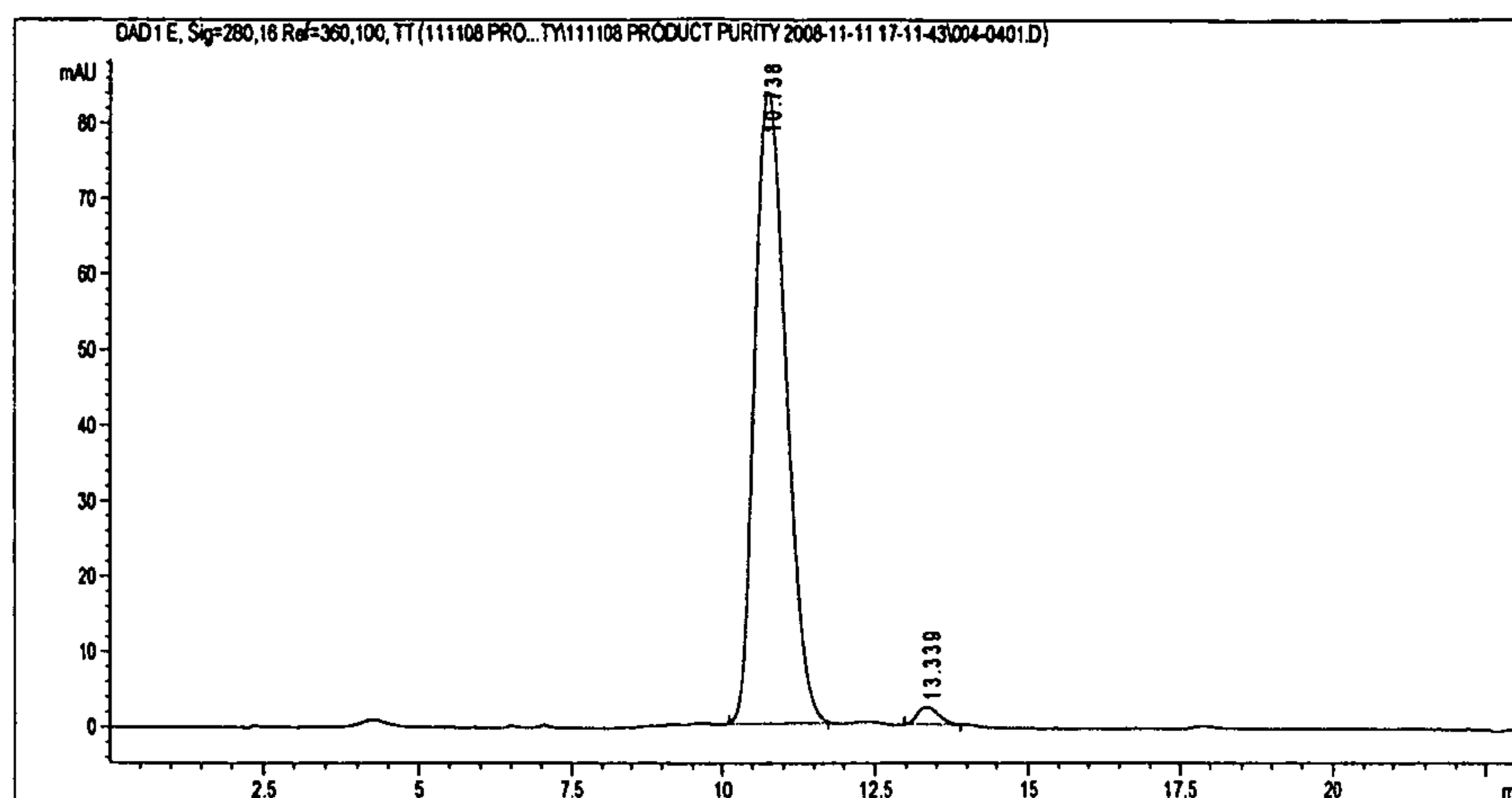
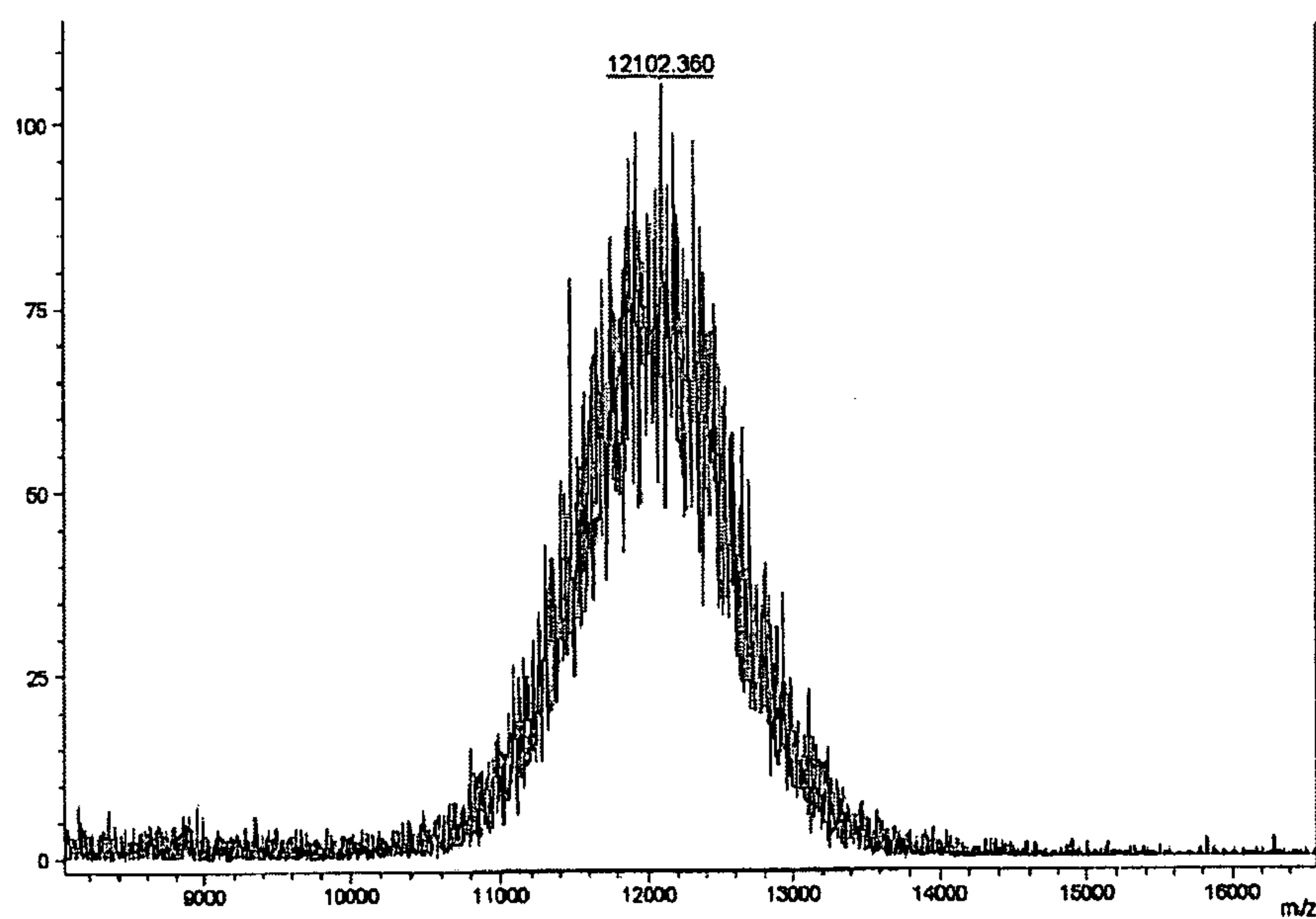


Figure KISS2.2



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12102.360	70.9	1020	280	104.11	1191

Figure 2.3

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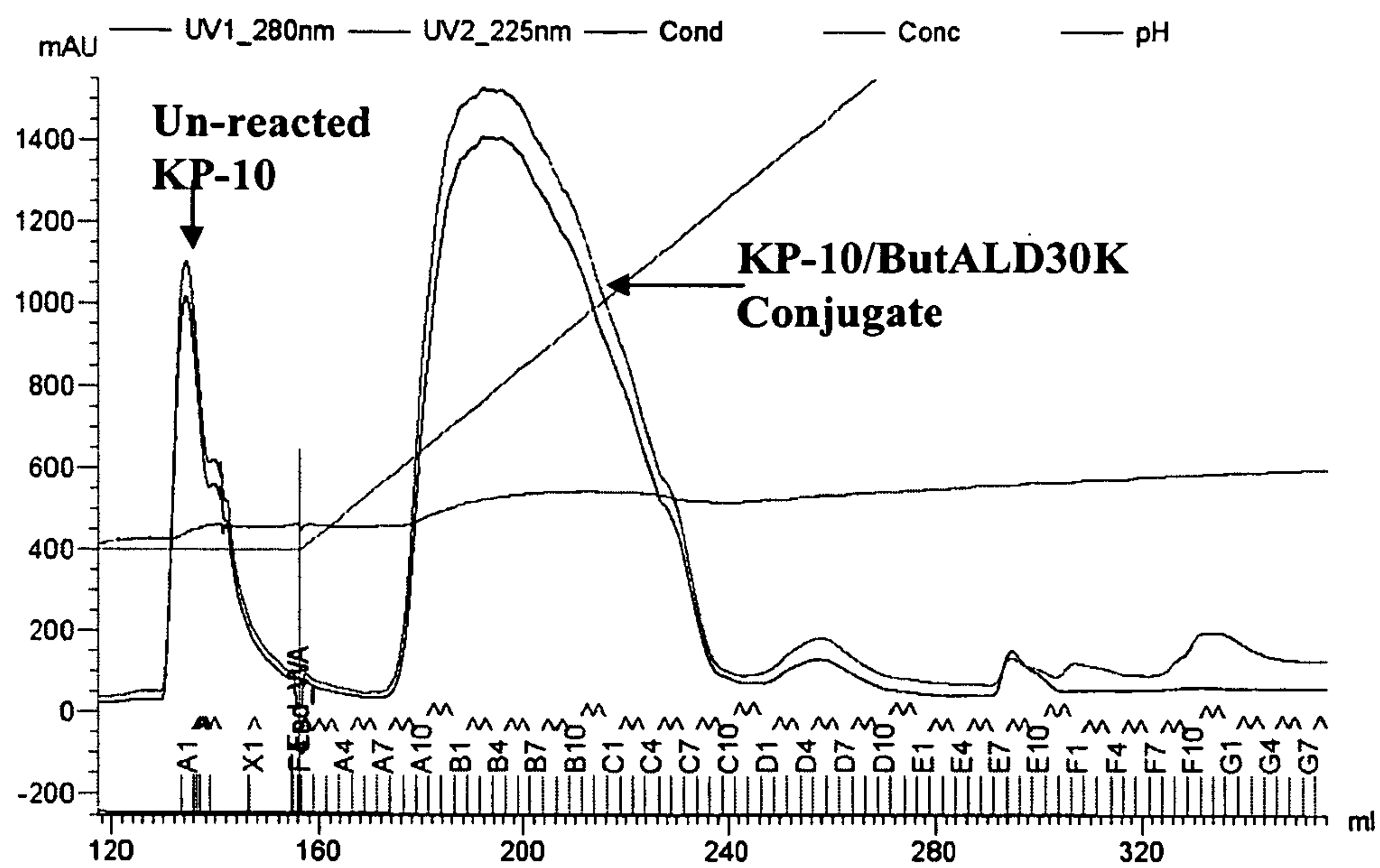


Figure KISS3.1

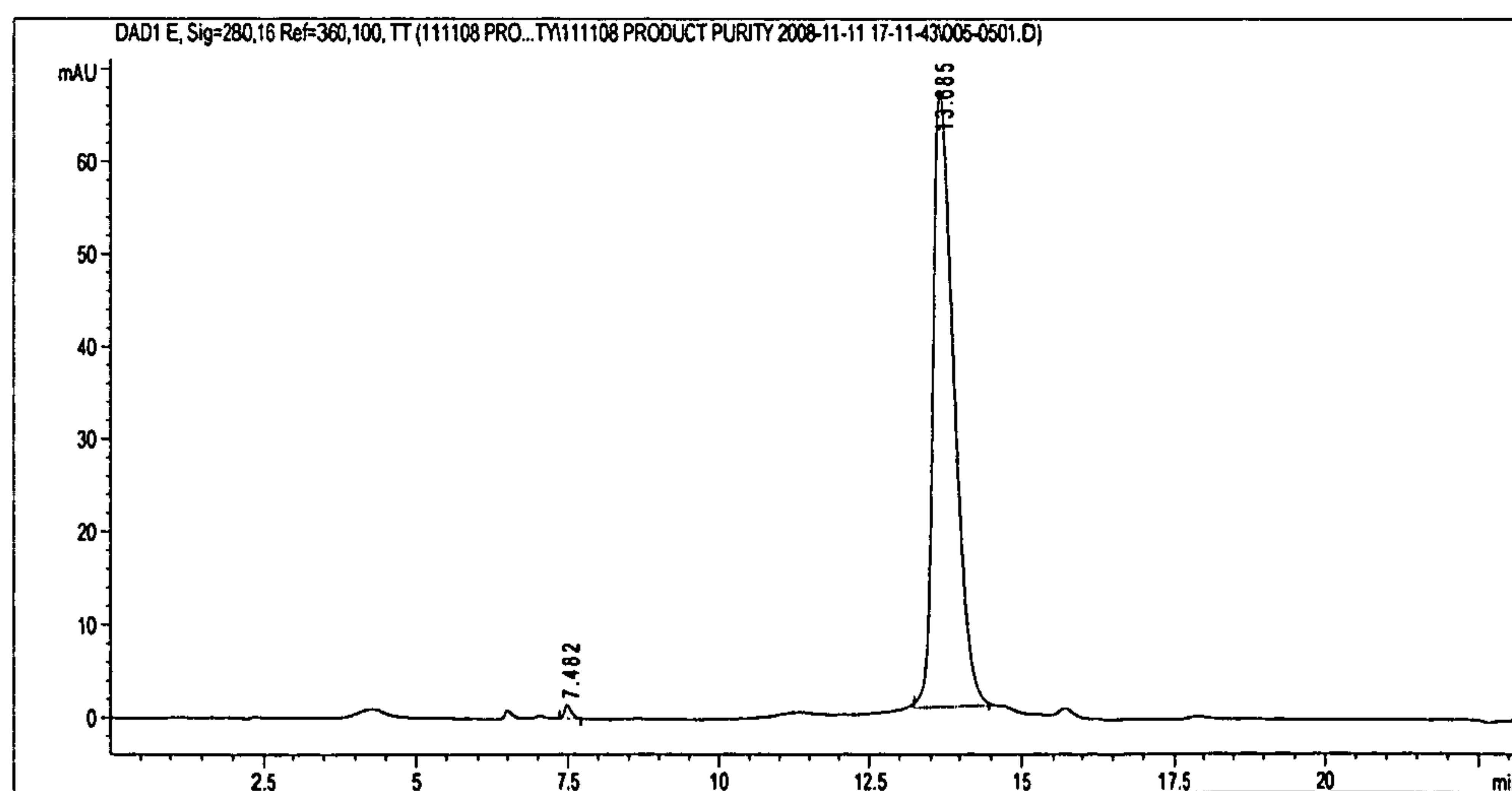
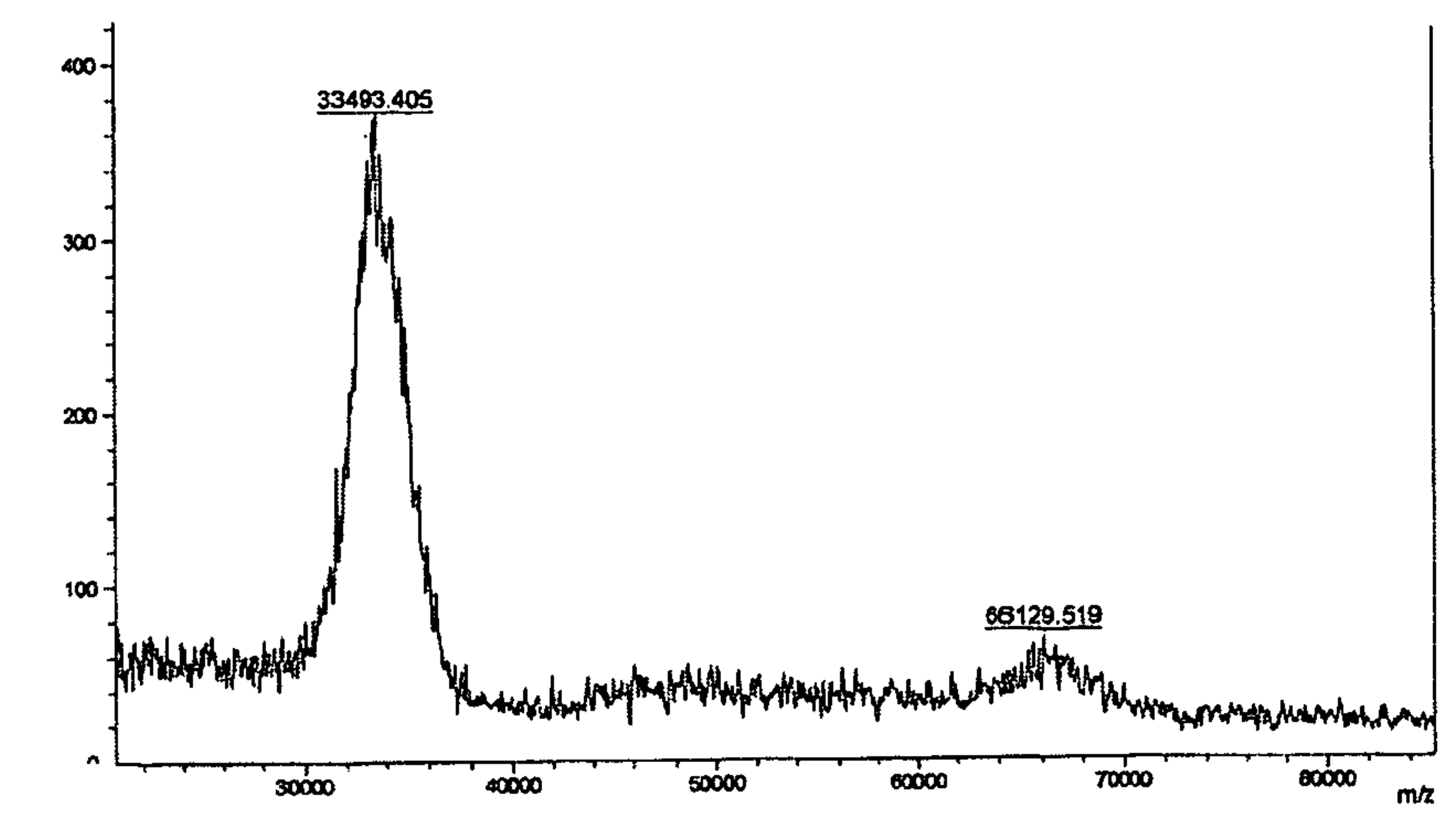


Figure KISS3.2

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m/z	SN	Quality Fac.	Res.	Intens.	Area
33493.405	349.1	54639	11	337.66	553818
66129.519	72.1	172	14	69.76	19387

Figure KISS3.3

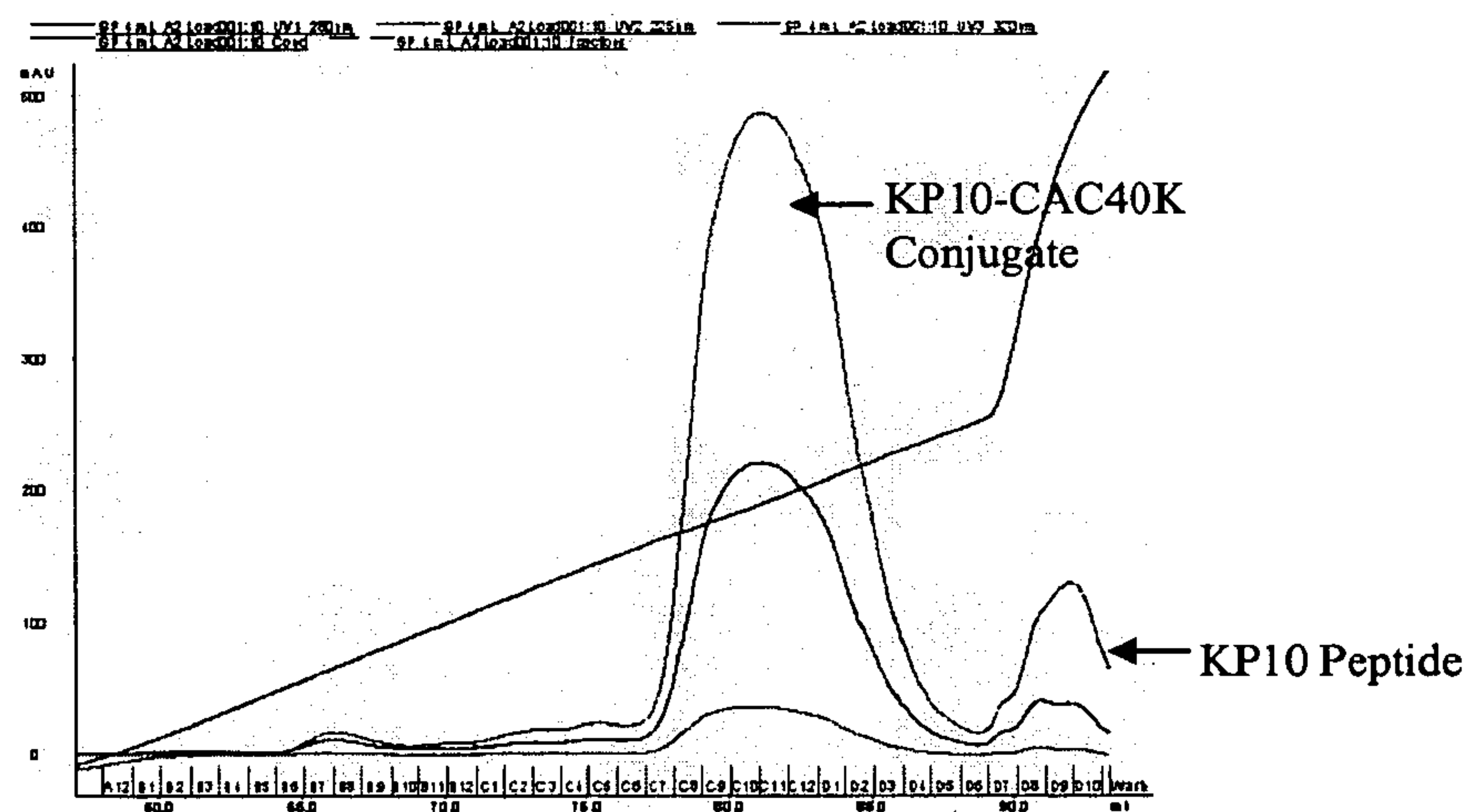


Figure KISS4.1

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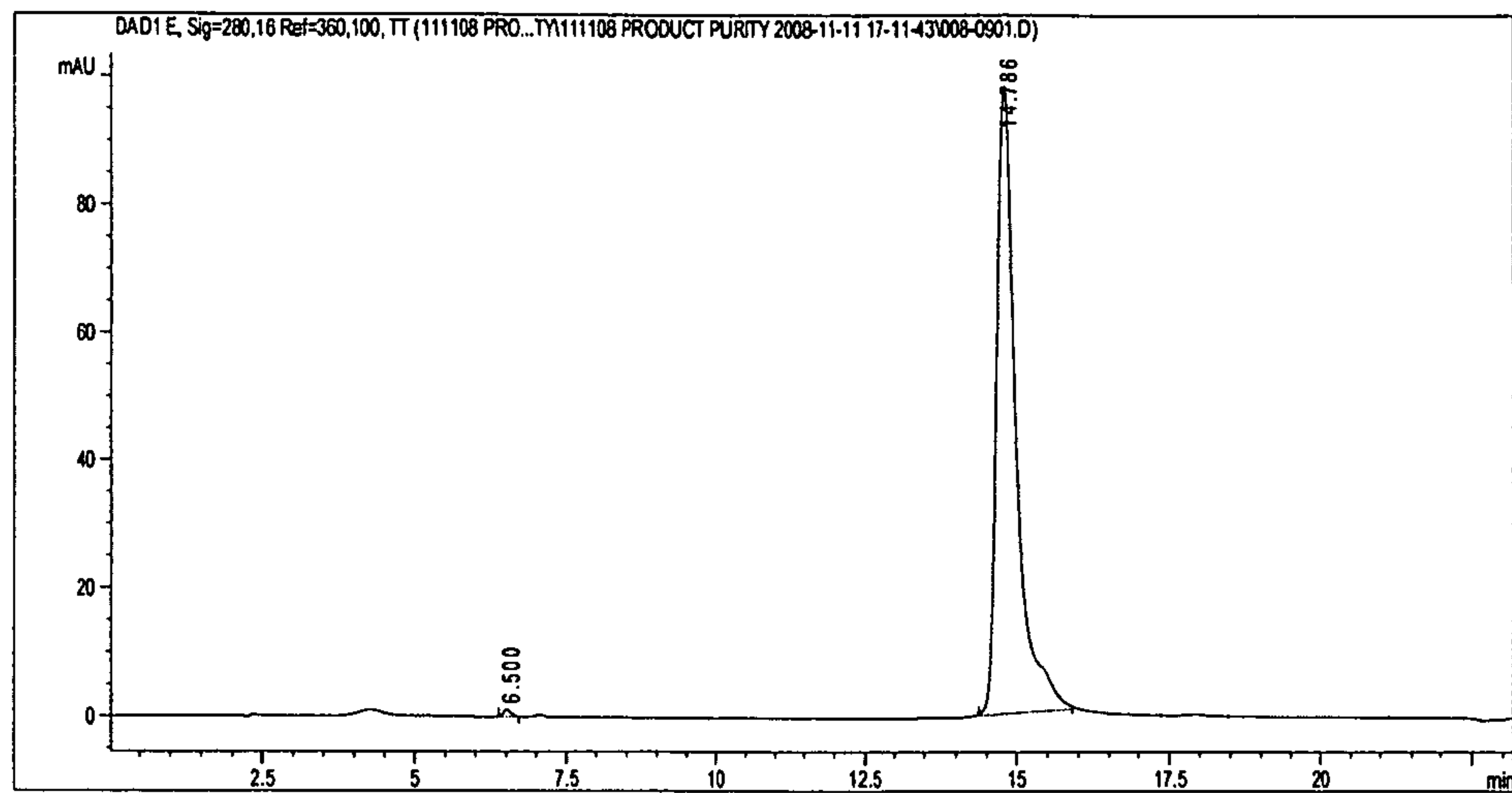
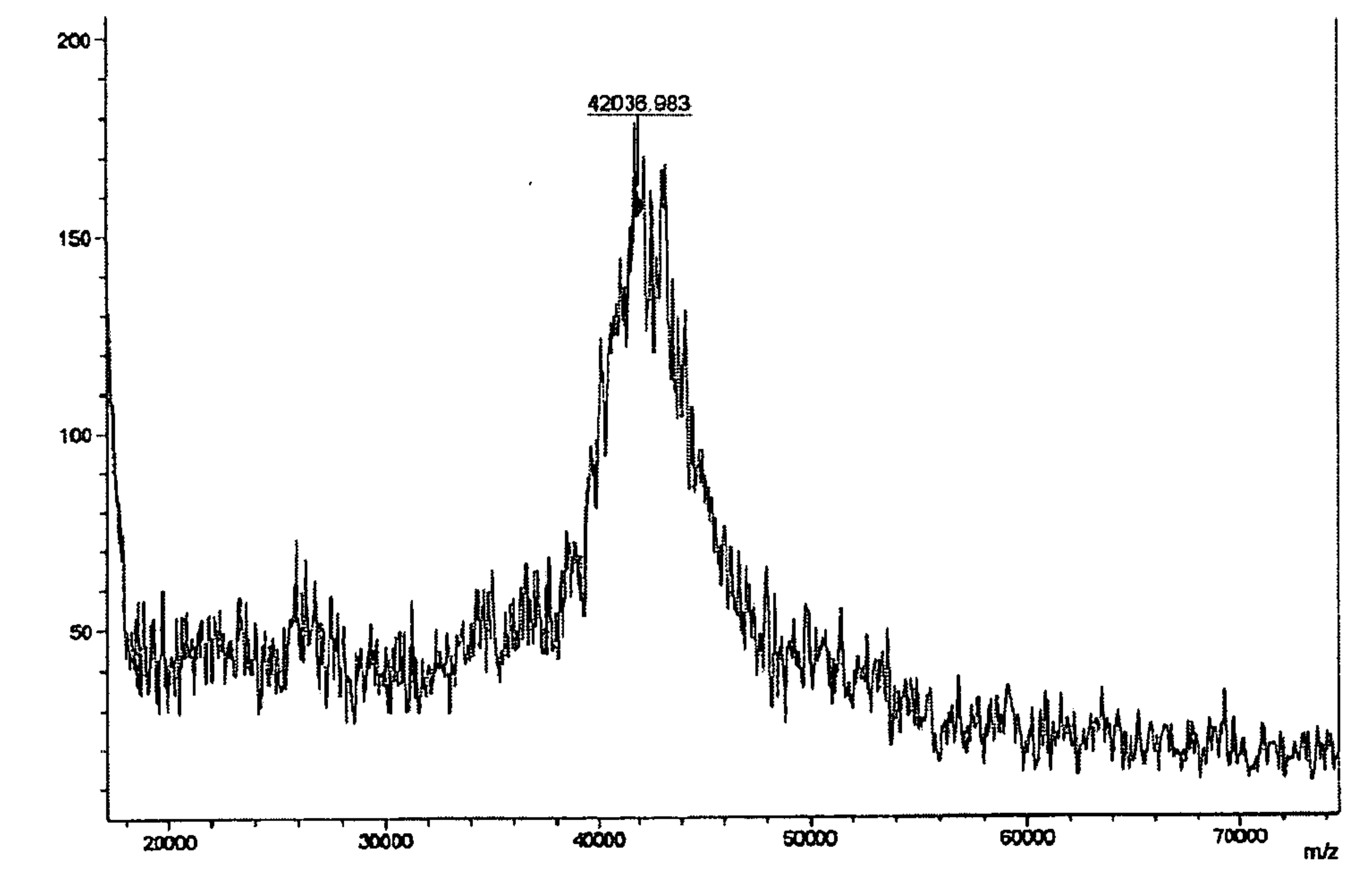


Figure KISS4.2



m/z	SN	Quality Fac.	Res.	Intens.	Area
42036.983	198.8	2429	10	179.04	105035

Figure KISS4.3

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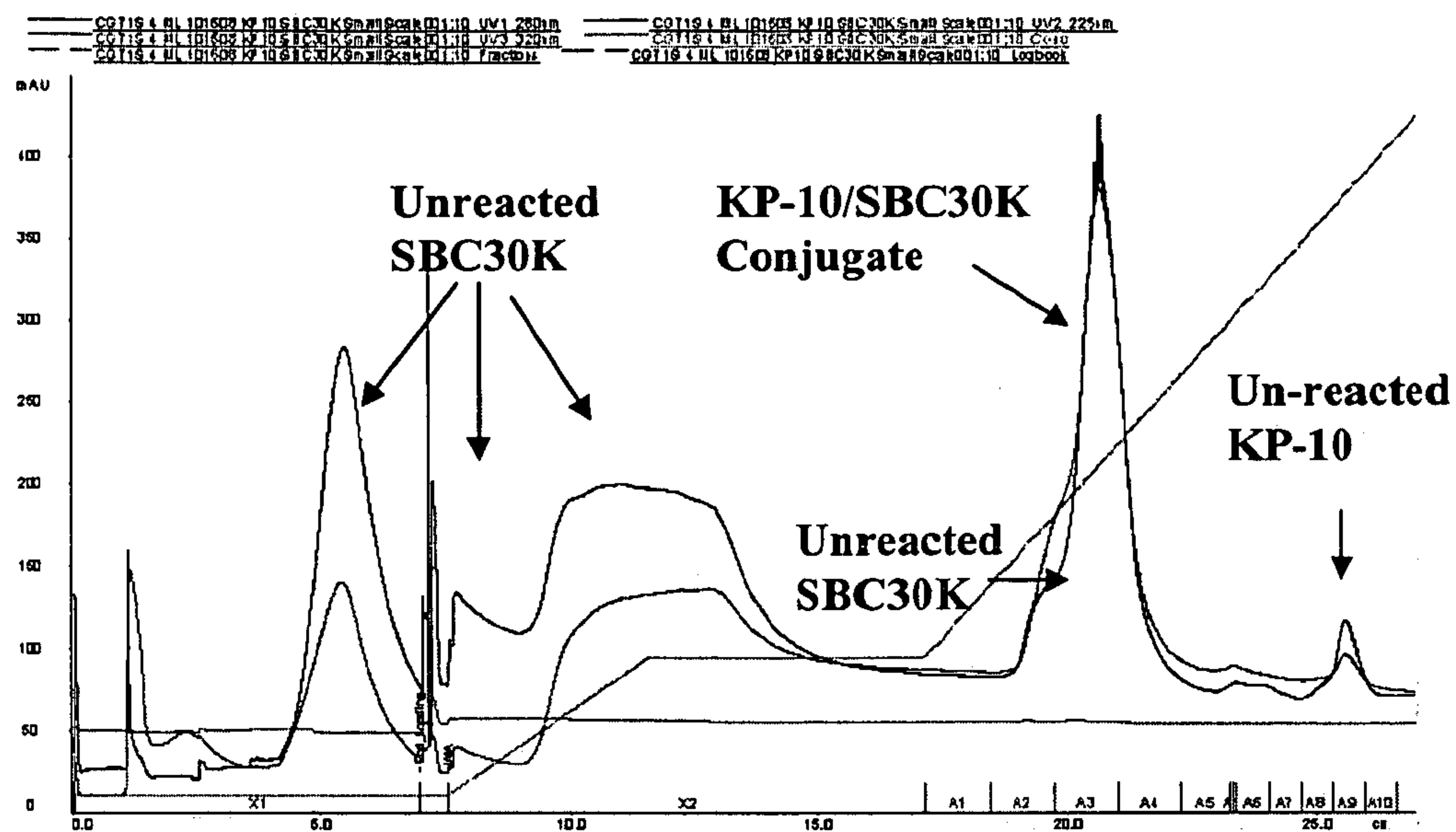


Figure KISS5.1

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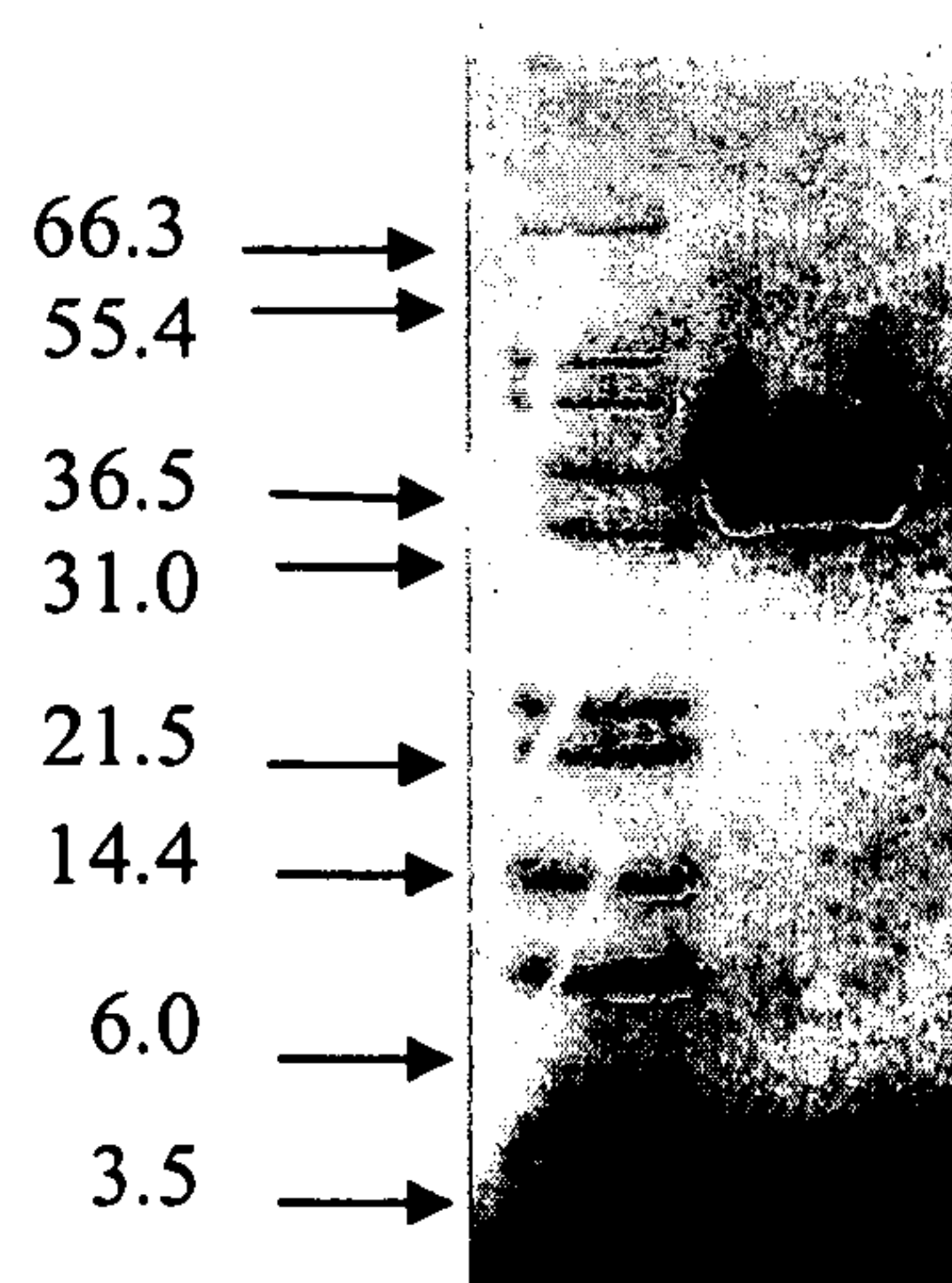


Figure KISS5.2

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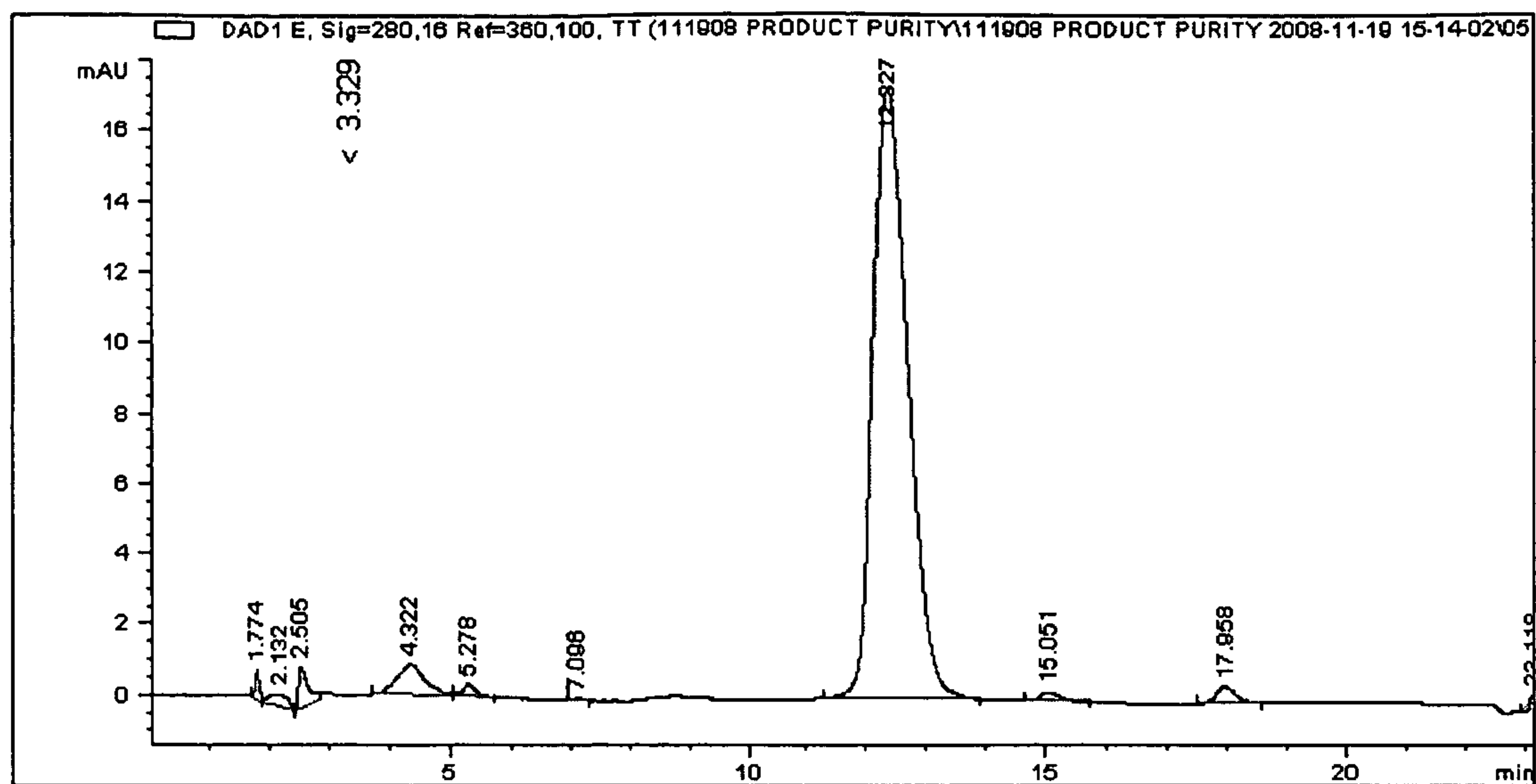


Figure KISS5.3

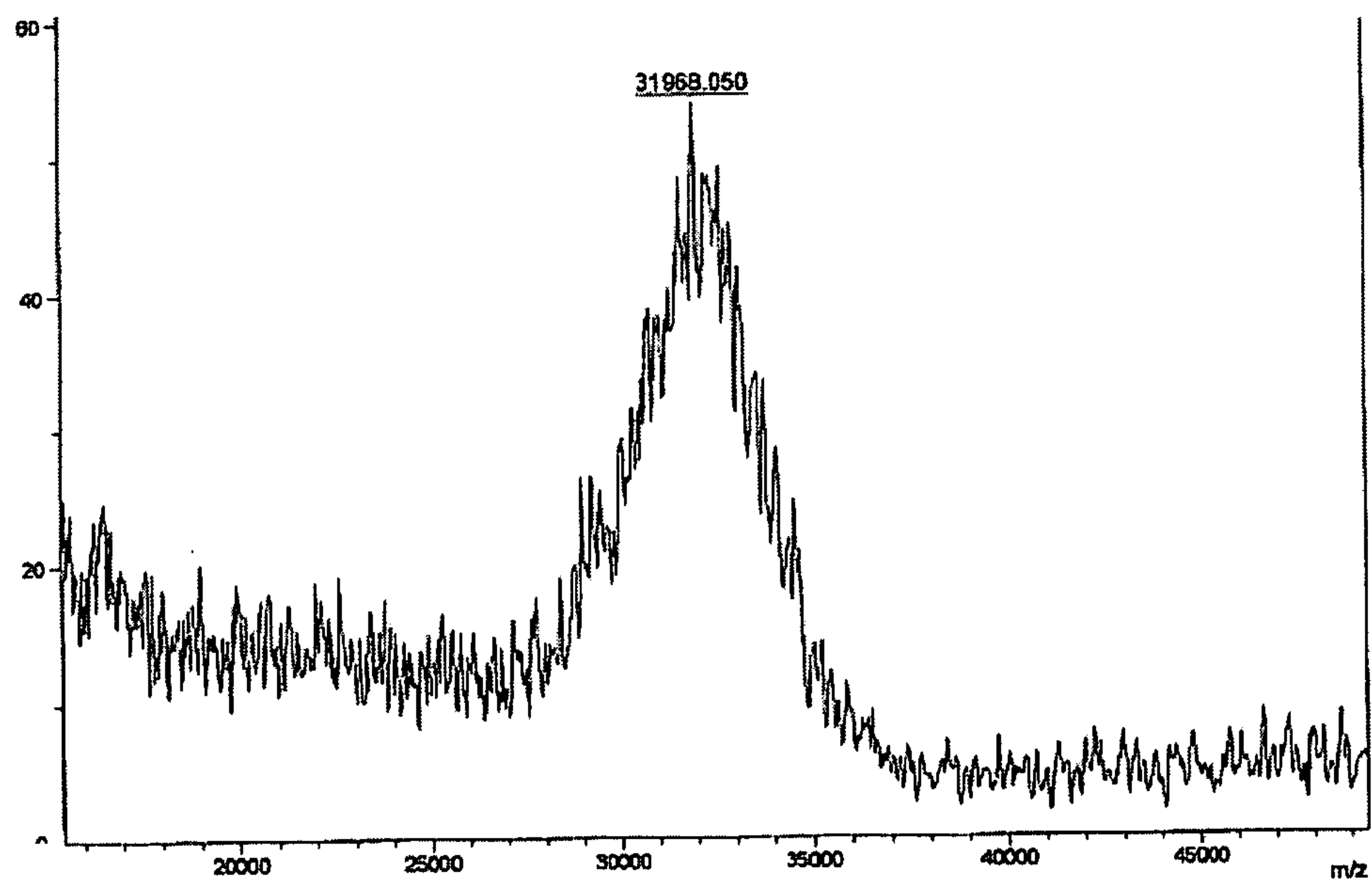


Figure KISS5.4

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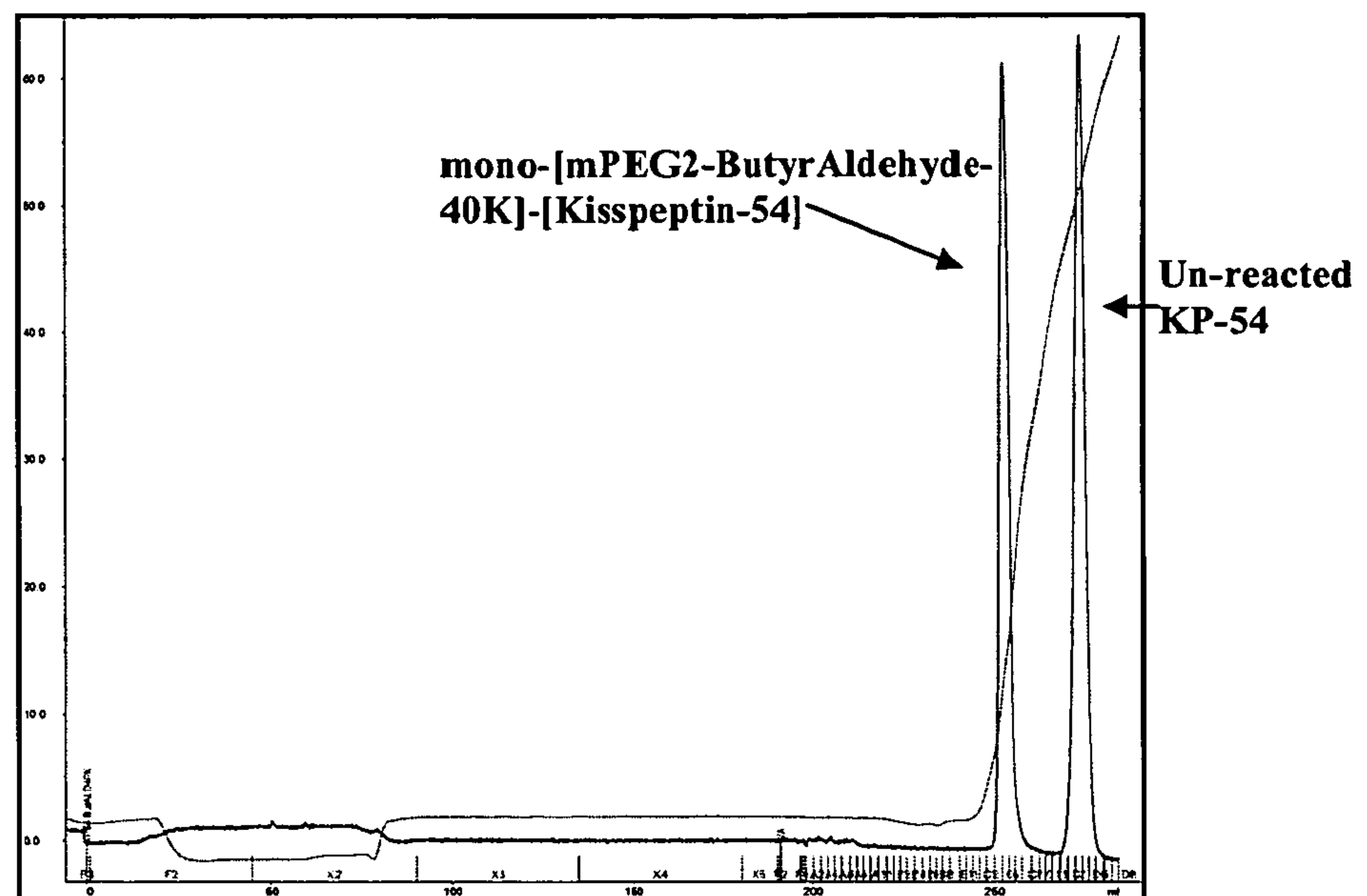


Figure KISS6.1

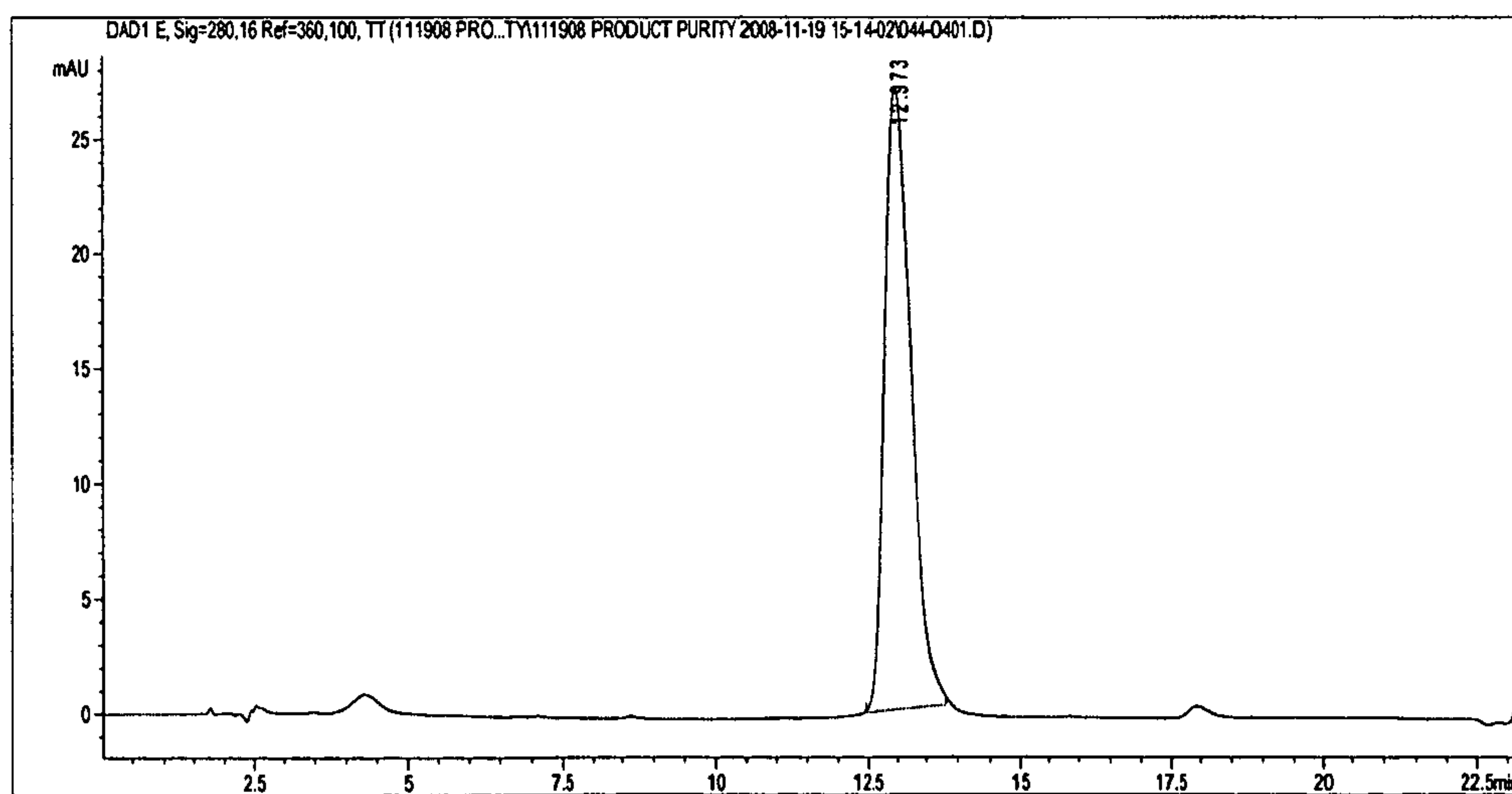


Figure KISS6.2

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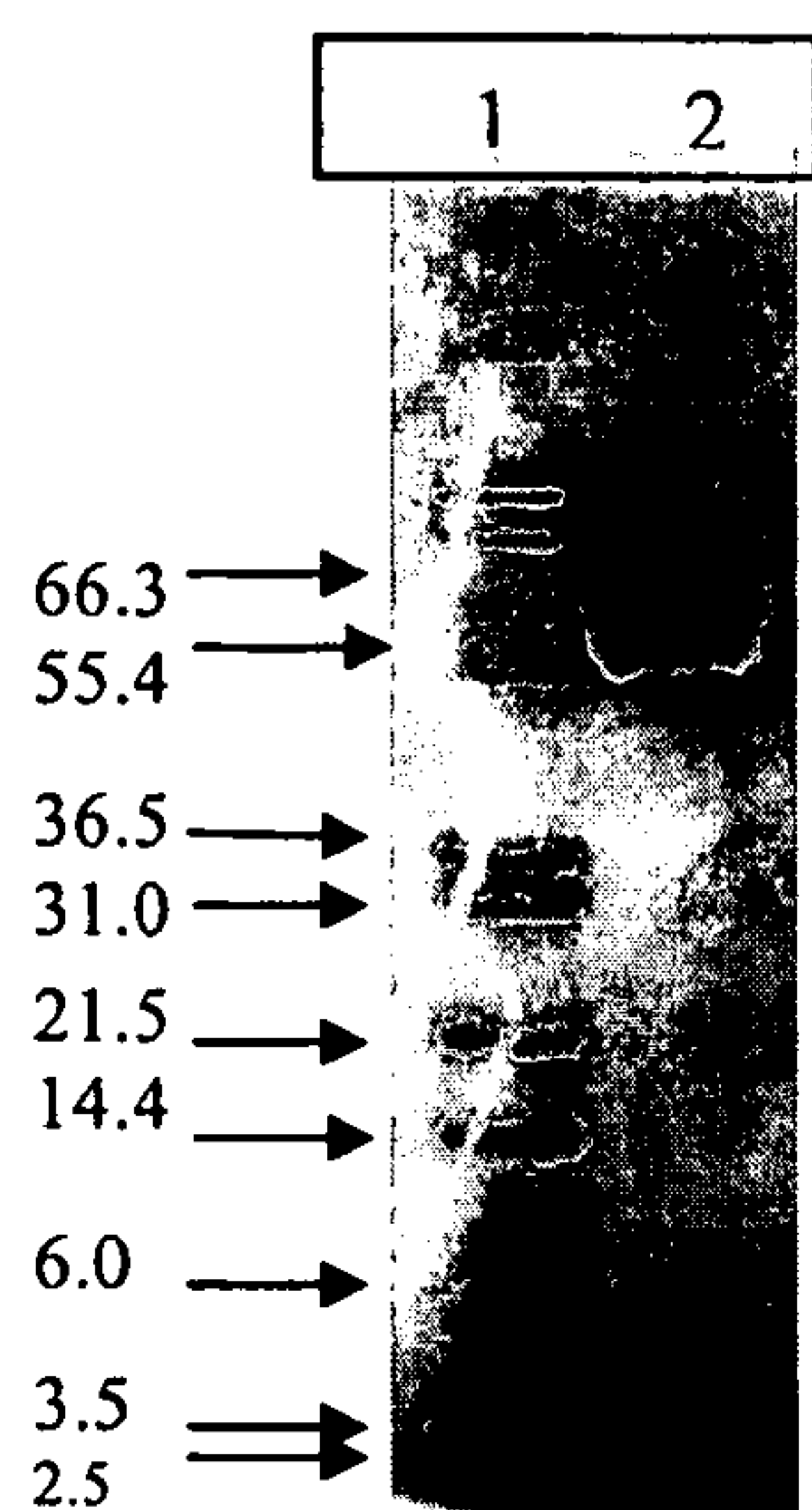


Figure KISS6.3

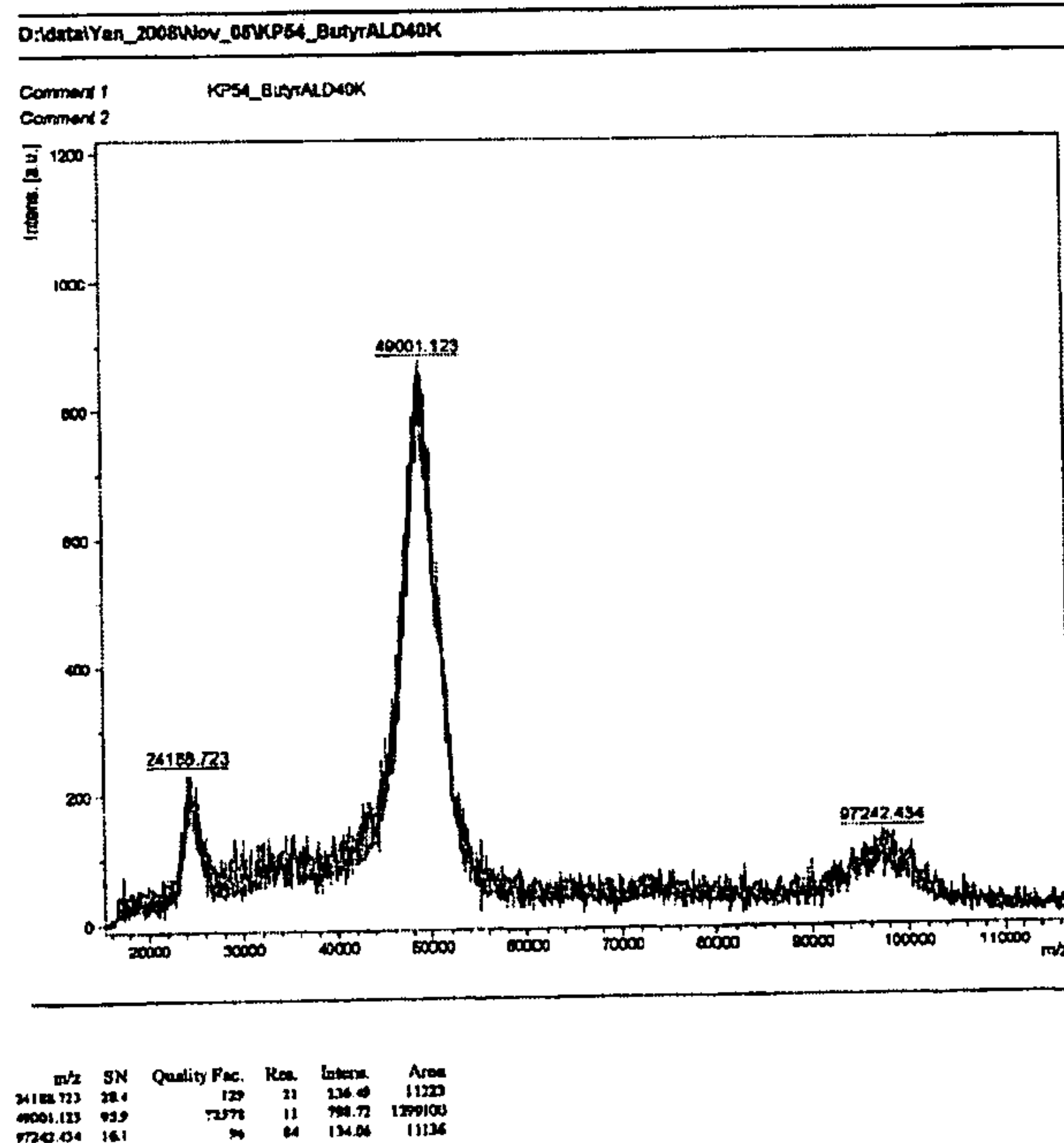


Figure KISS6.4

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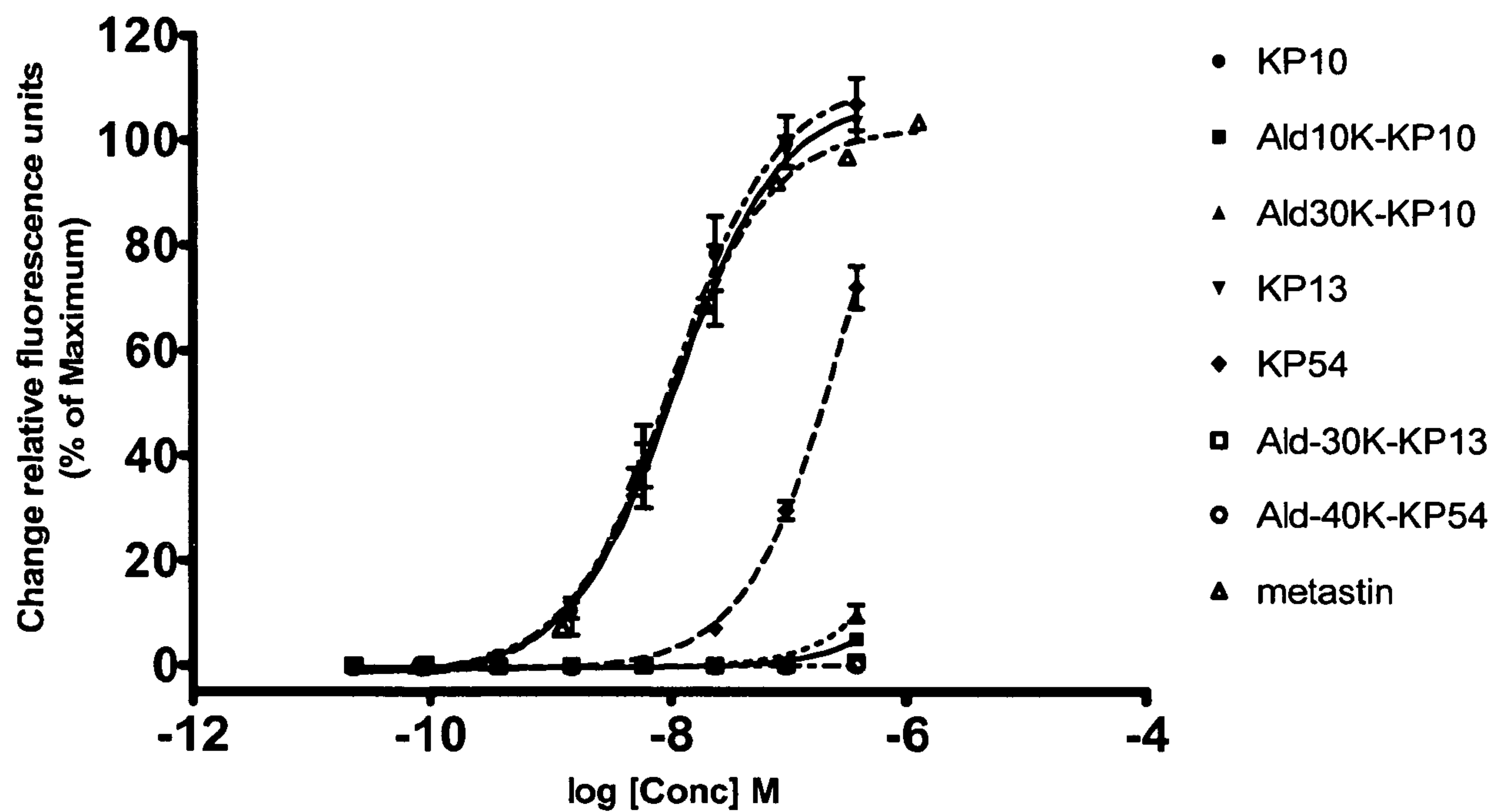


Figure KISS8.1

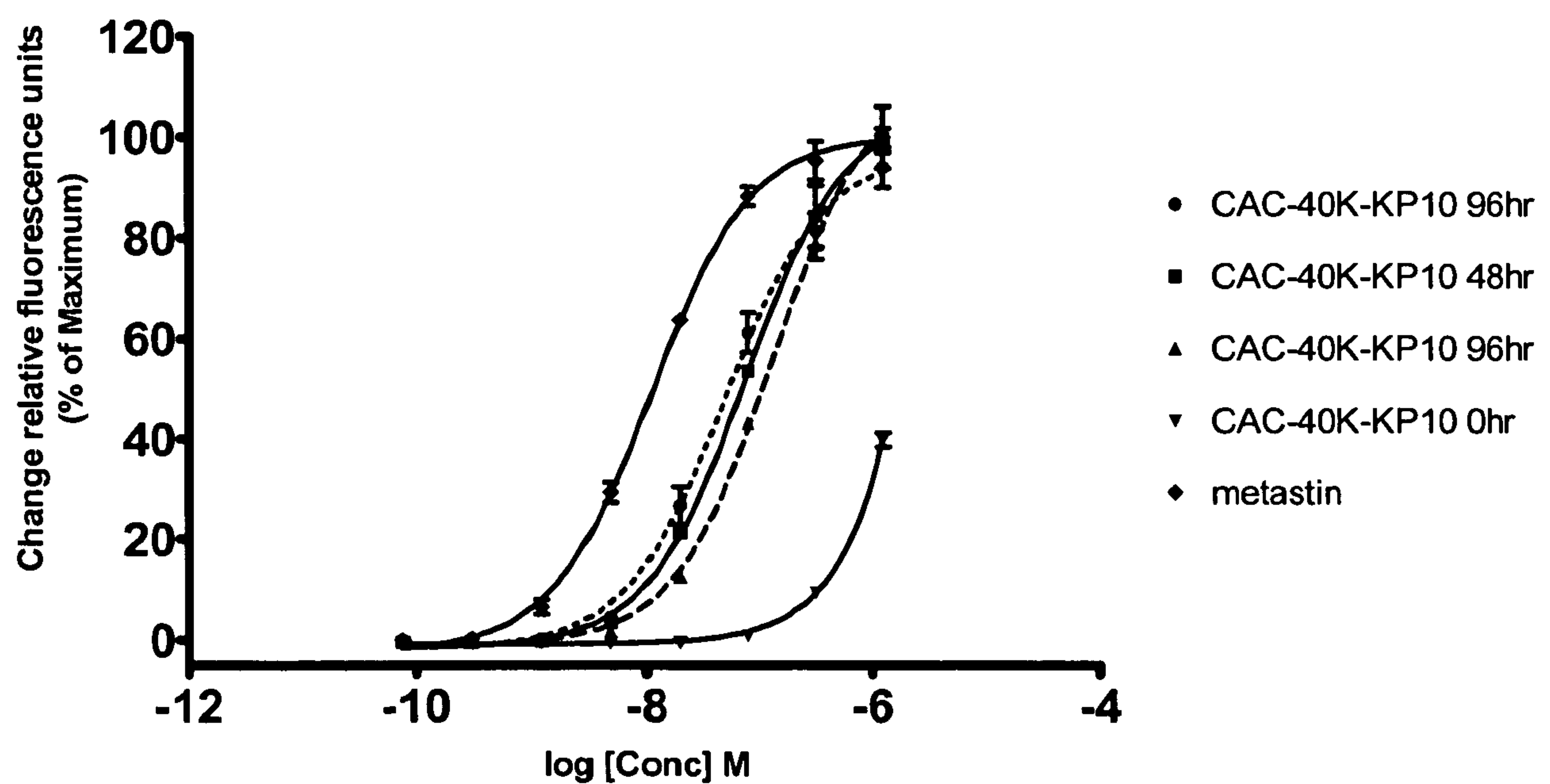


Figure KISS8.2

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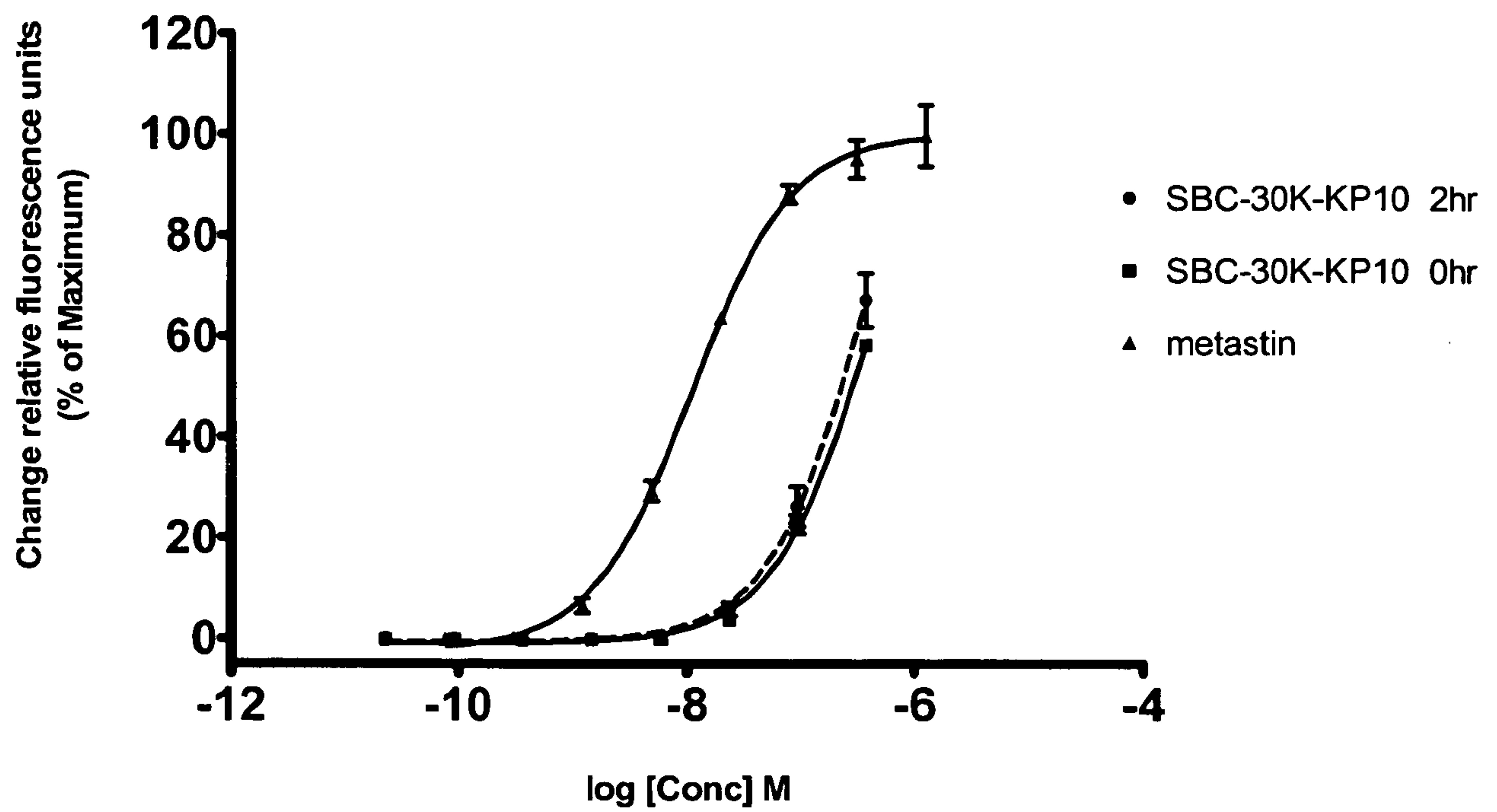


