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(54) **Titre : METHODES ET SUBSTANCES POUR TRAITER LE DIABETE OU LA STEATOSE HEPATIQUE**
(54) **Title: METHODS AND MATERIALS FOR TREATING DIABETES OR LIVER STEATOSIS**

(57) **Abrégé/Abstract:**

This document provides methods and materials for treating diabetes and/or liver steatosis. For example, methods for using compositions containing a potato polysaccharide preparation to reduce one or more symptoms of diabetes or liver steatosis are provided. In some cases, a composition containing a potato polysaccharide preparation provided herein can be used to treat fatty liver disease.



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(54) Title: METHODS AND MATERIALS FOR TREATING DIABETES OR LIVER STEATOSIS

(57) Abstract: This document provides methods and materials for treating diabetes and/or liver steatosis. For example, methods for using compositions containing a potato polysaccharide preparation to reduce one or more symptoms of diabetes or liver steatosis are provided. In some cases, a composition containing a potato polysaccharide preparation provided herein can be used to treat fatty liver disease.

METHODS AND MATERIALS FOR TREATING DIABETES OR LIVER STEATOSIS

BACKGROUND

5 1. *Technical Field*

 This document relates to methods and materials for treating diabetes and/or liver steatosis. For example, this document relates to using compositions containing a potato polysaccharide preparation to reduce one or more symptoms of diabetes or liver steatosis. In some cases, this document relates to using compositions containing
10 a potato polysaccharide preparation to reduce triglyceride levels, to reduce serum glucose levels, to reduce water consumption, to reduce urine production, to reduce kidney weight, to reduce liver weight, and/or to increase abdominal fat.

2. *Background Information*

 Potatoes are starchy, edible tubers obtained from potato plants and form an
15 integral part of much of the world's food supply. In fact, potatoes are the fourth largest food crop in the world. The main potato species worldwide is *Solanum tuberosum*.

SUMMARY

20 This document provides methods and materials for treating diabetes and/or liver steatosis. For example, this document provides methods for using compositions containing a potato polysaccharide preparation to reduce one or more symptoms of diabetes or liver steatosis. In some cases, a composition containing a potato polysaccharide preparation provided herein can be used to reduce triglyceride levels,
25 to reduce serum glucose levels, to reduce water consumption, to reduce urine production, to reduce kidney weight, to reduce liver weight, and/or to increase abdominal fat. In some cases, a composition containing a potato polysaccharide preparation provided herein can be used to treat fatty liver disease.

 Having the ability to use a composition containing a potato polysaccharide
30 preparation described herein to reduce one or more symptoms of diabetes or liver steatosis can provide clinicians and patients with an effective treatment regime for these conditions.

This document also provides compositions (e.g., nutritional supplement compositions) that contain a potato polysaccharide preparation. For example, this document provides nutritional supplement compositions containing a potato polysaccharide preparation, methods for obtaining potato polysaccharide preparations, methods for making nutritional supplement compositions containing a potato polysaccharide preparation, and methods for increasing or decreasing expression of polypeptides involved with mitochondria activity or function.

In some cases, the compositions provided herein (e.g., nutritional supplement compositions and potato polysaccharide preparations provided herein) can be used to increase or decrease expression of polypeptides involved with mitochondria activity or function. For example, a composition containing a potato polysaccharide preparation provided herein or a potato polysaccharide preparation provided herein can be used to increase expression of a transcription factor A, mitochondrial polypeptide (a TFAM polypeptide), an ATP synthase, H⁺ transporting, mitochondrial F1 complex, alpha subunit 1 polypeptide (an ATP5A1 polypeptide), a pyruvate dehydrogenase (lipoamide) alpha 1 polypeptide (a PDHA1 polypeptide), a pyruvate dehydrogenase (lipoamide) alpha 2 polypeptide (a PDHA2 polypeptide), a thimet oligopeptidase 1 polypeptide (a THOP1 polypeptide), or a combination thereof. In some cases, a composition containing a potato polysaccharide preparation provided herein or a potato polysaccharide preparation provided herein can be used to decrease expression of a forkhead box O1 polypeptide (a FOXO1A polypeptide), a nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 polypeptide (a NFKB1 polypeptide), a pyruvate dehydrogenase kinase, isozyme 2 polypeptide (a PDK2 polypeptide), a pyruvate dehydrogenase kinase, isozyme 4 polypeptide (a PDK4 polypeptide), a 3-hydroxy-3-methylglutaryl-CoA reductase polypeptide (a HMGCR polypeptide), or a combination thereof. In some case, a composition containing a potato polysaccharide preparation provided herein or a potato polysaccharide preparation provided herein can be used to increase one or more polypeptides (e.g., one or more of a TFAM polypeptide, an ATP5A1 polypeptide, a PDHA1 polypeptide, a PDHA2 polypeptide, or a THOP1 polypeptide) and decrease one or more polypeptides (e.g., one or more of a FOXO1A polypeptide, a NFKB1 polypeptide, a PDK2 polypeptide, a PDK4 polypeptide, or a HMGCR polypeptide).

In some cases, a composition provided herein (e.g., a nutritional supplement composition or potato polysaccharide preparation provided herein) can be used to

increase or decrease expression of polypeptides involved with diabetes or liver steatosis. For example, a composition provided herein (e.g., a nutritional supplement composition containing a potato polysaccharide preparation provided herein or a potato polysaccharide preparation provided herein) can be used to increase expression

5 of a lipase, hormone-sensitive polypeptide (an LIPE polypeptide) in adipocytes, to increase expression of a phosphoenolpyruvate carboxykinase 2 (mitochondrial) polypeptide (a PCK2 polypeptide), to increase expression of a monoacylglycerol O-acyltransferase 1 polypeptide (an MOGAT1 polypeptide), to increase expression of a peroxisome proliferator-activated receptor gamma, coactivator 1 alpha polypeptide (a

10 PPARGC1a polypeptide), to increase expression of a peroxisome proliferator-activated receptor gamma, coactivator 1 beta polypeptide (a PPARGC1b polypeptide), to increase expression of a superoxide dismutase 2, mitochondrial polypeptide (an SOD2 polypeptide), to increase expression of a nuclear receptor subfamily 4, group A, member 1 polypeptide (an NR4A1 polypeptide) in adipocytes,

15 to increase expression of an acetyl-CoA acetyltransferase 2 polypeptide (an ACAT2 polypeptide), to increase expression of a 3-hydroxy-3-methylglutaryl-CoA reductase polypeptide (an HMGCR polypeptide) in muscle cells, or a combination thereof. In some cases, a composition provided herein (e.g., a nutritional supplement composition or potato polysaccharide preparation provided herein) can be used to decrease

20 expression of a 1-acylglycerol-3-phosphate O-acyltransferase 1 polypeptide (an AGPAT1 polypeptide), to decrease expression of an oxidized low density lipoprotein (lectin-like) receptor 1 polypeptide (an OLR1 polypeptide), to decrease expression of a branched chain amino-acid transaminase 2, mitochondrial polypeptide (a BCAT2 polypeptide), to decrease expression of a nuclear factor of kappa light polypeptide

25 gene enhancer in B-cells 1 polypeptide (an NFKB1 polypeptide), to decrease expression of a SH2B adaptor protein 1 polypeptide (an SH2B1 polypeptide), to decrease expression of a lipoprotein lipase polypeptide (an LPL polypeptide), to decrease expression of a 3-hydroxy-3-methylglutaryl-CoA reductase polypeptide (an HMGCR polypeptide) in adipocytes, to decrease expression of a lipase, hormone-

30 sensitive polypeptide (an LIPE polypeptide) in muscle cells, to decrease expression of a nuclear receptor subfamily 4, group A, member 1 polypeptide (an NR4A1 polypeptide) in muscle cells, to decrease expression of a phosphatase and tensin homolog polypeptide (a PTEN polypeptide), to decrease expression of a caspase 8,

apoptosis-related cysteine peptidase polypeptide (a CASP8 polypeptide), or a combination thereof.

In some cases, a composition provided herein (e.g., a nutritional supplement composition or potato polysaccharide preparation provided herein) can be used to increase one or more polypeptides (e.g., one or more of an LIPE polypeptide (in adipocytes), a PCK2 polypeptide, an MOGAT1 polypeptide, a PPARGC1a polypeptide, a PPARGC1b polypeptide, an SOD2 polypeptide, an NR4A1 polypeptide (in adipocytes), an ACAT2 polypeptide, or an HMGCR polypeptide (in muscle cells)) and decrease one or more polypeptides (e.g., one or more of an AGPAT1 polypeptide, an OLR1 polypeptide, a BCAT2 polypeptide, an NFKB1 polypeptide, an SH2B1 polypeptide, an LPL polypeptide, an HMGCR polypeptide (in adipocytes), an LIPE polypeptide (in muscle cells), an NR4A1 polypeptide (in muscle cells), a PTEN polypeptide, or a CASP8 polypeptide).

In general, one aspect of this document features a method for treating diabetes. The method comprises, or consists essentially of, (a) identifying a mammal with diabetes, and (b) administering to the mammal a composition comprising a potato polysaccharide preparation obtained from raw potatoes, wherein the severity of a symptom of the diabetes is reduced. The composition can comprise the potato polysaccharide preparation in an amount that results in between 0.05 mg and 50 mg of the potato polysaccharide component of the potato polysaccharide preparation being administered to the mammal per kg of body weight of the mammal. The composition can comprise between 1 mg and 100 mg of the potato polysaccharide preparation. The composition can comprise between 6 mg and 20 mg of the potato polysaccharide preparation. The composition can comprise between 1 mg and 100 mg of the potato polysaccharide component of the potato polysaccharide preparation. The composition can comprise between 6 mg and 20 mg of the potato polysaccharide component of the potato polysaccharide preparation. The composition can be in the form of a tablet. The composition can comprise alpha lipoic acid. The composition can comprise alpha tocopherol. The potato polysaccharide preparation can be in an amount that results in between 0.075 mg and 0.5 mg of the potato polysaccharide component of the potato polysaccharide preparation being administered to the mammal per kg of body weight of the mammal. At least about 80 percent of the potato polysaccharide preparation can be potato polysaccharide. At least about 90 percent of the potato polysaccharide preparation can be potato polysaccharide. At least about 95 percent of

the potato polysaccharide preparation can be potato polysaccharide. The mammal can be a human.

In another aspect, this document features a method for treating a fatty liver disease. The method comprises, or consists essentially of, (a) identifying a mammal
5 with a fatty liver disease, and (b) administering to the mammal a composition comprising a potato polysaccharide preparation obtained from raw potatoes, wherein the severity of a symptom of the fatty liver disease is reduced. The composition can comprise the potato polysaccharide preparation in an amount that results in between 0.05 mg and 50 mg of the potato polysaccharide component of the potato
10 polysaccharide preparation being administered to the mammal per kg of body weight of the mammal. The composition can comprise between 1 mg and 100 mg of the potato polysaccharide preparation. The composition can comprise between 6 mg and 20 mg of the potato polysaccharide preparation. The composition can comprise between 1 mg and 100 mg of the potato polysaccharide component of the potato
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20 0.5 mg of the potato polysaccharide component of the potato polysaccharide preparation being administered to the mammal per kg of body weight of the mammal. At least about 80 percent of the potato polysaccharide preparation can be potato polysaccharide. At least about 90 percent of the potato polysaccharide preparation can be potato polysaccharide. At least about 95 percent of the potato polysaccharide
25 preparation can be potato polysaccharide. The mammal can be a human.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present
30 invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

5 Figure 1 is an HPLC chromatogram of a 10% ACN extract of raw potato (Russet Burbank).

Figure 2 is an HPLC chromatogram of collected and re-purified 3.5 minute peak material from a 10% ACN extract of raw potato shown in Figure 1.

10 Figure 3 is a representative real time PCR amplification plot for TFAM expression.

Figure 4 is an LC/MS trace of 3.5 minute HPLC peak material.

Figure 5 is a full NMR spectrum of 3.5 minute HPLC peak material.

Figure 6 is an expanded NMR spectrum of 3.5 minute HPLC peak material.

15 Figure 7 is a total ion chromatogram of derivatized carbohydrate fragments of 3.5 minute HPLC peak material obtained from raw potato Russet Burbank).

Figure 8 is a fragmentation pattern of diacetamide. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

20 Figure 9 is a fragmentation pattern of 3-acetoxy pyridine. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 10 is a fragmentation pattern of 3,4-furan dimethanol, diacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

25 Figure 11 is a fragmentation pattern of 1,2,3-propanetriol diacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

30 Figure 12 is a fragmentation pattern of imidazole, 2-acetamino-5-methyl. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 13 is a fragmentation pattern of 6,7-dihydro-5H-pyrrol[2,1,c][1,2,4] triazole-3-carboxylic acid. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 14 is a fragmentation pattern of acetic acid, 1-(2-methyltetrazol-5-yl) ethenyl ester. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

5 Figure 15 is a fragmentation pattern of 1,2,3,4-butanetriol, tetraacetate (isomer 1). The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

10 Figure 16 is a fragmentation pattern of 1,2,3,4-butanetriol, tetraacetate (isomer 2). The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

15 Figure 17 is a fragmentation pattern of pentaerythritol tetraacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 18 is a fragmentation pattern of 1,2,3,4,5-penta-o-acetyl-D-xylitol (isomer 1). The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

20 Figure 19 is a fragmentation pattern of 1,2,3,4,5-penta-o-acetyl-D-xylitol (isomer 2). The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

25 Figure 20 is a fragmentation pattern of 3,5-diacetoxy benzyl alcohol. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

30 Figure 21 is a fragmentation pattern of β -D-galactopyranose, pentaacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 22 is a fragmentation pattern of D-mannitol hexaacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 23 is a fragmentation pattern of galacticol, hexaacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 24 is a fragmentation pattern of cyclohexane carboxylic acid, 1,2,4,5-tetrakis(acetoxy), (1 α ,3 α ,4 α ,5 β)-(-). The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 25 is a fragmentation pattern of muco-inositol, hexaacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 26 is a fragmentation pattern of D-glucitol-hexaacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 27 is a fragmentation pattern of myo-inositol, hexaacetate. The peak fragmentation pattern is in the top panel, the compound library fragmentation match is in the bottom panel, and an overlay of the two is in the center panel.

Figure 28 is an HPLC chromatogram of a 10% ACN extract of raw Organic Yellow potato.

Figure 29 is an HPLC chromatogram of a 10% ACN extract of raw Purple potato.

Figure 30 is an HPLC chromatogram of a 10% ACN extract of raw Idaho Russet potato.

Figure 31 is an HPLC chromatogram of a 10% ACN extract of raw Yukon Gold potato.

Figure 32 is an HPLC chromatogram of a 10% ACN extract of raw sweet potato.

Figure 33 is an HPLC chromatogram of a 10% ACN extract of boiled Purple potato.

Figure 34 is an HPLC chromatogram of two pooled fraction collections from Idaho Russet potatoes.

Figure 35 is an HPLC chromatogram of fractions collections from 3 g of purple potatoes.

Figure 36 is an HPLC chromatogram of media collected from cells exposed to a potato polysaccharide preparation for 4 hours.

Figure 37 is a schematic of the study design used to test the use of a potato polysaccharide preparation to reduce diabetes and obesity parameters within living mammals.

Figure 38 is a graph plotting mean body weights for ZDF rats (Fa/Fa) and lean
5 ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 39 is a graph plotting mean triglyceride levels for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 40 is a graph plotting mean LDL levels for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

10 Figure 41 is a graph plotting mean serum glucose levels for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 42 is a graph plotting mean water consumption levels for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide
15 preparation (SNY).

Figure 43 is a graph plotting mean urine volumes for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 44 is a graph plotting mean blood glucose levels for fasted ZDF rats (Fa/Fa) and fasted, lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide
20 preparation (SNY).

Figure 45 is a graph plotting mean abdominal fat weight to body weight ratios for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 46 is a graph plotting mean kidney weight to body weight ratios for
25 ZDF rats (Fa/Fa) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 47 is a graph plotting mean liver weight to body weight ratios for ZDF rats (Fa/Fa) and lean ZDF rats (+/?) treated with vehicle or a potato polysaccharide preparation (SNY).

Figure 48 is a real time PCR amplification plot for TFAM demonstrating
30 differences in threshold cycle numbers between potato polysaccharide preparation-treated ZDF rats and untreated control ZDF rats. The lower cycle number for the treated rats equates to a higher gene expression.

Figure 49 is a graph plotting the fold change in expression of TFAM in treated versus untreated rats.

DETAILED DESCRIPTION

This document provides methods and materials for treating diabetes and/or liver steatosis. For example, this document provides methods for using compositions
5 containing a potato polysaccharide preparation to reduce one or more symptoms of diabetes or liver steatosis. In some cases, a composition containing a potato polysaccharide preparation provided herein can be used to reduce triglyceride levels, to reduce serum glucose levels, to reduce water consumption, to reduce urine
10 production, to reduce kidney weight, to reduce liver weight, and/or to increase abdominal fat. In some cases, a composition containing a potato polysaccharide preparation provided herein can be used to treat fatty liver disease.

As described herein, a composition containing a potato polysaccharide preparation provided herein (e.g., a nutritional supplement composition provided herein) can be administered to any appropriate mammal to reduce one or more
15 symptoms of diabetes, liver steatosis, and/or fatty liver disease. For example, a composition containing a potato polysaccharide preparation provided herein can be administered to a rat, mouse, dog, cat, horse, cow, goat, pig, chicken, duck, rabbit, sheep, monkey, or human to reduce one or more symptoms of diabetes and/or liver steatosis. Examples of diabetes symptoms include, without limitation, excessive fluid
20 intake, frequent urination, elevated blood glucose, elevated urinary glucose, ketosis, and vascular degeneration. Examples of liver steatosis symptoms include, without limitation, hepatomegaly (enlarged liver), steatohepatitis, and malnutrition. Examples of fatty liver disease symptoms include, without limitation, cirrhosis, jaundice, and esophageal bleeding.

25 Any appropriate route of administration (e.g., oral or parenteral administration) can be used to administer a composition containing a potato polysaccharide preparation provided herein (e.g., a nutritional supplement composition provided herein) to a mammal. For example, a composition containing a potato polysaccharide preparation provided herein can be administered orally.

30 A composition provided herein (e.g., a nutritional supplement composition) can include one or more potato polysaccharide preparations. A potato polysaccharide preparation can be a preparation that is obtained from a water extract of potato and that contains polysaccharide material having the ability to be eluted from a C18 cartridge (e.g., a Sep-Pak Plus C-18 cartridge) with 10% acetonitrile. In some cases, a

potato polysaccharide preparation can be a preparation that is obtained from potato and that contains polysaccharide material having HPLC characteristics of that of the peak eluted at 3.5 minutes as described in Example 1 (see, also, Figures 1, 2, and 28-34). In some cases, a polysaccharide of a potato polysaccharide preparation provided
5 herein can be a polar, water-soluble polysaccharide. In some cases, a polysaccharide of a potato polysaccharide preparation provided herein can be a highly substituted complex xyloglucan material.

In some cases, a potato polysaccharide preparation can be a preparation that is obtained from potato and that contains polysaccharide material that, when derivatized,
10 results in at least the following acylated carbohydrates as assessed using GC/MS: (a) myo-inositol (set to 1X to serve as an internal standard), (b) glucose at about 40X to about 60X the myo-inositol content (e.g., glucose at about 50X the myo-inositol content), (c) xylose at about 10X to about 20X the myo-inositol content (e.g., xylose at about 15X the myo-inositol content), (d) mannose at about 5X to about 15X the
15 myo-inositol content (e.g., mannose at about 10X the myo-inositol content), and (e) galactose at about 3X to about 7X the myo-inositol content (e.g., galactose at about 5X the myo-inositol content). The derivatization procedure can include forming a dry residue of the polysaccharide material that is then hydrolyzed using trifluoroacetic acid. The resulting material is then reduced using sodium borohydride, and after
20 borate removal, the end product is acylated using acetic anhydride and pyridine. The end products of the reaction are then injected directly on GC/MS to identify the acylated carbohydrates.

In some cases, a potato polysaccharide preparation can be a preparation that is obtained from potato and that contains polysaccharide material that, when derivatized
25 and assessed using GC/MS, results in at least four major components (3,4-furan dimethanol, diacetate; 1,2,3,4,5-penta-o-acetyl-D-xylitol (isomer 1); 3,5-diacetoxy-benzyl alcohol; and D-glucitol-hexaacetate). See, e.g., Example 1. In some cases, a potato polysaccharide preparation can be a preparation that is obtained from potato and that contains polysaccharide material that, when derivatized and assessed using
30 GC/MS, results in the compounds listed in Table 3 or results in the profile shown in Figure 7.

In some cases, a potato polysaccharide preparation provided herein can be a substantially pure potato polysaccharide preparation. Typically, a substantially pure potato polysaccharide preparation is a preparation that contains a single peak of

material (e.g., a single peak of polysaccharide material) when assessed using, for example, HPLC (see, e.g., Figures 2 and 34). In some cases, greater than 60, 70, 75, 80, 85, 90, 95, or 99 percent of a potato polysaccharide preparation provided herein can be polysaccharide material obtained from a potato.

5 Any appropriate potato species or variety can be used to obtain a potato polysaccharide preparation provided herein. For example, *Solanum tuberosum*, *Ipomoea batatas*, *S. acaule*, *S. bukasovii*, *S. leptophyes*, *S. megistacrolobum*, *S. commersonii*, or *S. infundibuliforme* can be used to obtain a potato polysaccharide preparation provided herein. In some cases, potato varieties of *S. tuberosum* such as

10 Organic Yellow, Purple or blue varieties, Cream of the Crop, Adirondack Blue, Adirondack Red, Agata, Almond, Andes Gold, Andes Sun, Apline, Alturas, Amandine, Annabelle, Anya, Arran Victory, Atlantic, Avalanche, Bamberg, Bannock Russet, Belle de Fontenay, BF-15, Bildtstar, Bintje, Blazer Russet, Blue Congo, Bonnotte, British Queens, Cabritas, Camota, Canela Russet, Cara, Carola, Chelina,

15 Chiloé, Cielo, Clavela Blanca, Désirée, Estima, Fianna, Fingerling, Flava, German Butterball, Golden Wonder, Goldrush, Home Guard, Innovator, Irish Cobbler, Jersey Royal, Kennebec, Kerr's Pink, Kestrel, Keuka Gold, King Edward, Kipfler, Lady Balfour, Langlade, Linda, Marcy, Marfona, Maris Piper, Marquis, Megachip, Monalisa, Nicola, Pachacoña, Pike, Pink Eye, Pink Fir Apple, Primura, Ranger

20 Russet, Ratte, Record, Red LaSoda, Red Norland, Red Pontiac, Rooster, Russet Burbank, Russet Norkotah, Selma, Shepody, Sieglinde, Silverton Russet, Sirco, Snowden, Spunta, Up to date, Stobrawa, Superior, Vivaldi, Vitelotte, Yellow Finn, or Yukon Gold can be used to obtain a potato polysaccharide preparation provided herein.

25 Any appropriate method can be used to obtain a potato polysaccharide preparation provided herein. For example, raw potato material can be homogenized (e.g., homogenized with a Polytron homogenizer) in water and maintained at room temperature for a period of time (e.g., about 1 hour) with occasional shaking. The homogenate can be centrifuged (e.g., centrifuged at 4000 g for 10 minutes) to remove

30 any larger solid material. The resulting supernatant can be loaded onto a Solid Phase Extraction cartridge (e.g., a C18 cartridge such as a Sep-Pak Plus C-18 cartridge), and the polysaccharide material eluted with 10 percent acetonitrile. Once eluted, the polysaccharide material can be dried and stored (e.g., stored at about 4°C).

This document also provides nutritional supplement compositions containing one or more potato polysaccharide preparations provided herein. For example, a potato polysaccharide preparation provided herein obtained from Idaho Russet potatoes can be formulated into a nutritional supplement composition.

5 Any appropriate dose of a potato polysaccharide preparation provided herein can be used to formulate a composition provided herein (e.g., a nutritional supplement composition or potato polysaccharide preparation provided herein). For example, a potato polysaccharide preparation provided herein can be used to formulate a composition for treating diabetes and/or liver steatosis such that the composition
10 contains between about 1 mg and about 750 mg (e.g., between about 1 mg and about 500 mg, between about 1 mg and about 250 mg, between about 5 mg and about 40 mg, between about 5 mg and about 30 mg, between about 5 mg and about 20 mg, between about 6 mg and about 50 mg, between about 6 mg and about 20 mg, between about 10 mg and about 25 mg, or between about 15 mg and about 20 mg) of the
15 potato polysaccharide component of the potato polysaccharide preparation. In some cases, a composition (e.g., a nutritional supplement composition) can be formulated to deliver about 0.05 mg of the potato polysaccharide component per kg of body weight to about 0.5 mg of the potato polysaccharide component per kg of body weight to a mammal (e.g., a human) per day. For example, a nutritional supplement composition
20 can be formulated into a single oral composition that a human can swallow once a day to provide between about 0.05 mg of the potato polysaccharide component per kg of body weight to about 0.5 mg of the potato polysaccharide component per kg of body weight.

Any appropriate method can be used to formulate a composition provided
25 herein (e.g., a nutritional supplement composition or potato polysaccharide preparation provided herein). For example, common formulation mixing and preparation techniques can be used to make a composition (e.g., a nutritional supplement composition) having the components described herein. In addition, a composition provided herein (e.g., a nutritional supplement composition or potato
30 polysaccharide preparation provided herein) can be in any form. For example, a composition provided herein (e.g., a nutritional supplement composition or potato polysaccharide preparation provided herein) can be formulated into a pill, capsule, tablet, gelcap, nutritional shake, nutritional bar, rectal suppository, sublingual suppository, nasal spray, inhalant, or injectable ampule. In some cases, a composition

provided herein (e.g., a nutritional supplement composition) can include one or more potato polysaccharide preparations provided herein alone or in combination with other ingredients including, without limitation, gelatin, cellulose, starch, sugar, bentonite, lactic acid, mannitol, alpha lipoic acid, alpha tocopherol, L-ascorbate, or combinations thereof.

This document also provides methods for increasing or decreasing expression of polypeptides involved with mitochondria activity or function. For example, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase or decrease expression of polypeptides involved with mitochondria activity or function. In some cases, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase expression of a TFAM polypeptide, an ATP5A1 polypeptide, a PDHA1 polypeptide, a PDHA2 polypeptide, a THOP1 polypeptide, or a combination thereof. In some cases, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to decrease expression of a FOXO1A polypeptide, a NFKB1 polypeptide, a PDK2 polypeptide, a PDK4 polypeptide, a HMGCR polypeptide, or a combination thereof. In some case, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase one or more polypeptides (e.g., one or more of a TFAM polypeptide, an ATP5A1 polypeptide, a PDHA1 polypeptide, a PDHA2 polypeptide, or a THOP1 polypeptide) and decrease one or more polypeptides (e.g., one or more of a FOXO1A polypeptide, a NFKB1 polypeptide, a PDK2 polypeptide, a PDK4 polypeptide, or a HMGCR polypeptide).

In humans, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase one or more human polypeptides (e.g., one or more of a human TFAM polypeptide, a human ATP5A1 polypeptide, a human PDHA1 polypeptide, a human PDHA2 polypeptide, a human THOP1 polypeptide, a human LIPE polypeptide (in adipocytes), a human PCK2 polypeptide, a human MOGAT1 polypeptide, a human PPARGC1a polypeptide, a vPPARGC1b polypeptide, an human SOD2 polypeptide, a human NR4A1 polypeptide (in adipocytes), a human ACAT2 polypeptide, or a human HMGCR polypeptide (in muscle cells)) and/or decrease one or more human polypeptides (e.g., one or more of a human FOXO1A polypeptide, a human NFKB1

polypeptide, a human PDK2 polypeptide, a human PDK4 polypeptide, a human HMGCR polypeptide (in adipocytes), a human AGPAT1 polypeptide, a human OLR1 polypeptide, a human BCAT2 polypeptide, a human SH2B1 polypeptide, a human LPL polypeptide, a human HMGCR polypeptide (in adipocytes), a human LIPE polypeptide (in muscle cells), a human NR4A1 polypeptide (in muscle cells), a human PTEN polypeptide, or a human CASP8 polypeptide).

A human TFAM polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG28581.1 (GI No. 47115243) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_003201.1 (GI No. 4507400). A human ATP5A1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH08028.2 (GI No. 34782901) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001001937.1 (GI No. 50345983). A human PDHA1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. ABQ58815.1 (GI No. 148300624) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001173454.1 (GI No. 291084741). A human PDHA2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH94760.1 (GI No. 66267554) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_005390.4 (GI No. 134031963). A human THOP1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH00583.2 (GI No. 38014202) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_003249.3 (GI No. 34222291). A human LIPE polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH70041.1 (GI No. 47124456) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_005357.2 (GI No. 21328445). A human PCK2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG33194.1 (GI No. 48145943) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_004563.1 (GI No. 66346720). A human MOGAT1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_477513.2 (GI No. 148746191) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_058165.1 (GI No. 148746190). A human PPARGC1a polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_037393.1 (GI No. 7019499) and can be encoded by the nucleic acid sequence set

forth in GenBank[®] Accession No. NM_013261.2 (GI No. 116284374). A human
 PPARGC1b polypeptide can have the amino acid sequence set forth in GenBank[®]
 Accession No. AAI44252.1 (GI No. 219518198) and can be encoded by the nucleic
 acid sequence set forth in GenBank[®] Accession No. NM_133263.2 (GI No.
 5 289577087). A human SOD2 polypeptide can have the amino acid sequence set forth
 in GenBank[®] Accession No. AAH16934.1 (GI No. 16877367) and can be encoded by
 the nucleic acid sequence set forth in GenBank[®] Accession No. NM_000636.1 (GI
 No. 67782304). A human NR4A1 polypeptide can have the amino acid sequence set
 forth in GenBank[®] Accession No. CAG32985.1 (GI No. 48145525) and can be
 10 encoded by the nucleic acid sequence set forth in GenBank[®] Accession No.
 NM_173158.1 (GI No. 320202954). A human ACAT2 polypeptide can have the
 amino acid sequence set forth in GenBank[®] Accession No. AAH00408.1 (GI No.
 12653279) and can be encoded by the nucleic acid sequence set forth in GenBank[®]
 Accession No. NM_005891.1 (GI No. 148539871). A human FOXO1A polypeptide
 15 can have the amino acid sequence set forth in GenBank[®] Accession No. NP_002006.2
 (GI No. 9257222) and can be encoded by the nucleic acid sequence set forth in
 GenBank[®] Accession No. NM_002015.3 (GI No. 133930787). A human NFkB1
 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No.
 CAB94757.1 (GI No. 8574070) and can be encoded by the nucleic acid sequence set
 20 forth in GenBank[®] Accession No. NM_001165412.1 (GI No. 25955301). A human
 PDK2 polypeptide can have the amino acid sequence set forth in GenBank[®]
 Accession No. NP_002602.2 (GI No. 19923736) and can be encoded by the nucleic
 acid sequence set forth in GenBank[®] Accession No. NM_00211.4 (GI No.
 315630394). A human PDK4 polypeptide can have the amino acid sequence set forth
 25 in GenBank[®] Accession No. AAH40239.1 (GI No. 25955471) and can be encoded by
 the nucleic acid sequence set forth in GenBank[®] Accession No. NM_002612.2 (GI
 No. 94421466). A human HMGCR polypeptide can have the amino acid sequence set
 forth in GenBank[®] Accession No. AAH33692.1 (GI No. 21707182) and can be
 encoded by the nucleic acid sequence set forth in GenBank[®] Accession No.
 30 NM_000859.2 (GI No. 196049378). A human AGPAT1 polypeptide can have the
 amino acid sequence set forth in GenBank[®] Accession No. NP_116130.2 (GI No.
 15100175) and can be encoded by the nucleic acid sequence set forth in GenBank[®]
 Accession No. NM_006411.3 (GI No. 301336168). A human OLR1 polypeptide can
 have the amino acid sequence set forth in GenBank[®] Accession No. NP_002534.1 (GI

No. 4505501) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_002543.2 (GI No. 119392084). A human BCAT2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH04243.2 (GI No. 48257075) and can be encoded by the nucleic acid sequence set forth in

5 GenBank[®] Accession No. NM_001190.1 (GI No. 258614013). A human SH2B1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH10704.1 (GI No. 14715079) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001145797.1 (GI No. 224926829). A human LPL polypeptide can have the amino acid sequence set forth in GenBank[®] Accession

10 No. CAG33335.1 (GI No. 4814622) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_000237.1 (GI No. 145275217). A human HMGCR polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH33692.1 (GI No. 21707182) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001130996.1 (GI No.

15 196049379). A human PTEN polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAD13528.1 (GI No. 4240387) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_000314.2 (GI No. 110224474). A human CASP8 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH68050.1 (GI No. 45751586) and can be

20 encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001228.4 (GI No. 122056470).

In addition, this document provides methods for increasing expression of polypeptides involved in mitochondrial biogenesis linked to enhanced protein and nucleic acid biosynthesis. For example, a potato polysaccharide preparation provided

25 herein or a nutritional supplement composition provided herein can be used to increase expression of polypeptides involved with mitochondrial biogenesis linked to enhanced protein and nucleic acid biosynthesis. In some cases, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase expression of a Slc25a33 polypeptide, an

30 Tomm40 polypeptide, a Mrpl3 polypeptide, a Mrps18b polypeptide, a Mrps9 polypeptide, a Fars2 polypeptide, a Mrpl15 polypeptide, a Mrps23 polypeptide, a Mrps2 polypeptide, a Mrpl17 polypeptide, a TFAM polypeptide, or a combination thereof.

This document also provides methods for increasing expression of polypeptides involved in mitochondrial energy production. For example, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase expression of polypeptides involved with
 5 mitochondrial energy production. In some cases, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase expression of a Prodh polypeptide, an Slc25a1 polypeptide, a Hmgcl polypeptide, a Cps1 polypeptide, a Aldh4a1 polypeptide, a Mdh2 polypeptide, a Atp5b polypeptide, a Slc25a22 polypeptide, a Slc25a19 polypeptide, a Uqcrc2
 10 polypeptide, a Abcf2 polypeptide, or a combination thereof.

This document also provides methods for increasing or decreasing expression of polypeptides involved with lipogenesis, triglyceride assembly, and mitochondrial lipolysis. For example, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase or
 15 decrease expression of polypeptides involved with lipogenesis, triglyceride assembly, and mitochondrial lipolysis. In some cases, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase expression of an Acbd4 polypeptide, a Fads1 polypeptide, a Gnpat polypeptide, a Lypla1 polypeptide, a Cpt2 polypeptide, or a combination thereof. In
 20 some cases, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to decrease expression of a Pck2 polypeptide, an Agpat4 polypeptide, an Acaca polypeptide, or a combination thereof. In some case, a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein can be used to increase one or more
 25 polypeptides (e.g., one or more of an Acbd4 polypeptide, a Fads1 polypeptide, a Gnpat polypeptide, a Lypla1 polypeptide, a Cpt2 polypeptide) and decrease one or more polypeptides (e.g., one or more of a Pck2 polypeptide, an Agpat4 polypeptide, an Acaca polypeptide).

In humans, a potato polysaccharide preparation provided herein or a
 30 nutritional supplement composition provided herein can be used to increase one or more human polypeptides (e.g., one or more of a Slc25a33 polypeptide, an Tomm40 polypeptide, a Mrpl3 polypeptide, a Mrps18b polypeptide, a Mrps9 polypeptide, a Fars2 polypeptide, a Mrpl15 polypeptide, a Mrps23 polypeptide, a Mrps2 polypeptide, a Mrpl17 polypeptide, a TFAM polypeptide, a Prodh polypeptide, an

Slc25a1 polypeptide, a Hmgcl polypeptide, a Cps1 polypeptide, a Aldh4a1 polypeptide, a Mdh2 polypeptide, an Atp5b polypeptide, a Slc25a22 polypeptide, a Slc25a19 polypeptide, a Uqcrc2 polypeptide, an Abcf2 polypeptide, an Acbd4 polypeptide, a Fads1 polypeptide, a Gnpat polypeptide, a Lypla1 polypeptide, and a Cpt2 polypeptide (in liver cells)) and/or decrease one or more human polypeptides (e.g., one or more of a Pck2 polypeptide, an Agpat4 polypeptide, and an Acaca polypeptide (in liver cells)).

A human Slc25a33 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. XP_005263560.1 (GI No. 530360655) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. XM_005263503.1 (GI No. 530360654). A human Tomm40 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH47528.1 (GI No. 28839408) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001128916.1 (GI No. 193083119). A human Mrpl3 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG33001.1 (GI No. 48145557) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_007208.3 (GI No. 312147300). A human Mrps18b polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. BAD13700.1 (GI No. 46091143) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_014046.3 (GI No. 186928836). A human Mrps9 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH47784.1 (GI No. 29126836) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_182640.2 (GI No. 186910309). A human Fars2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_006558.1 (GI No. 5729820) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_006567.3 (GI No. 126513133). A human Mrpl15 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG38562.1 (GI No. 49065488) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_014175.3 (GI No. 169403971). A human Mrps23 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_057154.2 (GI No. 16554604) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_016070.3 (GI No. 312222785). A human Mrps2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH04905.2 (GI No. 33872889).

and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_016034.4 (GI No. 389565494). A human Mrpl17 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG33458.1 (GI No. 48146471) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_022061.3 (GI No. 169403966). A human Prodh polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAD24775.1 (GI No. 4581877) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_016335.4 (GI No. 304766735). A human Slc25a1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_005975.1 (GI No. 21389315) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_005984.3 (GI No. 374713106). A human Hmgcl polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG33165.1 (GI No. 48145885) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_000191.2 (GI No. 62198231). A human Cps1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH20695.1 (GI No. 116283350) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001122633.2 (GI No. 327532712). A human Aldh4a1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. ACN89883.1 (GI No. 225421341) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. FJ462711.1 (GI No. 225421340). A human Mdh2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG38785.1 (GI No. 49168580) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. CR536548.1 (GI No. 49168579). A human Atp5b polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. ABD77240.1 (GI No. 89574029) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001686.3 (GI No. 50345985). A human Slc25a22 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_001177990.1 (GI No. 300796991) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001191060.1 (GI No. 300796969). A human Slc25a19 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_001119594.1 (GI No. 186928860) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001126121.1 (GI No. 186928857). A human Uqcrc2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH00484.1

(GI No. 12653427) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_003366.2 (GI No. 50592987). A human Abcf2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_009120.1 (GI No. 27881506) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_007189.2 (GI No. 525345247). A human Acbd4 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH41143.1 (GI No. 26996542) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_001135704.1 (GI No. 209364588). A human Fads1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AFL91689.1 (GI No. 390432195) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. AK314199.1 (GI No. 164697148). A human Gnpat polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_055051.1 (GI No. 7657134) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_014236.3 (GI No. 170650722). A human Lypla1 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. CAG33384.1 (GI No. 48146323) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. CR457103.1 (GI No. 48146322). A human Cpt2 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. NP_000089.1 (GI No. 4503023) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. NM_000098.2 (GI No. 169790951). A human Agpat4 polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH13410.1 (GI No. 38196950) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. XM_005267052.1 (GI No. 530383869). A human Acaca polypeptide can have the amino acid sequence set forth in GenBank[®] Accession No. AAH31485.1 (GI No. 32425437) and can be encoded by the nucleic acid sequence set forth in GenBank[®] Accession No. XM_005257266.1 (GI No. 530412017).

The potato polysaccharide preparations provided herein or nutritional supplement compositions provided herein can be administered to any appropriate mammal (e.g., rat, mouse, dog, cat, horse, cow, goat, pig, chicken, duck, rabbit, sheep, monkey, or human). In addition, any appropriate route of administration (e.g., oral or parenteral administration) can be used to administer a potato polysaccharide preparation provided herein or a nutritional supplement composition provided herein to a mammal. For example, a potato polysaccharide preparation provided herein or a

nutritional supplement composition provided herein can be administered orally.

The document will provide addition description in the following examples, which do not limit the scope of the invention described in the claims.

5

EXAMPLES

Example 1 – Identification of a potato polysaccharide preparation having the ability to alter expression of polypeptides involved with mitochondria activity and function

6 grams of a Russet potato variety of the *Solanum tuberosum* species were homogenized with a Polytron homogenizer in 20 mL water in a 50 mL centrifuge tube and kept at room temperature for 1 hour. The homogenate was centrifuged at 4000 rpm for 10 minutes. A Sep-Pak Plus C-18 cartridge was activated with 10 mL 100% acetonitrile (ACN) and washed with 10 mL 0.05% trifluoroacetic acid in water (TFA water). 10 mL of the supernatant was loaded onto the cartridge, and all H₂O that passes through cartridge was collected in 1.5 mL Eppendorf tubes. Next, 10 mL of 2% ACN (in 0.05%TFA water) was passed through the column, and the elutriate was collected in 1.5 mL Eppendorf tubes. Next, 10 mL of 5% ACN (in 0.05%TFA water) was used to wash the column, and the elutriate was collected in 1.5 mL Eppendorf tubes. Finally, 10 mL of 10% ACN (in 0.05% TFA water) was collected in 1.5 mL Eppendorf tubes after passing through the column. All of the fractions were dried, and the dried fractions of the same ACN concentration were reconstituted into 1 tube in 1 mL of 0.05% TFA water for further purification via HPLC or reconstituted in 1 mL of phosphate buffered saline for use in cell treatments.

A Waters 2695 separations module with a photodiode array detector was used to purify the 10% ACN extract. An XterraRP C18 column (4.6 X 150 mm) was used for the separation with 0.05% TFA water as the mobile phase. Each HPLC run was a 20 minute gradient ranging from 0 to 2.5% ACN. The injection volume was 100 µL, and the flow rate was 0.5 mL/minute. HPLC fractionation of the 10% ACN extract yielded three major UV absorbing peaks eluted at 3.5, 3.9, and 12.1 minutes (Figure 1). Collection and HPLC re-purification of the 3.5 minute fraction yielded a symmetrical peak displaying a maximum absorbance at 198.3 nm (Figure 2).

The three peaks were evaluated to determine whether or not they obtained material having the ability to alter the expression levels of polypeptides involved in mitochondria activity and function. Briefly, 5 x 10⁵ neuroblastoma cells obtained from American Type Culture Collection (ATCC) were plated into each well of 6-well

plates with 2 mL of RPMI media and incubated for 4 hours in the presence or absence of different aliquots of the HPLC purified material. Following the incubation, total RNA was isolated and purified using the RNeasy mini kit (Qiagen, Valencia, CA). In particular, pelleted cells were resuspended in 600 μ L of RLT lysis buffer (Qiagen) and homogenized by passing the lysate 20 times through a 1 mL pipette tip. The samples were then processed according to the manufacturer's instructions (Qiagen, Valencia, Ca). In the final step, the RNA was eluted with 40 μ L of RNase-free water by centrifugation for 1 minute at 13,000g. The RNA was analyzed on a model 2100 bioanalyzer (Agilent, Santa Clara, CA) using a total RNA nanochip according to the manufacturer's protocol. Afterwards, 2 μ g of total RNA was reverse transcribed using Superscript III reverse transcriptase and random primers.

DNA microarray analyses also were performed using a system provided by Agilent. Arrays included four arrays per chip (Agilent 4X44K chips). Total RNA was reverse transcribed (400 ng) using T7 primers and labeled and transcribed using Cyanine-3 dye. Each array was hybridized with at least 1.65 μ g of labeled cRNA at 65°C for 18 hours. Arrays were scanned using an Agilent array scanner. A 10% or greater change in gene expression was capable of being determined using both microarray platforms.

Incubation of cultured cells with the HPLC purified fraction eluted at 3.5 minutes produced changes in the expression of mitochondrial and cellular metabolic genes (Table 1). The extracted potato material that eluted at 3.5 minutes is referred to herein as potato polysaccharide material, a potato polysaccharide preparation, or a potato polysaccharide since it was determined to be a polysaccharide as indicated below. The 3.5 minute fraction (a potato polysaccharide preparation) was the only fraction of the three determined to possess significant biological activity when tested using real time PCR for TFAM, NFkB, and HMGCR expression.

Table 1. Gene expression changes in HTB-11 cells as determined by microarray following a four-hour incubation with a potato polysaccharide preparation.

Gene symbol	Gene name	% change
TFAM	transcription factor A, mitochondrial	+15
FOXO1A	forkhead box O1	-28
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	-14
ATP5A1	ATP synthase, H ⁺ transporting, mitochondrial F1 complex, alpha subunit 1	+30
PDHA1	pyruvate dehydrogenase (lipoamide) alpha 1	+8
PDHA2	pyruvate dehydrogenase (lipoamide) alpha 2	+41
PDK2	pyruvate dehydrogenase kinase, isozyme 2	-24
PDK4	pyruvate dehydrogenase kinase, isozyme 4	-41
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase	-18
THOP1	thimet oligopeptidase 1	+23

Real-time PCR was performed in triplicate with TFAM, HMGCR, and NFKB1 detector sets. Beta-actin or GAPDH was used as a reference gene. The real-time PCR master mix included 25 μ L 2x universal master mix, 2.5 μ L 20x detector set (with the primer and probe), and 21.5 μ L of water. PCR was performed in an Applied Biosystems 7500 sequence detection system. The thermocycler conditions included denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 60 seconds. Forty cycles of PCR were preceded by 95°C for 10 minutes. Reactions were performed in triplicate. The relative quantities of TFAM were found using the formula $2^{-\Delta\Delta C_t}$ using the Applied Biosystems 7500 software. Validation of some of the microarray results by real time PCR used TFAM, HMGCR, and NFKB1 as candidate genes. A representative real time PCR amplification plot demonstrated that TFAM mRNA was present and was differentially expressed (Figure 3). The potato polysaccharide preparation had a profound effect on TFAM expression and was able to upregulate it by 57% (Table 2). Both HMGCR and NFKB1 gene expression were reduced by approximately 20%, consistent with and validating the DNA microarray data (Table 2).

Table 2. Validation of gene expression changes by real time PCR. HTB-11 cells treated for 4 hours with a potato polysaccharide preparation.

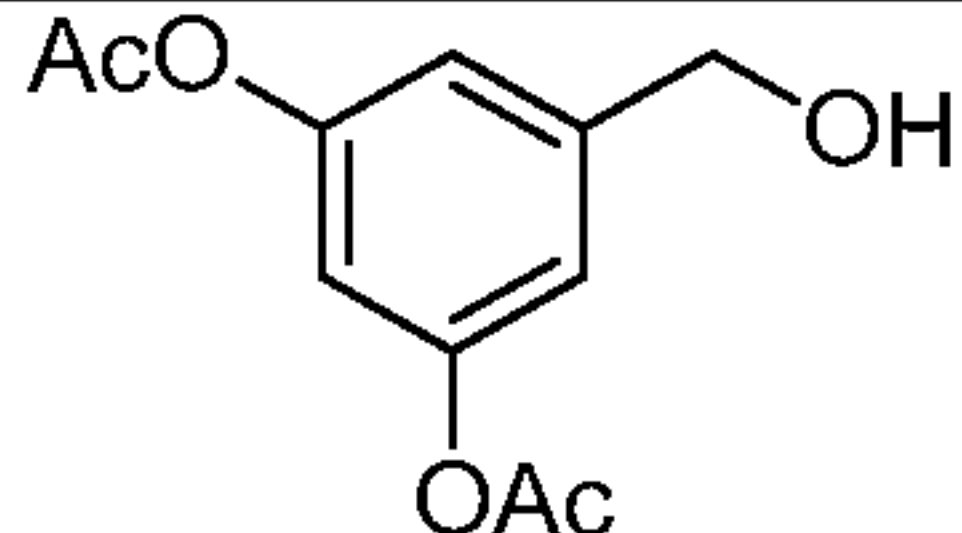
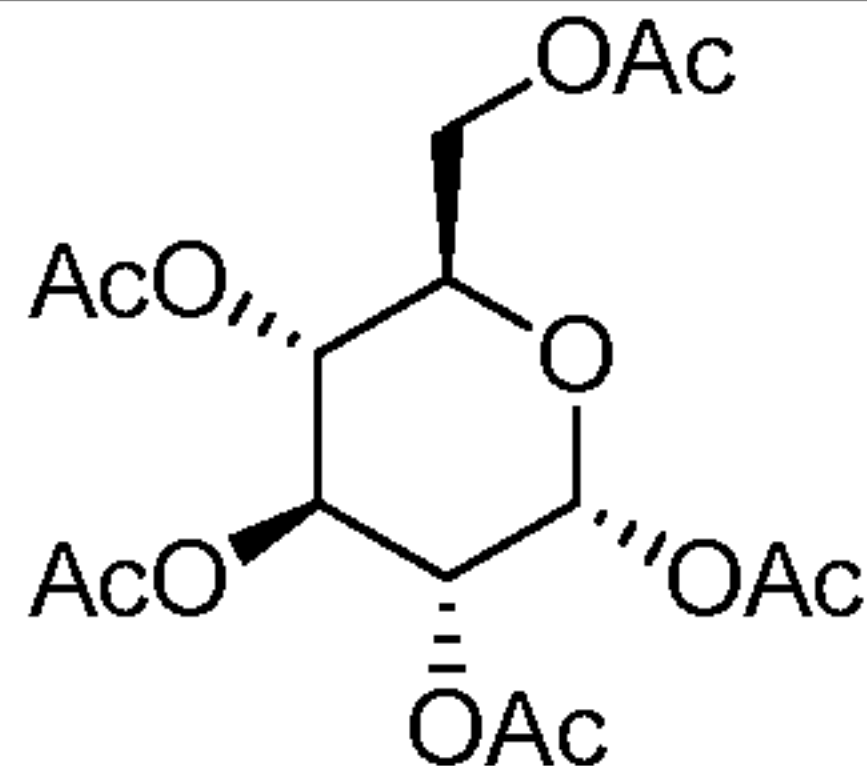
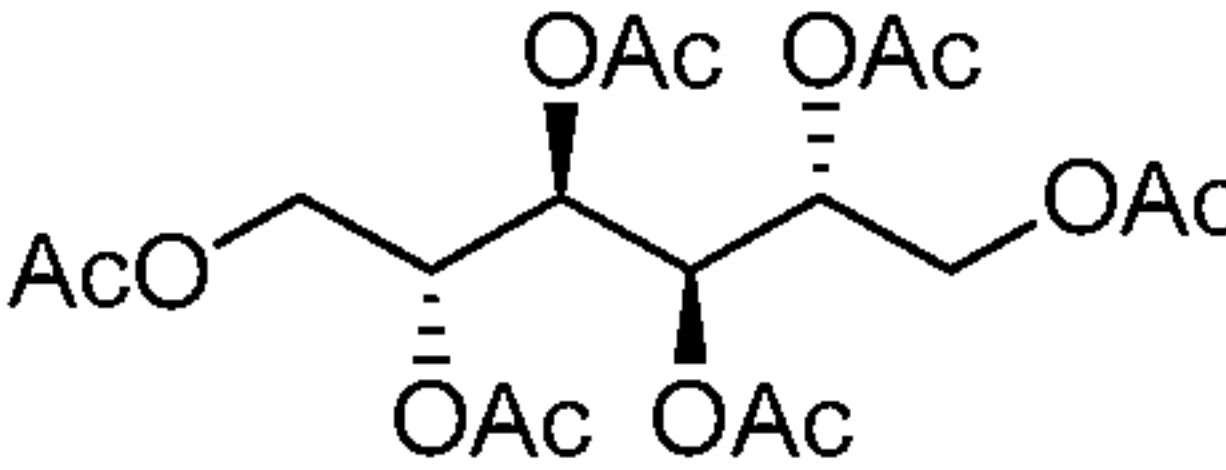
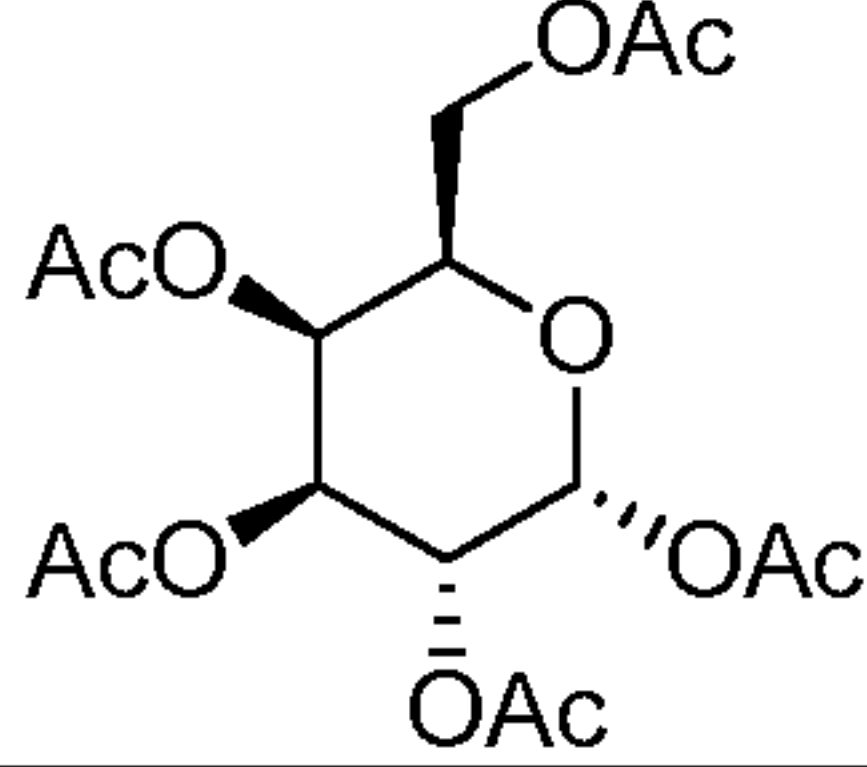
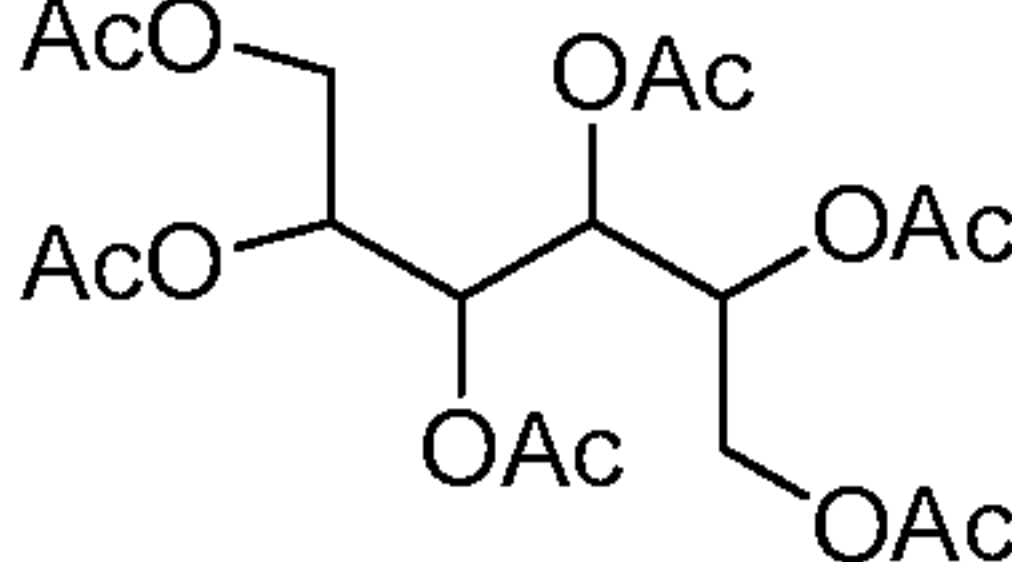
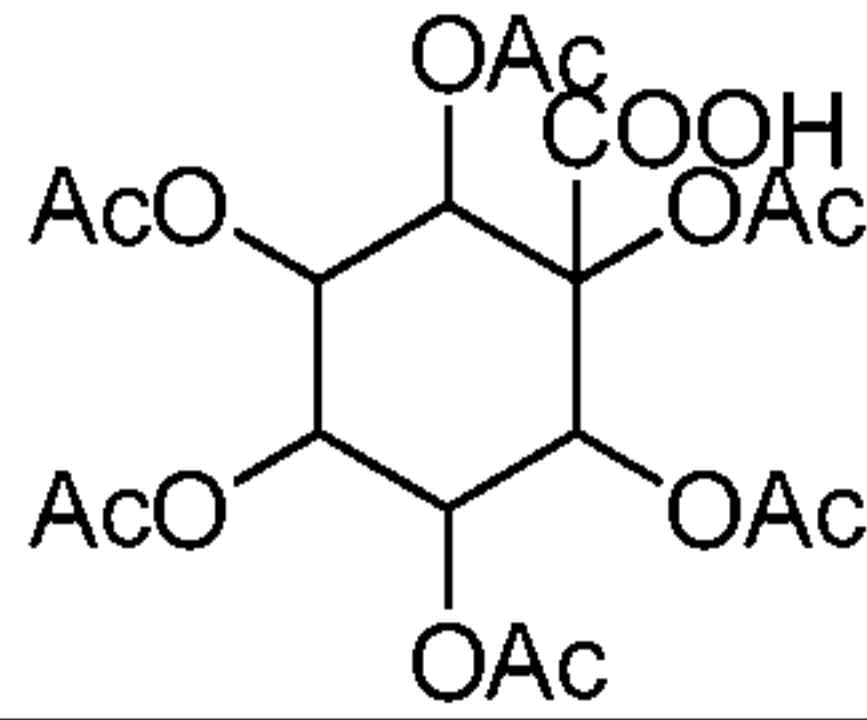
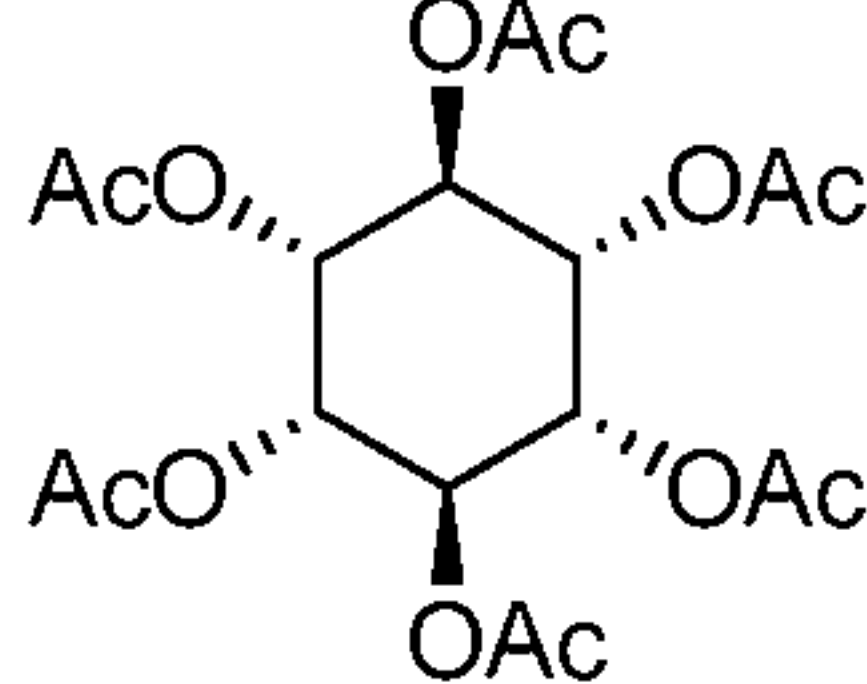
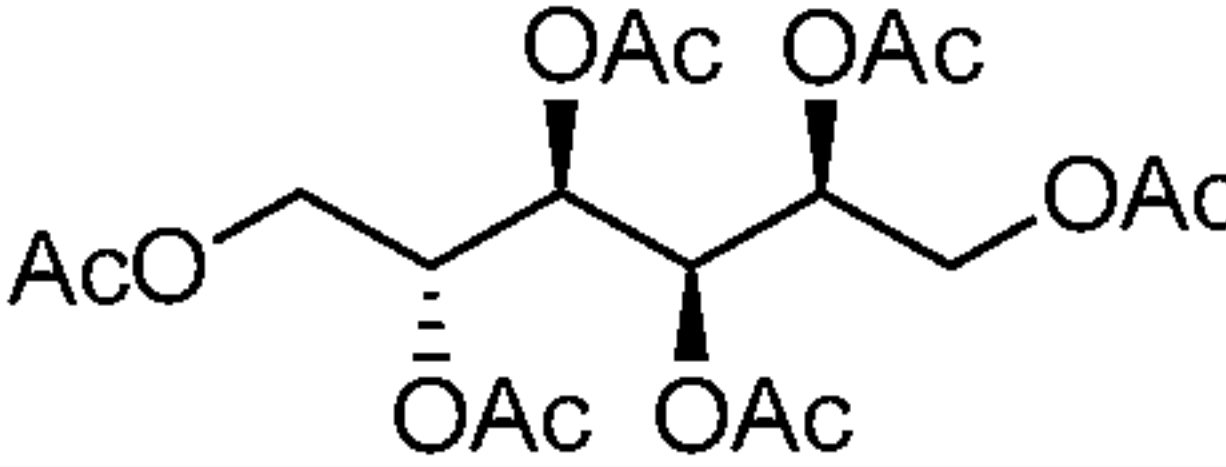
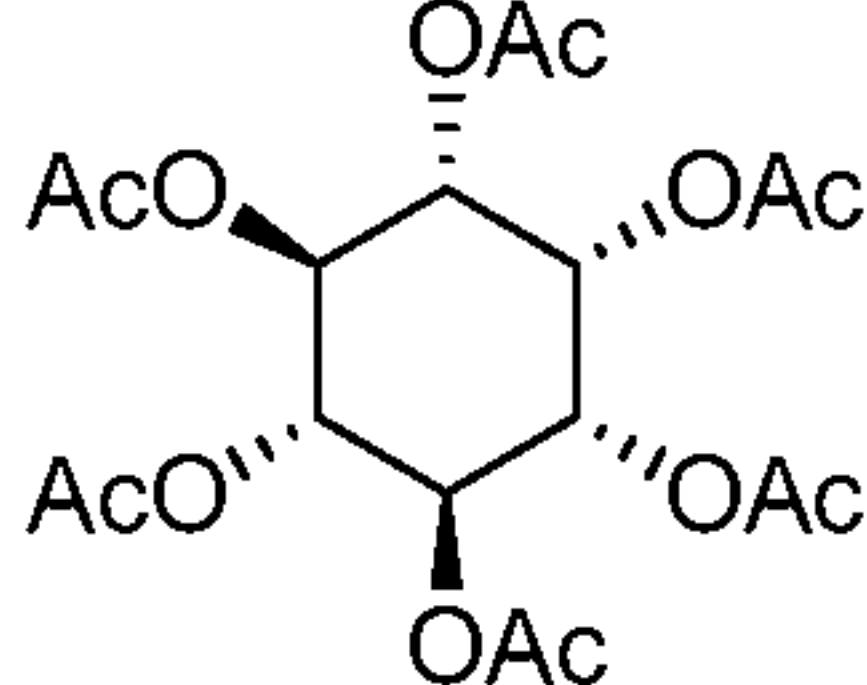
Gene Symbol	% change
TFAM	+57 $\pm$ 9
NFKB1	-20 $\pm$ 5
HMGCR	-19 $\pm$ 4

Further chemical characterization of the symmetrical 3.5 minute HPLC peak material was performed. Pooled 3.5 minute HPLC fractions were dried and reconstituted in 1 mL TFA water and subjected to tandem LC/MS/MS (Figure 4) and NMR chemical analyses (Figures 5 and 6). For the NMR analysis, ¹H-NMR was run on the sample using deuterium oxide (D₂O) as a solvent to further analyze the sample. The water peak at 4.65 PPM was solvent-suppressed, and the spectrum was acquired for several hours. Acetamide was detected at 3.2 PPM, along with acetonitrile at 1.9 PPM. Minor peaks were detected at 1.05 PPM, 1.17 PPM (broad peak), 1.189 PPM, and 1.864 PPM. One characteristic of polymeric materials in a proton NMR was the broadening of peaks such as the shift at 1.17 PPM. These shifts on the NMR could represent the peak at 4.8 PPM and suggested a polar, water-soluble polymer such as a polysaccharide. Taken together, these results confirmed the presence of high molecular weight polysaccharide material contained in HPLC purified fractions eluting at 3.5 minutes.

Further analysis confirmed that the HPLC purified fraction eluting at 3.5 minutes contains polysaccharide material (e.g., highly substituted complex xyloglucan material). To make the polysaccharide material analyzable by gas chromatography/mass spectroscopy (GC/MS), it was converted into its derivatized carbohydrate fragments. Briefly, the sample was concentrated to a dry residue that was hydrolyzed using trifluoroacetic acid. This was then reduced using sodium borohydride, and after borate removal, the end product was acylated using acetic anhydride and pyridine. The end products of the reaction were injected directly on GC/MS to identify any acylated carbohydrates. Based on the end analysis, a larger carbohydrate existed in the sample. The total ion chromatogram (TIC) is shown below in Figure 7 with appropriate peak labels below in Table 3. The major components identified are indicated in bold (peaks 3, 12, 14, and 21). The corresponding fragmentation for each compound is provided in Figures 8-27. For each fragmentation, the peak fragmentation pattern is on the top, the compound library fragmentation match is on the bottom, and an overlay of the two is in the center. Finally, unlabeled peaks were either column bleed or did not have a sufficient match to the compound library.

Table 3: Summary of GC/MS results.

Peak	Retention Time (min)	Compound Name	Structure
1	10.731	Diacetamide	
2	13.669	3-Acetoxy pyridine	
3	19.568	3,4-Furan dimethanol, diacetate	
4	19.950	1,2,3-propanetriol diacetate	
5	23.387	Imidazole, 2-acetamino-5-methyl	
6	23.499	6,7-dihydro-5H-pyrrol[2,1,c][1,2,4] triazole-3-carboxylic acid	
7	24.304	Acetic acid, 1-(2-methyltetrazol-5-yl) ethenyl ester	
8	25.538	1,2,3,4-butanetriol, tetraacetate	
9	27.412	(1,5)β(1,3)triacyl D-galactosan (stereoisomer 1)	
10	28.188	(1,5)β(1,3)triacyl D-galactosan (stereoisomer 2)	
11	29.210	Pentaerythritol tetraacetate	
12	29.727	1,2,3,4,5-penta-o-acetyl-D-xylitol (isomer 1)	
13	30.697	1,2,3,4,5-penta-o-acetyl-D-xylitol (isomer 2)	

14	32.477	3,5-diacetoxy-benzyl alcohol	
15	32.677	β -D-glucopyranose, pentaacetate	
16	33.012	D-mannitol hexaacetate	
17	33.106	β -D-galactopyranose, pentaacetate	
18	33.206	Galacticol, hexaacetate	
19	33.364	Cyclohexane carboxylic acid, 1,2,4,5-tetrakis(acetoxy), (1 α ,3 α ,4 α ,5 β)-(-)	
20	33.582	Muco-inositol, hexaacetate	
21	33.006	D-glucitol-hexaacetate	
22	34.463	Myo-inositol, hexaacetate	

These results demonstrate the presence of sugar monomers that serve as building blocks for a larger carbohydrate. It appeared from these multiple lines of analysis that the potato polysaccharide preparation is a highly substituted complex xyloglucan.

Example 2 – Sweet potatoes and multiple varieties of potatoes exhibit the presence of potato polysaccharide material

Six grams of potato material from multiple varieties of *Solanum tuberosum* (Organic yellow, Purple, Idaho Russet, and Yukon Gold) and six grams of material
5 from sweet potatoes (*Ipomoea batatas*) were extracted in 20 mL of water. 10 mL of that water was then loaded onto a sep-pak cartridge, and the cartridge was then eluted with 10 mL of 10% ACN. The ACN was then dried, and the residue was dissolved in 1 mL of water. A 100 µL injection of this water was assessed using HPLC.

The HPLC chromatograms demonstrated that the amount of the first peak (at
10 3.5 minutes at 210 nm) was the same for all five types of potatoes tested (Figures 28-32).

In another experiment, material was extracted from a boiled Purple potato and analyzed. The peak at 3.5 minutes was not reduced in the boiled potato (Figure 33).

The 3.5 minute peak from two pooled fraction collections from Idaho Russet
15 potatoes was collected, dried, and reconstituted in 100 µL of water. The material was then injected into the HPLC yielding a single peak at 3.5 minutes (Figure 34). Taken together, these results demonstrate that potatoes within the *Solanum tuberosum* and *Ipomoea batatas* species contain potato polysaccharide material.

20 Example 3 – Highly substituted complex xyloglucan from potato material alters expression of polypeptides in human omental apidocytes obtained from diabetic patients

Human omental apidocytes obtained from normal and diabetic patients were purchased from Zen-Bio, Inc (Research Triangle Park, NC). The cells were either
25 untreated or treated with 62.5 µg/mL of the 3.5 minute peak from purple potatoes for four hours. After the four hour incubations, the cells were harvested, and a microarray analysis was performed to measure changes in gene expression.

Incubation of human omental apidocytes from diabetic patients with the HPLC purified fraction eluted at 3.5 minutes produced changes in the expression of genes
30 involved in obesity and/or diabetes (Table 4). Incubation of human omental apidocytes from normal humans produced minimal changes in the expression of the genes listed in Table 4 (Table 5).

Table 4. Gene expression changes as determined by microarray following a four-hour incubation of human omental adipocytes from diabetic patients with a potato polysaccharide preparation.

Gene symbol	% change
AGPAT1	-1
OLR1	-45
BCAT2	-9
NFKB1	-6
SH2B1	-17
LPL	-24
HMGCR	-9
LIPE	+15
PCK2	+5
MOGAT1	+52
PPARGC1a	+59
PPARGC1b	+44
SOD2	+18
NR4A1	+12
ACAT2	+13

5

Table 5. Gene expression changes as determined by microarray following a four-hour incubation of human omental adipocytes from normal humans with a potato polysaccharide preparation.

Gene symbol	% change
AGPAT1	None detected
OLR1	-18
BCAT2	None detected
NFKB1	-56
SH2B1	-33
LPL	+18
HMGCR	+16
LIPE	+32
PCK2	+30
MOGAT1	+22
PPARGC1a	+26
PPARGC1b	+26
SOD2	+23
NR4A1	+45
ACAT2	+17

10

Real-time PCR was performed in triplicate with AGPAT1, OLR1, BCAT2, NR4A1, and ACAT2 detector sets. Beta-actin or GAPDH was used as a reference gene. The real-time PCR master mix included 25 μ L 2x universal master mix, 2.5 μ L 20x detector set (with the primer and probe), and 21.5 μ L of water. PCR was performed in an Applied Biosystems 7500 sequence detection system. The

thermocycler conditions included denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 60 seconds. Forty cycles of PCR were preceded by 95°C for 10 minutes. Reactions were performed in triplicate. Validation of some of the microarray results by real time PCR used AGPAT1, OLR1, BCAT2, NR4A1, and ACAT2 as candidate genes. Real time PCR amplification plots demonstrated that AGPAT1, OLR1, BCAT2, NR4A1, and ACAT2 mRNAs were present and were differentially expressed (Table 6).

Table 6. Validation of gene expression changes by real time PCR. Human omental apidocytes from diabetic patients treated for 4 hours with a potato polysaccharide preparation.

Gene Symbol	% change
AGPAT1	-13 ± 1
OLR1	-9 ± 1
BCAT2	-4 ± 1
NR4A1	+34 ± 3
ACAT2	+12 ± 2

Example 4 – Highly substituted complex xyloglucan from potato material alters expression of polypeptides in mouse myocytes

Mouse myoblasts were seeded in 2 mL aliquots into two 75 cm² tissue culture flasks. Cells were left to differentiate into myocytes for 4 days in 5% CO₂ at 37 °C.

Myocytes were detached from flask walls using gentle agitation. Suspended cells were transferred to a 15mL conical tube and centrifuged at 500g for 3 minutes. 2 mL aliquots were seeded into 75 cm² tissue culture flasks for both control and diabetic model cells. The mouse cells were obtained from normal mice and from mice treated with low dose alloxan. The diabetic mice had high blood glucose compared to the normal mice. A potato polysaccharide preparation (62.5 µg/mL of the 3.5 minute peak from purple potatoes) was added to one control and one diabetic flask, and the cells were incubated for 24 hours.

After the 24 hour incubation, the cells were harvested, and a microarray analysis was performed to measure changes in gene expression. In addition, images were taken of the cells after treatment using a Nikon EclipseTE300 (Morell) inverted microscope coupled with an Optronics digital cameraware at 20x. The images were analyzed on ImageJ software for cell mortality and fiber size. Cell mortality was calculated using a ratio of the number of inactive cells to the number of active cells.

Fiber size was calculated using a polygonal lasso tracer and measured in pixel area.

Incubation of mouse myocytes from the diabetic model with the HPLC purified fraction eluted at 3.5 minutes produced changes in the expression of genes involved in obesity and/or diabetes (Table 7). Incubation of mouse myocytes from normal mice produced minimal changes in the expression of the genes listed in Table 7 (Table 8).

Table 7. Gene expression changes as determined by microarray following a 24-hour incubation of mouse myocytes from the diabetic model with a potato polysaccharide preparation.

Gene symbol	% change
NFKB1	-46
SH2B1	-35
LPL	-16
HMGCR	+25
LIPE	-46
PCK2	none
SOD2	+74
NR4A1	-33
ACAT2	none
PTEN	-22
CASP8	not detected

Table 8. Gene expression changes as determined by microarray following a 24-hour incubation of mouse myocytes from normal mice with a potato polysaccharide preparation.

Gene symbol	% change
NFKB1	37
SH2B1	202
LPL	139
HMGCR	105
LIPE	147
PCK2	118
SOD2	None detected
NR4A1	200
ACAT2	75
PTEN	96
CASP8	104

Real-time PCR was performed in triplicate with PTEN and CASP8 detector sets. Beta-actin or GAPDH was used as a reference gene. The real-time PCR master mix included 25 μ L 2x universal master mix, 2.5 μ L 20x detector set (with the primer and probe), and 21.5 μ L of water. PCR was performed in an Applied Biosystems

7500 sequence detection system. The thermocycler conditions included denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 60 seconds. Forty cycles of PCR were preceded by 95°C for 10 minutes. Reactions were performed in triplicate. Validation of some of the microarray results by real time PCR used PTEN and CASP8 as candidate genes. Real time PCR amplification plots demonstrated that PTEN and CASP8 mRNAs were present and were differentially expressed (Table 9).

Table 9. Validation of gene expression changes by real time PCR. Mouse myocytes from the diabetic model treated for 24 hours with a potato polysaccharide preparation.

Gene Symbol	% change
PTEN	-31 ± 4
CASP8	-72 ± 8

Example 5 – Analysis of a potato polysaccharide preparation

A potato polysaccharide preparation was purified using HPLC from 3 g of purple potato. The potato polysaccharide peak was eluted at about 5 minutes (Figure 35). This peak was obtained using a different chromatographic column (10 mm x150 mm) as compared to the column used to obtain the 3.5 minute peak. Since the column was a larger preparative column and the flow rate was 1.5 mL/minute, the elution time of the potato polysaccharide was 5 minutes.

The obtained peak was collected, dried, and reconstituted in 60 µL of water. The reconstituted potato polysaccharide material was then added to HTB-11 cells in culture flasks for 4 hours. The post treatment media was collected and added to another flask of HTB-11 cells. Each group of cells was analyzed for gene expression changes. The initially treated cells exhibited the expected changes in mitochondrial gene expression. No changes were detected in the cells exposed to the post treatment media for 4 hours.

In a separate experiment, the post treatment media was extracted using the techniques used to originally purify the potato polysaccharide. A chromatogram of the extracted post treatment media demonstrated the absence of a peak at 5 minutes.

Example 6 – Using a potato polysaccharide preparation to treat obesity

Class I-III obese humans are identified based on the criteria of Table 10.

5 Table 10. Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks.

			Disease Risk* Relative to Normal Weight and Waist Circumference	
	BMI (kg/m²)	Obesity Class	Men 102 cm (40 in) or less Women 88 cm (35 in) or less	Men > 102 cm (40 in) Women > 88 cm (35 in)
Underweight	< 18.5		-	-
Normal	18.5– 24.9		-	-
Overweight	25.0– 29.9		Increased	High
Obesity	30.0– 34.9	I	High	Very High
	35.0– 39.9	II	Very High	Very High
Extreme Obesity	40.0 +	III	Extremely High	Extremely High

Once identified, a Class I-III obese patient is treated as follows. Potato polysaccharide is formulated in the presence of alpha lipoic acid or alpha tocopherol or both. Formulated potato polysaccharide is added to 90% by weight inert binder material and is administered by the oral parenteral route in the form of a tablet, capsule, or liquid, twice daily (bid). Maximal concentrations of potato polysaccharide are initially administered bid over the course of one month. Positive outcome measures include: (1) significant reduction of BMI, (2) augmentation of serum LDL/HDL ratio, (3) lowering serum triglyceride concentration, (4) lowering systolic and diastolic blood pressure, and (5) lowering fasting blood glucose.

Example 7 – Using a potato polysaccharide preparation to treat type II diabetes

Once a type II diabetes patient is identified, the patient is treated as follows. Potato polysaccharide is formulated in the presence of alpha lipoic acid or alpha tocopherol or both. Formulated potato polysaccharide is added to 90% by weight inert binder material and is administered by the oral parenteral route in the form of a tablet, capsule, or liquid, twice daily (bid). Maximal concentrations of potato polysaccharide are initially administered bid over the course of one month. Positive outcome measures include: (1) restoration of normal fasting blood glucose, (2) significant weight loss and lowering of BMI, (3) augmentation of serum LDL/HDL ratio, (4) lowering serum triglyceride concentration, (5) lowering serum concentration of free fatty acids, (6) lowering systolic and diastolic blood pressure, (7) enhancement of insulin sensitivity, and (8) lowering insulin requirement in Type II diabetes patients.

Example 8 – Using a potato polysaccharide preparation to treat a polycystic ovary syndrome

Once a polycystic ovary syndrome (POS) patient is identified, the patient is treated as follows. Potato polysaccharide is formulated in the presence of alpha lipoic acid or alpha tocopherol or both. Formulated potato polysaccharide is added to 90% by weight inert binder material and is administered by the oral parenteral route in the form of a tablet, capsule, or liquid, twice daily (bid). Maximal concentrations of potato polysaccharide are initially administered bid over the course of one month. Positive outcome measures include: (1) restoration of normal reproductive function, (2) restoration of normal ovarian follicle maturation, (3) restoration of normal fasting blood glucose levels, (4) significant weight loss and lowering of BMI, (5) augmentation of serum LDL/HDL ratio, (6) lowering serum triglyceride concentration, (7) lowering serum concentration of free fatty acids, (8) lowering systolic and diastolic blood pressure, (9) enhancement of insulin sensitivity, and (10) lowering insulin requirement in comorbid POS patients with type II diabetes.