Figure KISS8.3

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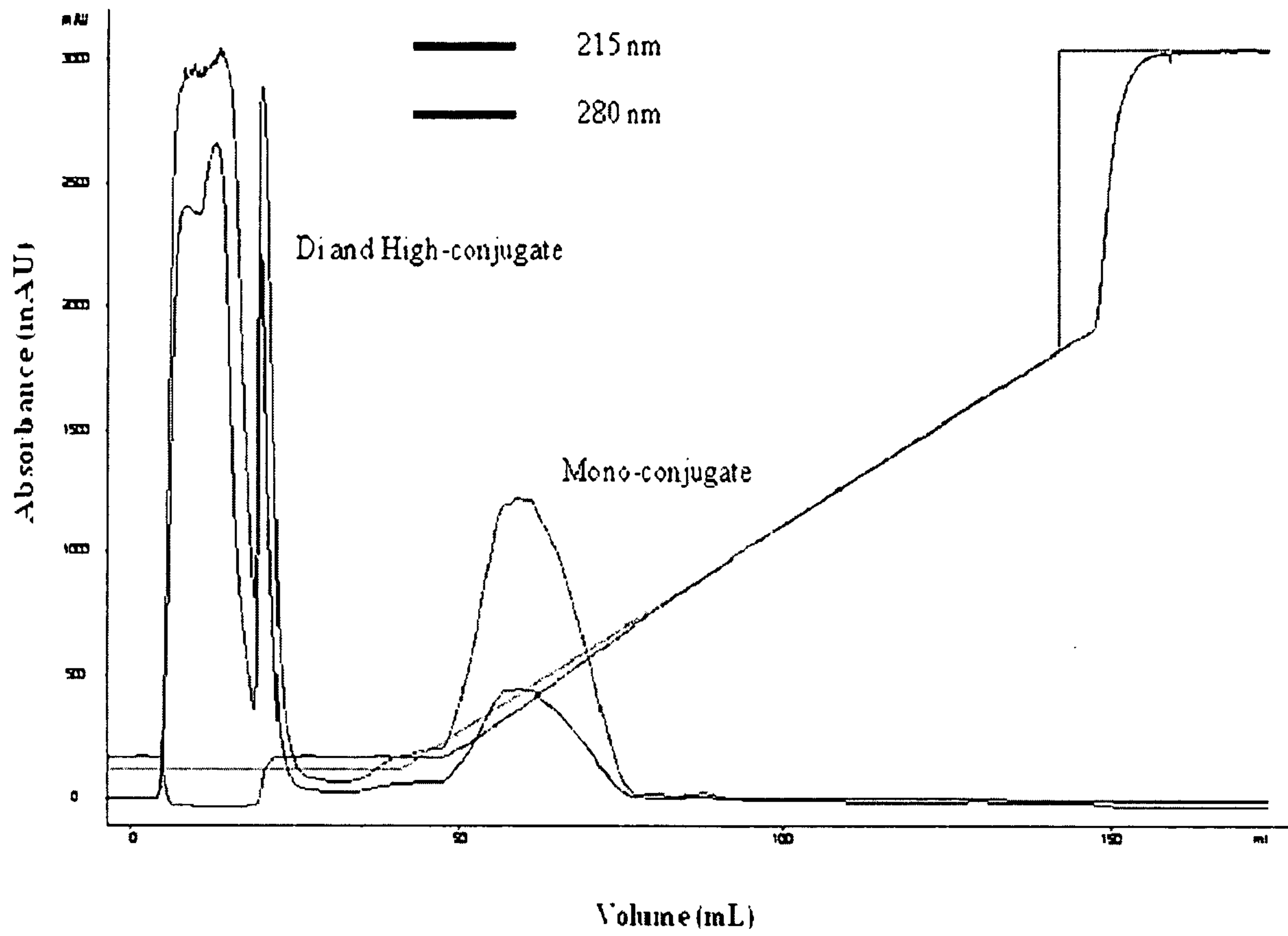


Figure ZIC2.1

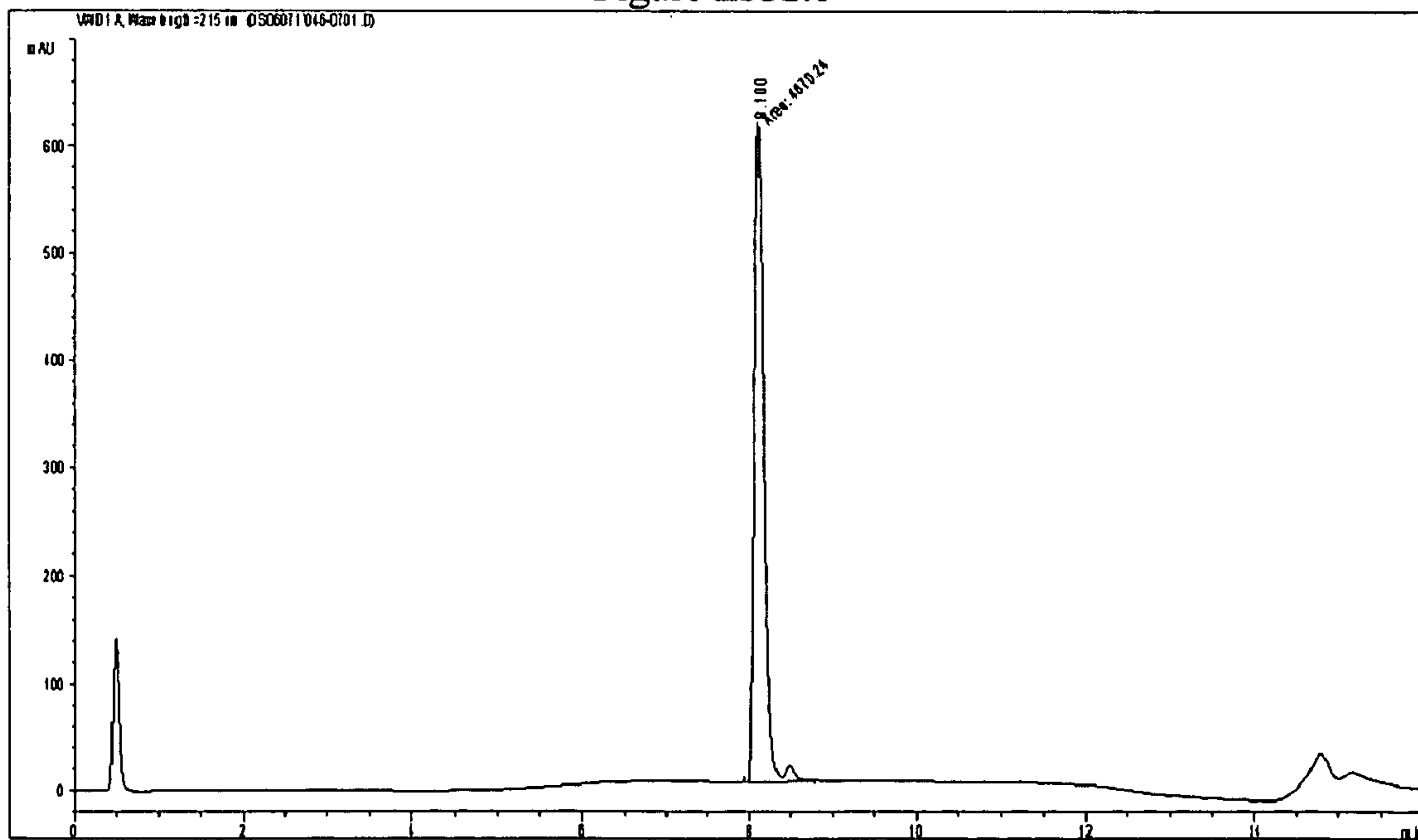


Figure ZIC2.2

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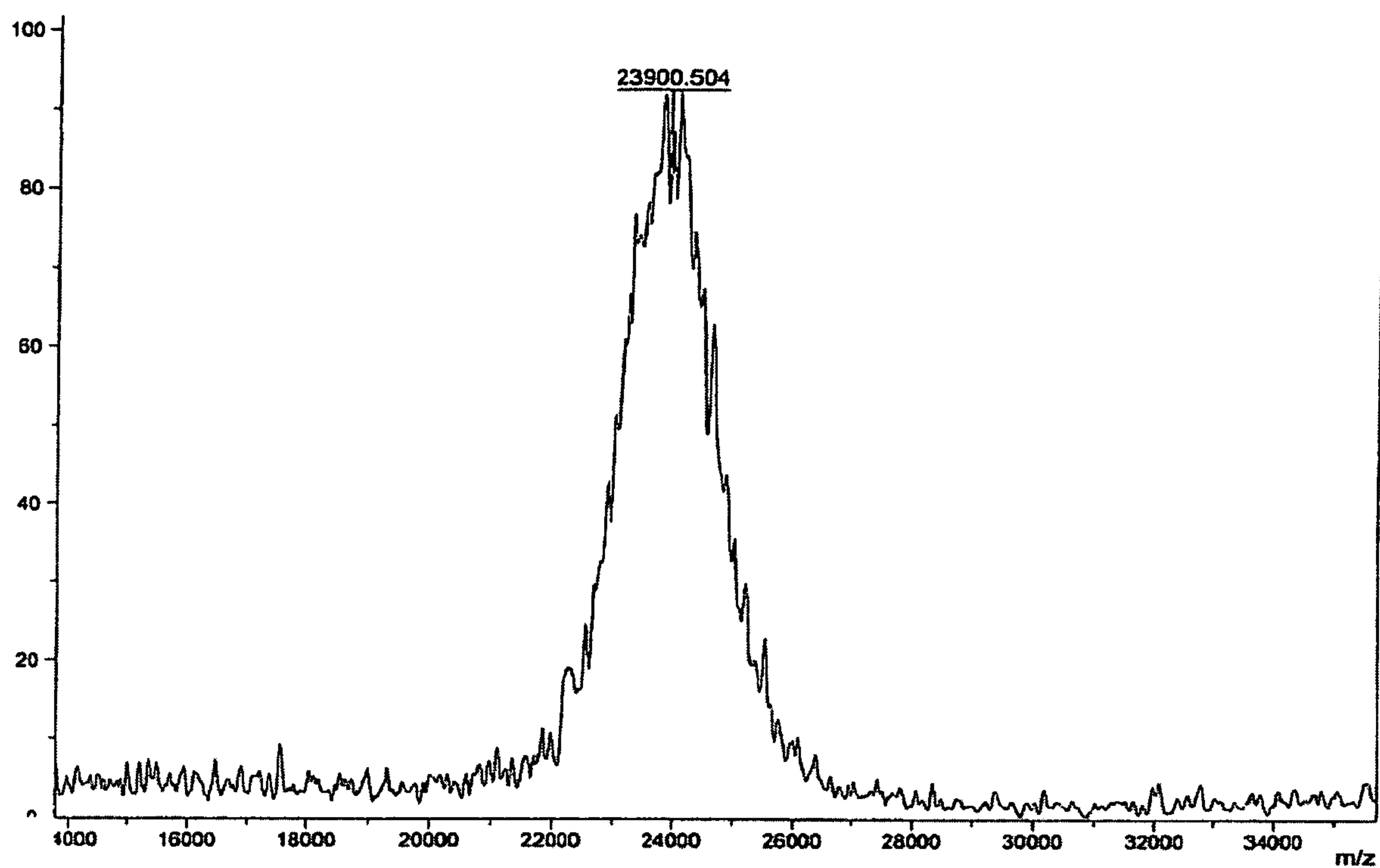


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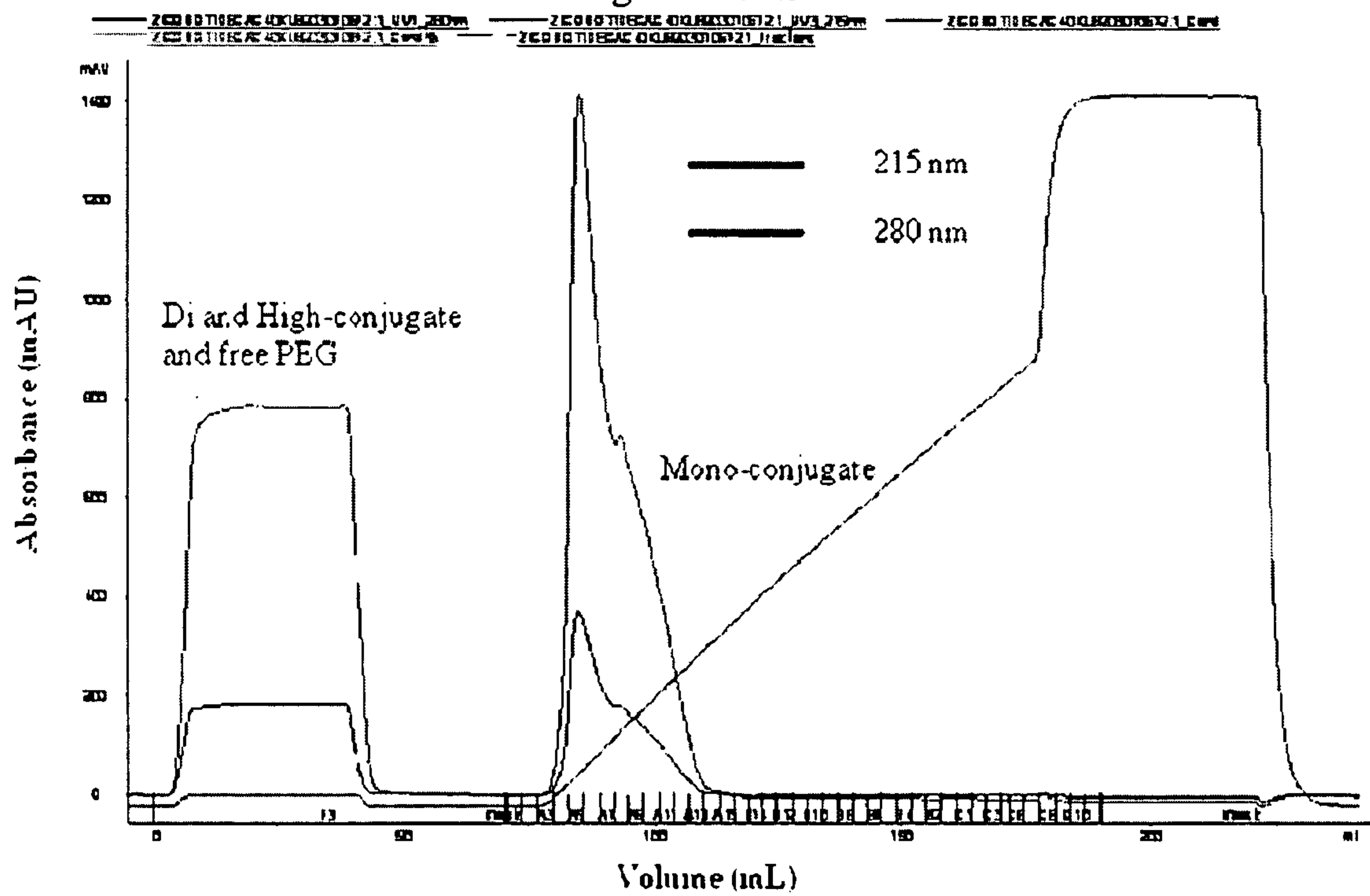


Figure ZIC3.1

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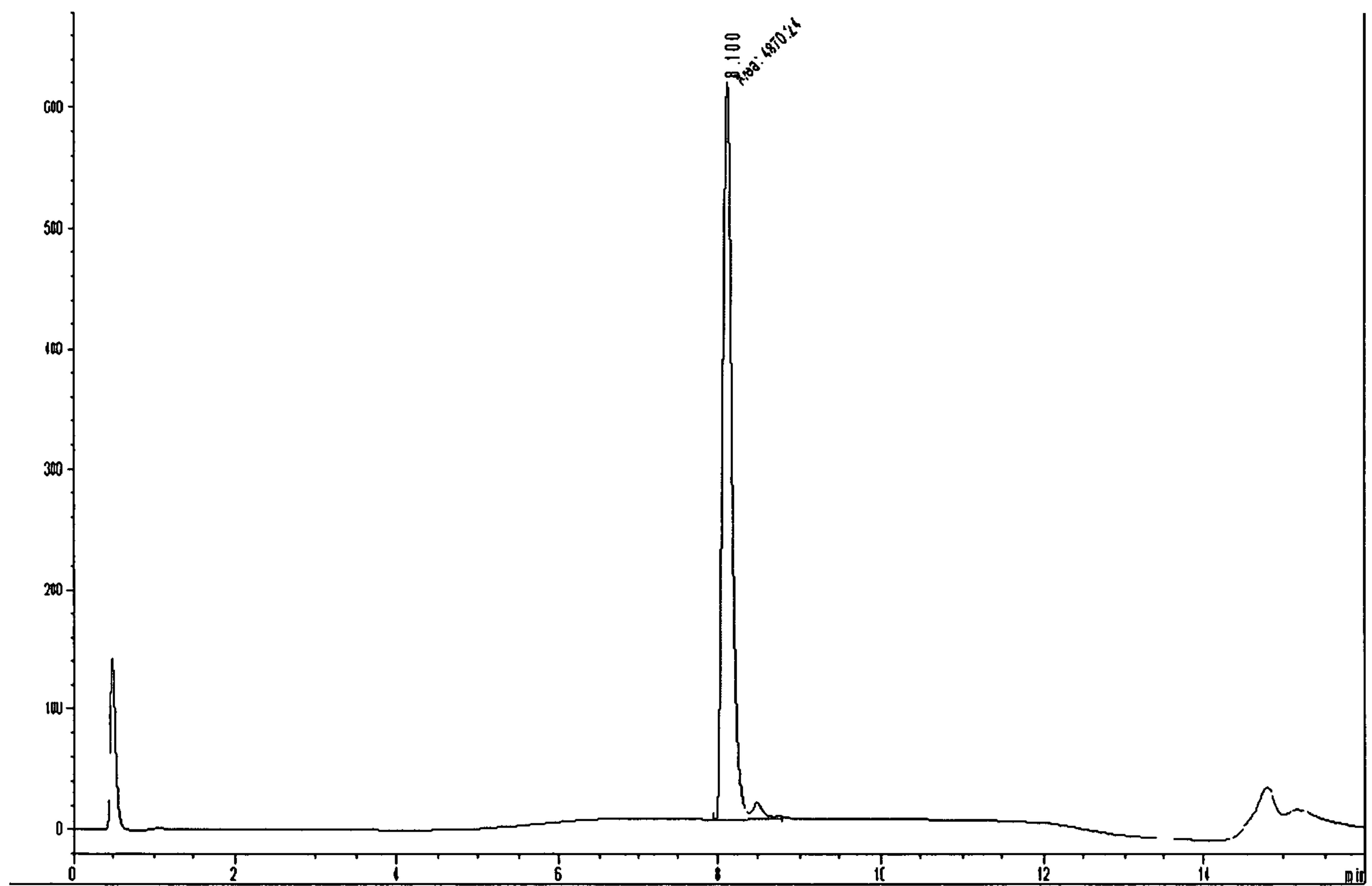


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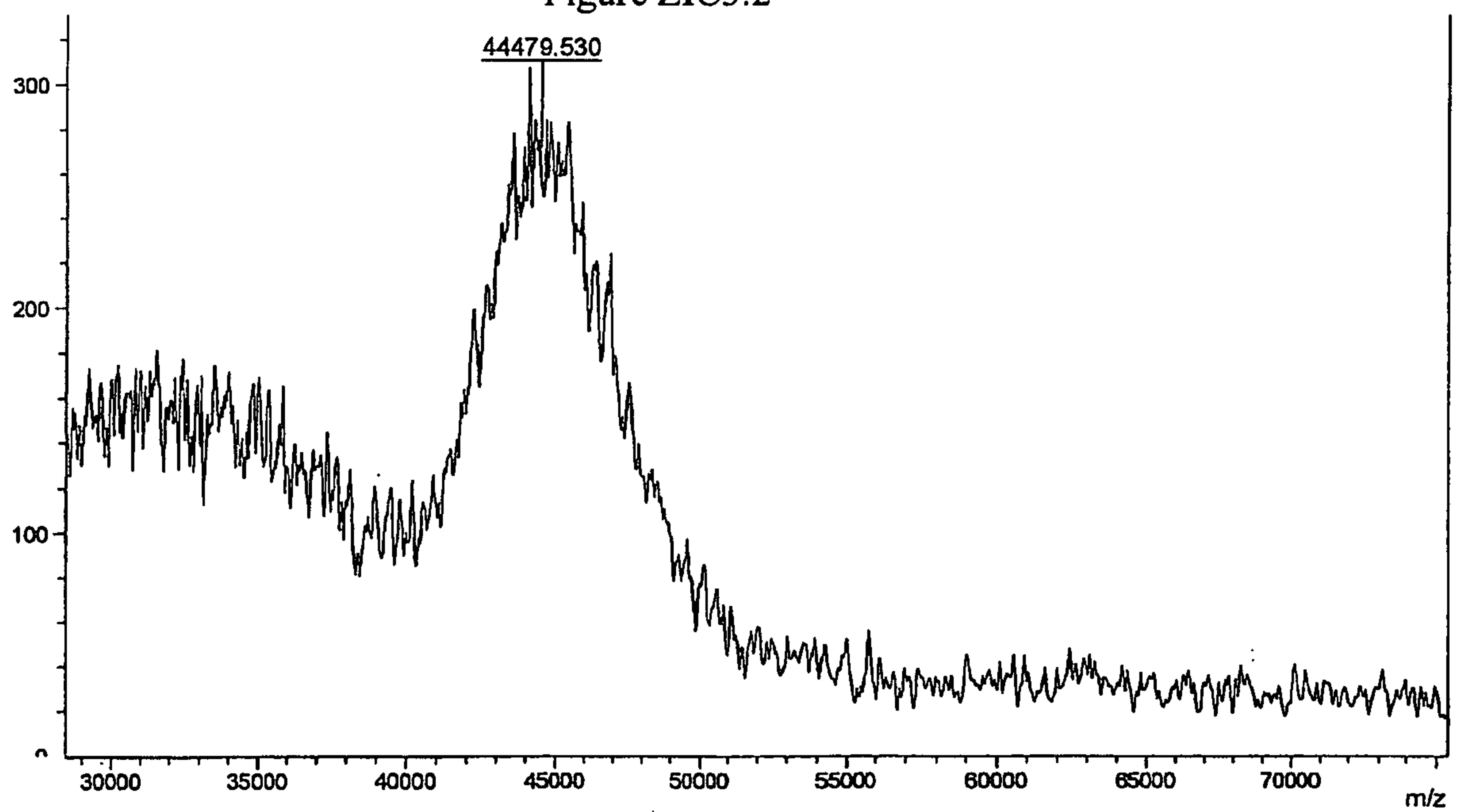


Figure ZIC3.3

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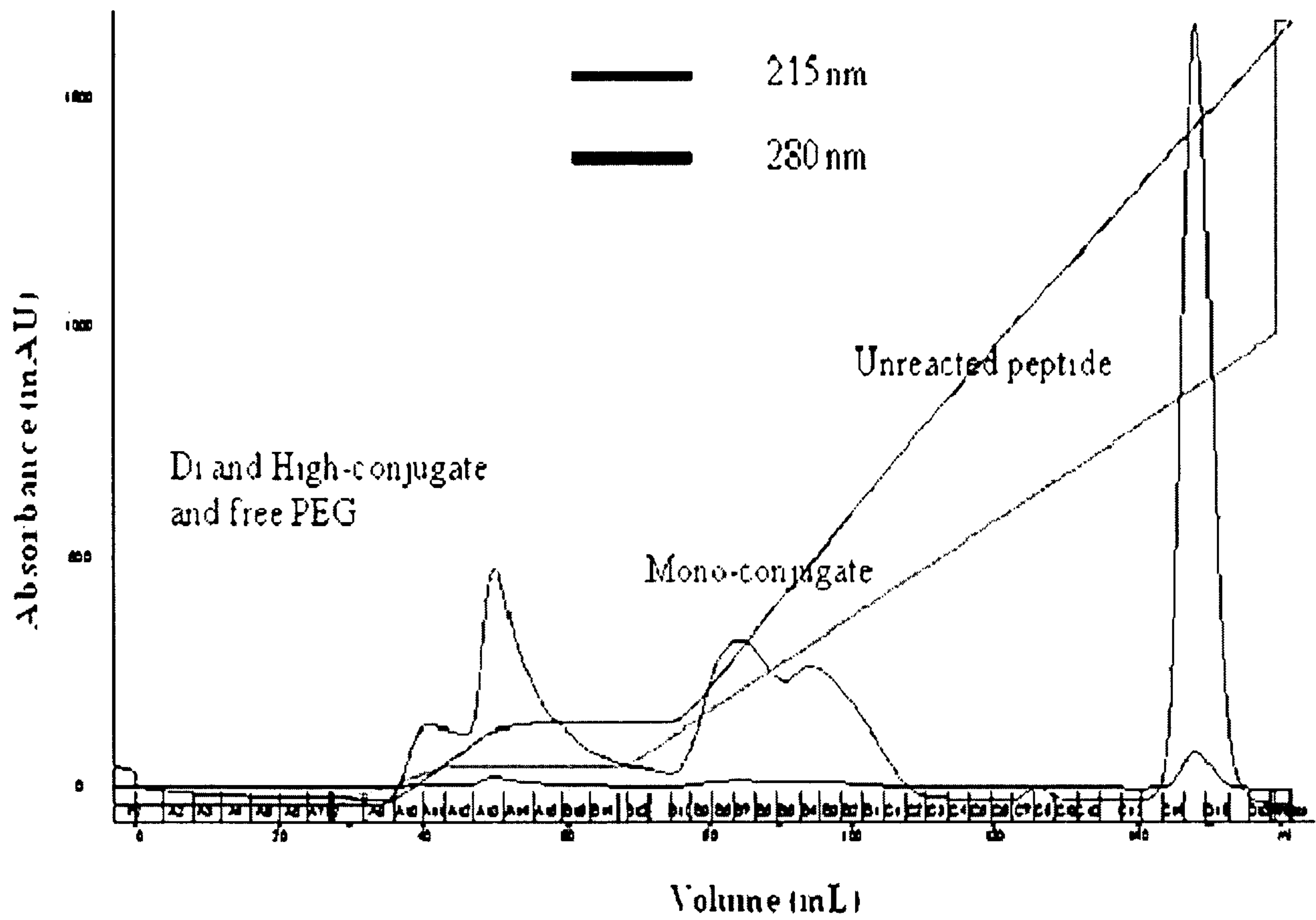


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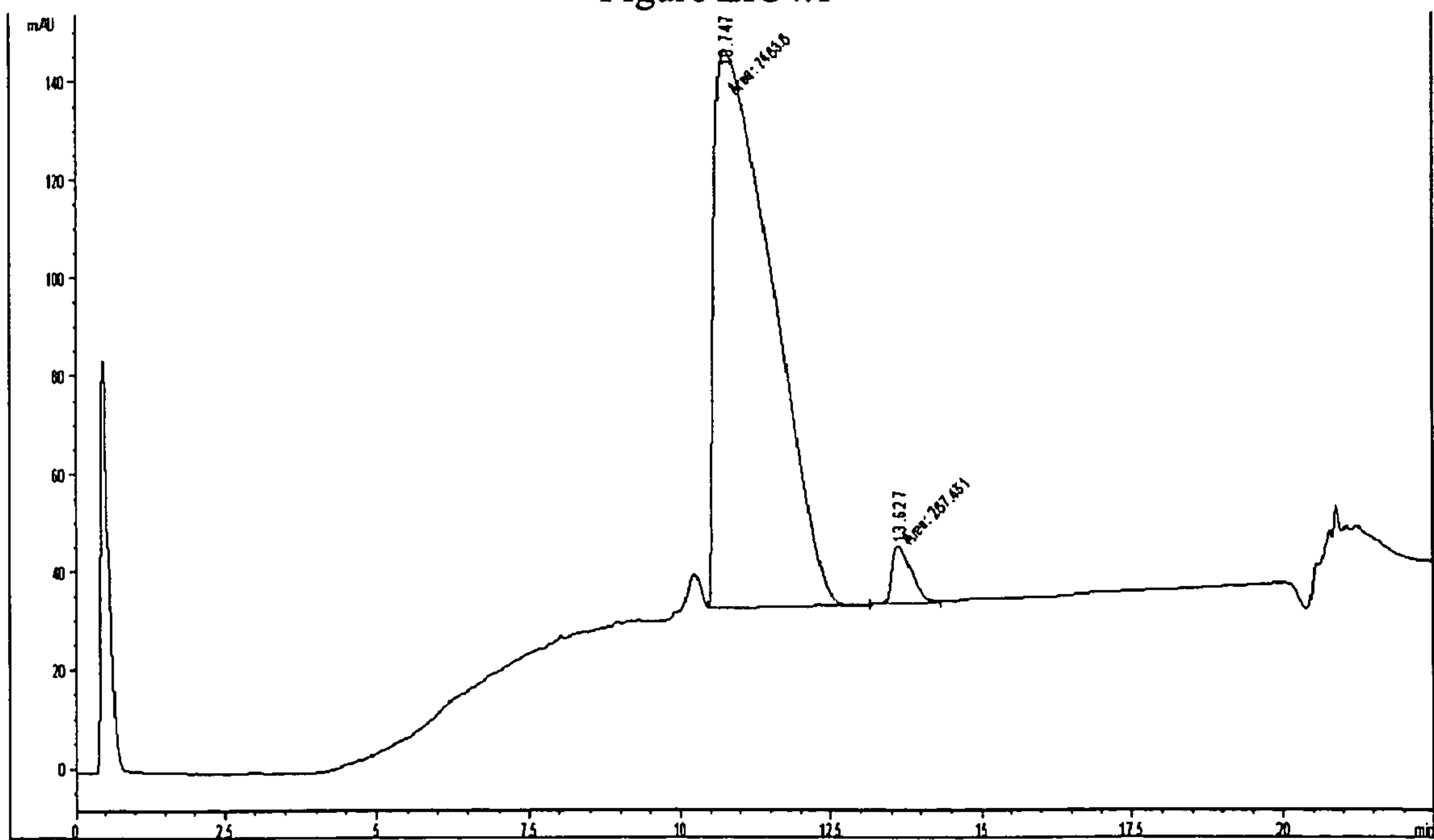


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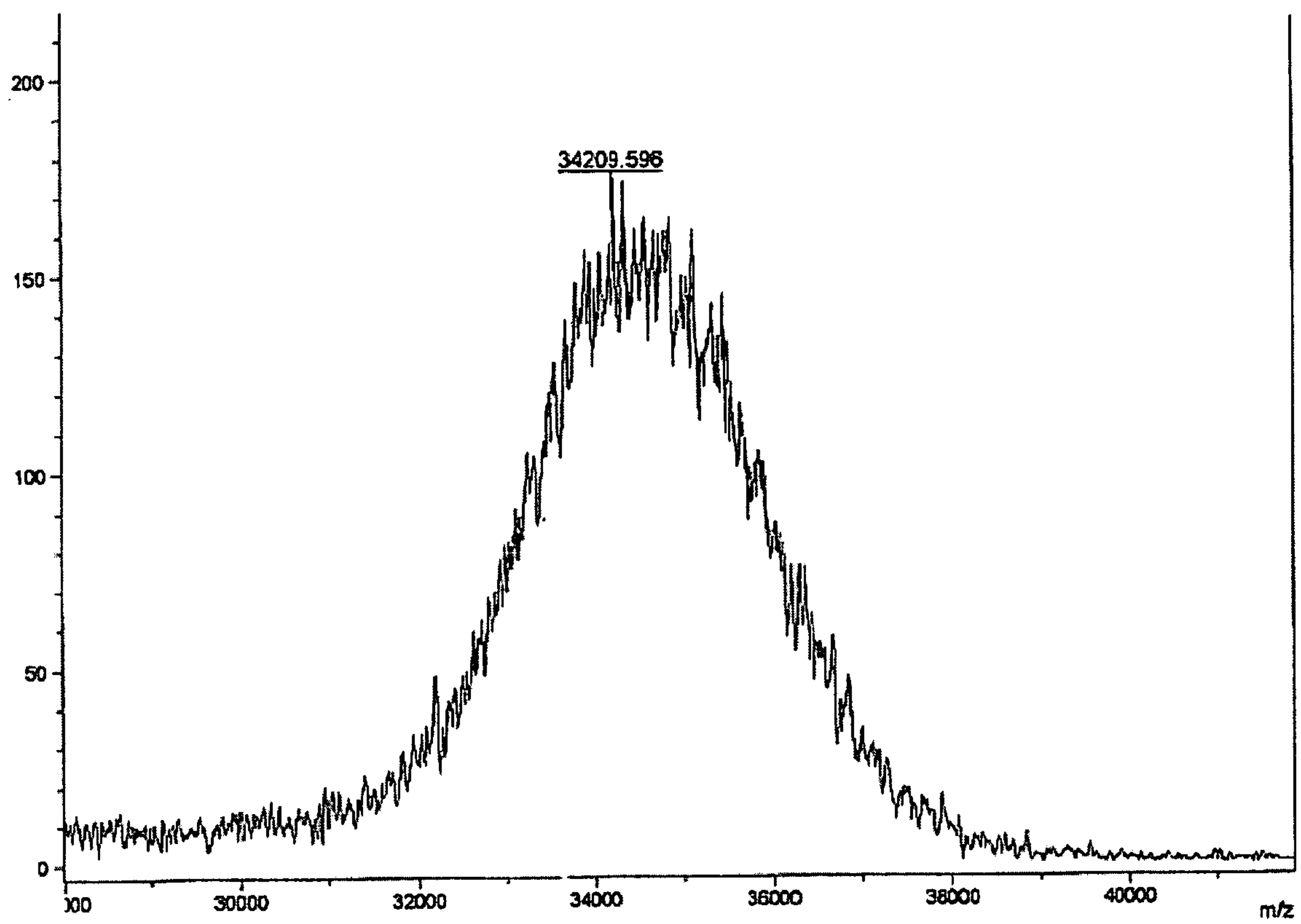


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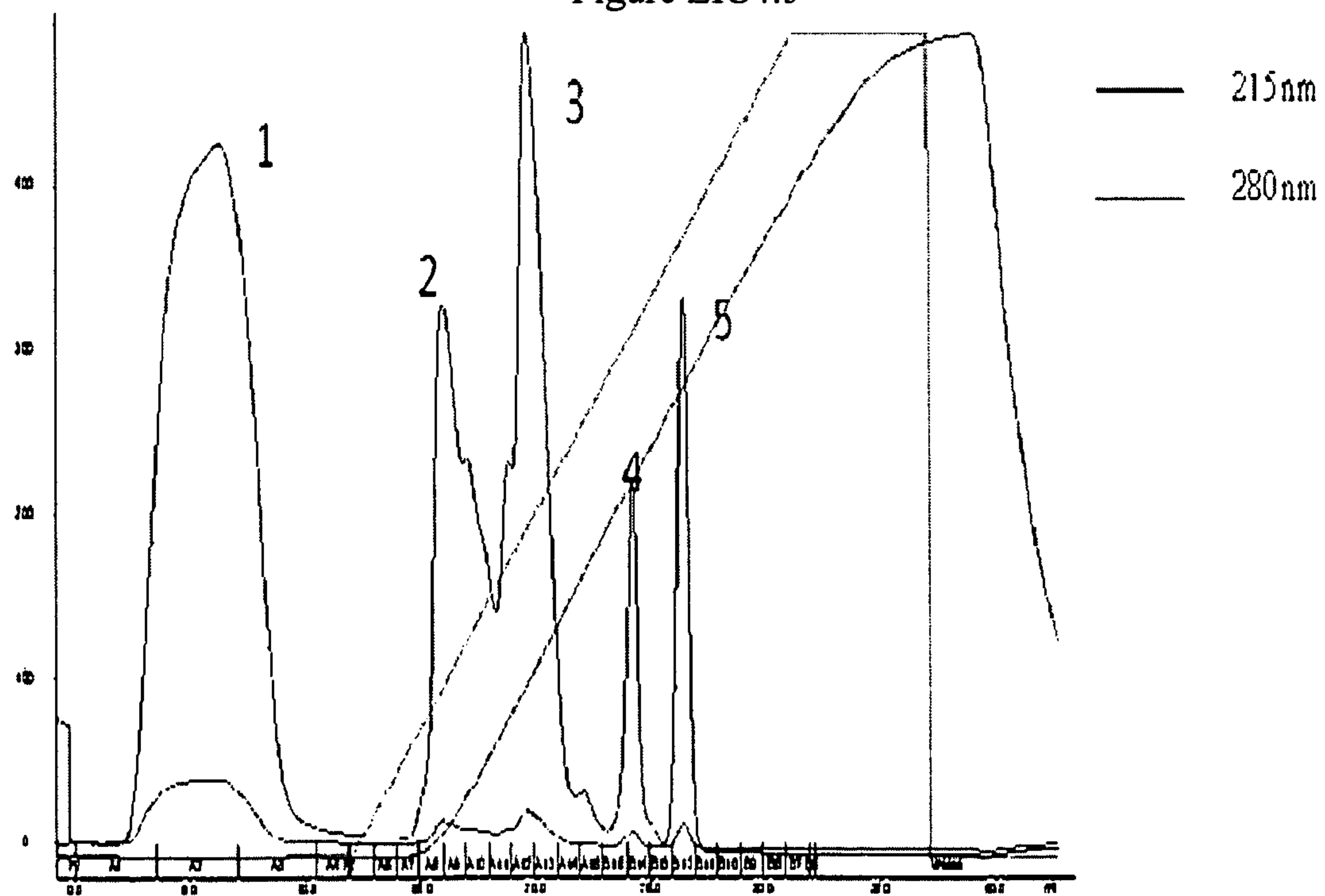


Figure ZIC5.1

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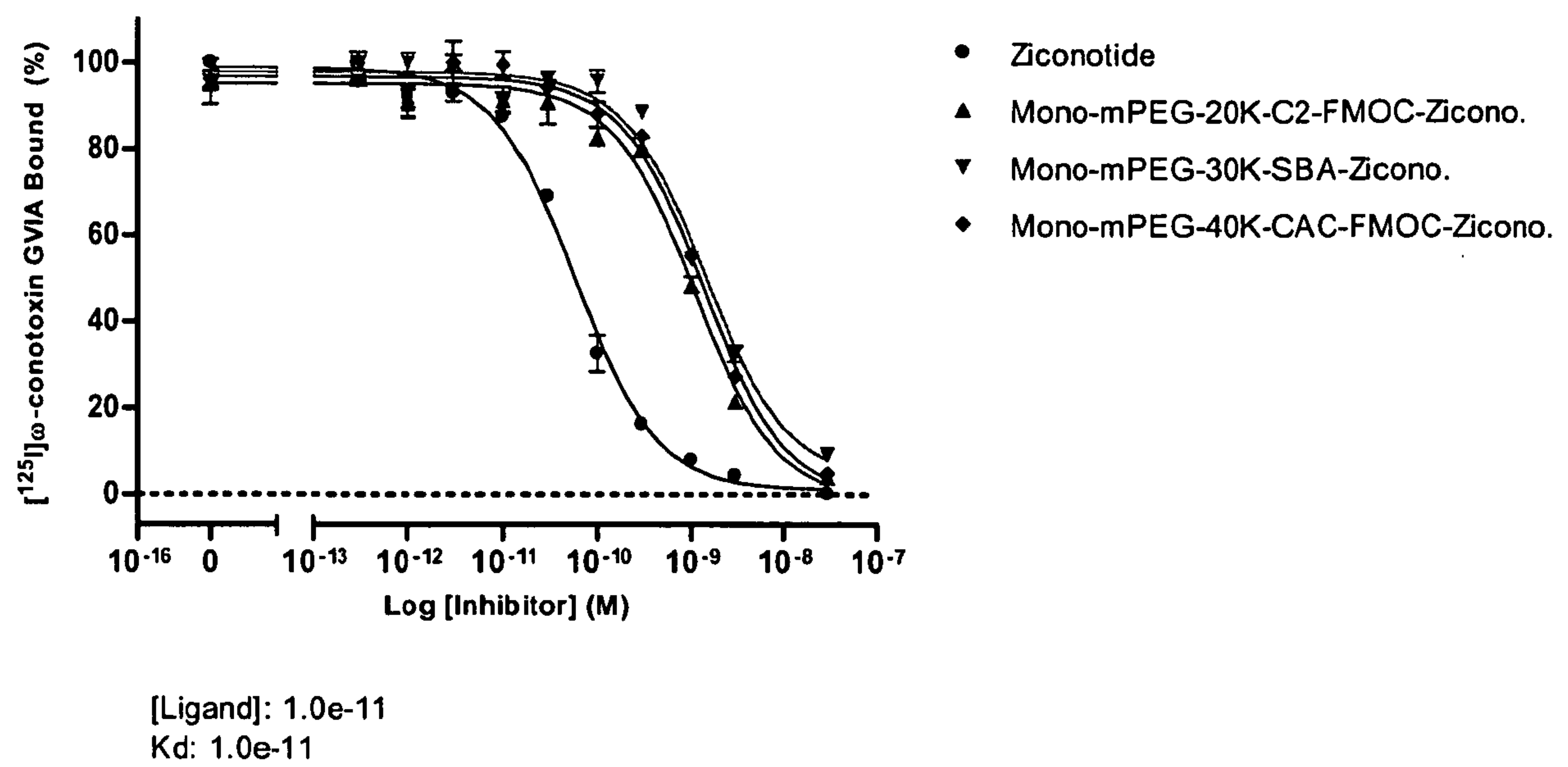


Figure ZIC6.1

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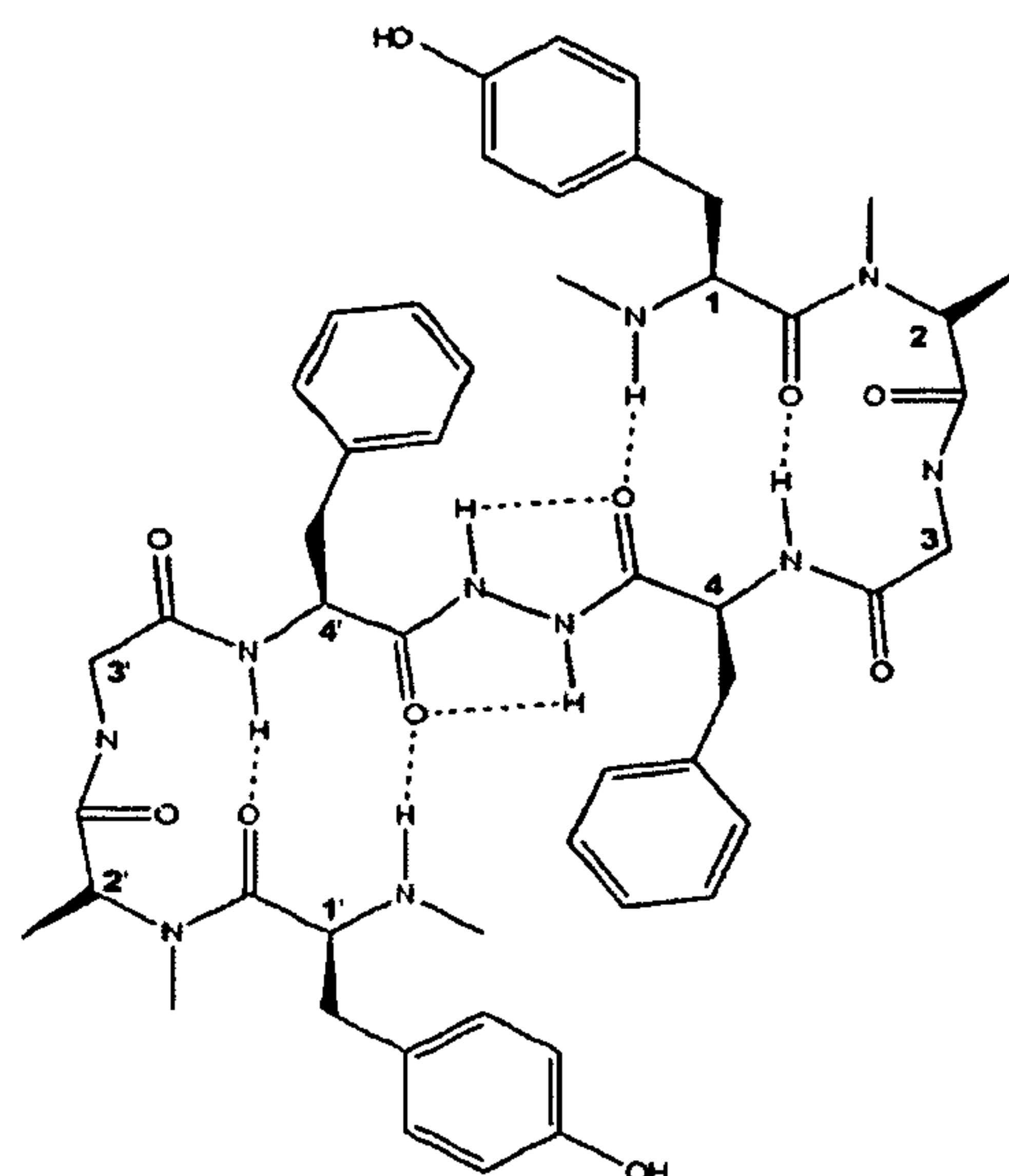


Figure BIP1. Biphalin structure

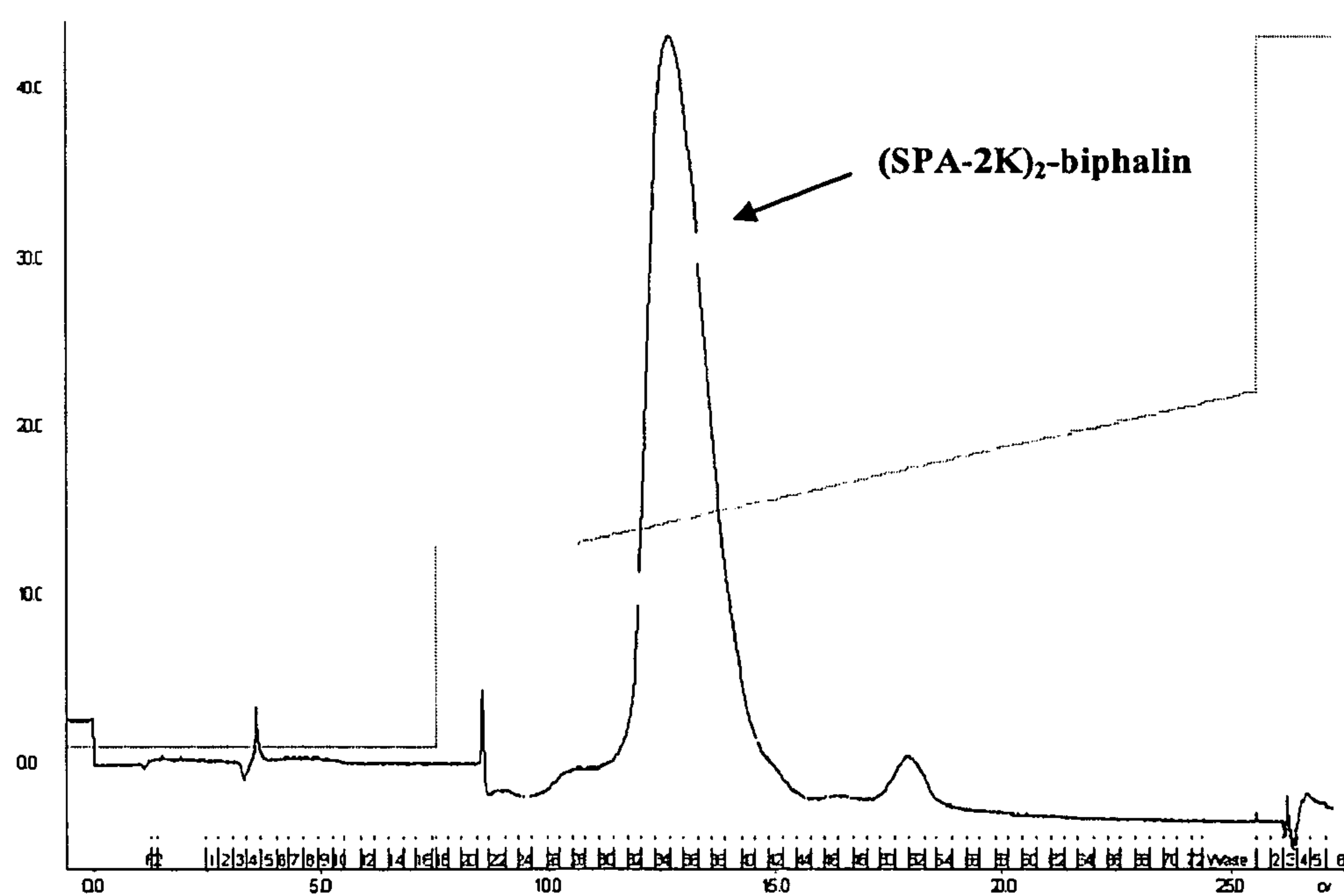


Figure BIP2.1

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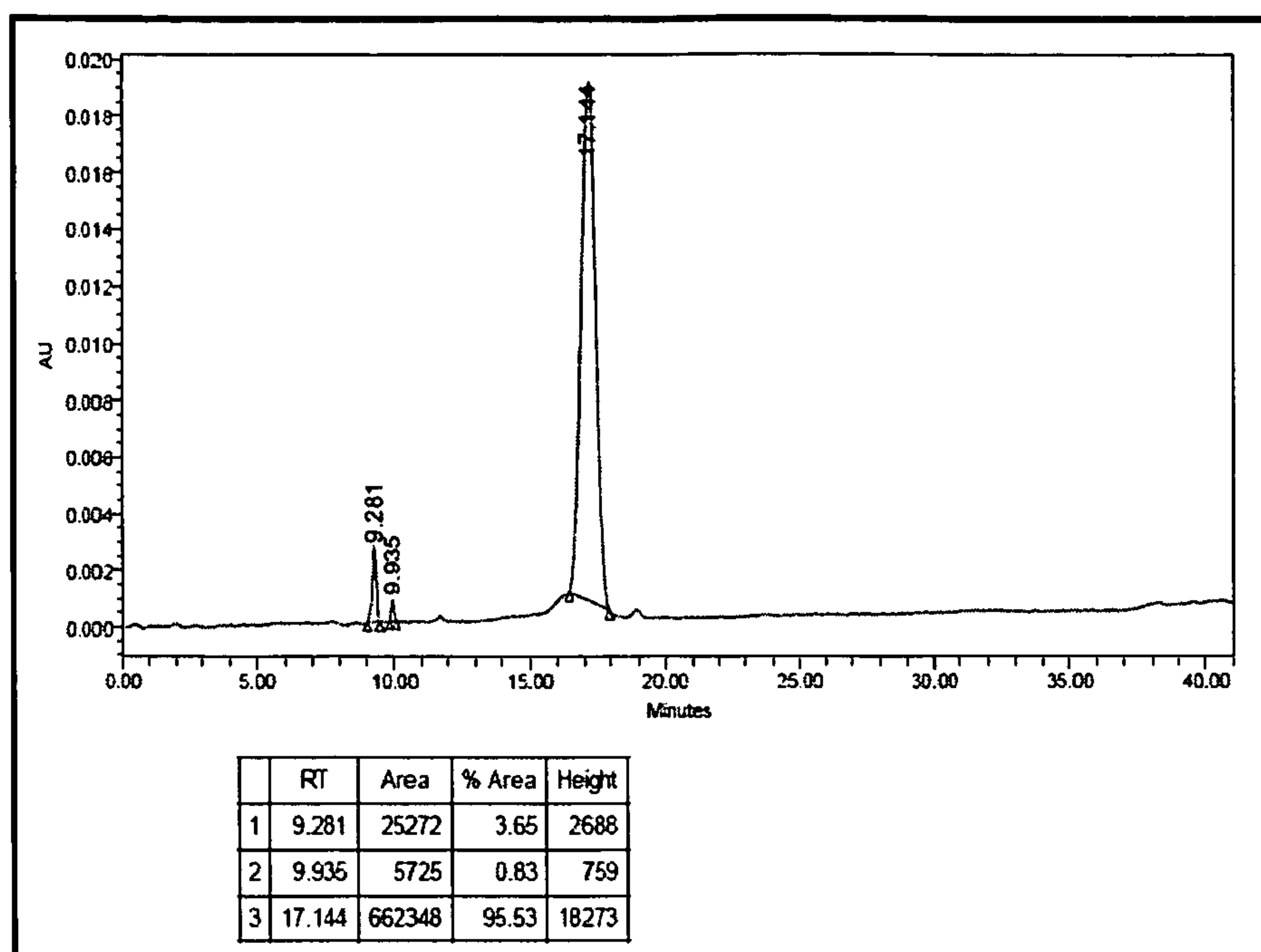


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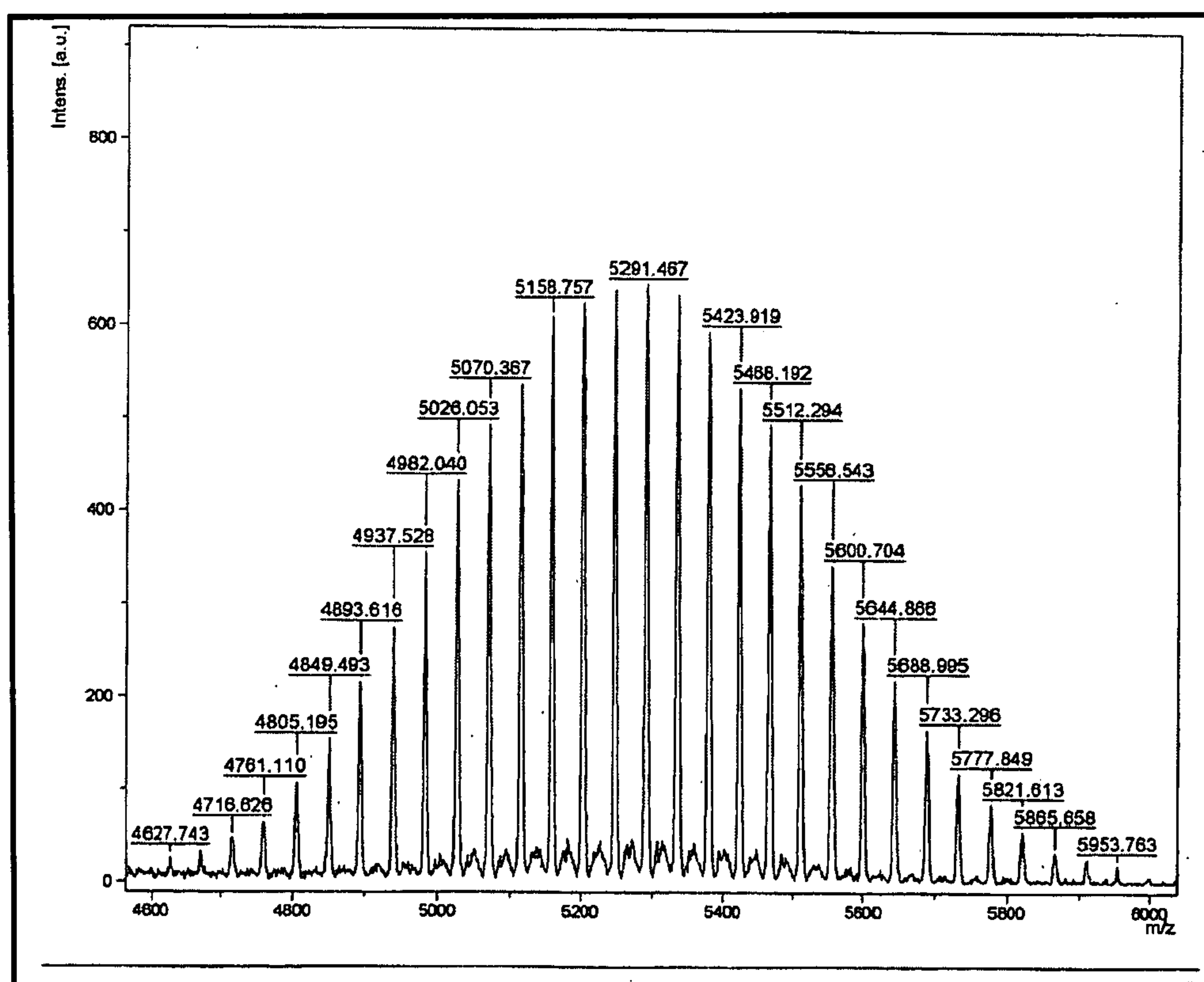


Figure BIP2.3

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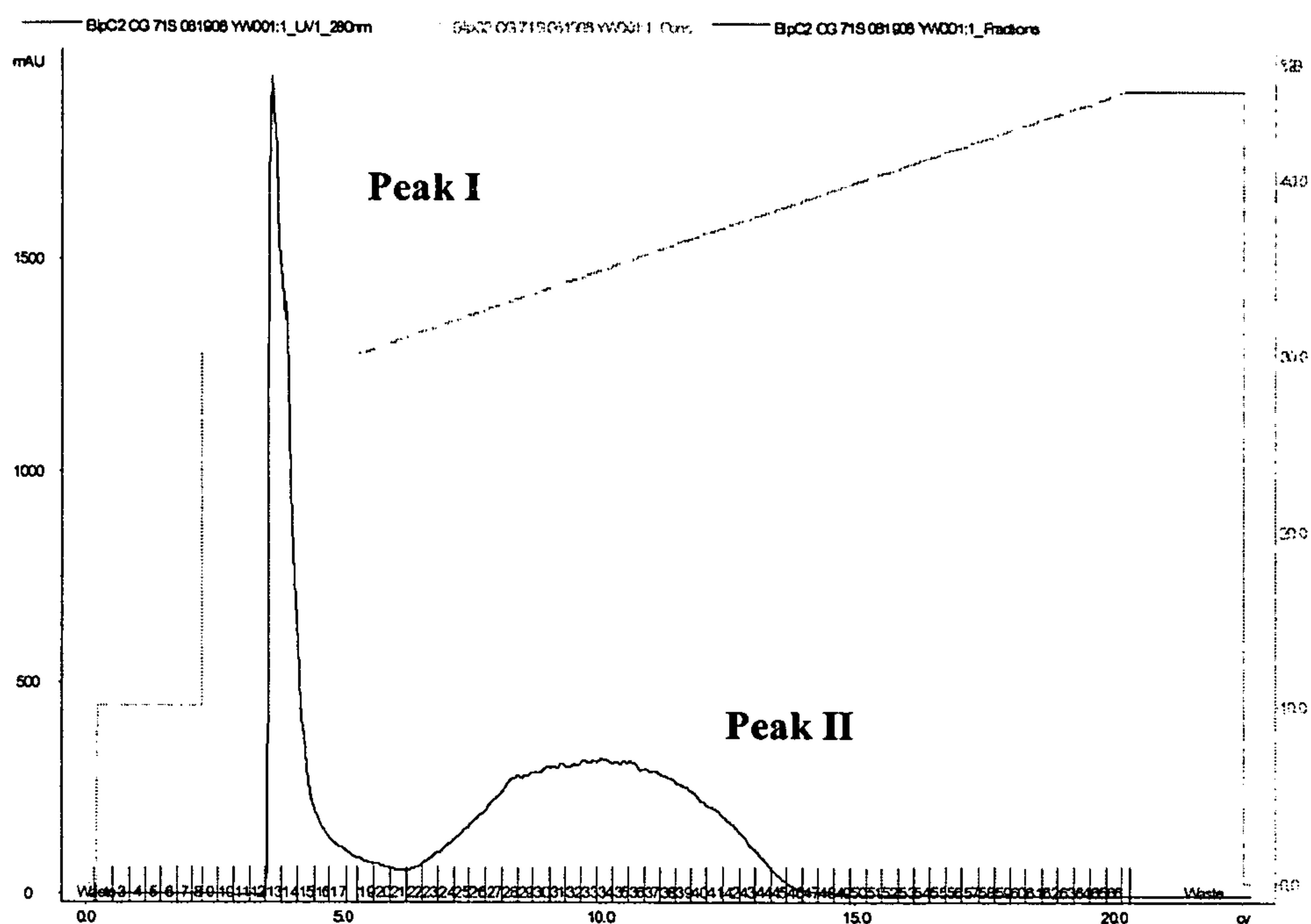


Figure BIP3.1

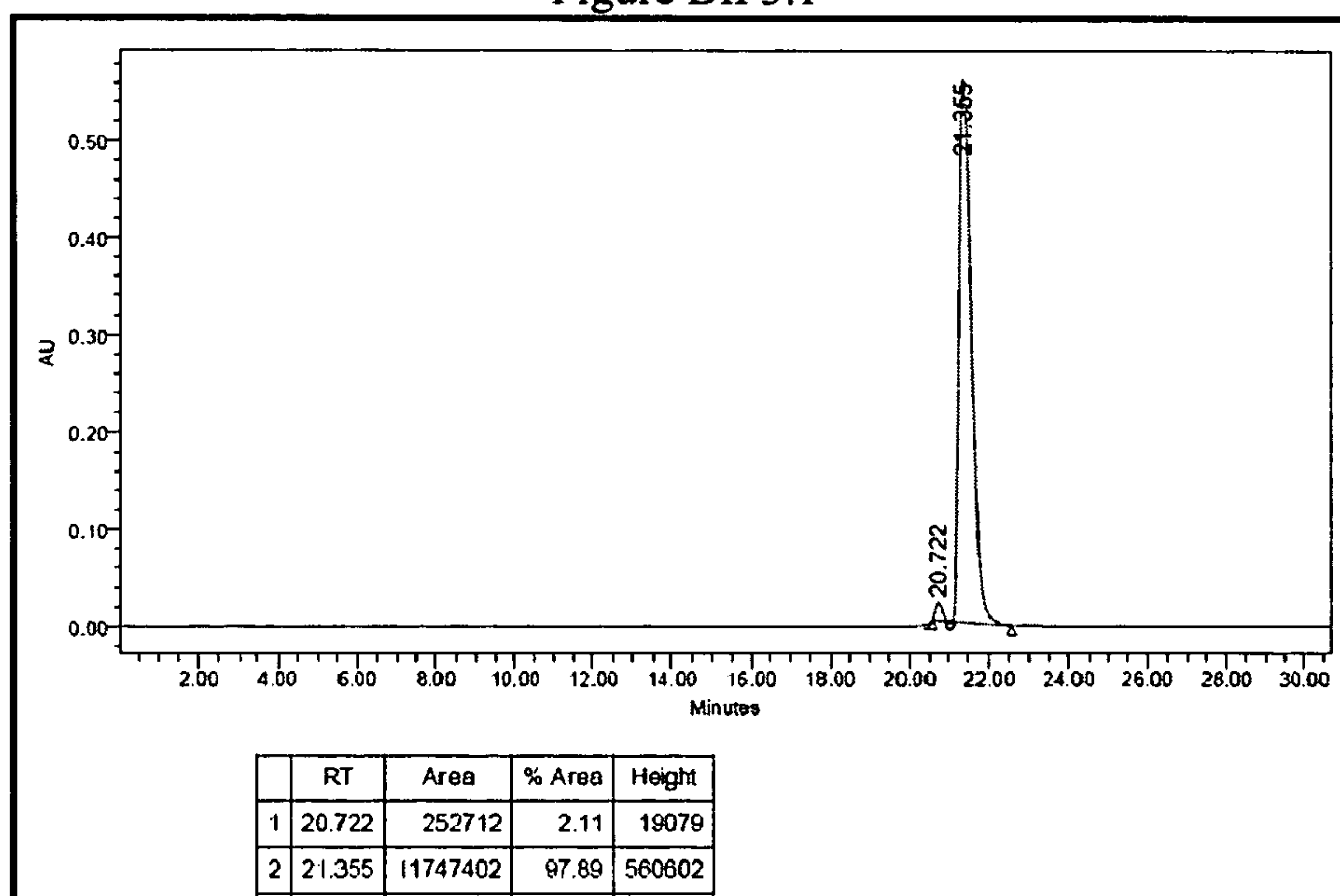


Figure BIP3.2

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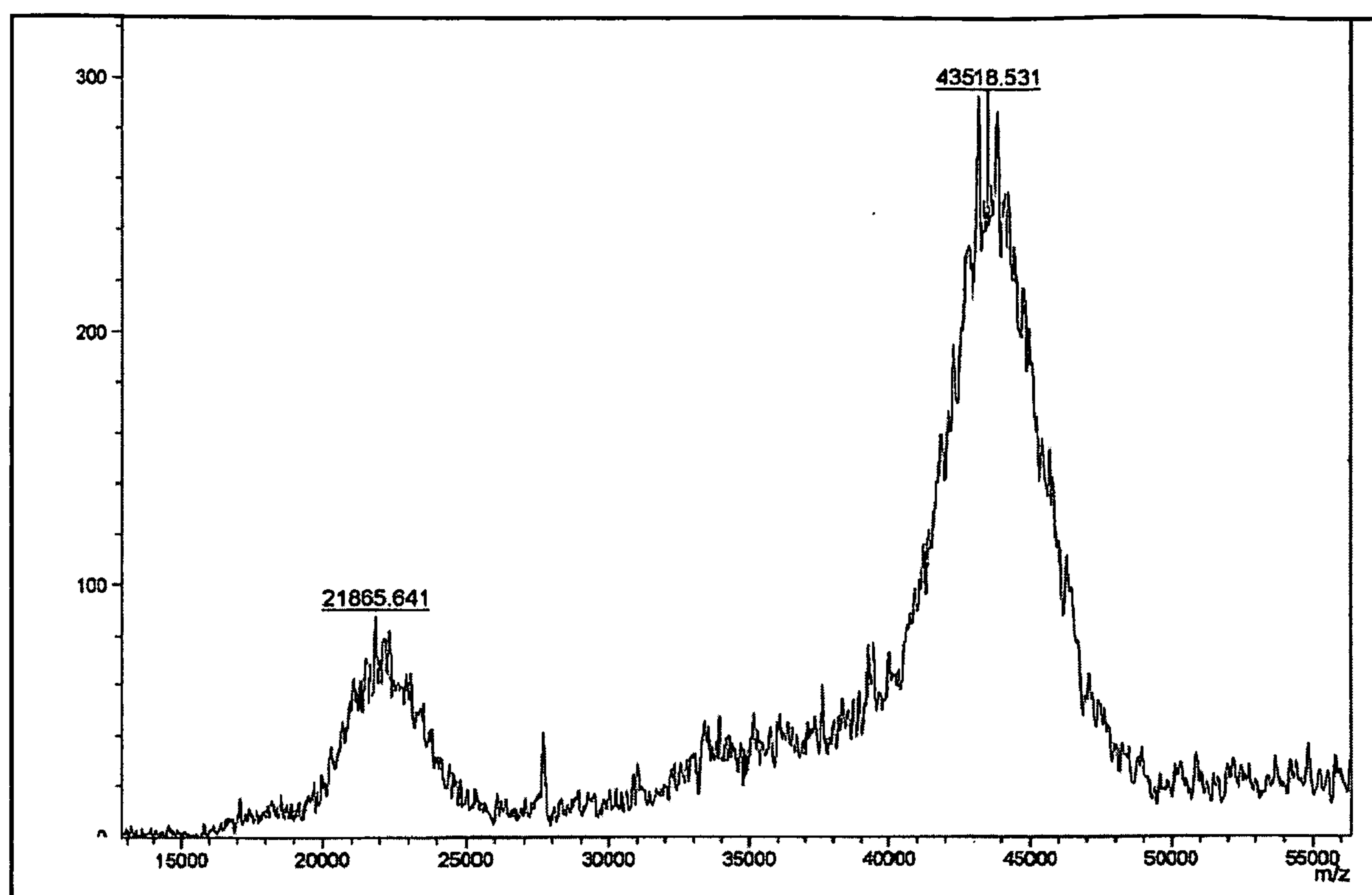