30

Example 9 – Maintaining and restoring insulin sensitivity
and glucose homeostasis in living mammals

In vivo animal model

The Zucker Diabetic Fatty (ZDF) rat model was used (Carley and Severson,
5 *Biochim. Biophys. Acta*, 1734:112-26 (2005)). Positive results in the ZDF rat model
can indicate a potential for positive treatment outcomes in human Type II diabetics.
In particular, circulating plasma triglyceride concentrations, circulating plasma
glucose concentrations, abdominal fat, water utilization, urine secretion, and organ
weights were examined in cohorts of ZRF rats treated with a potato polysaccharide
10 preparation or with vehicle.

Dosing and grouping

Two types of rats were used for the study (ZDF/ZDF rats (n=20) and
heterozygous lean rats (n=20)). The rats within the groups were then chosen at
15 random and divided into groups of 10. Group 1 included the ZDF vehicle fed rats,
group 2 included the ZDF potato polysaccharide fed rats, group 3 included the lean
vehicle fed rats, and group 4 included the lean potato polysaccharide fed rats. The
vehicle was distilled water, and the potato polysaccharide was given daily each
morning via oral gavage at a dosage of 0.05 mg per animal. The dose was usually
20 given in 1 mL of water. Rats were caged in groups and maintained in 12 hour light/12
hour dark (7 am to 7 pm). The study lasted for 28 days.

Data collection

Body weights were recorded weekly. Whole blood, serum, and plasma were
25 collected at day 0 for baseline analysis. Plasma and serum was collected from fasting
rats at day 14. Water consumption was monitored starting at day 24 and continued
until termination. Urine collection for measurement of volume and protein content
was on day 27. Whole blood, serum, and plasma were collected at day 28
(termination). Fasted blood glucose was measured at day 28, and liver and abdominal
30 fat were collected and snap frozen in liquid nitrogen.

Total cholesterol (HDL, LDL, and triglycerides) and serum glucose were
measured at days 0, 14, and 28. Serum creatinine was measured at termination.
Whole blood was preserved in PAX RNA blood tubes for possible gene expression
analysis. Abdominal fat, liver, and kidneys were weighed and used in calculating

organ to body mass ratios. Plasma collected was stored from days 0, 14, and 28 for possible future analysis.

Experimental animals

5 Twenty-two 7-week old, male Zucker Diabetic Fatty rats (ZDF, Code: 370) and twenty-two 7-8 week old, male ZDF Lean rats (Code: 371) were purchased from Charles Rivers Laboratories (Wilmington, MA). The study animals were allowed an acclimation period of 4 days prior to baseline blood collections, at which time two extra animals from each strain were dropped from the study based on
10 baseline body weight. The rats were housed two rats per cage and maintained in the Innovive caging system (San Diego, CA) upon arrival. Cages were monitored daily to ensure the Innovive system maintained 80 air changes per hour and positive pressure. Rat rooms were maintained at temperatures of 66-75 °F and a relative humidity between 30 percent and 70 percent. The rooms were lit by artificial
15 light for 12 hours each day (7:00 am to 7:00 pm). Animals had free access to water and Purina 5008 rodent food (Waldschmidt's, Madison, WI) for the duration of the study except during fasted experiments.

Drug formulation

20 A potato polysaccharide preparation for animal testing was prepared as follows. Ten gram portions of raw potato material were homogenized with a Polytron homogenizer in ten volumes of distilled water and maintained at room temperature for 1 hour with occasional shaking. The raw potato homogenate was subsequently centrifuged at 4000 g for 10 minute in order to remove insoluble material. The
25 resulting supernatant was purified by Solid Phase Extraction utilizing a Sep-Pak Plus C-18 cartridge. Semipurified polysaccharide material contained in 10 percent acetonitrile and 0.05% trifluoroacetic acid was dried and purified to homogeneity by reverse phase HPLC.

 The eluted 3.5 minute HPLC fraction containing pure potato polysaccharide
30 preparation was dried and used in animal testing.

 The purified potato polysaccharide preparation (10 mL stock solution at 5 mg/mL concentration) was stored at 4 °C. The vehicle for the study was sterile water (Catalog number 002488, Butler Schein). Each week, the stock solution was diluted 1:100 in sterile water (0.05 mg/mL) and dispensed into daily aliquots. All vehicle and

drug solutions were stored at 4 °C and administered at room temperature daily by oral gavage (PO) in a volume of 1 mL/animal (0.15 mg/kg dose based on estimated body weight of 350 g).

5 *Body weights*

Animals were weighed weekly with a calibrated digital balance to monitor animal health. Body weights were taken in a fed state, except for the terminal body weight measurement.

10 *Blood Collection*

Blood was collected on Day 0 for baseline, Day 14 for Week 2, and Day 28 during termination for Week 4. Animals were fasted for 11.5 hours (10:00 pm - 9:30 am) prior to each blood collection, and if applicable, dosed 1 hour prior to the blood collection. Whole blood was collected into blood collection tubes for
15 baseline pooled blood analysis (1.0 mL of blood from each animal) and terminal blood analysis (2.5 mL of blood from each animal). For Baseline and Days 14 and 28, 850 µL of whole blood was collected into pre-chilled K2EDTA tubes with DPP4i (1:100 P8340, Sigma Aldrich) added and processed to plasma. For Baseline and Days 14 and 28, 250 µL whole blood was collected into a SST tube and
20 processed to serum.

Blood Analyses

Whole blood collected into blood tubes was frozen at -20 °C and shipped on ice packs for analyses. Plasma with DPP4i added were frozen at -20 °C and
25 shipped on dry ice for analyses. Serum was frozen at -20 °C and shipped for analysis. Baseline and Day 14 sera were analyzed for the standard lipid panel (cholesterol, triglycerides, HDL, and LDL) as well as glucose. Terminal serum samples were analyzed for the standard lipid panel, glucose, and creatinine content.

30 *Water consumption*

Beginning on Day 23, water consumption monitoring began and was continued for the remainder of the study. The difference in water weight (beginning weight of water in grams minus the end weight of water in grams) was divided by the number of animals per cage to determine the average amount of water in grams

consumed per animal per day. Water added was accounted for in the measurements, and calculations were converted to mL/animal/day. On Day 26, animals were placed into individual metabolic cages; therefore, water consumption was monitored per animal instead of per cage.

5

Urine collection

Urine was collected at room temperature for 24 hours from Day 26 to Day 27. Animals had free access to food and water throughout the procedure. Urine volumes were measured, and urine protein and creatinine were analyzed.

10

Fasted Glucose

Fasted blood glucose was measured at 9:30 am on Day 28, about 1 hour post-dose with 11.5 hours of fasting. Blood glucose was measured with a Bayer Contour glucometer. Termination immediately followed the blood glucose measurements.

15

Necropsy

All animals were euthanized by isoflurane overdose and thoracotomy following the collection of fasted blood glucose data on Day 28 of the study. Blood was collected via descending vena cava. Liver and abdominal fat were collected and weighed, and a portion of the left lateral liver lobe and abdominal fat were placed into individual histology cassettes and snap frozen in liquid nitrogen. General pathological observations were recorded.

20

Study design

Animals were recruited into treatment groups based on body weights collected on Day -1. Animals were fasted for 11.5 hours (10:00 pm - 9:30 am) prior to collection of blood on Day 0 for baseline parameter analyses. Each animal was anesthetized using isoflurane inhalant anesthetic with subsequent retro-orbital blood collection technique, followed by subcutaneous fluid replacement. Study animals received vehicle (sterile water) or a potato polysaccharide via oral gavage beginning on Day 1 and for the duration of the experiment. Animals were administered 1.0 mL of a 0.05 mg/mL solution to achieve a target dose of 0.15 mg/kg/ day.

25

30

At the end of Week 2, animals were fasted and dosed prior to collection of blood on Day 14 for mid-study parameter analyses. Each animal was anesthetized using isoflurane inhalant anesthetic with subsequent retro-orbital blood collection technique. Water consumption monitoring began on Day 23 and continued for the duration of the study. On Day 26, study animals were placed into individual metabolic cages for a 24-hour collection of urinary output. Urine volume was measured, and two clean, processed aliquots were retained for analysis.

At the end of Week 4, animals were fasted and dosed prior to measurement of blood glucose on Day 28. Fasted blood glucose was measured via tail clip blood collection, and termination began directly thereafter. Animals were euthanized using isoflurane inhalant anesthetic followed with a thoracotomy. Blood was collected via the descending vena cava and distributed into the appropriate tubes. The liver and abdominal fat were collected and weighed, and portions snap frozen in liquid nitrogen. The study design and treatments in the groups for the rats are presented in Figure 37 and Table 11.

Table 11. Treatment Groups.

Group 1: Fa/Fa Vehicle (Sterile Water), n=10
Group 2: Fa/Fa potato polysaccharide 0.05 mg/day, n=10
Group 3: Lean +/- Vehicle (Sterile Water), n=10
Group 4: Lean +/- potato polysaccharide 0.05 mg/day, n=10

+/- represents the ZDF lean rats that are heterozygotic with a normal leptin receptor allele and that display no abnormal metabolic symptoms.

20 *Statistical analysis*

Data were reported in mean + SEM. Statistical analysis was performed using the Prism 5.0d program by GraphPad Software. Analysis of variation for body weight, lipid panel parameters (cholesterol, triglycerides, HDL, and LDL), serum glucose, and water consumption were performed through a two-way ANOVA. Bonferroni post-tests were used to compare replicate means by row. Analysis of variation for blood glucose, urine parameters (urine volume, proteinuria, and creatinine clearance), liver-to-body weight ratio, and abdominal fat-to-body weight ratio were performed through a one-way ANOVA with a Bonferroni post-test to

compare all pairs of columns. Significance was determined when the p-value was less than an alpha of 0.05 with a confidence interval of 95%. Outliers were screened by testing the group's mean versus the standard error of the mean (SEM) for said time point. If the relationship of SEM to mean was in excess of 10%, then the data points of that group at that time point were carried through an outlier test. Data points outside a z-score variation of 3.0 were listed as outliers and not included in the mean or SEM for the group. In Group 1 for Day 6 body weight, one animal's value was considered an outlier and was removed from the graphs and statistical analysis.

10 *Results*

Mean body weight between the four groups did not change (Figure 38).

Comparing groups 1 and 2, the rats treated with a potato polysaccharide preparation exhibited a significant drop in triglyceride levels at day 14 ($P < 0.05$; Figure 39). On day 0, mean LDL was lower in Group 4 as compared to Group 3 (Figure 40).

15 serum glucose was statistically lower on day 28 for rats of Group 2 treated with the potato polysaccharide preparation (Figure 41). Rats of Group 2, which were treated with a potato polysaccharide preparation, exhibited a statistically significant reduction in water consumption and urine production (Figures 42 and 43) as compared to the rats of Group 1. Rats of Group 2 exhibited mean fasted glucose levels that were statistically lower than the levels observed for rats of Group 1 (Figure 44).

Abdominal fat in the potato polysaccharide preparation treated group was statistically elevated (Figure 45). In addition, the kidney weight to body weight ratio was lower for the rats of Group 2 as compared to those for the rats of Group 1 (Figure 46).

25 These results demonstrate that administration of a potato polysaccharide preparation can maintain the metabolic integrity of adipocytes during a critical developmental period of insulin desensitivity observed in vehicle-treated ZDF controls. In the vehicle-treated cohort, a developmental period highlighted by markedly increased plasma triglyceride concentrations is functionally linked to temporal development of insulin desensitization and diabetic levels of plasma glucose. In the cohort treated with a potato polysaccharide preparation, a statistically significant reduction of plasma triglyceride concentrations was observed at the 14 day time point, which is critically linked to significantly lower levels of fasting and non-fasting "true" glucose. Lower levels of plasma glucose were associated with

significantly reduced water intake and urine output, indicating a marked inhibition of the development of multiple type II diabetic symptoms.

These positive outcomes are directly translatable to inhibition of type II diabetes development in humans. Interestingly, levels of true glucose in vehicle-
5 treated ZDF controls were lower than those observed in treated ZDF rats at early time points. This was consistent with temporal development of insulin insensitivity in humans via presentation of prediabetic lowered plasma glucose levels. Administration of a potato polysaccharide preparation was observed to inhibit temporal development of prediabetic lowered levels of plasma glucose. In effect,
10 administration of a potato polysaccharide preparation maintained normal levels of plasma glucose via maintenance of insulin sensitivity. Maintenance of normal levels of plasma glucose was statistically linked to diminished circulating plasma triglycerides at the 14 day time point, which was functionally linked to higher levels of abdominal fat in treated animals that were normally observed in obese non-diabetic
15 humans. In summary, administration of a potato polysaccharide preparation as described herein maintained metabolic integrity of abdominal fat storage that is linked to temporal development of insulin insensitivity. This also indicates that a potato polysaccharide preparation can be used to stabilize metabolic processes in obese human populations, thereby permitting programmed dietary regimens to combat
20 obesity disorders effectively.

Example 10 – Use of potato polysaccharide preparations to treat fatty liver diseases

To assess the ability of potato polysaccharide preparations to treat fatty liver
25 diseases, the livers from the rats of the four groups of Example 9 were collected, weighed, and examined as described in this Example.

DNA microarray

Total RNA extracted from liver samples was isolated and purified using the
30 RNeasy mini kit (Qiagen, Valencia, CA). In particular, 100 mg of tissue was resuspended in 1.8 mL of RLT lysis buffer (Qiagen) and homogenized with a polytron homogenizer for 30 seconds. The samples were then processed according to the manufacturer's instructions (Qiagen, Valencia, Ca). In the final step, the RNA was eluted with 50 µL of RNase-free water by centrifugation for 1 minute at 13,000g. The

RNA was analyzed on a model 2100 bioanalyzer (Agilent, Santa Clara, CA) using a total RNA nanochip according to the manufacturer's protocol.

DNA microarray analyses were performed using a system provided by Agilent. Arrays included four arrays per chip (Agilent Rat gene expression 4X44K version 3 chips). Total RNA was reverse transcribed (700 ng) using T7 primers, labeled, and transcribed using Cyanine-3 dye. Each array was hybridized with 2 µg of labeled cRNA at 65 °C for 18 hours. Arrays were scanned using an Agilent array scanner.

10 *Results*

Oral administration of the potato polysaccharide preparation over a time course of 28 days produced a statistically significant reduction (about 40%) in the liver weight to body weight ratios in Zucker ZDF rats, as compared to control Zucker ZDF rats receiving vehicle (p=0.01, N=9).

15 In addition, daily oral administration of the potato polysaccharide preparation resulted in a coordinated enhancement of gene expression in liver tissue that is functionally linked to enhanced protein and nucleic acid biosynthesis (Table 12).

20 Table 12. Enhanced expression of genes driving mitochondrial biogenesis linked to enhanced protein and nucleic acid biosynthesis.

Gene Symbol	Gene Name	Fold Change	P value
Slc25a33	solute carrier family 25 (pyrimidine nucleotide carrier), member 33	3.6	0.00005
Tomm40	translocase of outer mitochondrial membrane 40 homolog (yeast)	2.4	0.0005
Mrpl3	mitochondrial ribosomal protein L3	2.4	0.000008
Mrps18b	mitochondrial ribosomal protein S18B	1.9	0.002
Mrps9	mitochondrial ribosomal protein S9	1.8	0.001
Fars2	phenylalanyl-tRNA synthetase 2, mitochondrial	1.8	0.001
Mrpl15	mitochondrial ribosomal protein L15	1.7	0.004
Mrps23	mitochondrial ribosomal protein S23	1.6	0.0003
Mrps2	mitochondrial ribosomal protein S2	1.6	0.003
Mrpl17	mitochondrial ribosomal protein L17	1.5	0.0001
TFAM	Transcription factor A	1.5	0.05

Daily oral administration of the potato polysaccharide preparation also resulted in a coordinated enhancement of gene expression in liver tissue that is functionally linked to enhanced TCA cycle activity and ATP production (Table 13).

5 Table 13. Enhanced expression of genes driving mitochondrial energy production.

Gene Symbol	Gene Name	Fold Change	P value
Prodh	proline dehydrogenase (oxidase) 1	2.9	0.003
Slc25a1	solute carrier family 25 (mitochondrial carrier, citrate transporter), member 1	2.3	0.00004
Hmgcl	3-hydroxymethyl-3-methylglutaryl-CoA lyase	2.2	0.0004
Cps1	carbamoyl-phosphate synthetase 1	2.0	0.0001
Aldh4a1	aldehyde dehydrogenase 4 family, member A1	1.9	0.0003
Mdh2	malate dehydrogenase 2, NAD (mitochondrial)	1.9	0.0002
Atp5b	ATP synthase, H ⁺ transporting, mitochondrial F1 complex, beta polypeptide	1.8	0.0002
Slc25a22	solute carrier family 25 (mitochondrial carrier, glutamate), member 22	1.6	0.0007
Slc25a19	solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19	1.6	0.00009
Uqcrc2	ubiquinol cytochrome c reductase core protein 2	1.6	0.0001
Abcf2	ATP-binding cassette, subfamily F (GCN20), member 2	1.6	0.004

Daily oral administration of the potato polysaccharide preparation resulted in differential expression of genes functionally involved in lipogenesis, triglyceride assembly, and mitochondrial lipolysis (Table 14).

Table 14. Differential expression of genes involved in lipogenesis, triglyceride assembly, and mitochondrial lipolysis.

Gene Symbol	Gene Name	Fold Change	P value
Acbd4	acyl-CoA binding domain containing 4	3.0	0.00003
Fads1	fatty acid desaturase 1	1.9	0.003
Gnpat	glyceronephosphate O-acyltransferase	1.6	0.002
Lypla1	lysophospholipase I	1.5	0.001
Cpt2	Carnitine palmitoyltransferase	1.2	0.04
Pck2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	-1.4	0.003
Agpat4	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	-1.8	0.001
Acaca	acetyl-CoA carboxylase alpha	-2.3	0.00007

Daily oral administration of the potato polysaccharide preparation did not result in any significant change in the expression of three hepatic reference or housekeeping genes (Congiu *et al.*, *Liver Int.*, 31:386-90 (2011); Table 15).

Table 15. Expression of hepatic reference or housekeeping genes.

Gene Symbol	Gene Name	Mean signal difference
Gapdh	glucuronidase, beta	0.1
Hprt	hypoxanthine phosphoribosyltransferase 1	0.06
Srsf4	serine/arginine-rich splicing factor 4	0.004

Real-time PCR analysis of TFAM expression was performed to validate the DNA microarray data sets. After rats were given the potato polysaccharide preparation for 28 days, real-time PCR was performed to measure changes in TFAM gene expression in ZDF rat livers. GAPDH was used as a reference gene. The real-

time PCR master mix included 25 μ L 2x universal master mix, 2.5 μ L 20x detector set (with the primer and probe), and 21.5 μ L of water. PCR was performed in an Applied Biosystems 7500 sequence detection system. The thermocycler conditions included denaturation at 95 °C for 15 seconds and annealing/extension at 60 °C for 60 seconds.

- 5 Forty cycles of PCR were preceded by 95 °C for 10 minutes. Reactions were performed in triplicate. The relative quantities of TFAM were determined using the formula $2^{-\Delta\Delta C_t}$ using the Applied Biosystems 7500 software. There was a 3.4 ± 0.5 fold change increase relative to the untreated rats (Figures 48 and 49).

- 10 Taken together, these results demonstrate that potato polysaccharide preparations can be used as anti-steatotic agents to treat fatty liver diseases.

OTHER EMBODIMENTS

- 15 It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for treating diabetes, wherein said method comprises:
 - (a) identifying a mammal with diabetes, and
 - 5 (b) administering to said mammal a composition comprising a potato polysaccharide preparation obtained from raw potatoes, wherein the severity of a symptom of said diabetes is reduced.
2. The method of claim 1, wherein said composition comprises said potato
10 polysaccharide preparation in an amount that results in between 0.05 mg and 50 mg of the potato polysaccharide component of said potato polysaccharide preparation being administered to said mammal per kg of body weight of said mammal.
3. The method of claim 1, wherein said composition comprises between 1 mg
15 and 100 mg of said potato polysaccharide preparation.
4. The method of claim 1, wherein said composition comprises between 6 mg and 20 mg of said potato polysaccharide preparation.
- 20 5. The method of claim 1, wherein said composition comprises between 1 mg and 100 mg of the potato polysaccharide component of said potato polysaccharide preparation.
6. The method of claim 1, wherein said composition comprises between 6 mg
25 and 20 mg of the potato polysaccharide component of said potato polysaccharide preparation.
7. The method of claim 1, wherein said composition is in the form of a tablet.
- 30 8. The method of claim 1, wherein said composition comprises alpha lipoic acid.
9. The method of claim 1, wherein said composition comprises alpha tocopherol.

10. The method of claim 1, wherein said potato polysaccharide preparation is in an amount that results in between 0.075 mg and 0.5 mg of the potato polysaccharide component of said potato polysaccharide preparation being administered to said mammal per kg of body weight of said mammal.

5

11. The method of claim 1, wherein at least about 80 percent of said potato polysaccharide preparation is potato polysaccharide.

12. The method of claim 1, wherein at least about 90 percent of said potato polysaccharide preparation is potato polysaccharide.

10

13. The method of claim 1, wherein at least about 95 percent of said potato polysaccharide preparation is potato polysaccharide.

14. The method of claim 1, wherein said mammal is a human.

15

15. A method for treating a fatty liver disease, wherein said method comprises:
 (a) identifying a mammal with a fatty liver disease, and
 (b) administering to said mammal a composition comprising a potato polysaccharide preparation obtained from raw potatoes, wherein the severity of a symptom of said fatty liver disease is reduced.

20

16. The method of claim 15, wherein said composition comprises said potato polysaccharide preparation in an amount that results in between 0.05 mg and 50 mg of the potato polysaccharide component of said potato polysaccharide preparation being administered to said mammal per kg of body weight of said mammal.

25

17. The method of claim 15, wherein said composition comprises between 1 mg and 100 mg of said potato polysaccharide preparation.

30

18. The method of claim 15, wherein said composition comprises between 6 mg and 20 mg of said potato polysaccharide preparation.

19. The method of claim 15, wherein said composition comprises between 1 mg and 100 mg of the potato polysaccharide component of said potato polysaccharide preparation.
- 5 20. The method of claim 15, wherein said composition comprises between 6 mg and 20 mg of the potato polysaccharide component of said potato polysaccharide preparation.
21. The method of claim 15, wherein said composition is in the form of a tablet.
- 10 22. The method of claim 15, wherein said composition comprises alpha lipoic acid.
23. The method of claim 15, wherein said composition comprises alpha
- 15 tocopherol.
24. The method of claim 15, wherein said potato polysaccharide preparation is in an amount that results in between 0.075 mg and 0.5 mg of the potato polysaccharide component of said potato polysaccharide preparation being administered to said
- 20 mammal per kg of body weight of said mammal.
25. The method of claim 15, wherein at least about 80 percent of said potato polysaccharide preparation is potato polysaccharide.
- 25 26. The method of claim 15, wherein at least about 90 percent of said potato polysaccharide preparation is potato polysaccharide.
27. The method of claim 15, wherein at least about 95 percent of said potato polysaccharide preparation is potato polysaccharide.
- 30 28. The method of claim 15, wherein said mammal is a human.

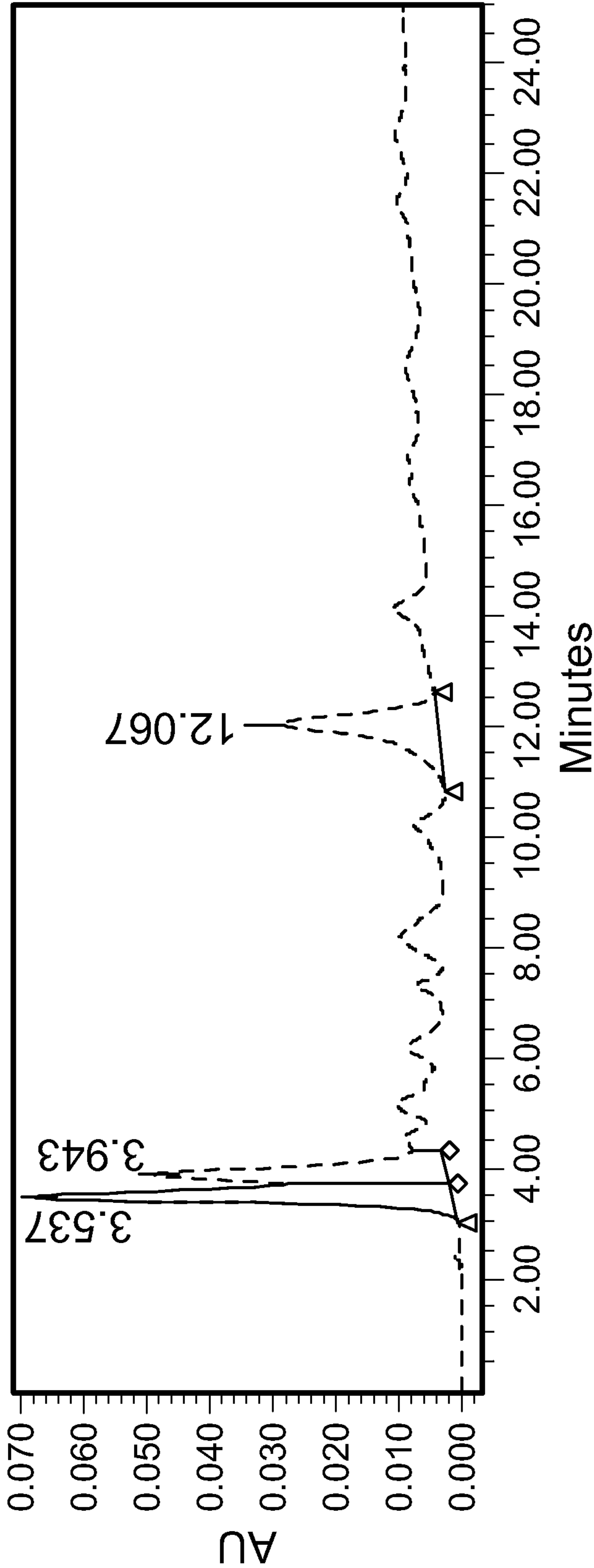


FIG. 1

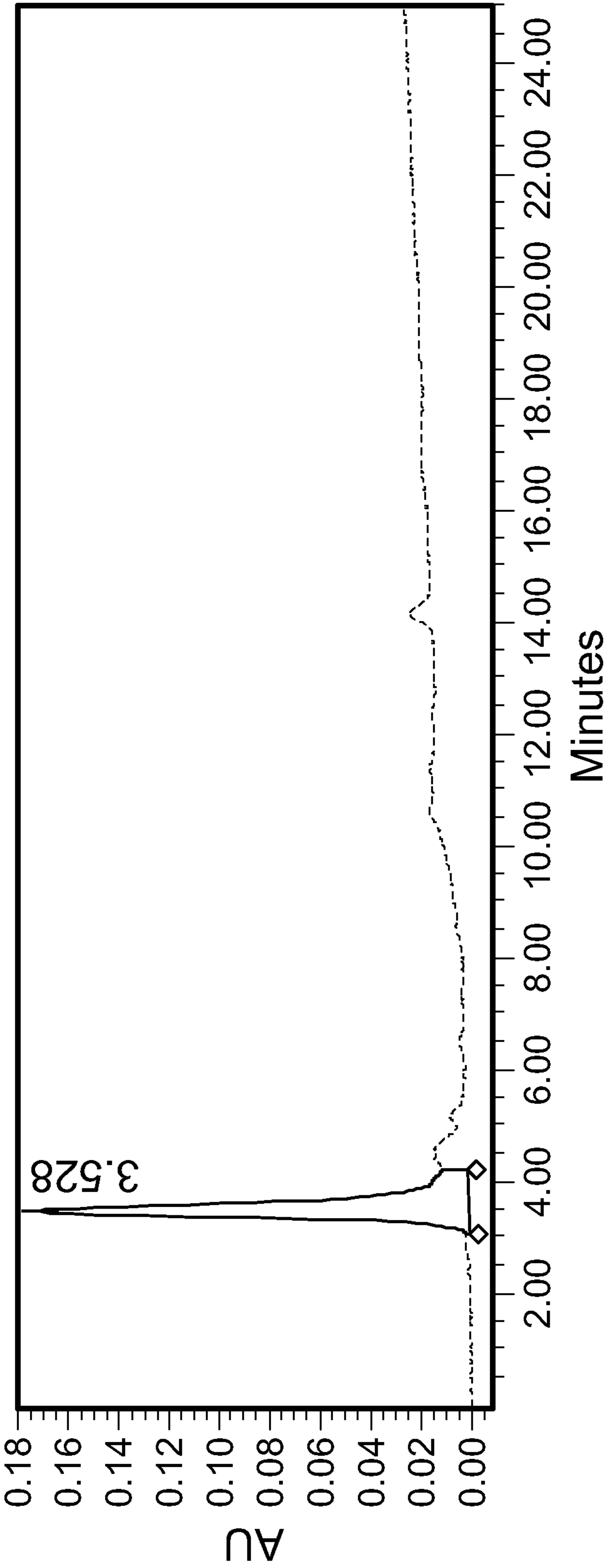


FIG. 2

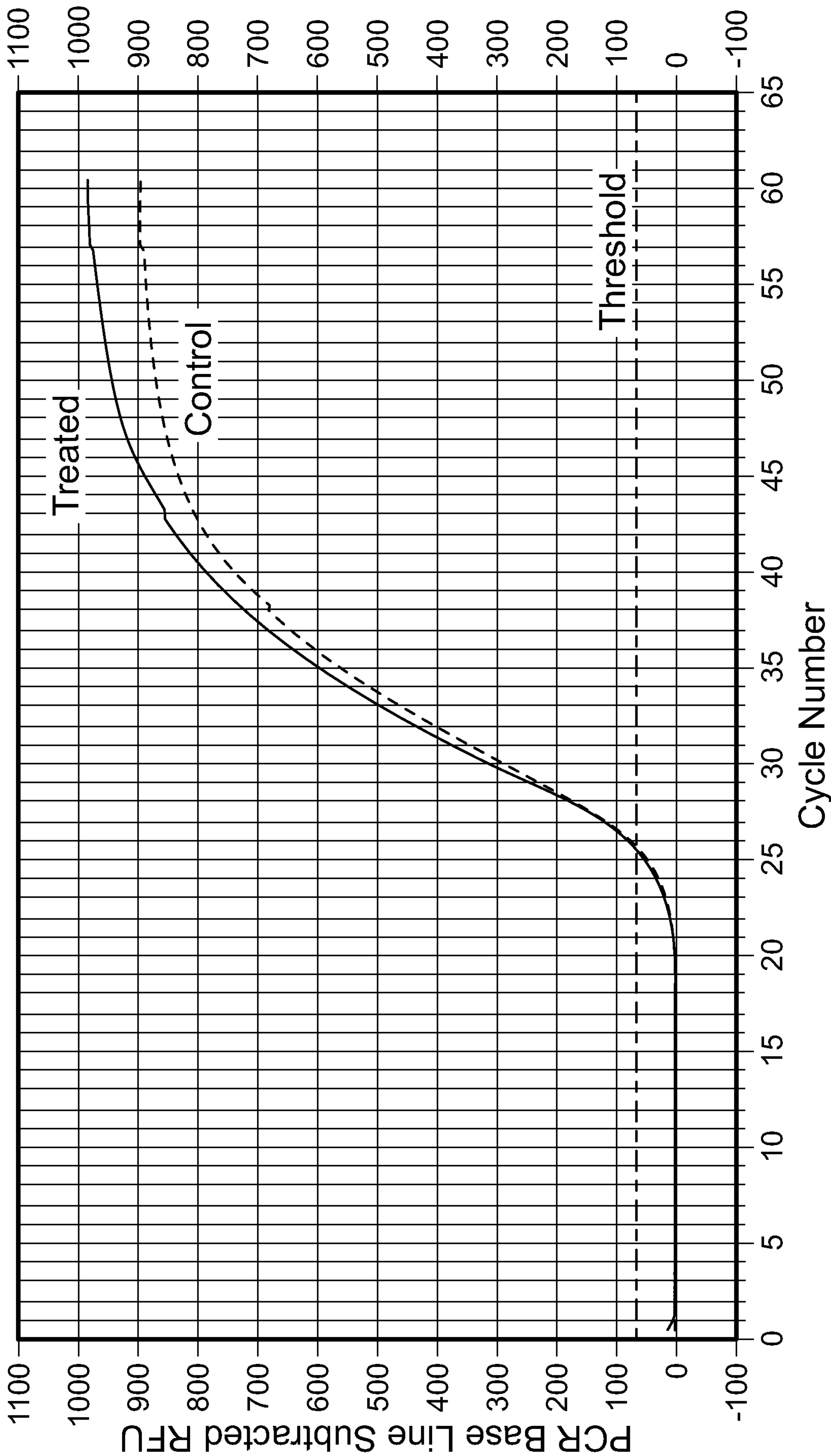


FIG. 3

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121611-NE479 Liquid

Instrument=LCmade 1 Operator=stlm Intel=LC Ionization=ESI+

Comment=90/10 H2O(HOAc)/MeOH - 100% MeOH

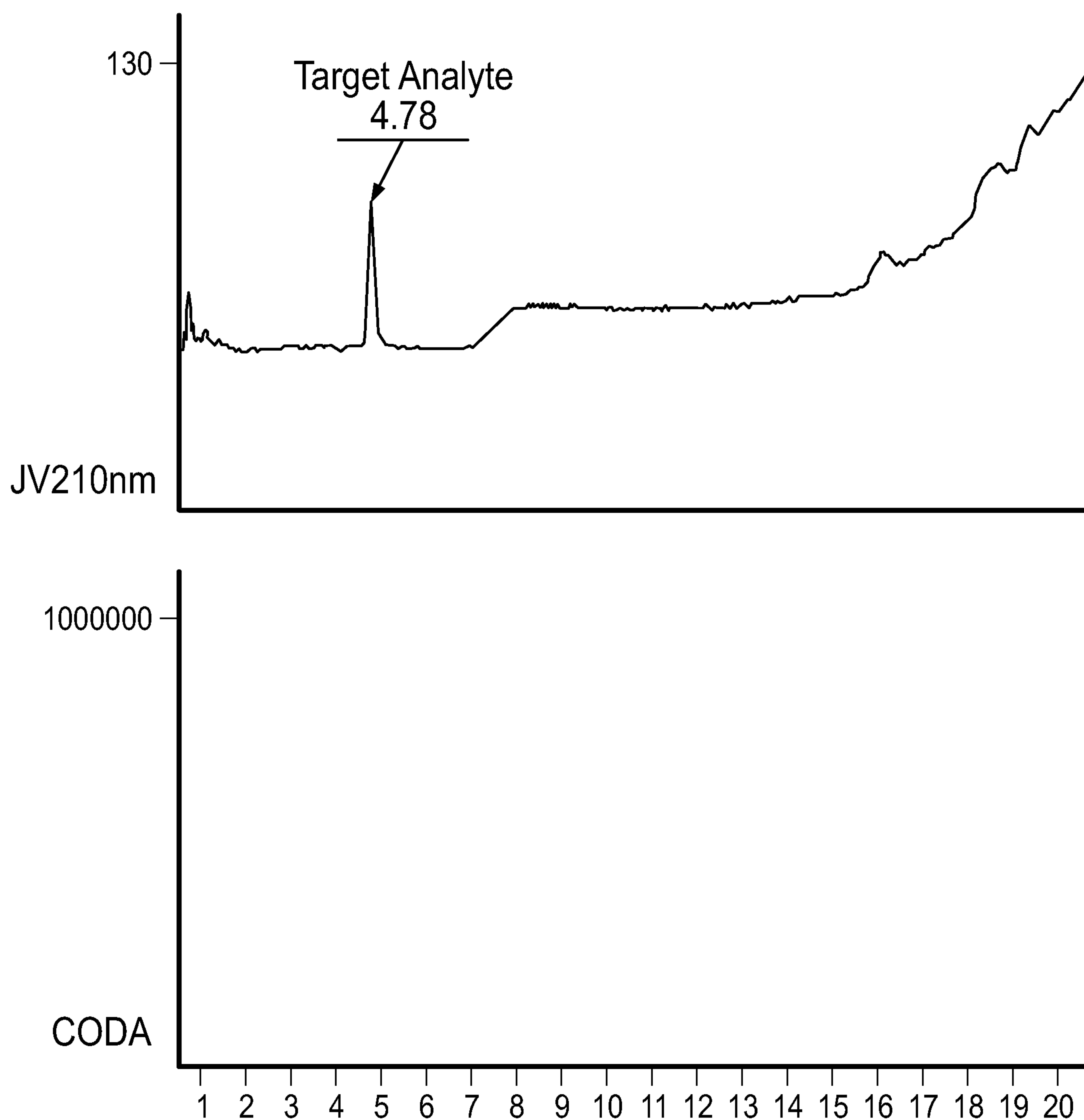
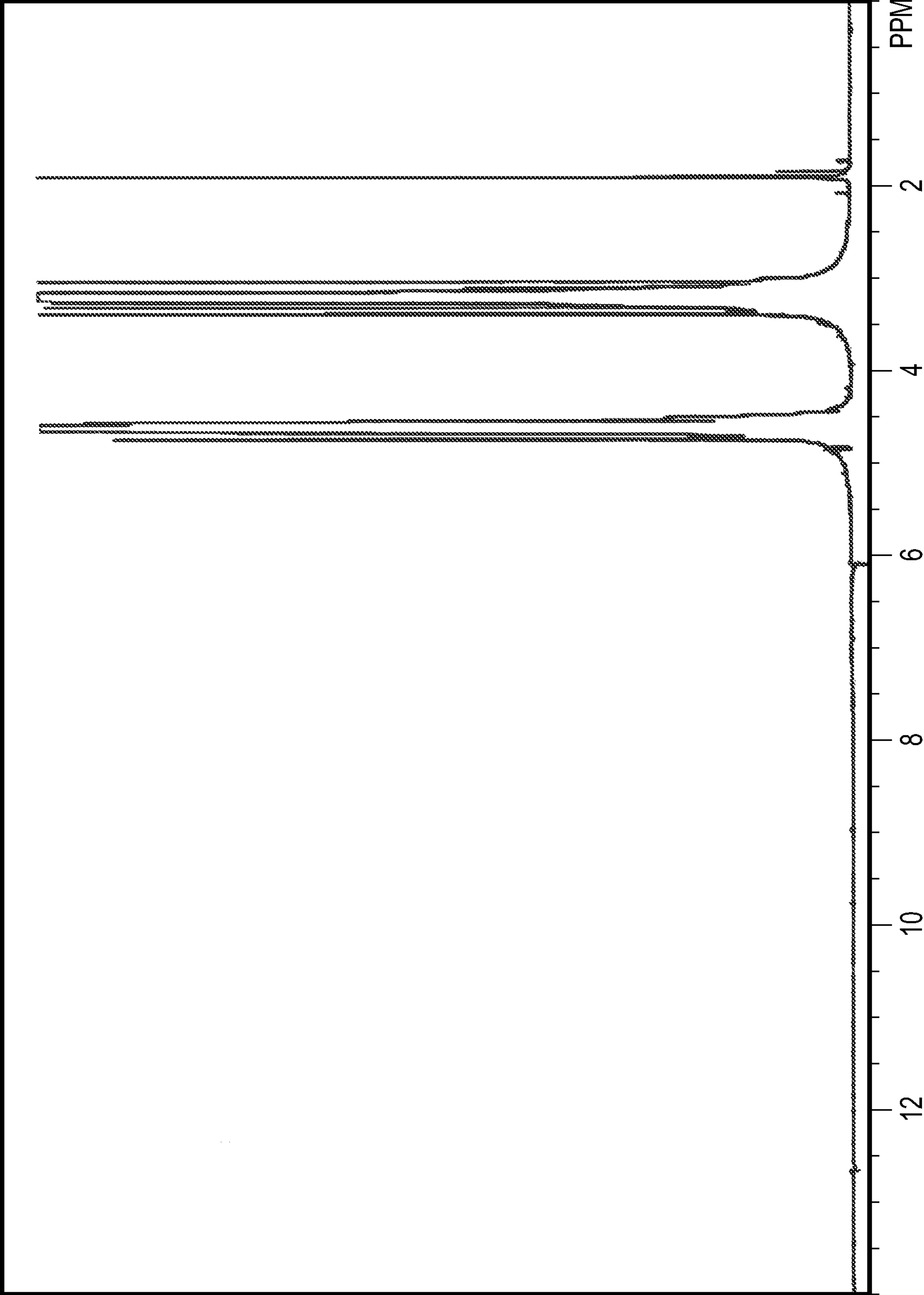


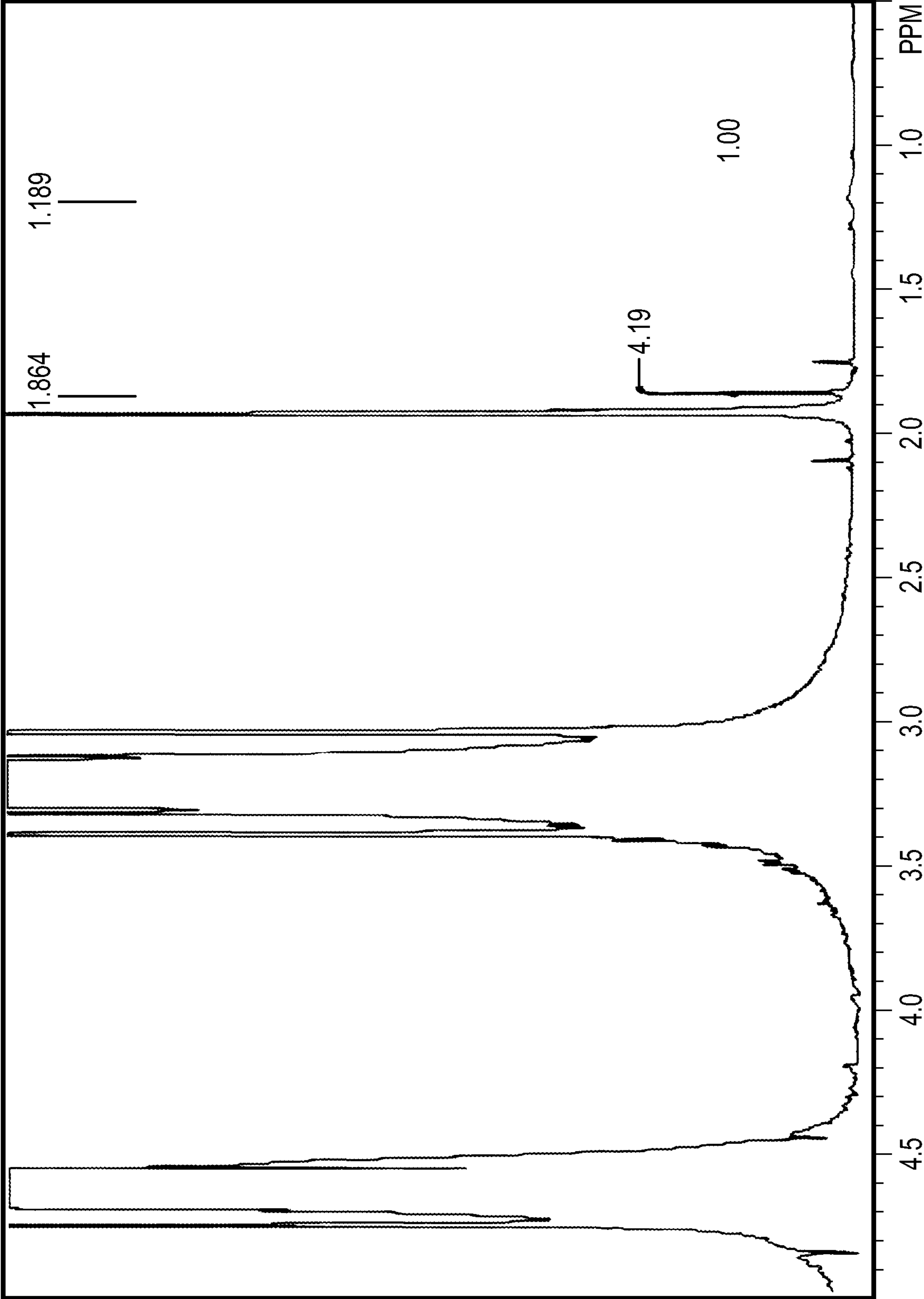
FIG. 4



NE479, D2O, 1H - presat, 400MHz

F1: 399.622	F2: 100.494	SW1: 7022	OF1: 2803.8	PTS1d: 17500 . 32768
EX: PRESAT		PW: 5.0 us	PD: 0.0 sec	NA: 1468
			LB: 1.0	Nuts - Savomz11.013 fid

FIG. 5



NE479, D2O, 1H - presat, 400MHz

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EX: PRESAT	PW: 6.0 us	PD: 0.0 sec	NA: 1468	LB: 1.0 Nuts - Savomz11.013 fid

FIG. 6

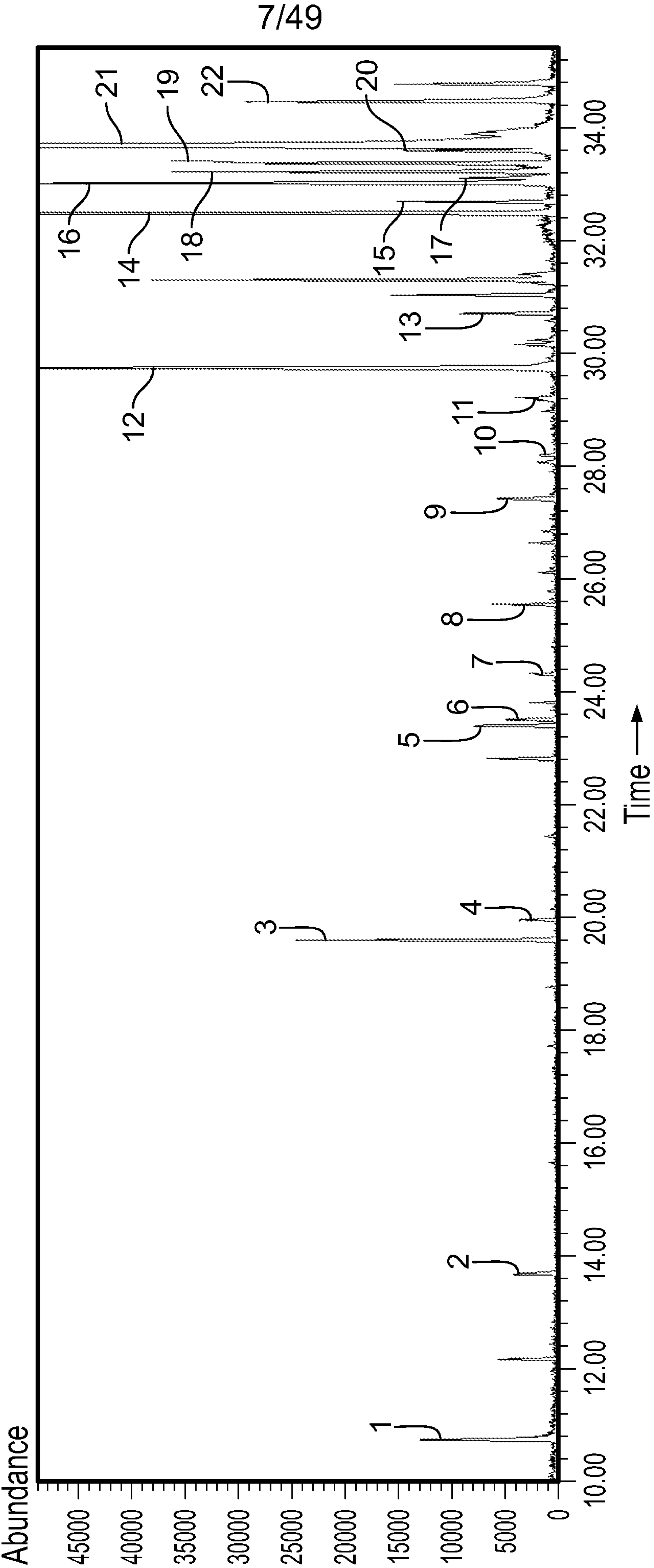


FIG. 7

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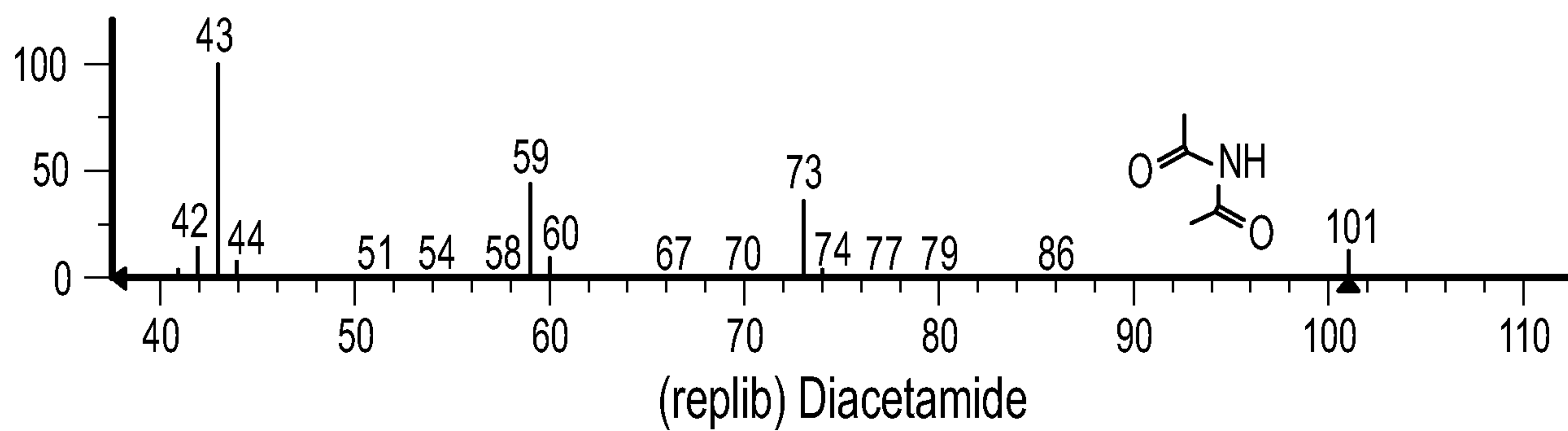
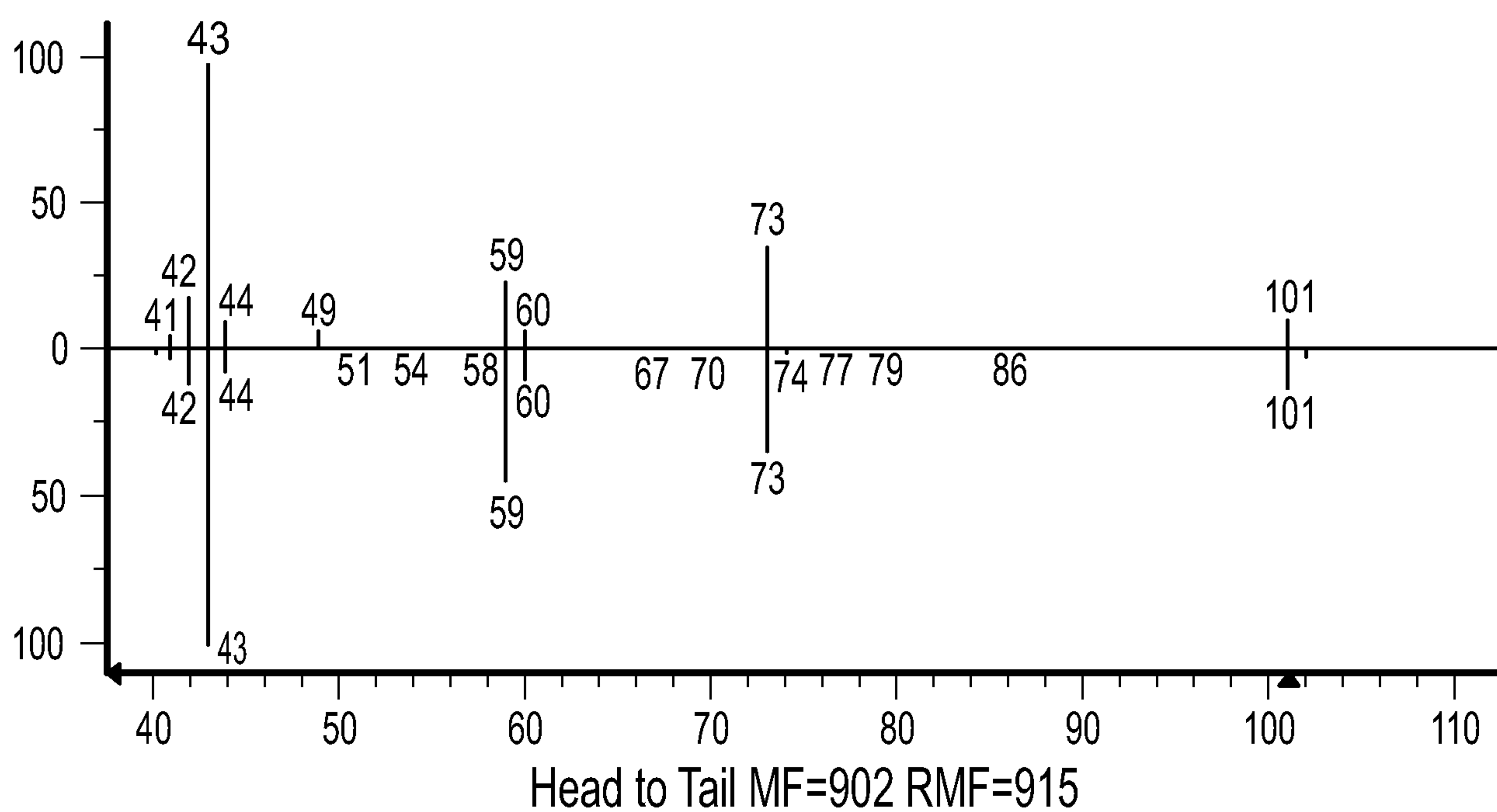
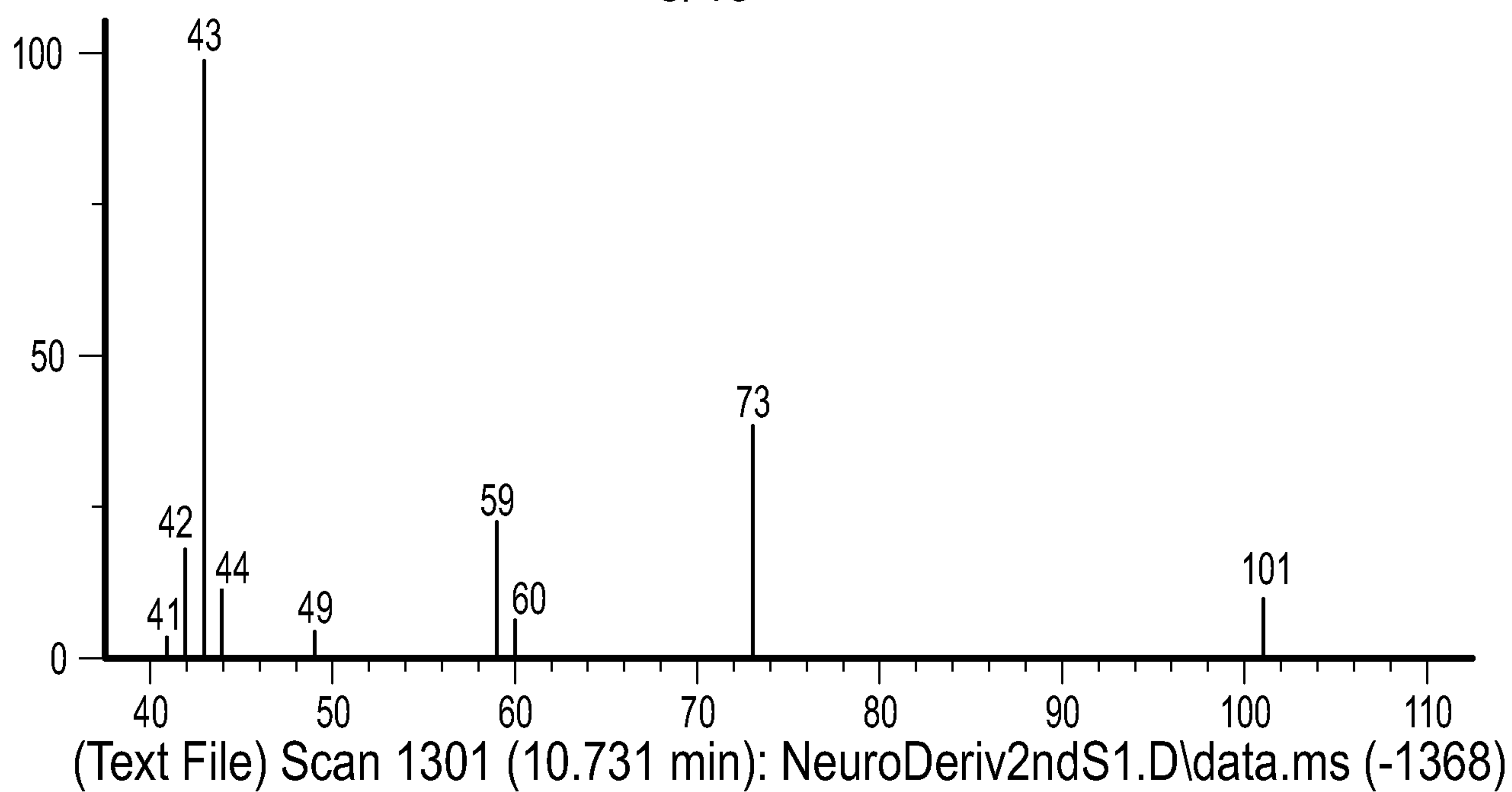


FIG. 8

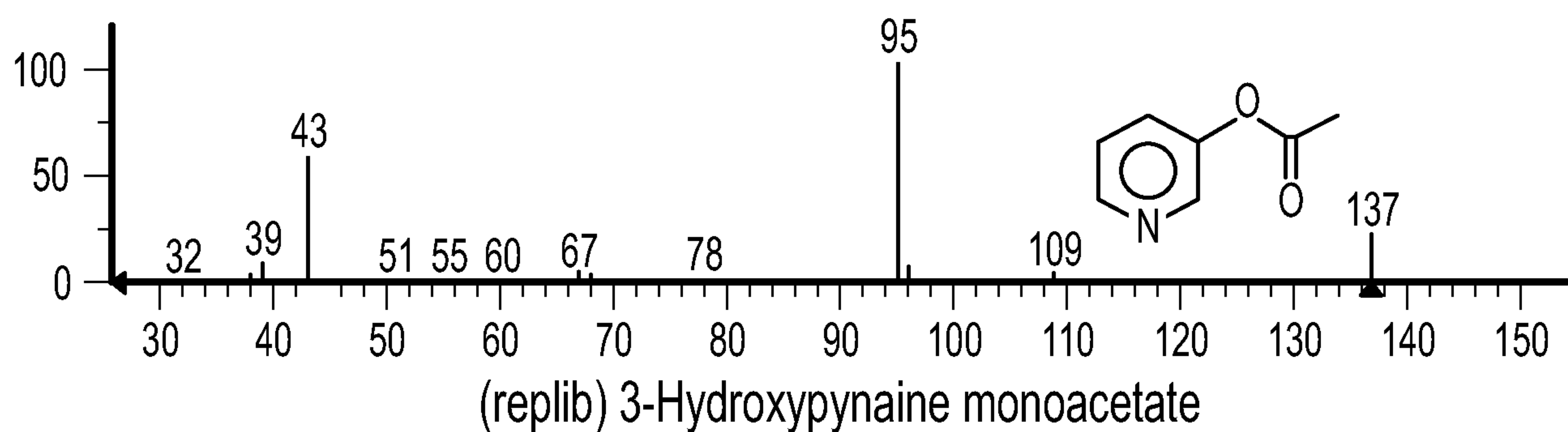
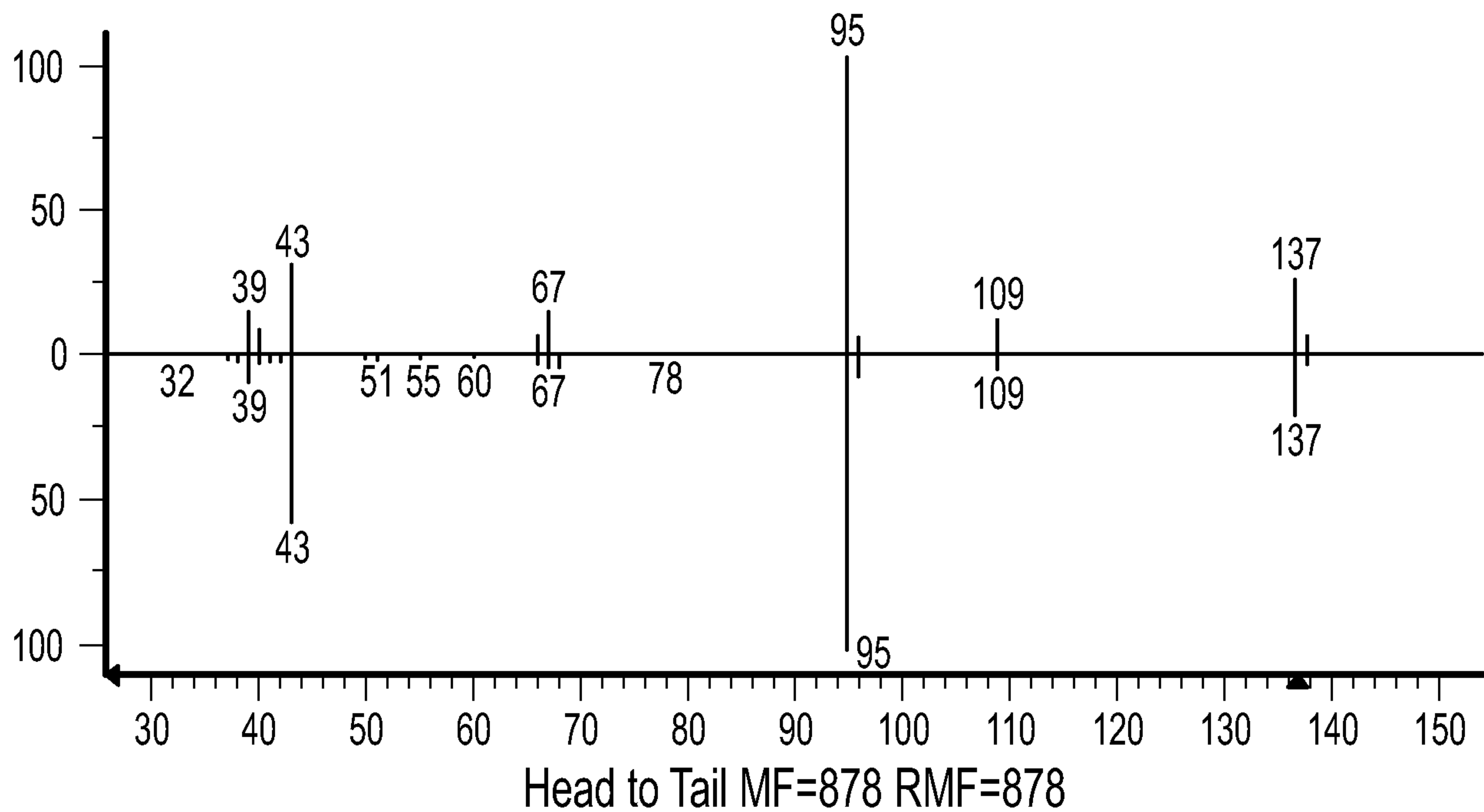
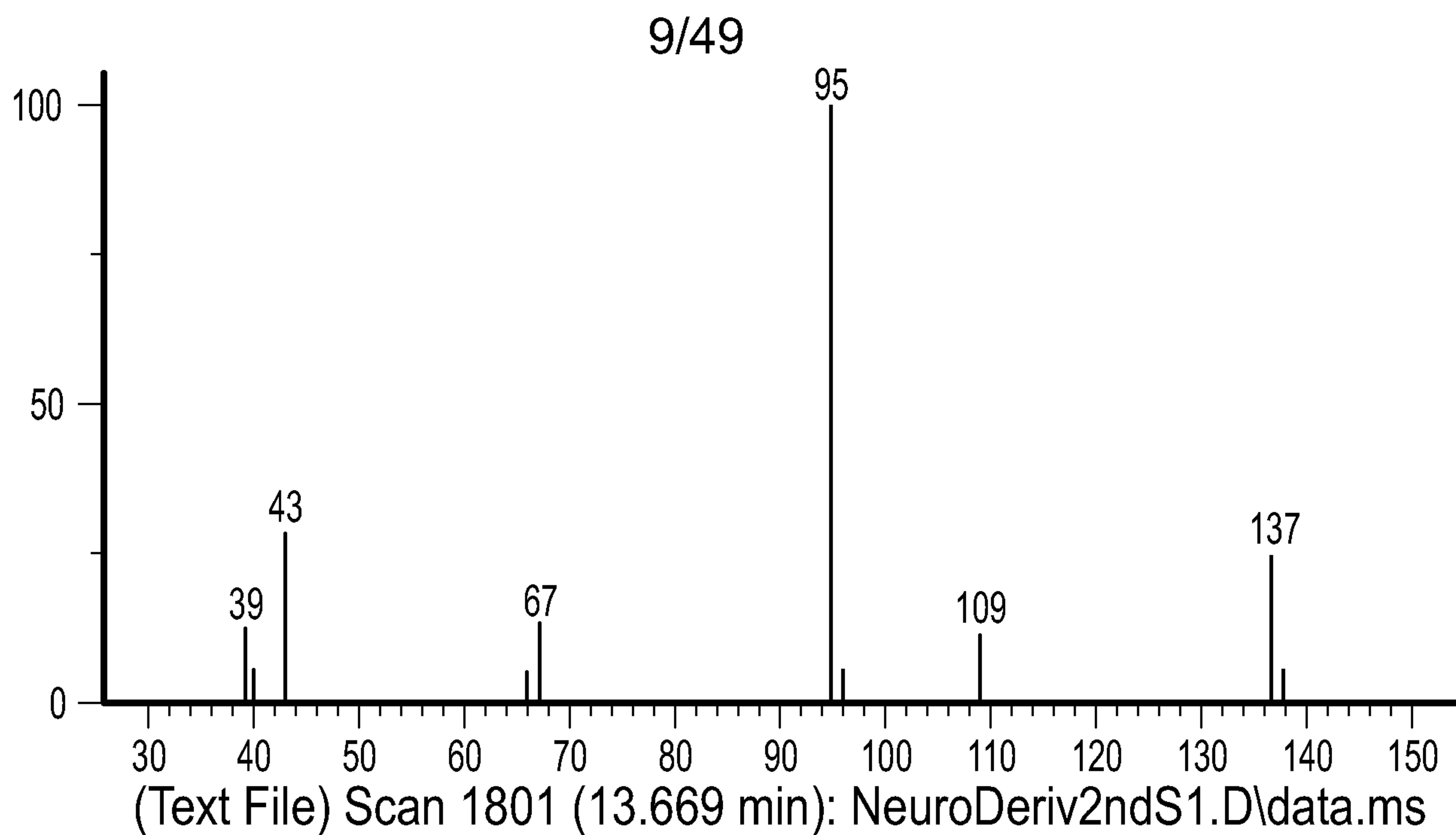


FIG. 9

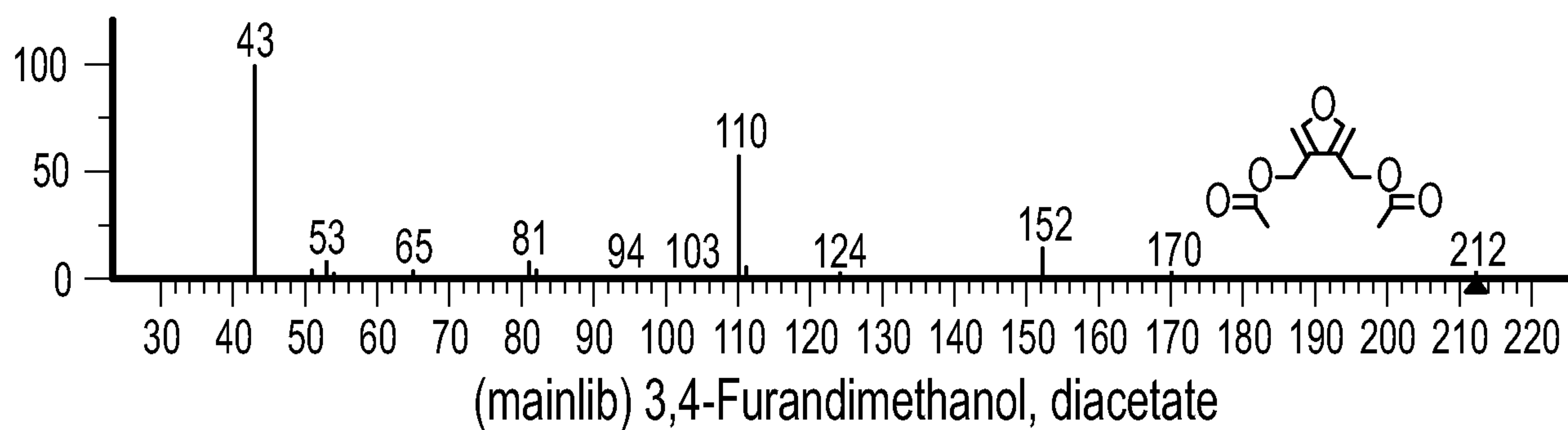
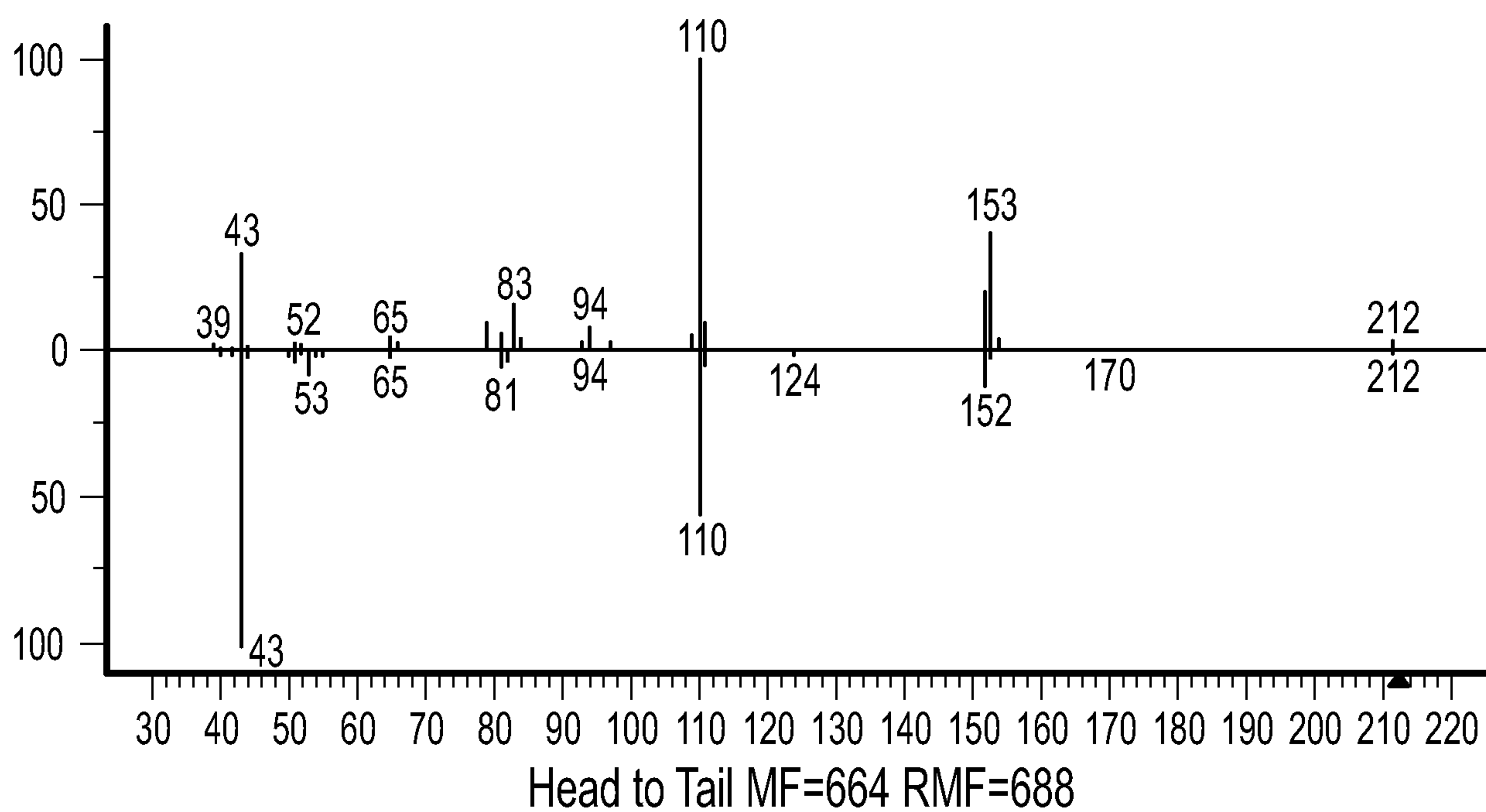
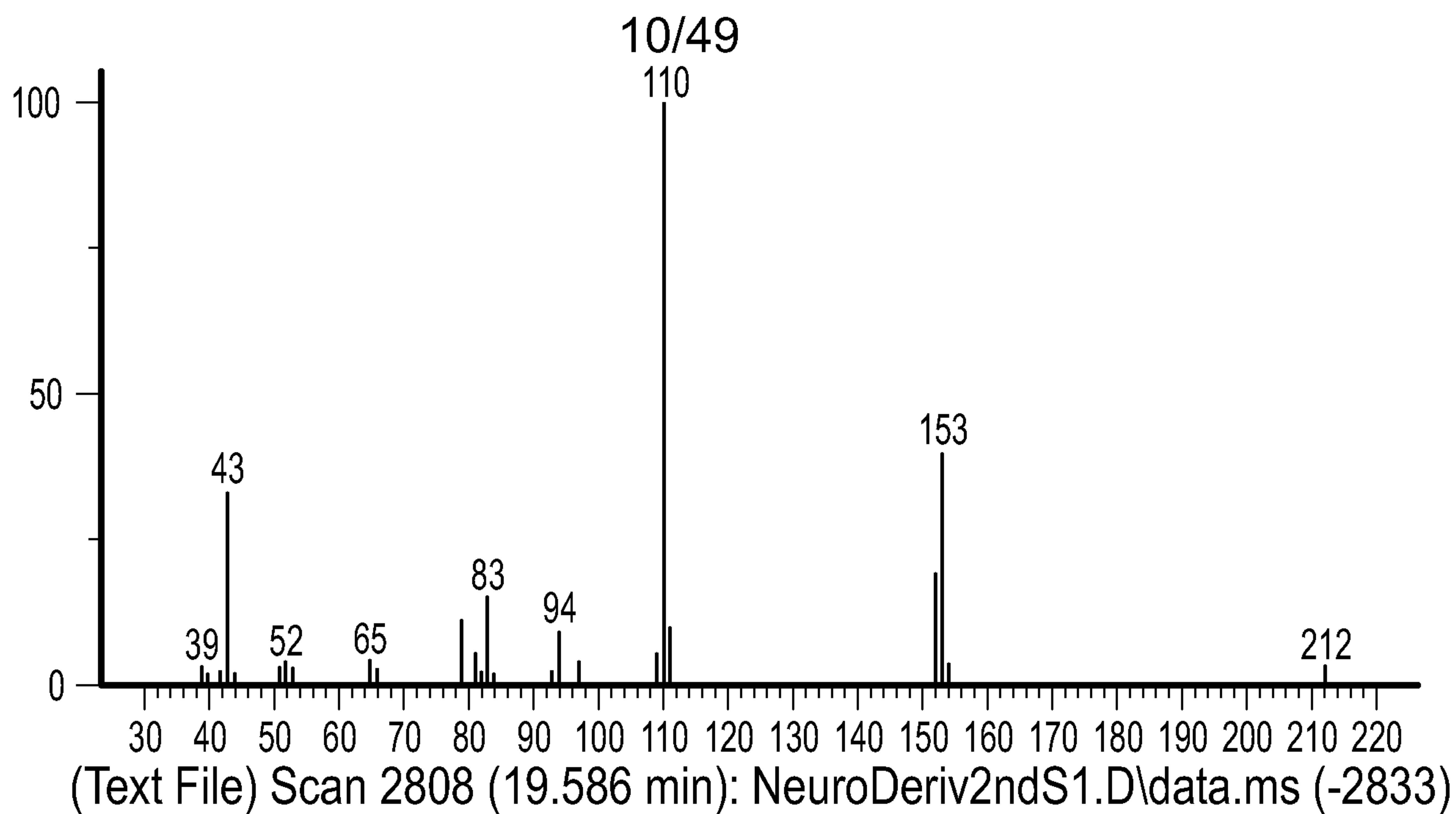