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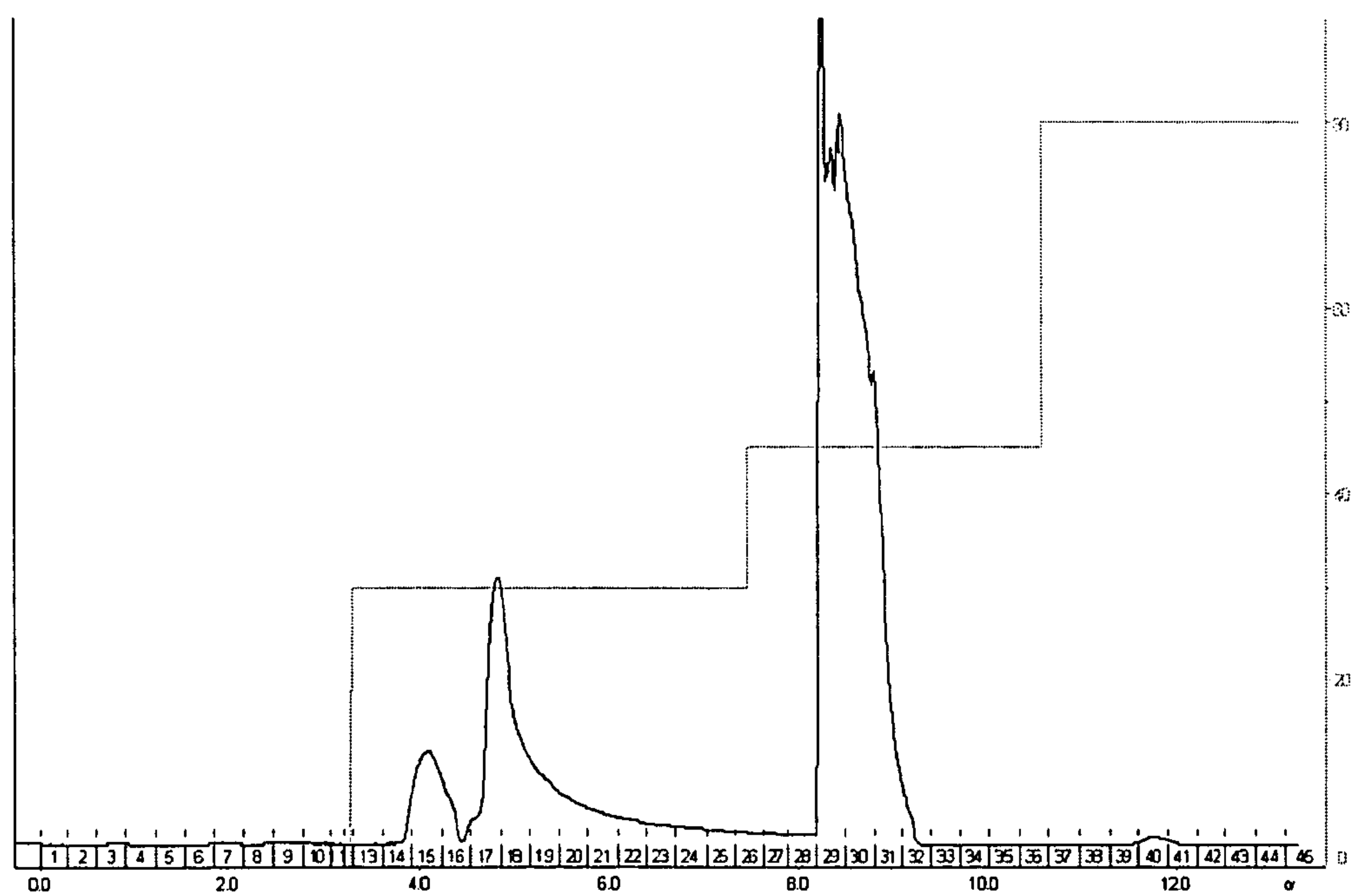


Figure BIP4.1

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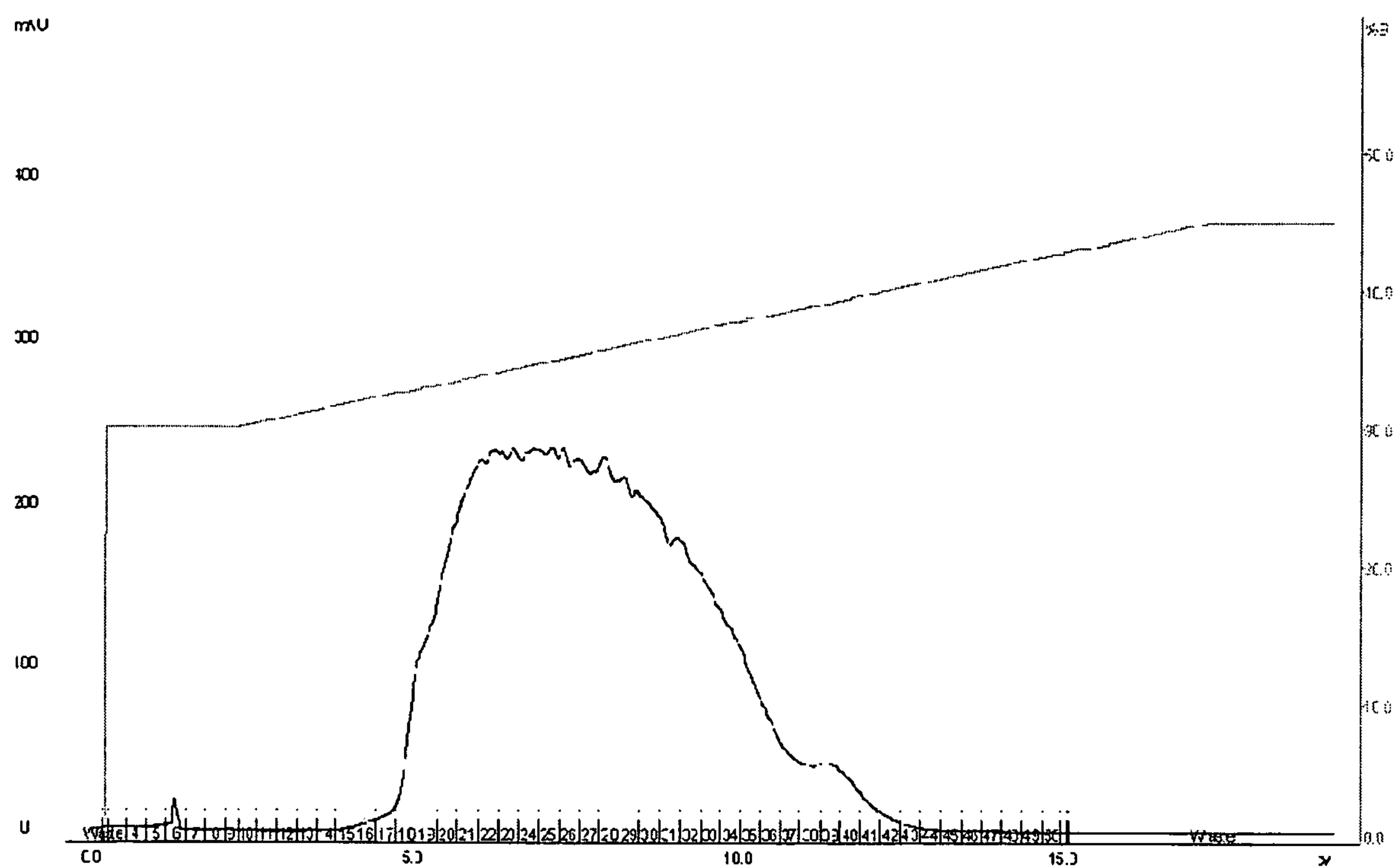


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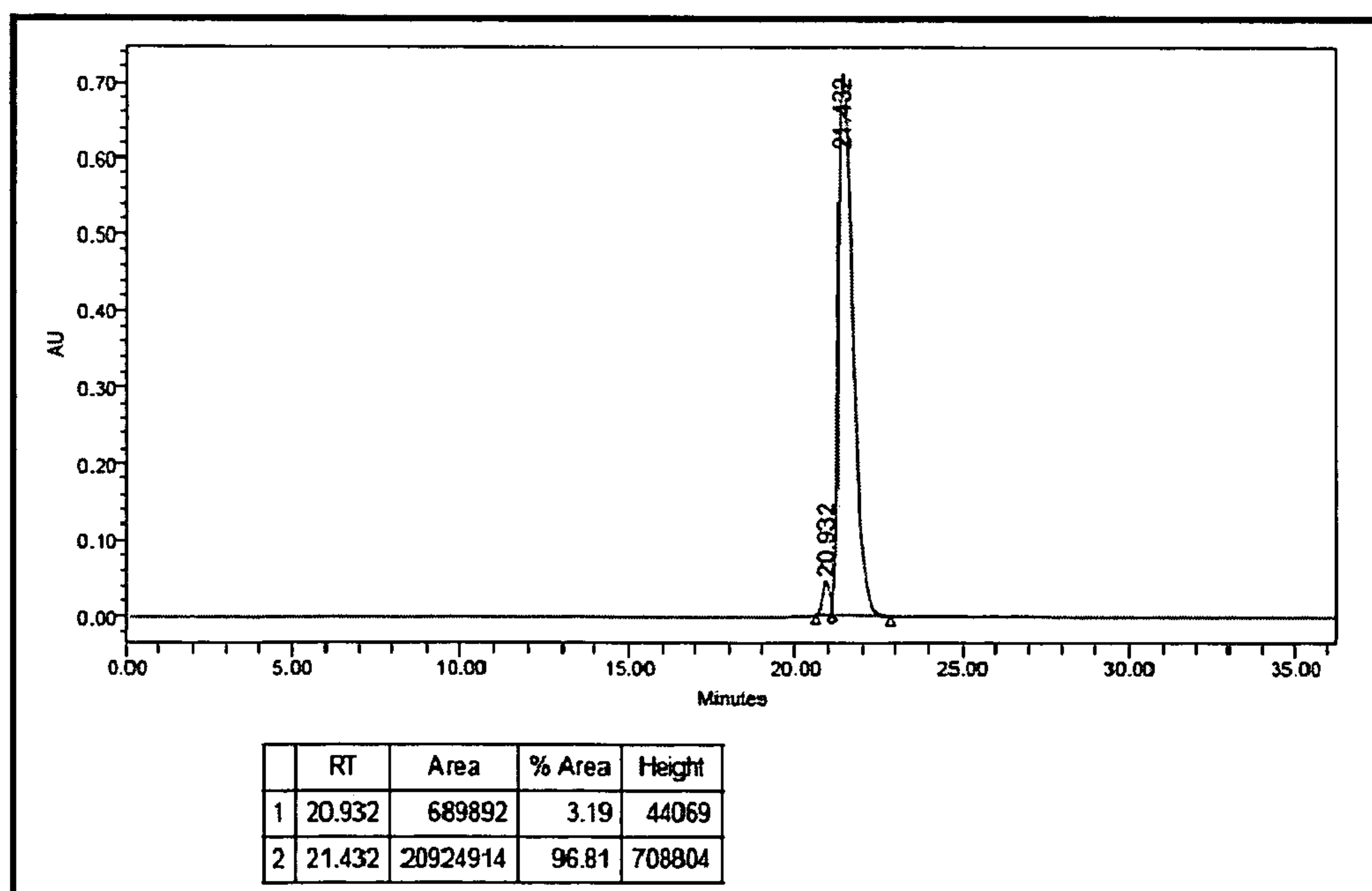


Figure BIP4.3

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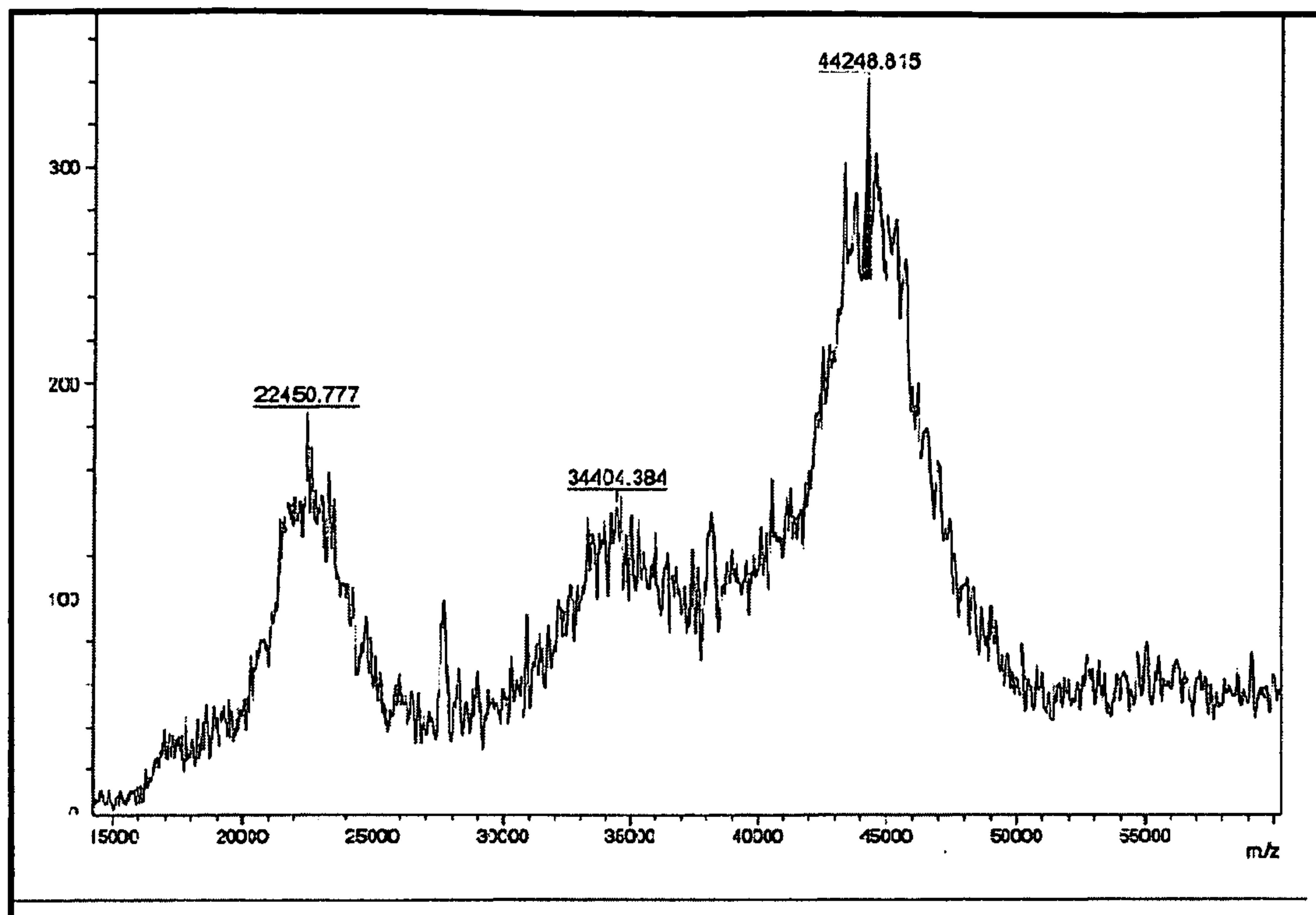


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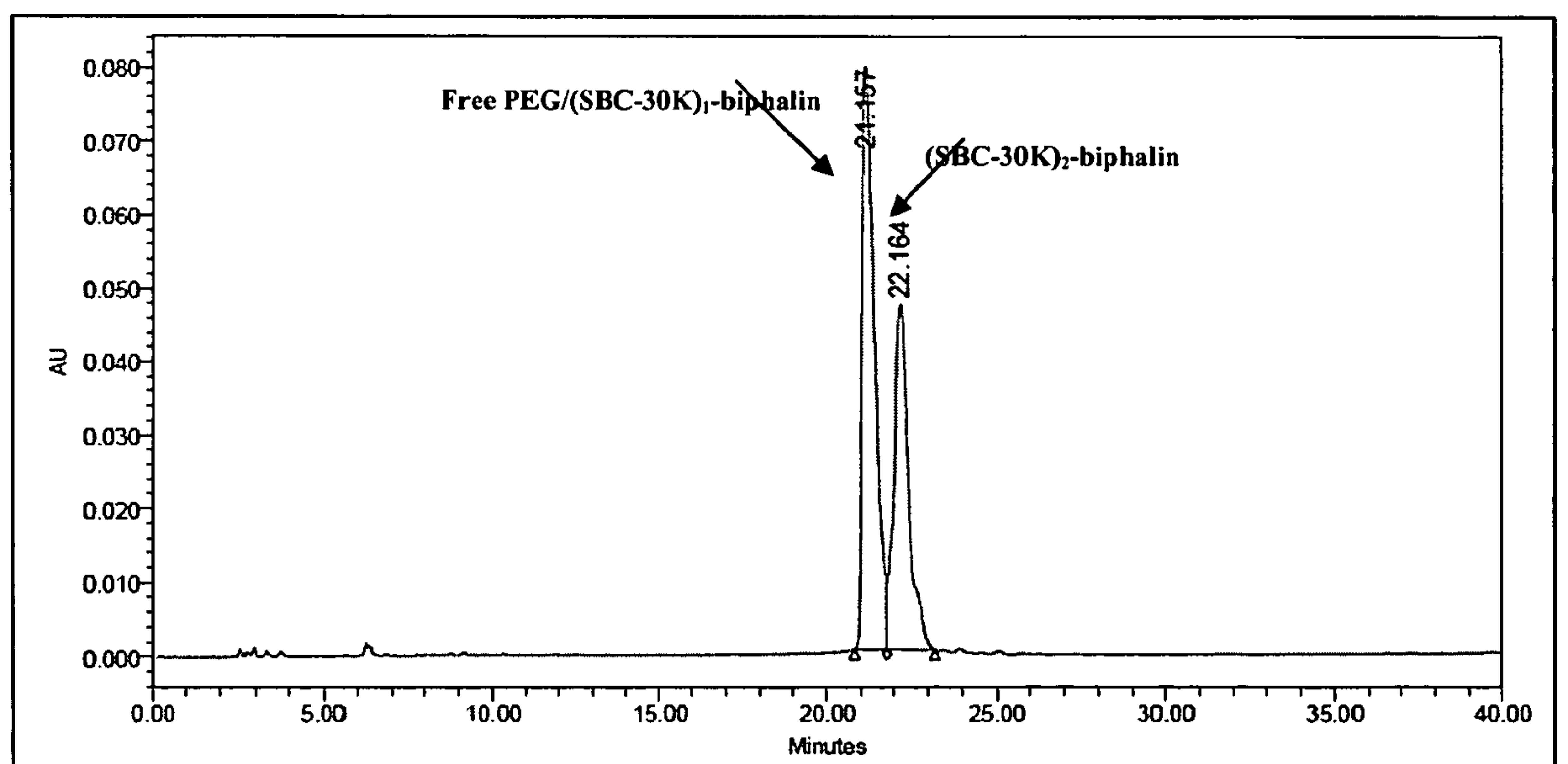


Figure BIP5.1

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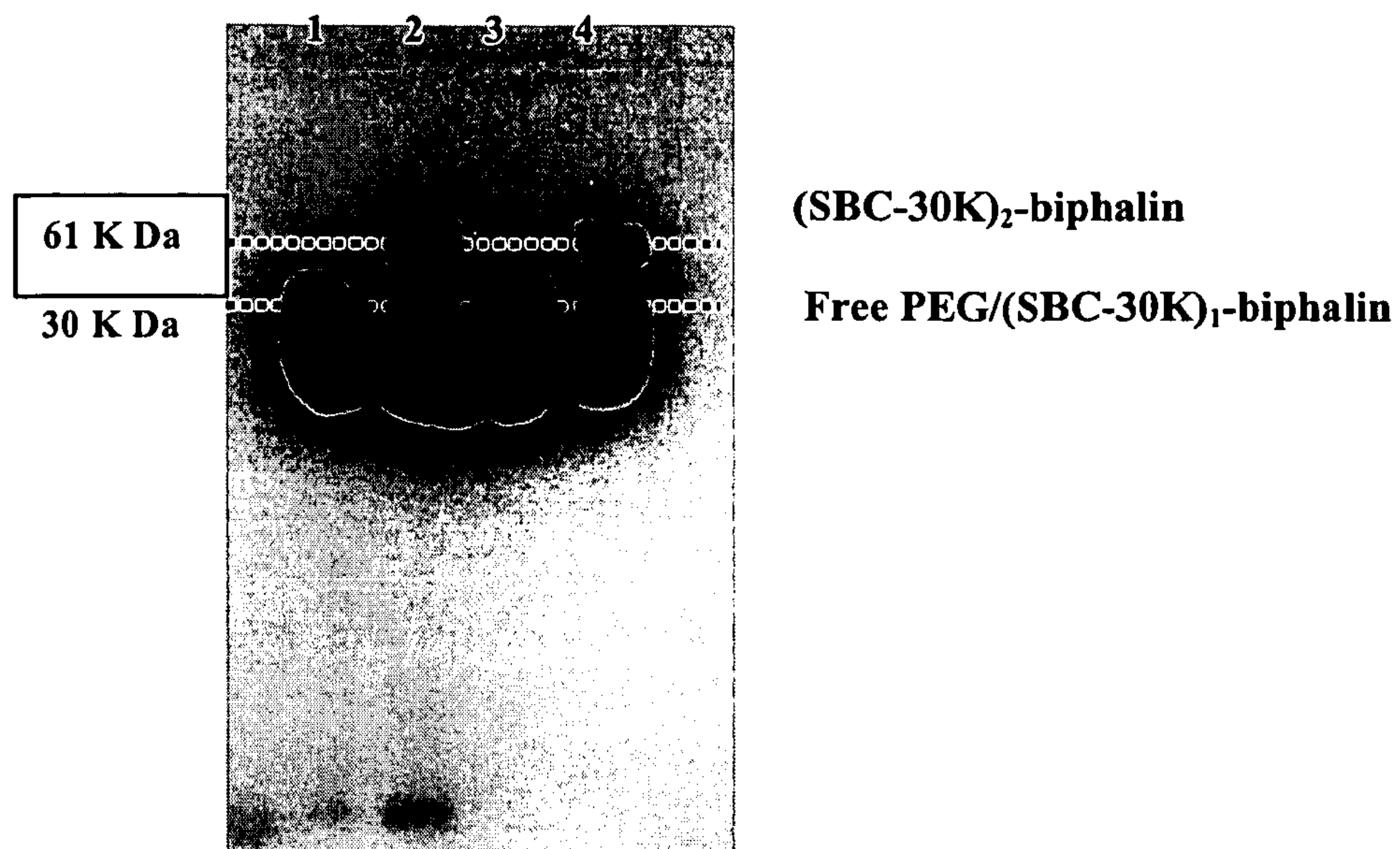


Figure BIP5.2

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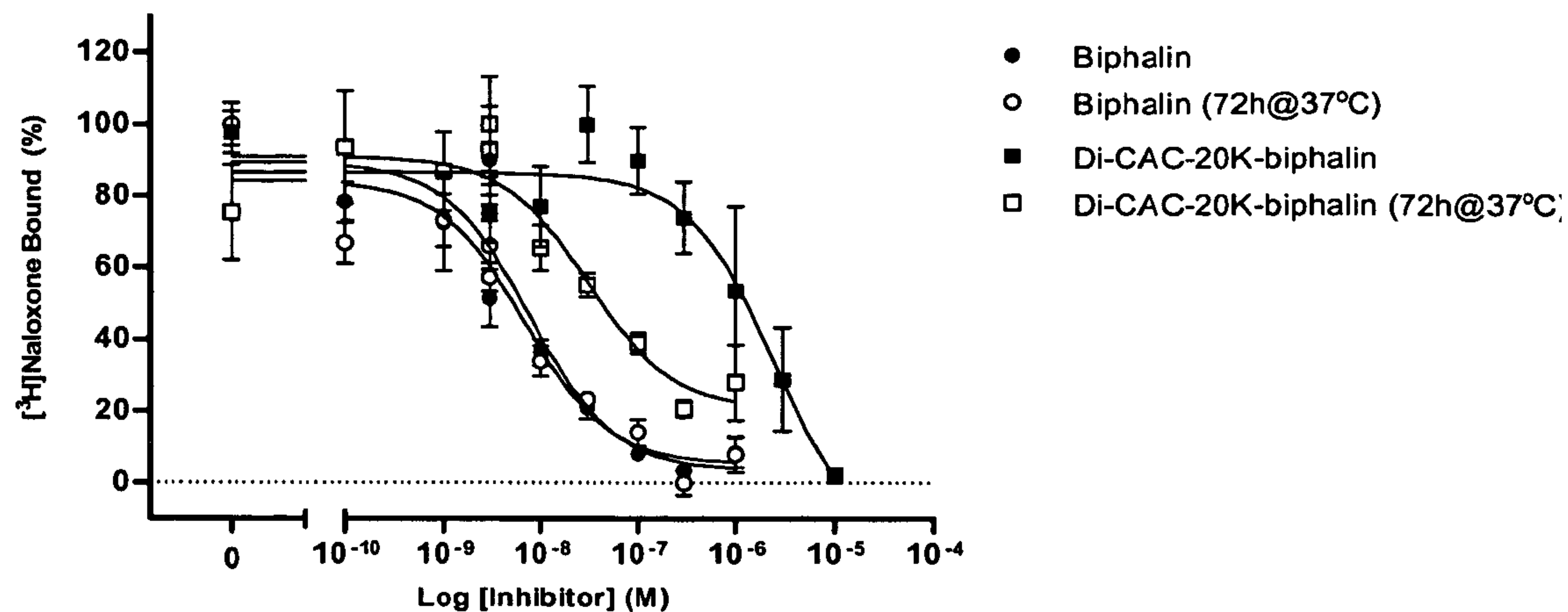
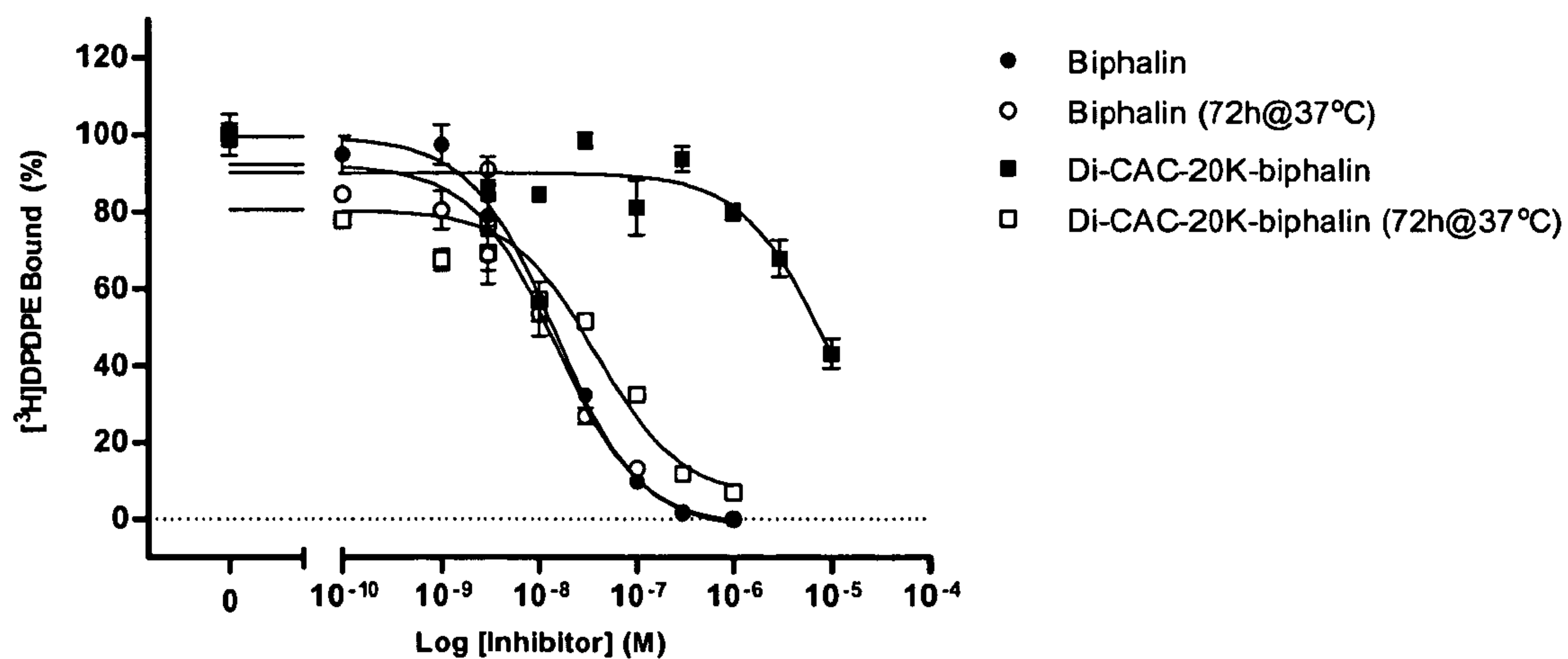
A **μ Opioid Receptor (Human Recombinant) Binding Assay****B** **δ Opioid Receptor (Human Recombinant) Binding Assay**

Figure BIP6.1

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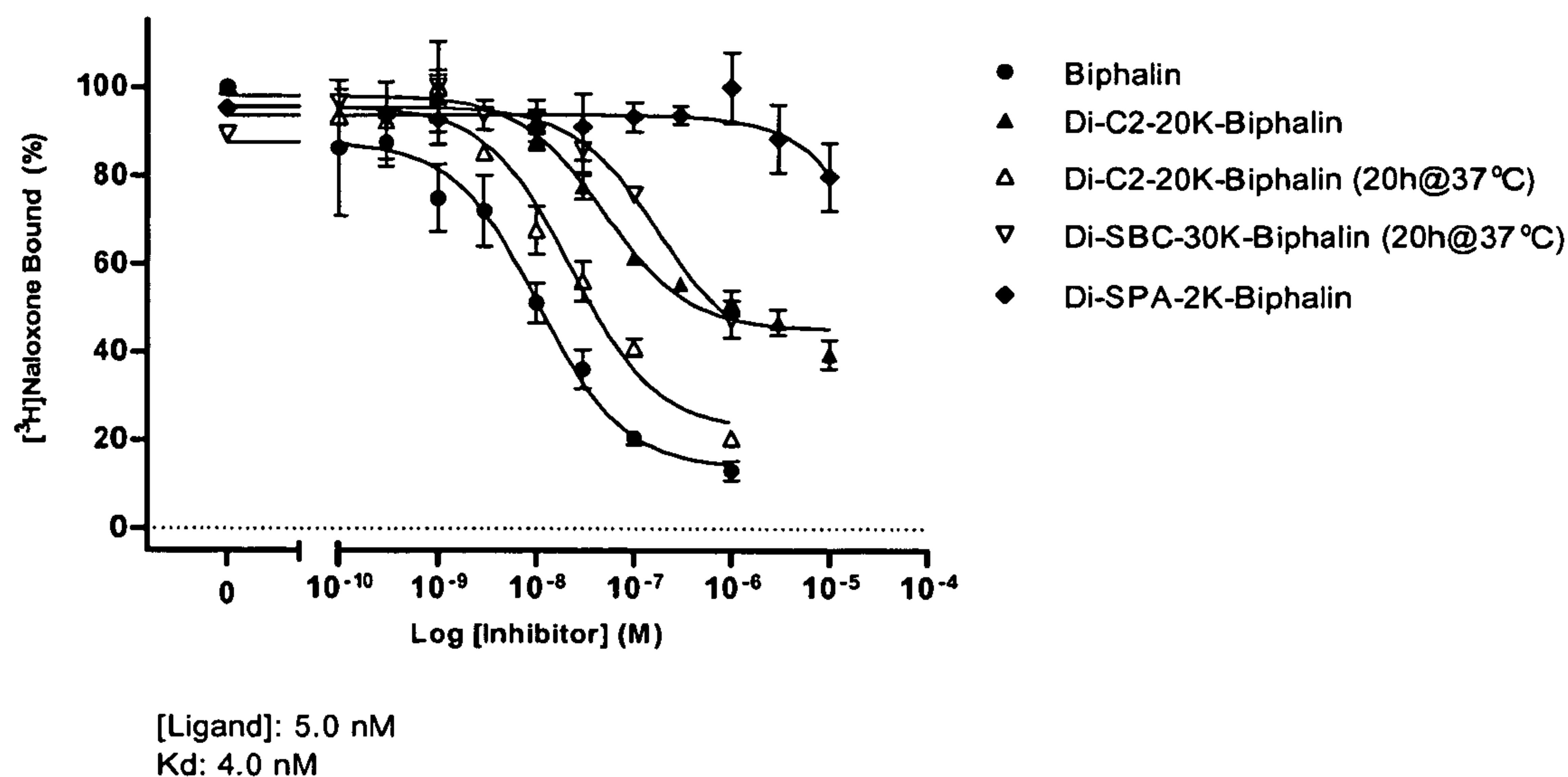
A **μ Opioid Receptor (Human Recombinant) Binding Assay**

Figure BIP6.2A

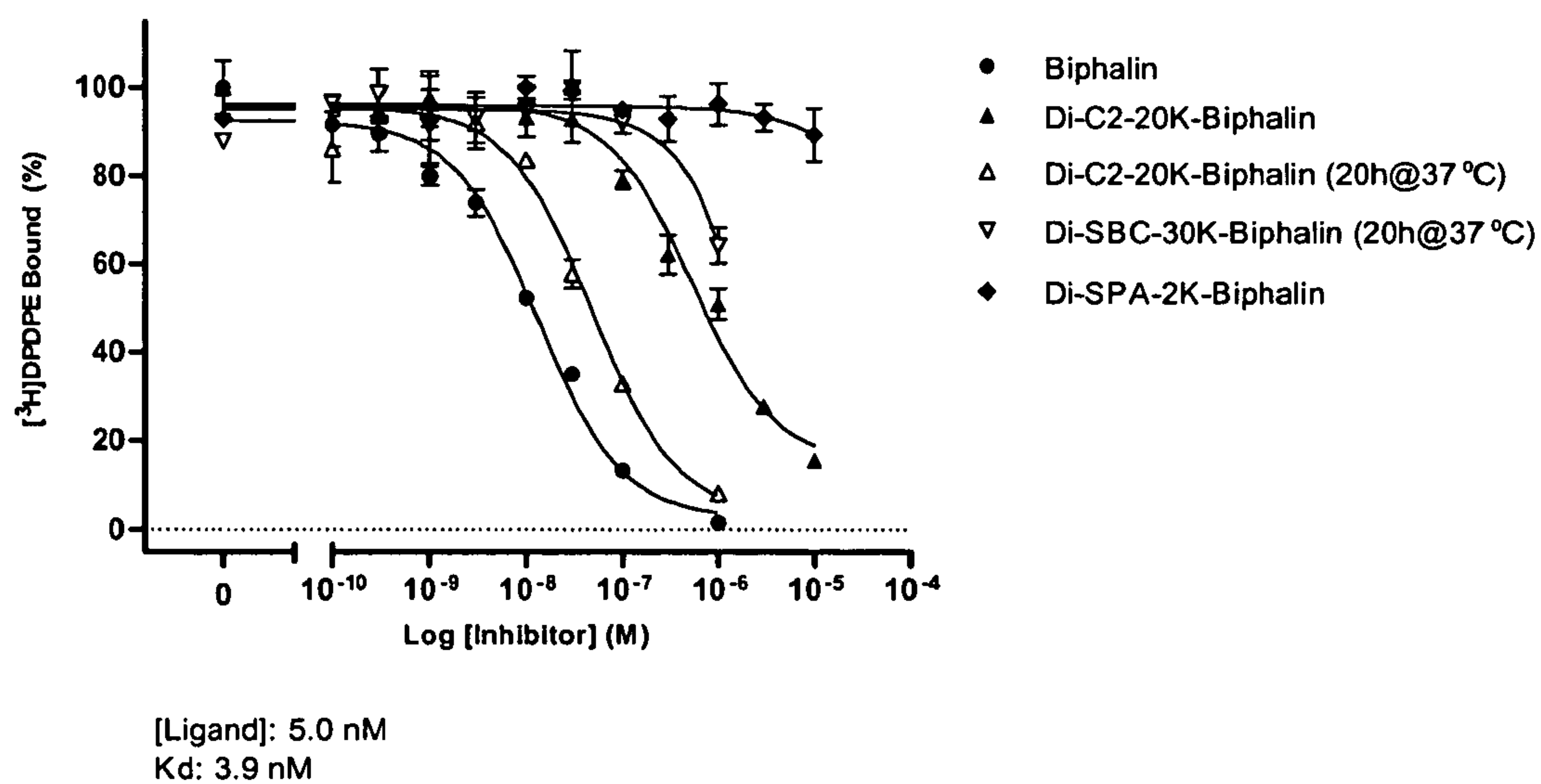
B **δ Opioid Receptor (Human Recombinant) Binding Assay**

Figure BIP6.2B

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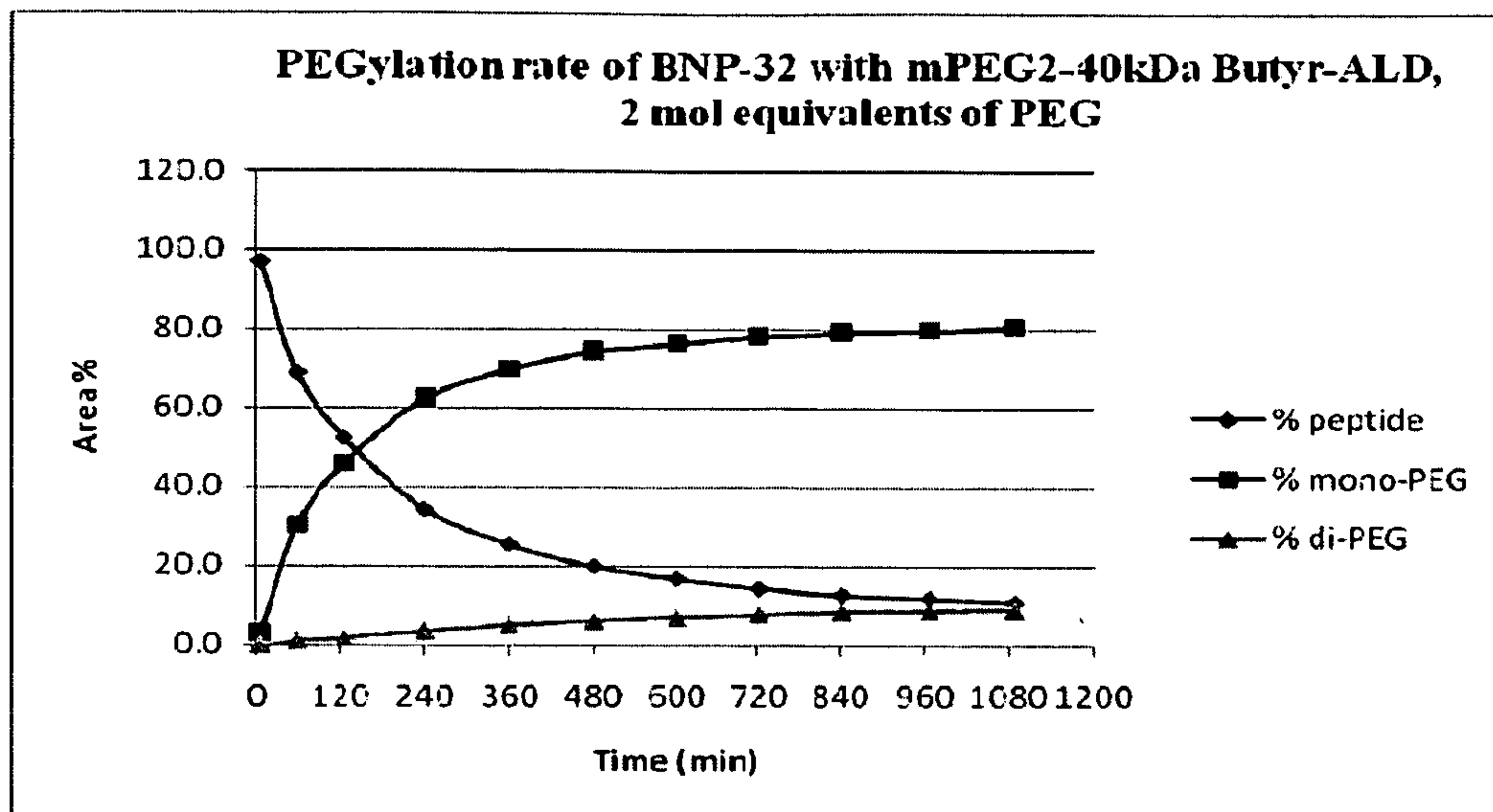


Figure BNP2.1

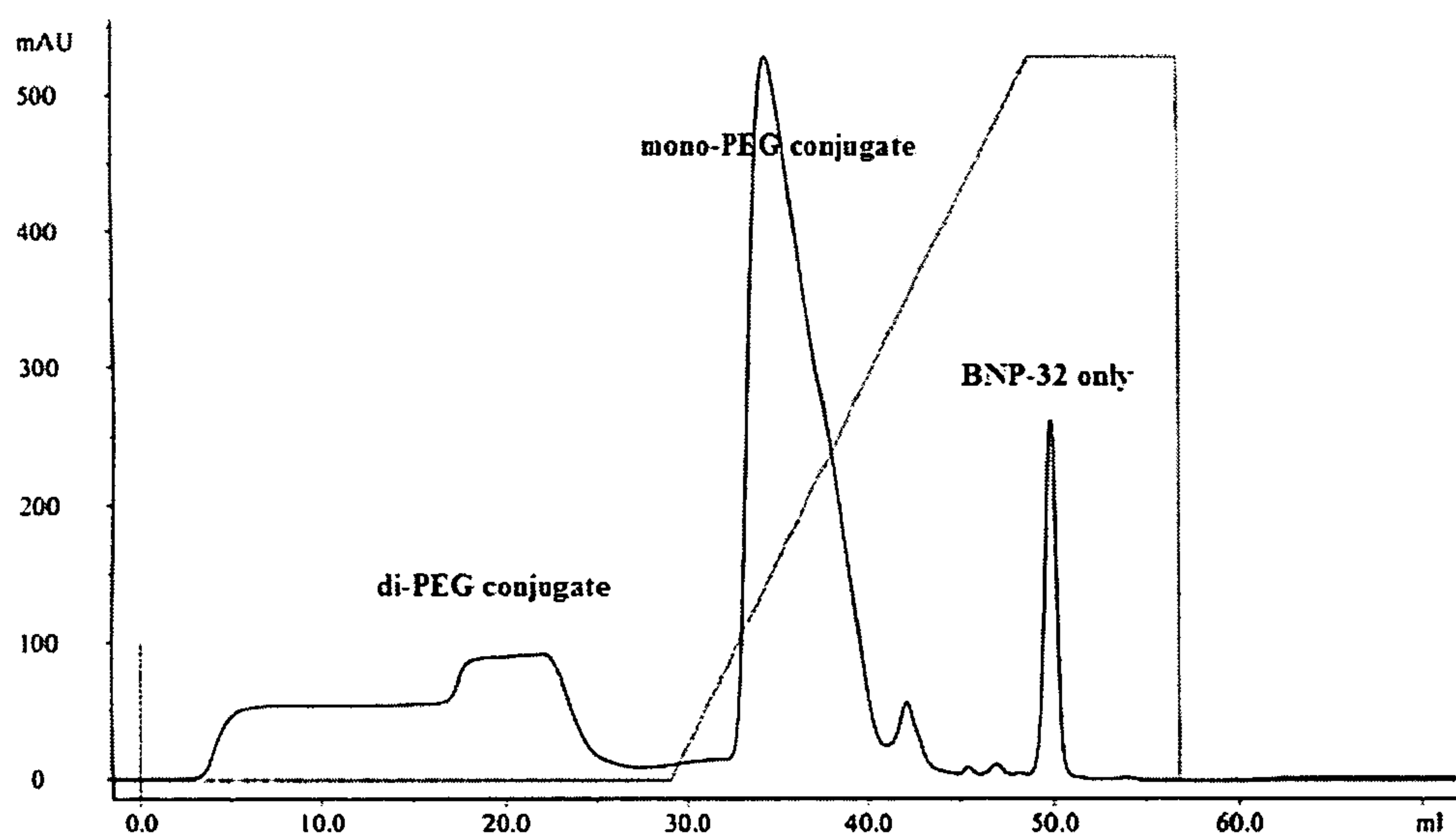


Figure BNP2.2

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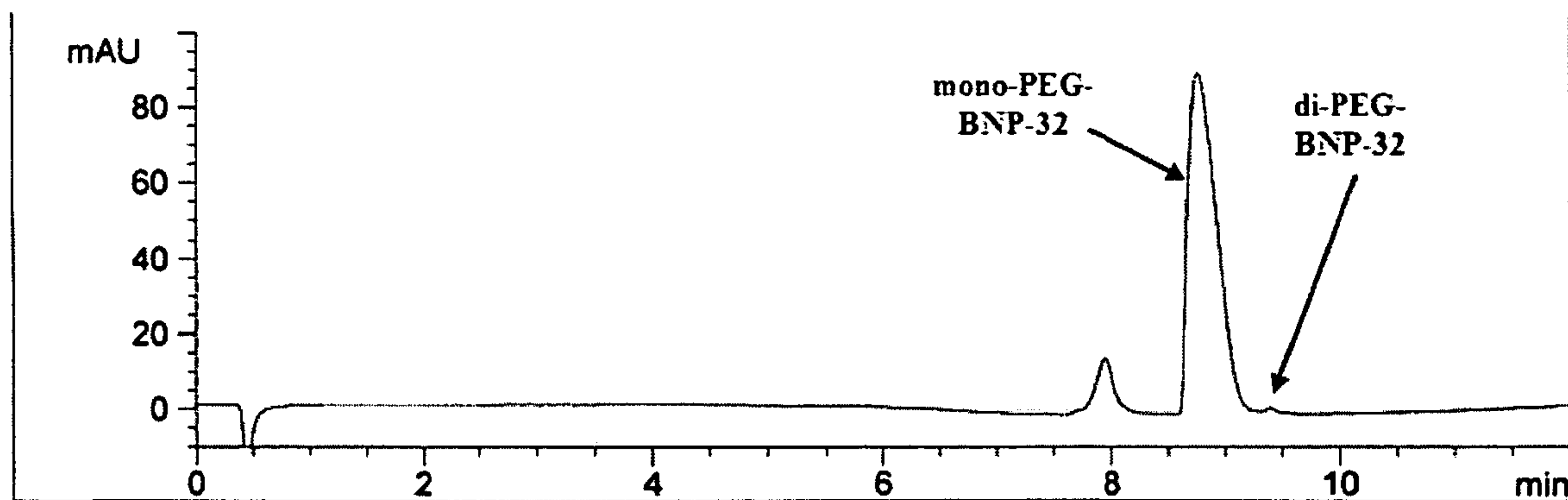


Figure BNP2.3

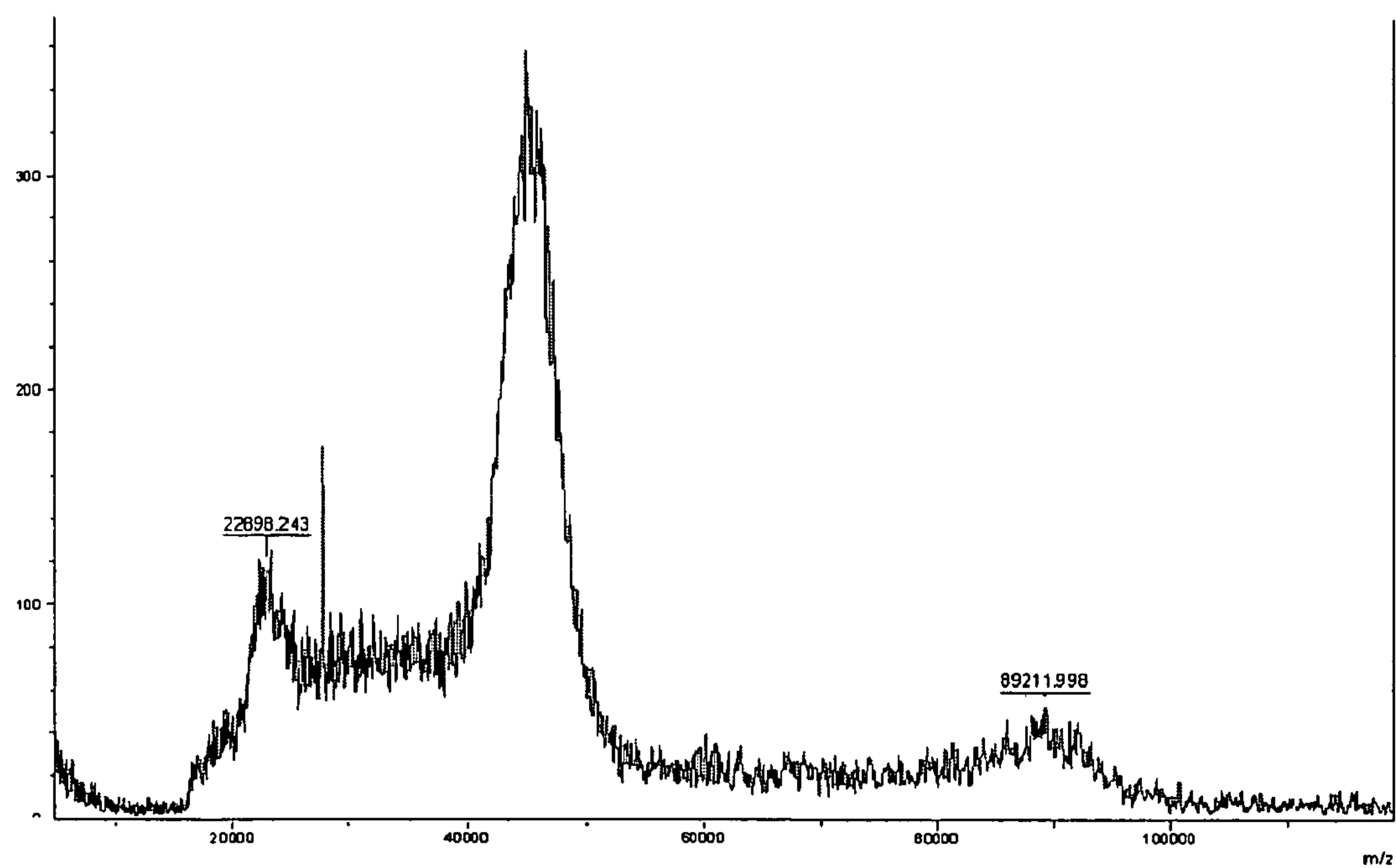


Figure BNP2.4

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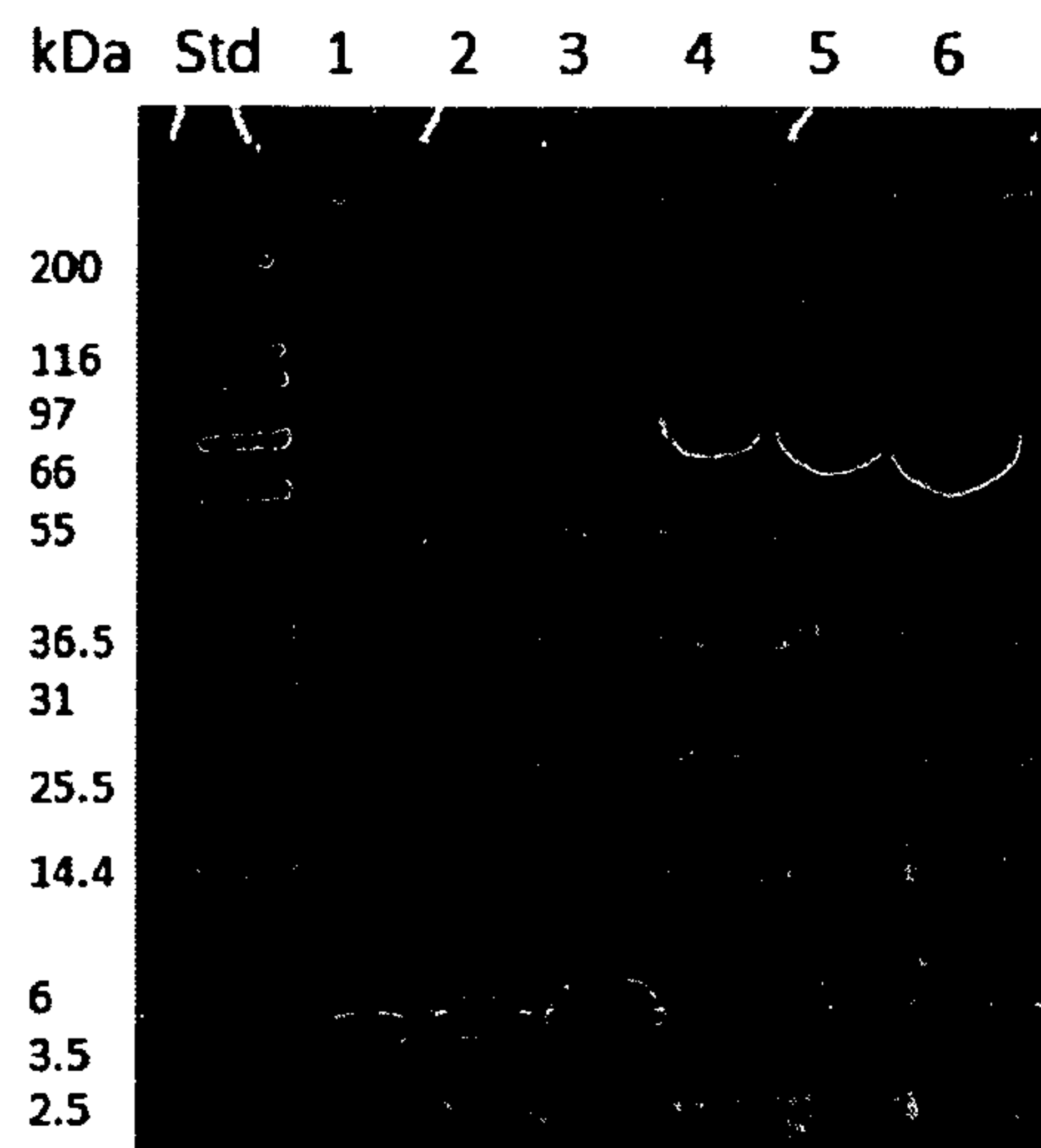


Figure BNP2.5

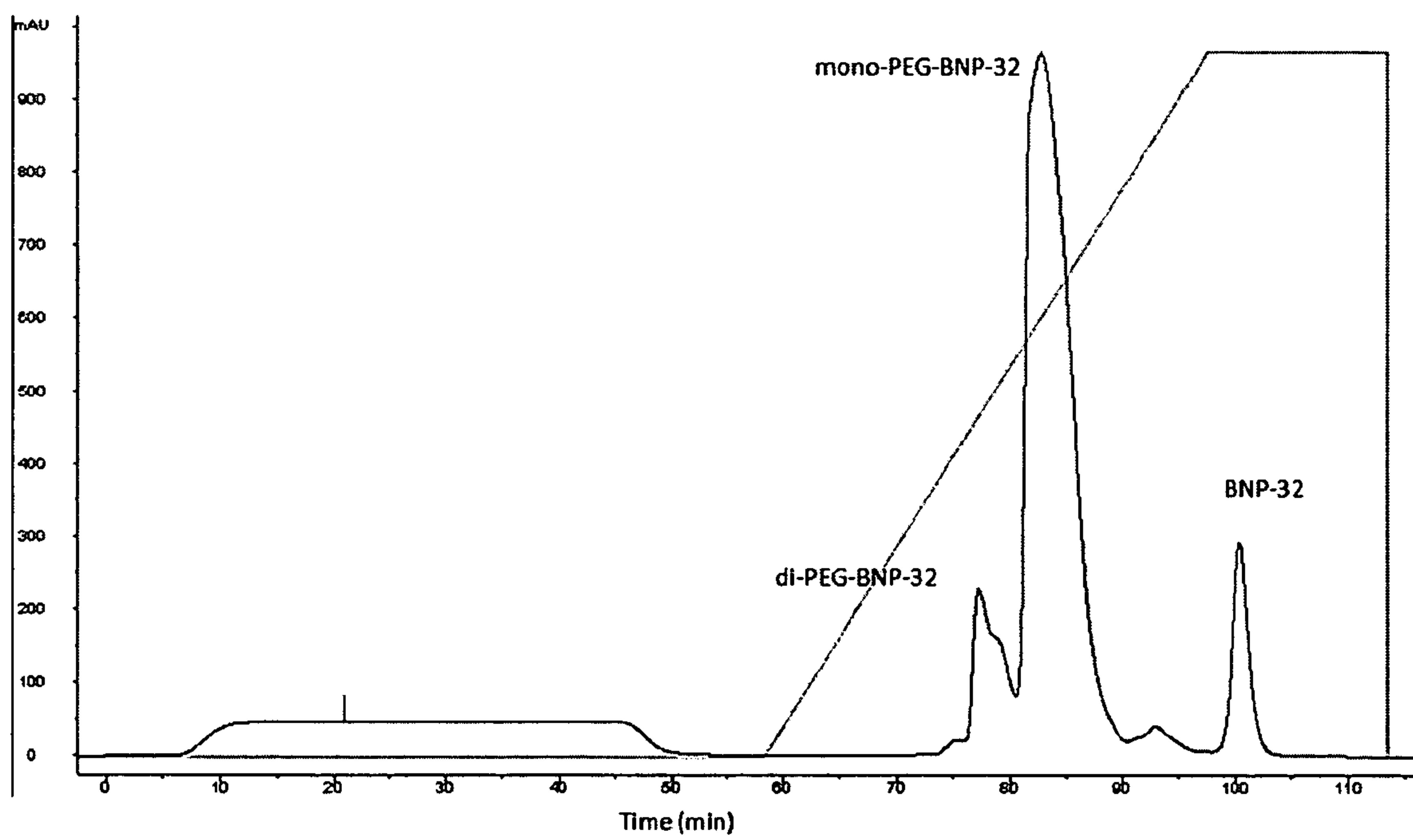


Figure BNP4.1

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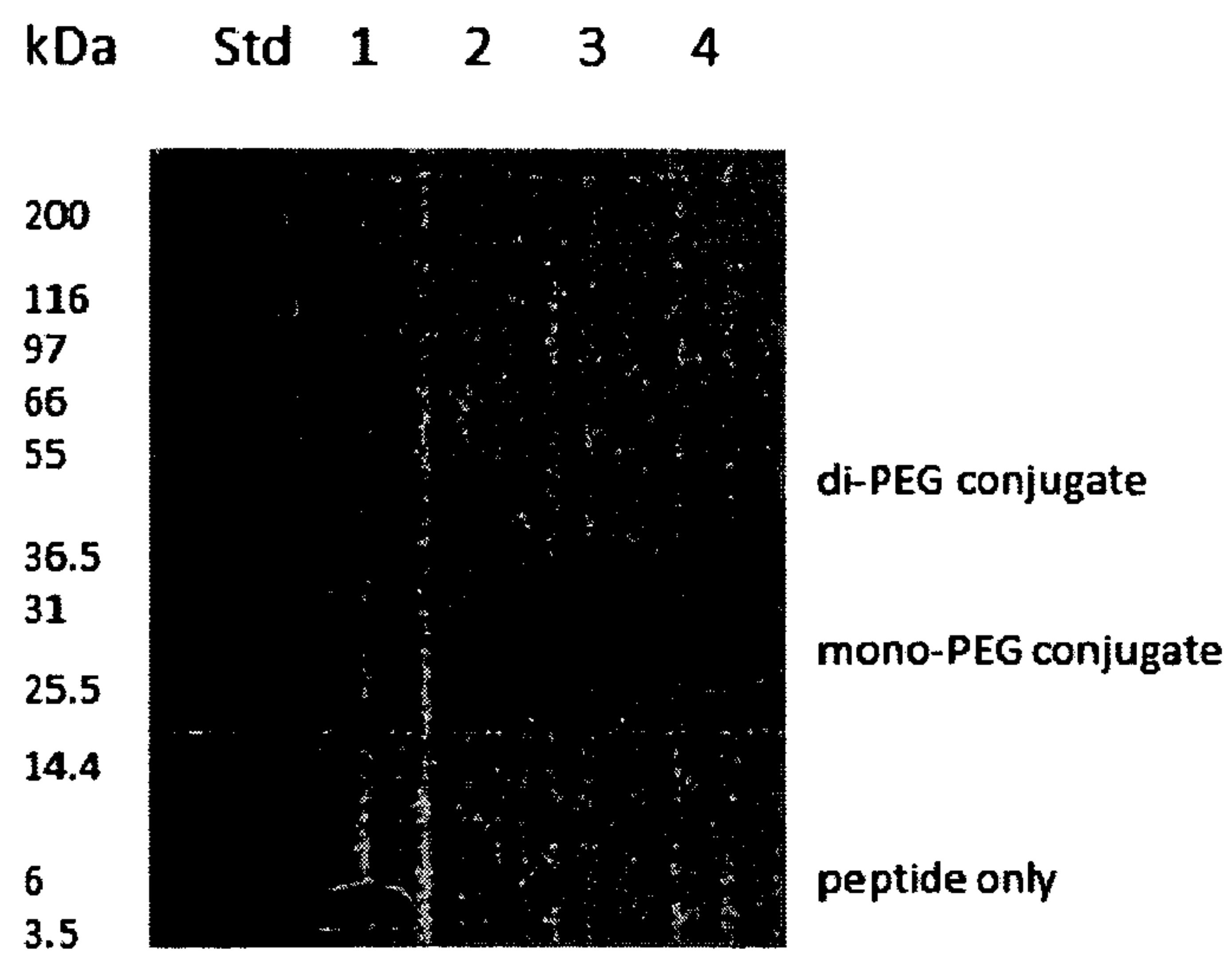


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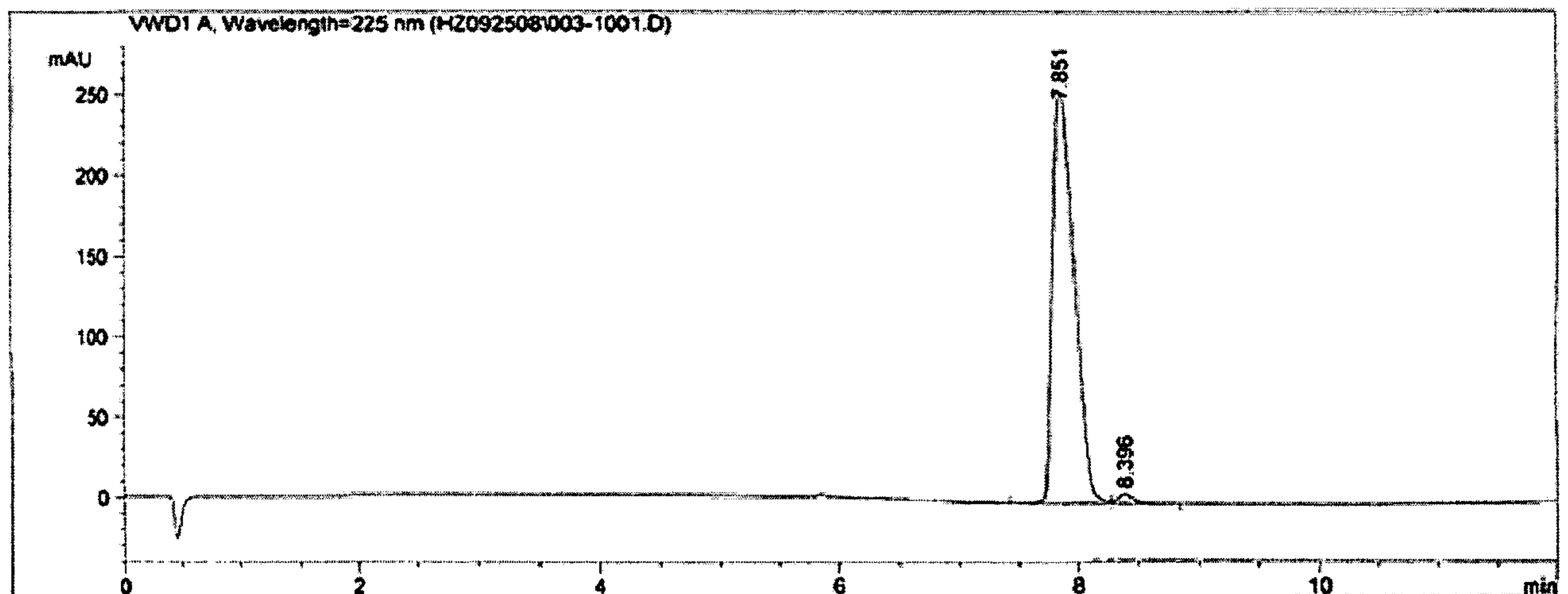


Figure BNP4.3

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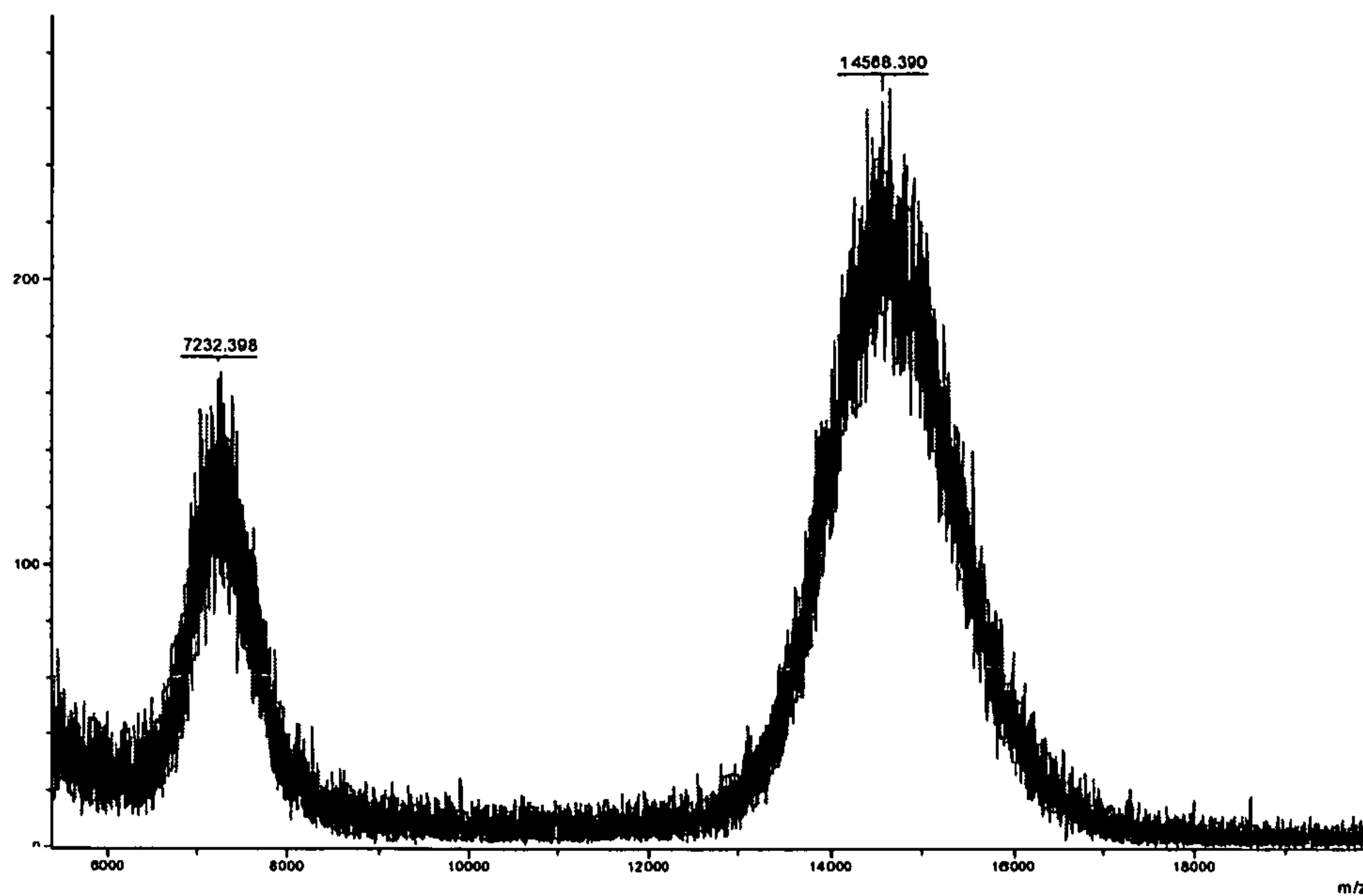