FIG. 10

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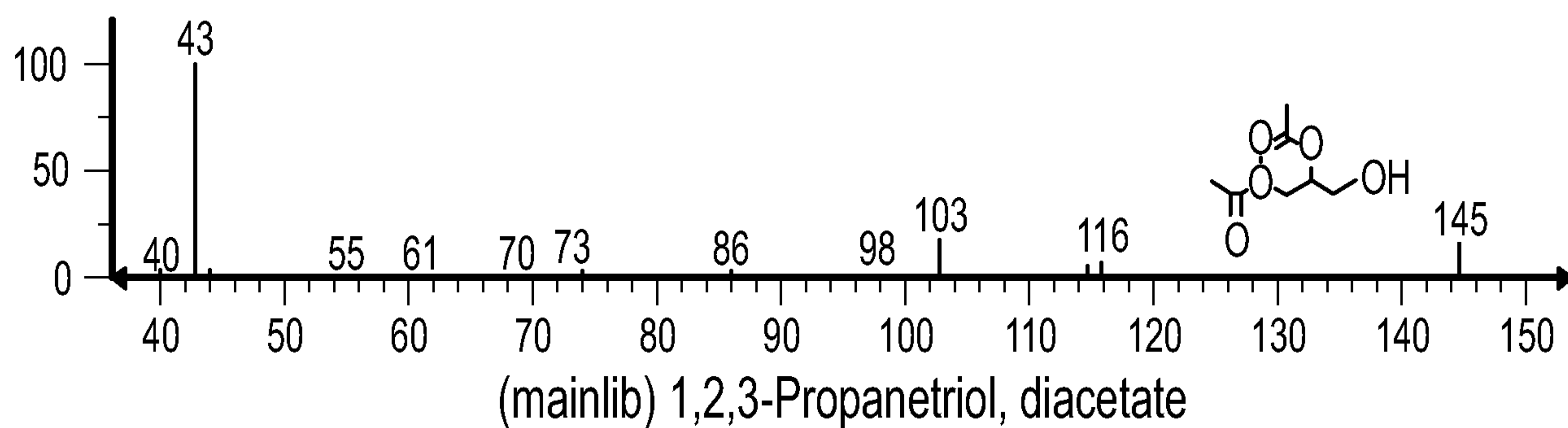
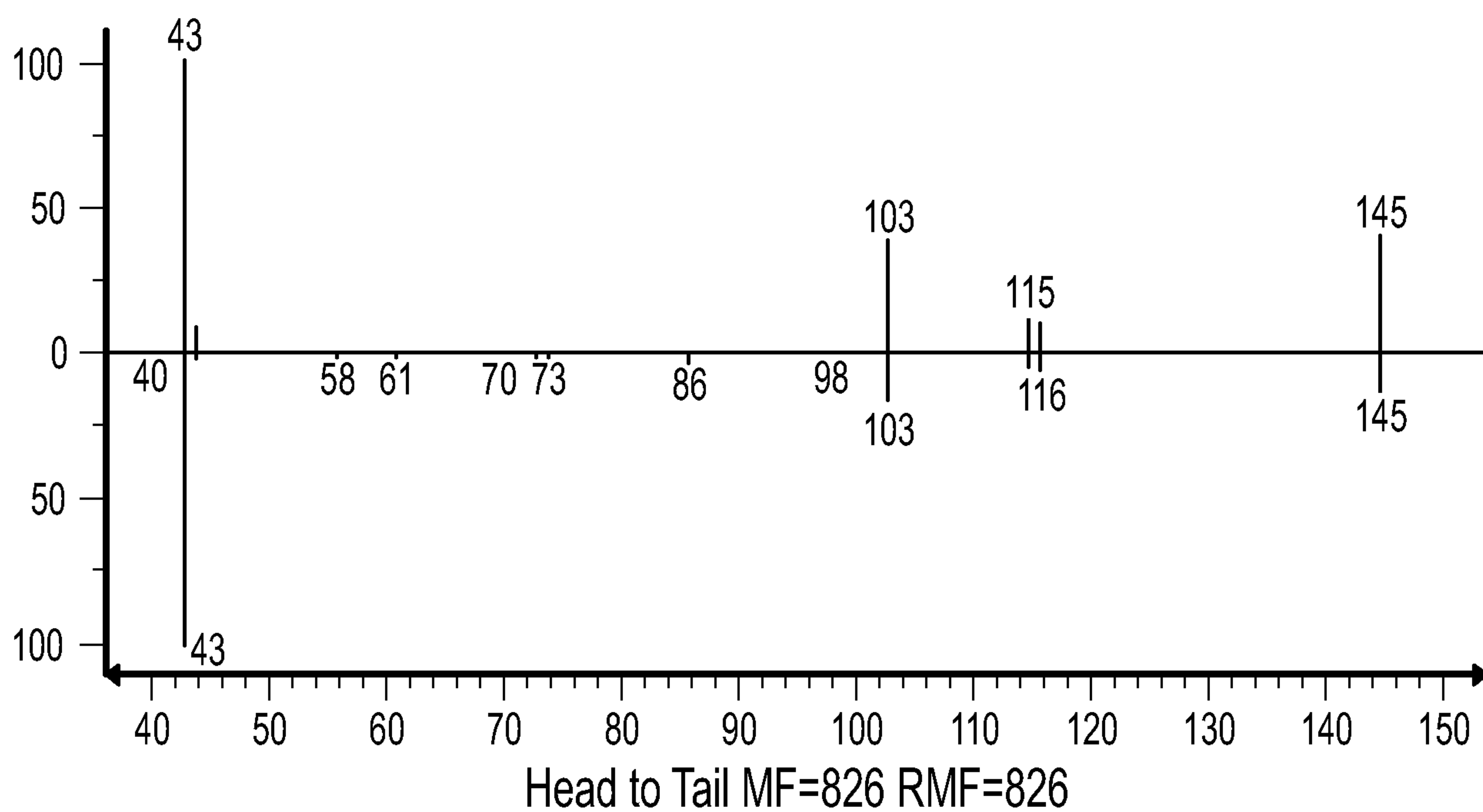
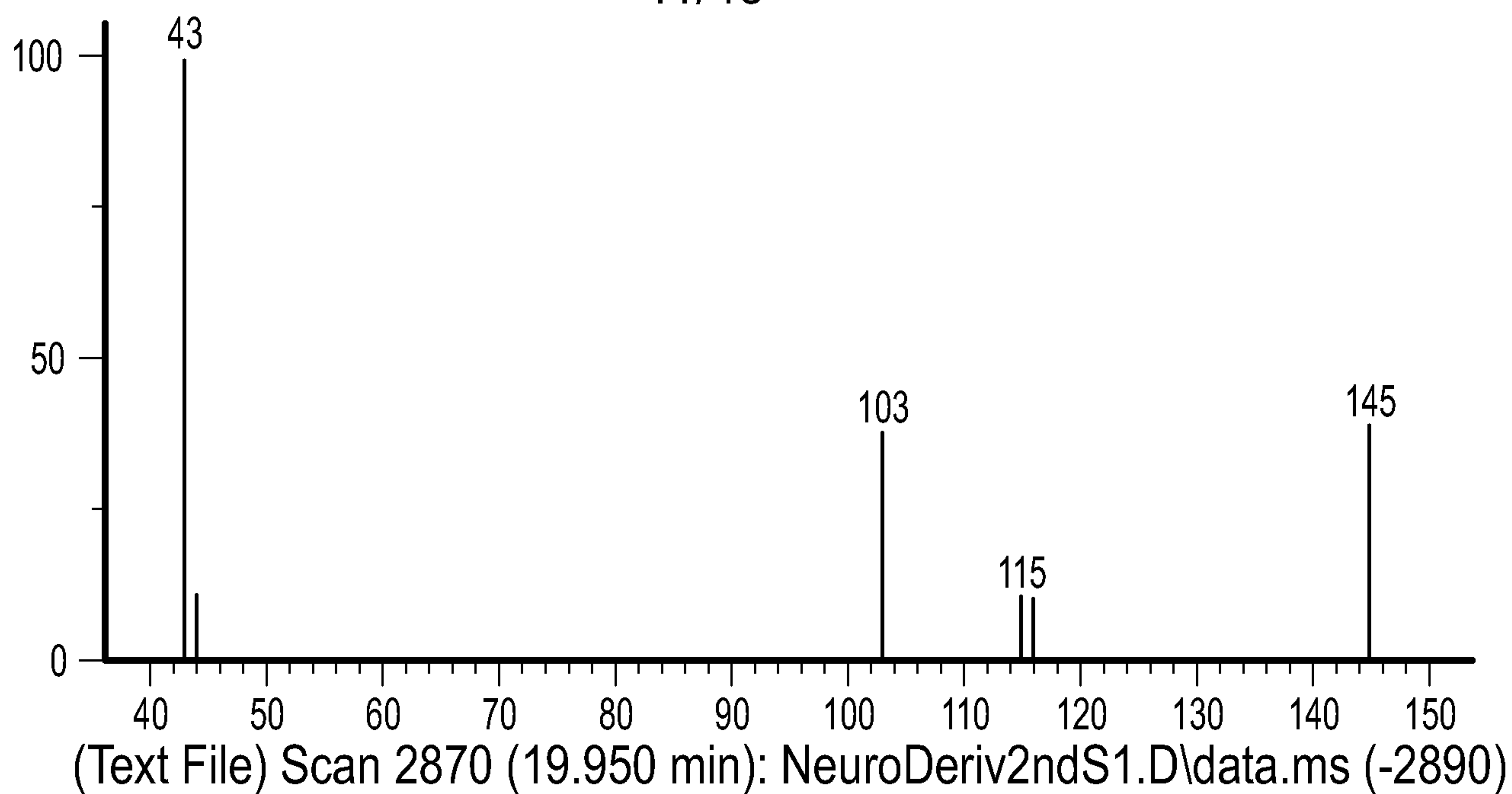


FIG. 11

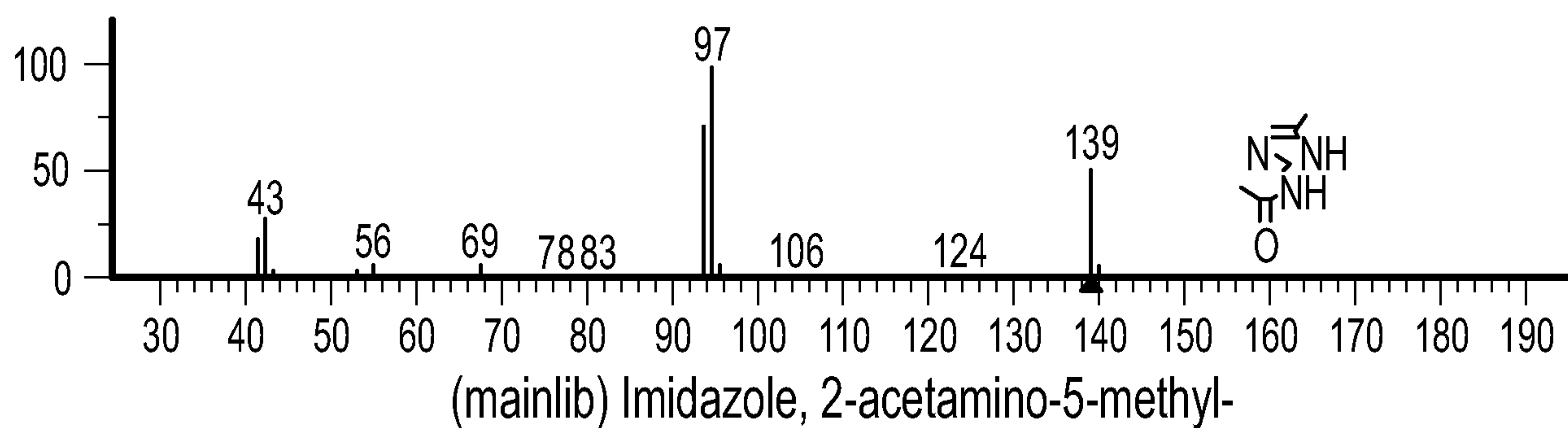
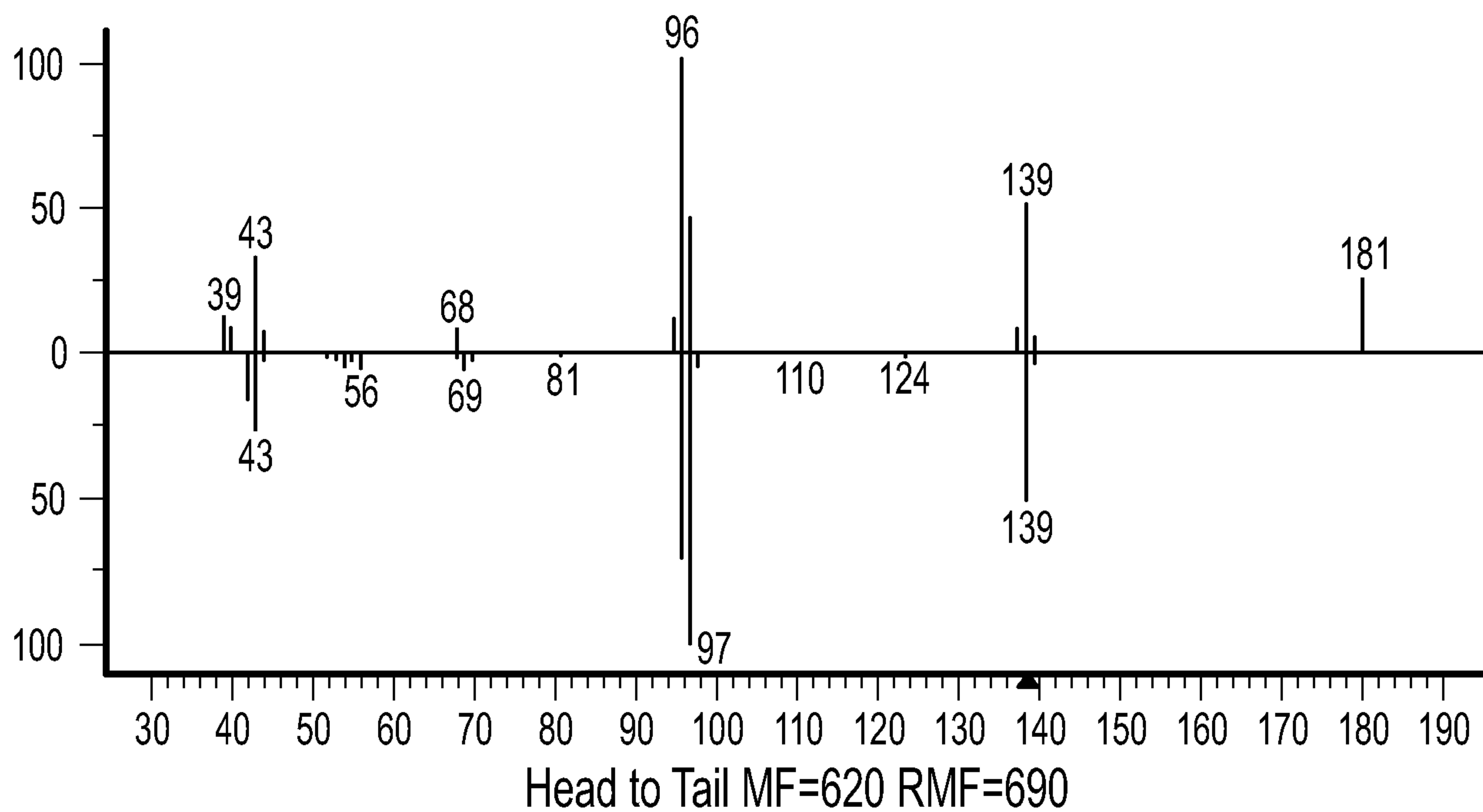
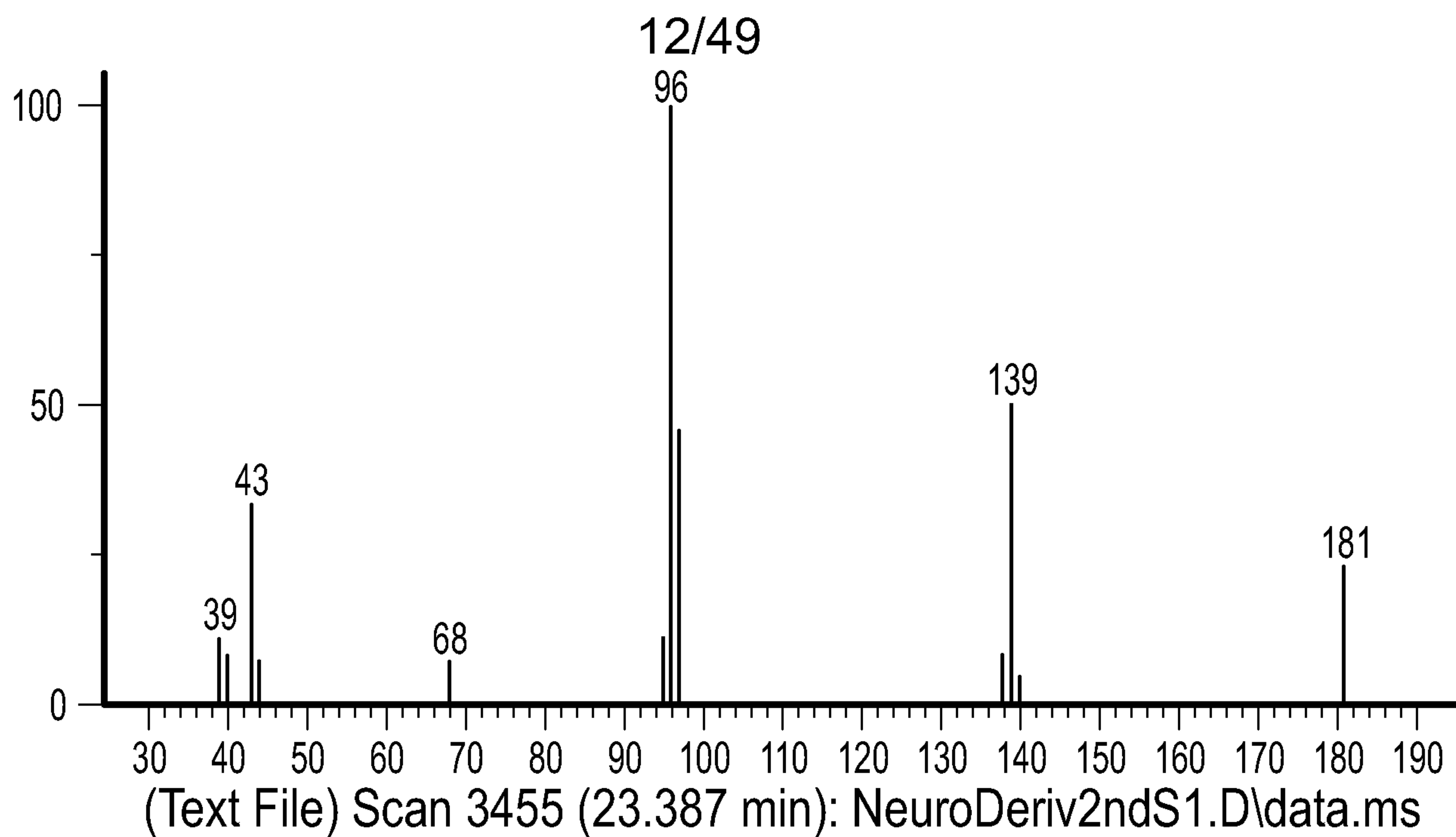


FIG. 12

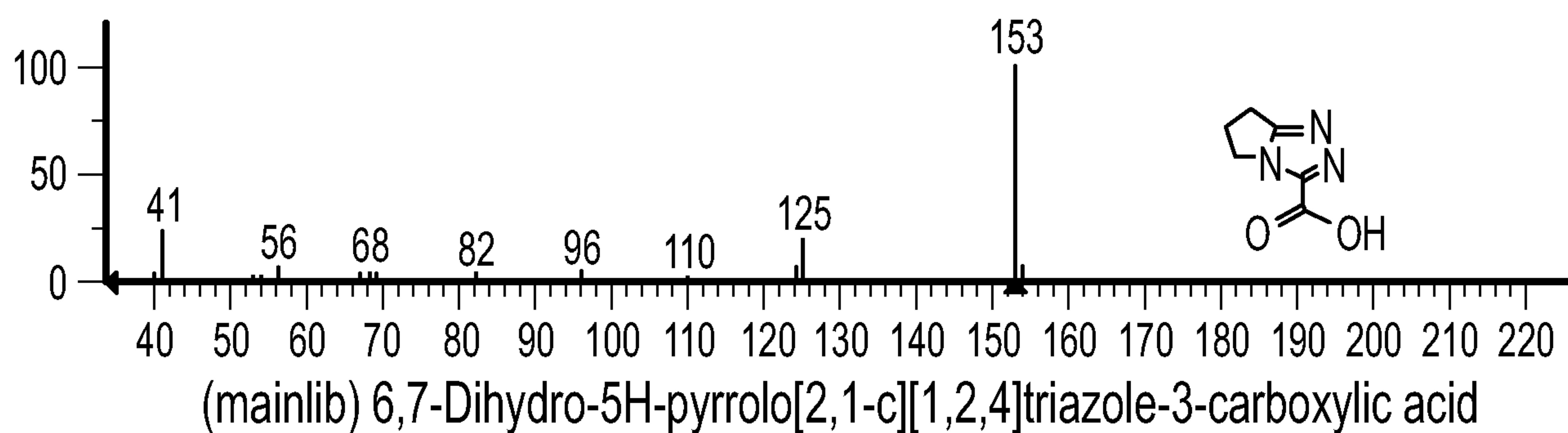
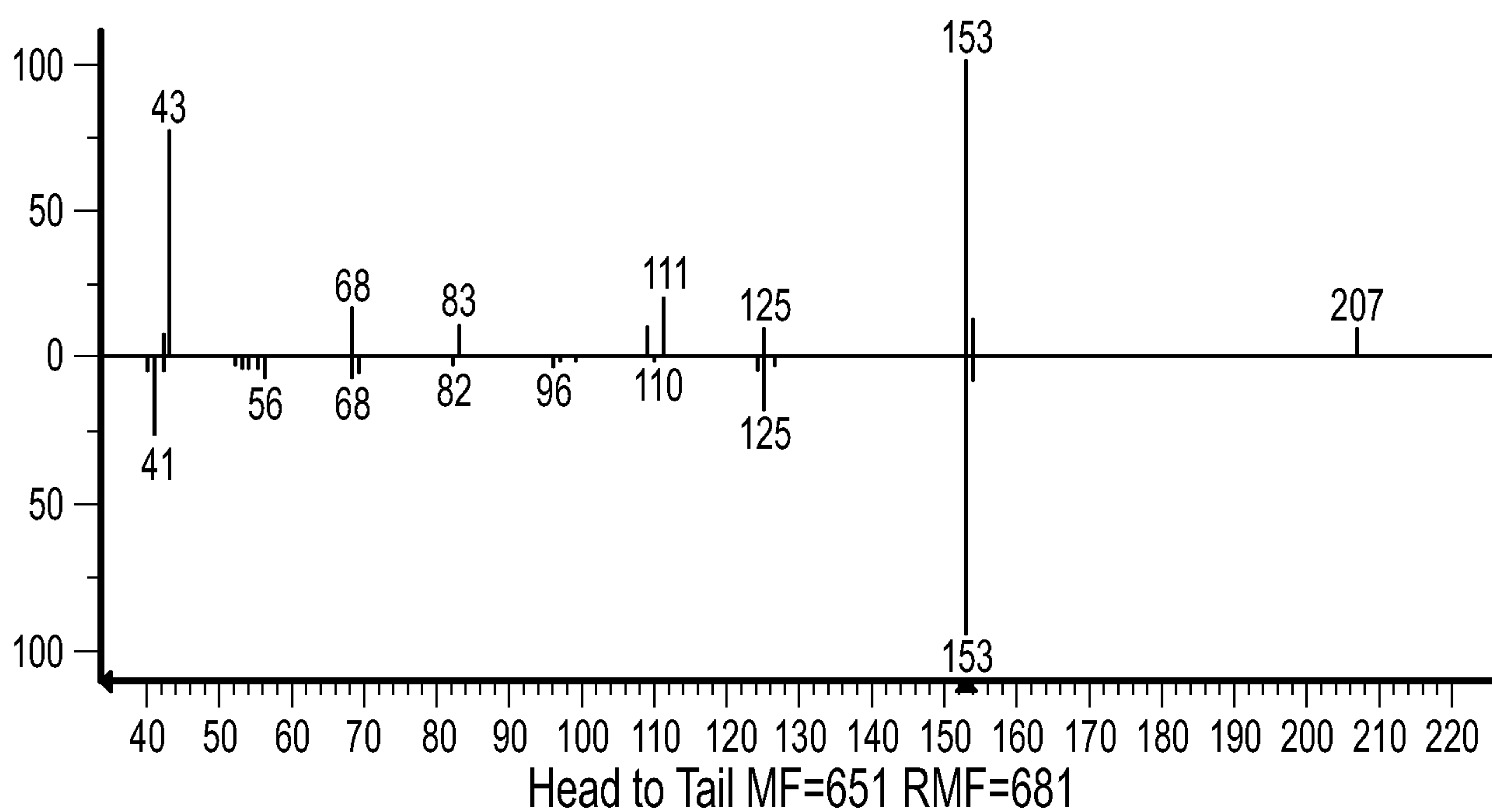
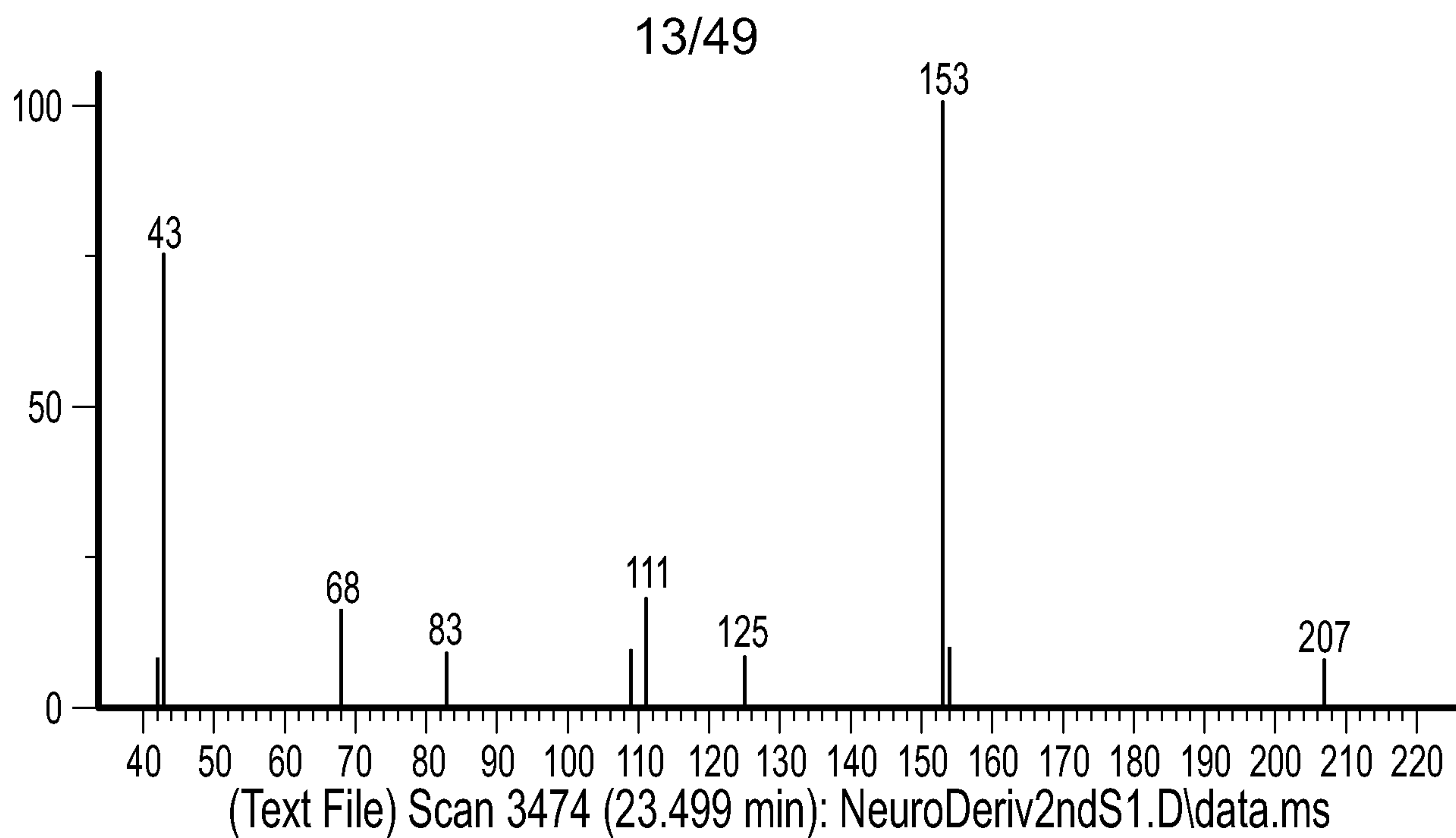


FIG. 13

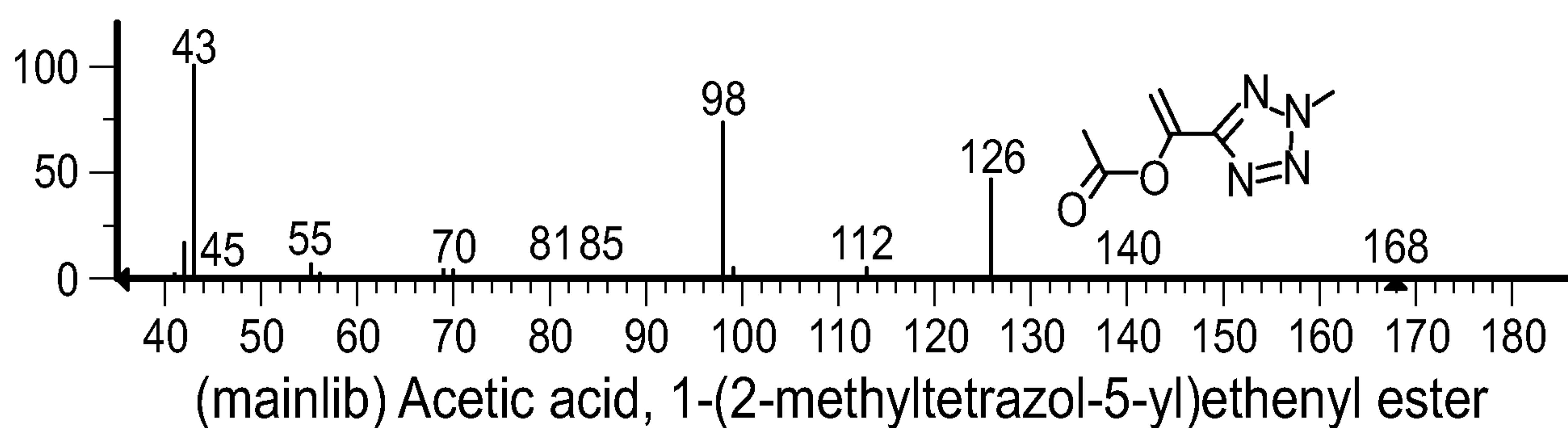
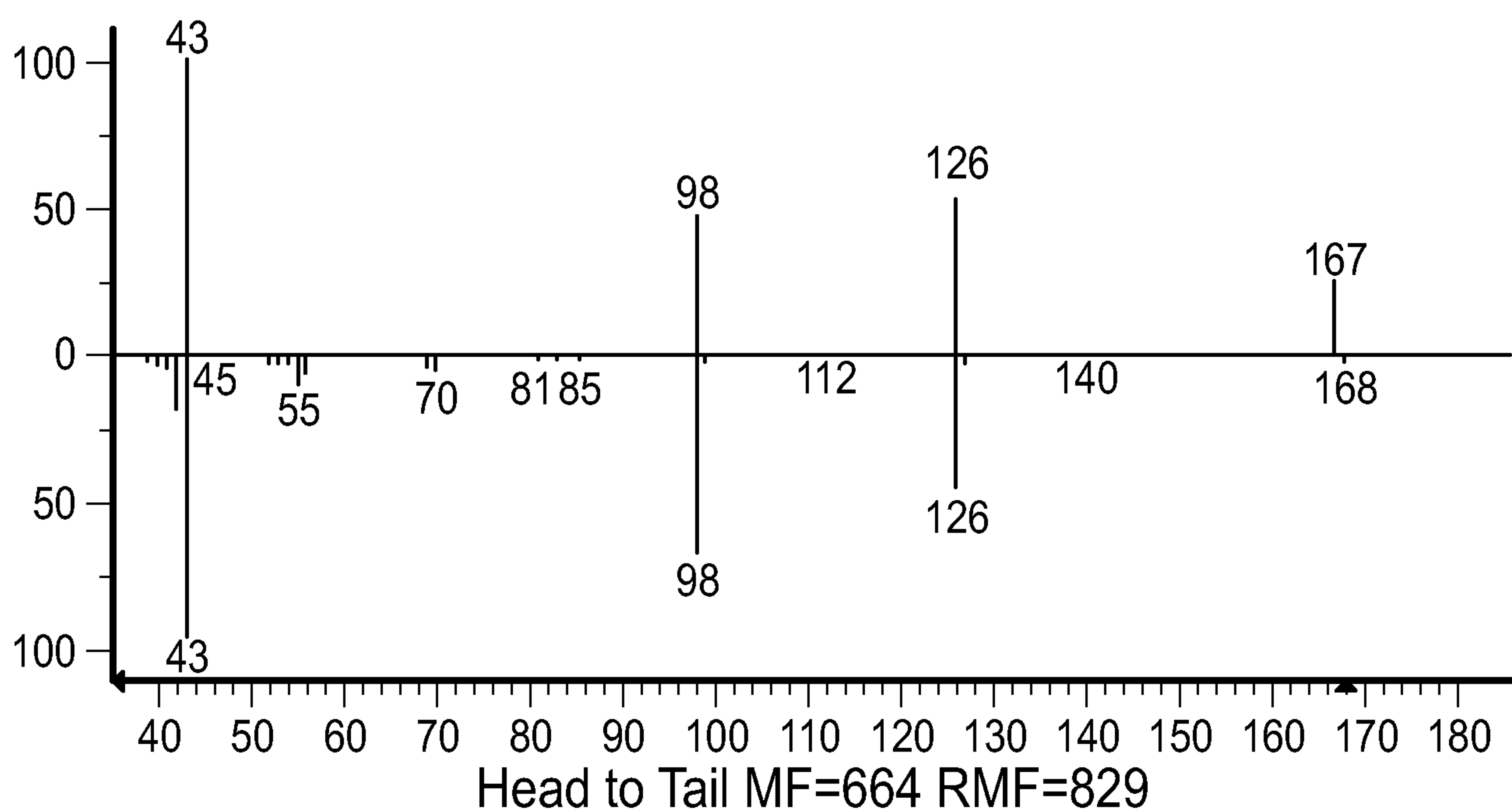
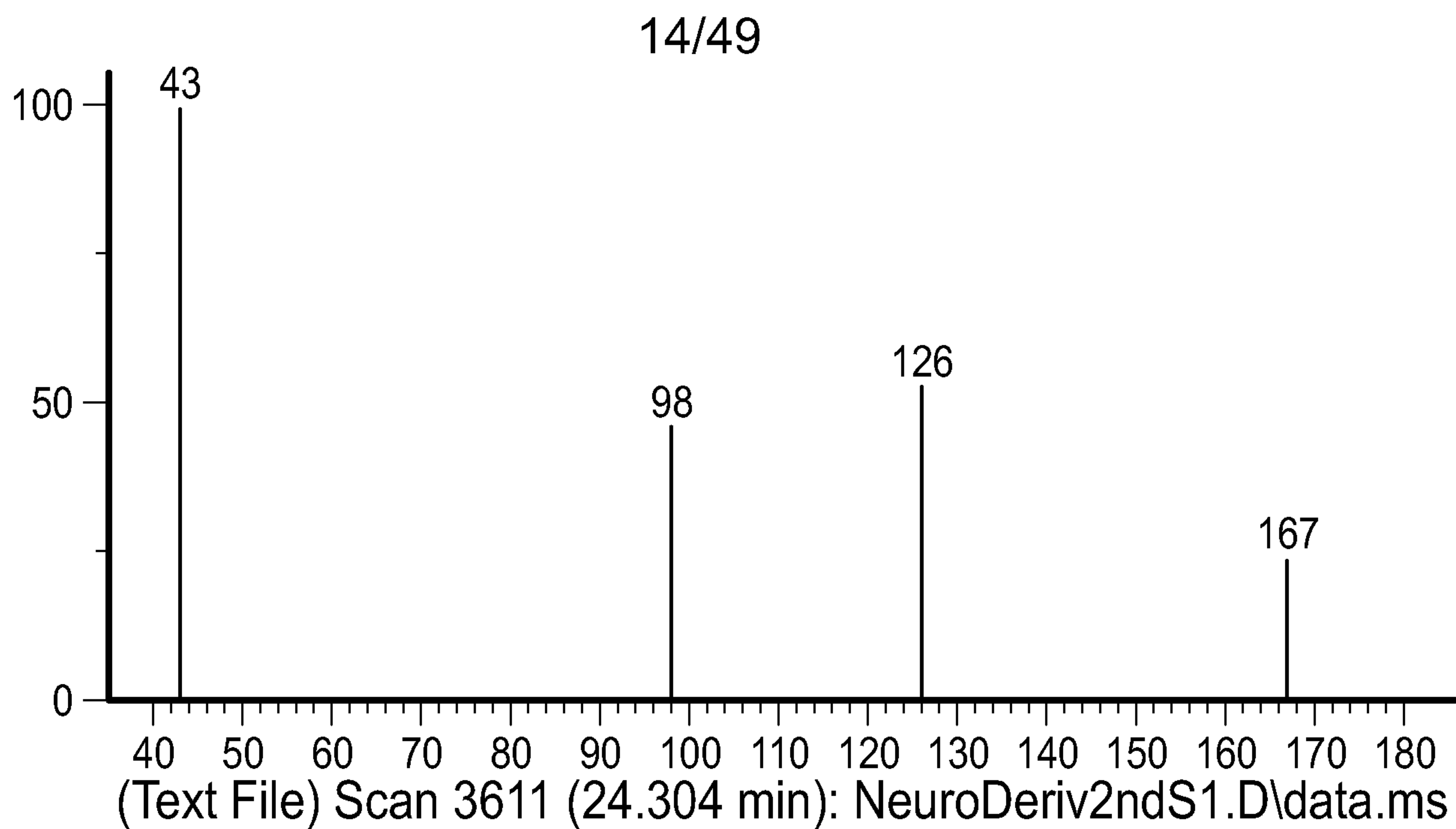