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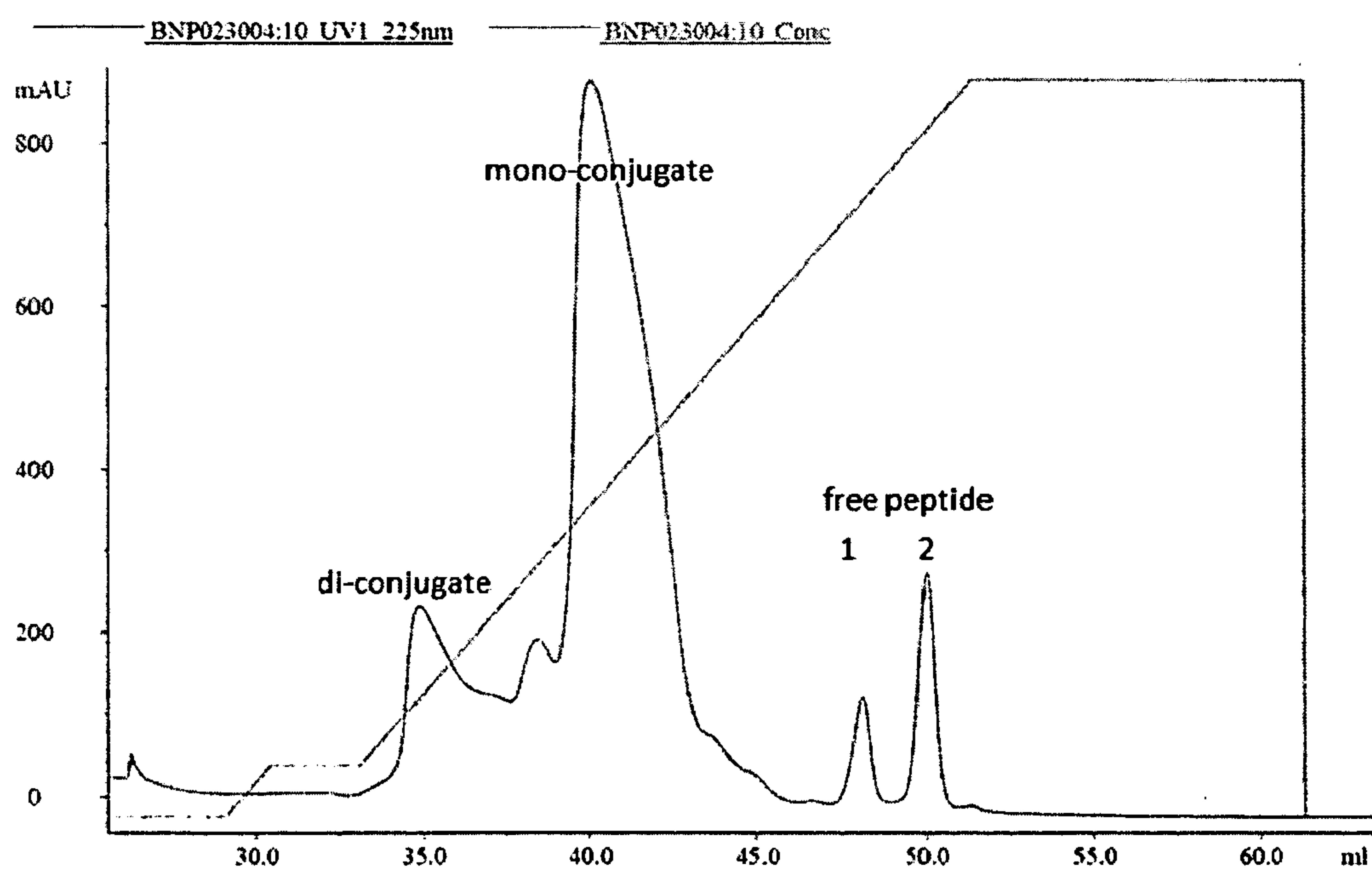


Figure BNP5.1

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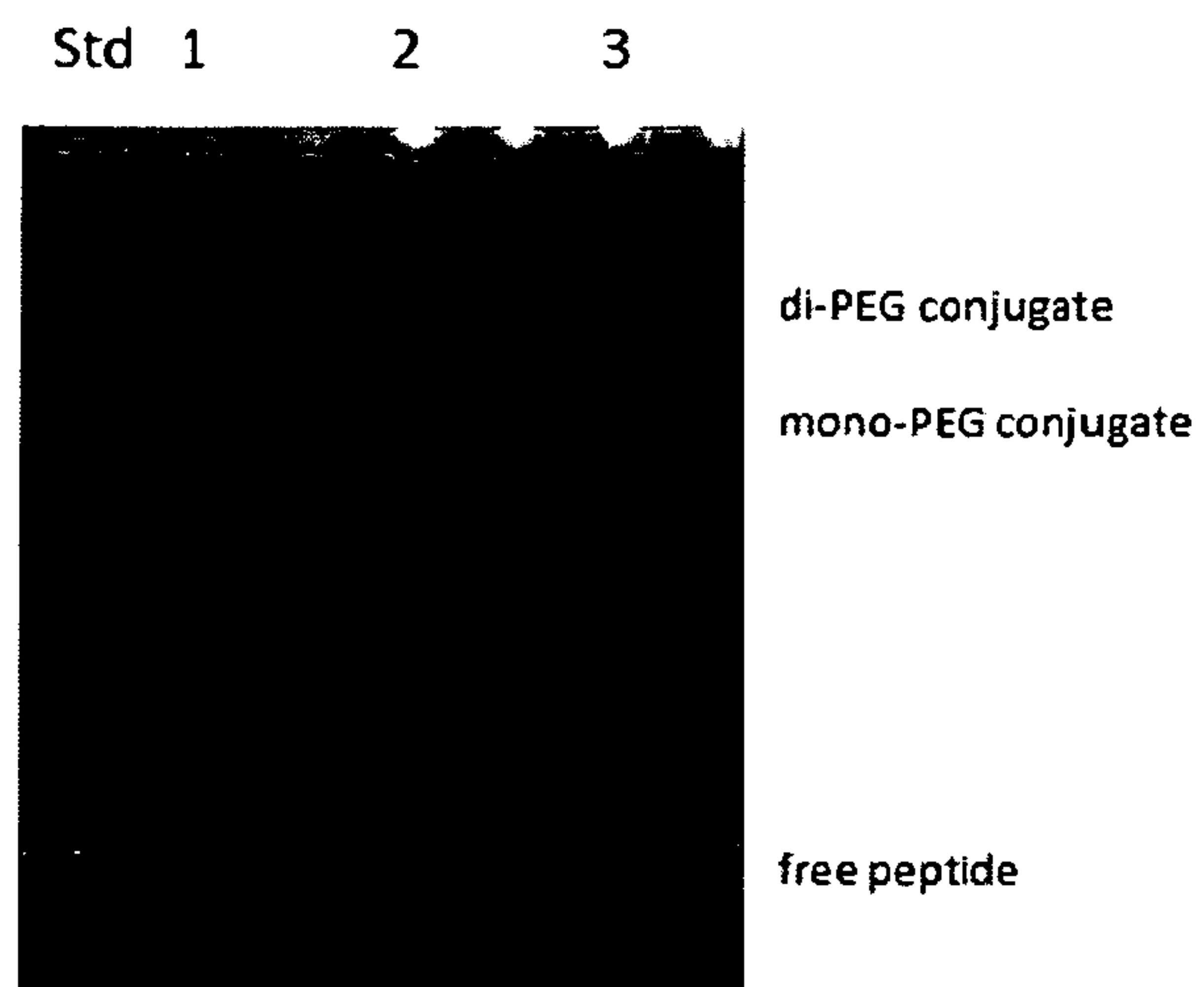


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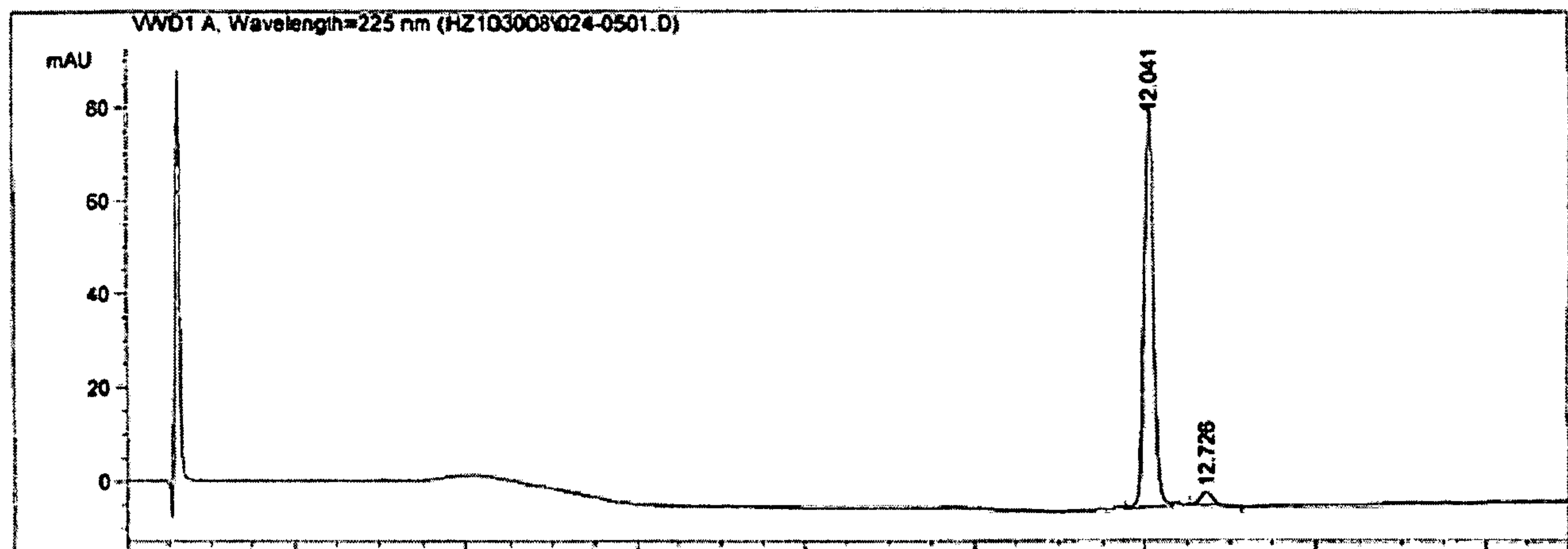


Figure BNP5.3

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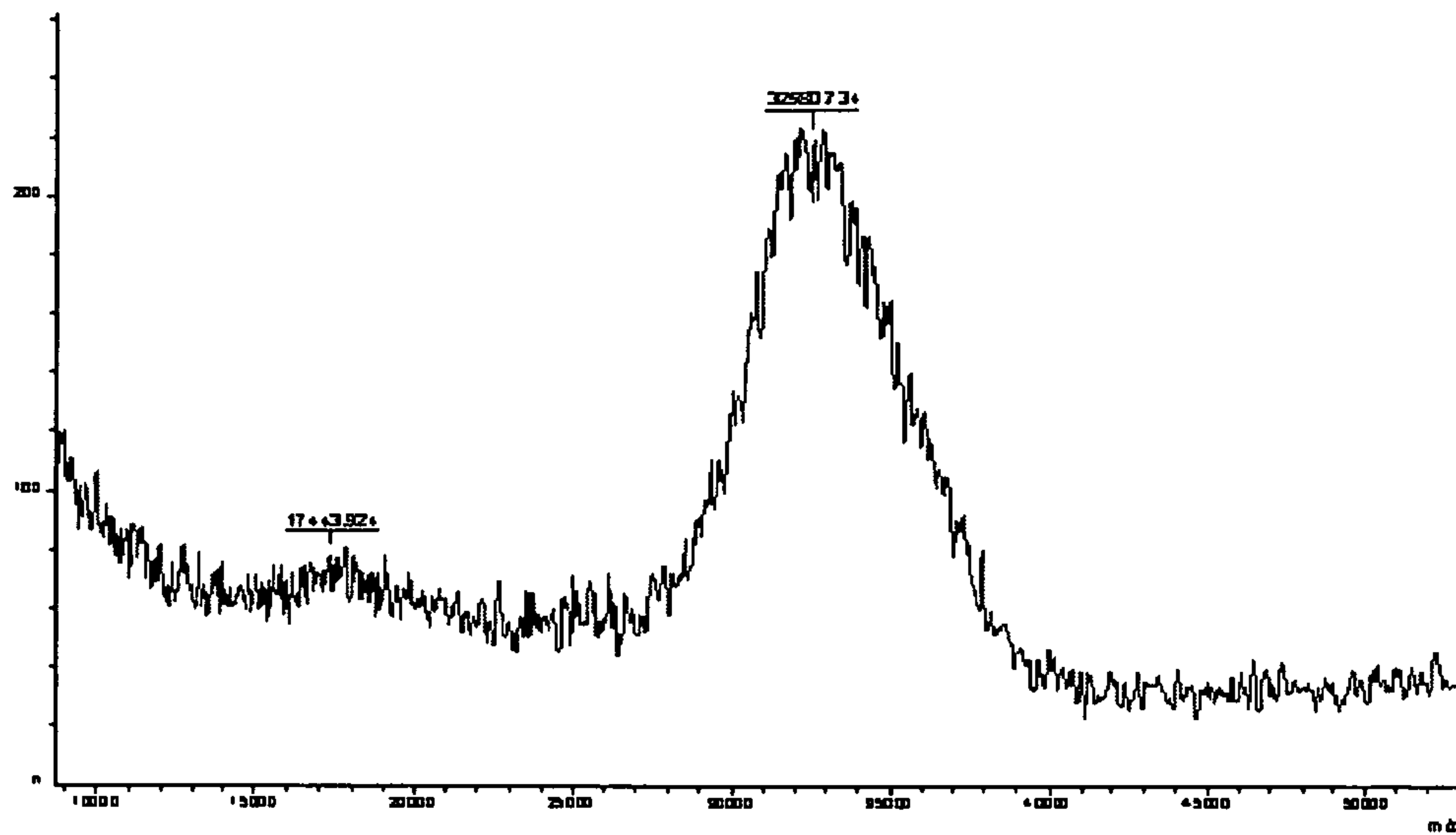


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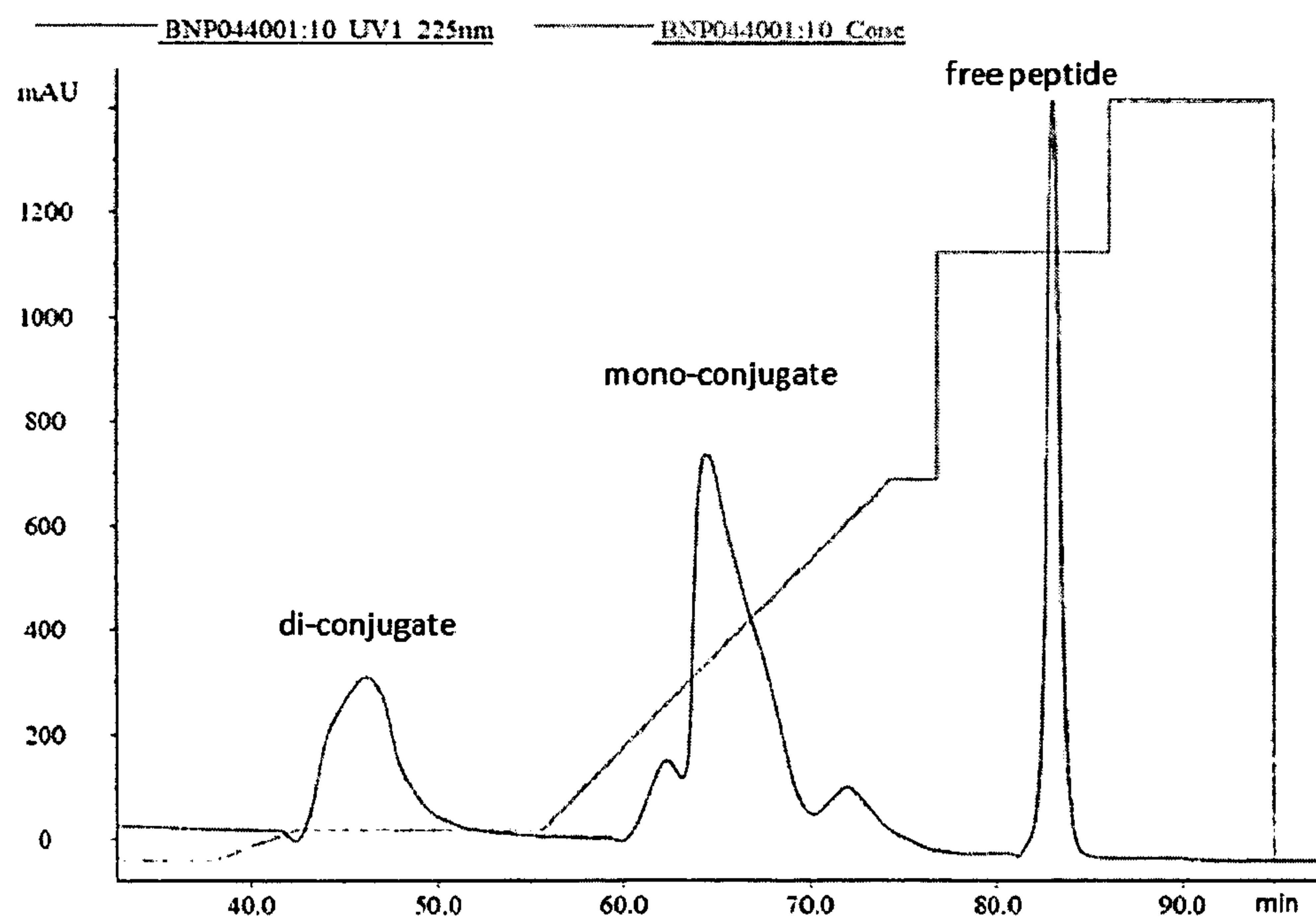


Figure BNP6.1

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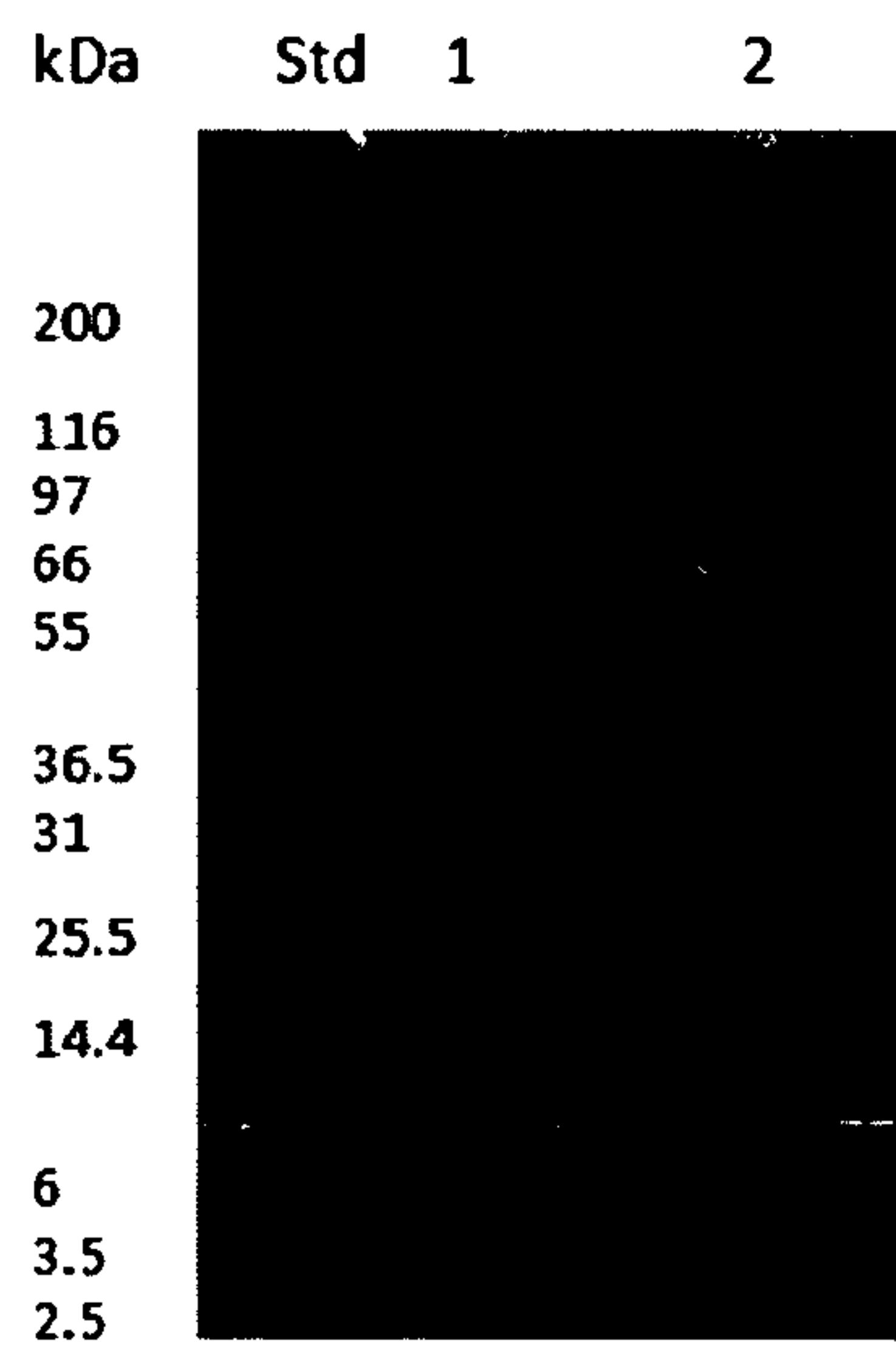


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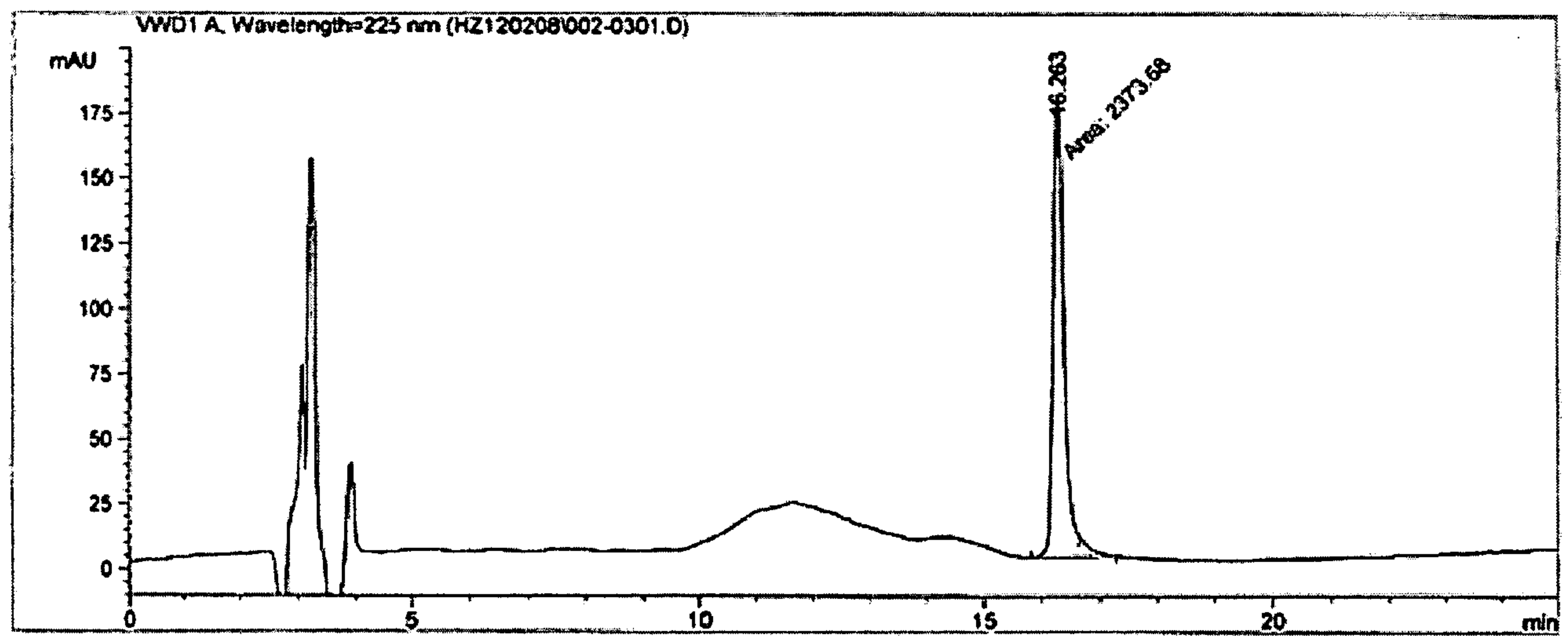


Figure BNP6.3

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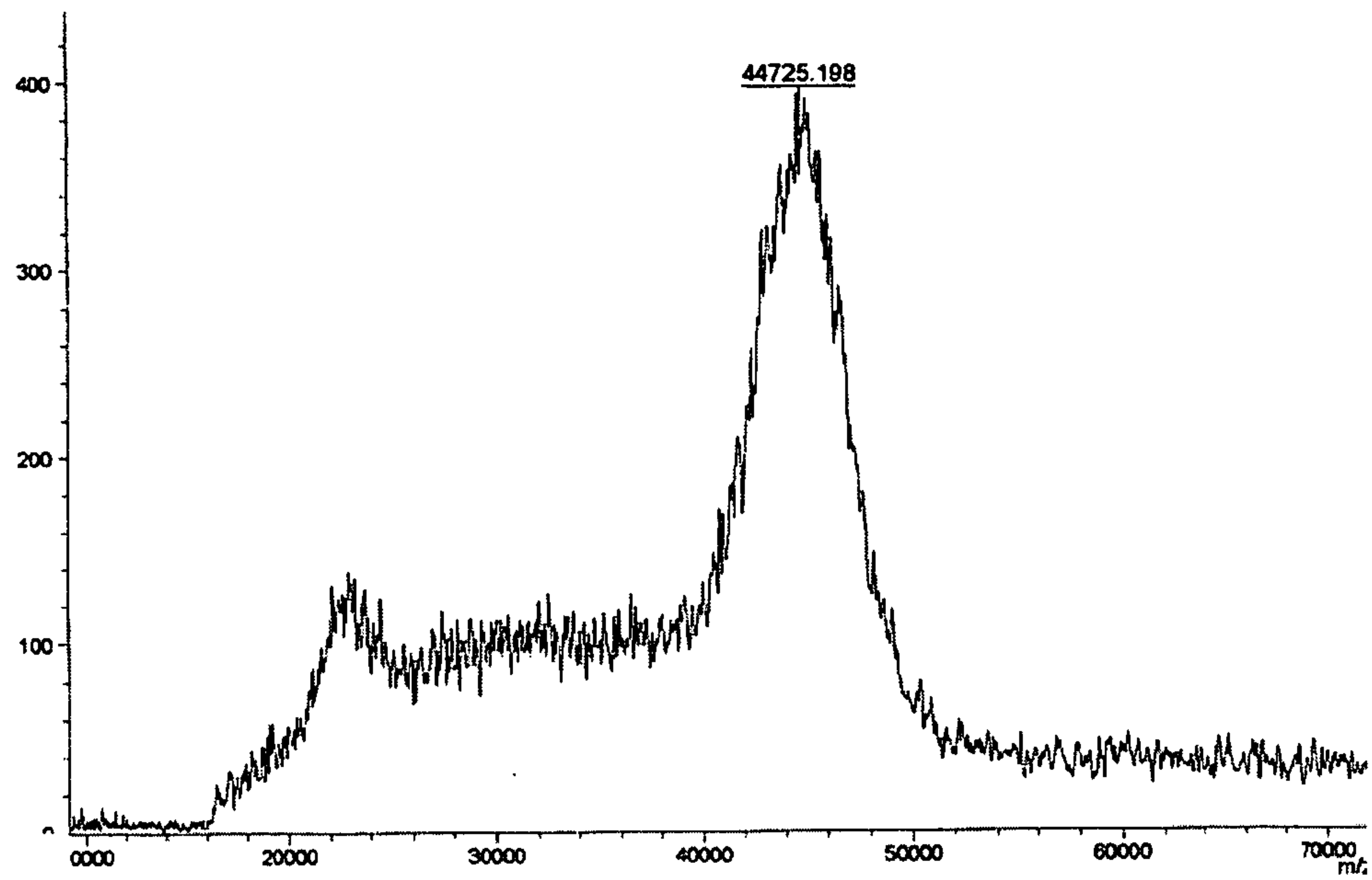


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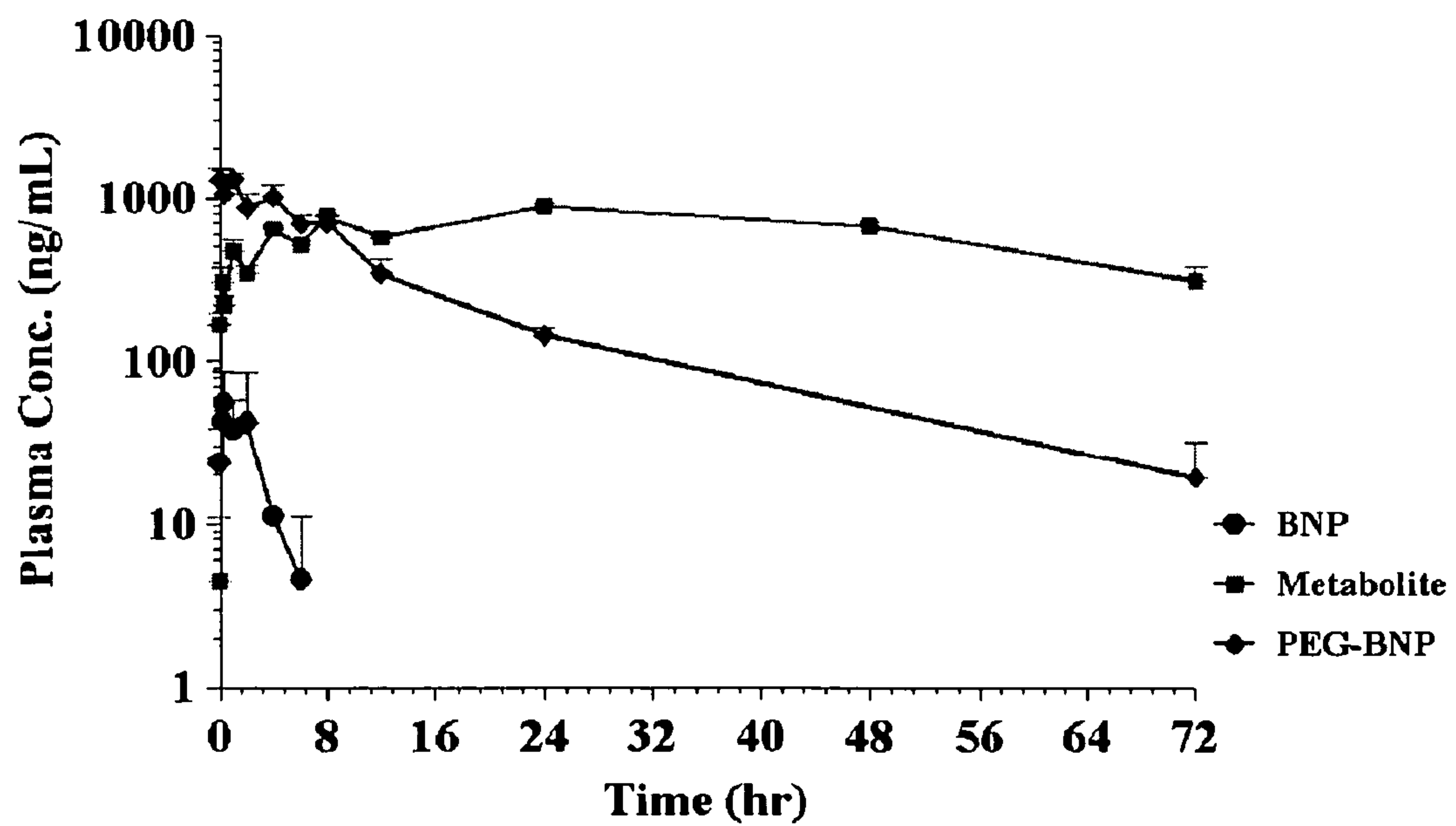


Figure BNP7.1

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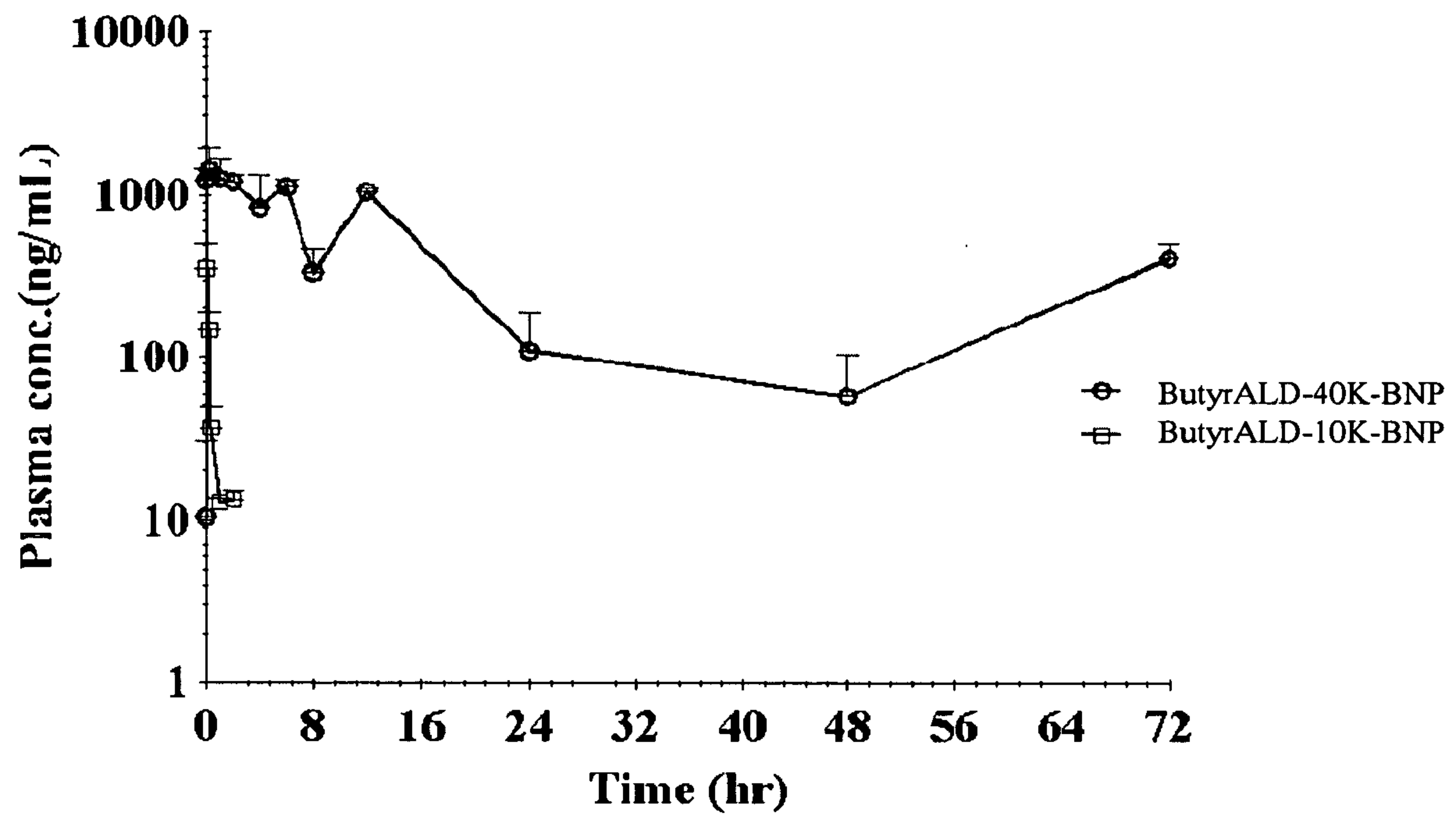


Figure BNP7.2

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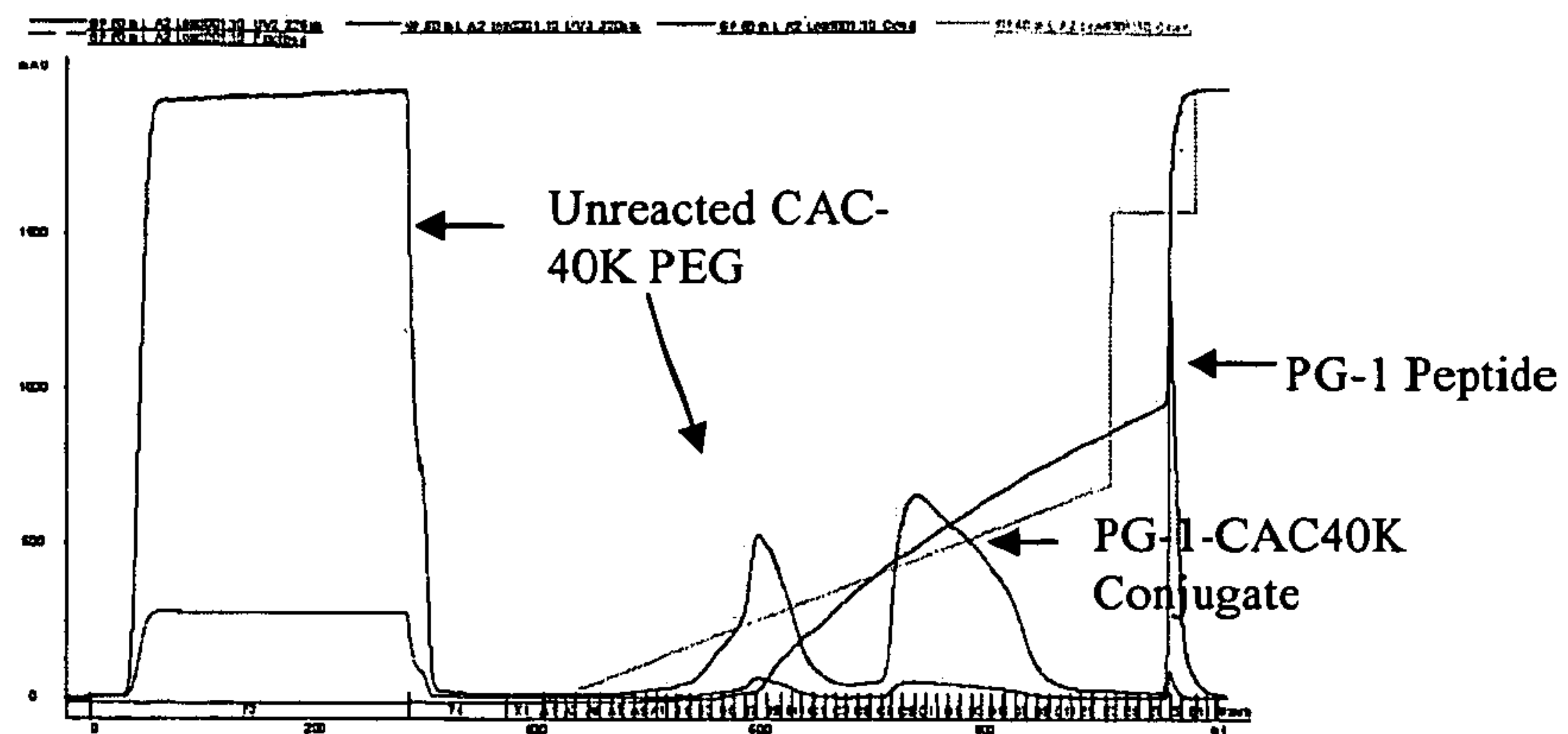


Figure PRO2.1

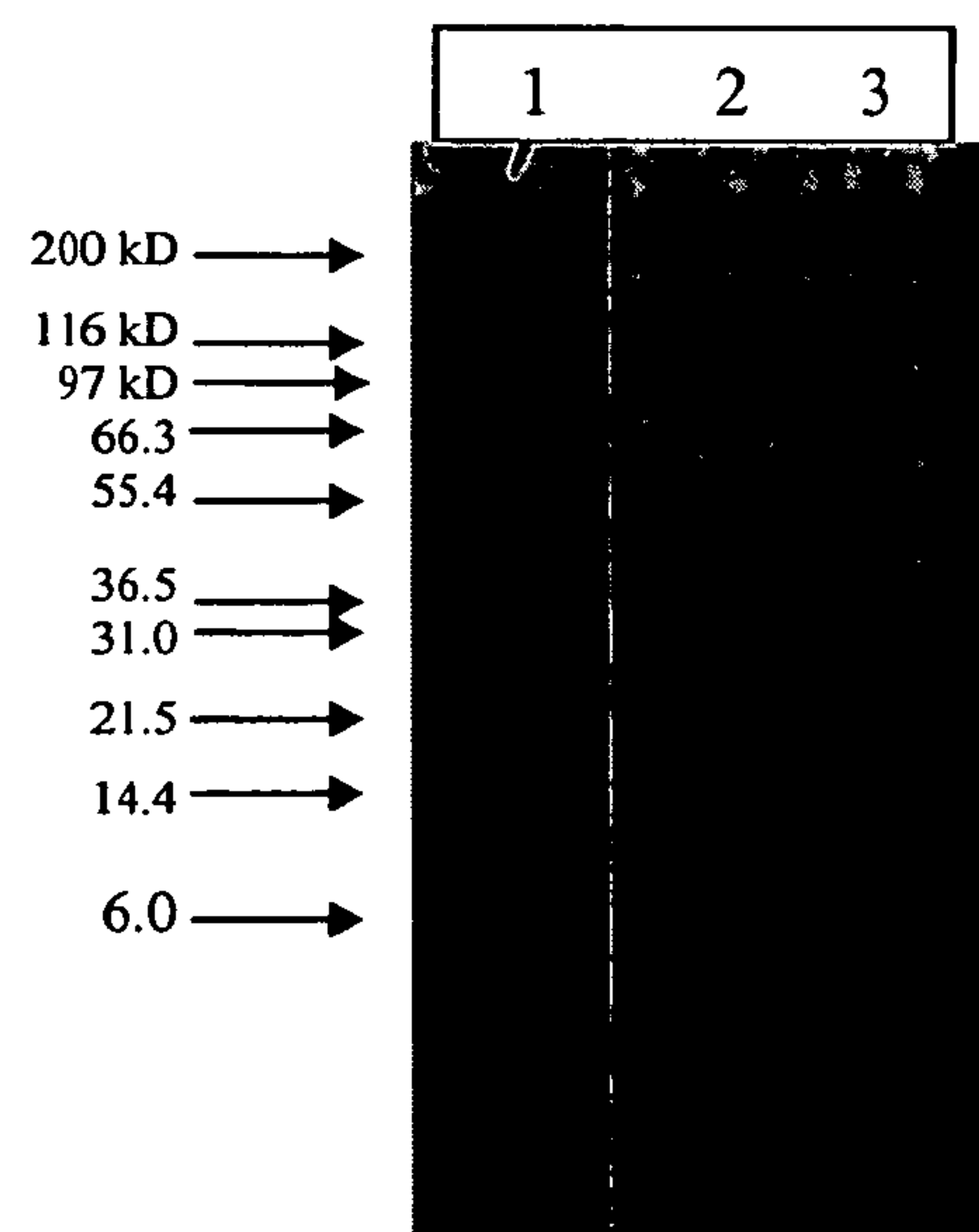


Figure PRO2.2

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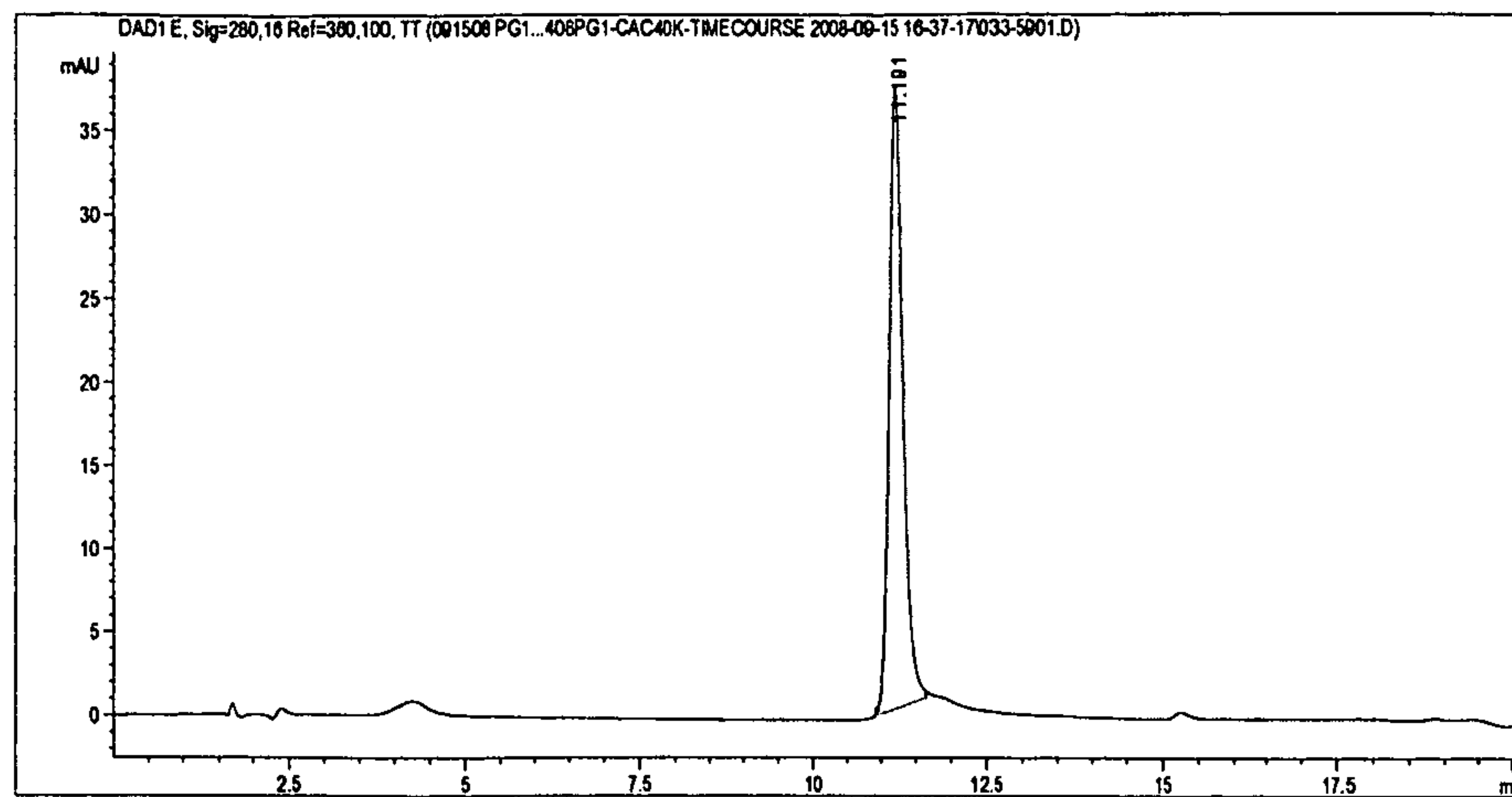


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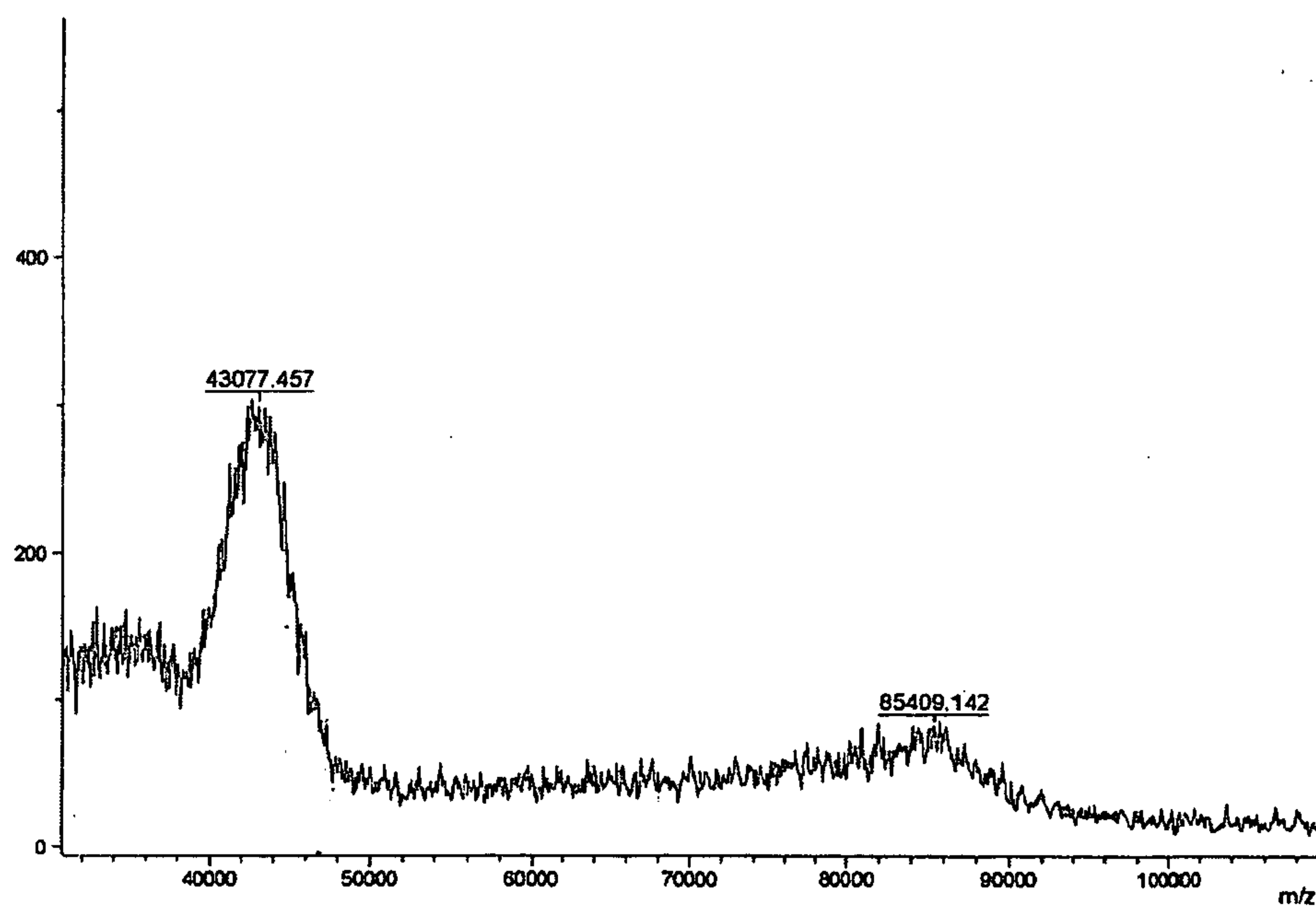


Figure PRO2.4

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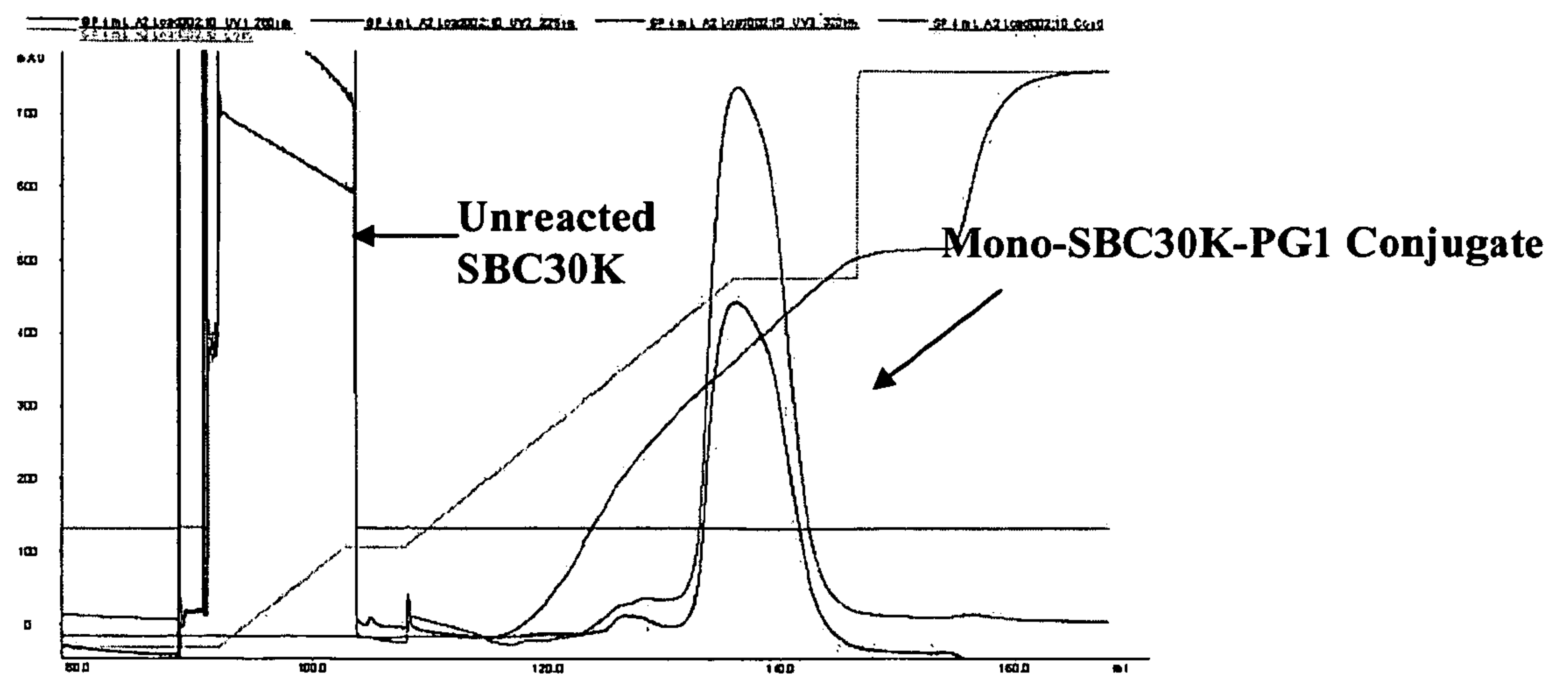


Figure PRO3.1

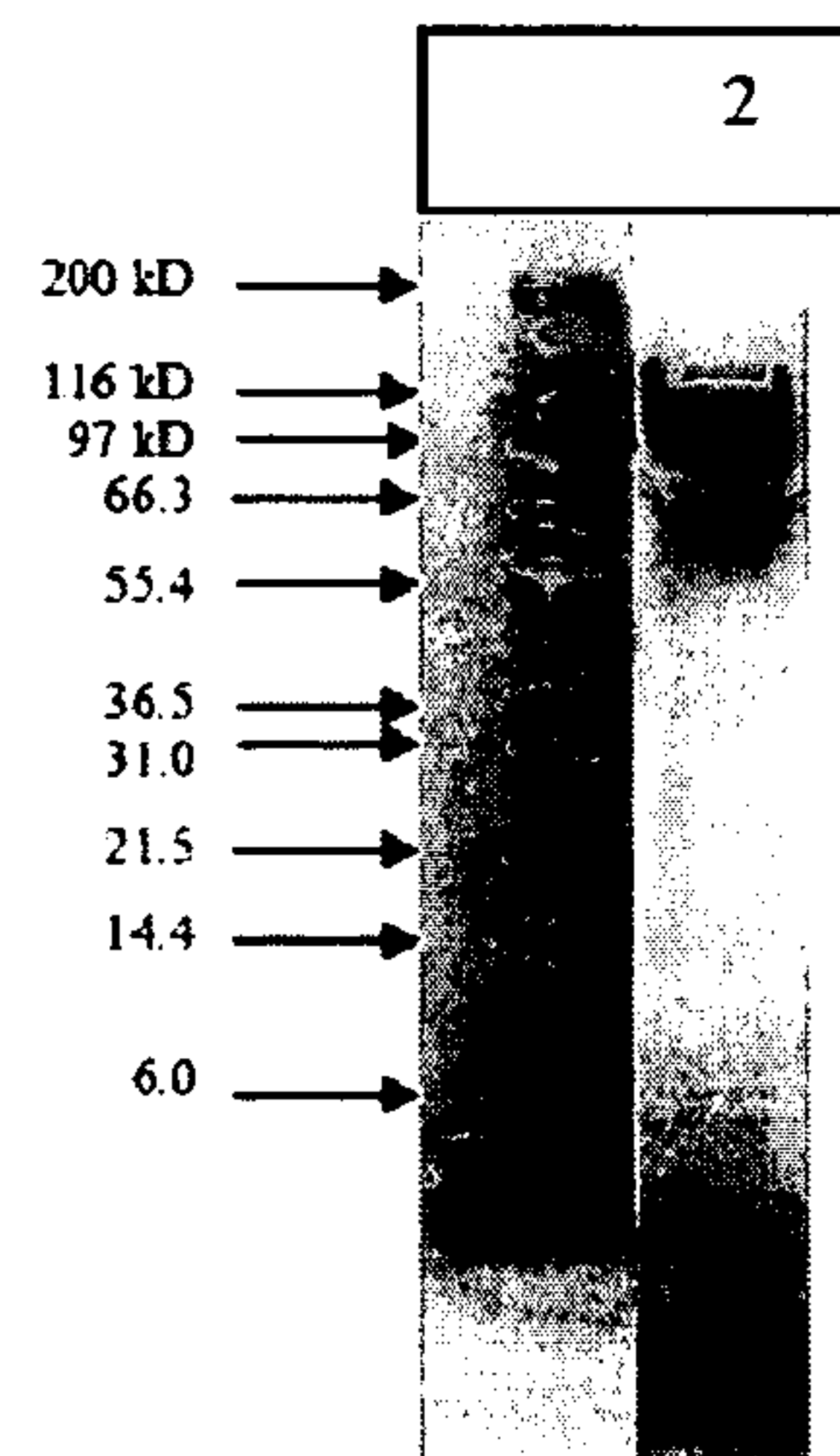


Figure PRO3.2

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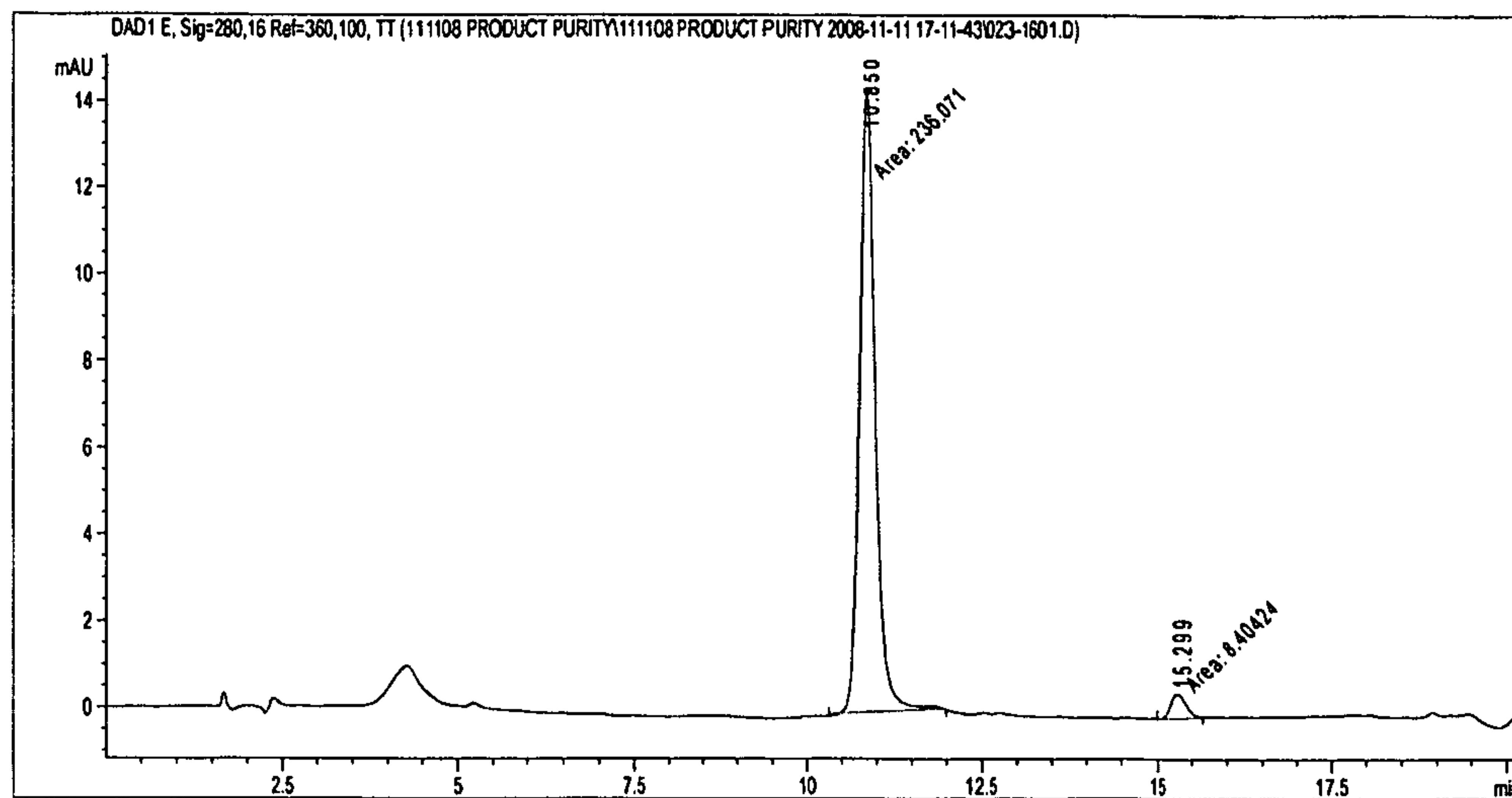


Figure PRO3.3

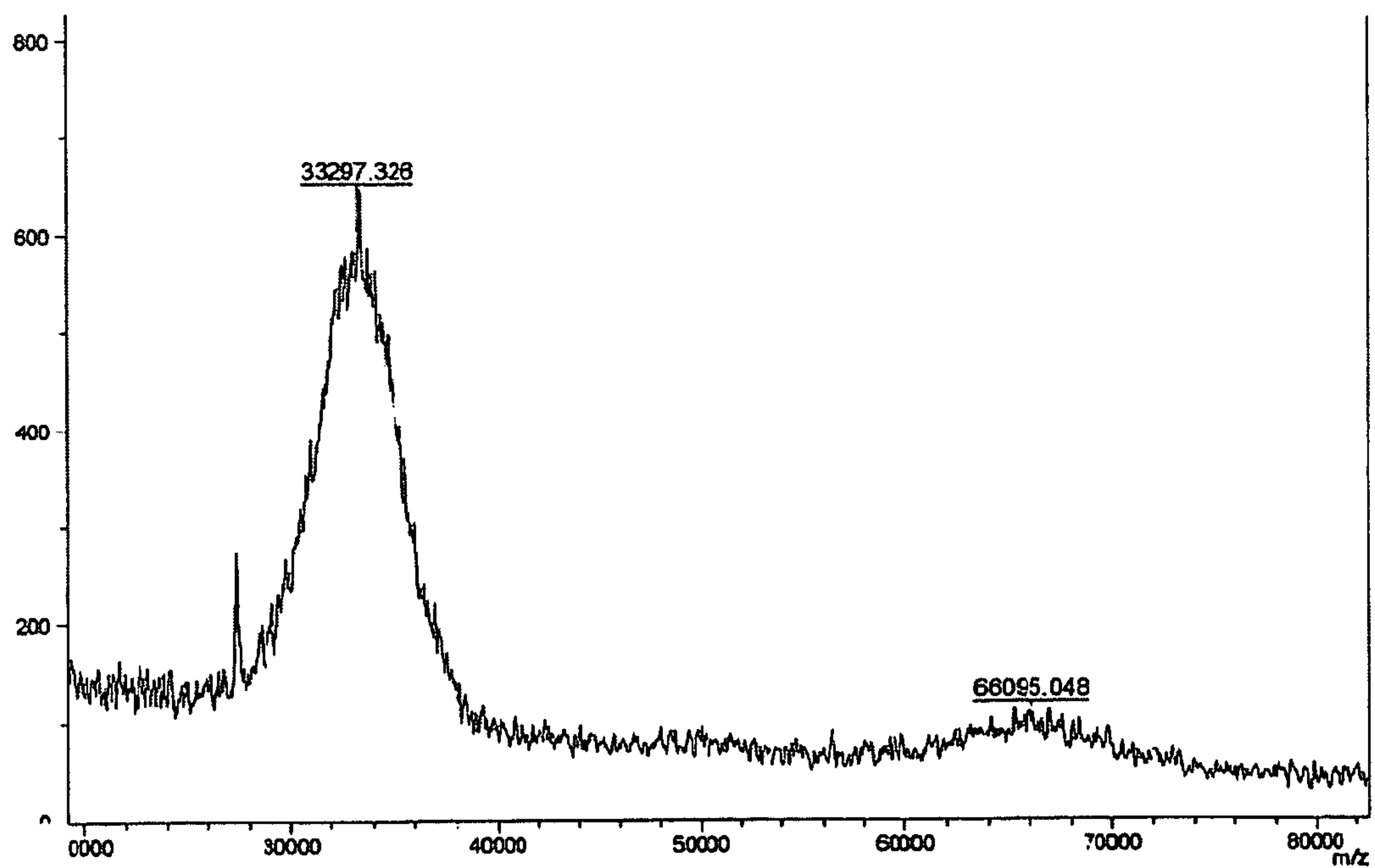


Figure PRO3.4

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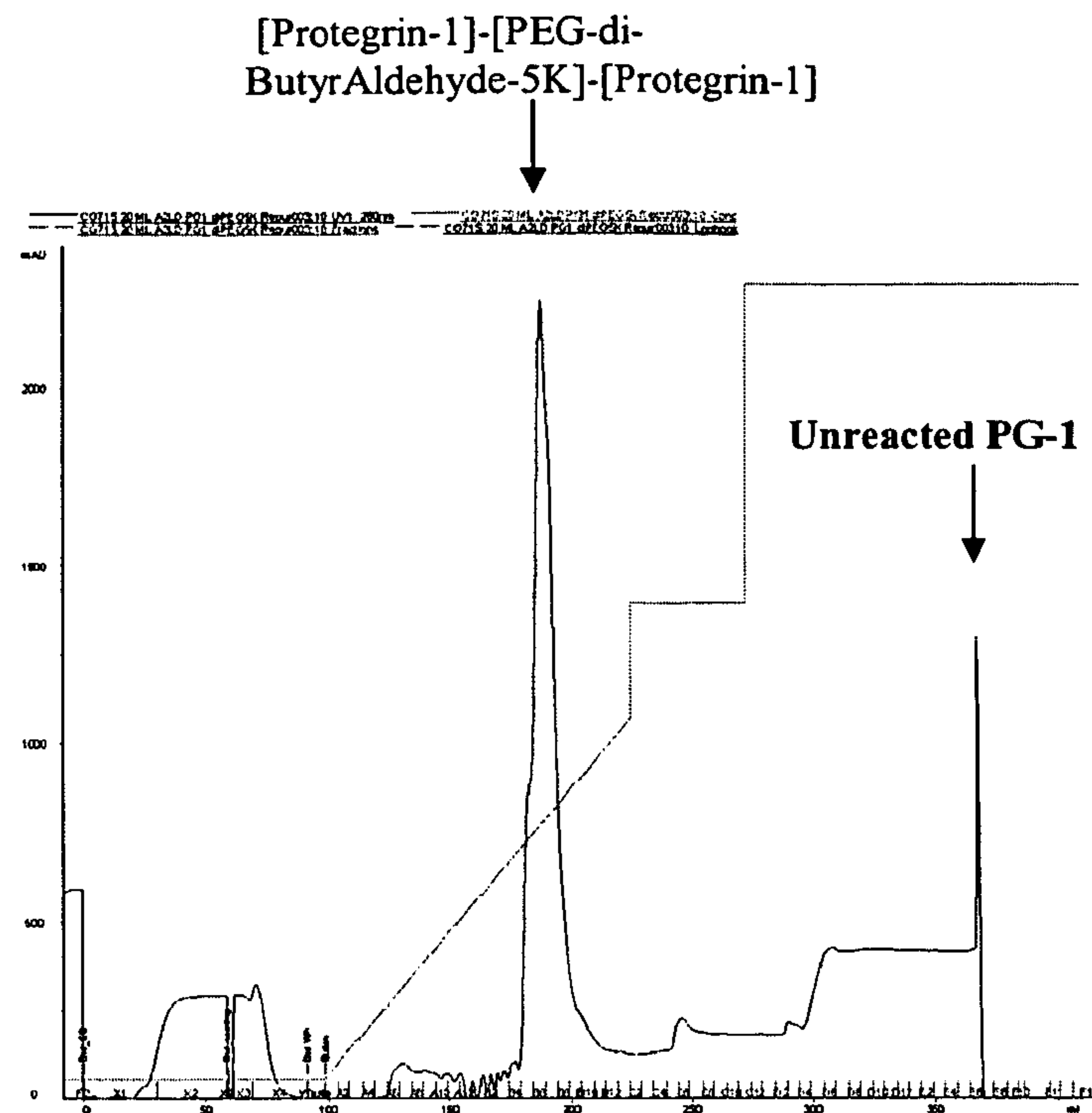


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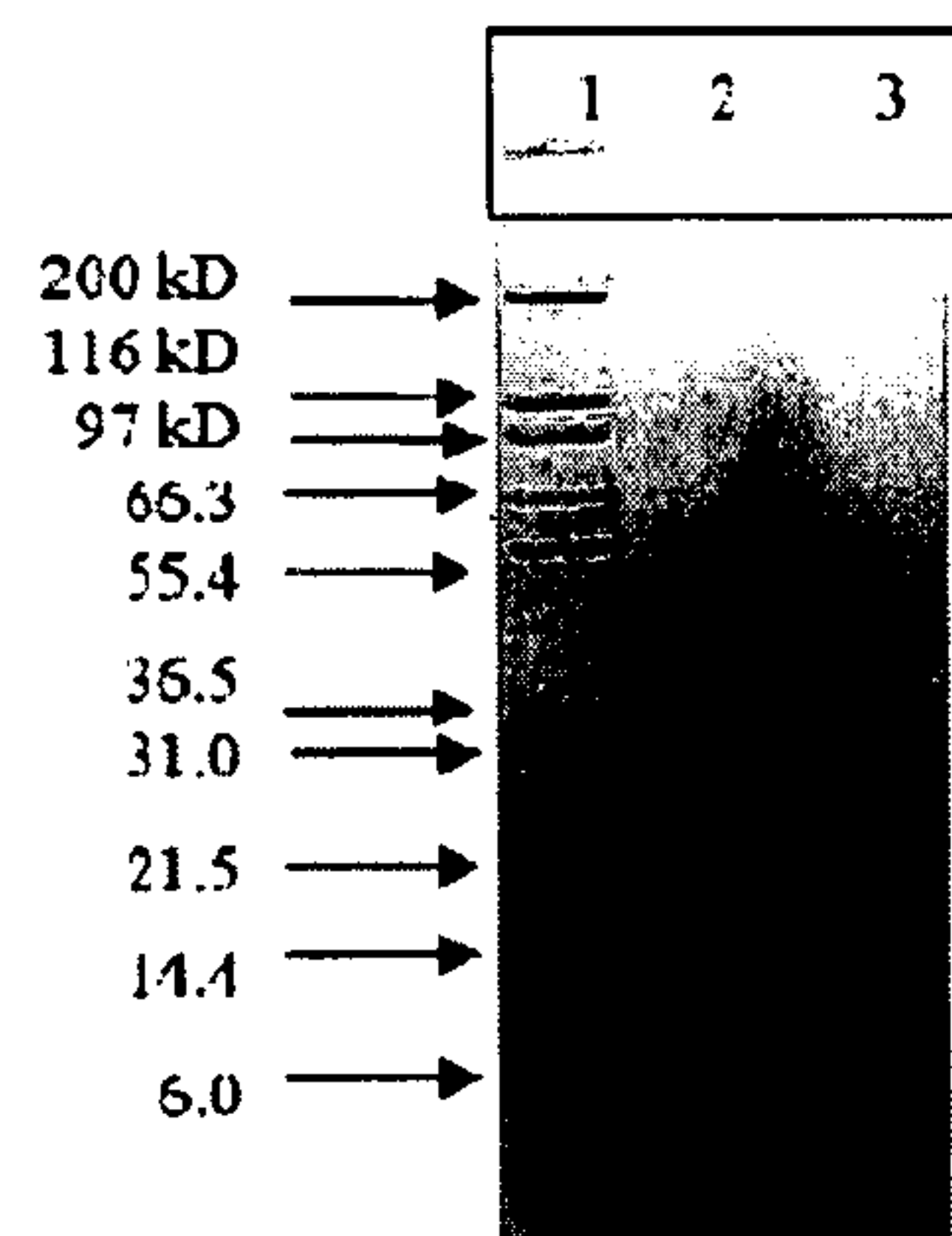


Figure PRO4.2

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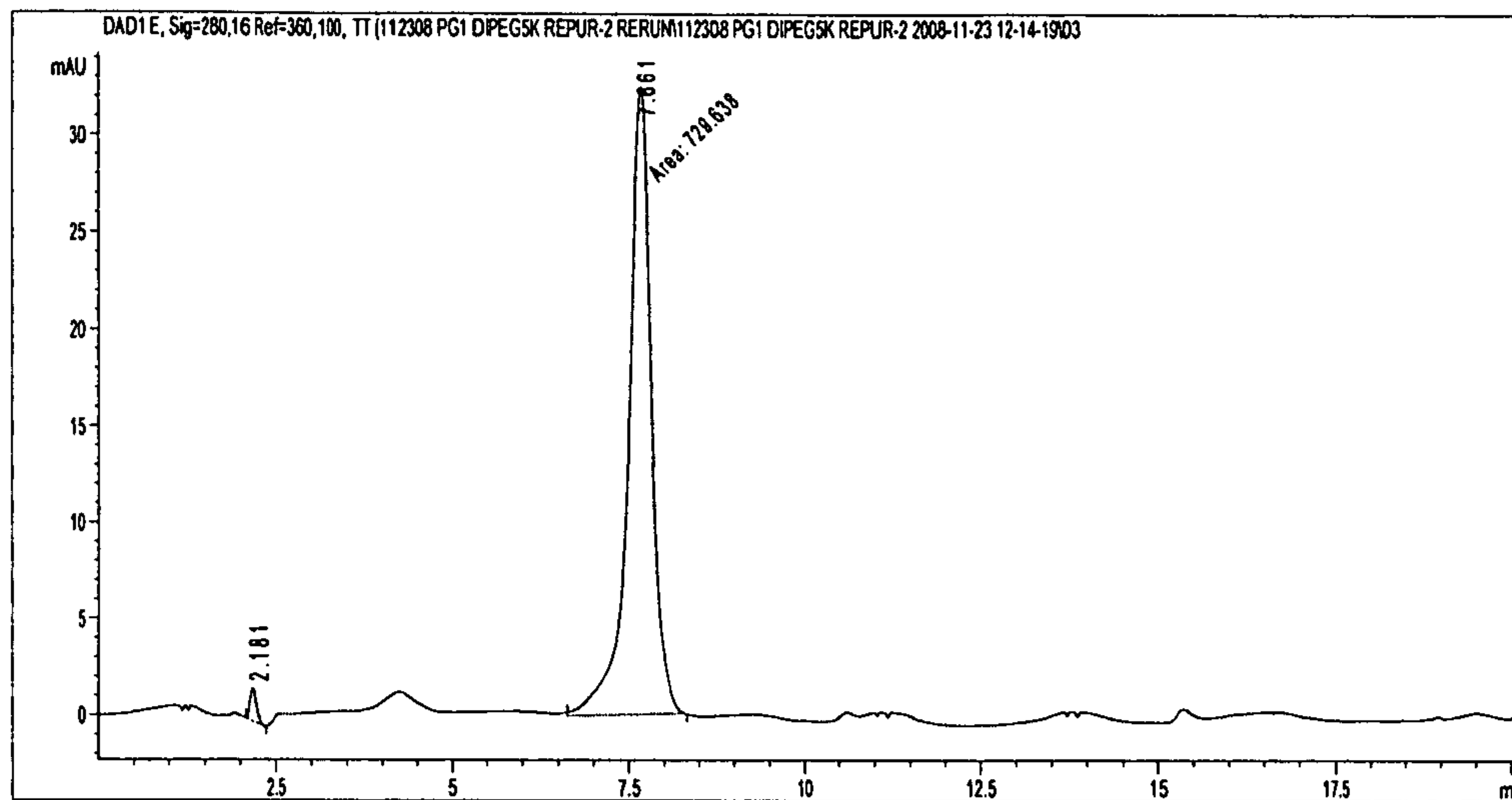


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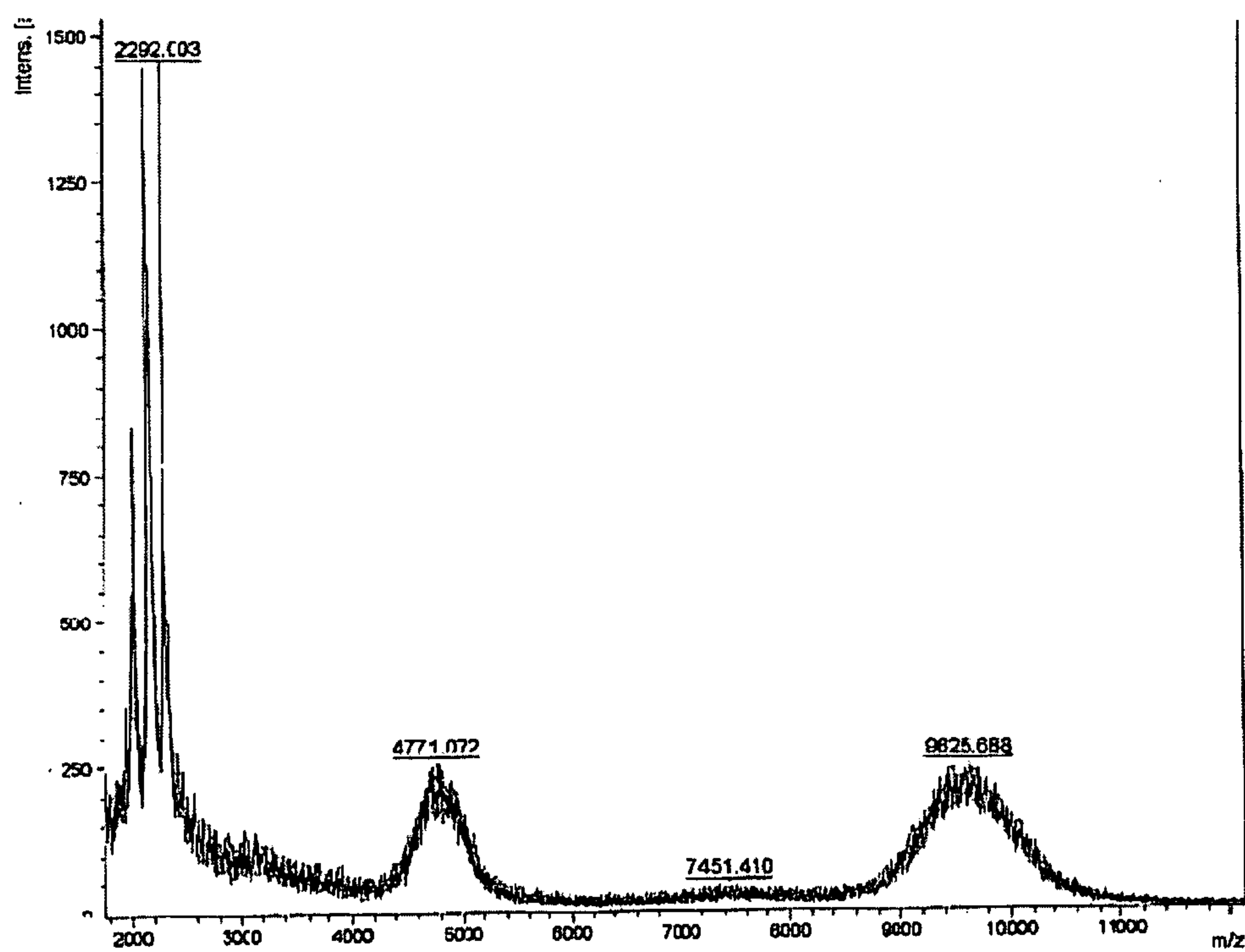


Figure PRO4.4

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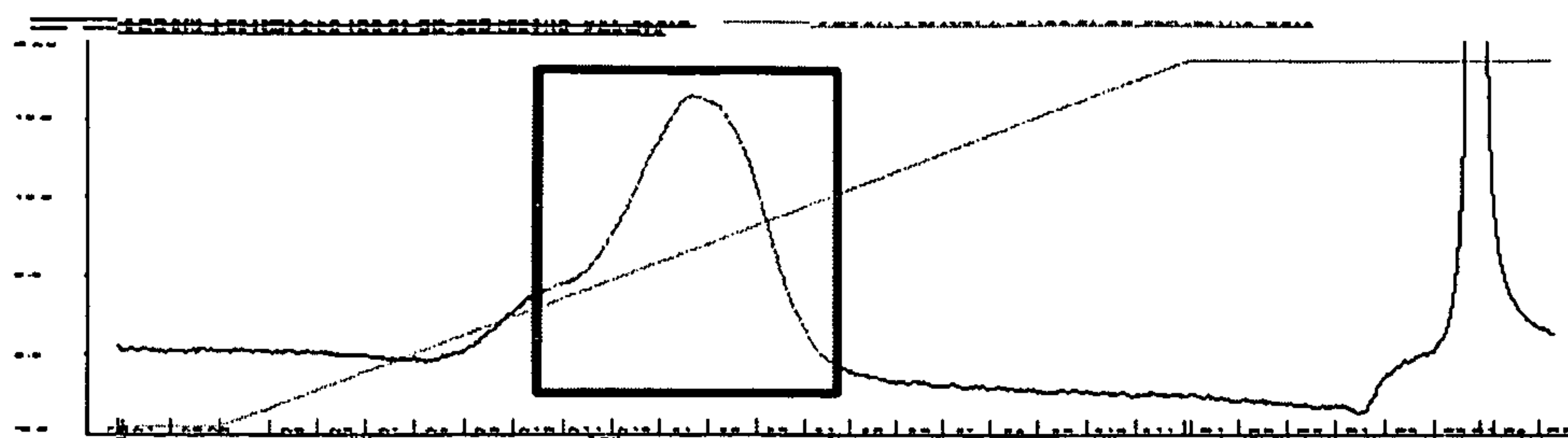


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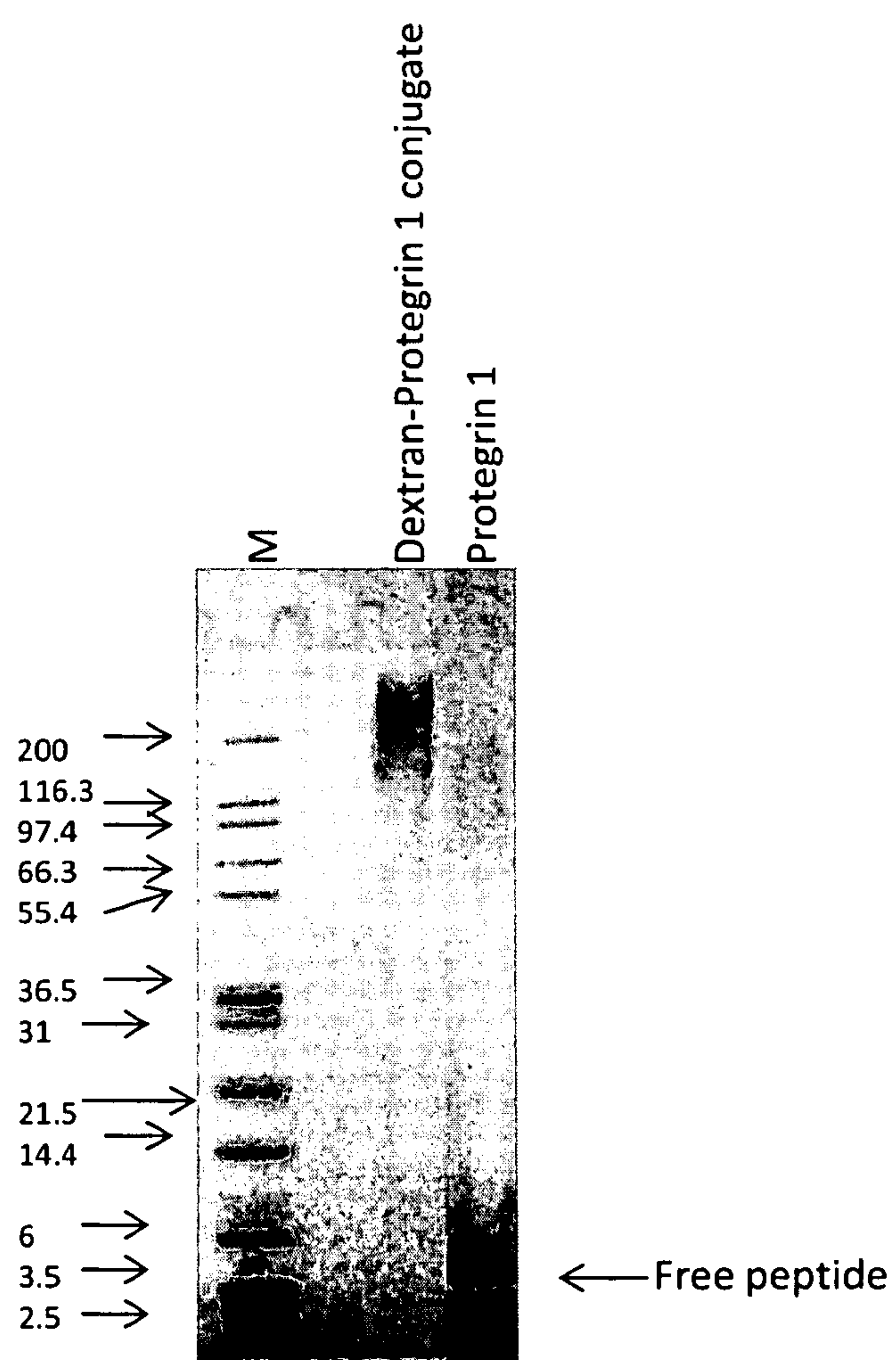


Figure PRO5.2

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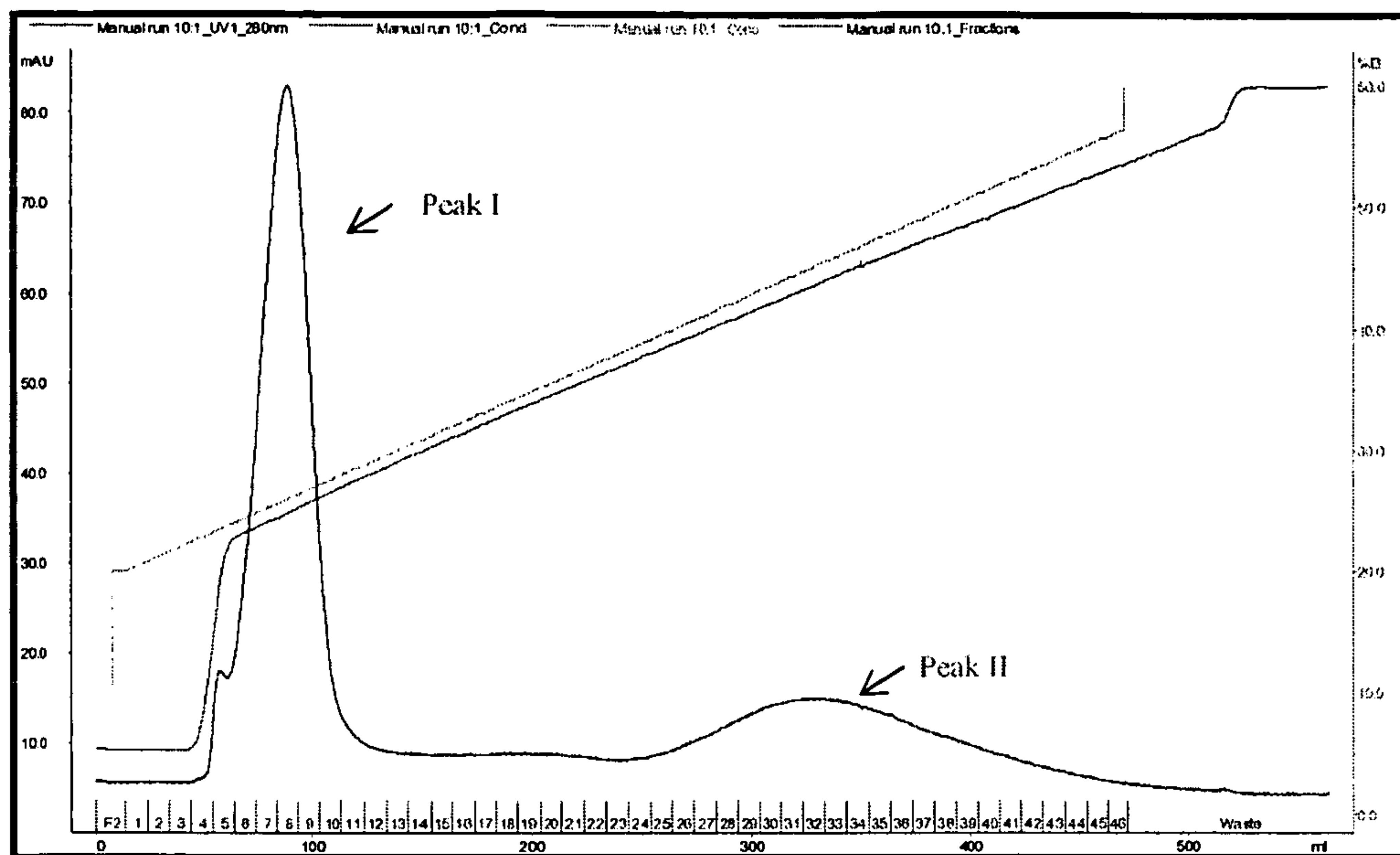


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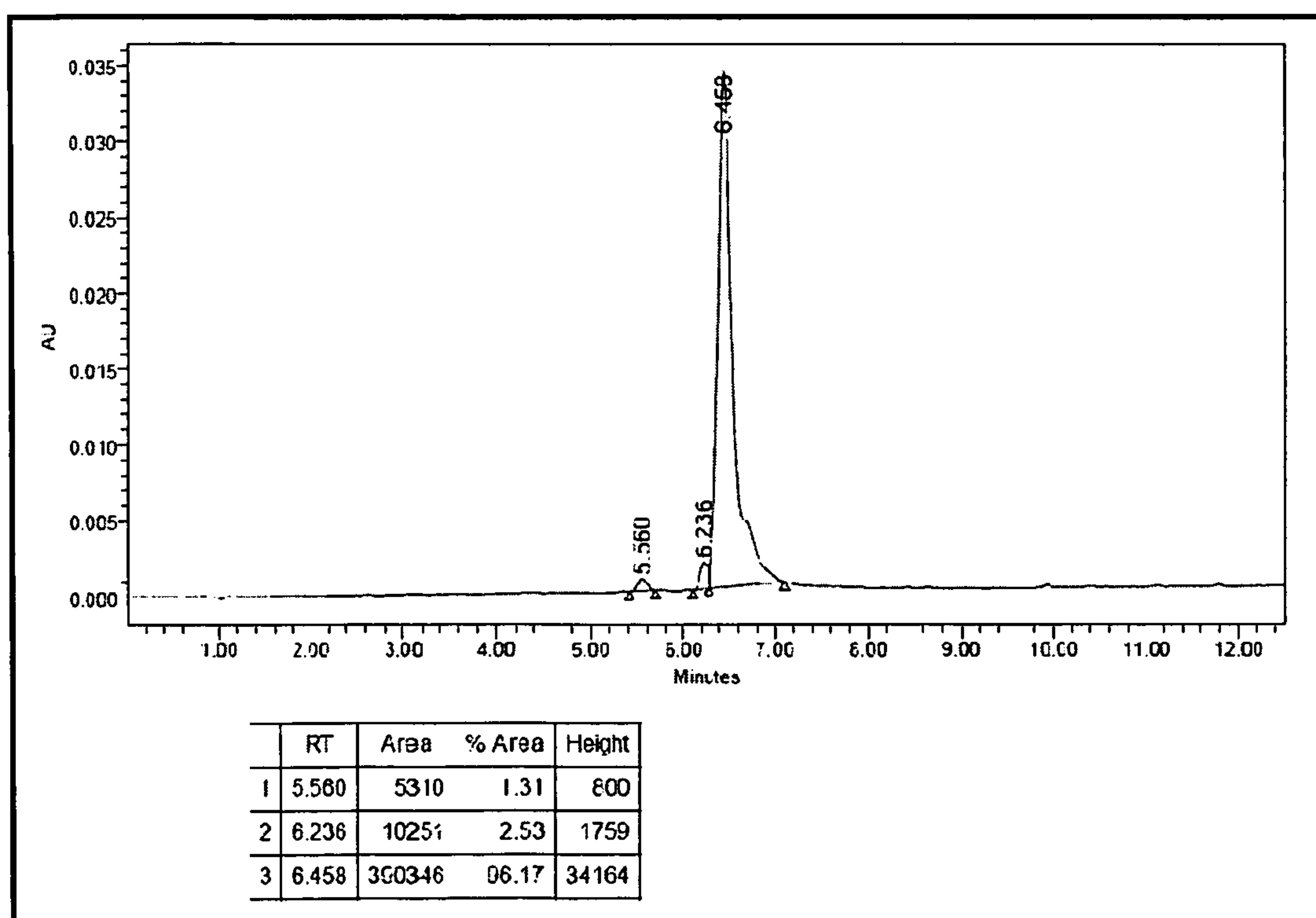


Figure PRO6.2

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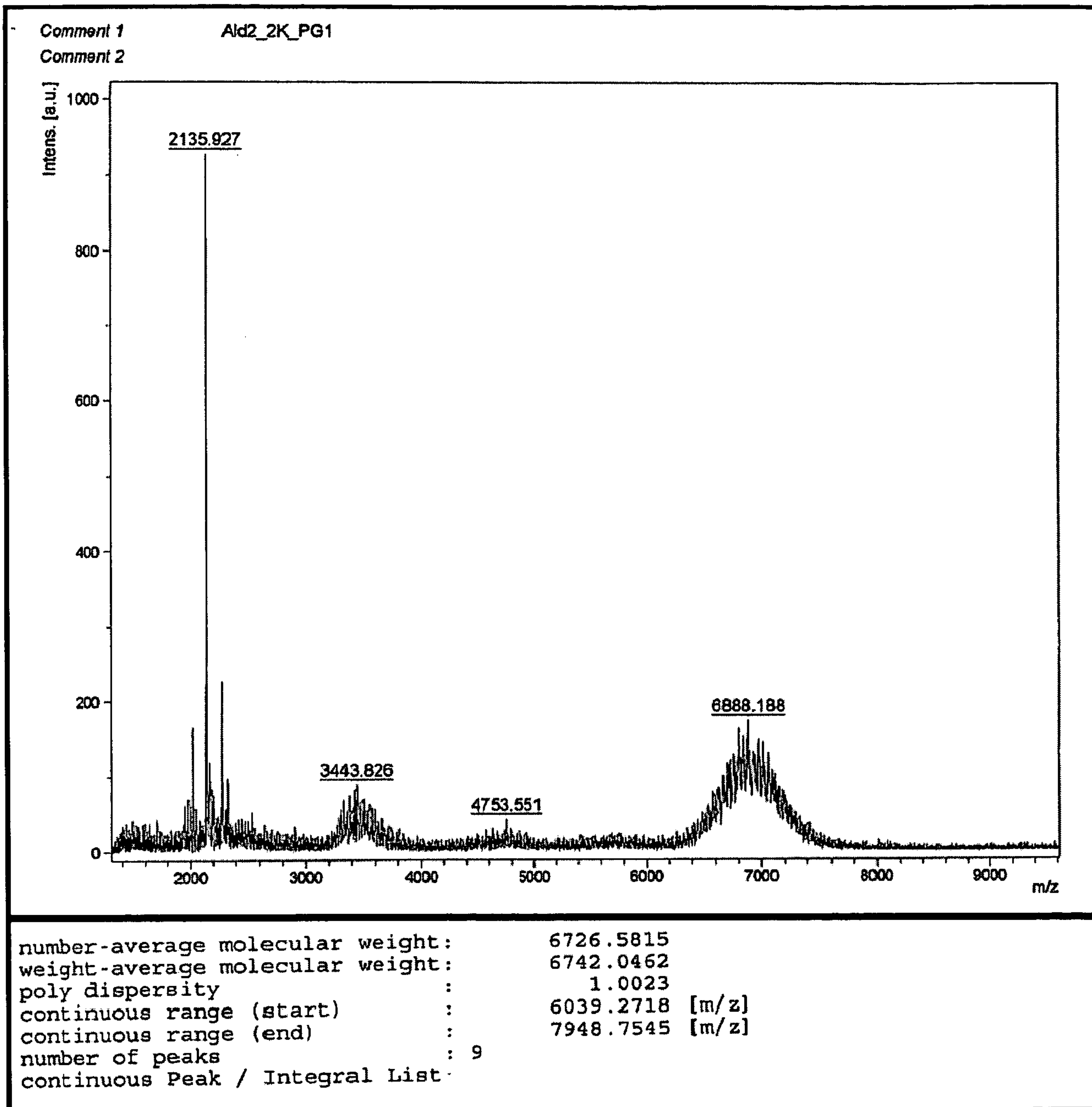


Figure PRO6.3

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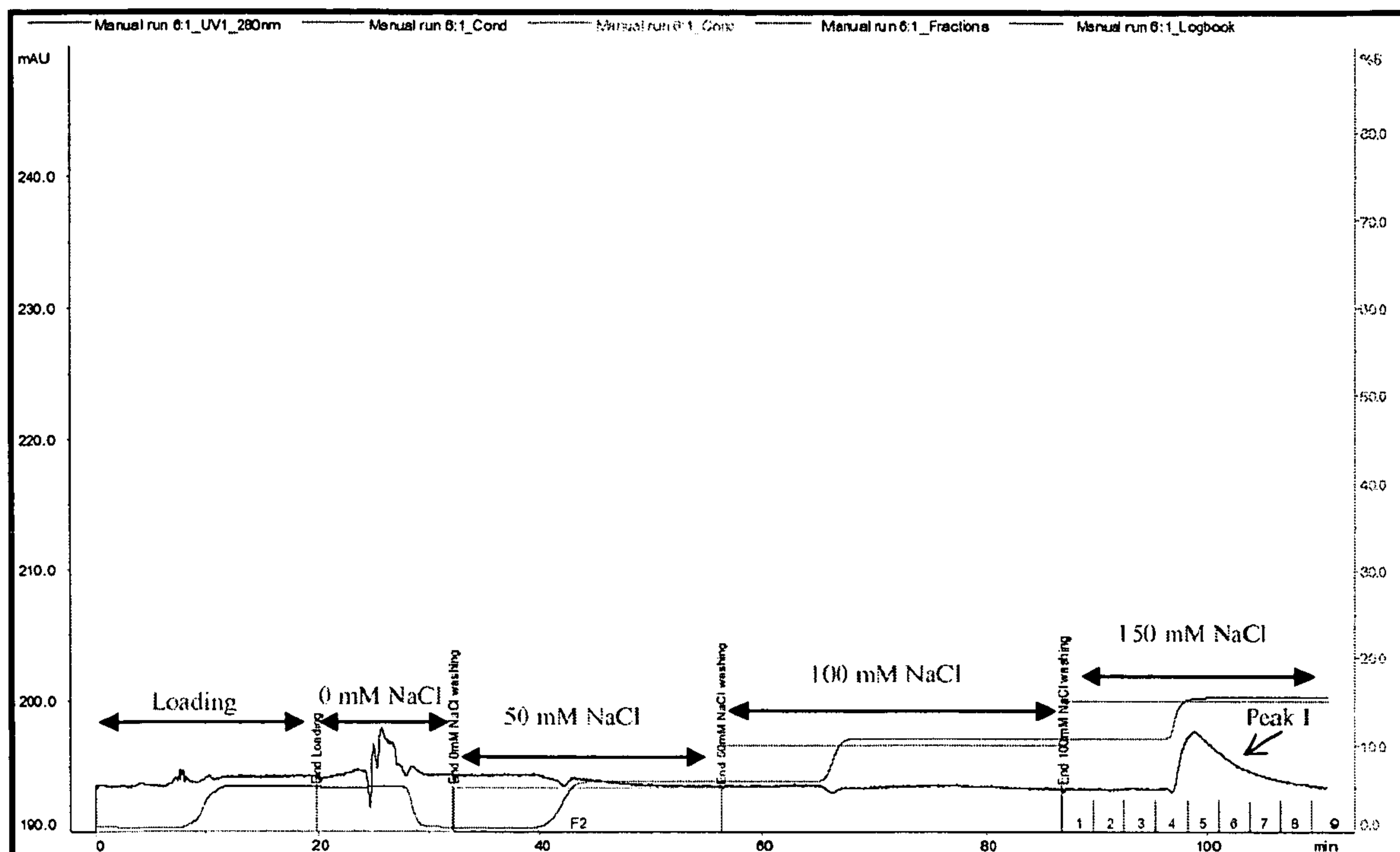


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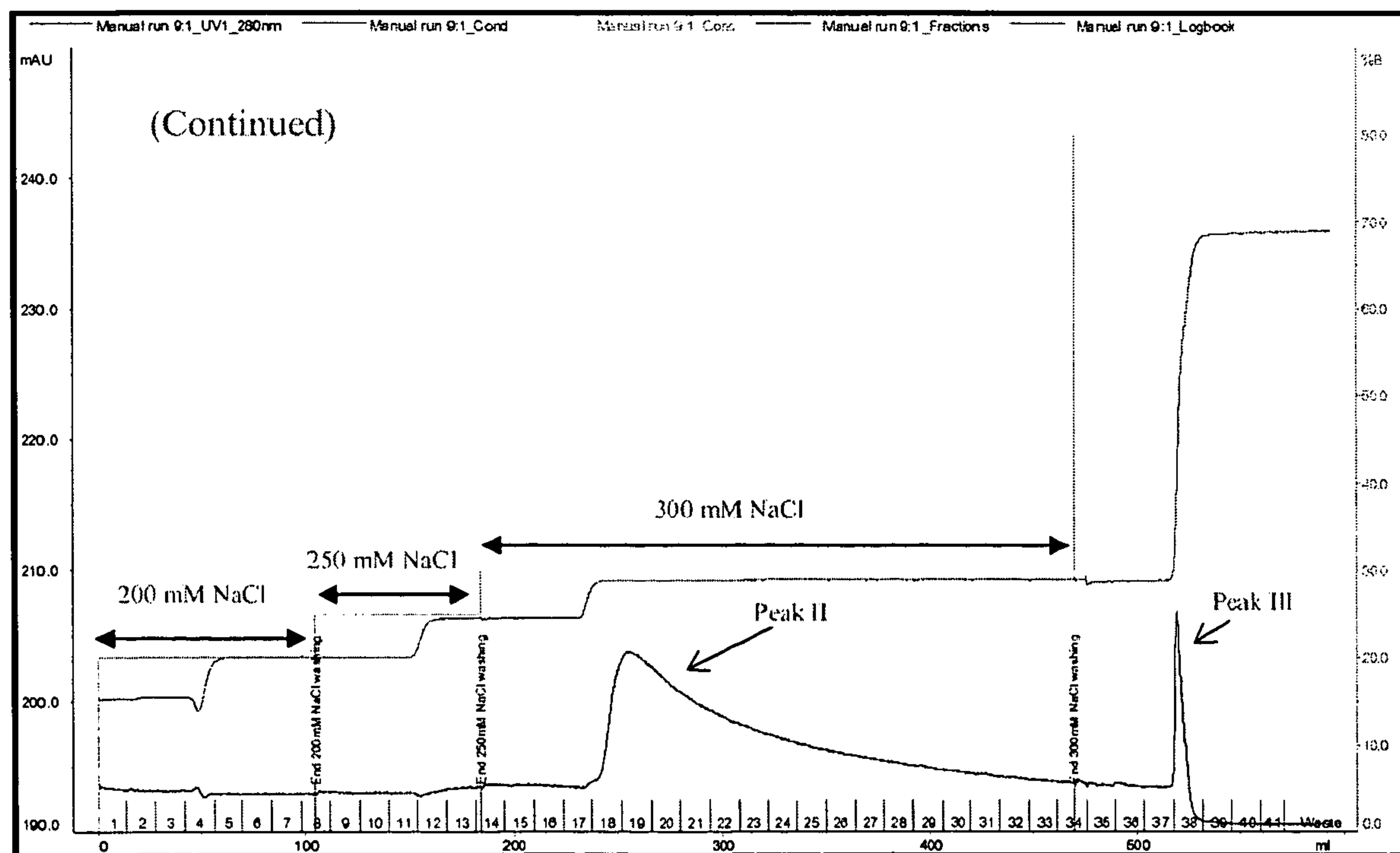


Figure 7.1.2

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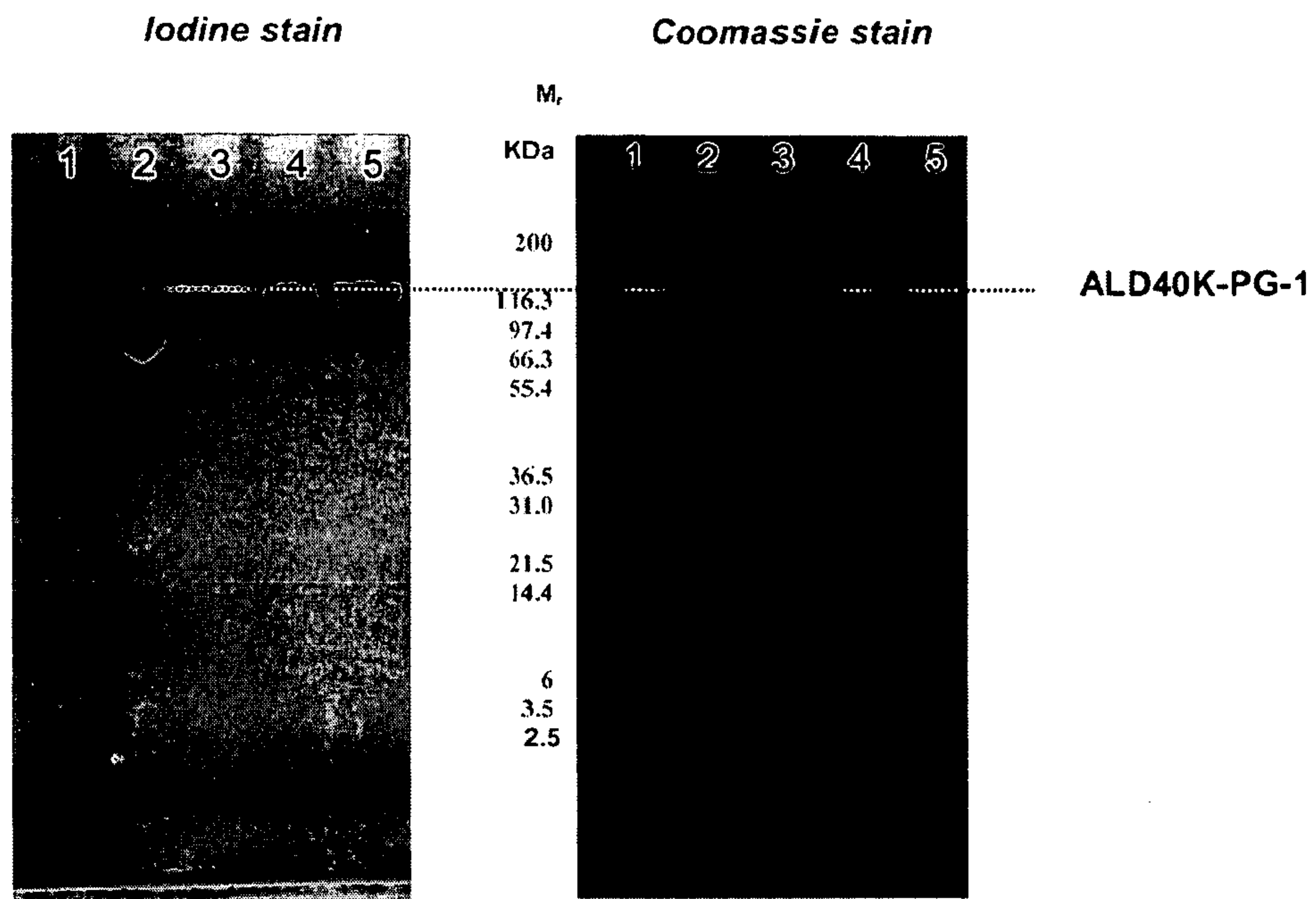


Figure PRO7.2

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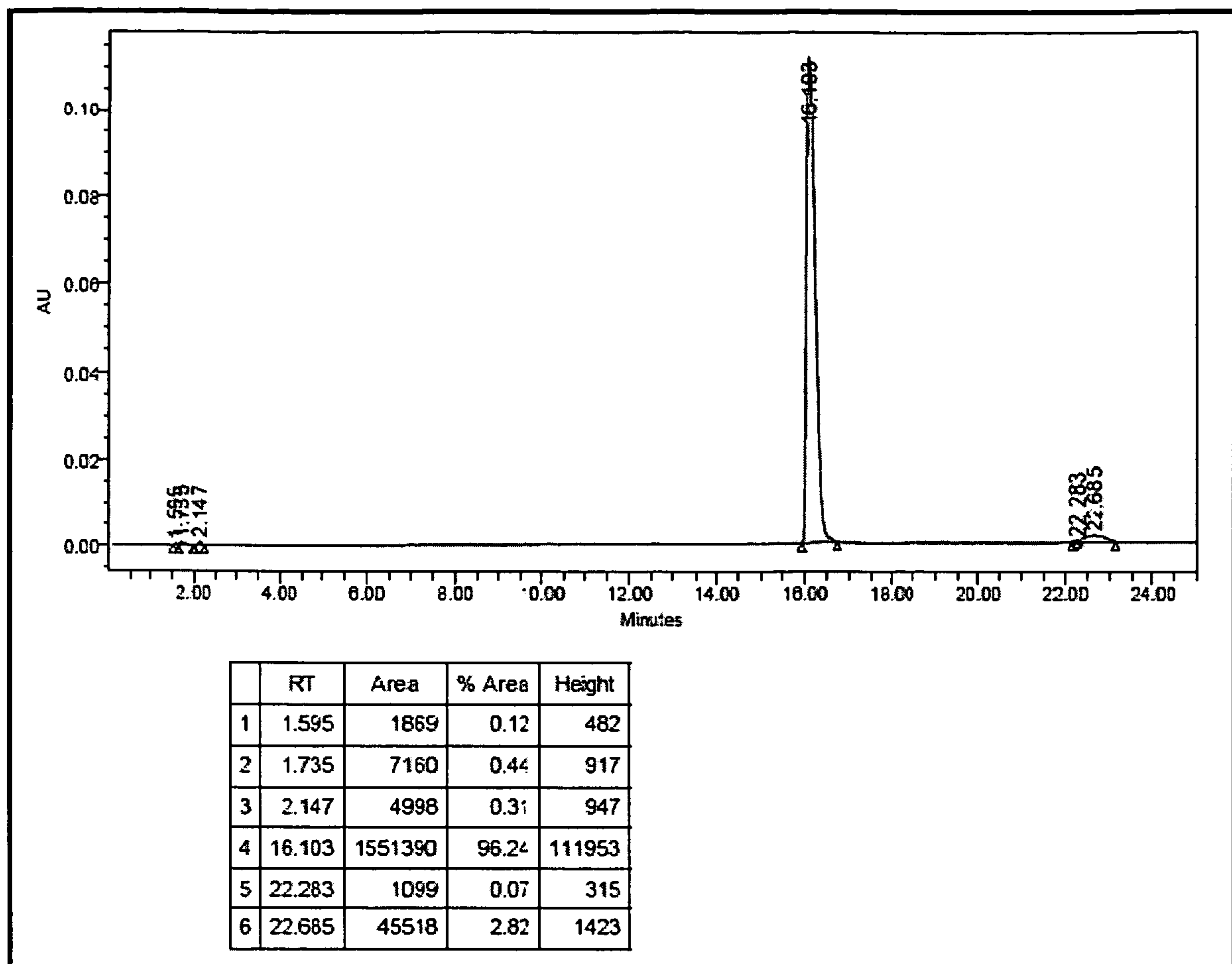


Figure PRO7.3

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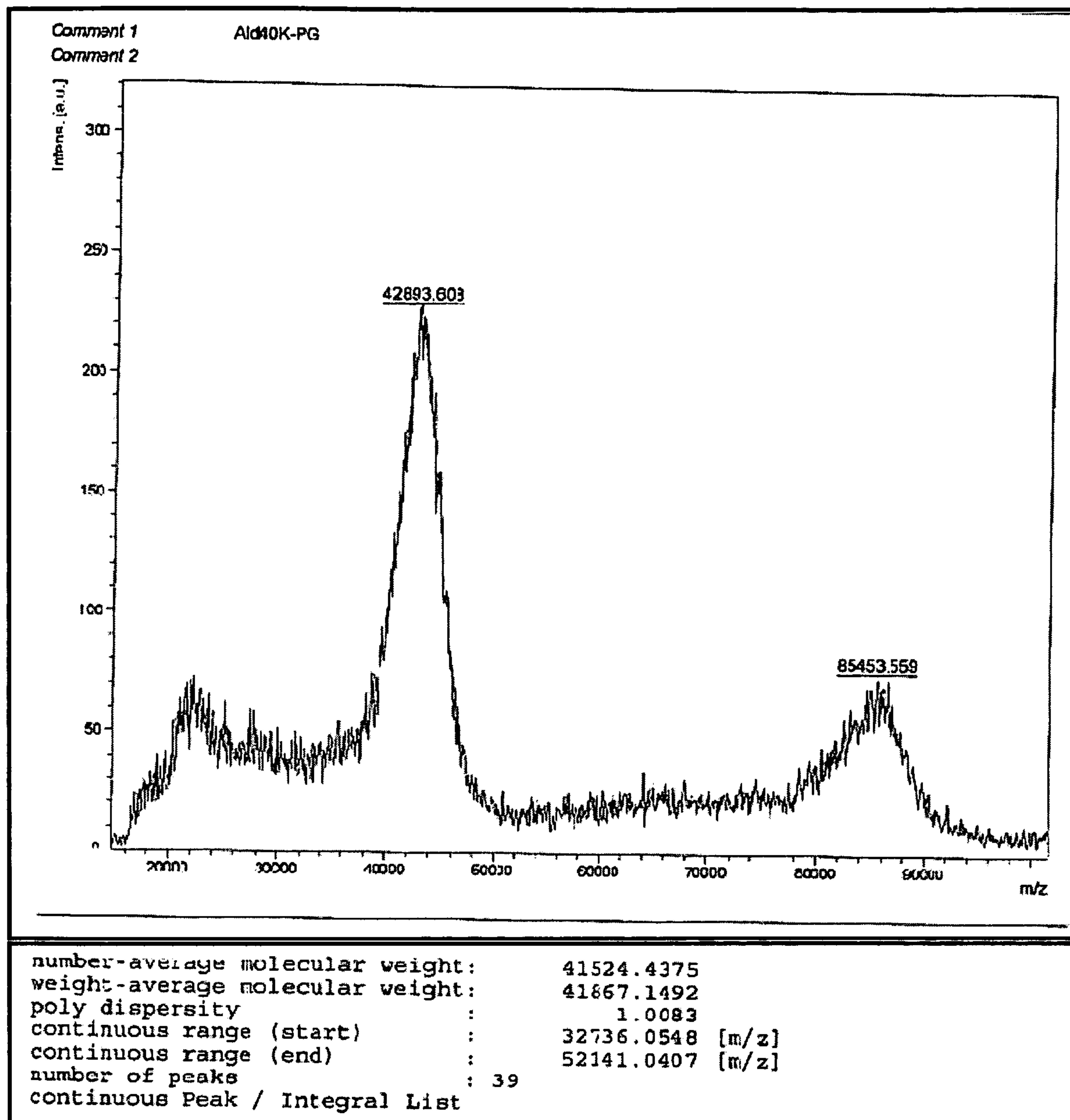


Figure PRO7.4

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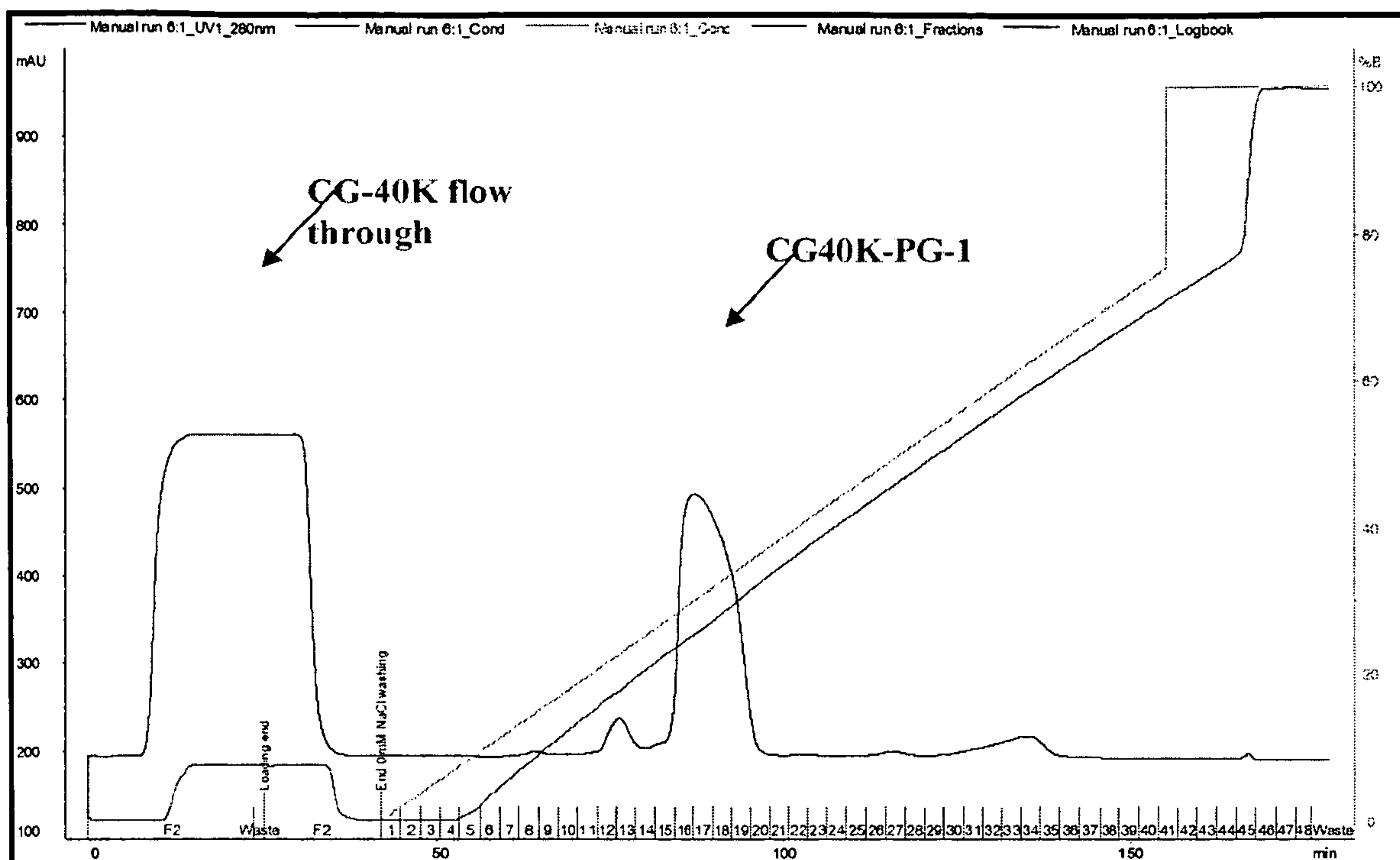


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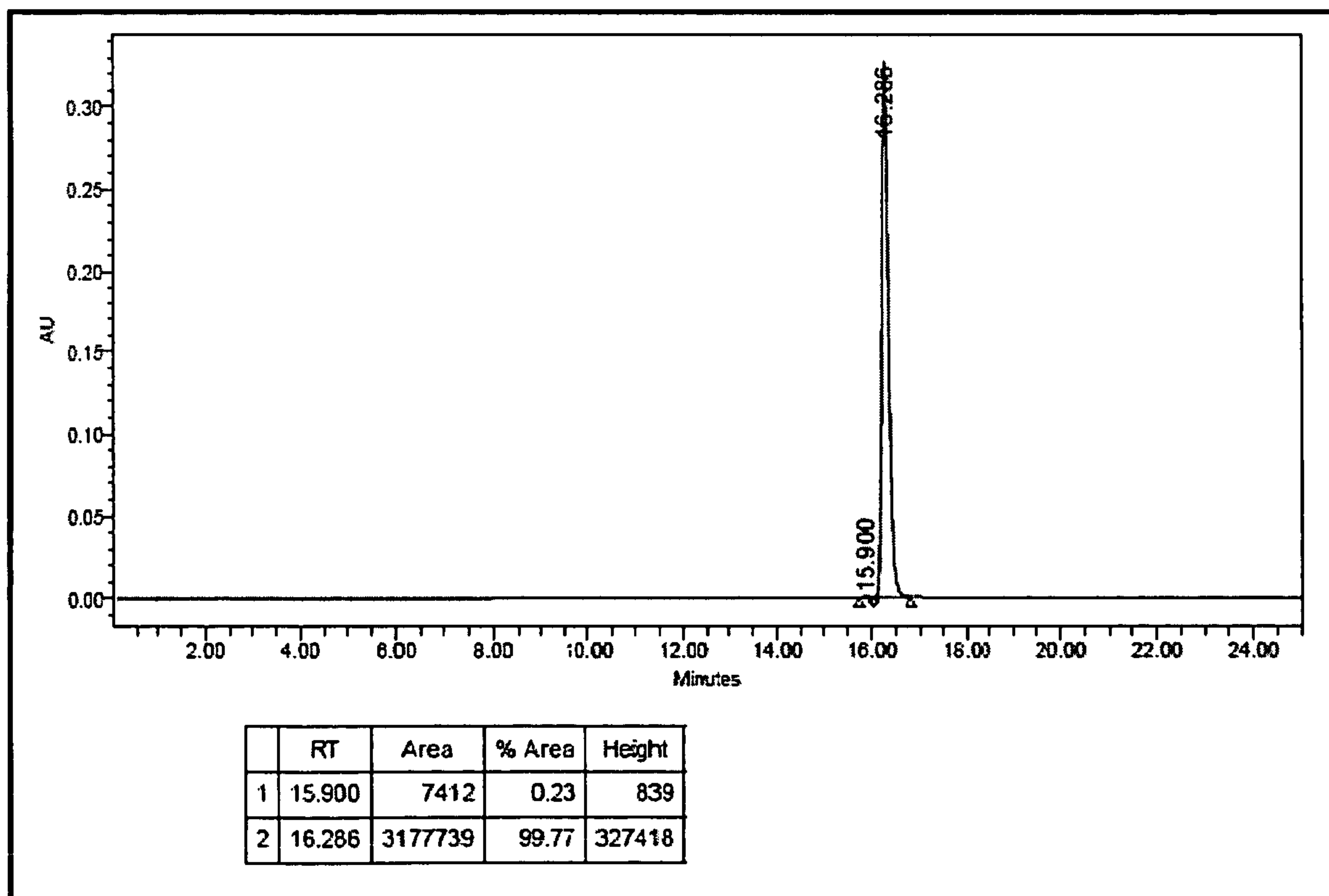


Figure PRO8.2

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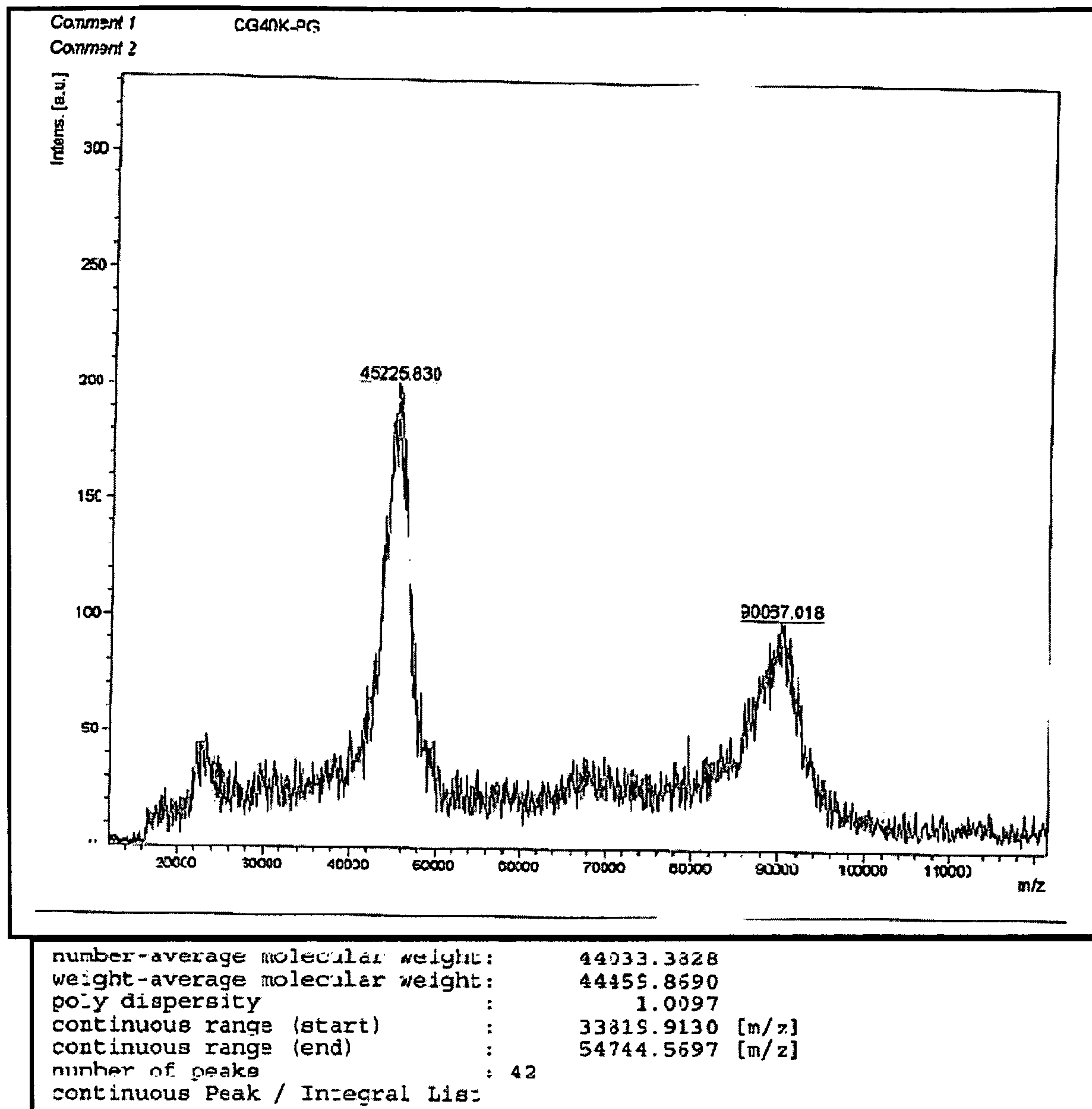


Figure PRO8.3

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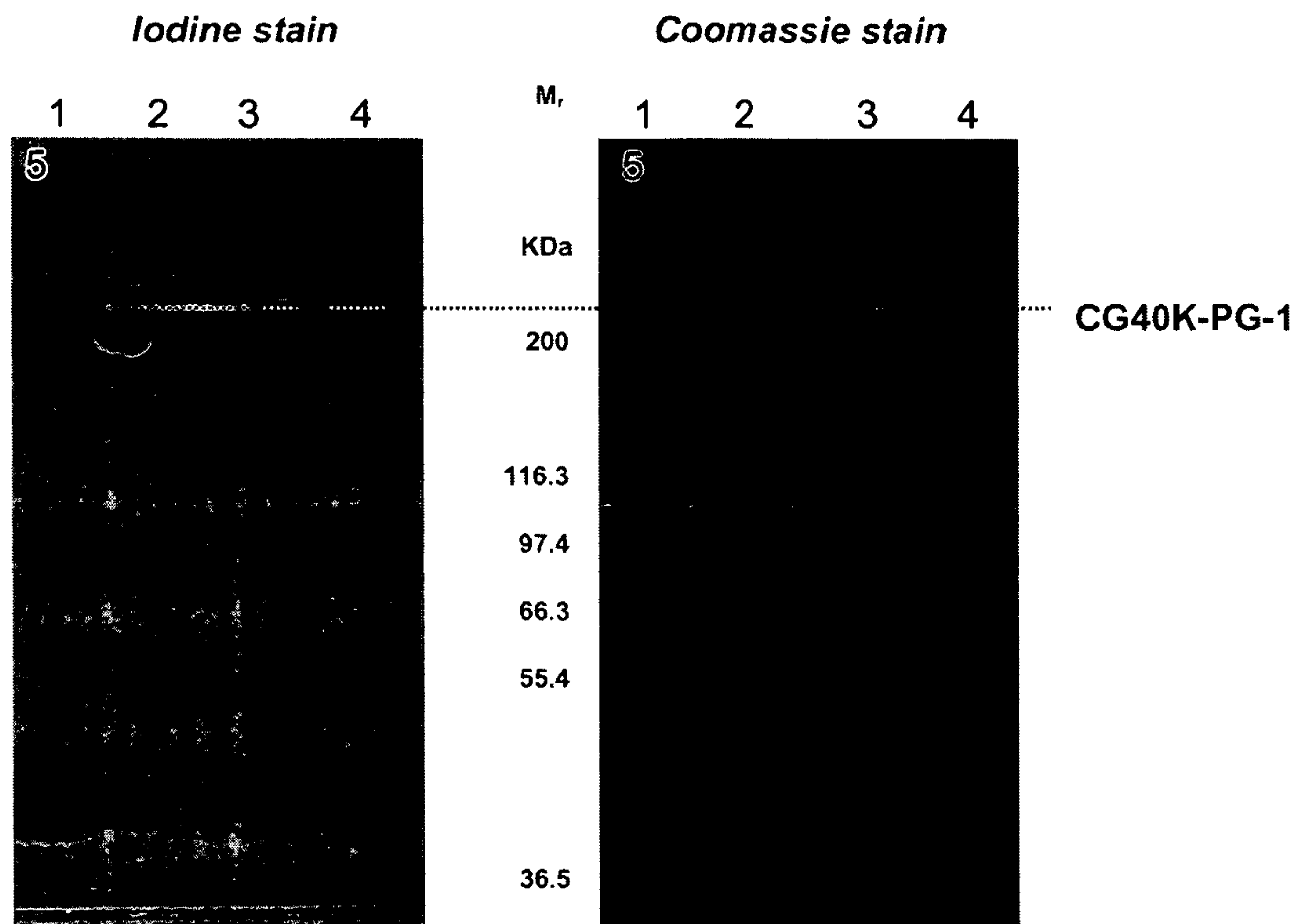


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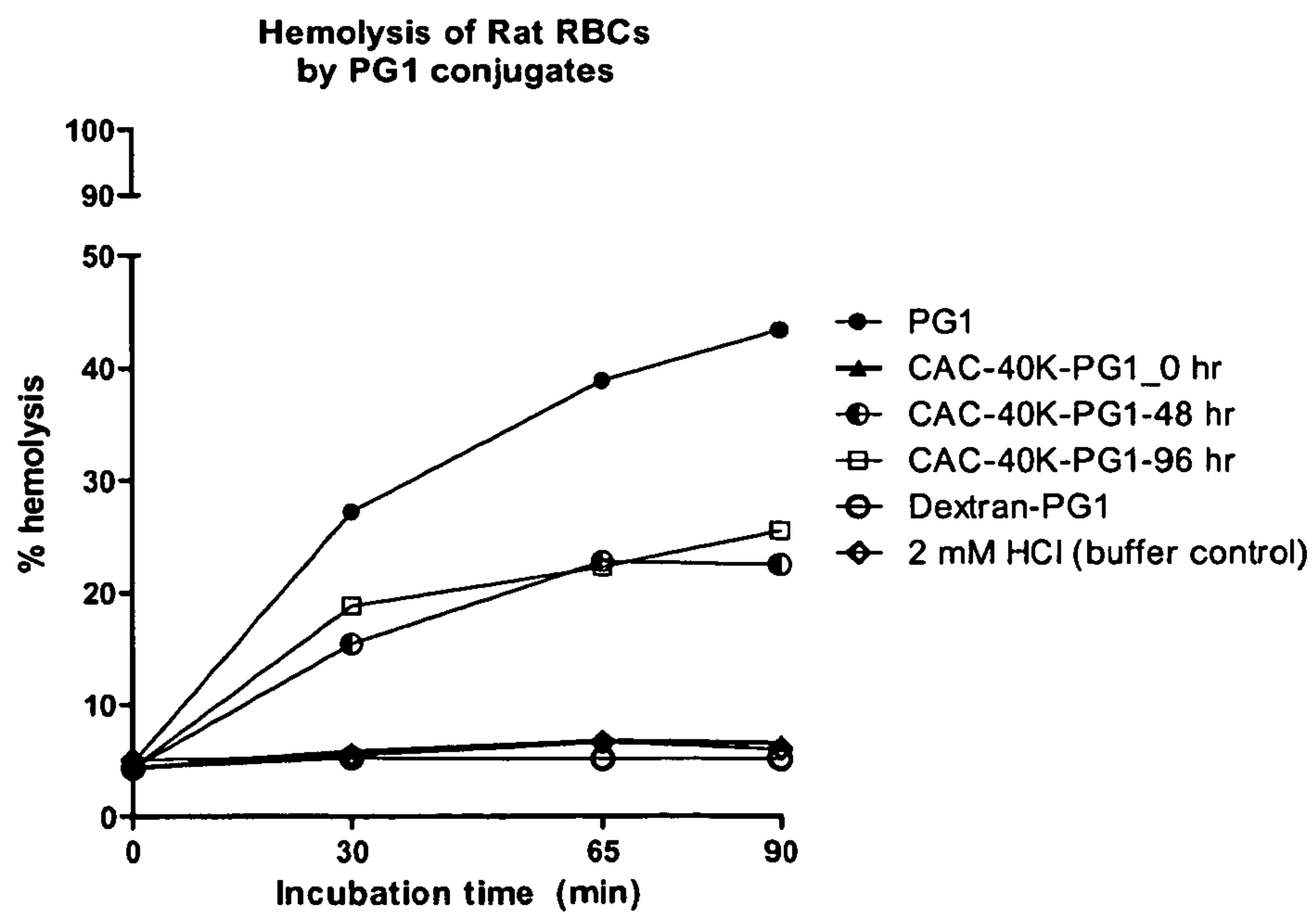