FIG. 14

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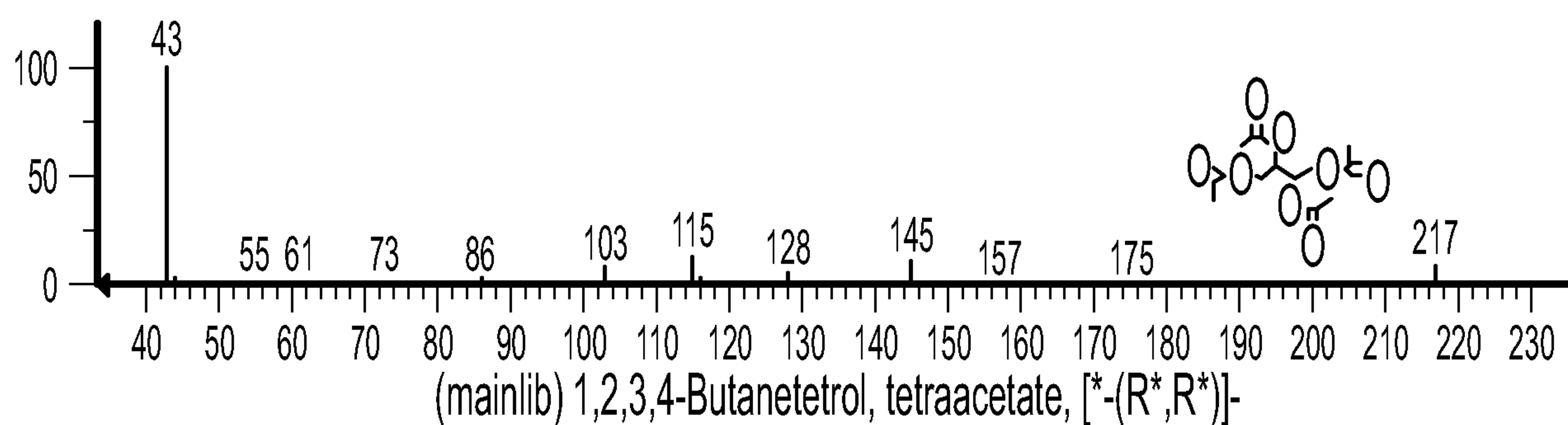
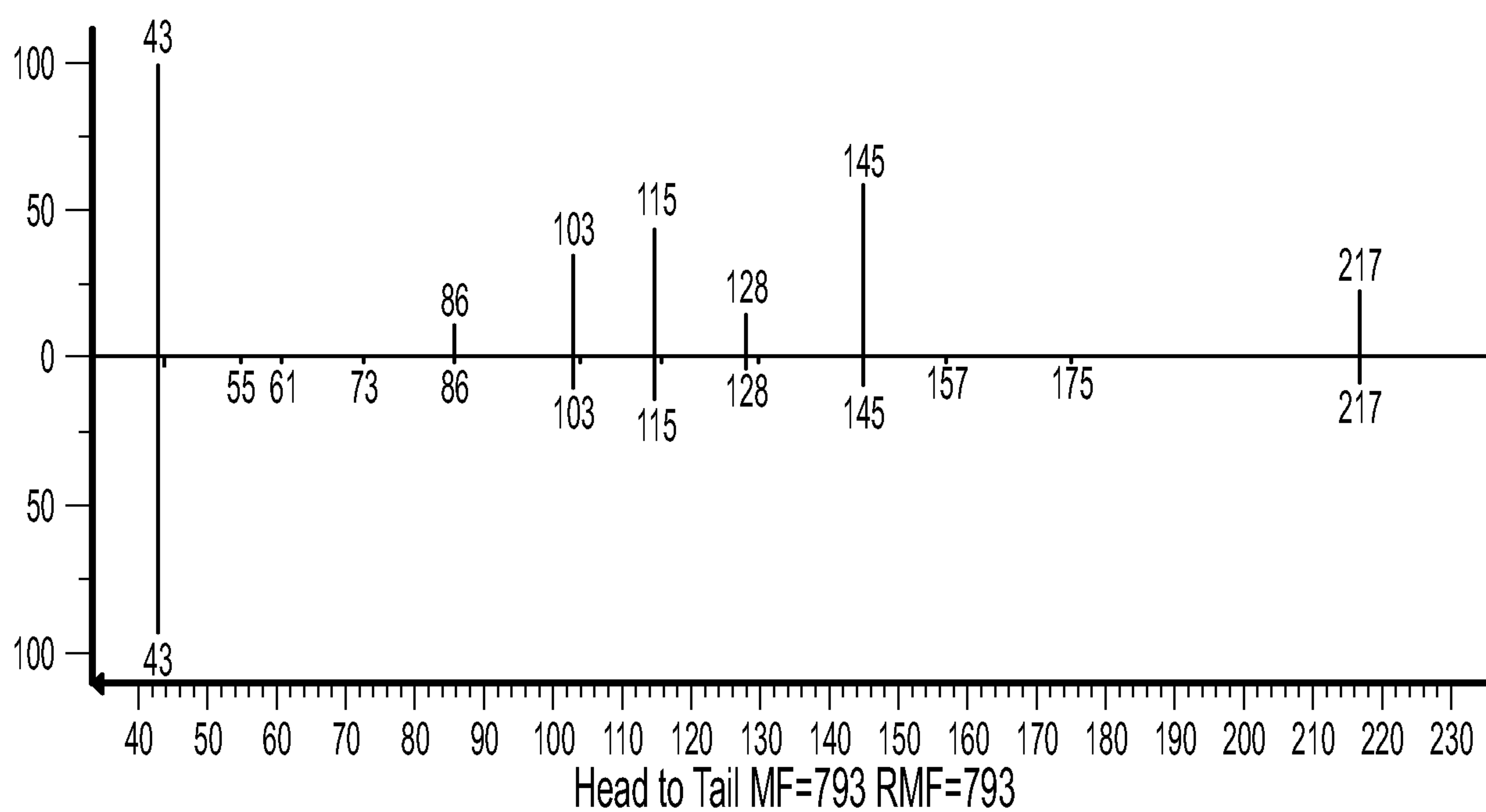
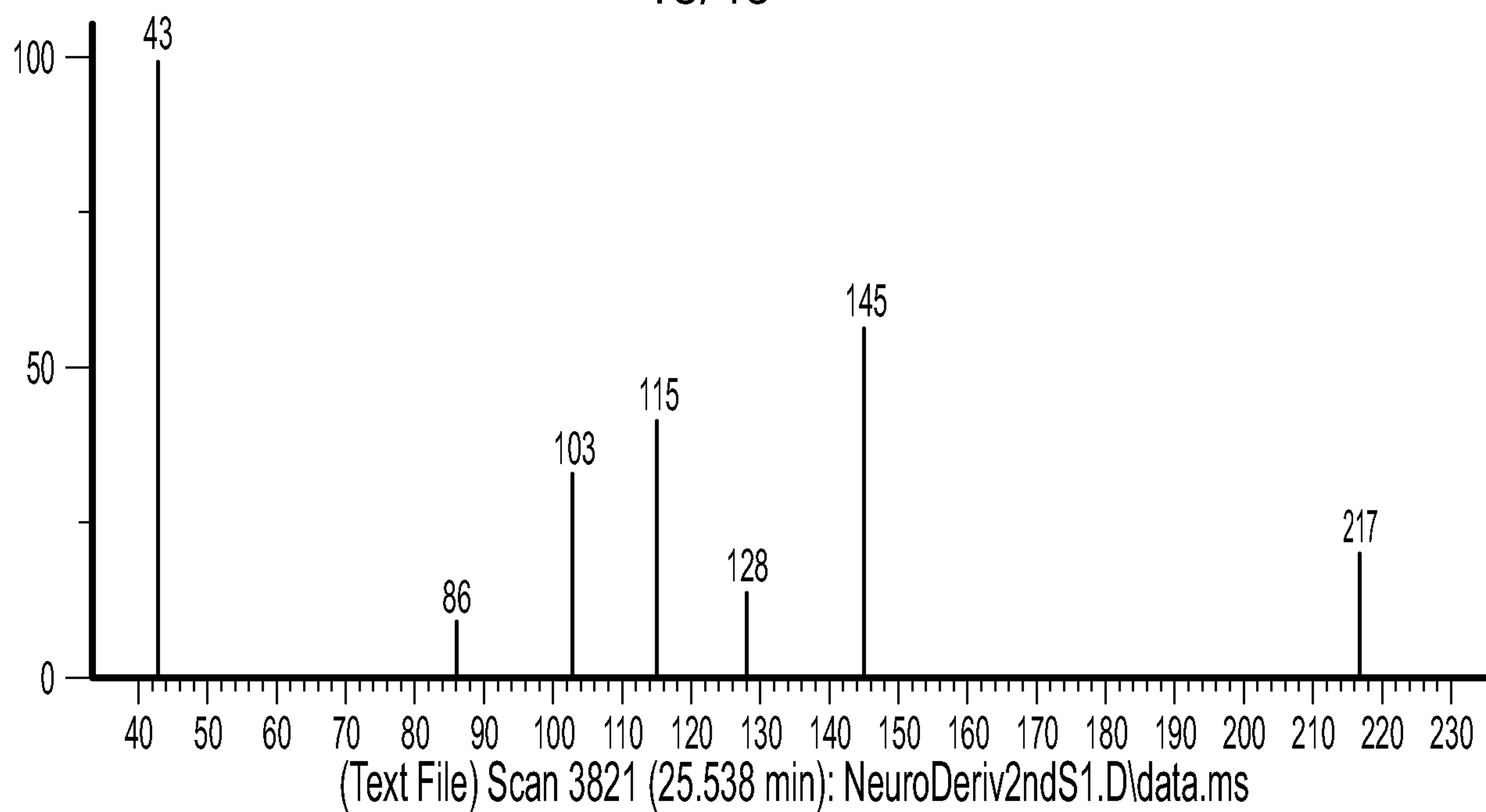


FIG. 15

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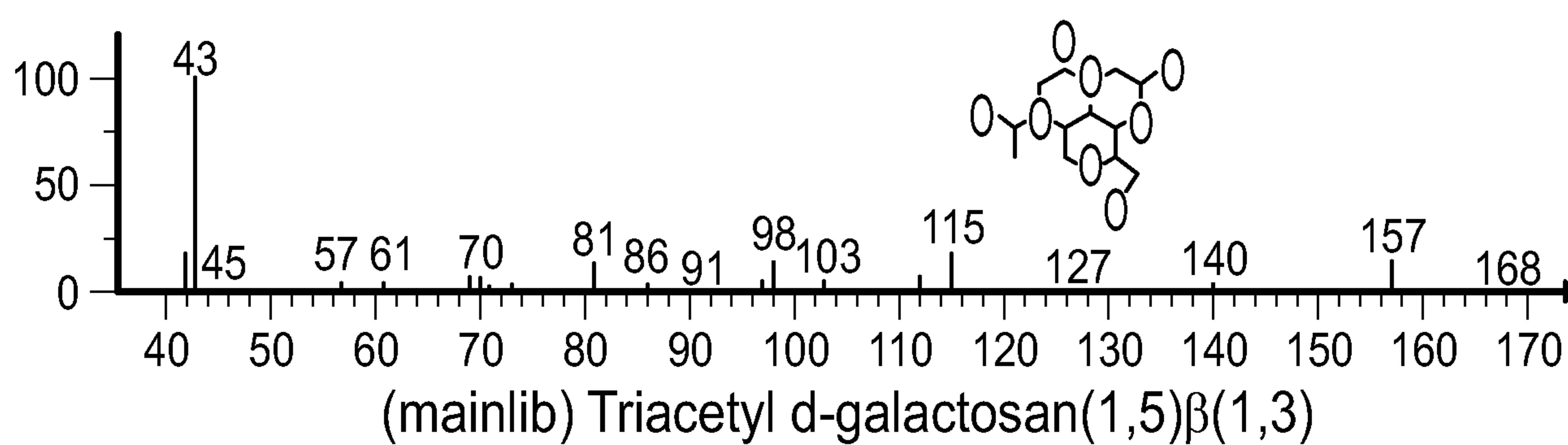
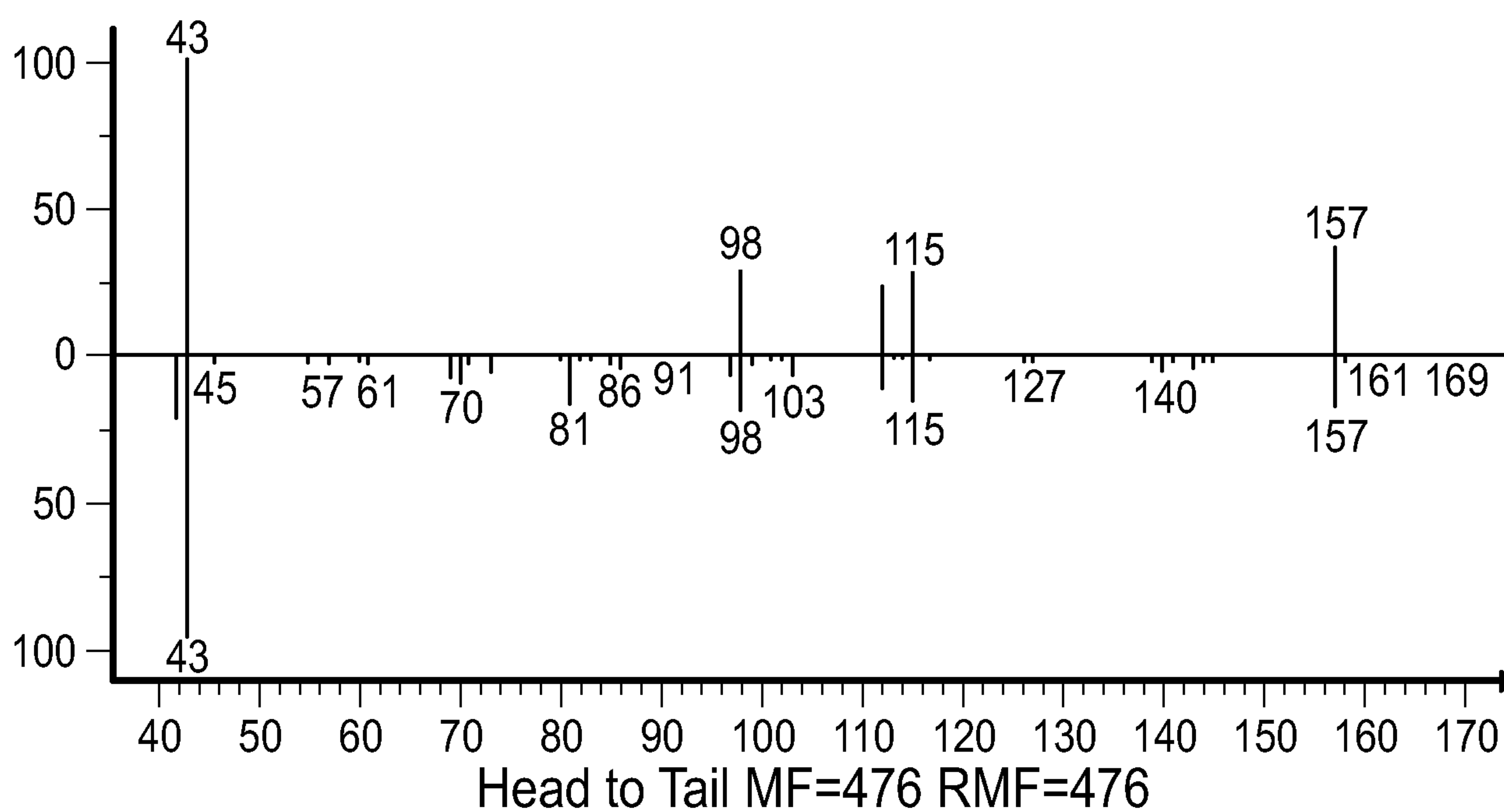
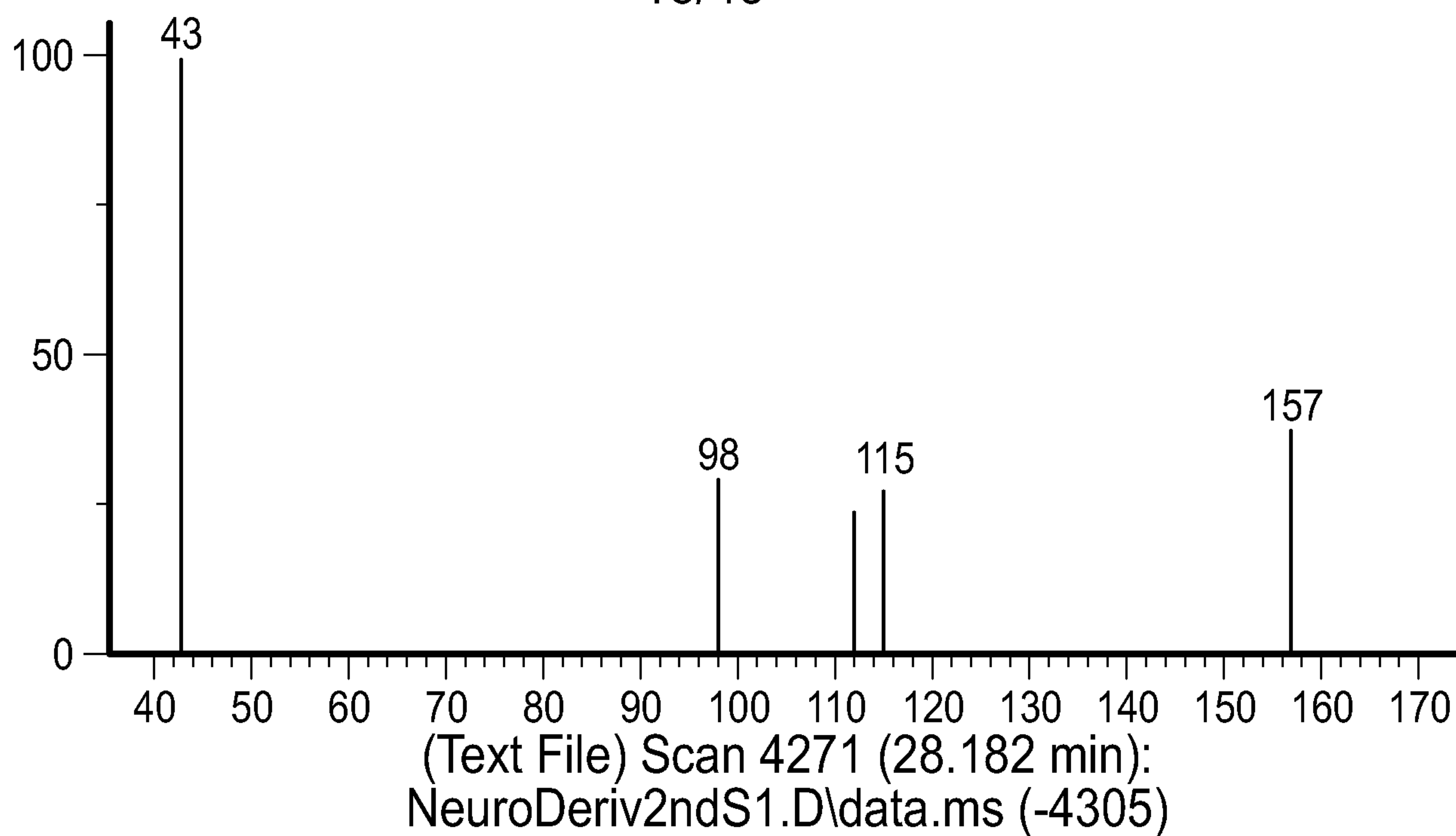


FIG. 16

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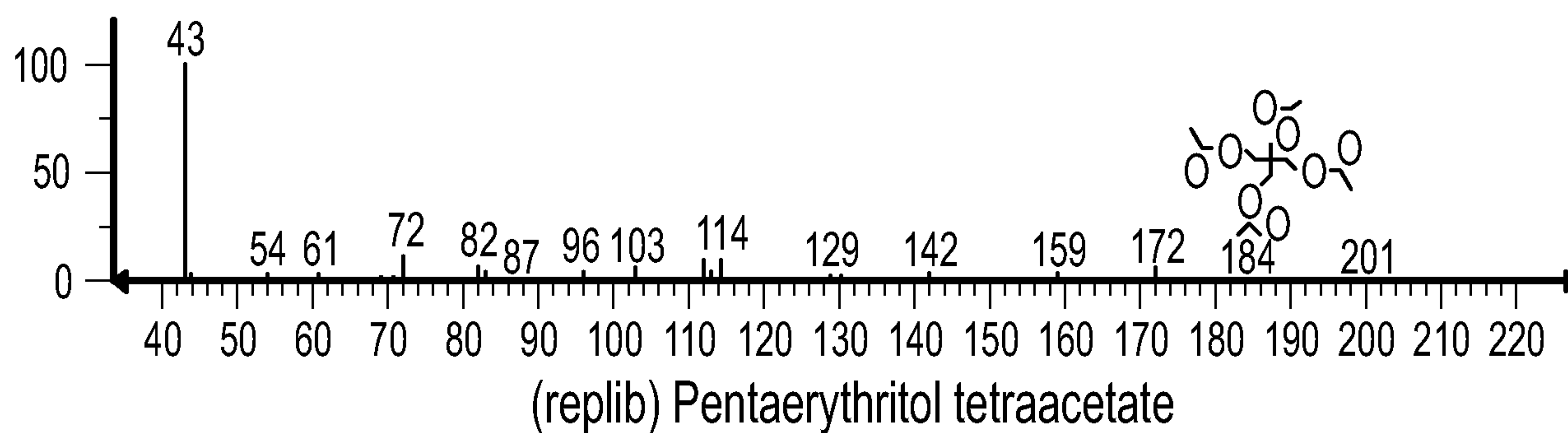
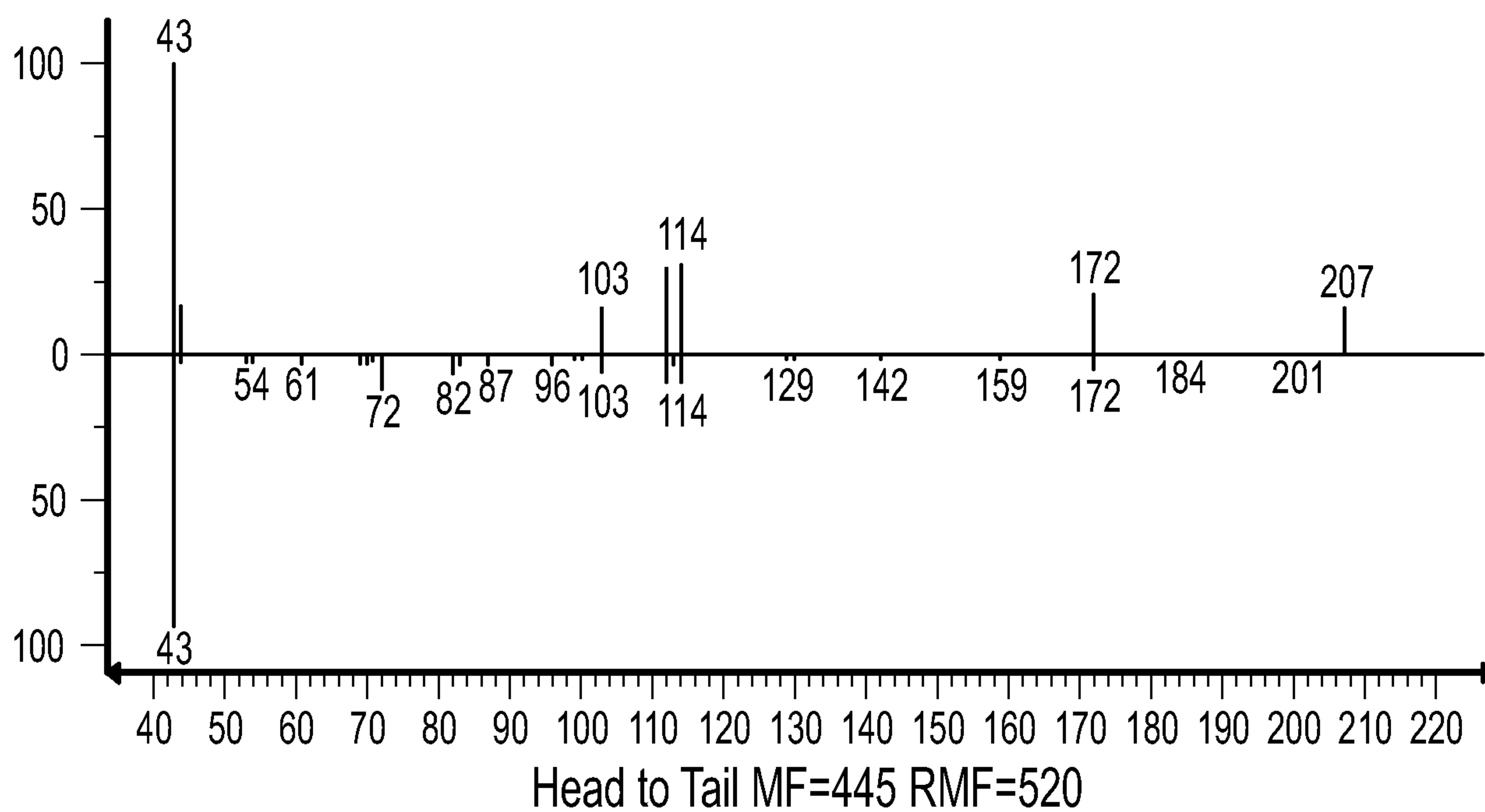
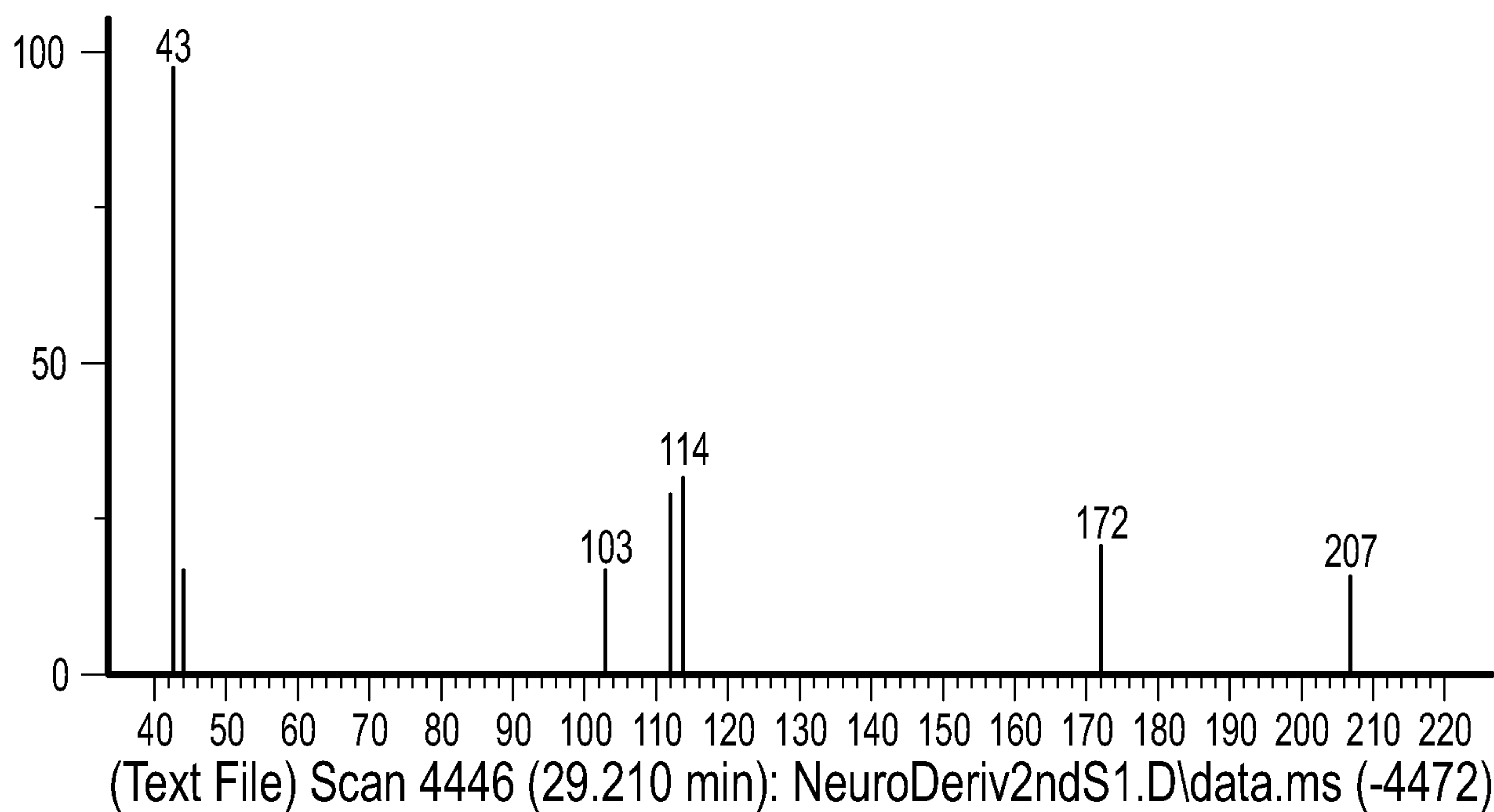


FIG. 17

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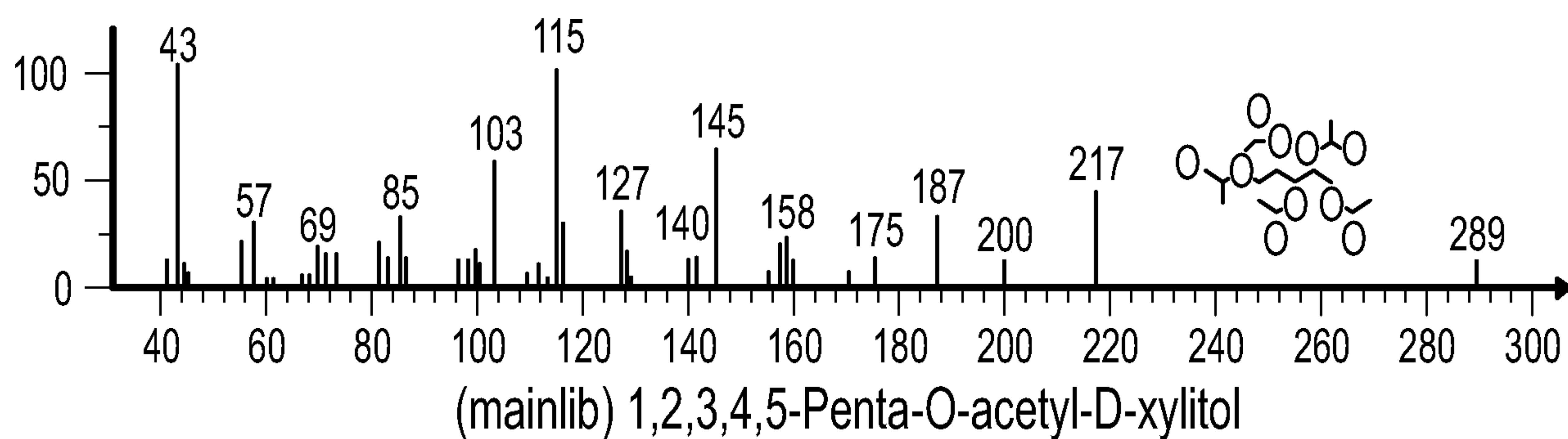
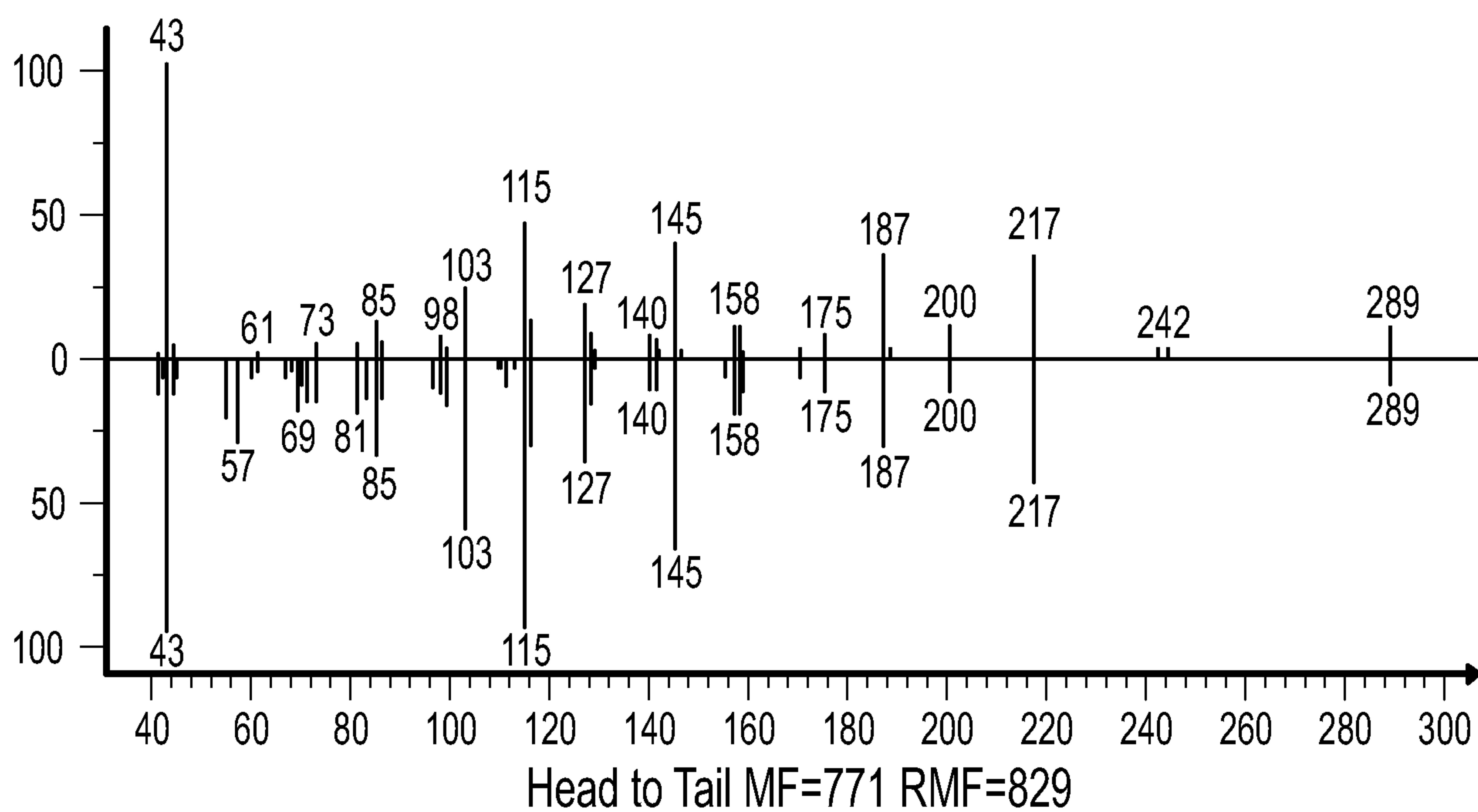
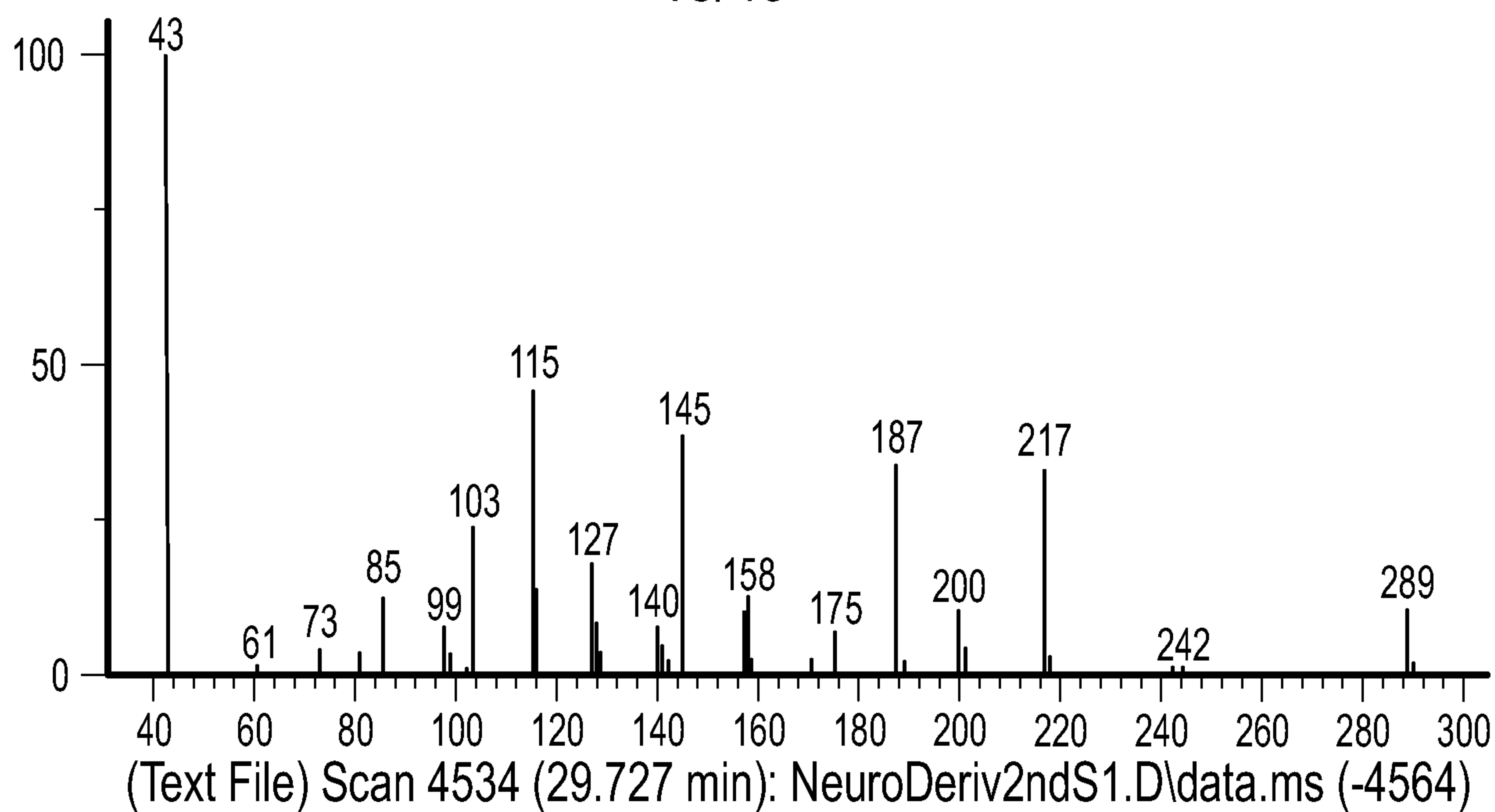