Figure PRO9.1

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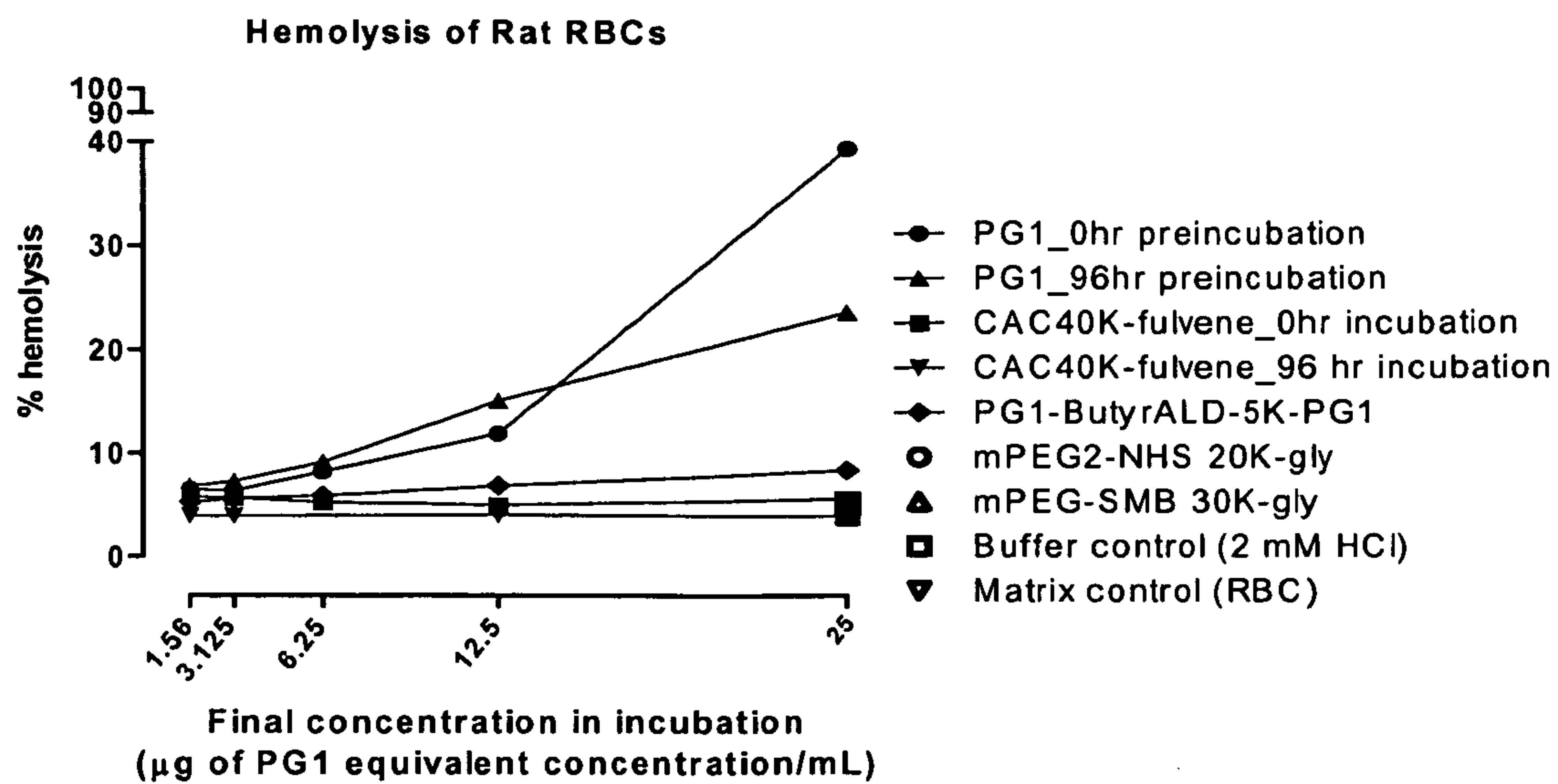


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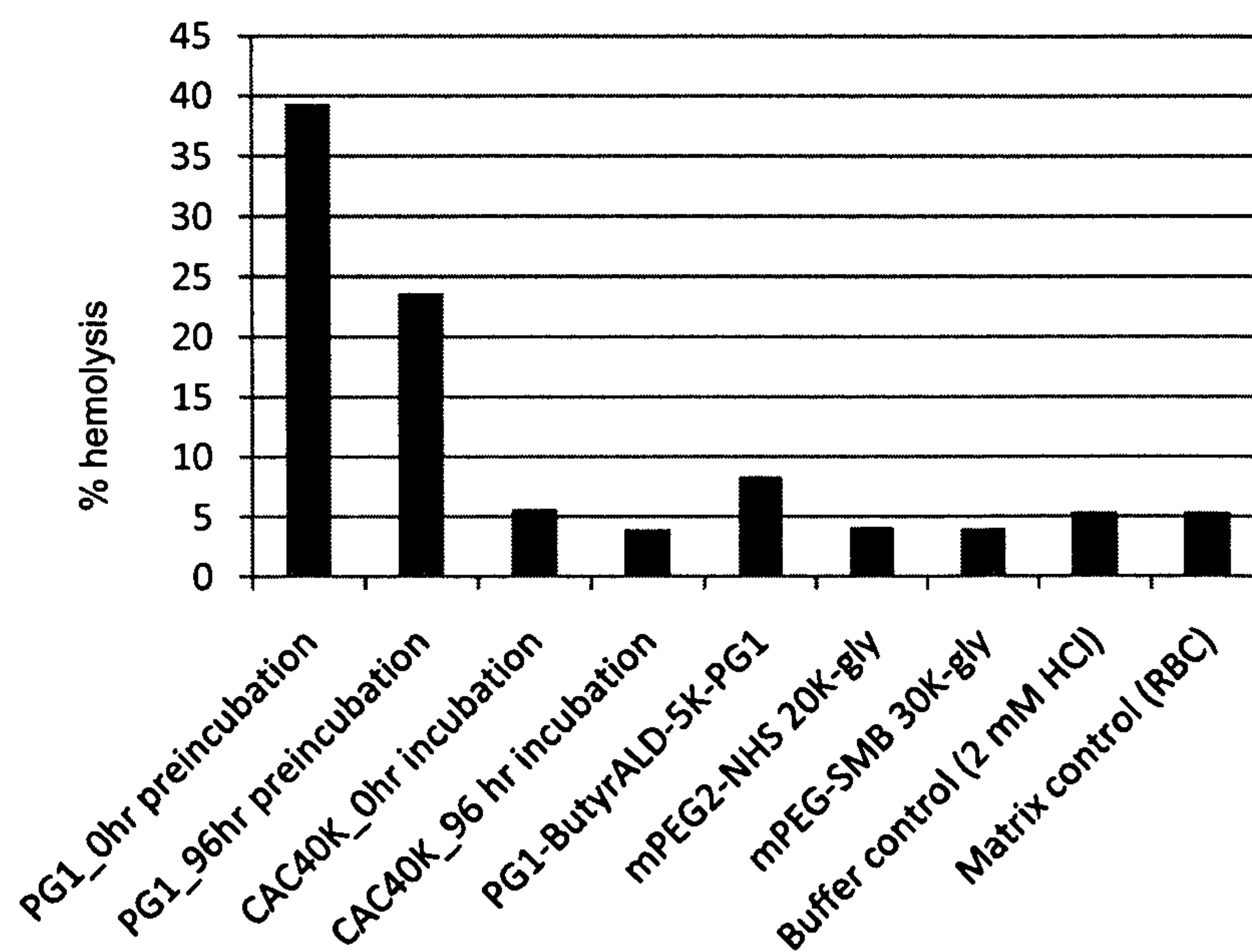


Figure PRO9.3

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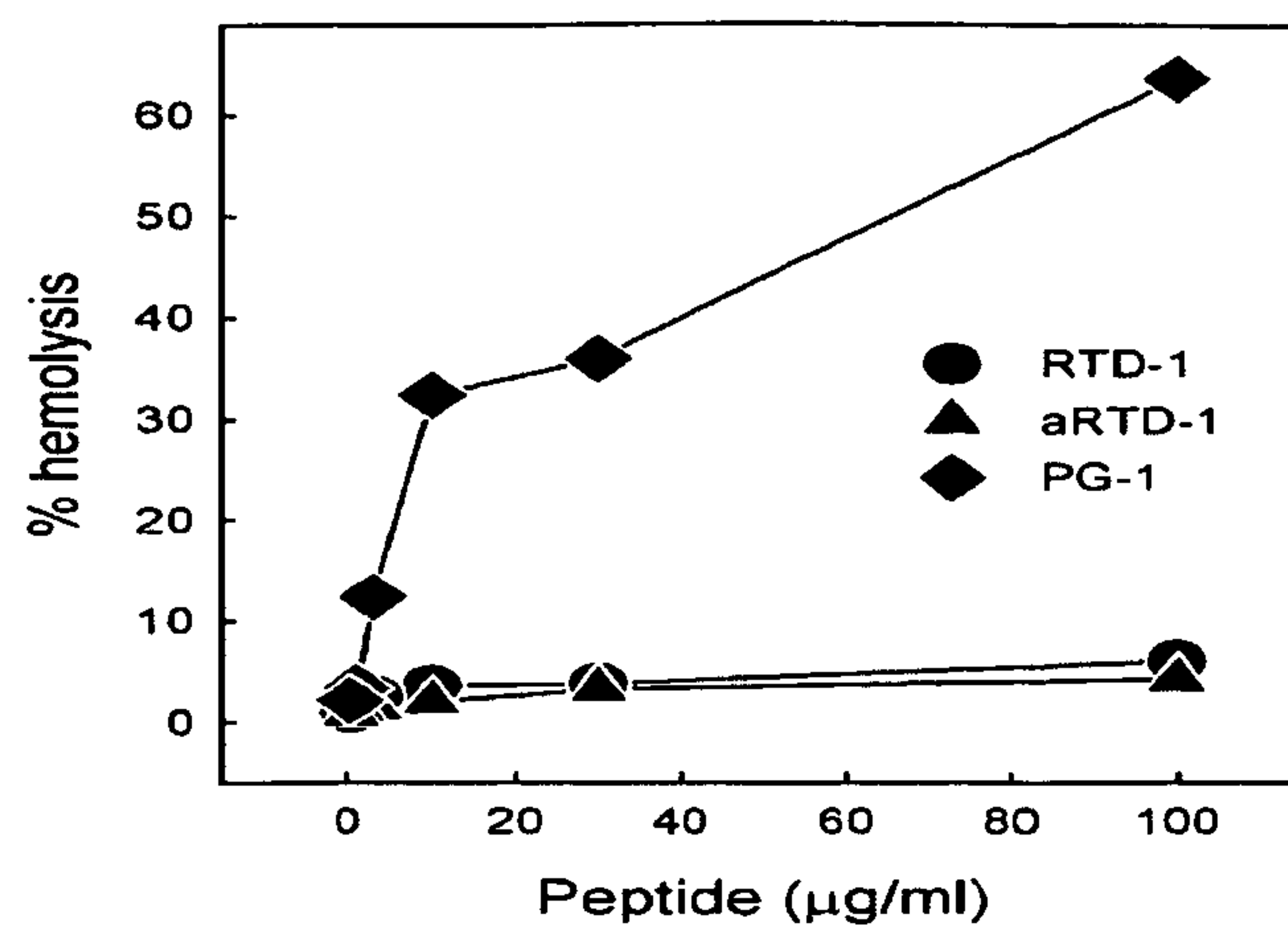


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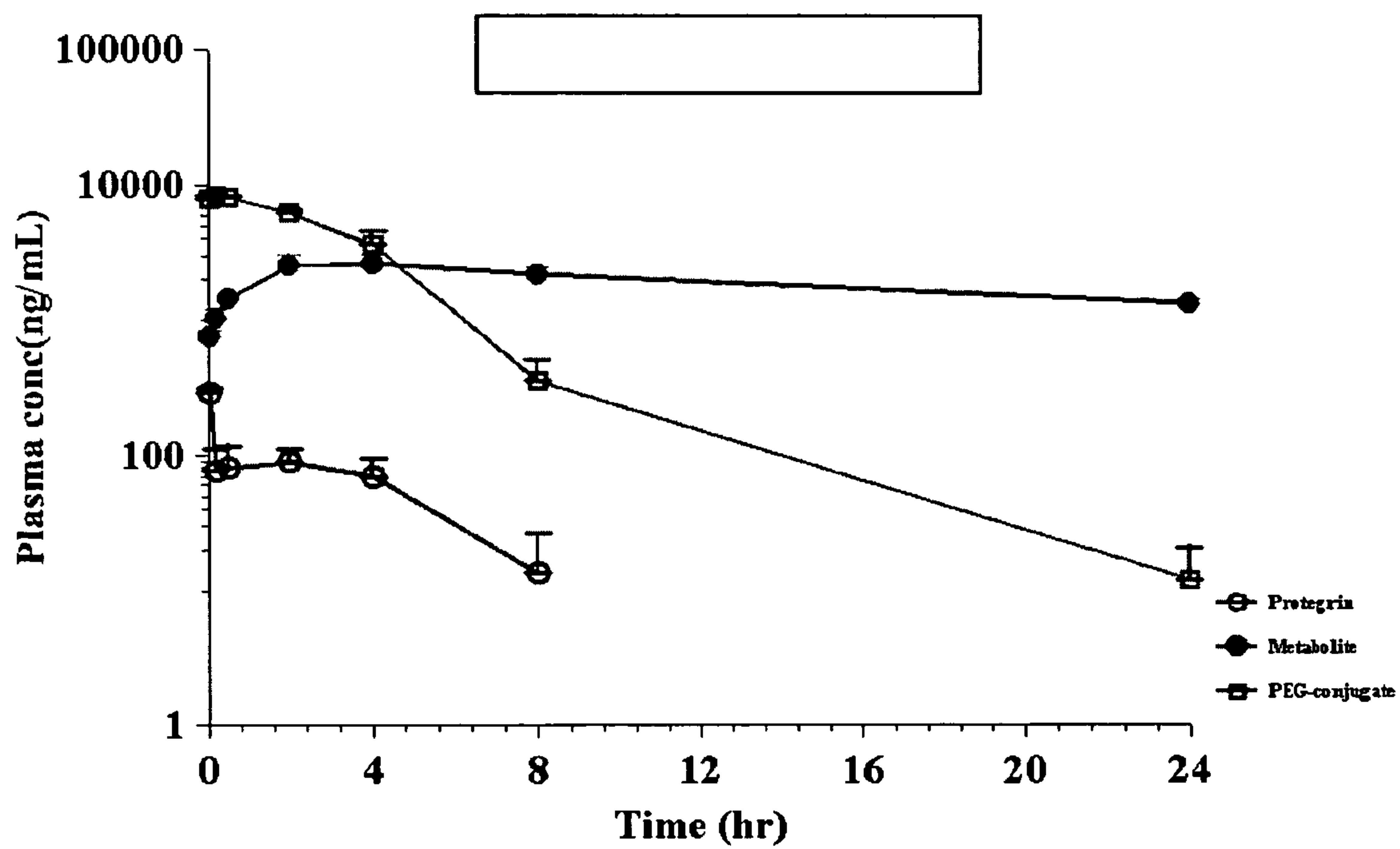


Figure PRO10.1

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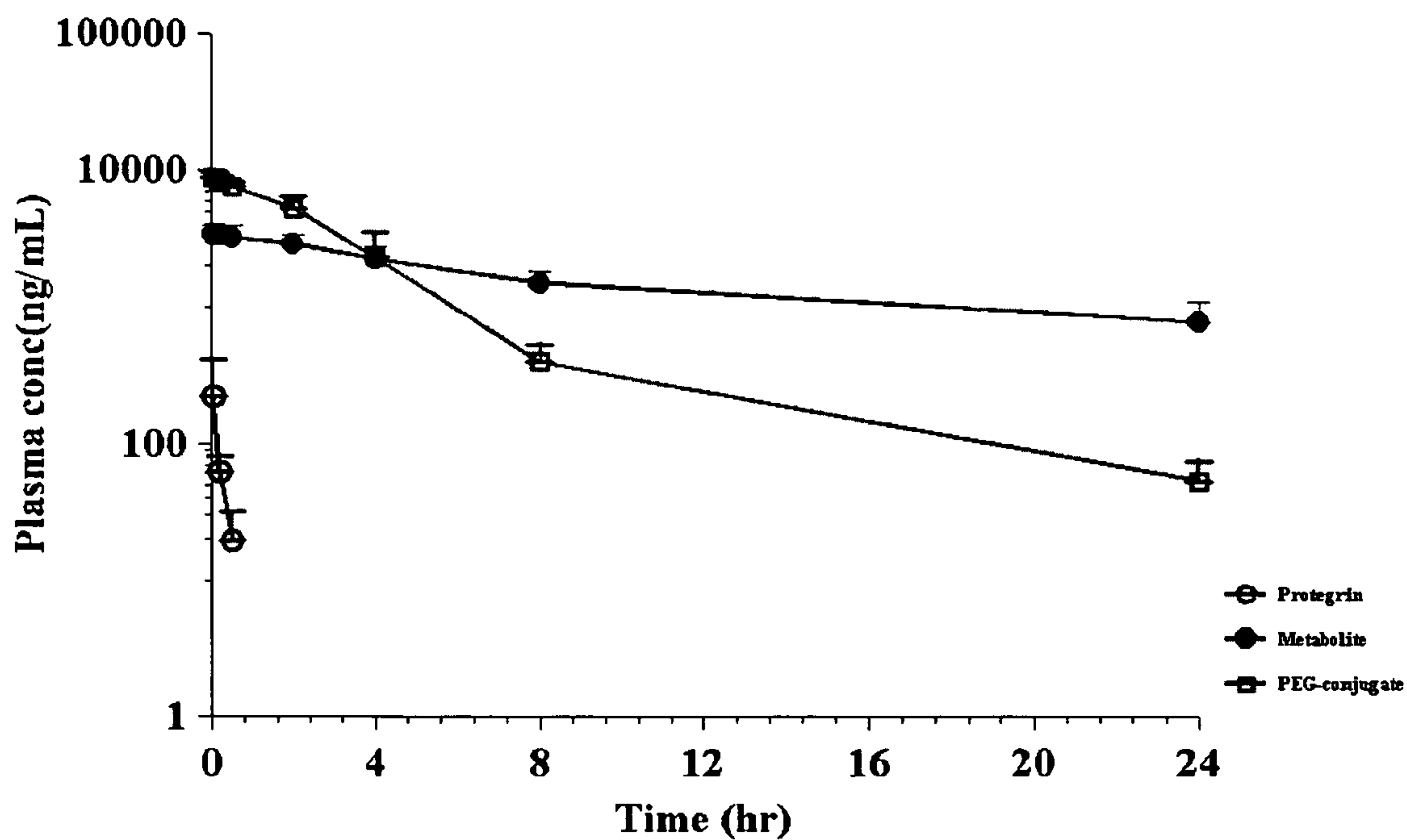


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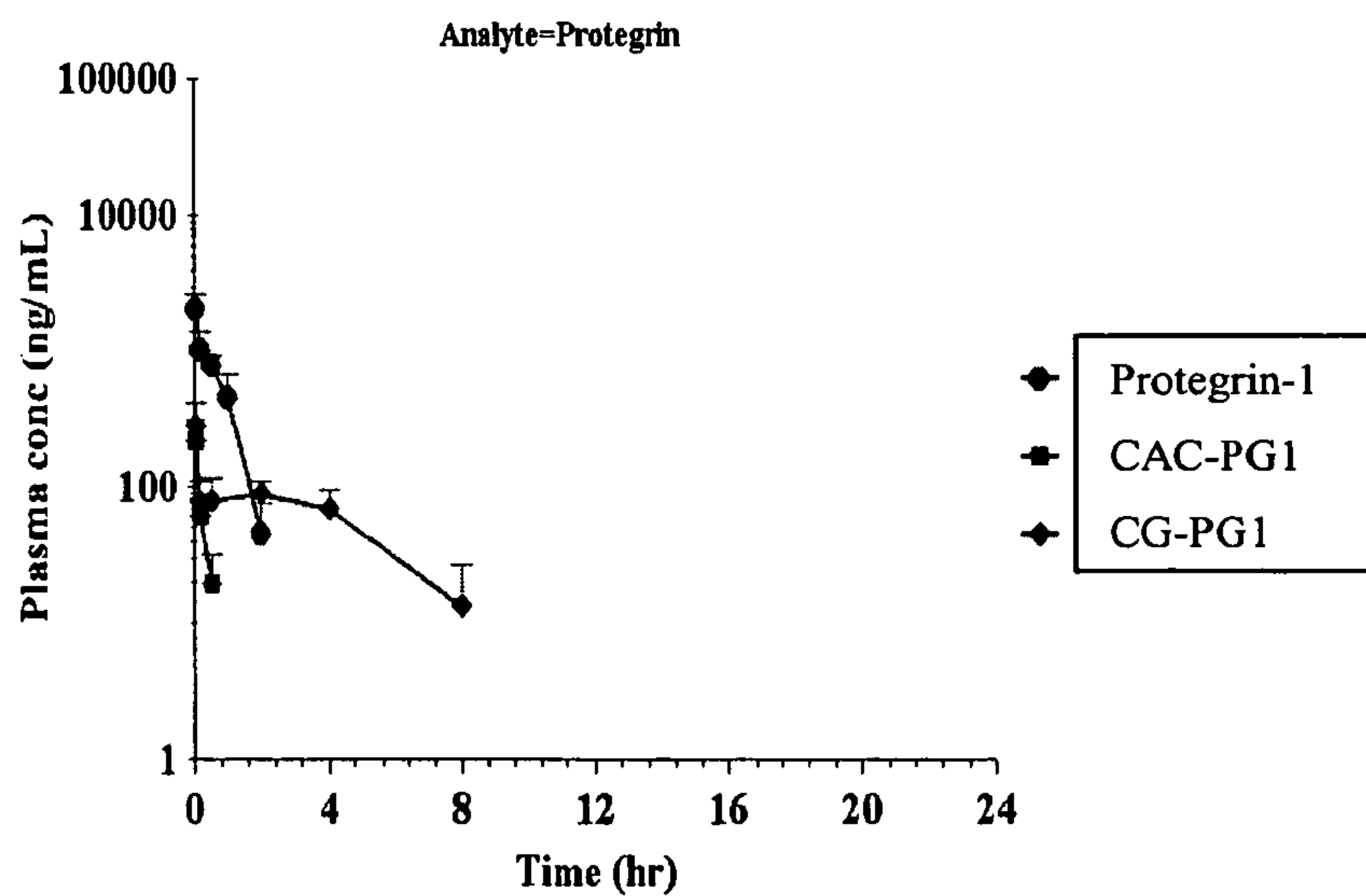


Figure PRO10.3

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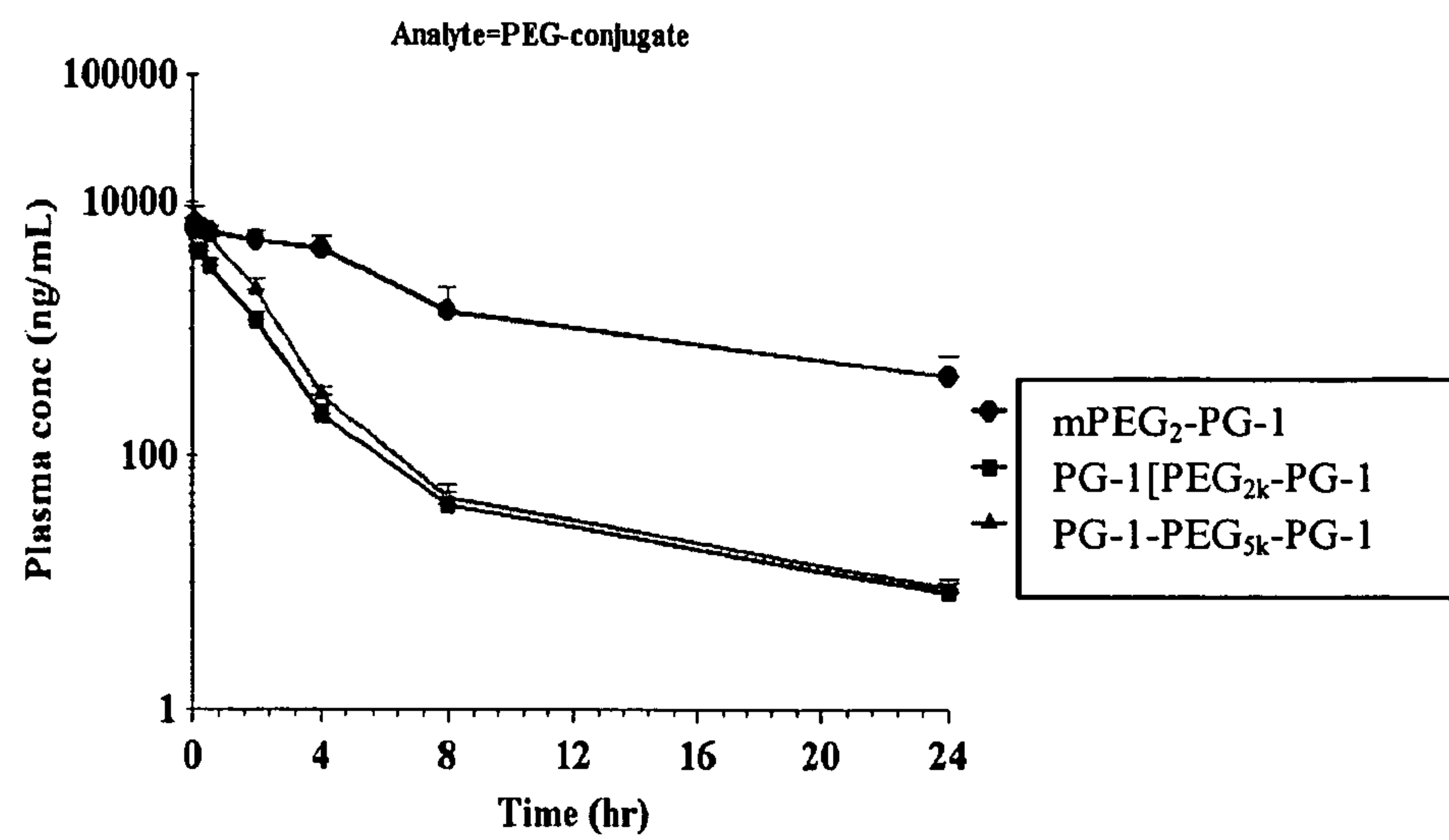
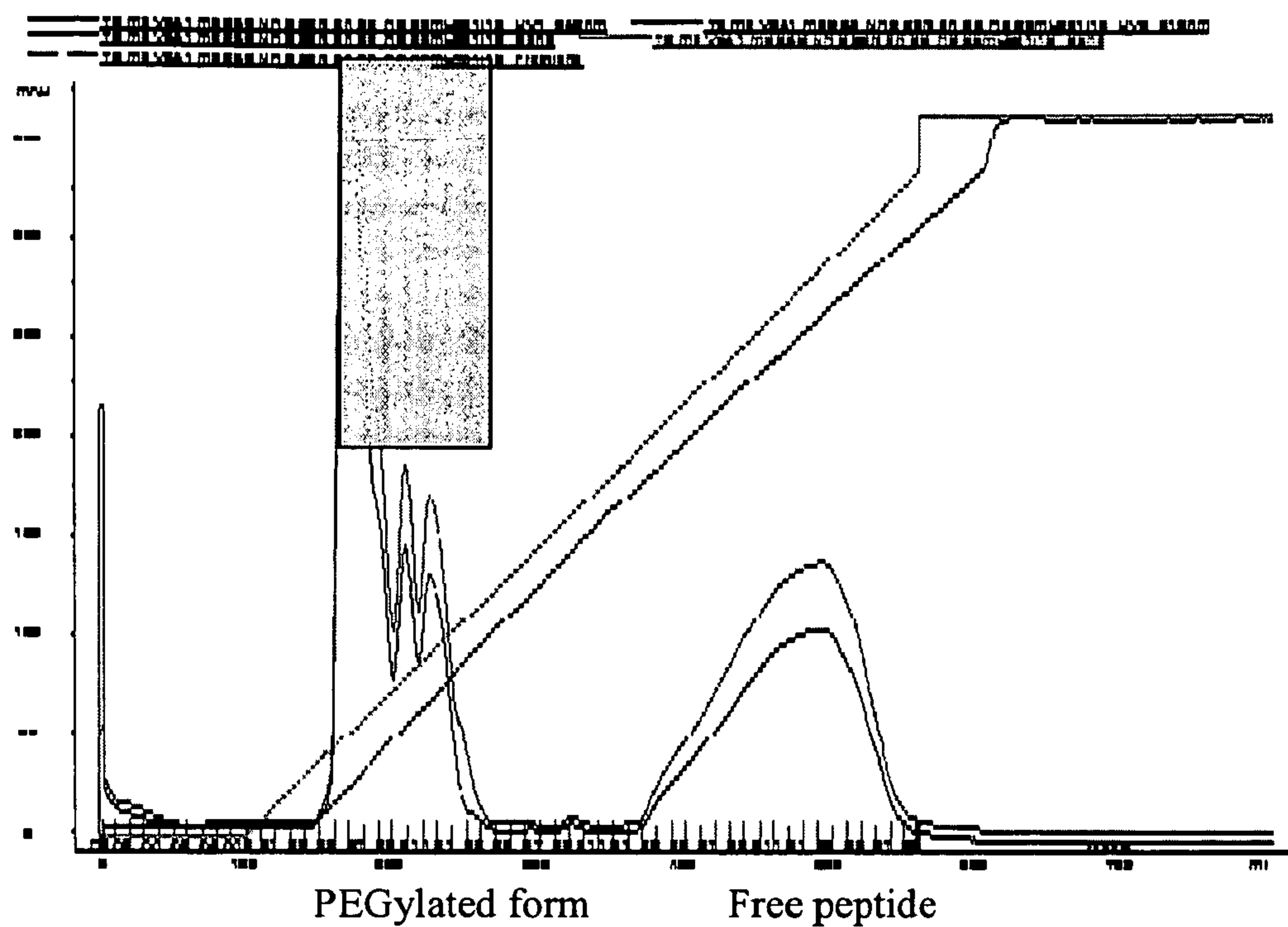
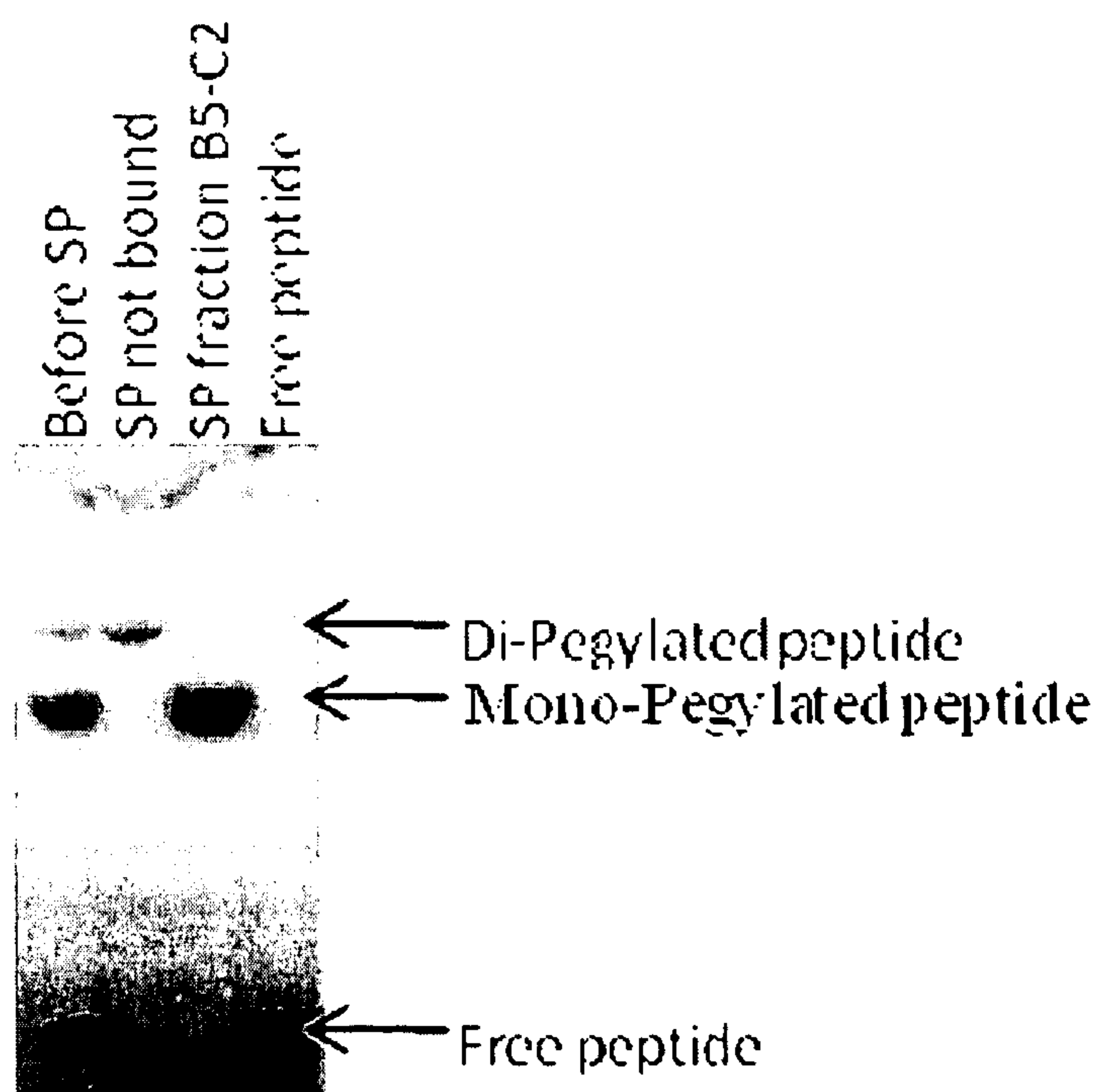


Figure PRO10.4

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**Figure V2.1****Figure V2.2**

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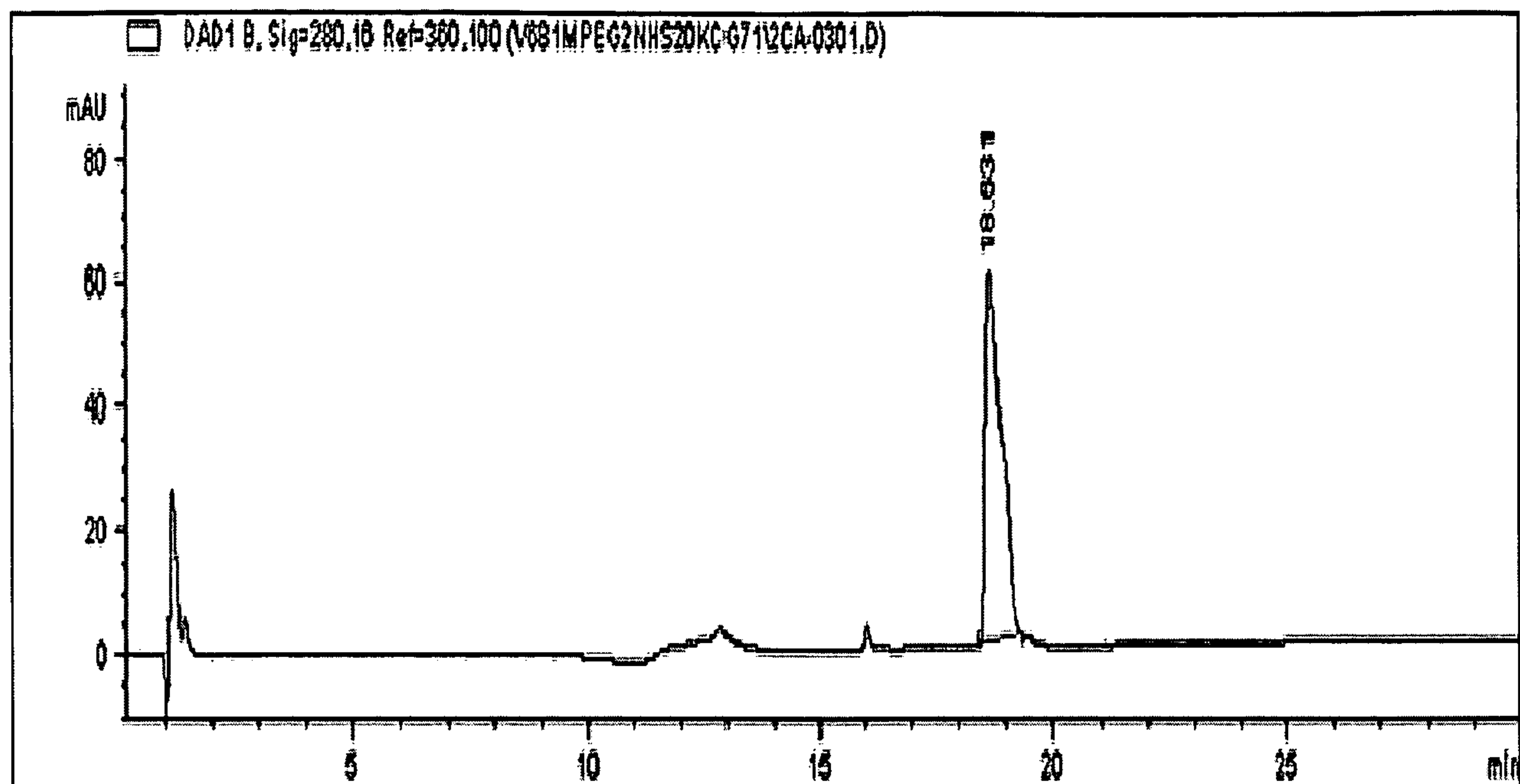


Figure V2.3

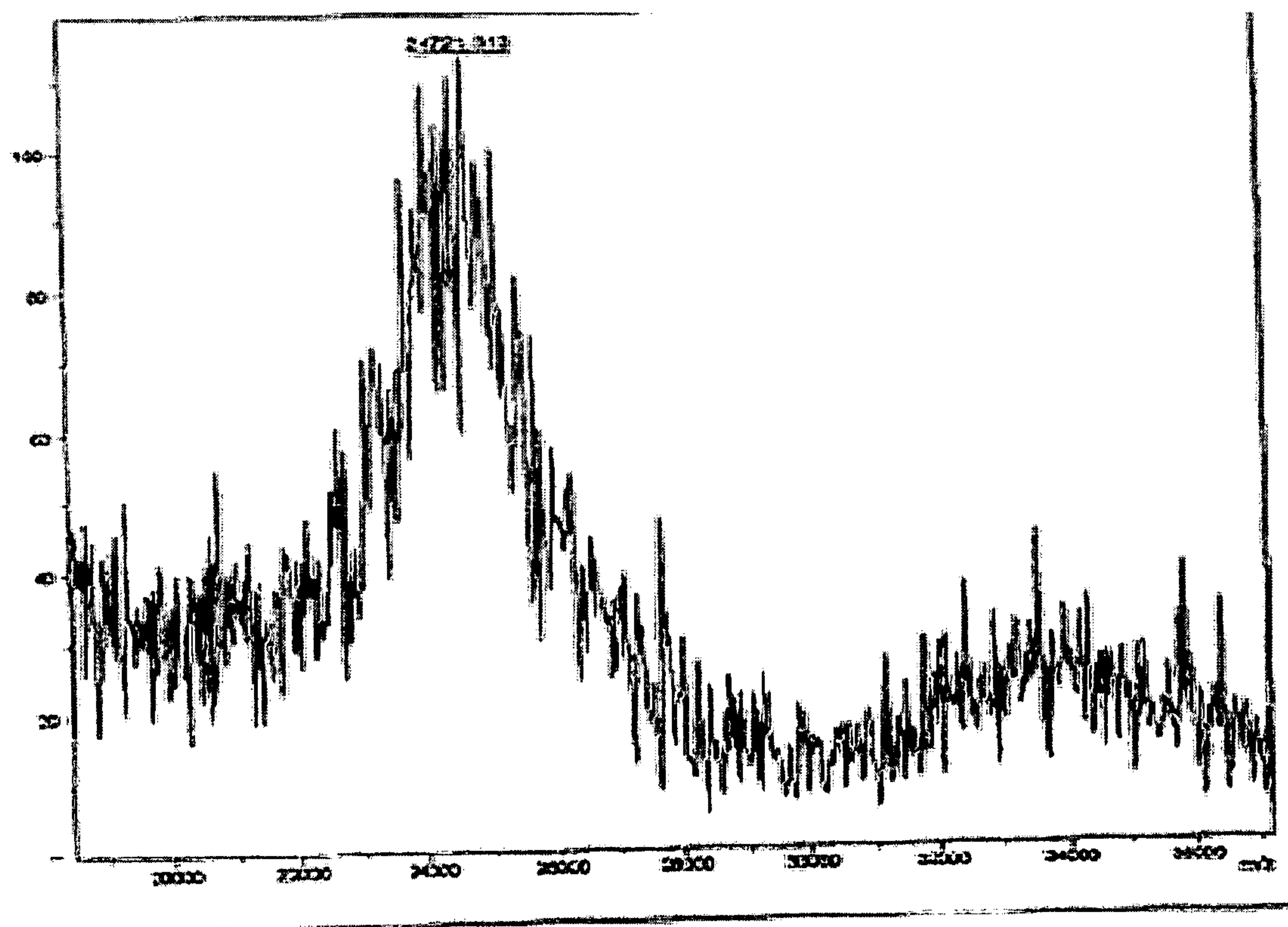


Figure V2.4

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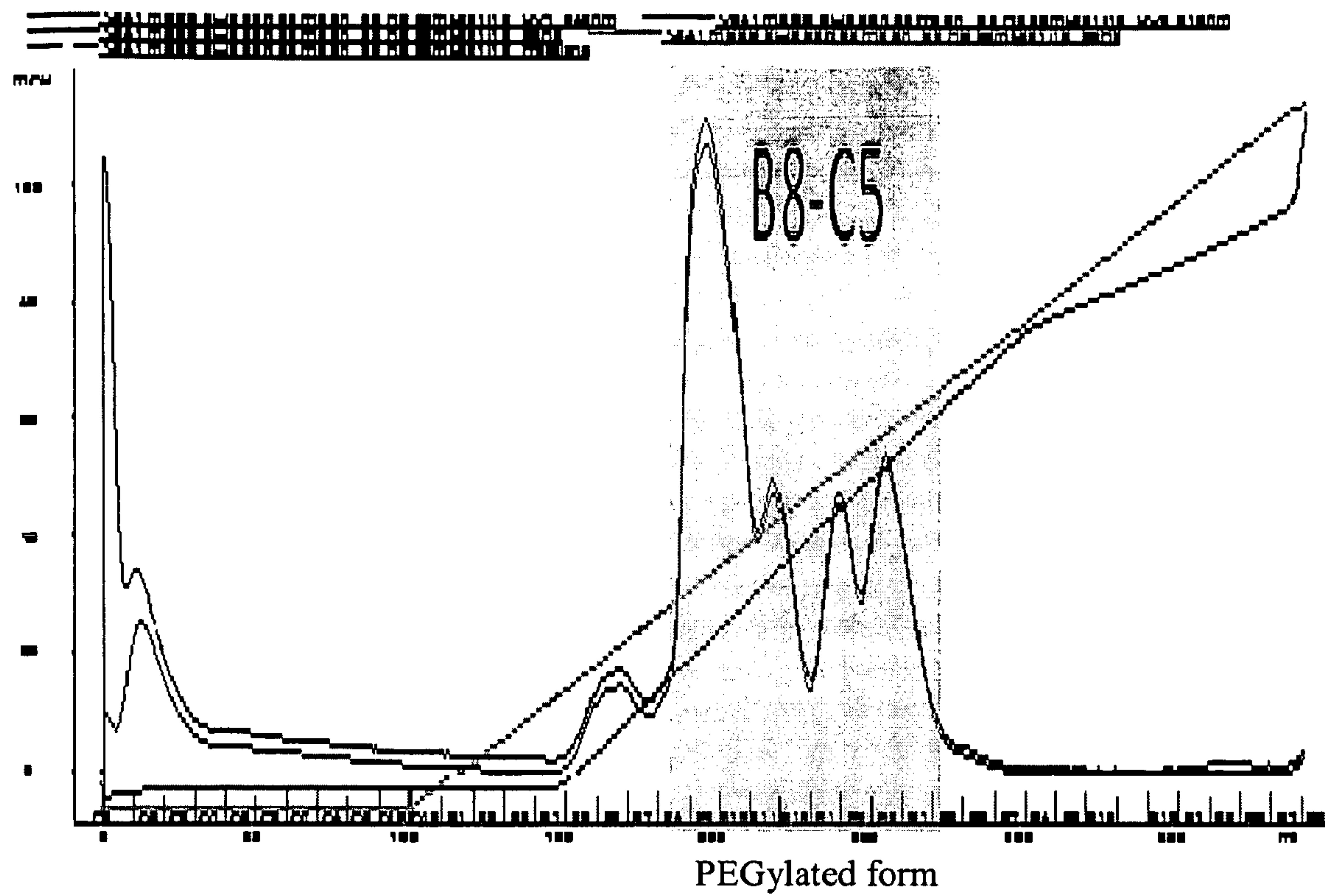


Figure V3.1

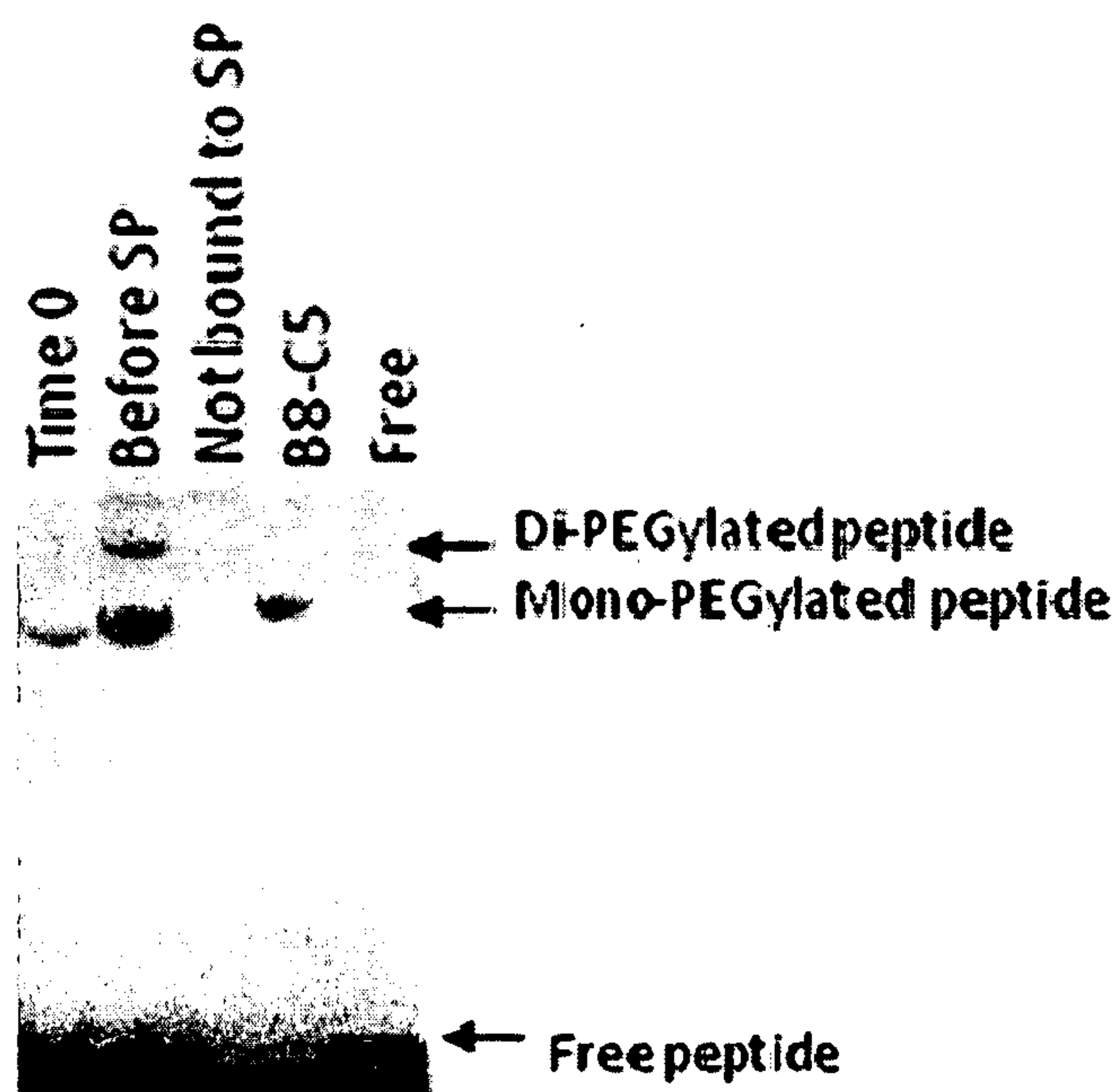


Figure V3.2

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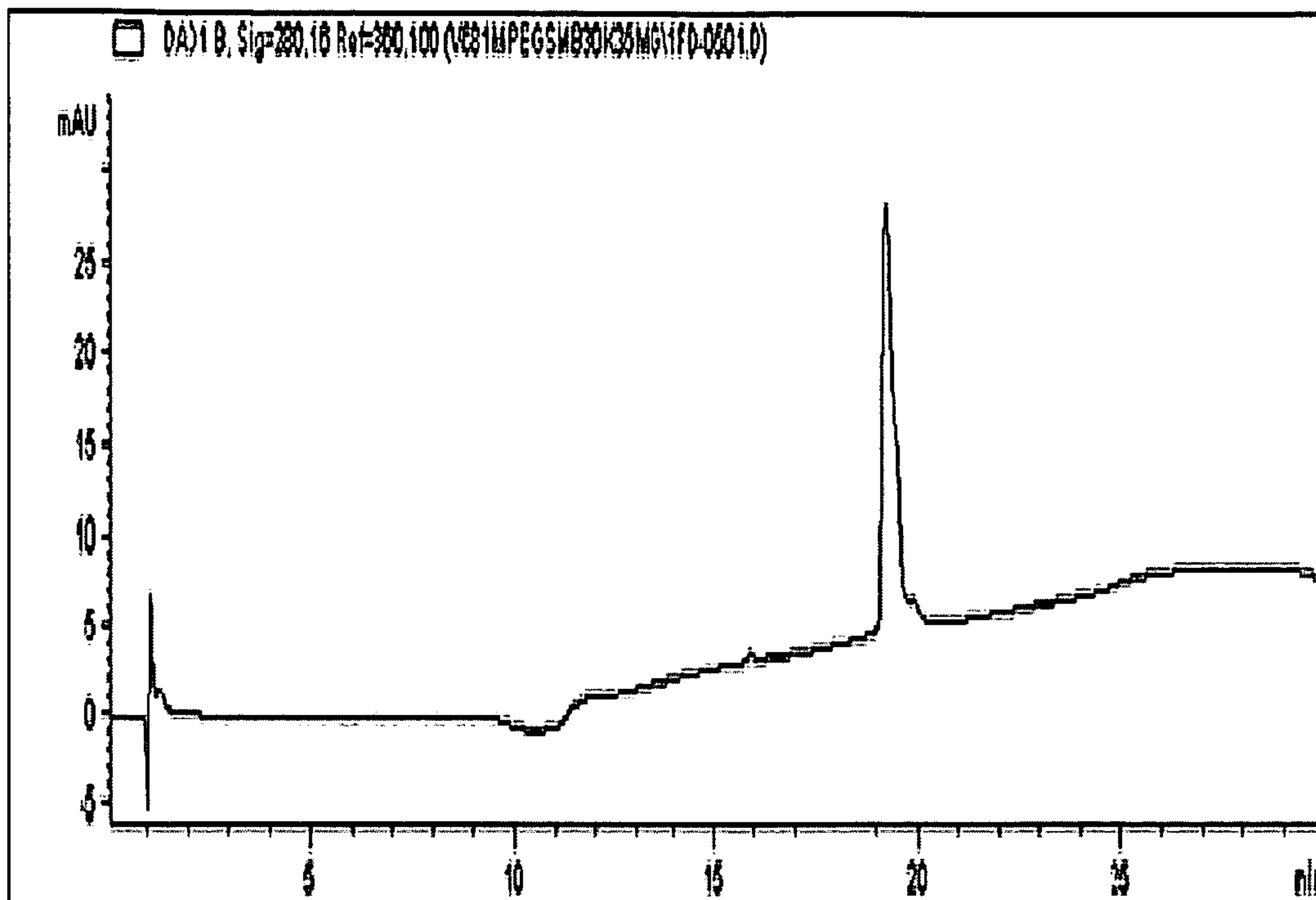


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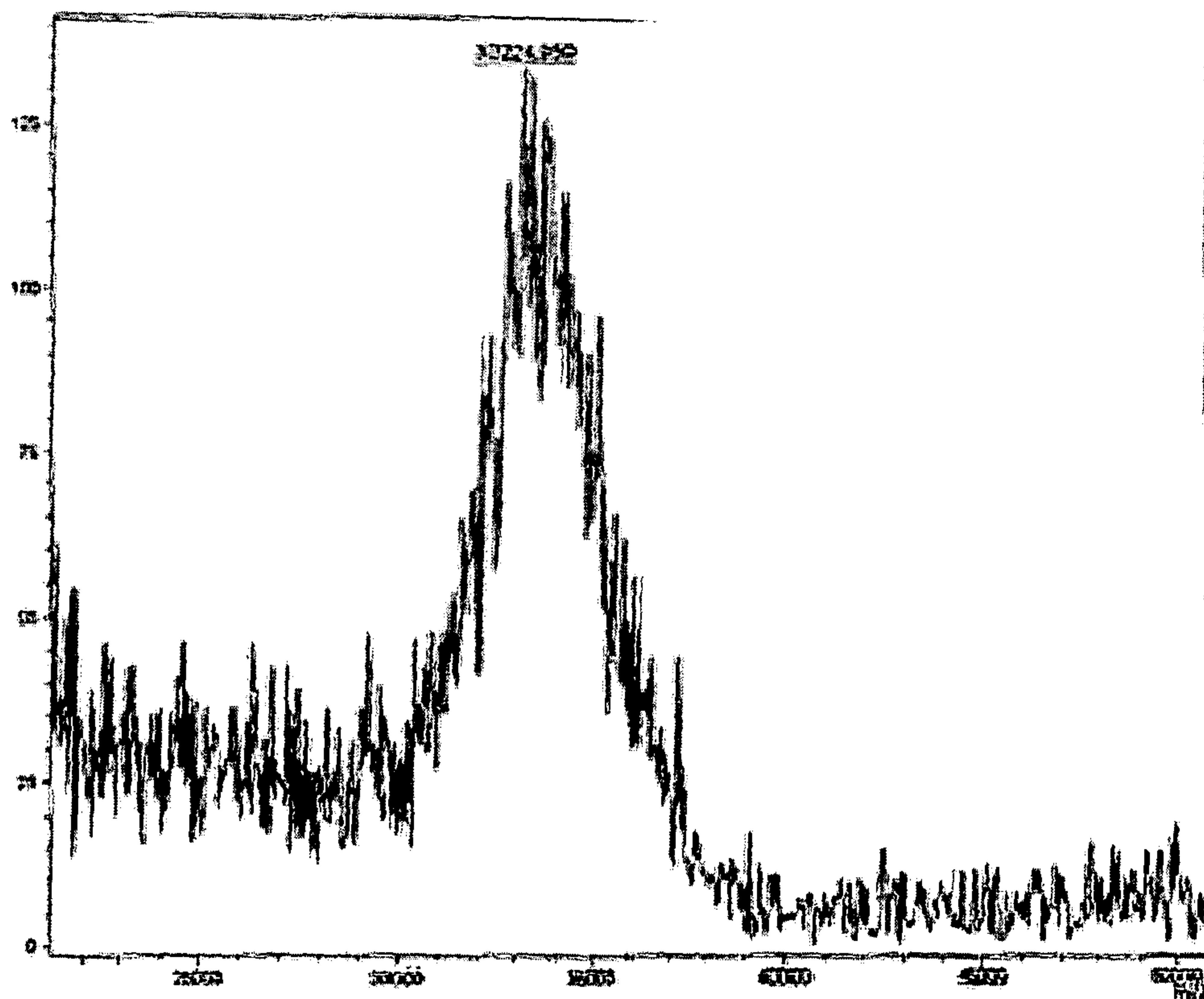
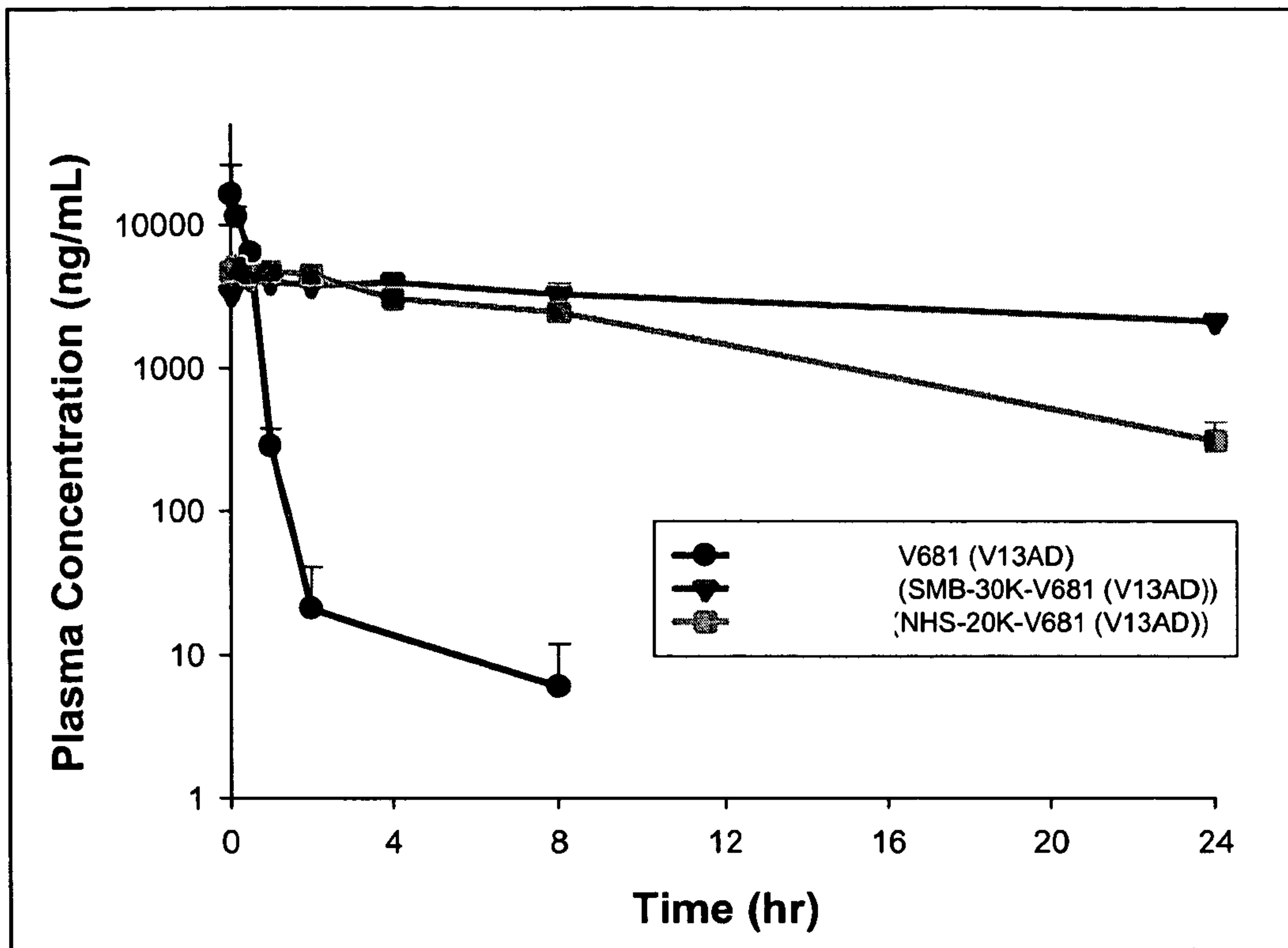
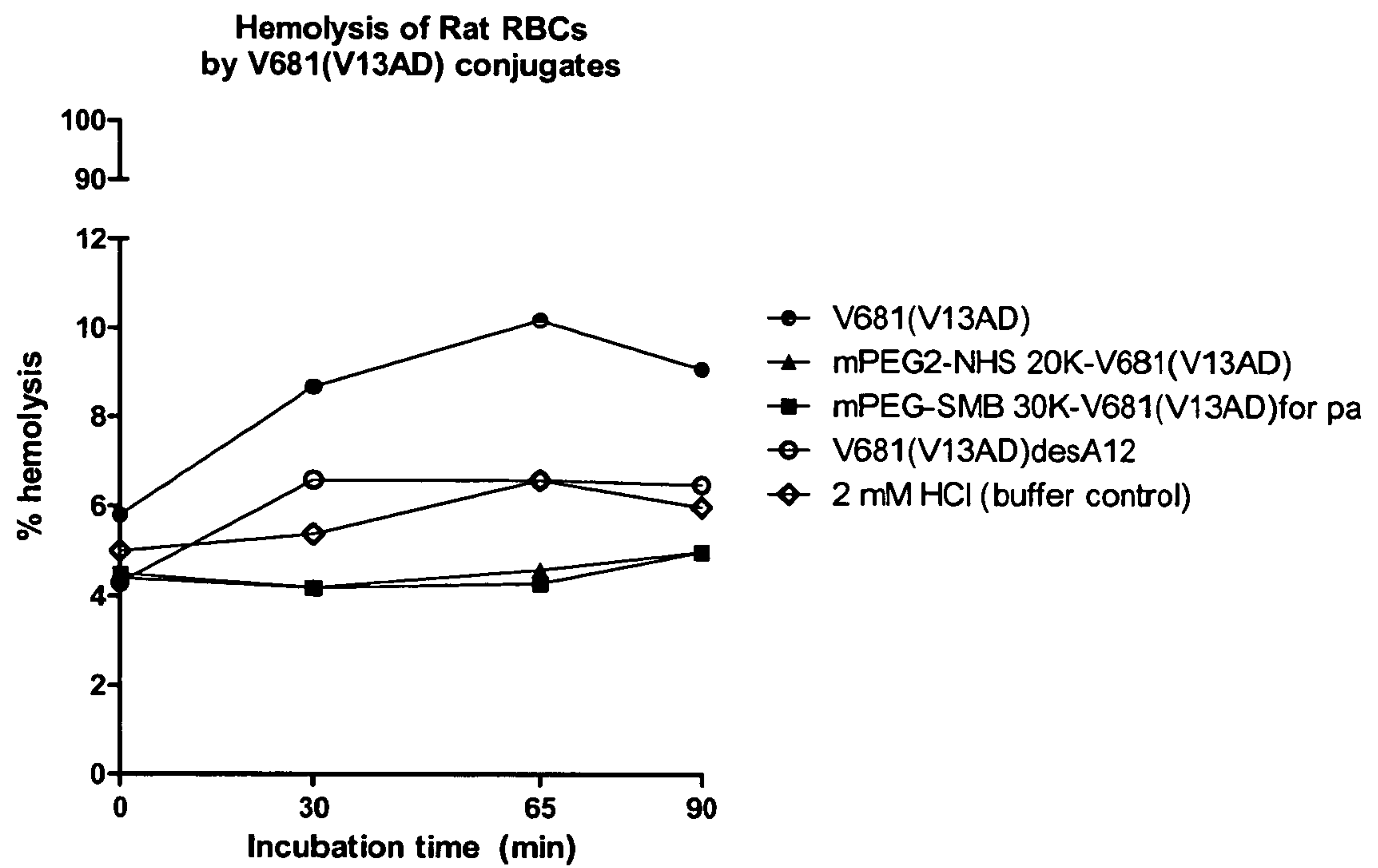


Figure V3.4

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**Figure V4.1**

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**Figure V5.1**

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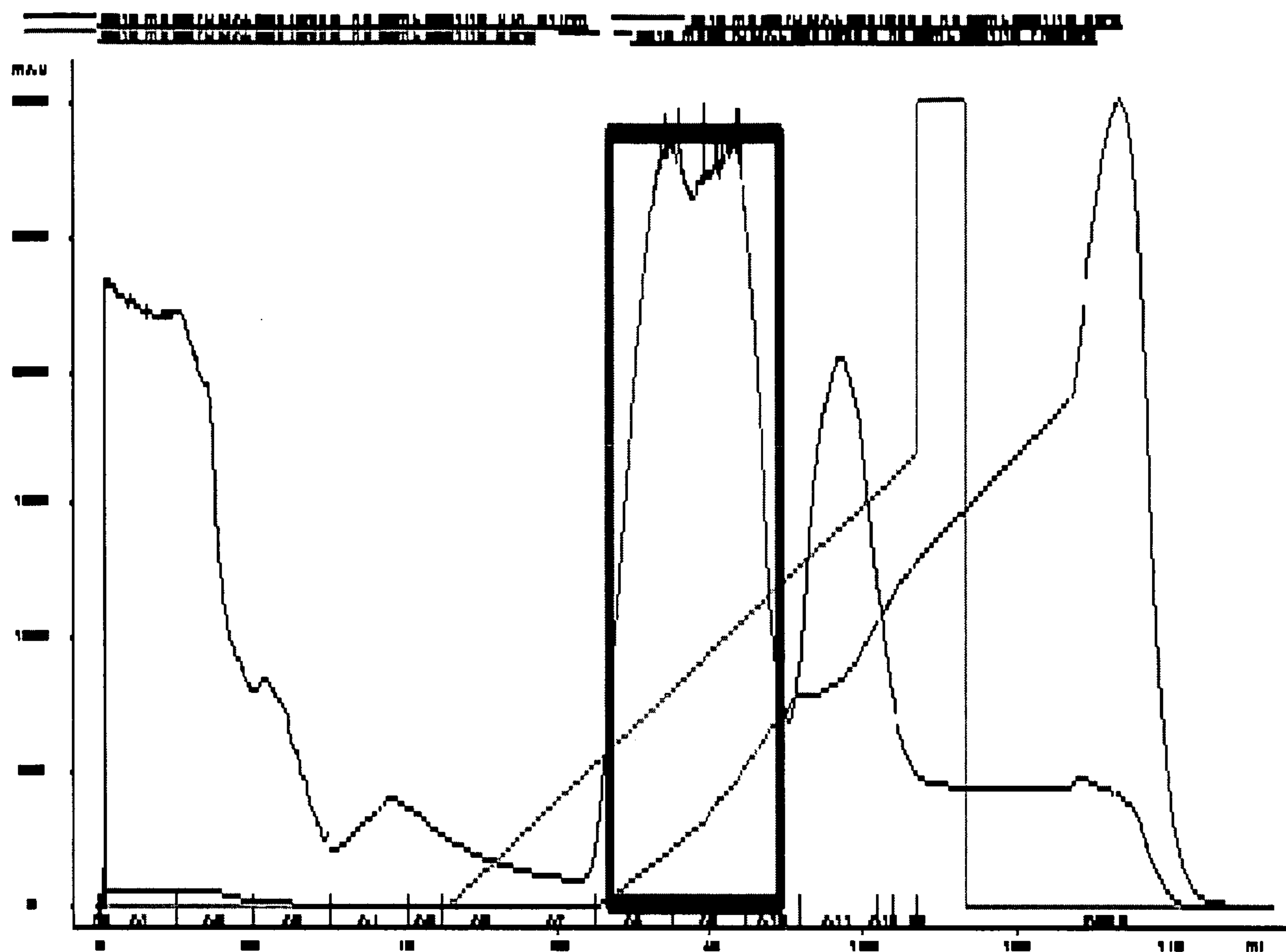