FIG. 18

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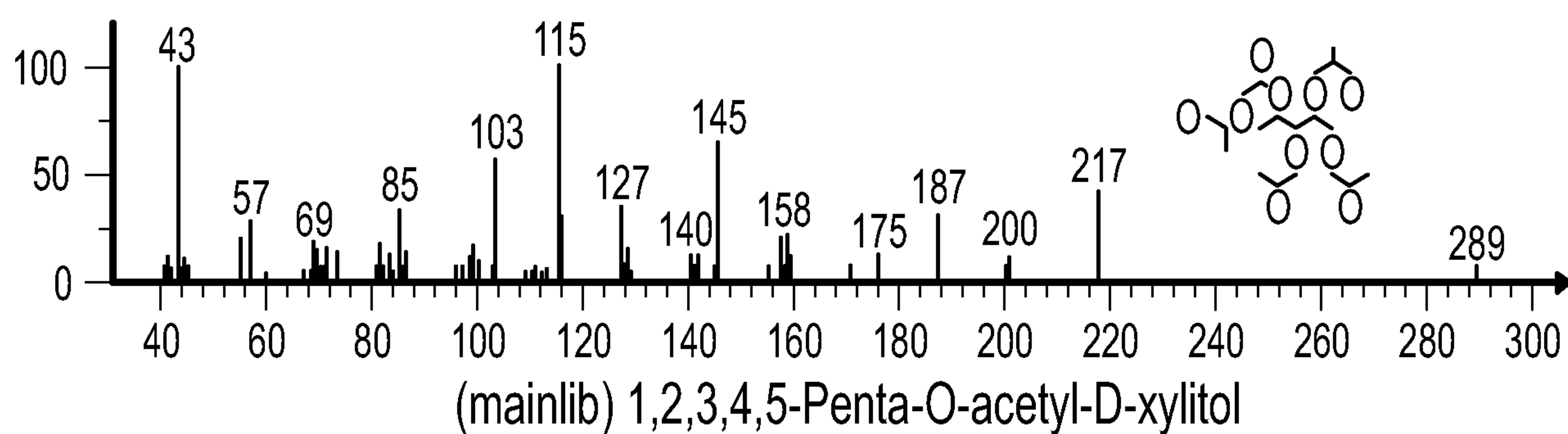
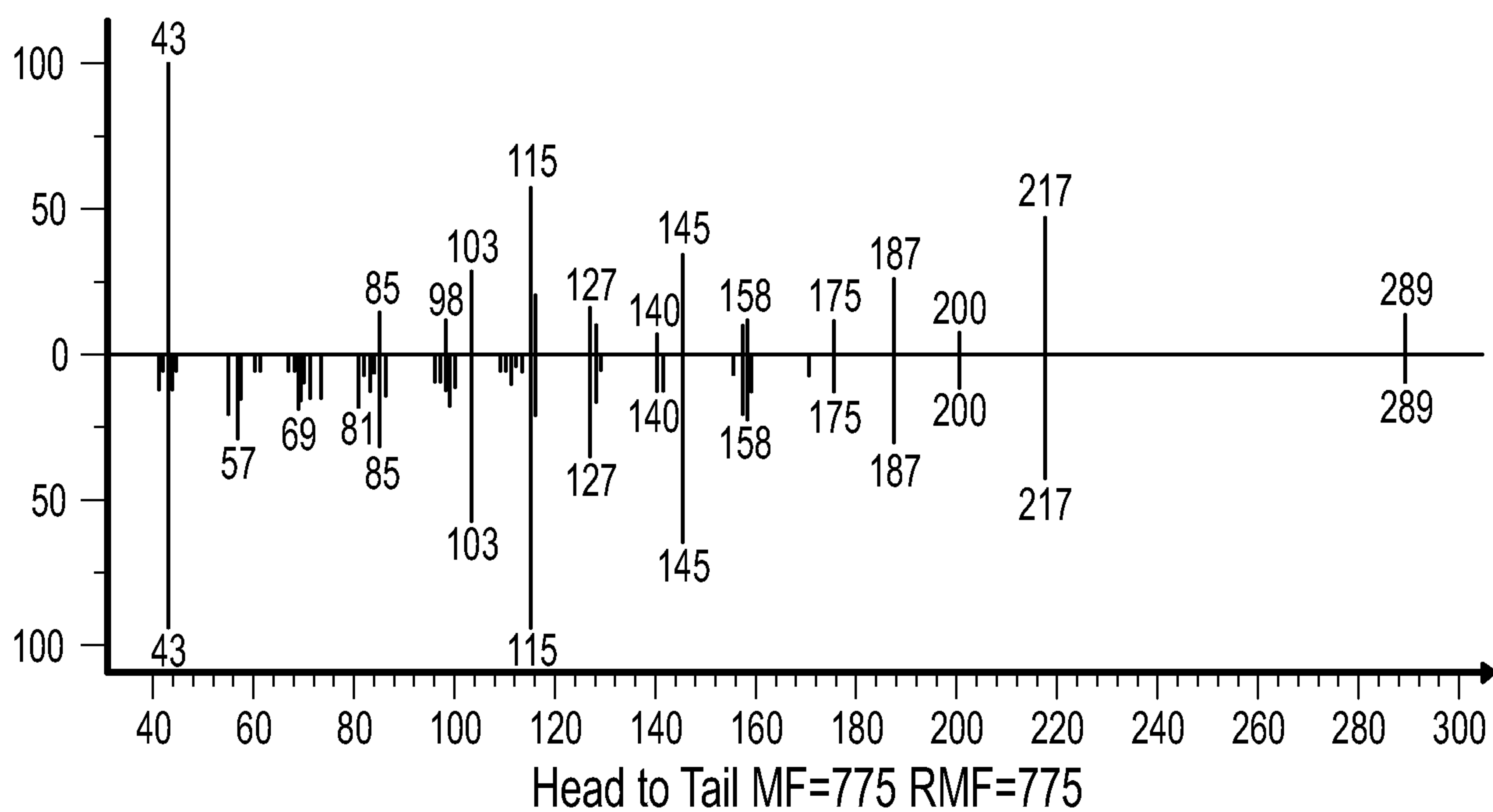
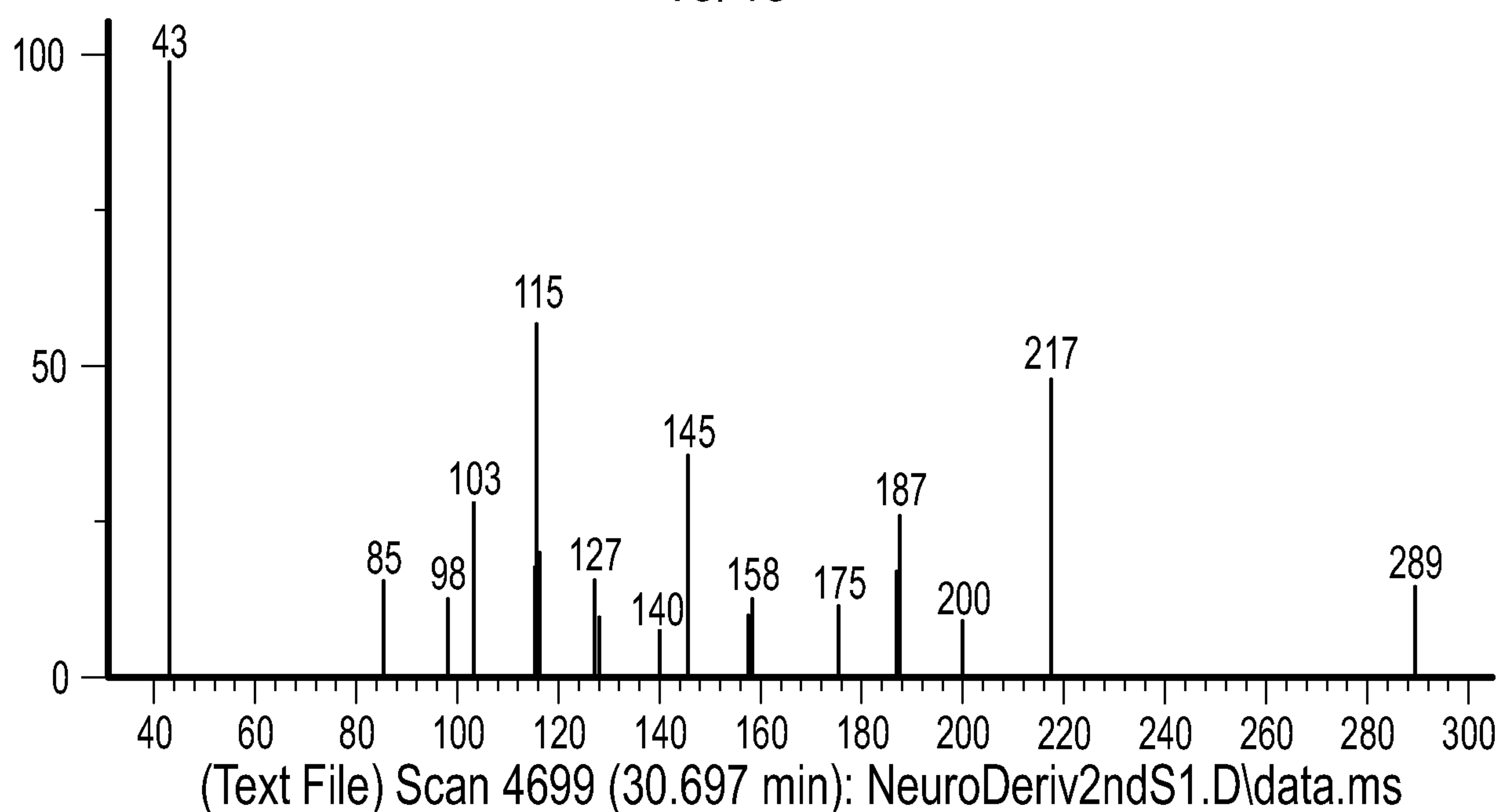


FIG. 19

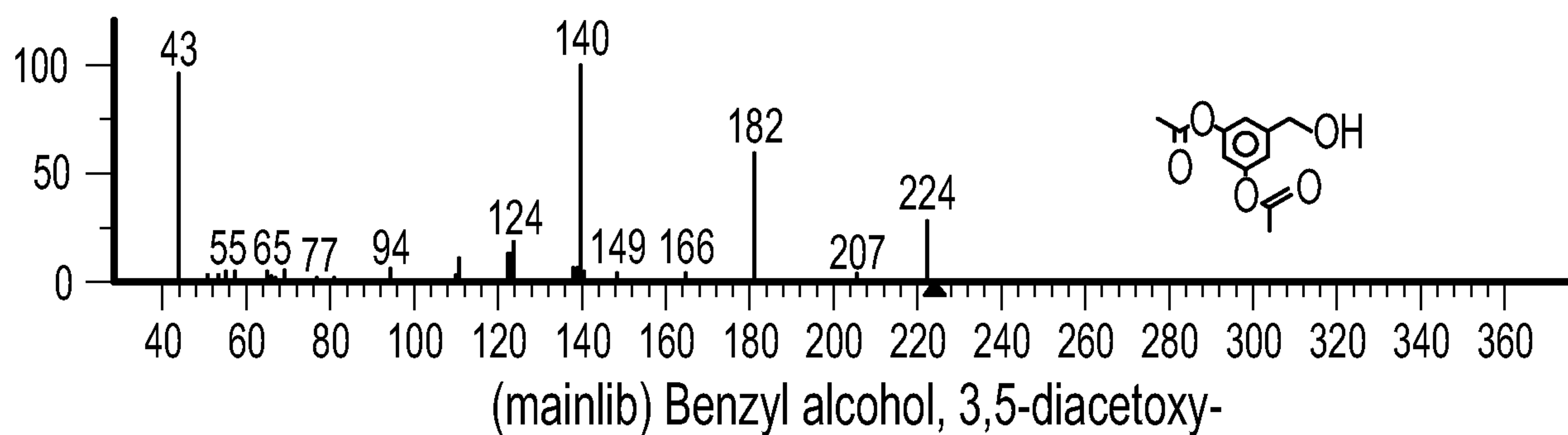
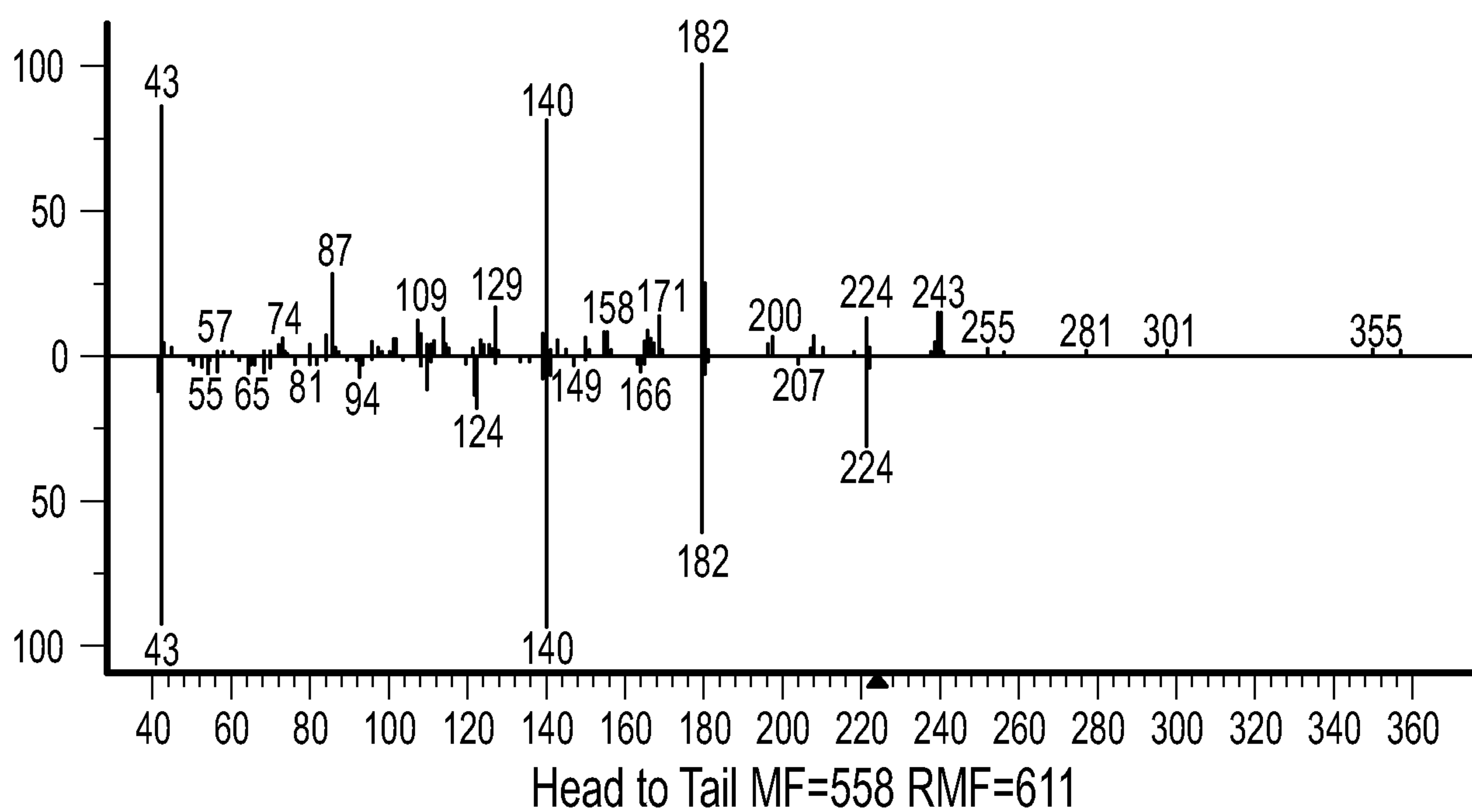
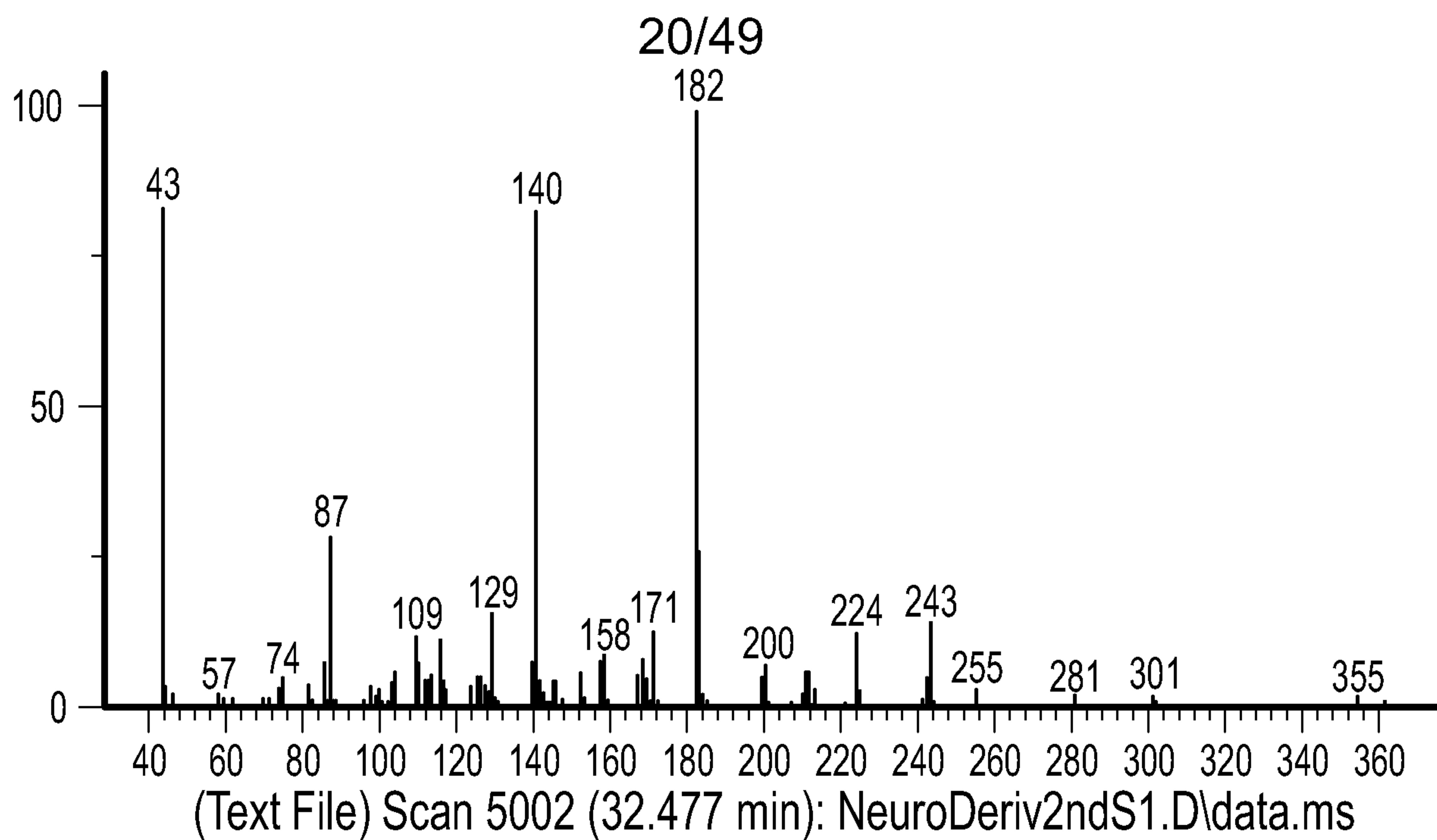


FIG. 20

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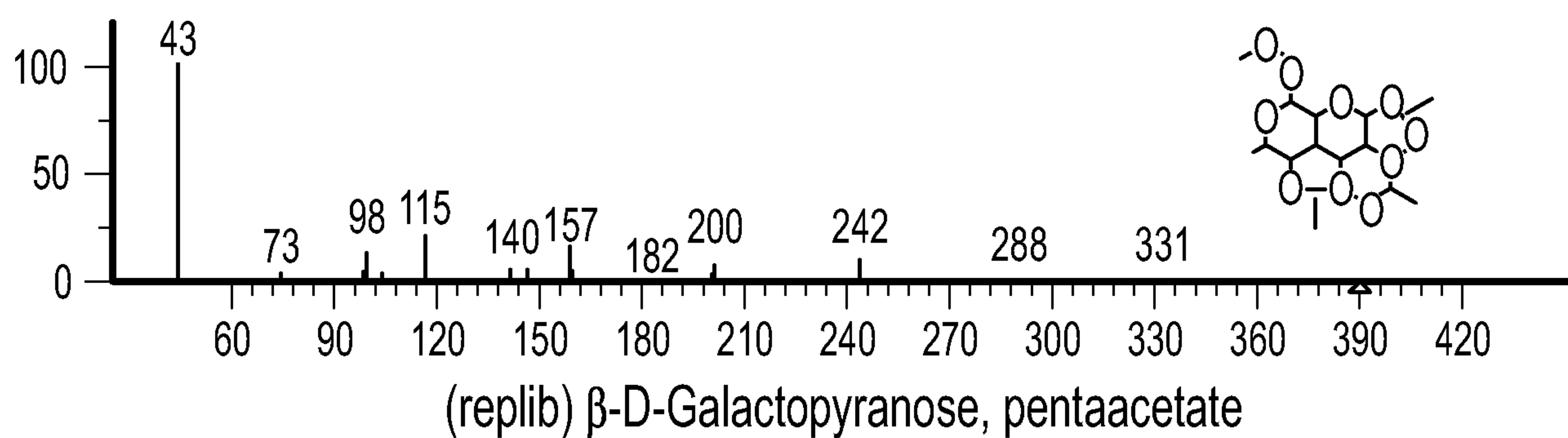
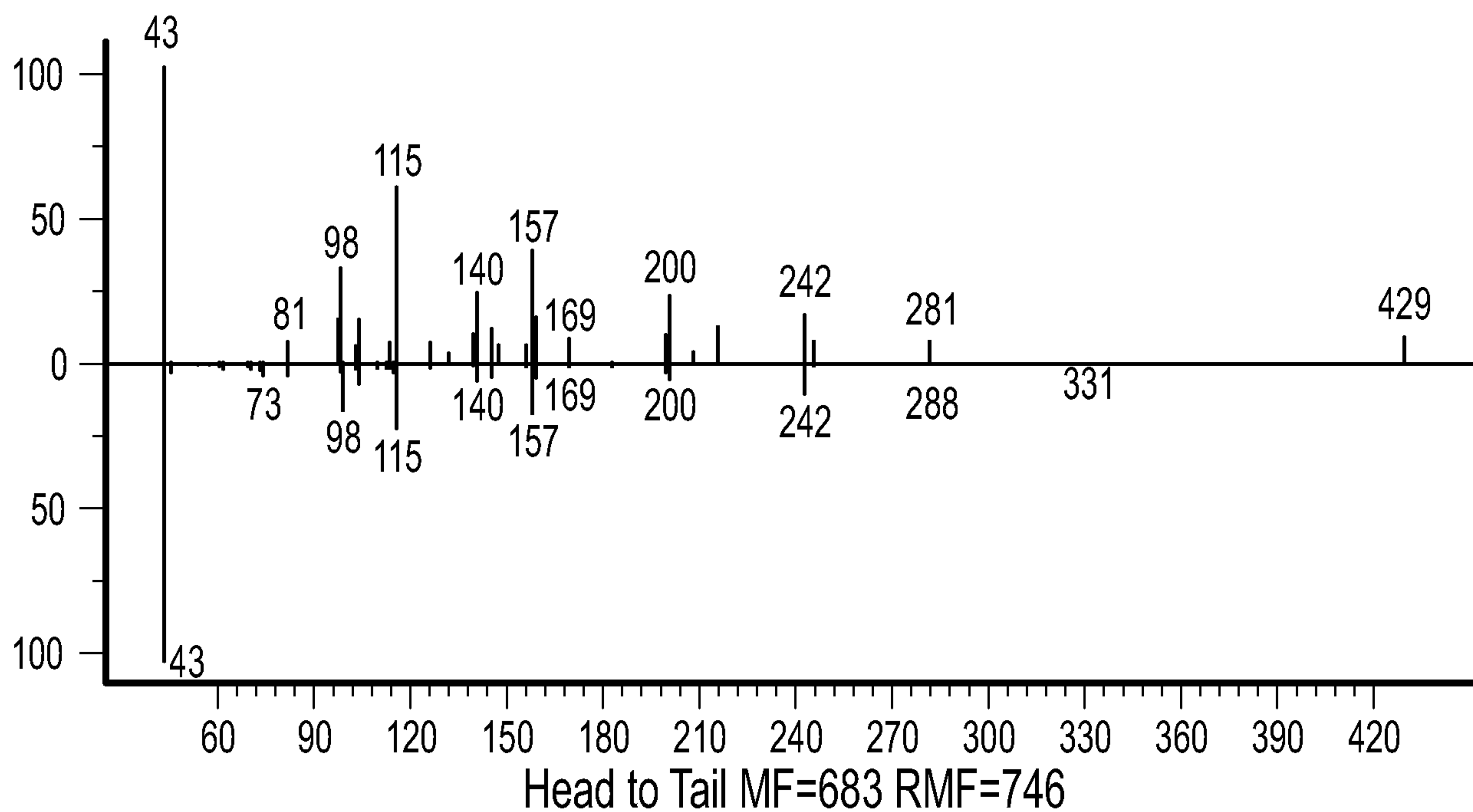
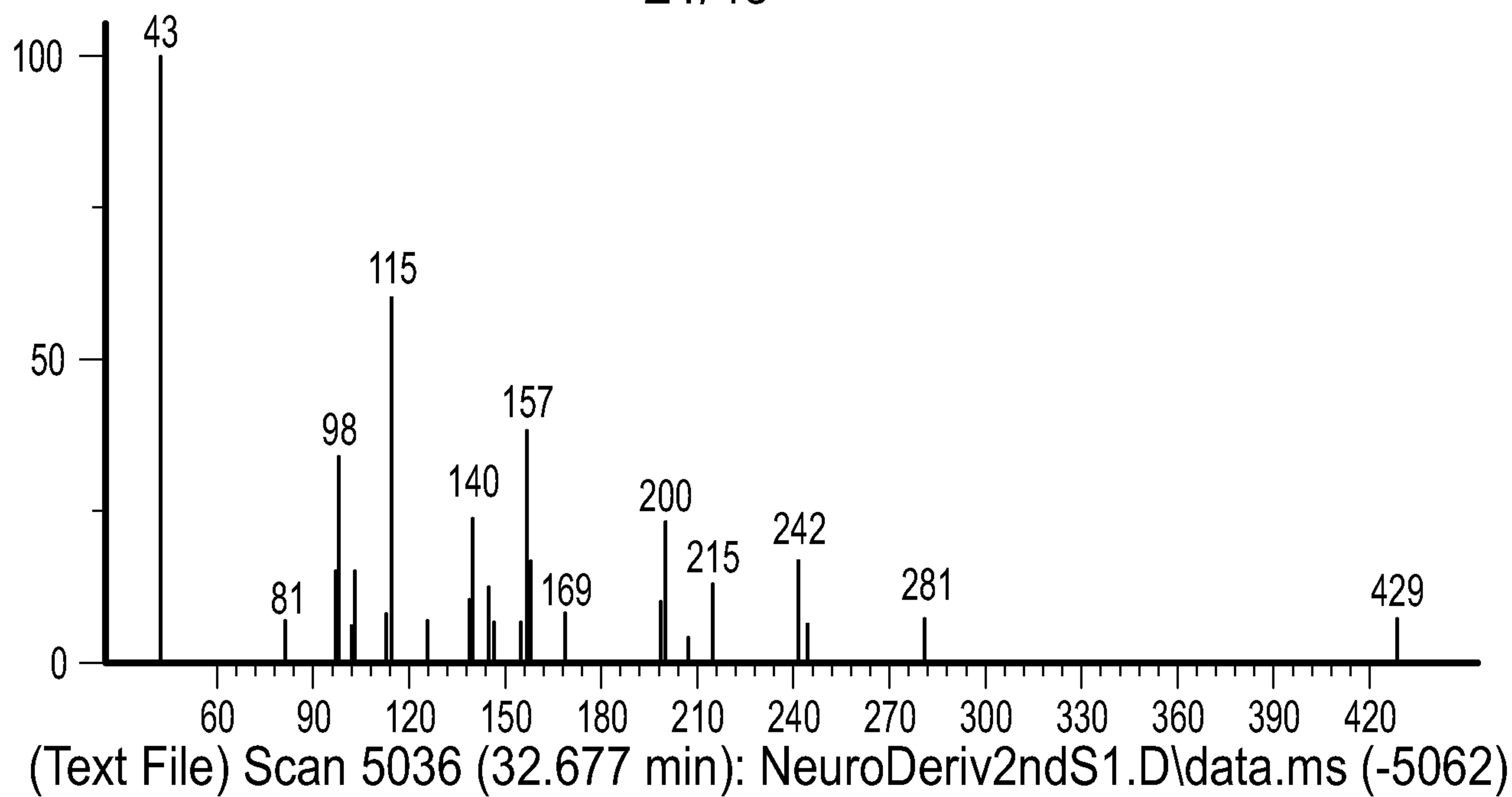


FIG. 21

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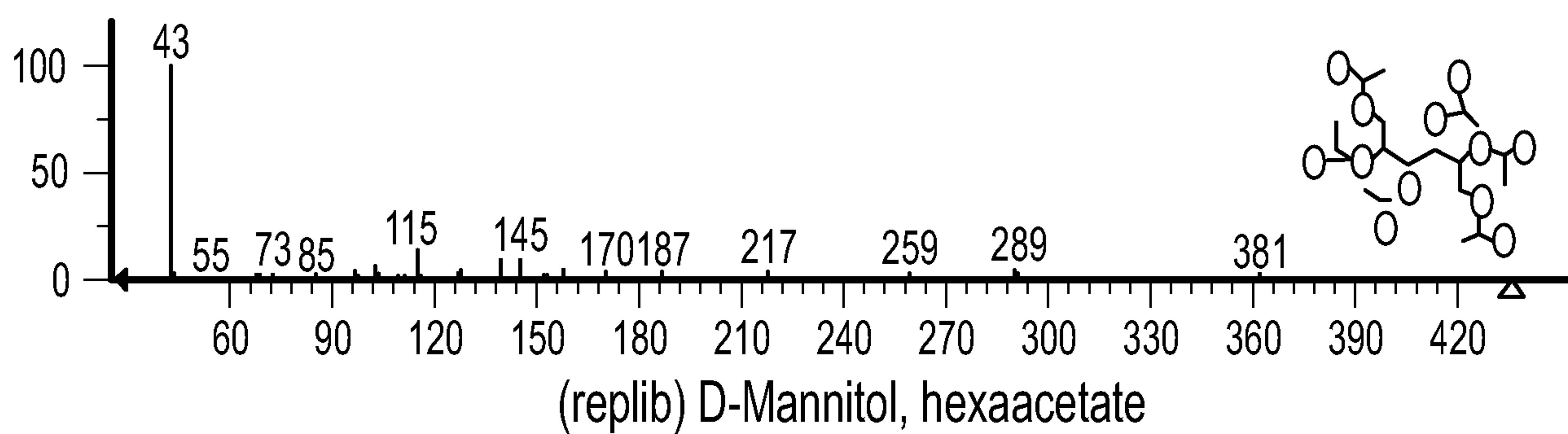
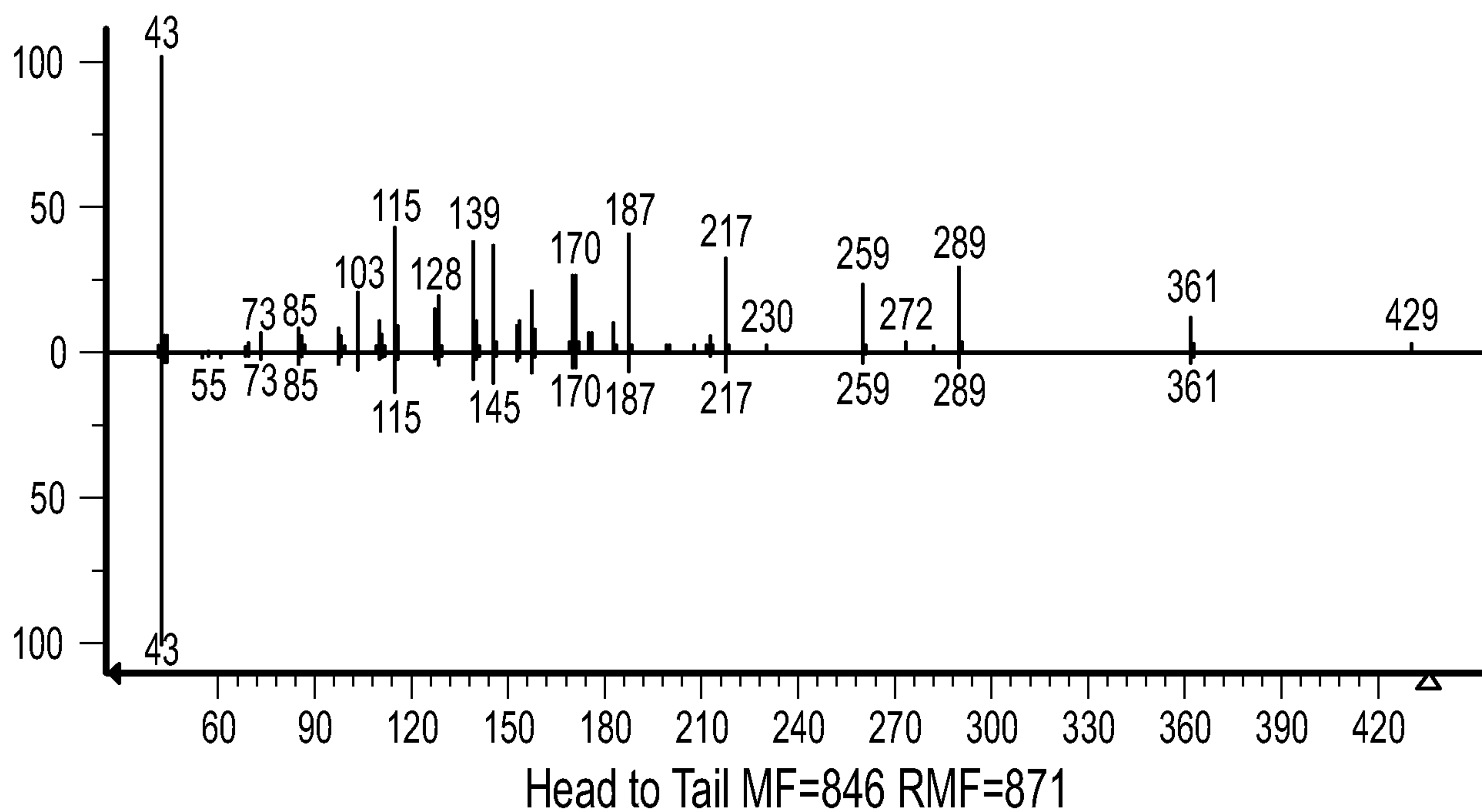
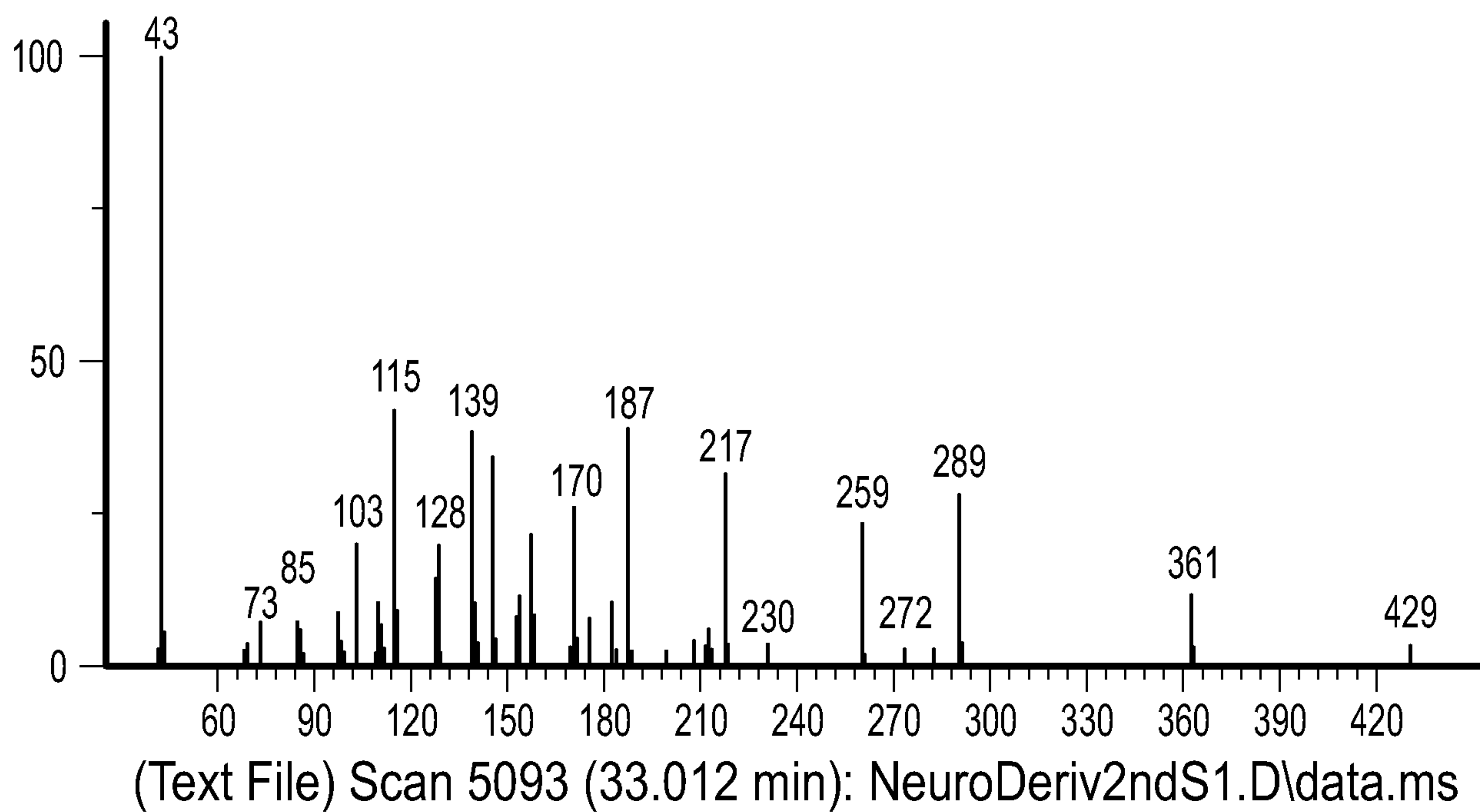