Figure C-PEP2.1

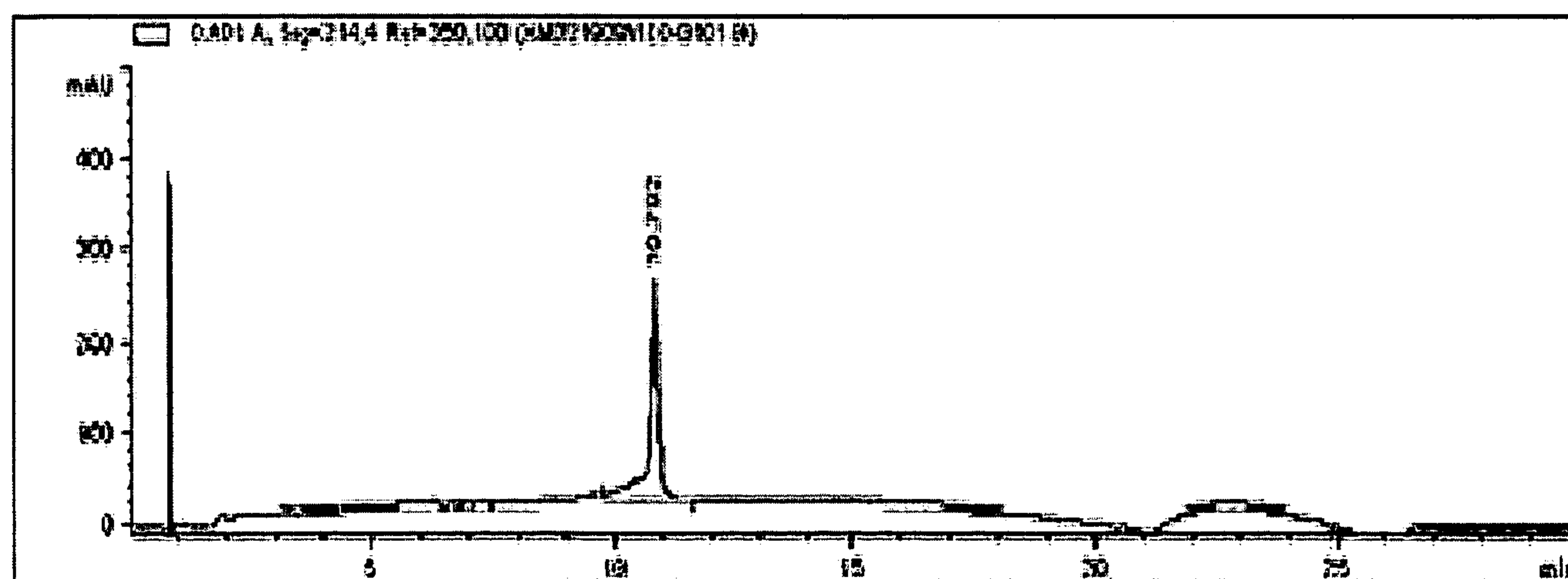


Figure C-PEP2.2

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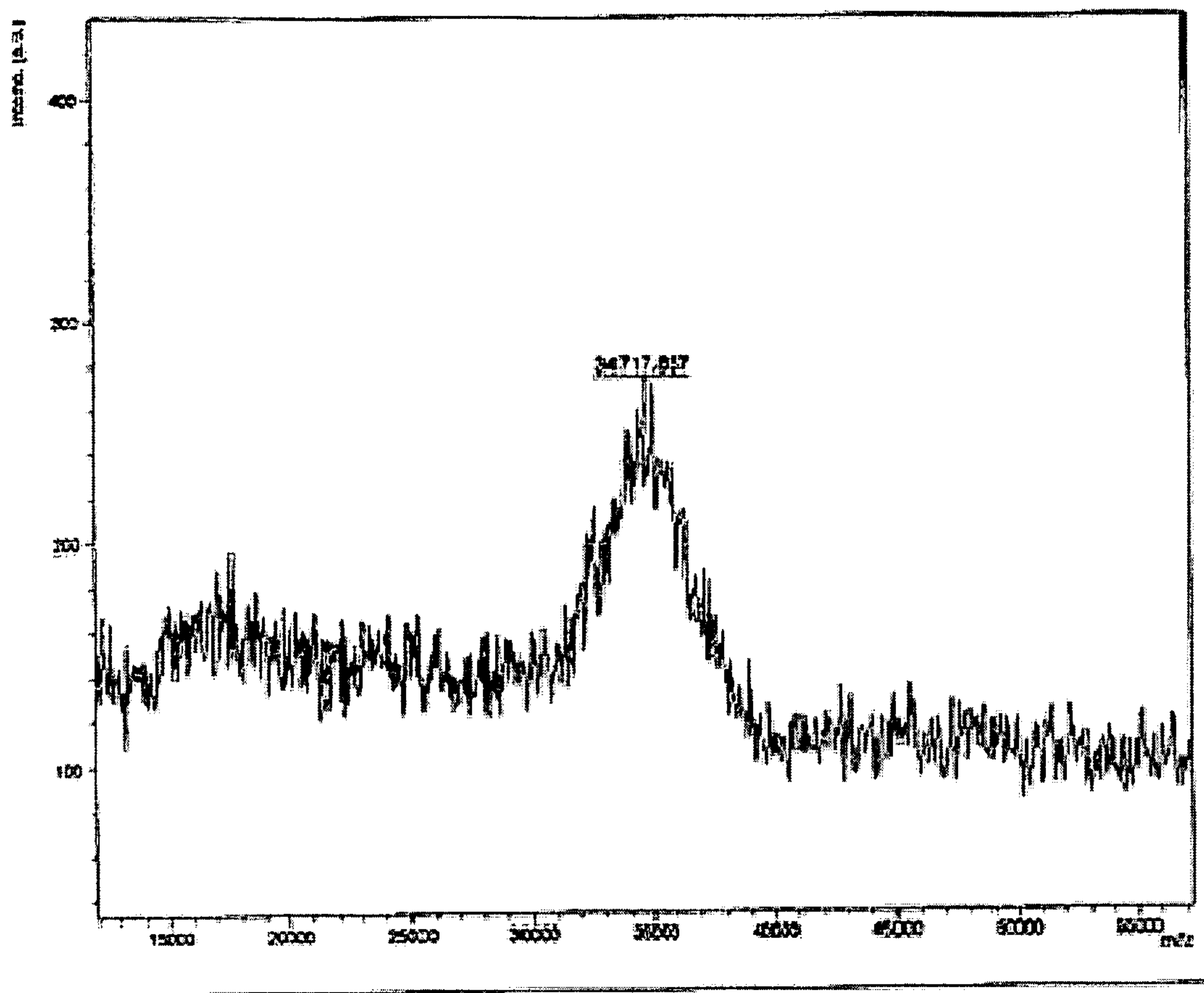


Figure C-PEP2.3

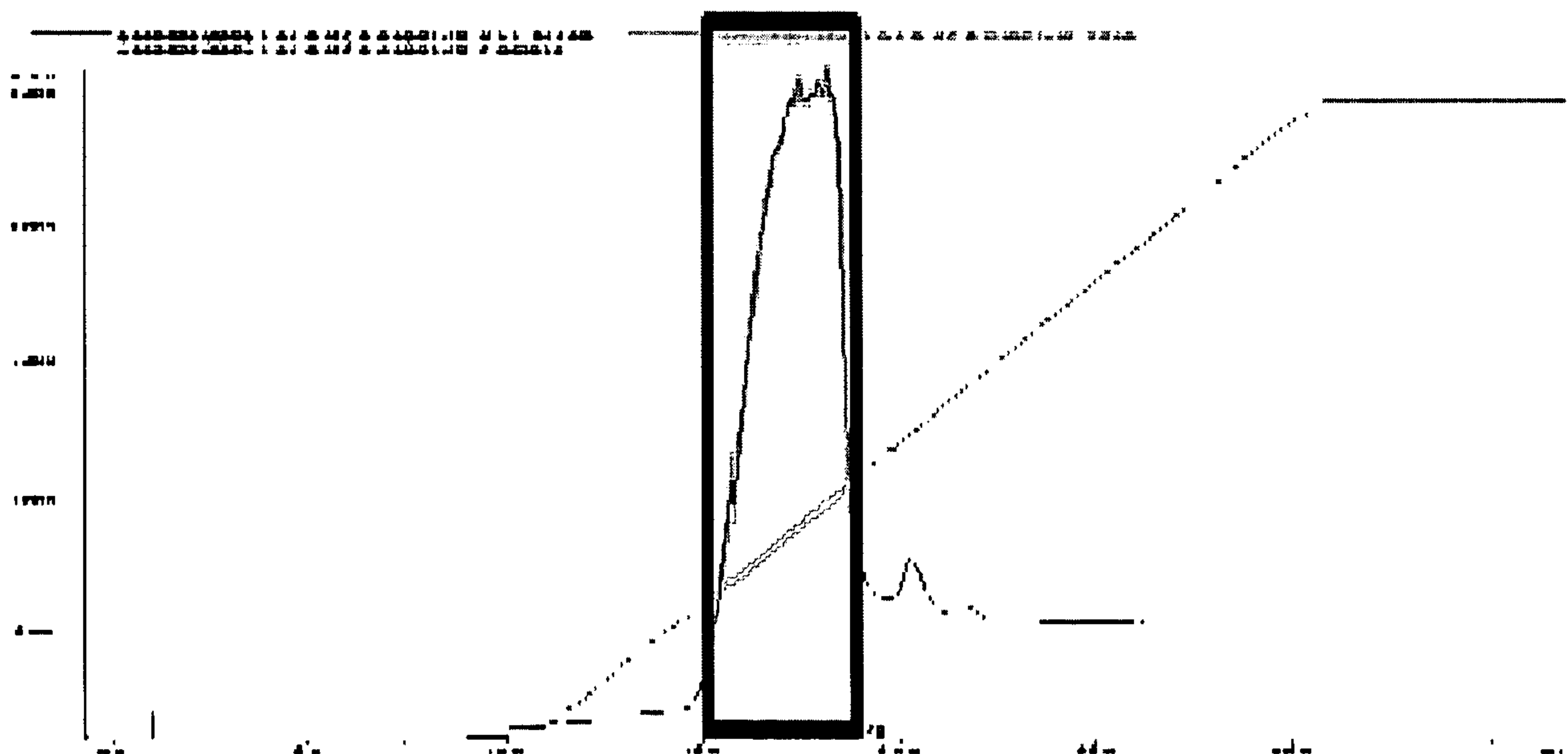


Figure C-PEP3.1

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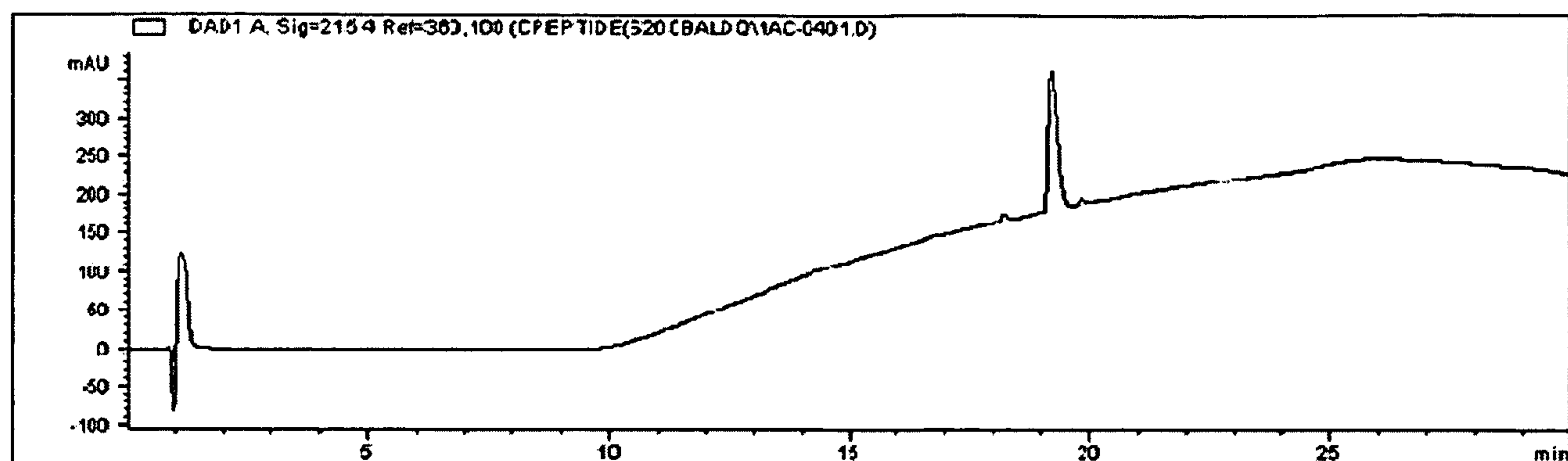


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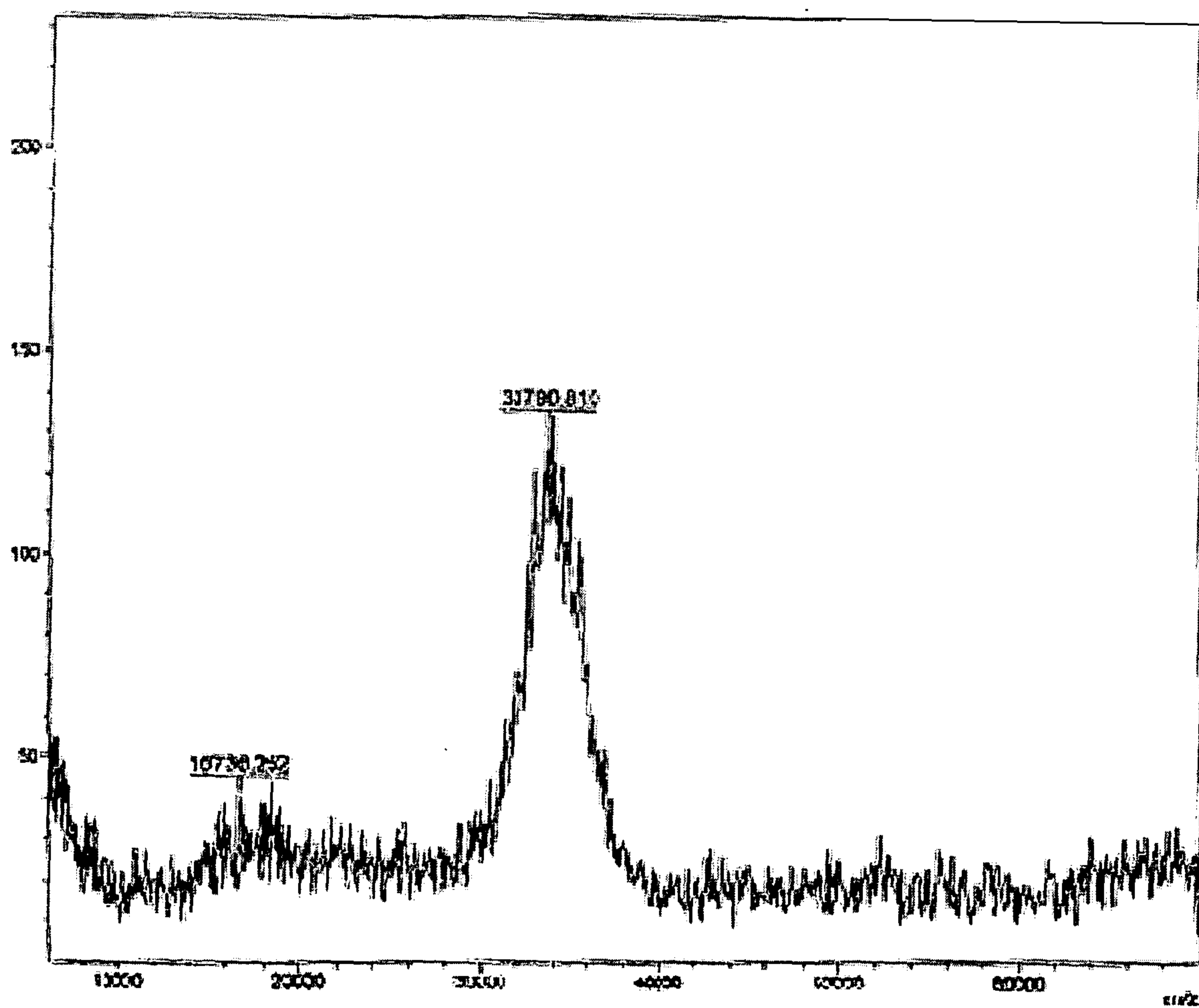


Figure C-PEP3.3

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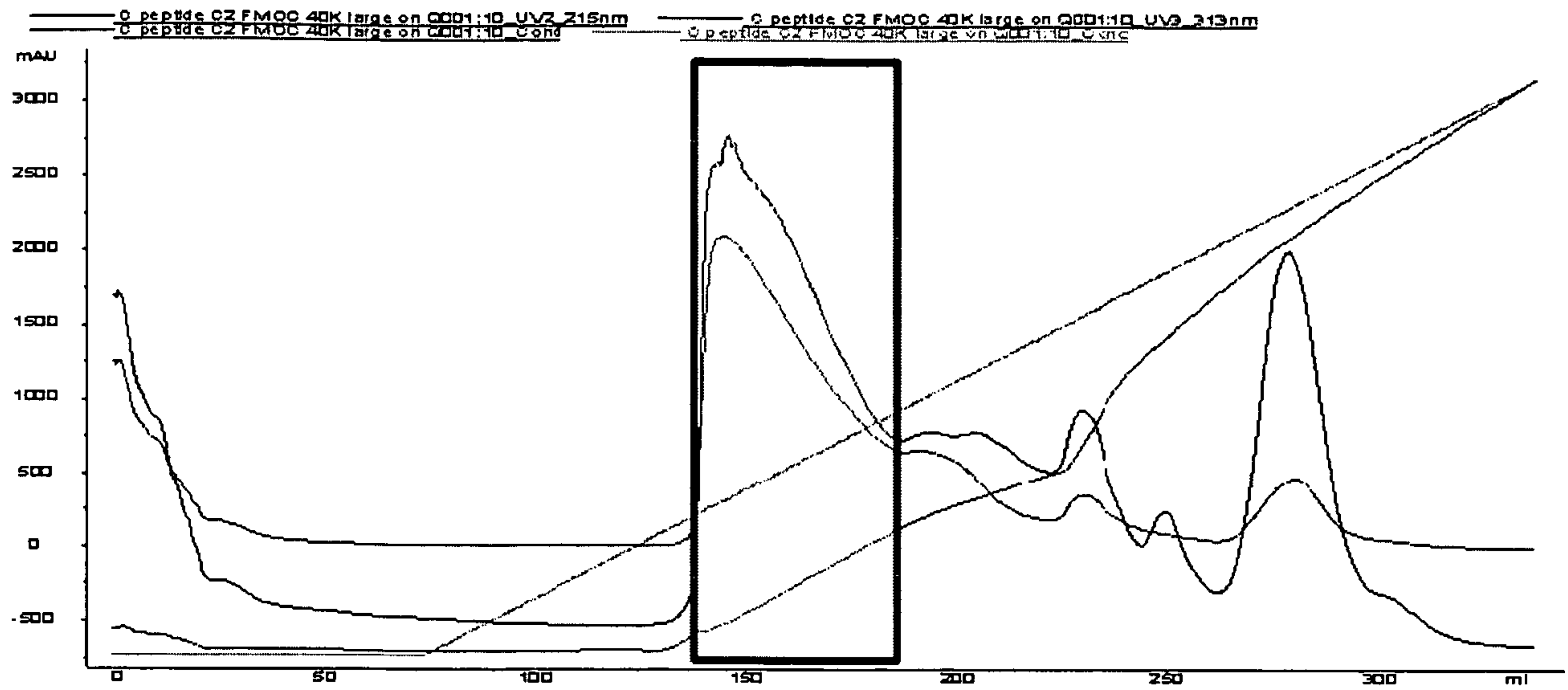


Figure C-PEP4.1

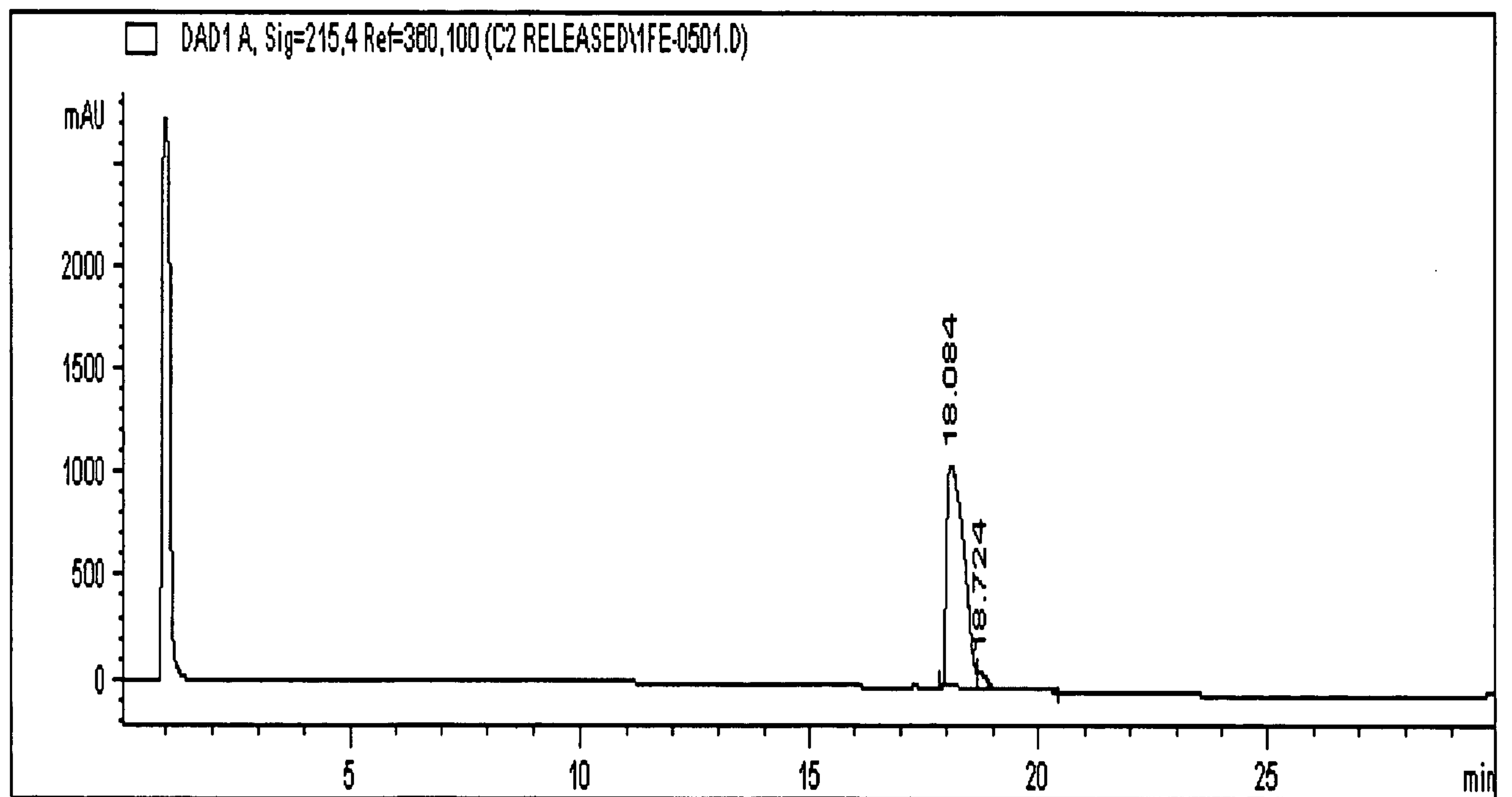


Figure C-PEP4.2

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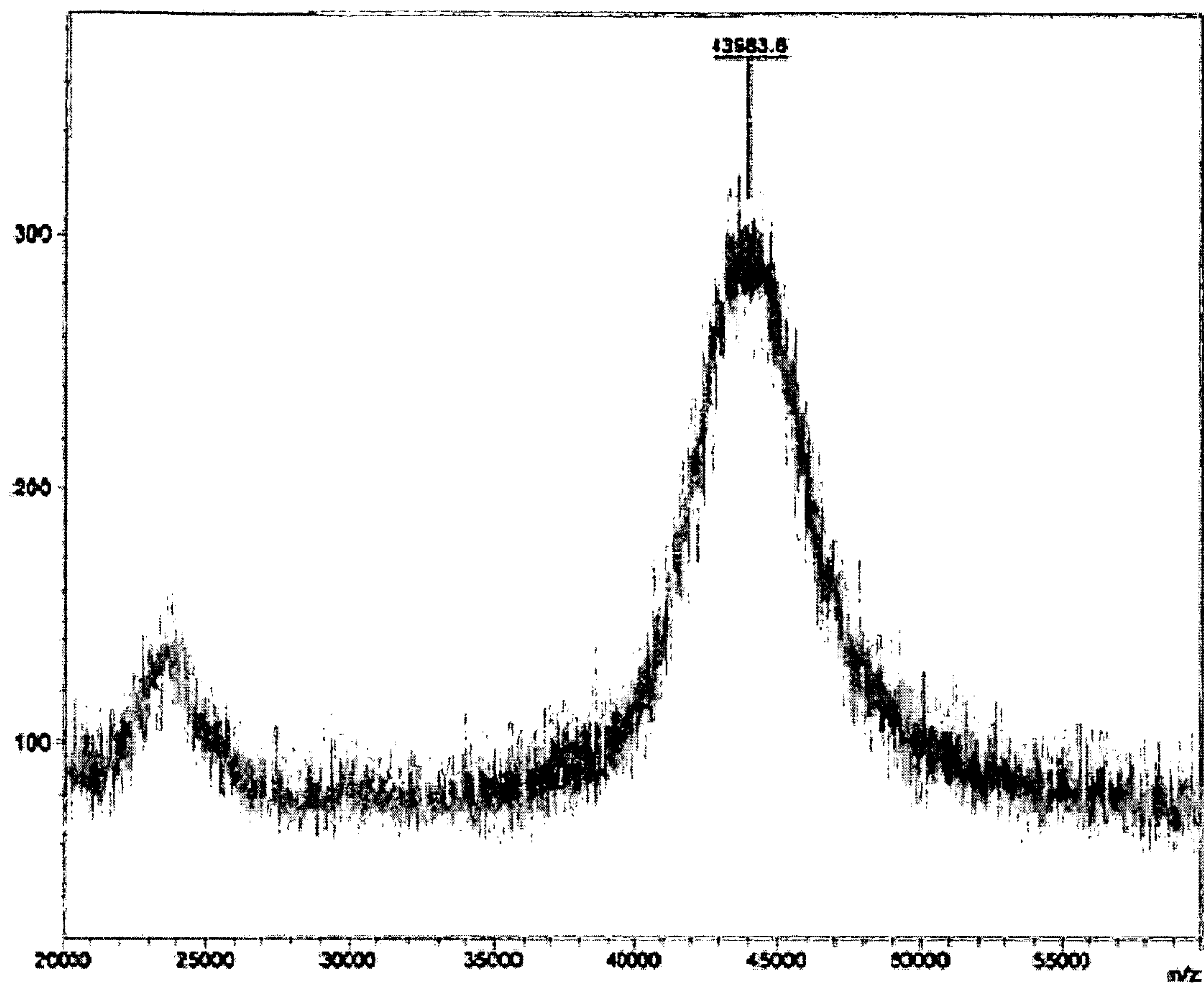


Figure C-PEP4.3

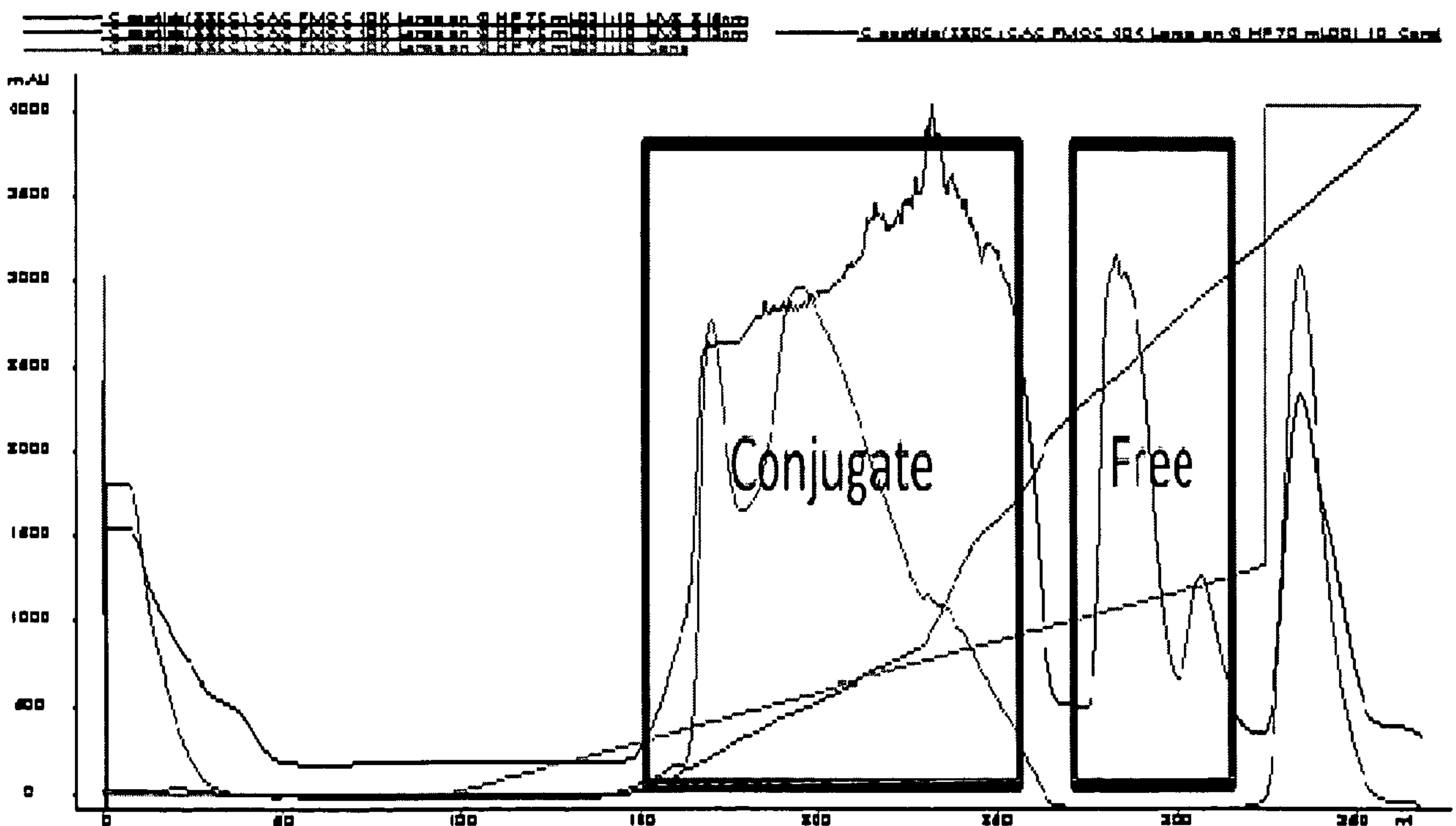


Figure C-PEP5.1

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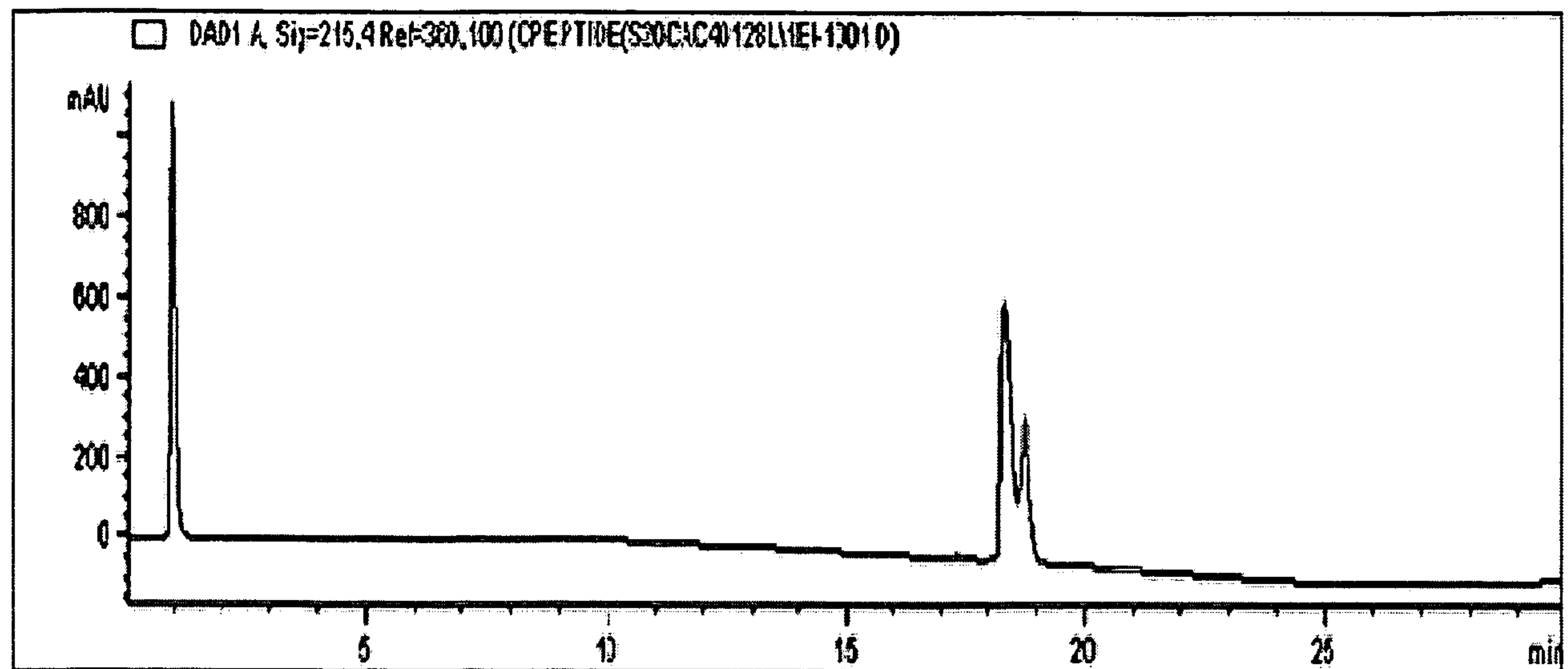


Figure C-PEP5.2

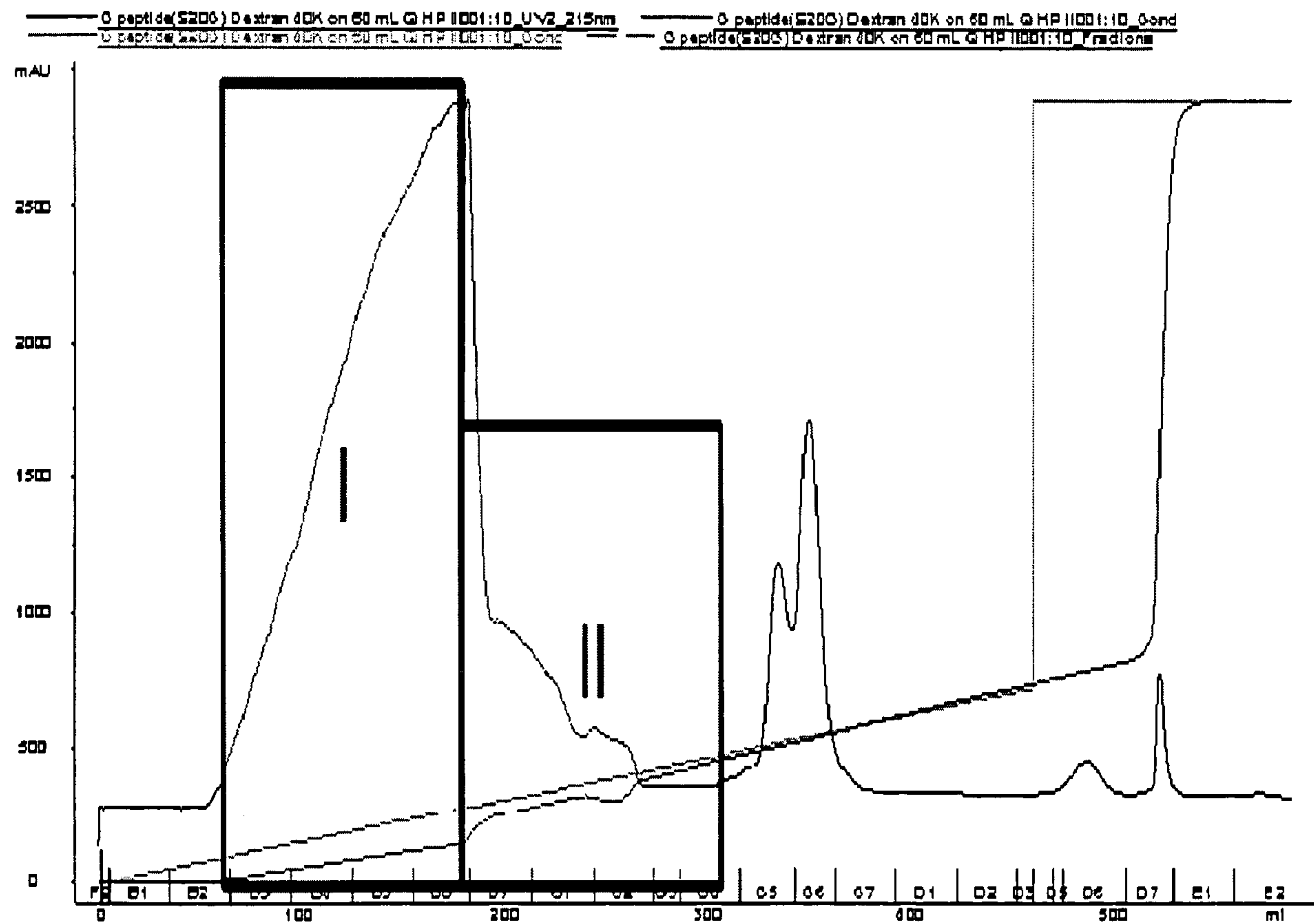


Figure C-PEP6.1

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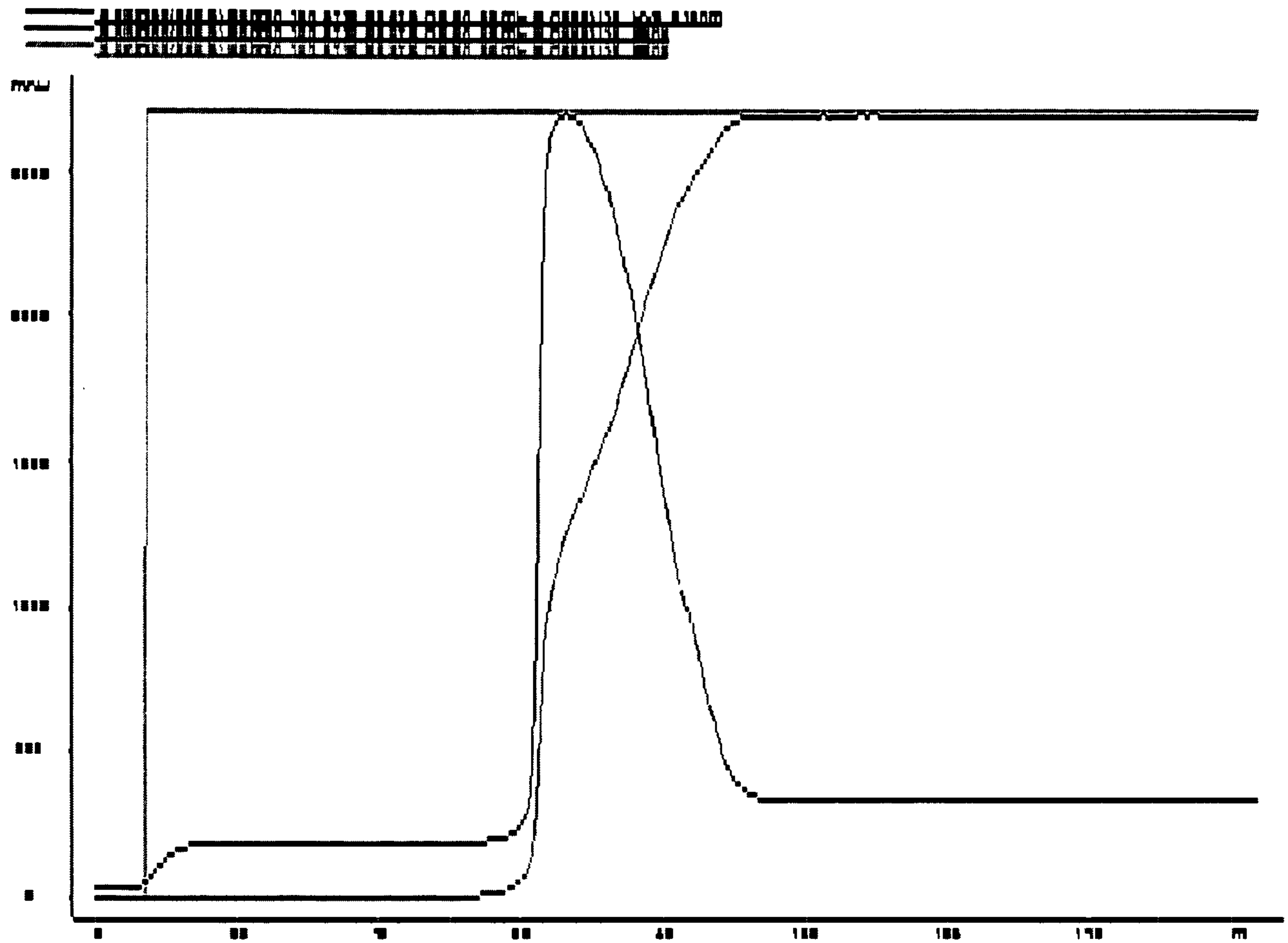


Figure C-PEP6.2

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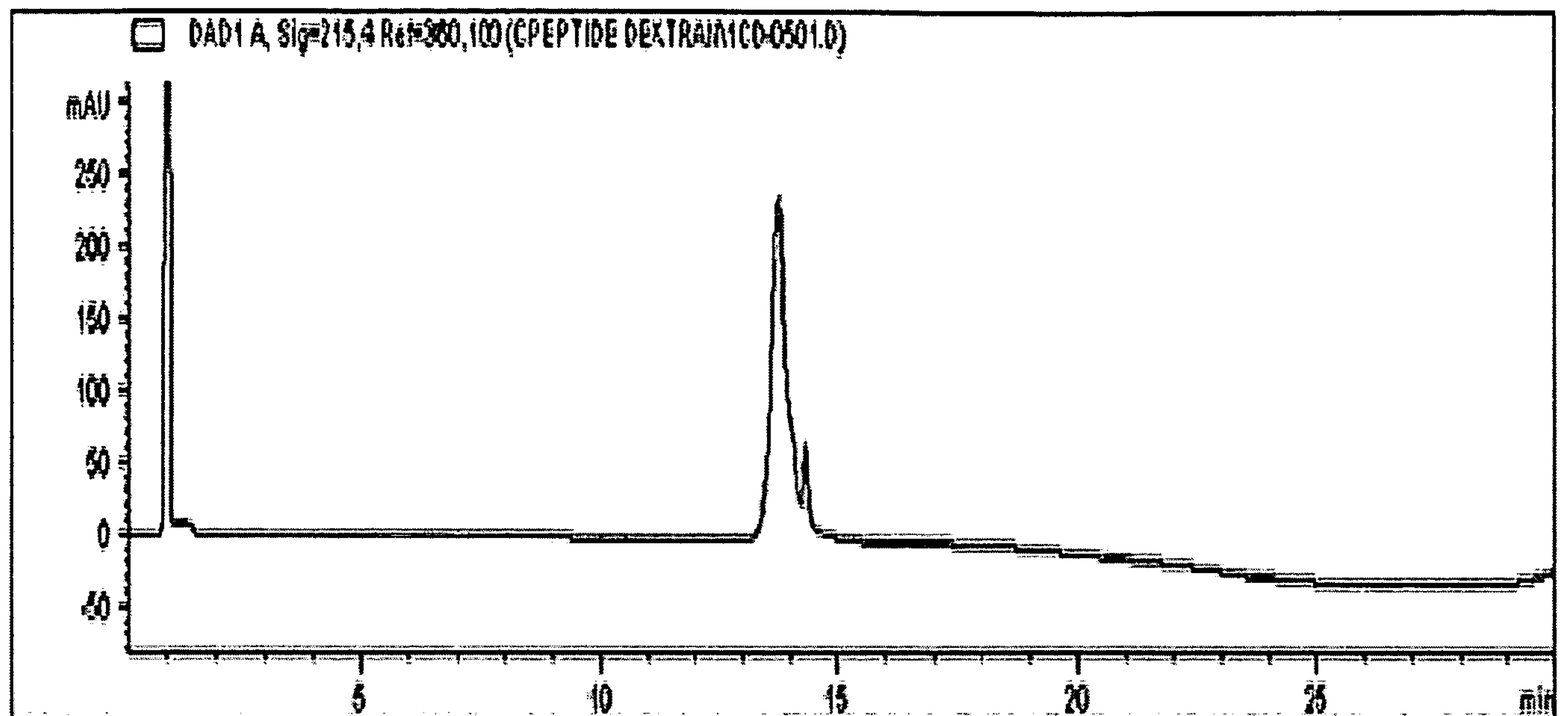


Figure C-PEP6.3

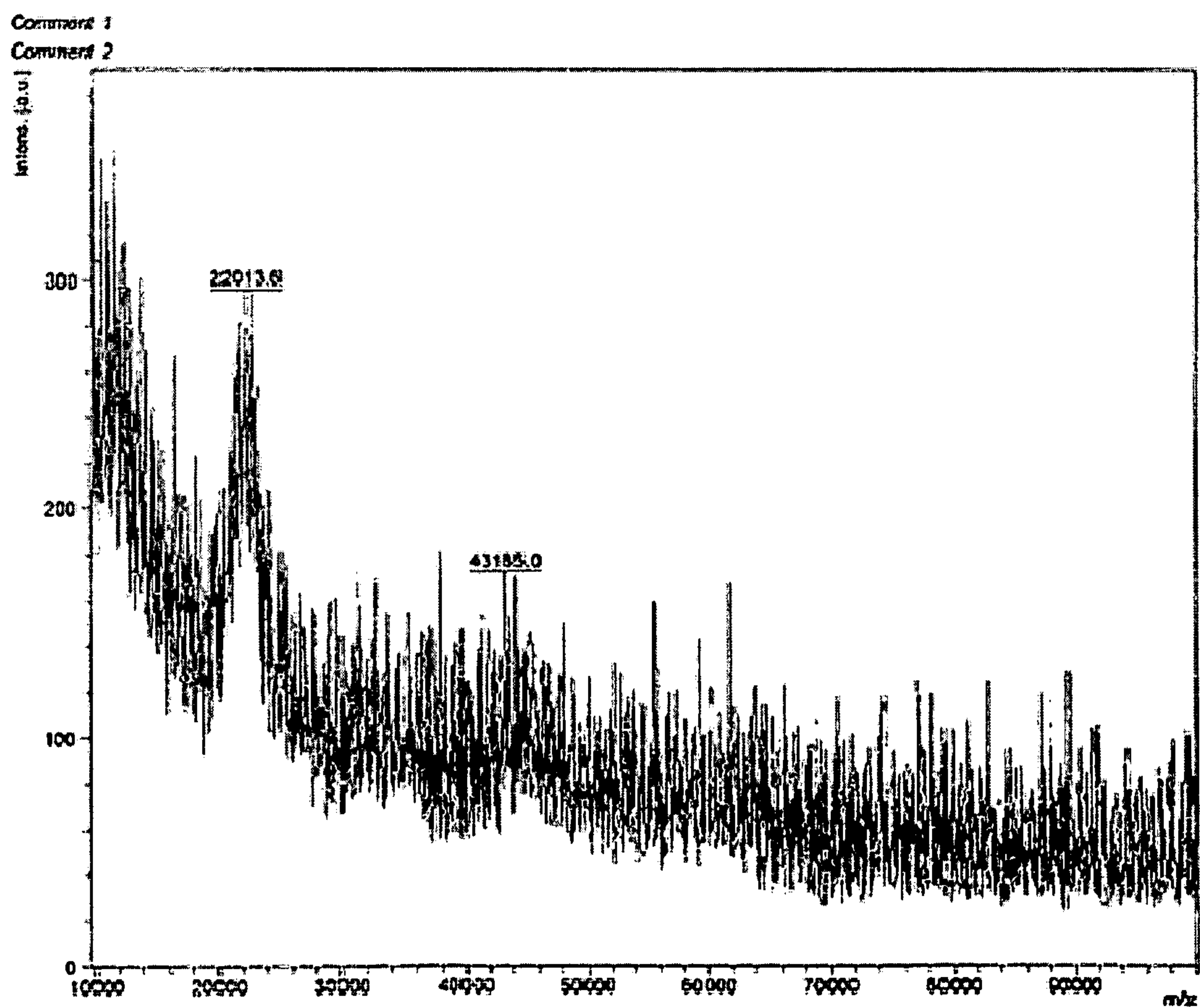


Figure C-PEP6.4

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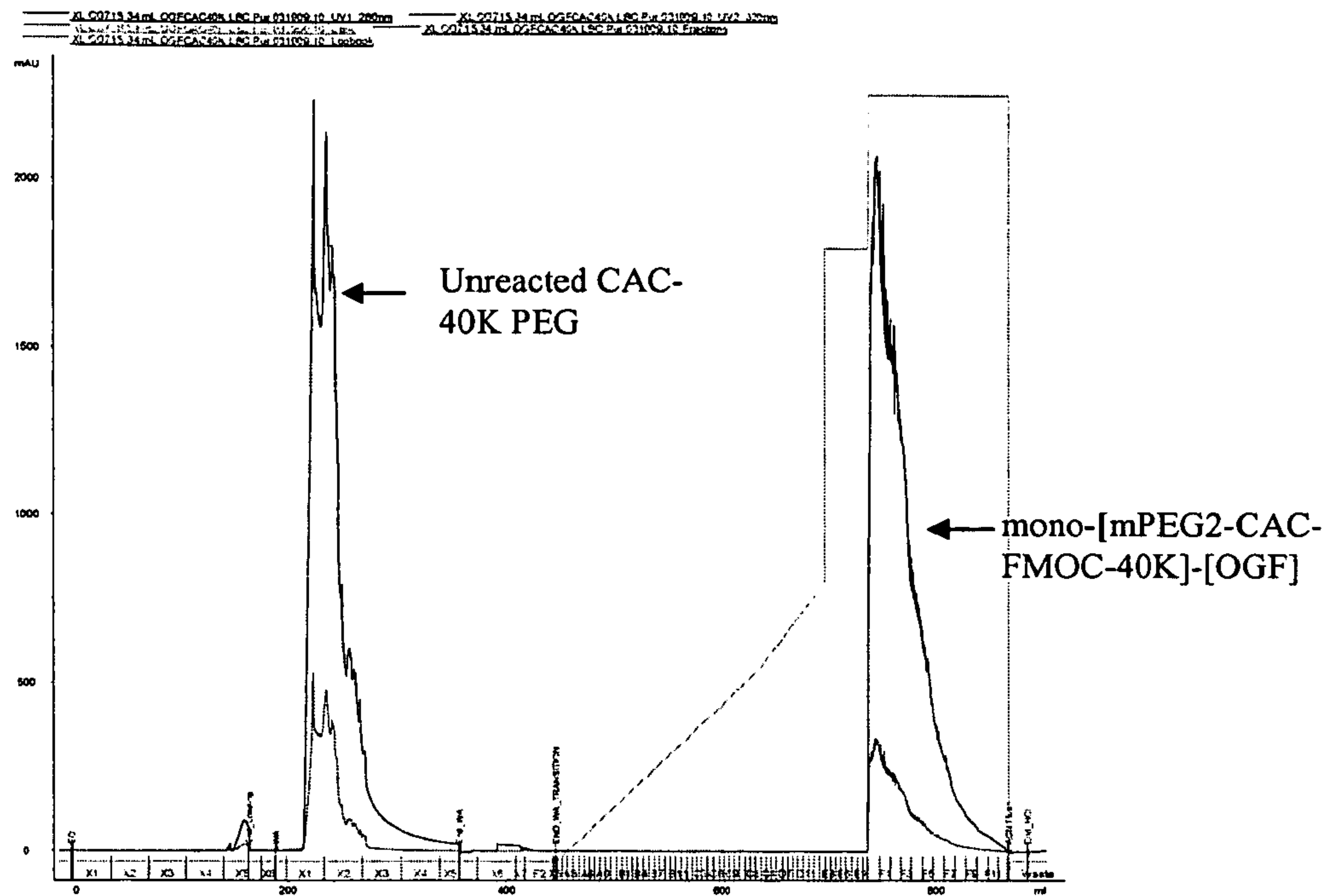


Figure OGF2.1

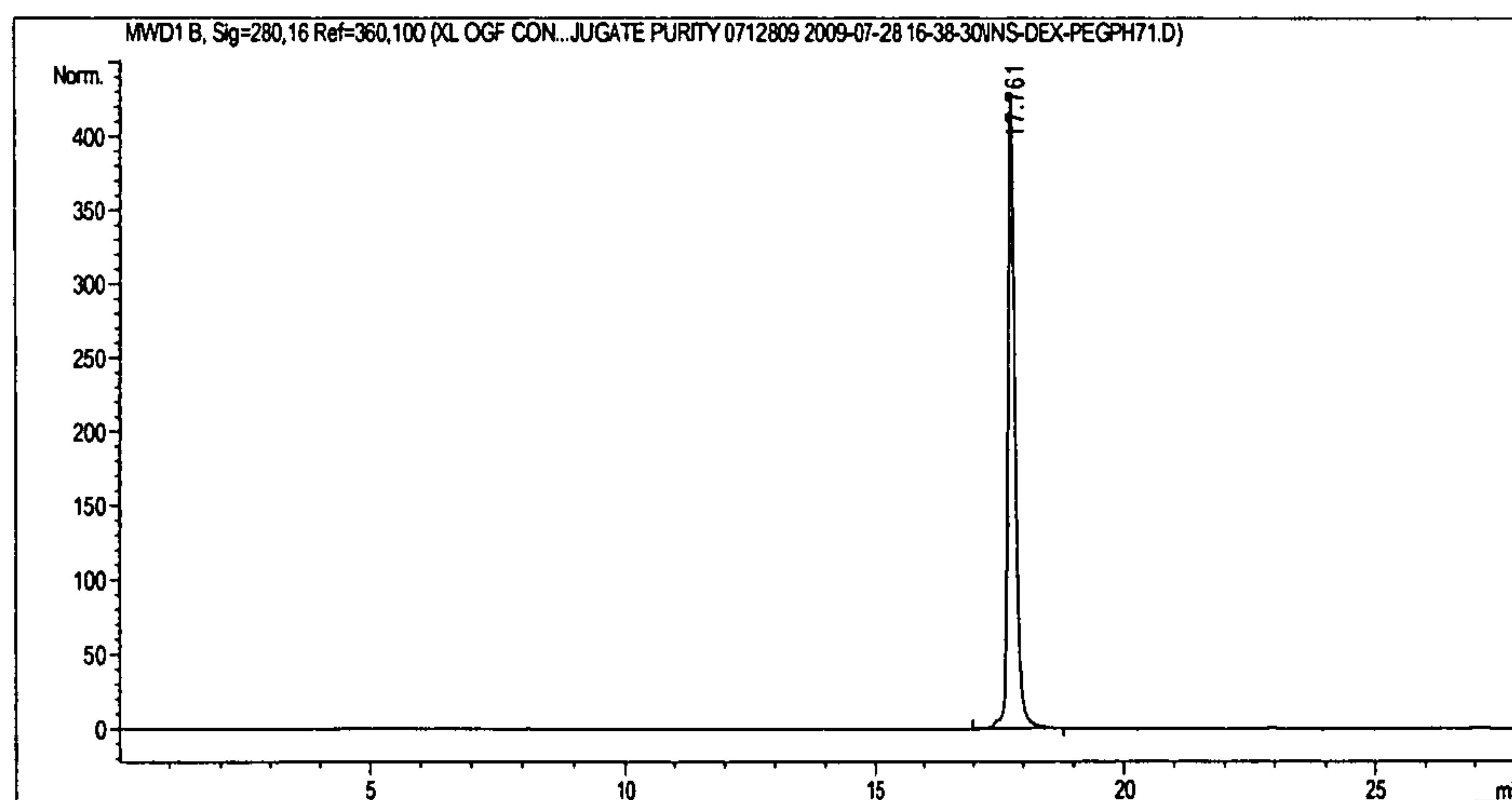


Figure OGF2.2

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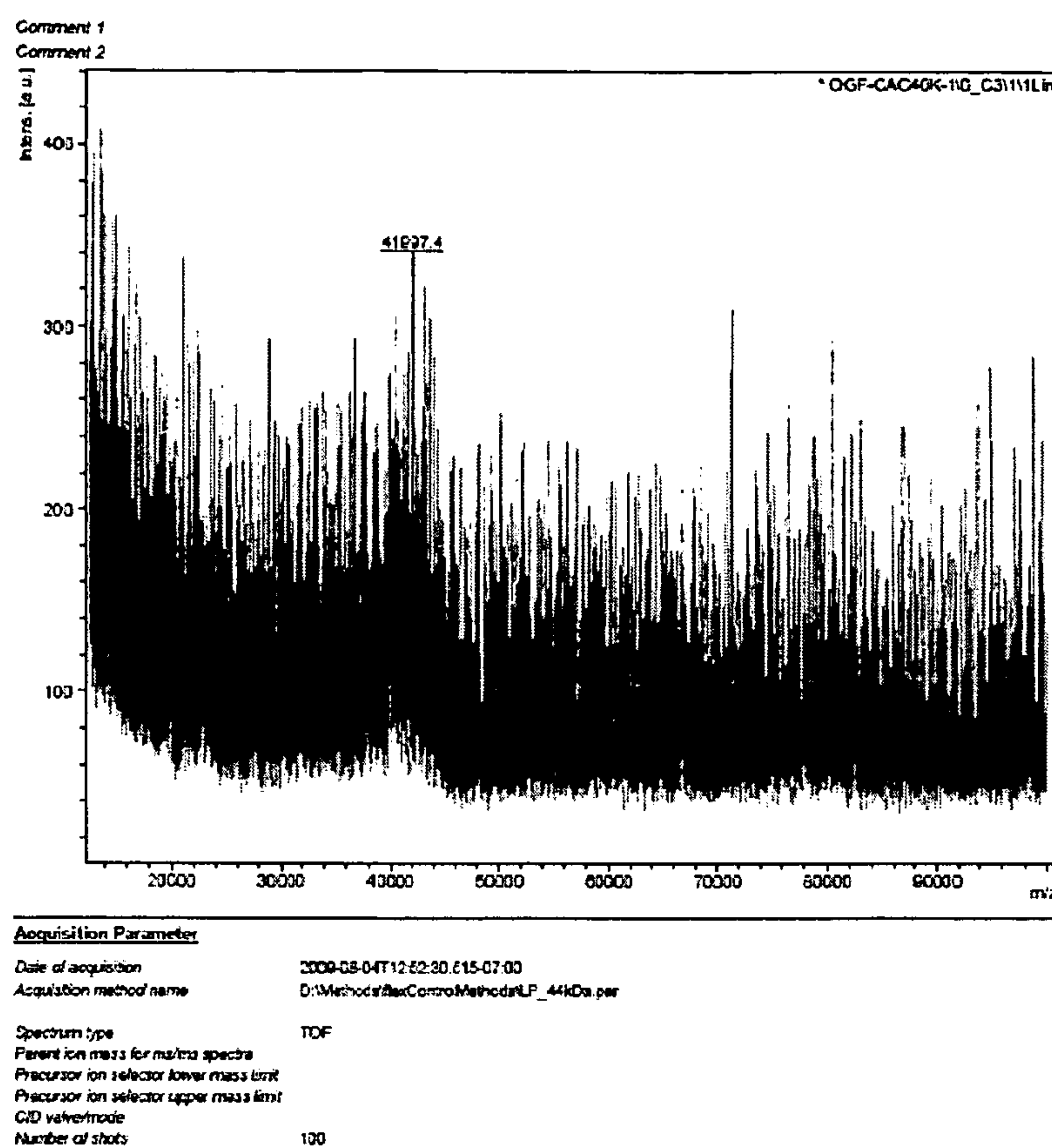


Figure OGF2.3

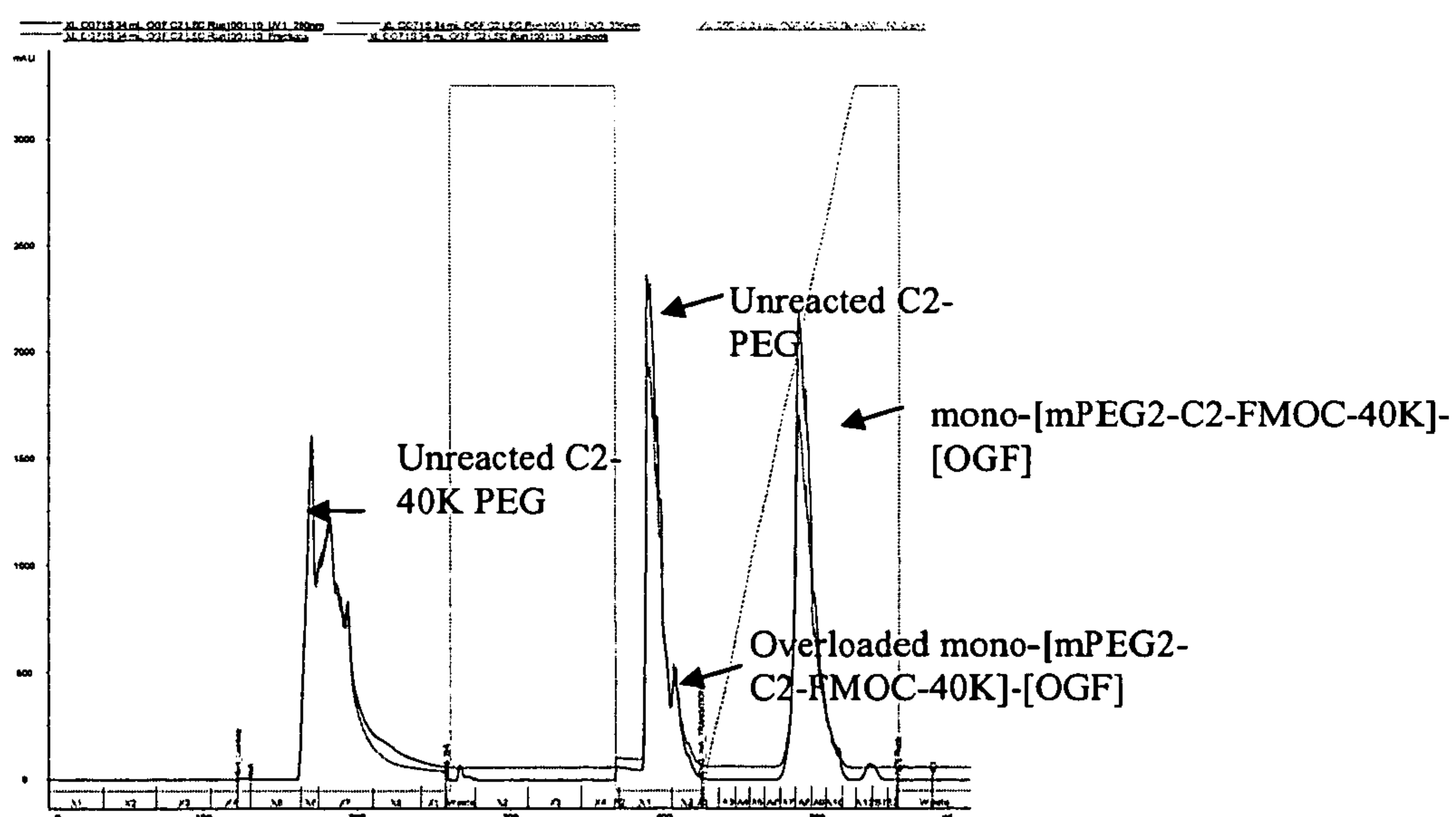


Figure OGF3.1

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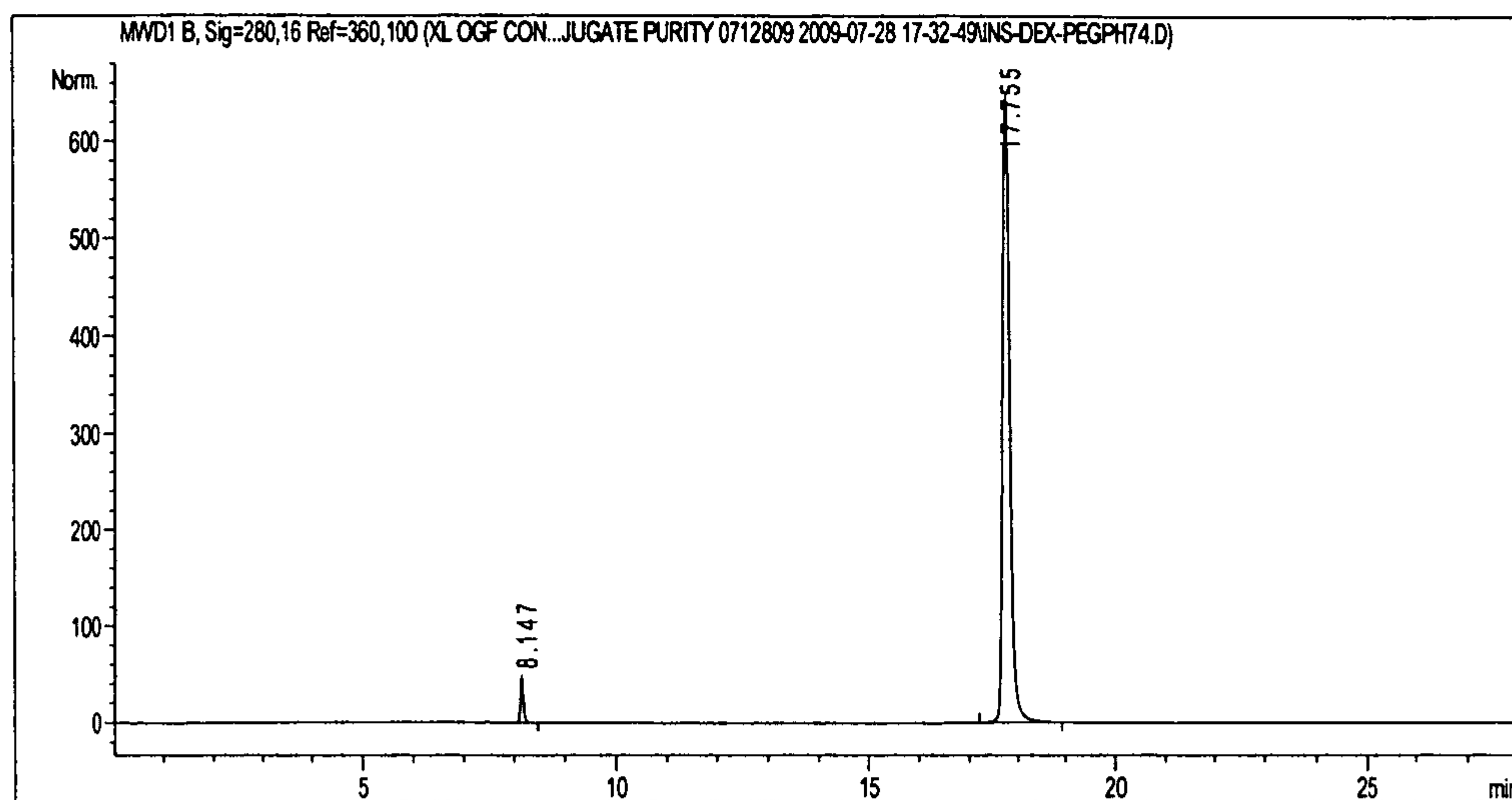
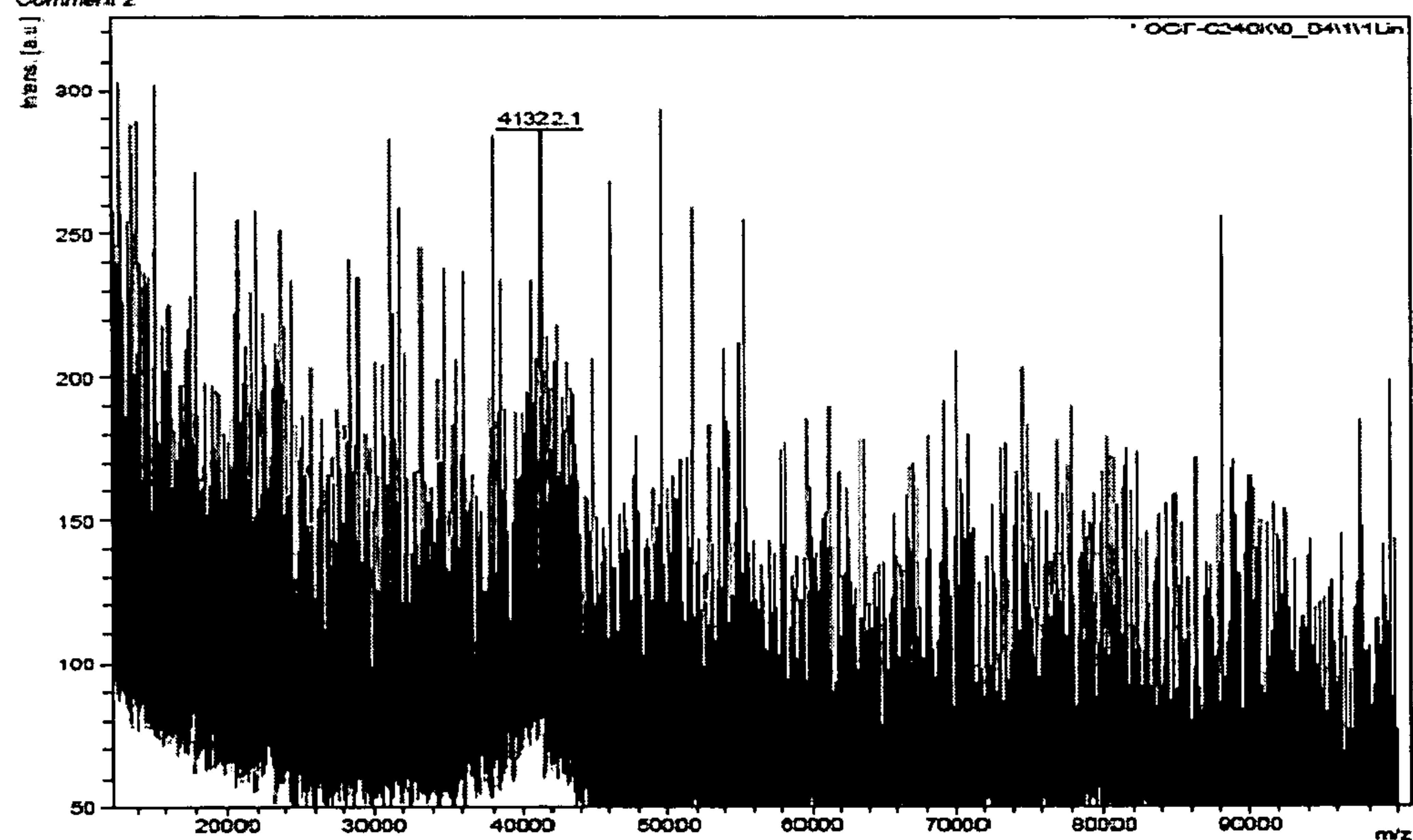


Figure OGF3.2

D:\Data\XL\OGF-C240K\0_B4\1

Comment 1

Comment 2

Acquisition Parameter

Date of acquisition	2009-03-04T12:56:37.087-07:00
Acquisition method name	D:\Methods\flexControl\Methods\LP_44kDa.par
Spectrum type	TOF
Parent ion mass for ms/ms spectra	
Precursor ion selector lower mass limit	
Precursor ion selector upper mass limit	
CID valve/mode	
Number of shots	100

Figure OGF3.3

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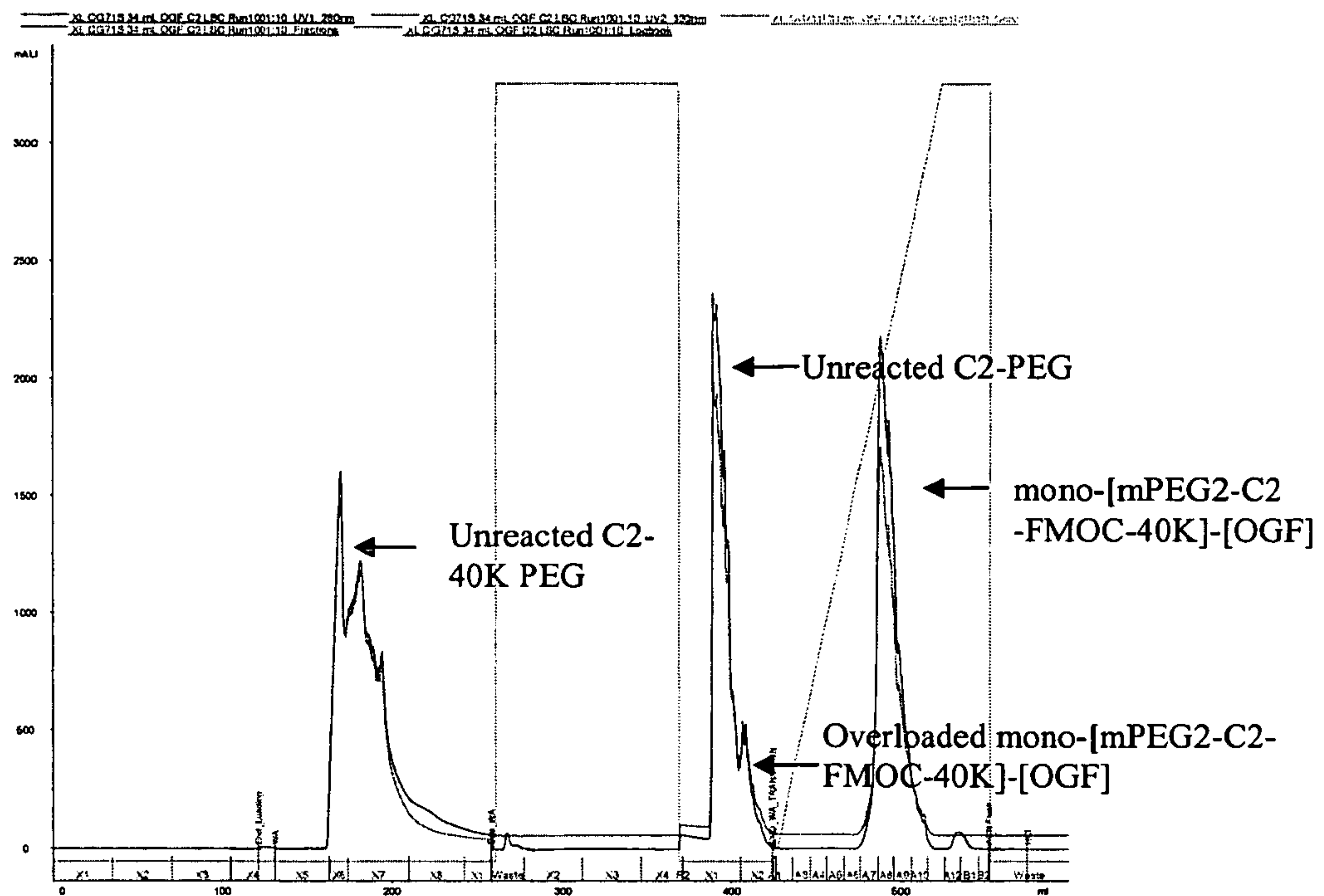


Figure OGF4.1

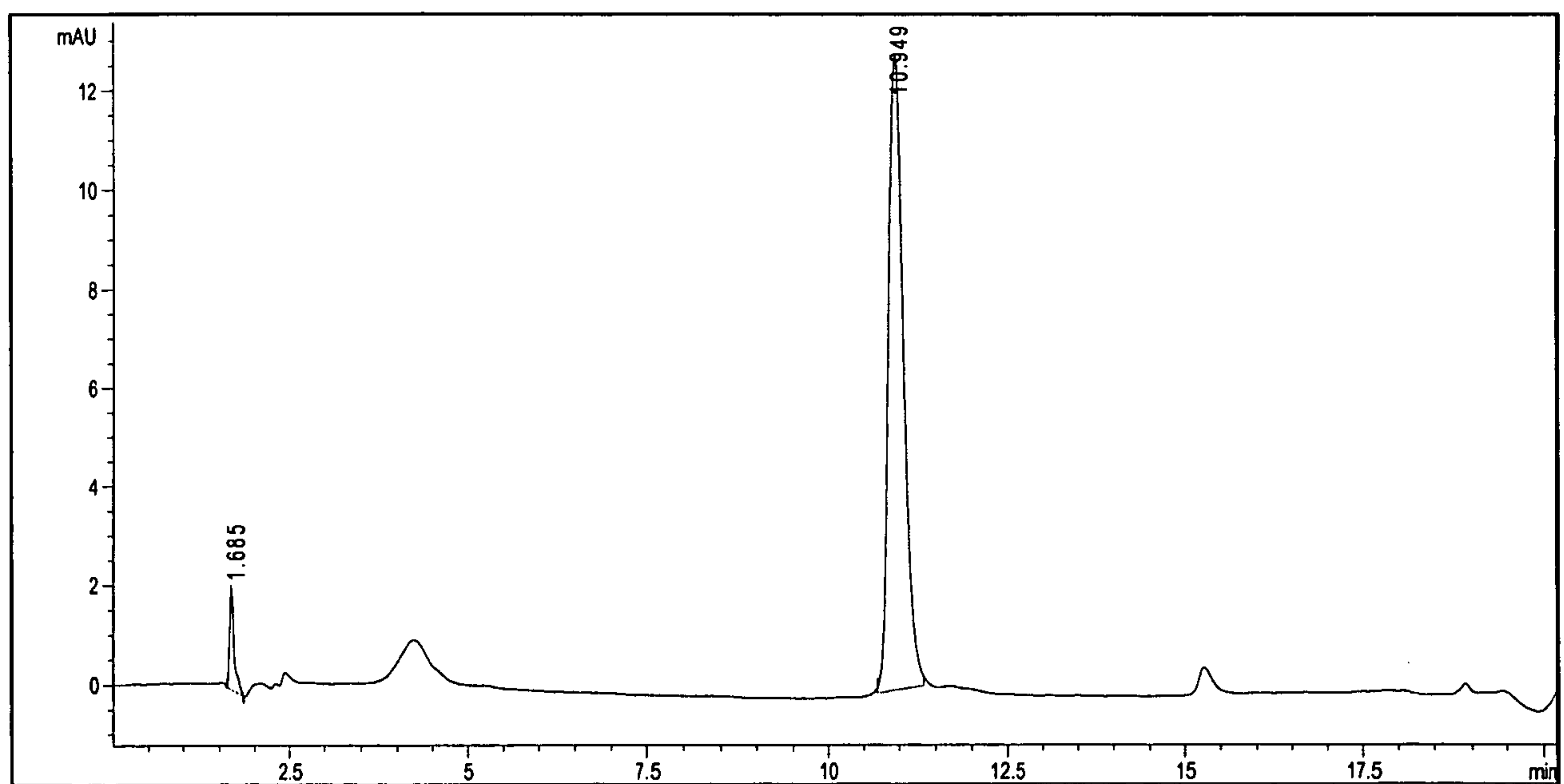


Figure OGF4.2

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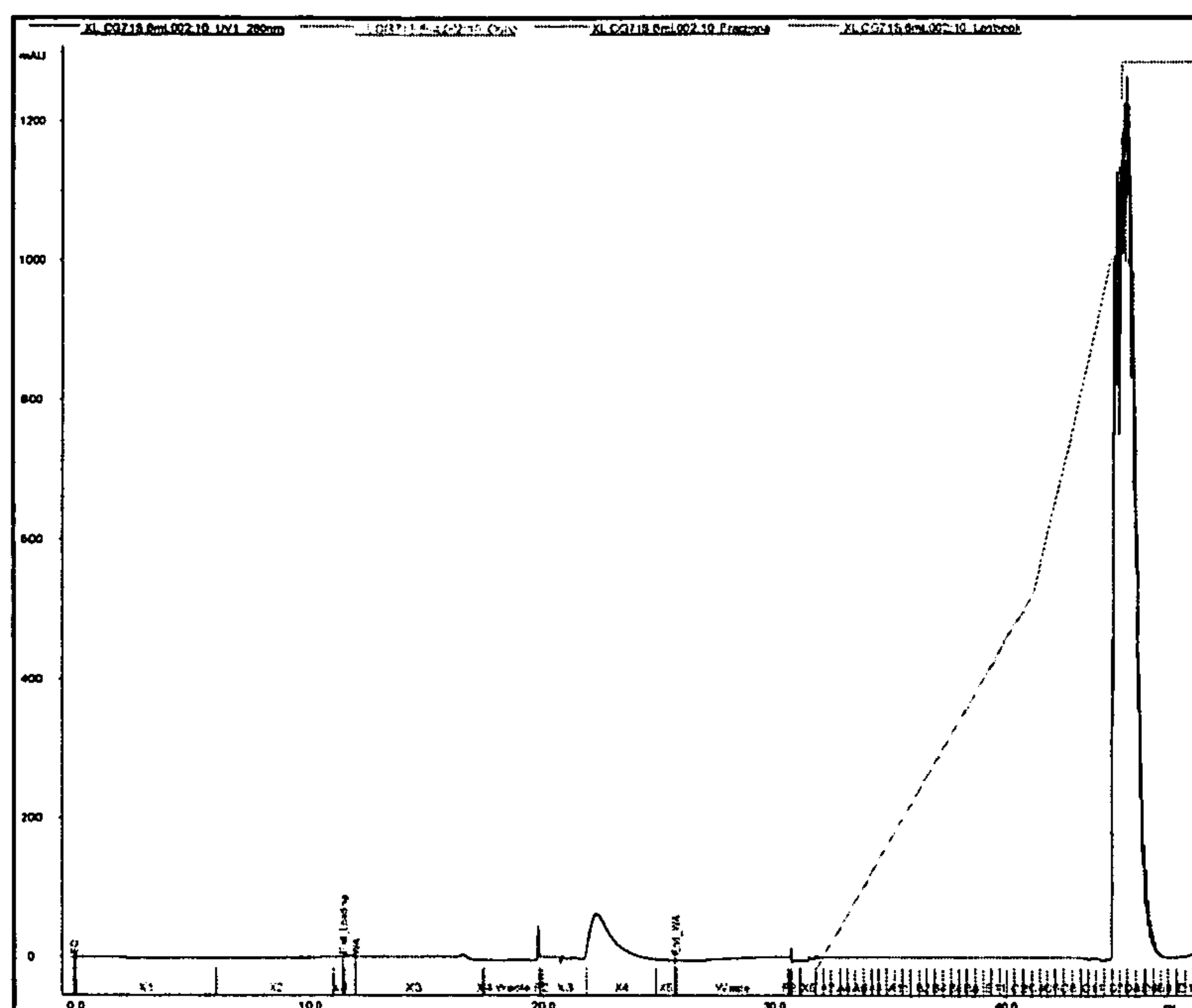


Figure OGF5.1

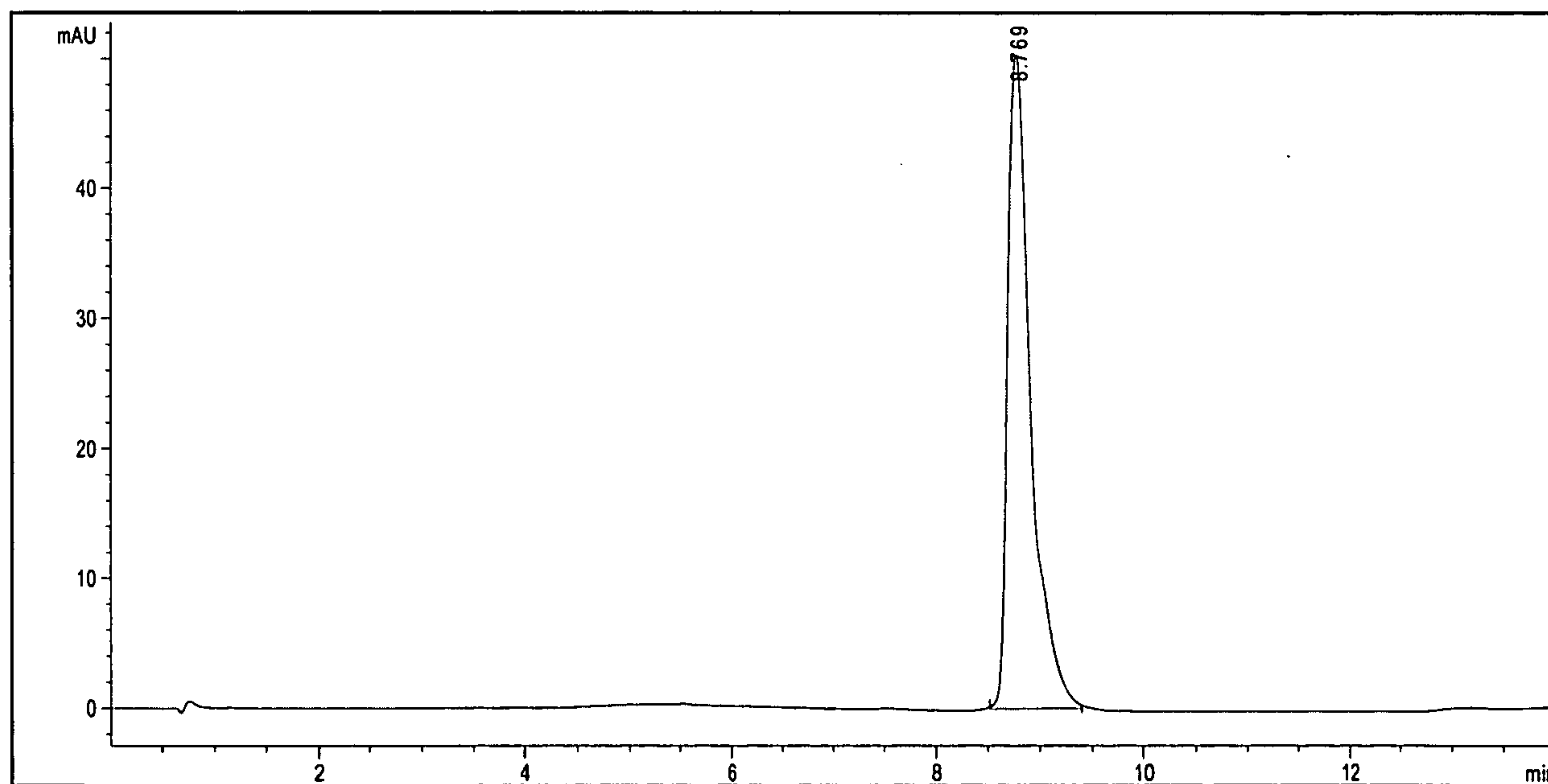


Figure OGF5.2

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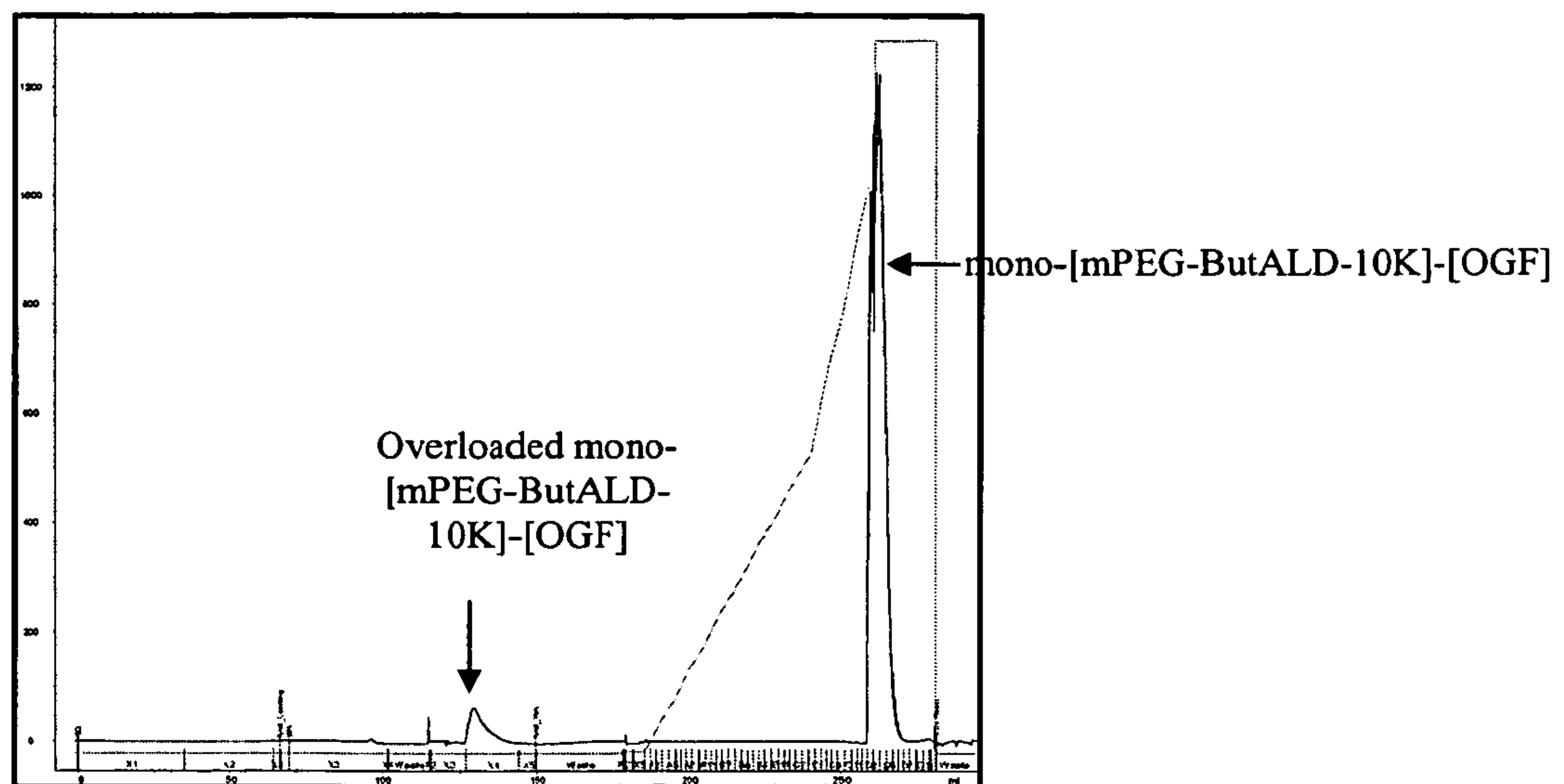


Figure OGF6.1

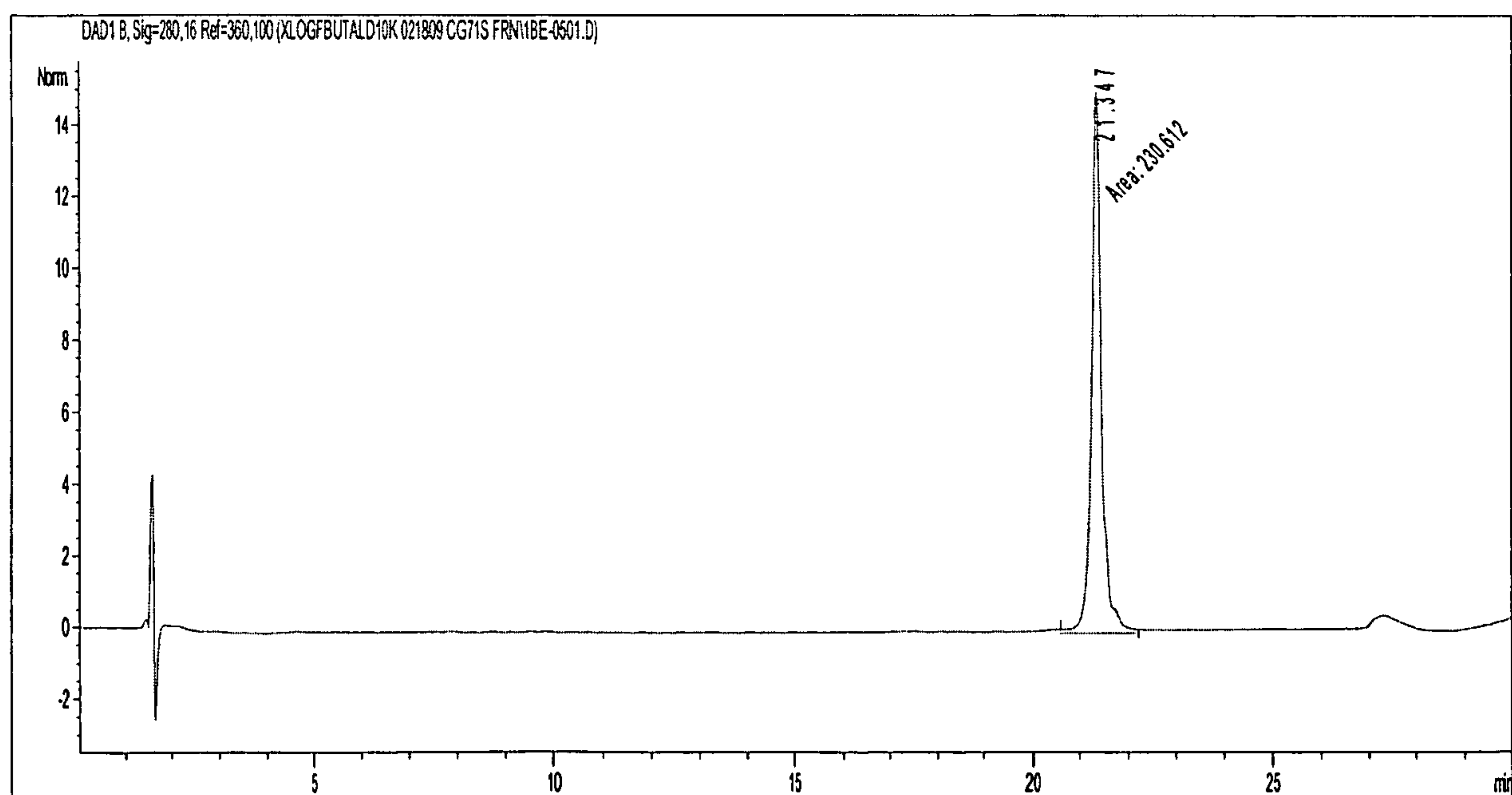


Figure OGF6.2

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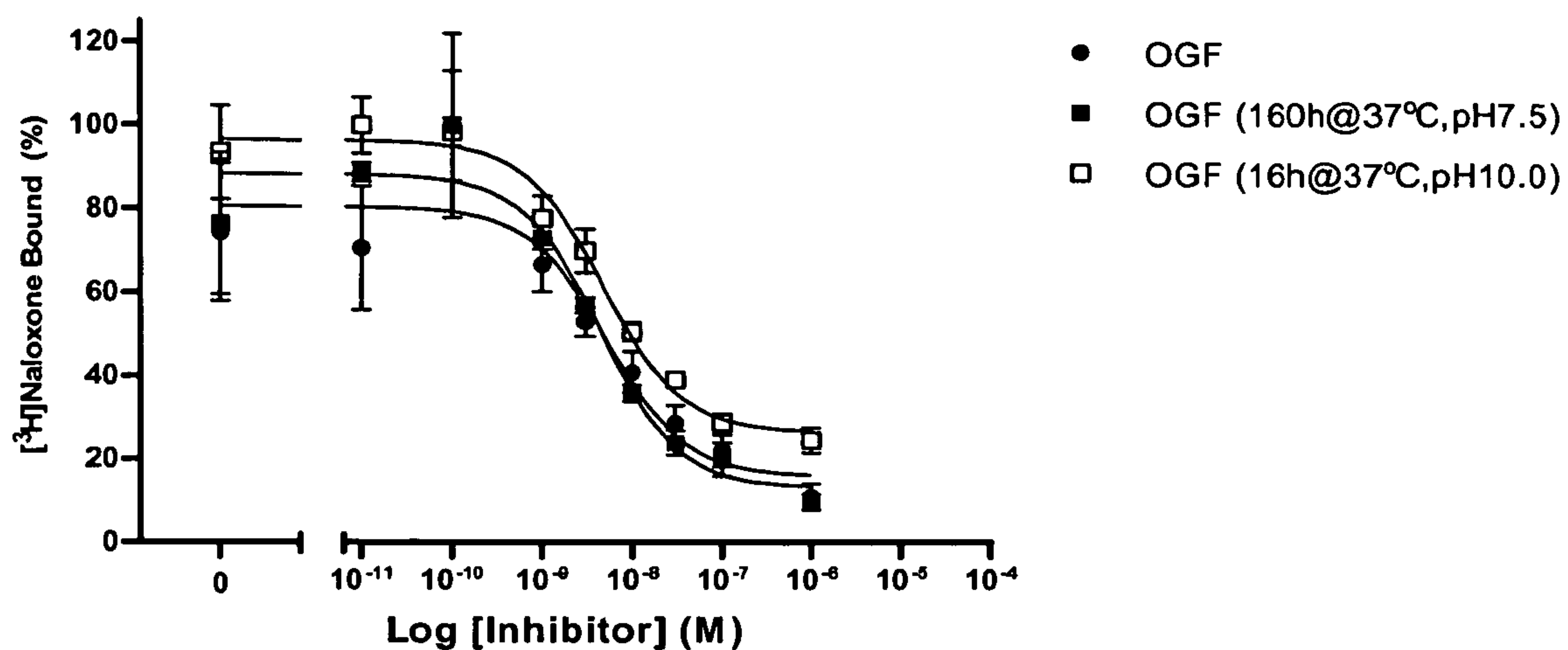
A **μ Opioid Receptor (Human Recombinant) Binding Assay**

Figure OGF7.1A

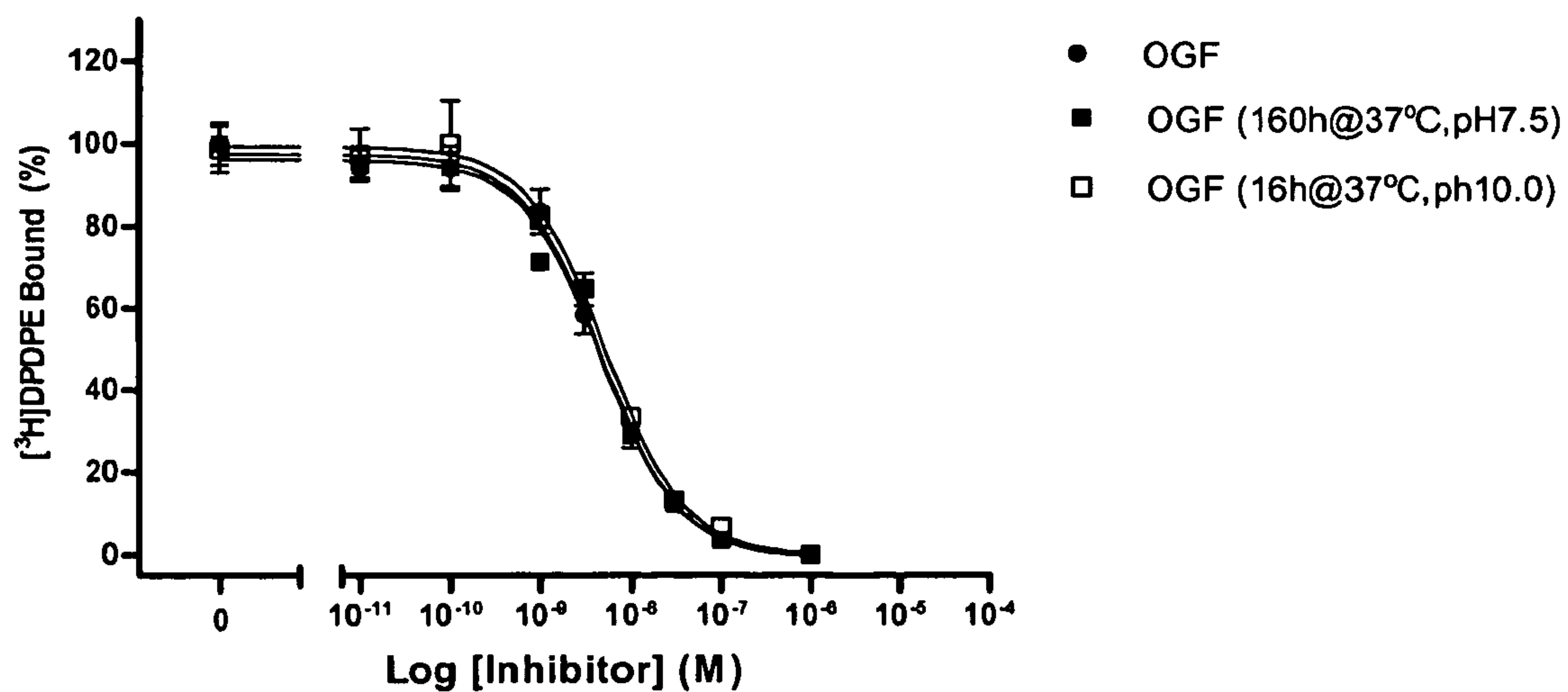
B **δ Opioid Receptor (Human Recombinant) Binding Assay**

Figure OGF7.1B

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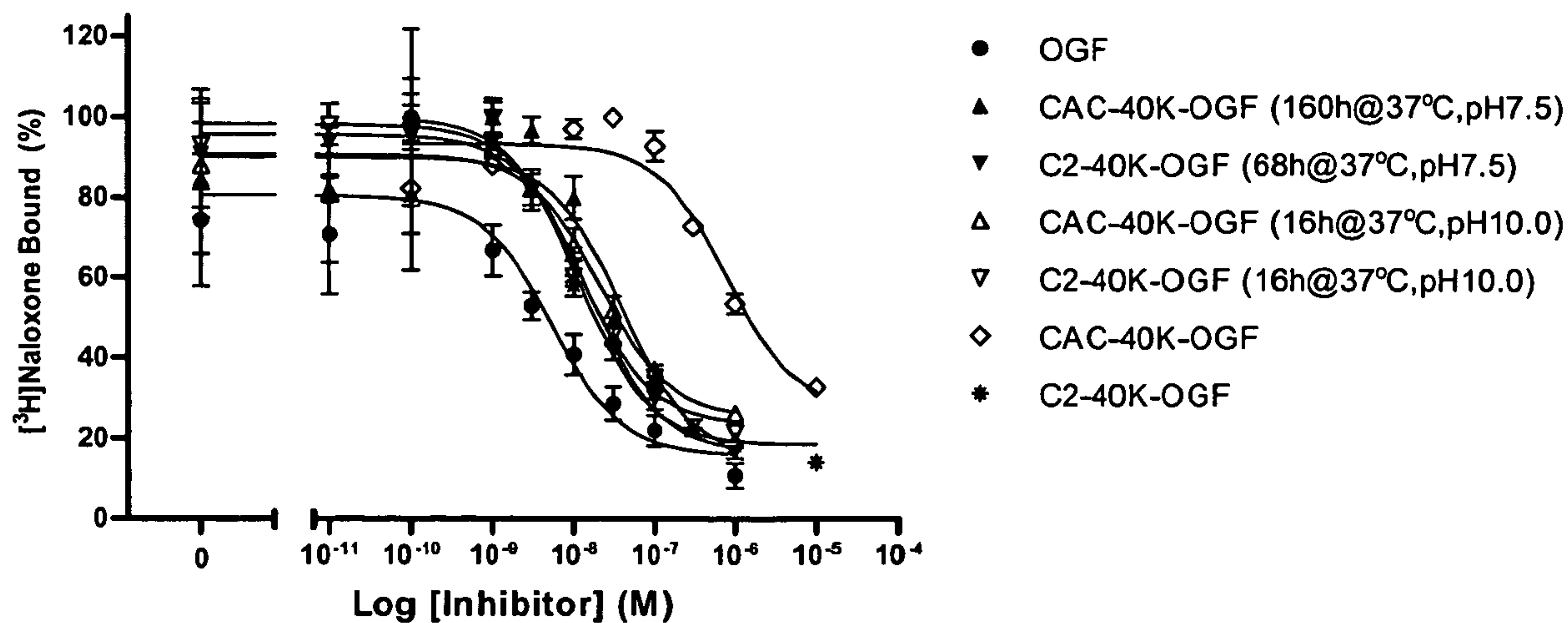
A **μ Opioid Receptor (Human Recombinant) Binding Assay**

Figure OGF7.2A

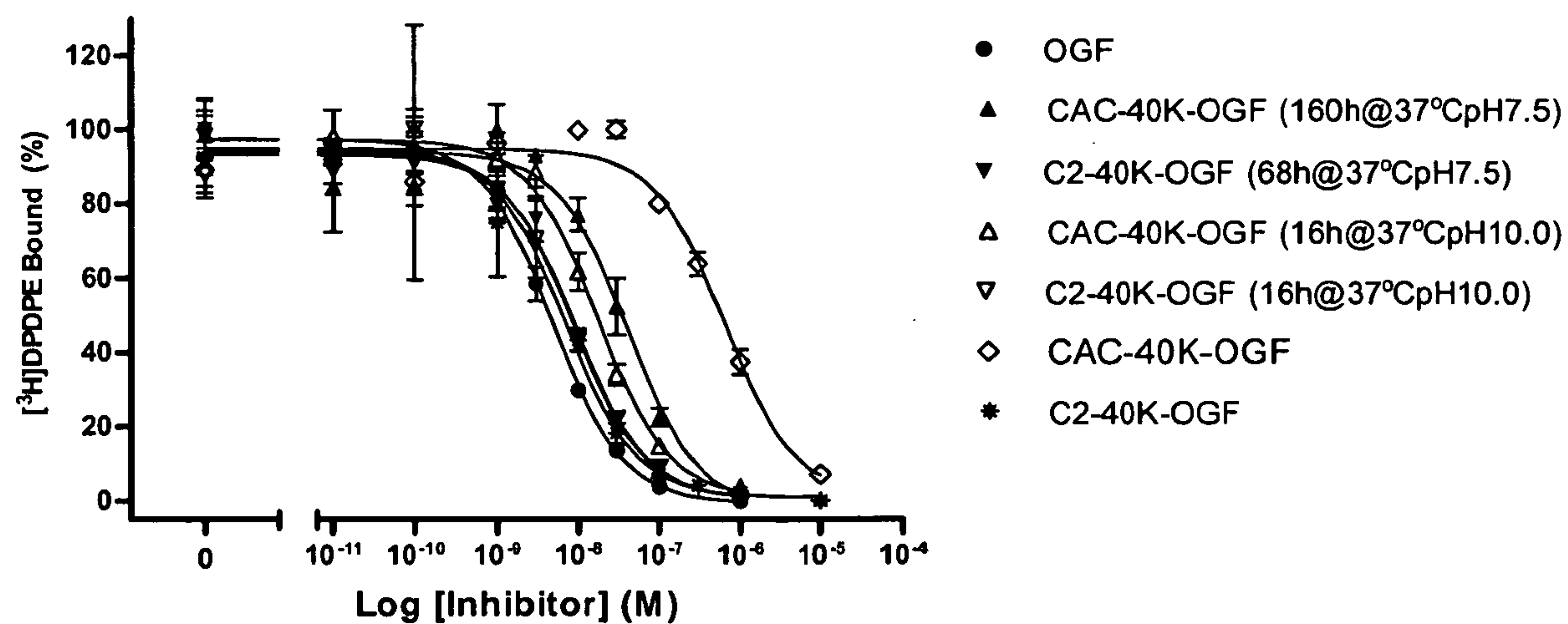
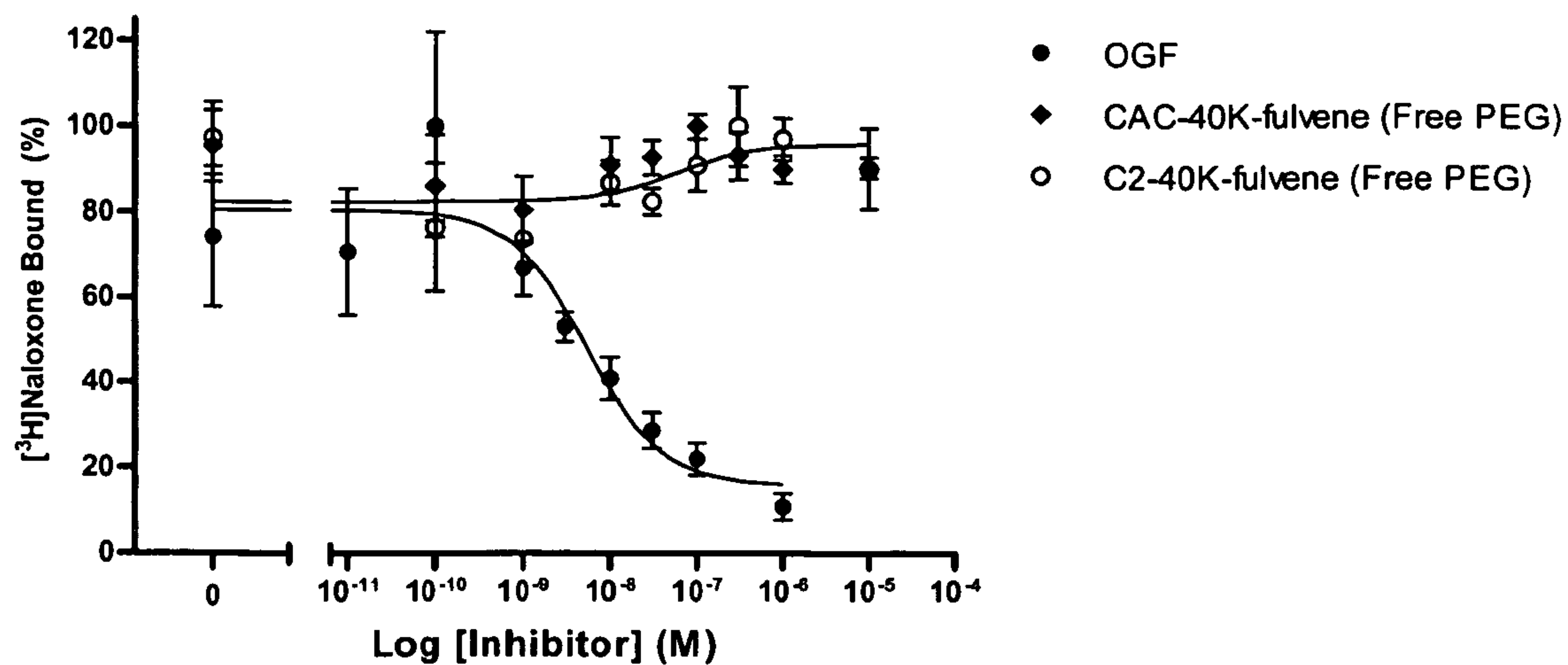
B **δ Opioid Receptor (Human Recombinant) Binding Assay**

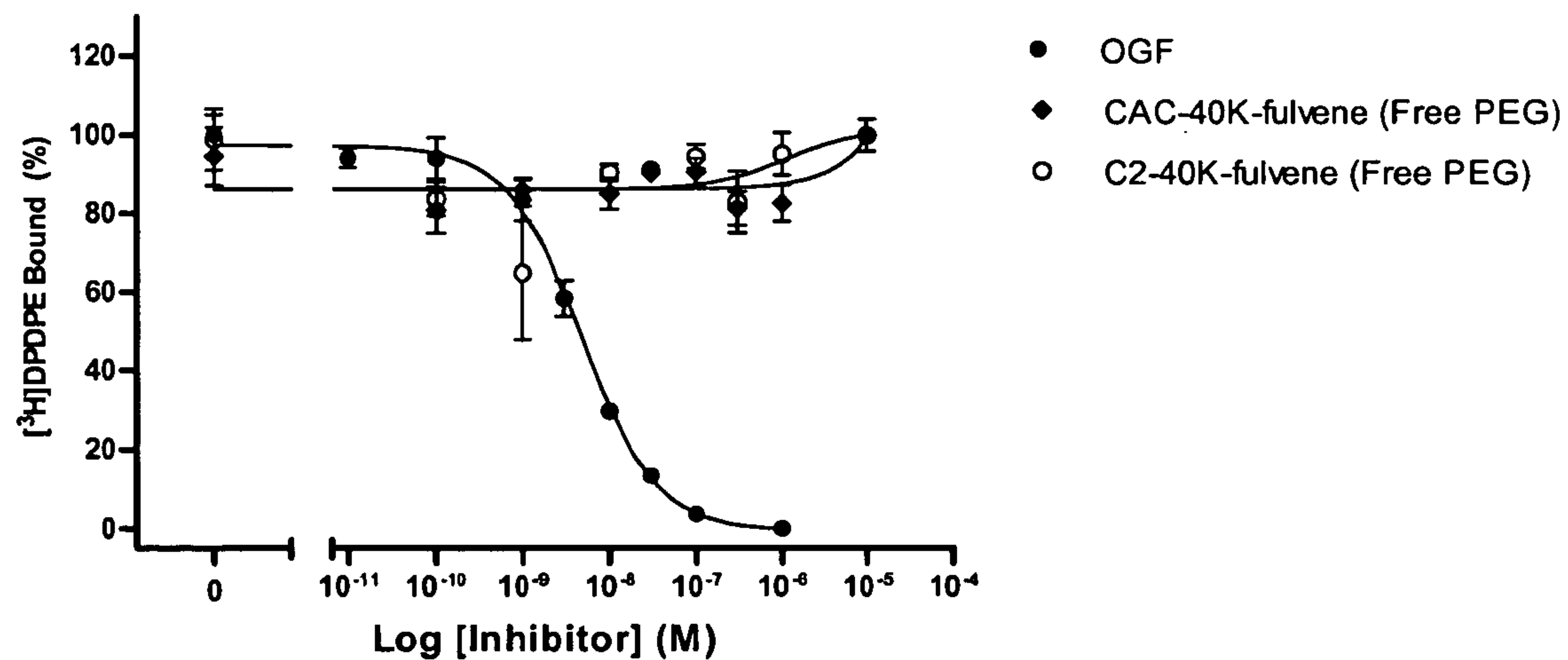
Figure OGF7.2B

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A **μ Opioid Receptor (Human Recombinant) Binding Assay**

[Ligand]: 5.0 nM
Kd: 2.0 nM

Figure OGF7.3A

B **δ Opioid Receptor (Human Recombinant) Binding Assay**

[Ligand]: 5.0 nM
Kd: 3.0 nM

Figure OGF7.3B

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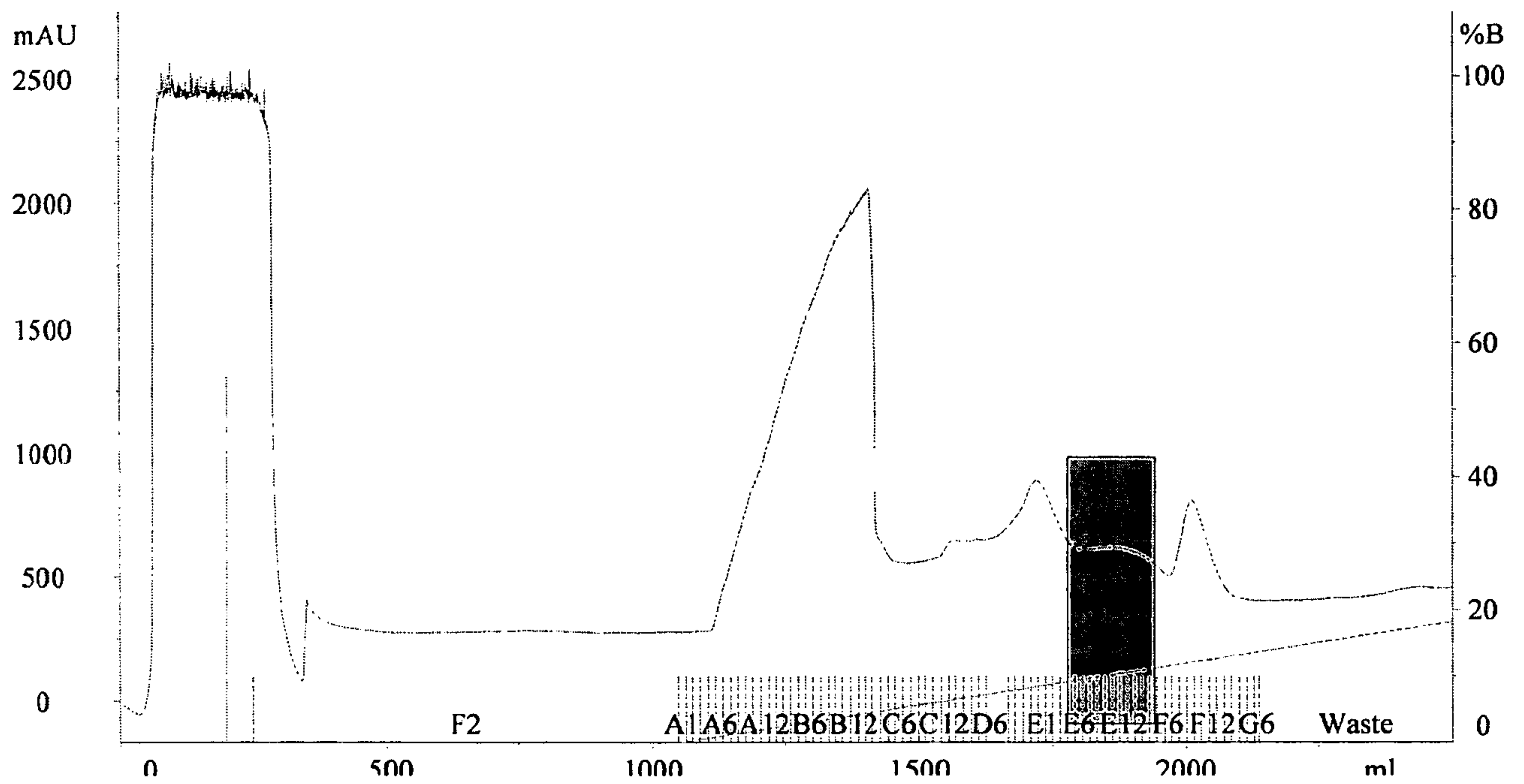


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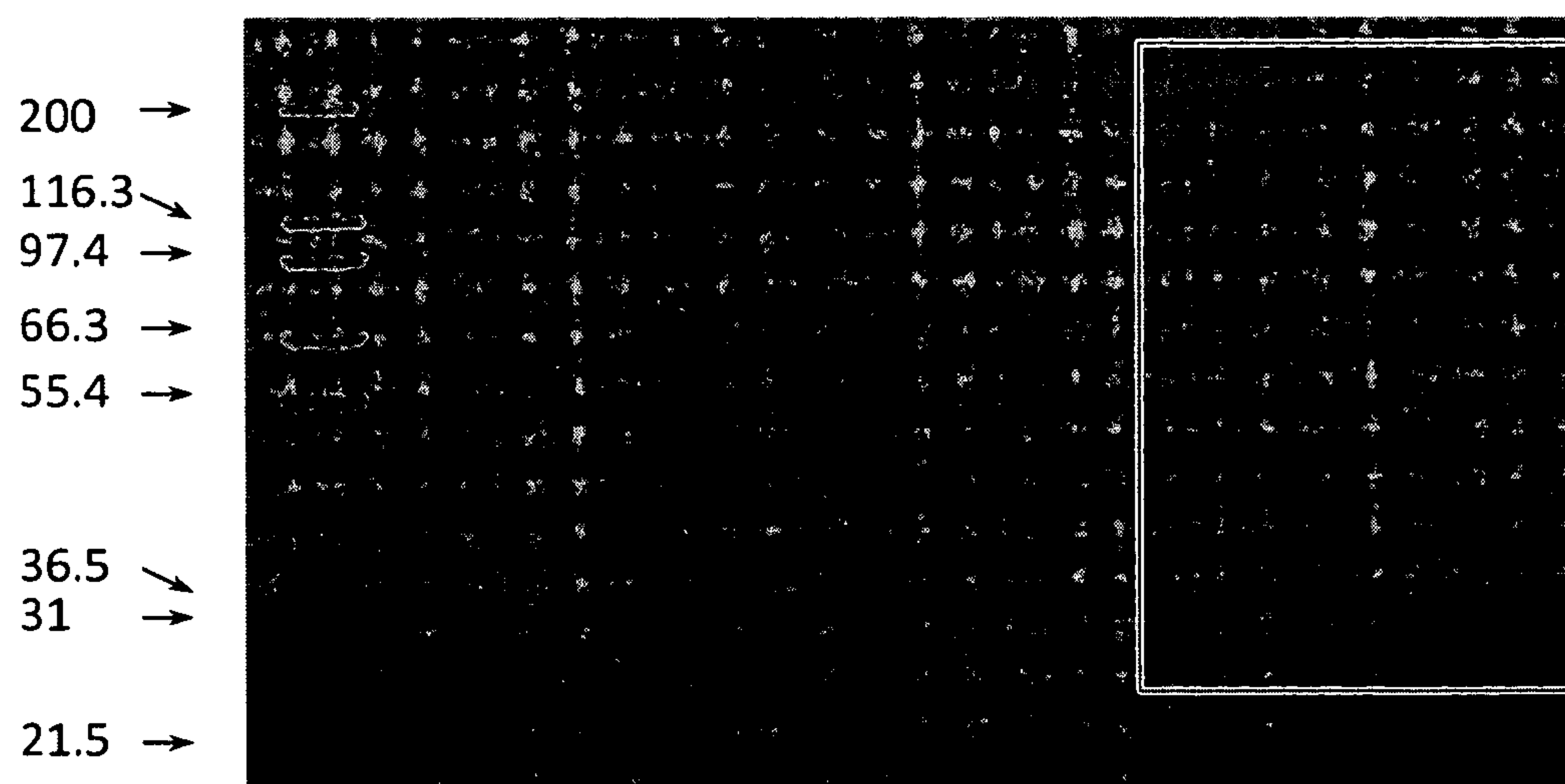


Figure INS1.2

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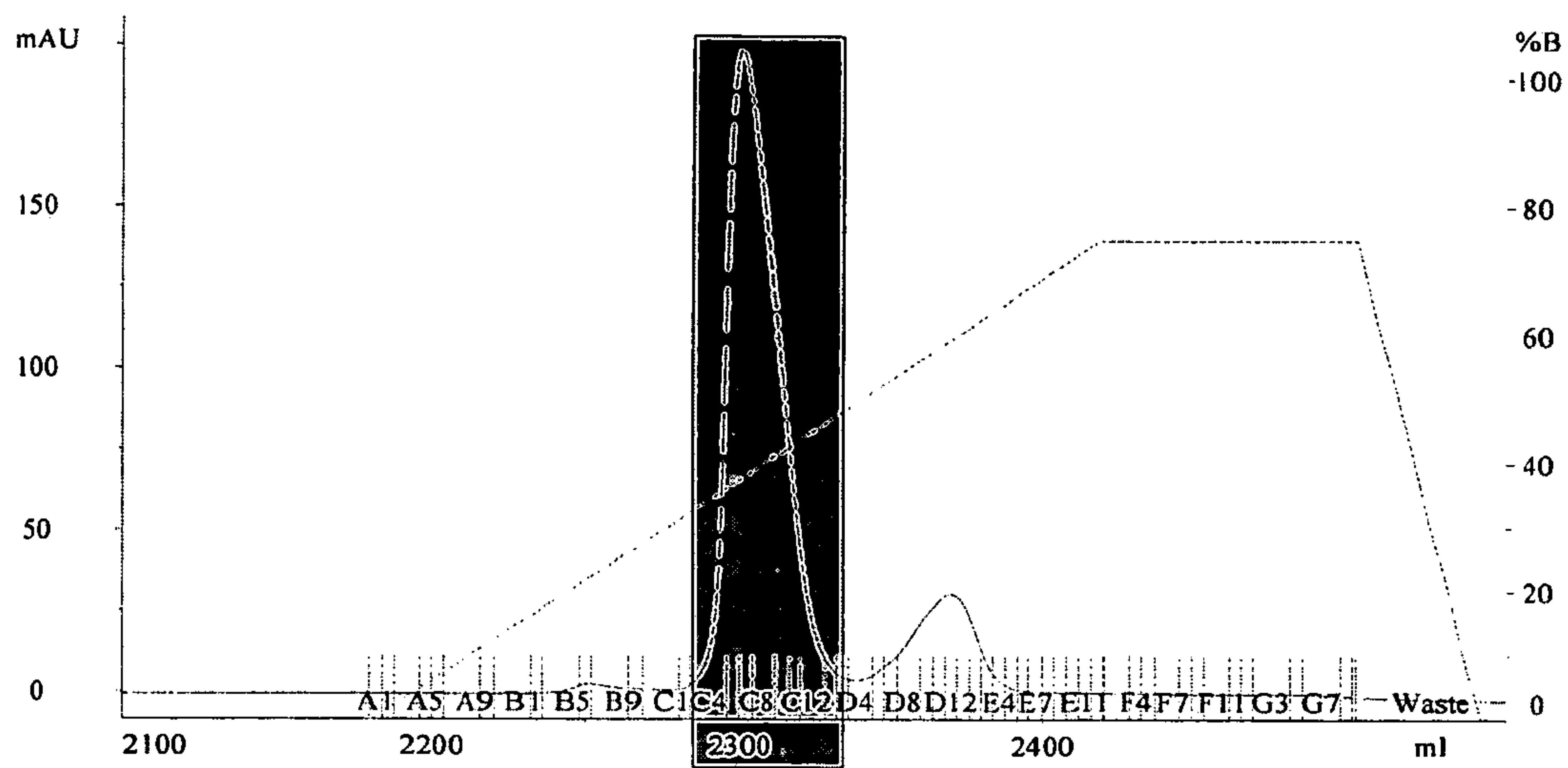


Figure INS1.3

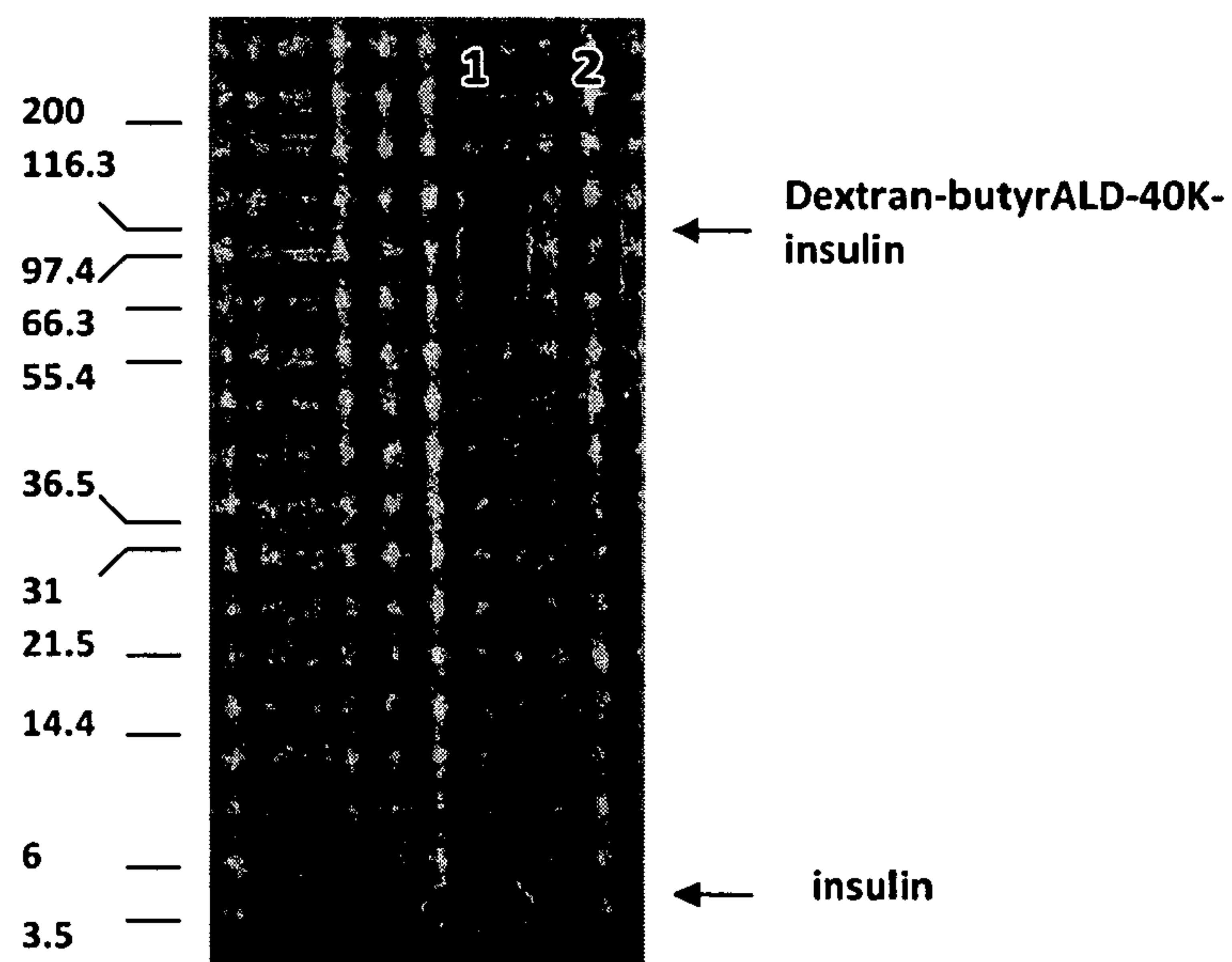


Figure INS1.4

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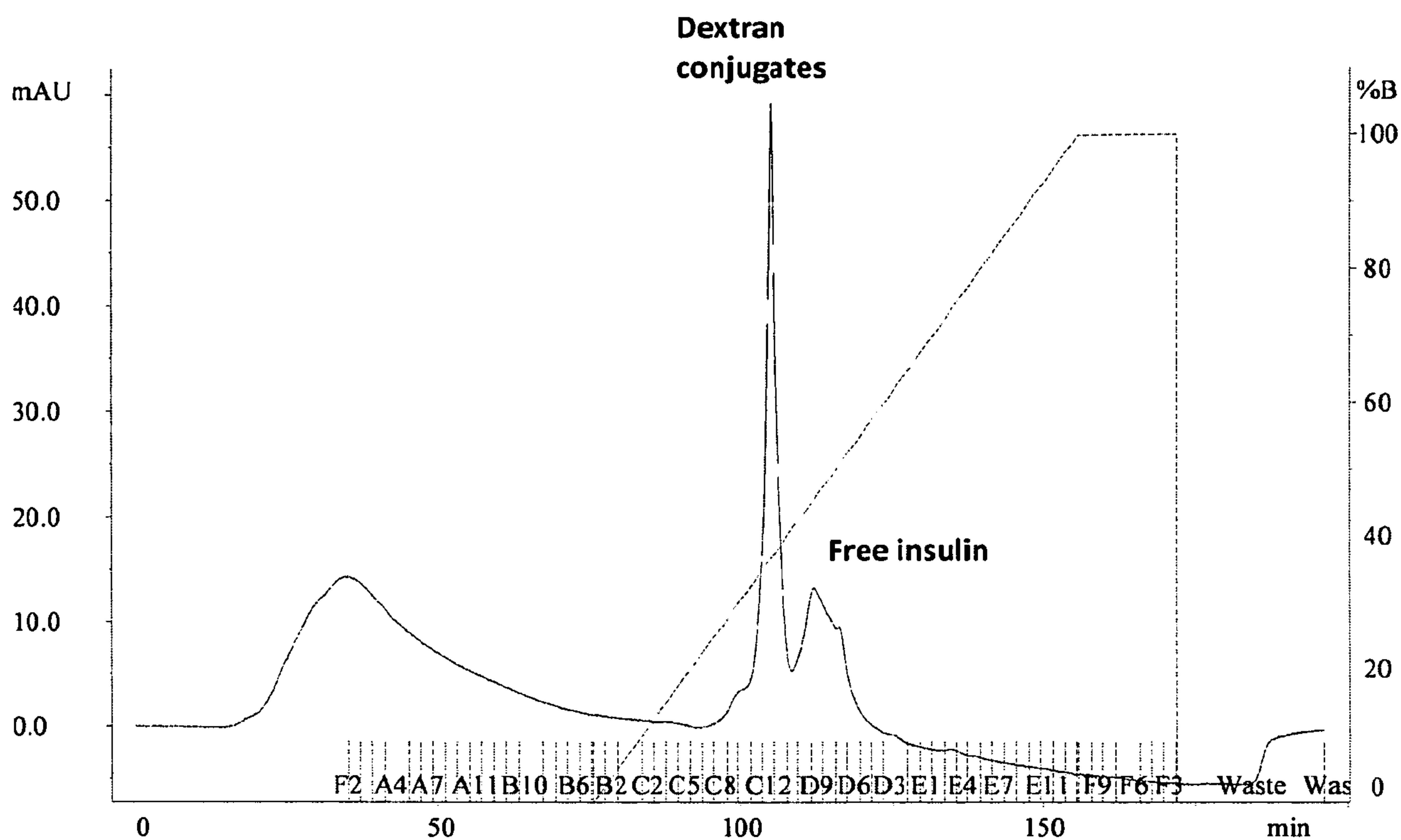


Figure INS1.5

**Competition binding assay
CHO-hIR (Clone 4.1)
02Sep09**

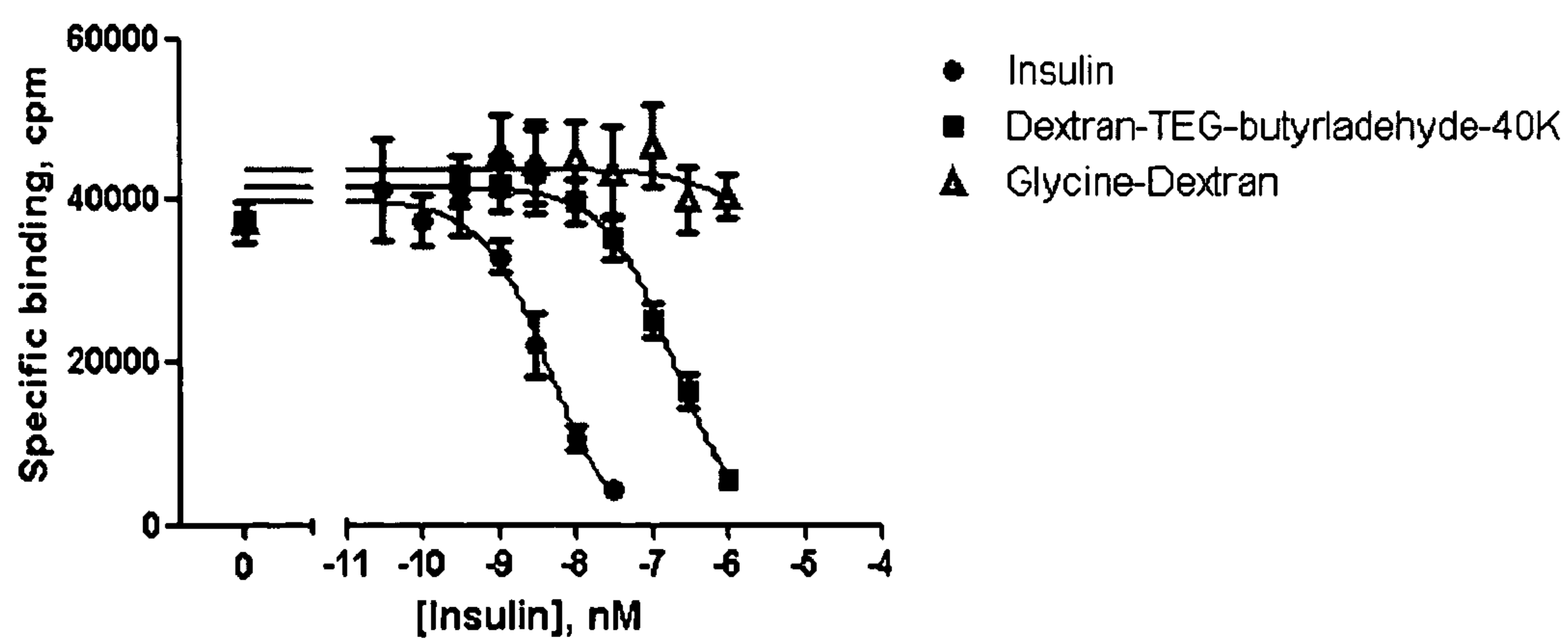


Figure INS2.1

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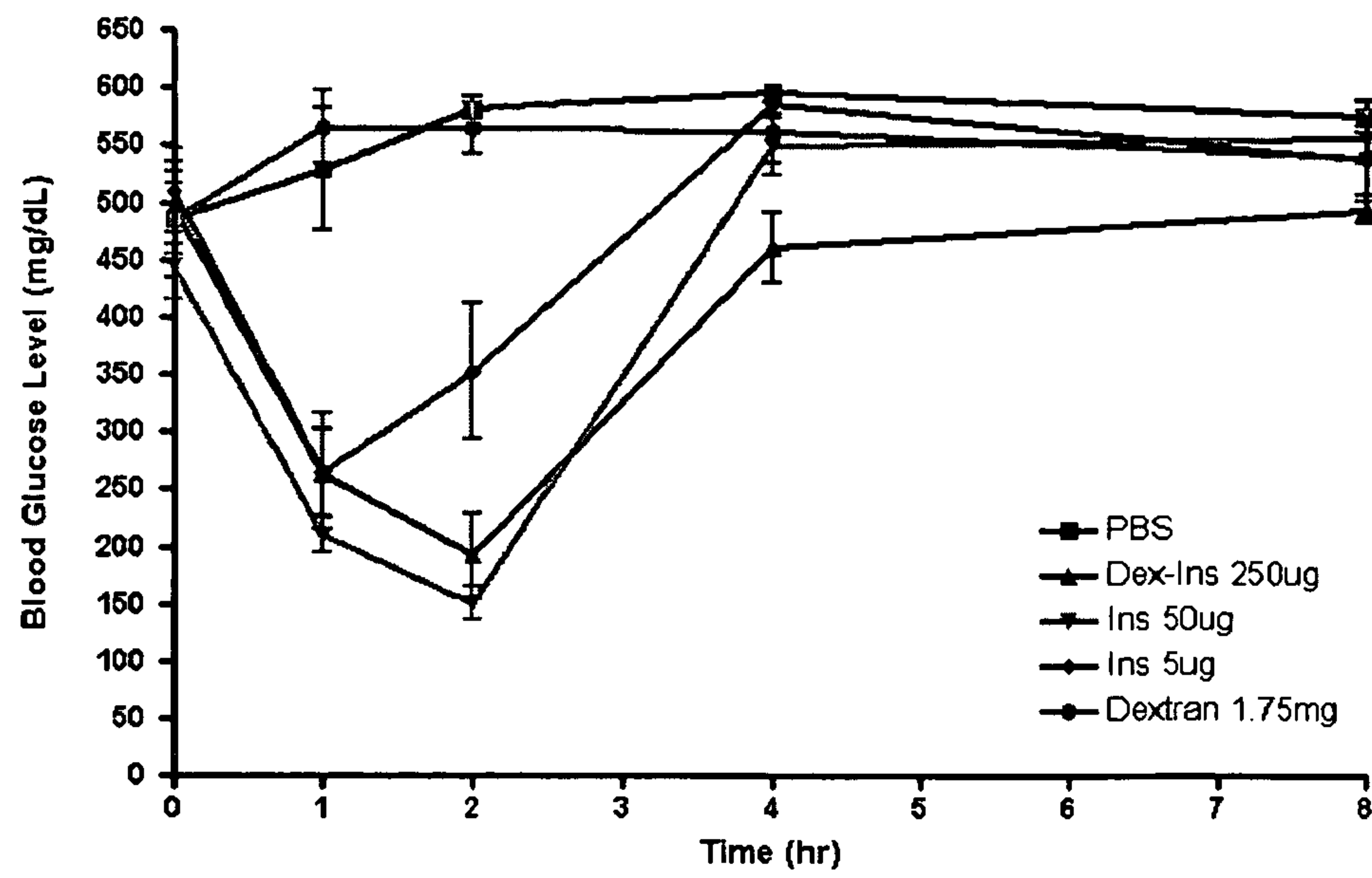


Figure INS3.1