FIG. 22

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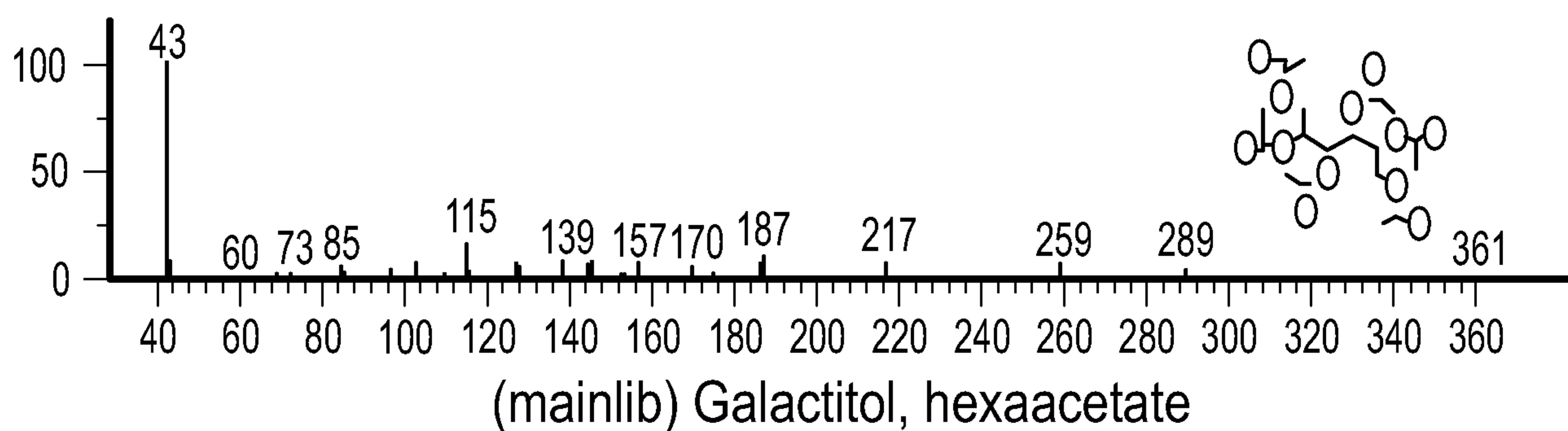
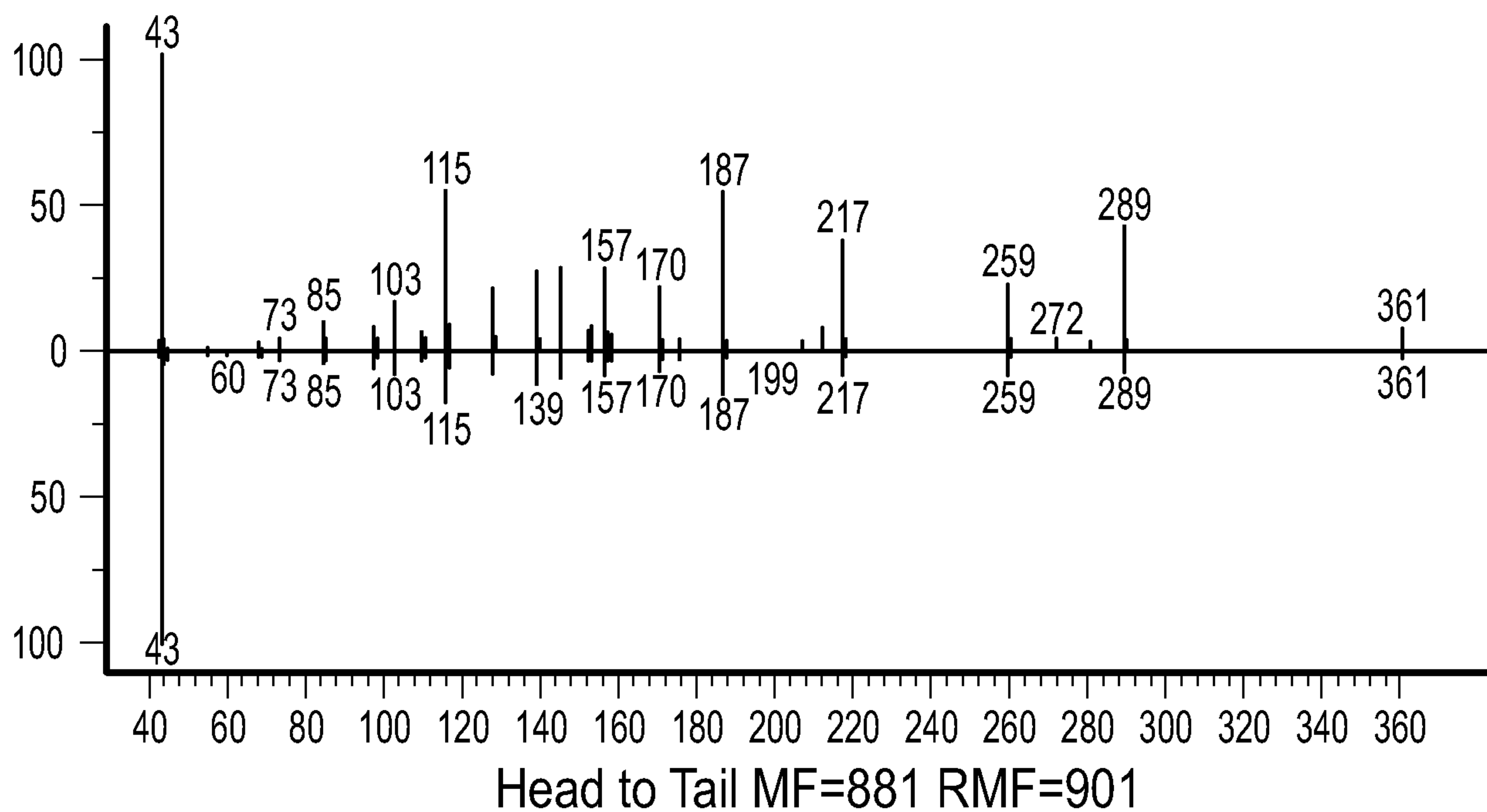
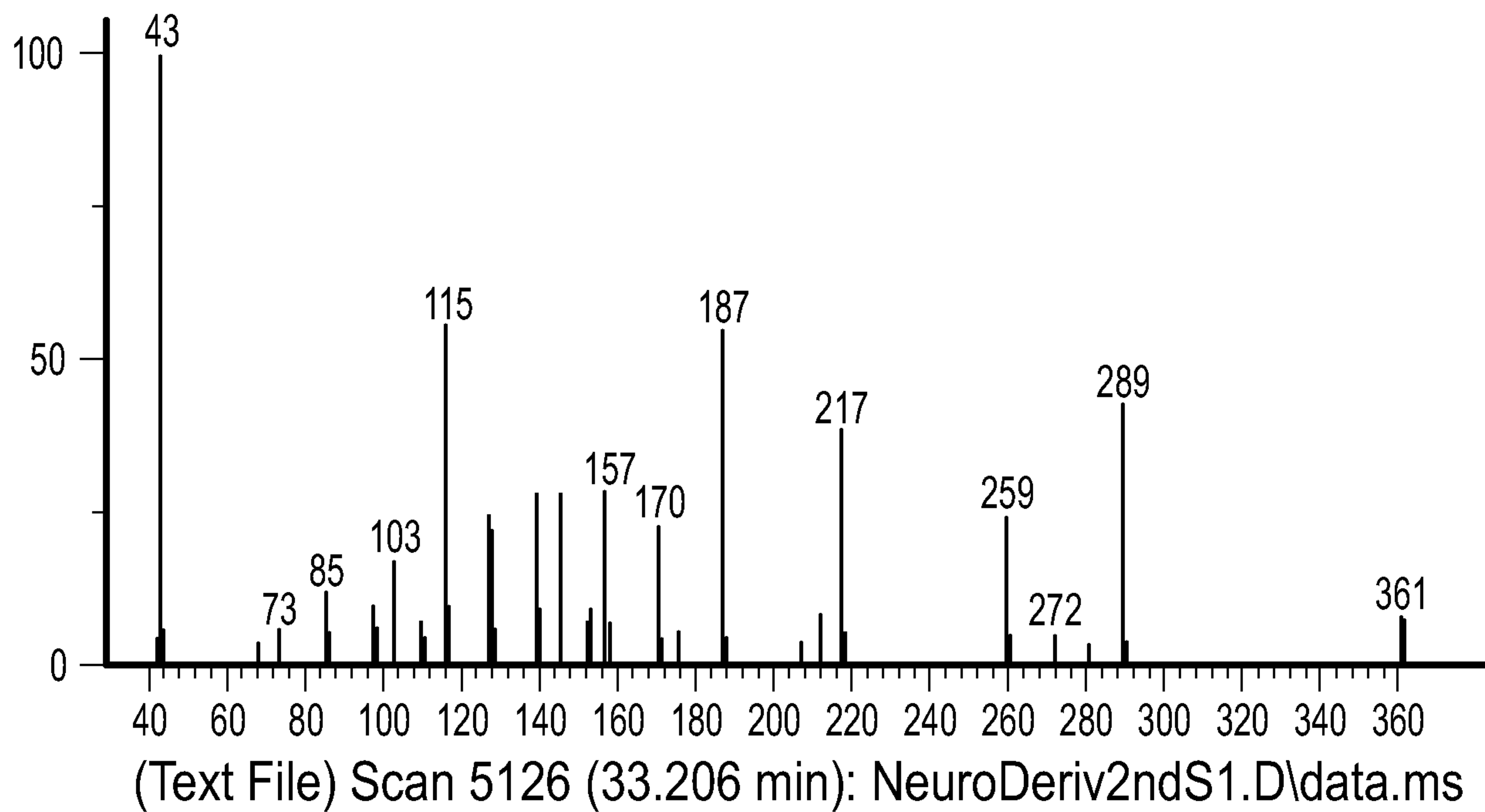


FIG. 23

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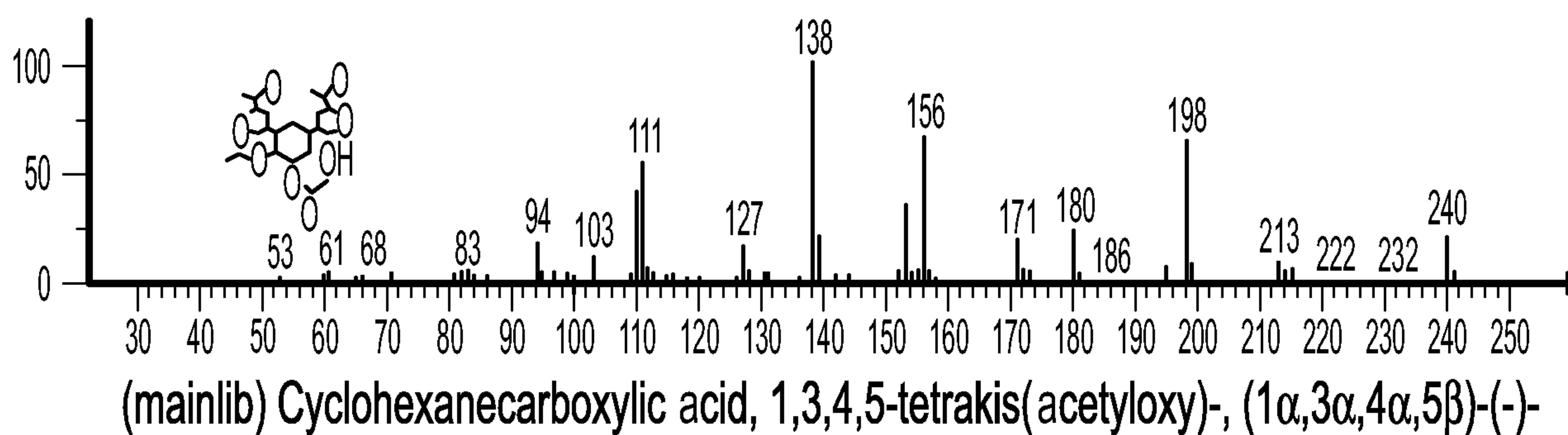
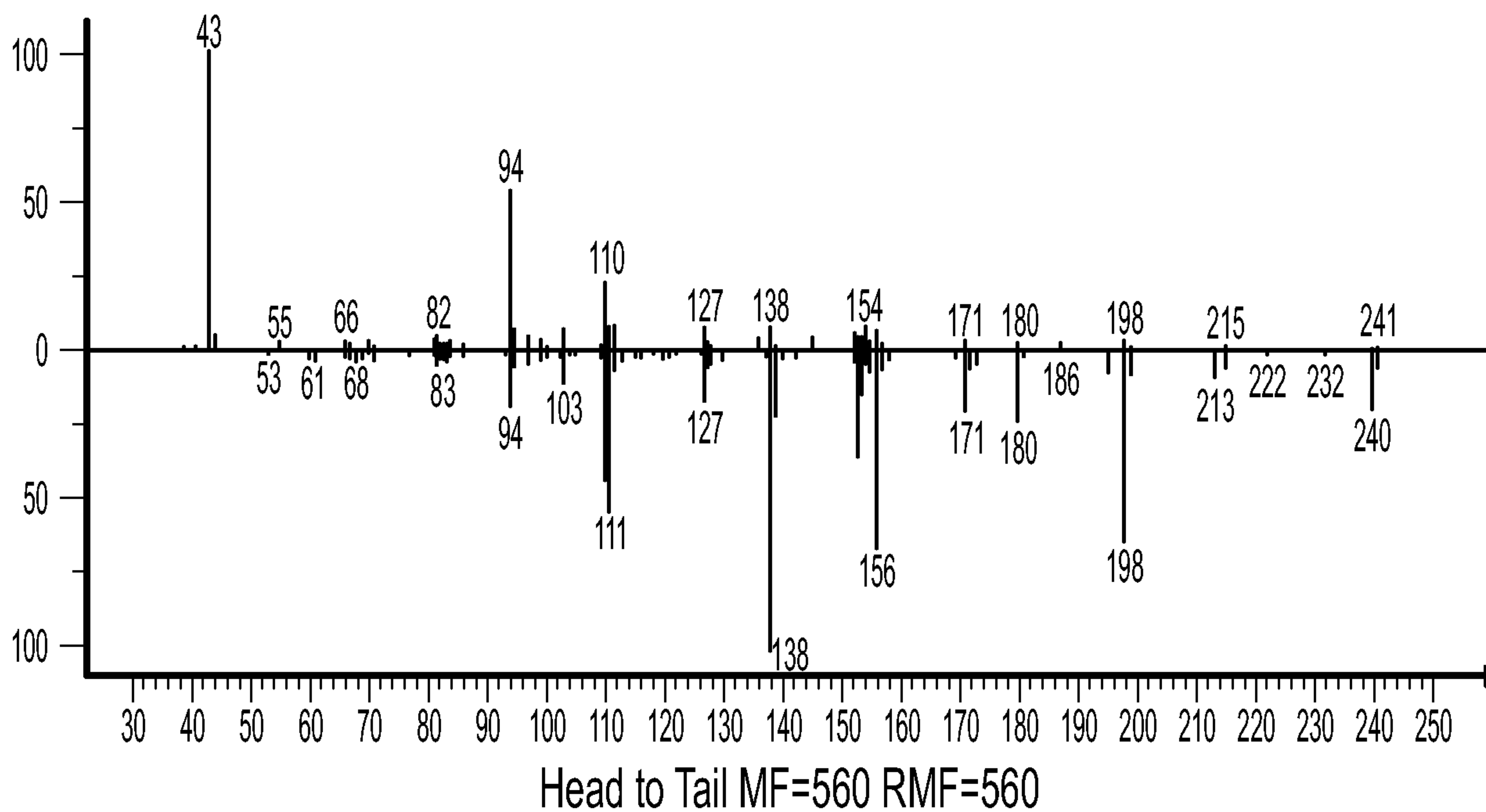
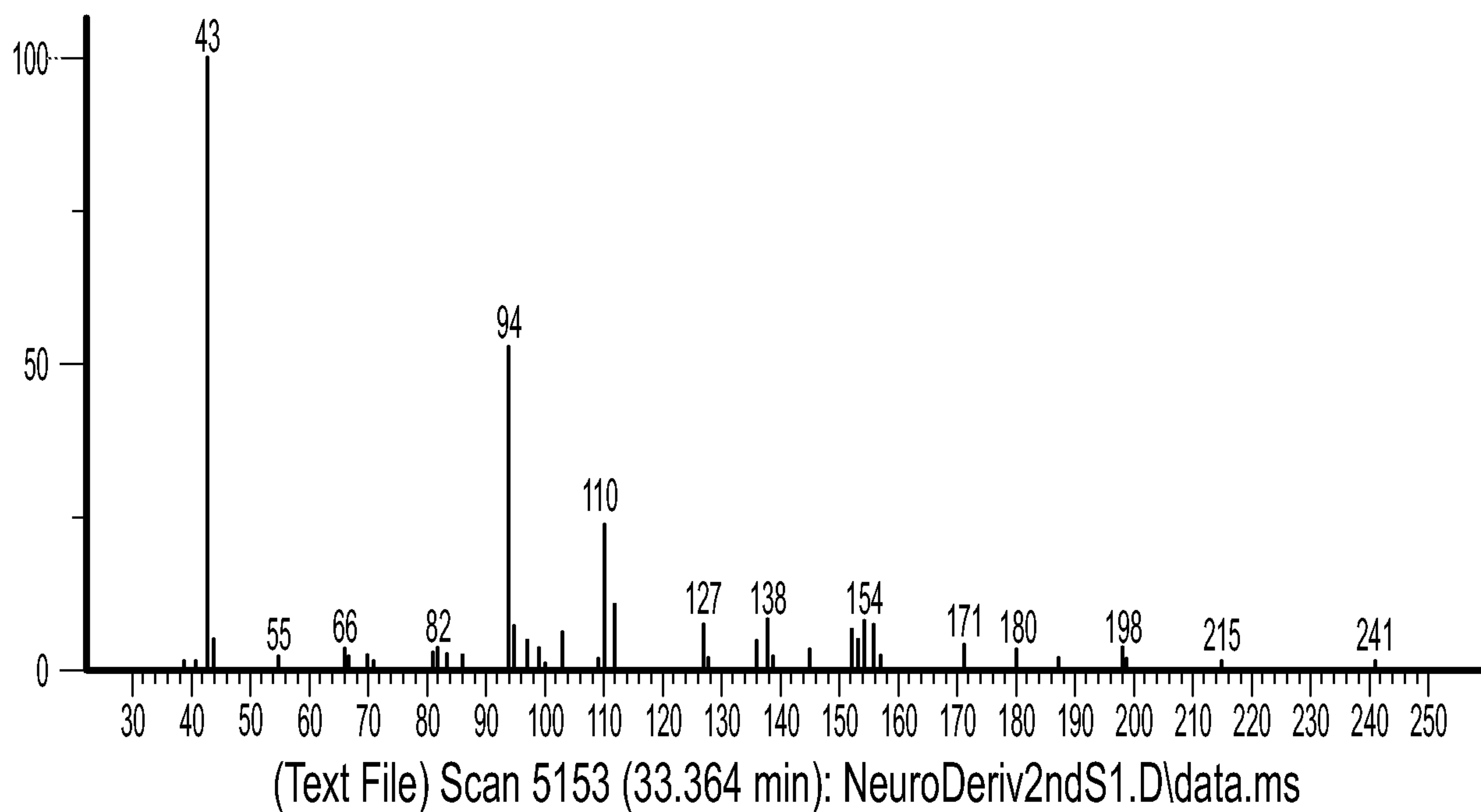


FIG. 24

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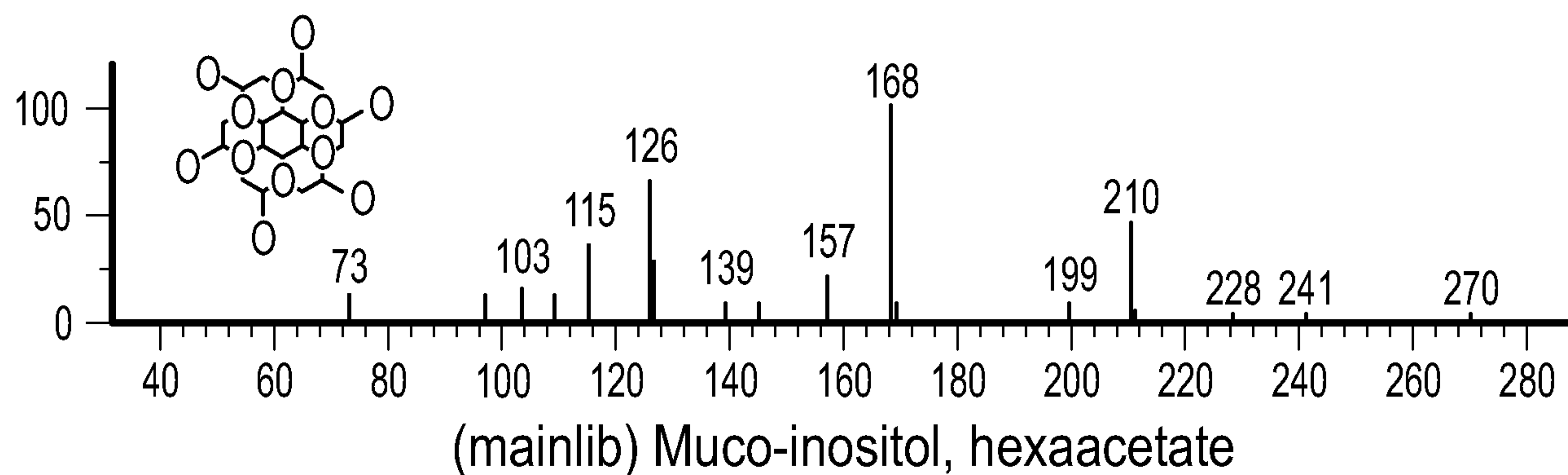
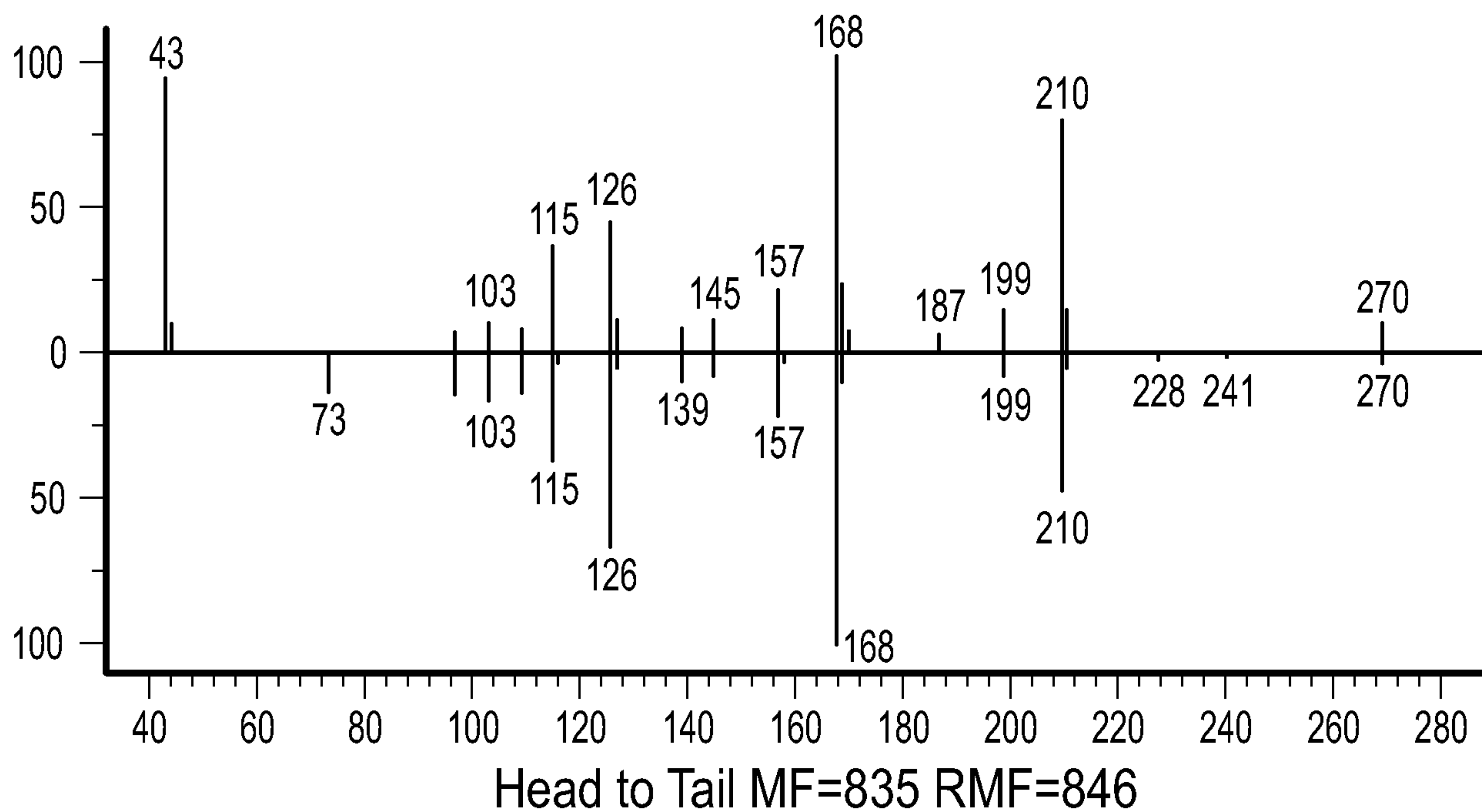
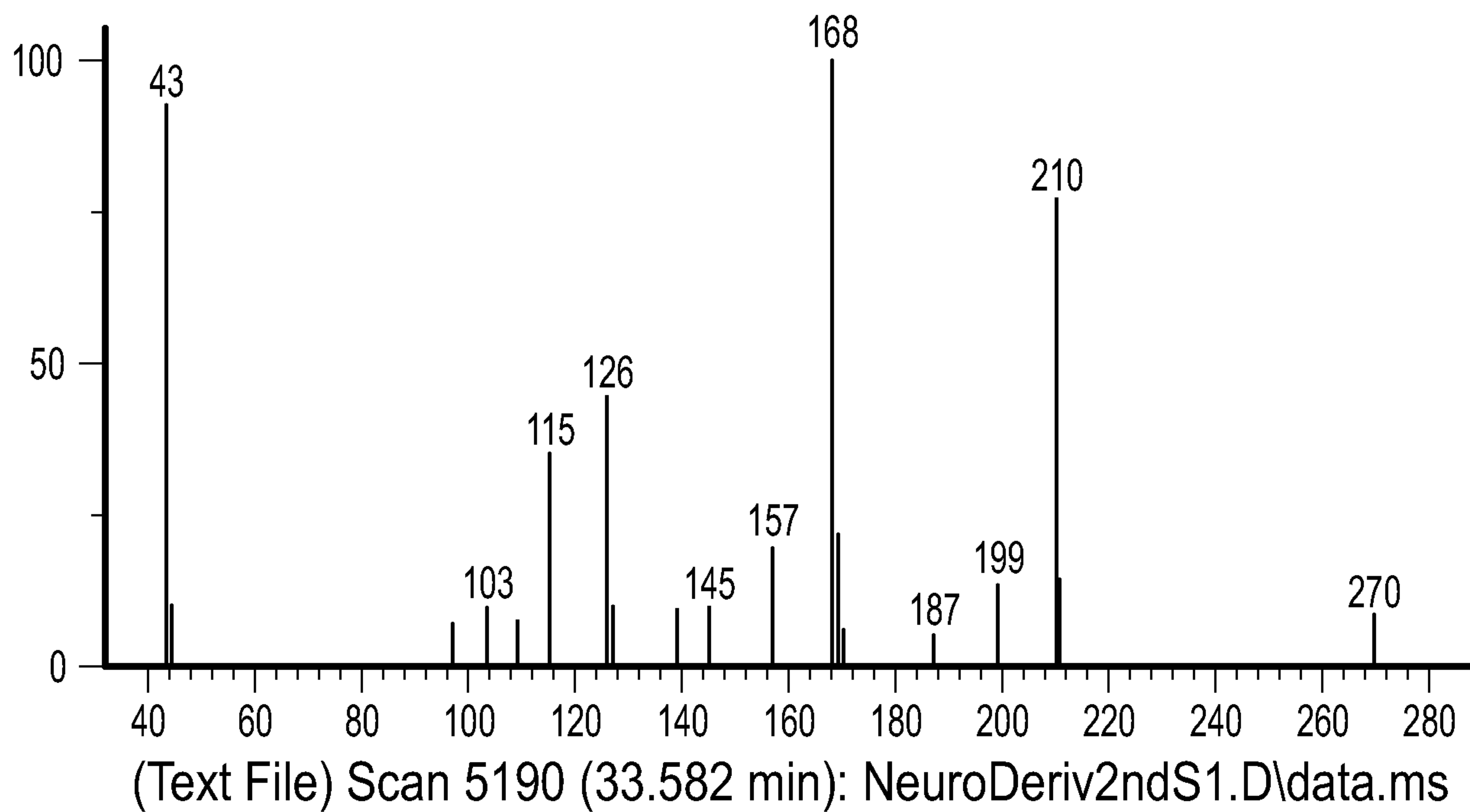


FIG. 25

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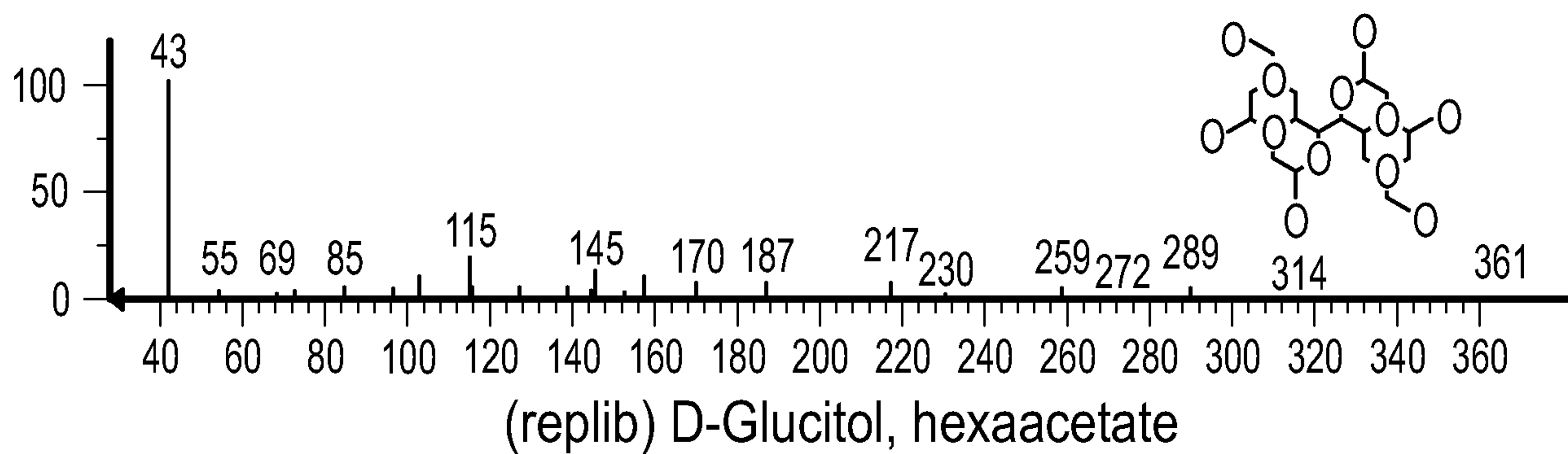
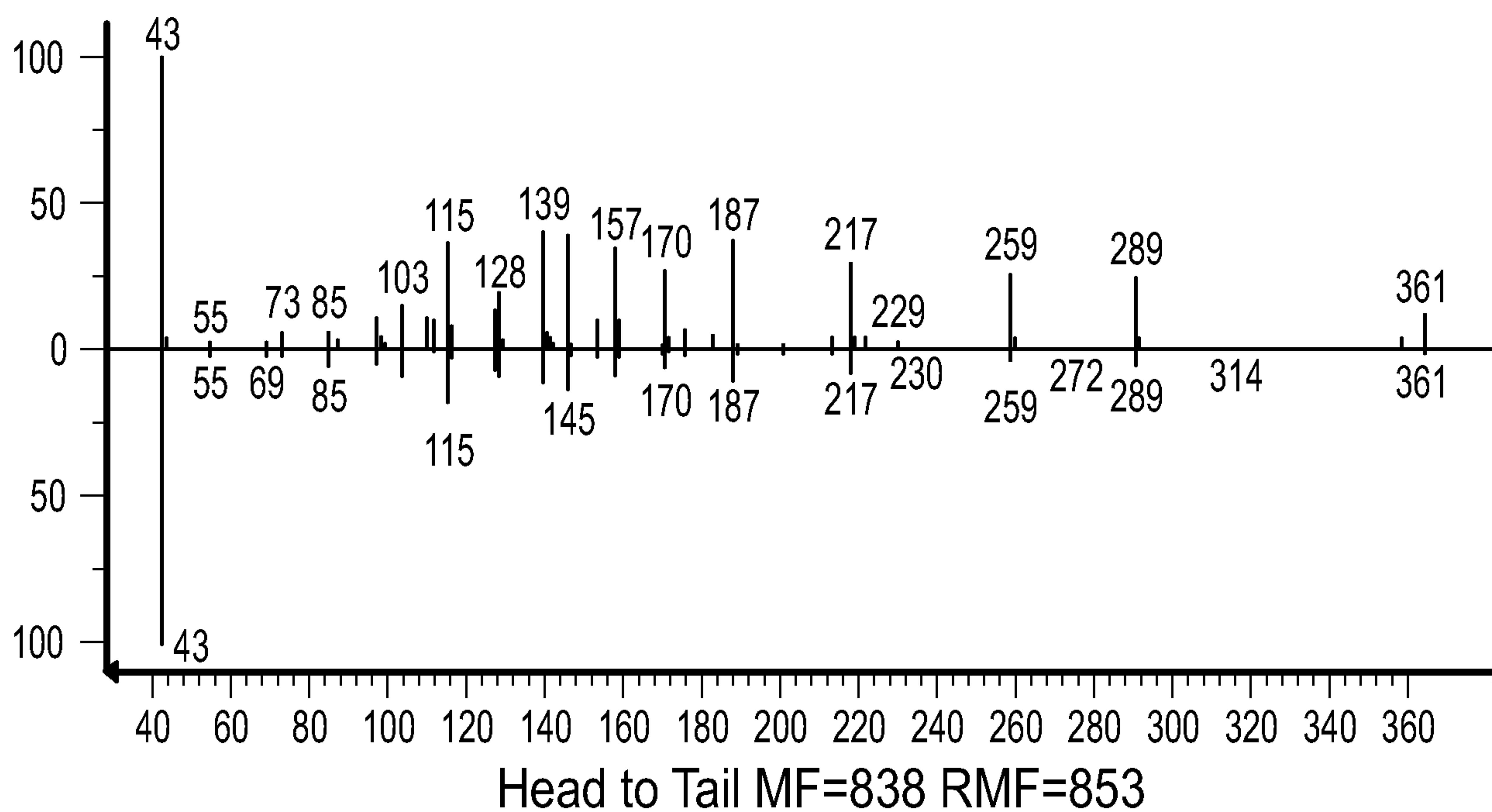
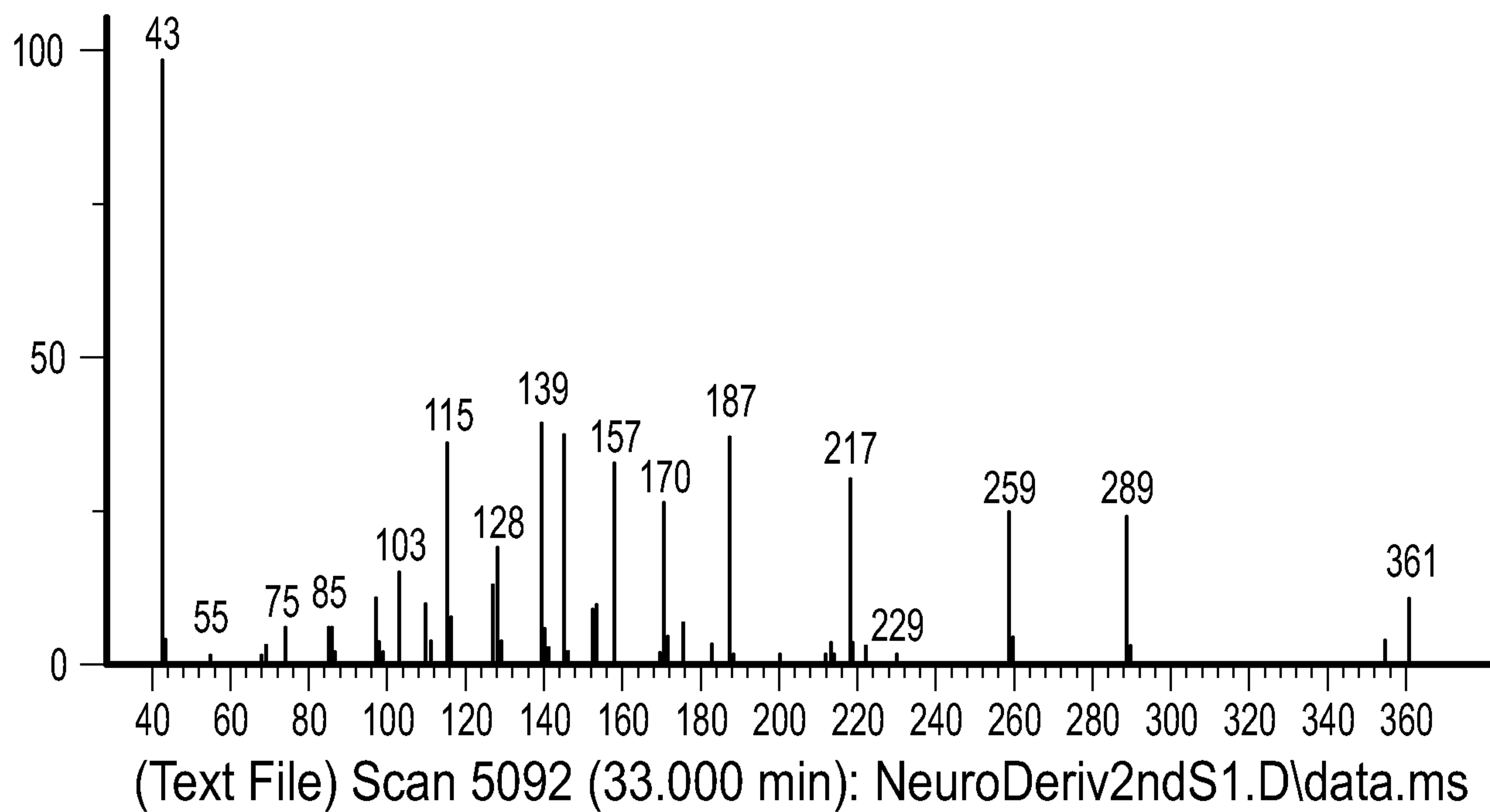


FIG. 26

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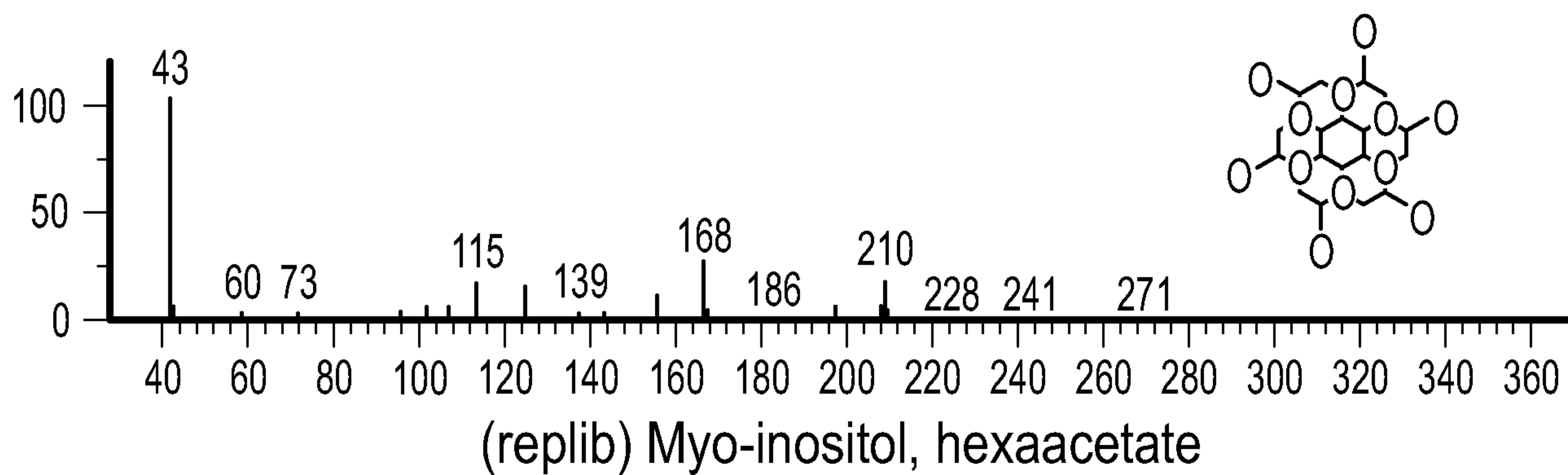
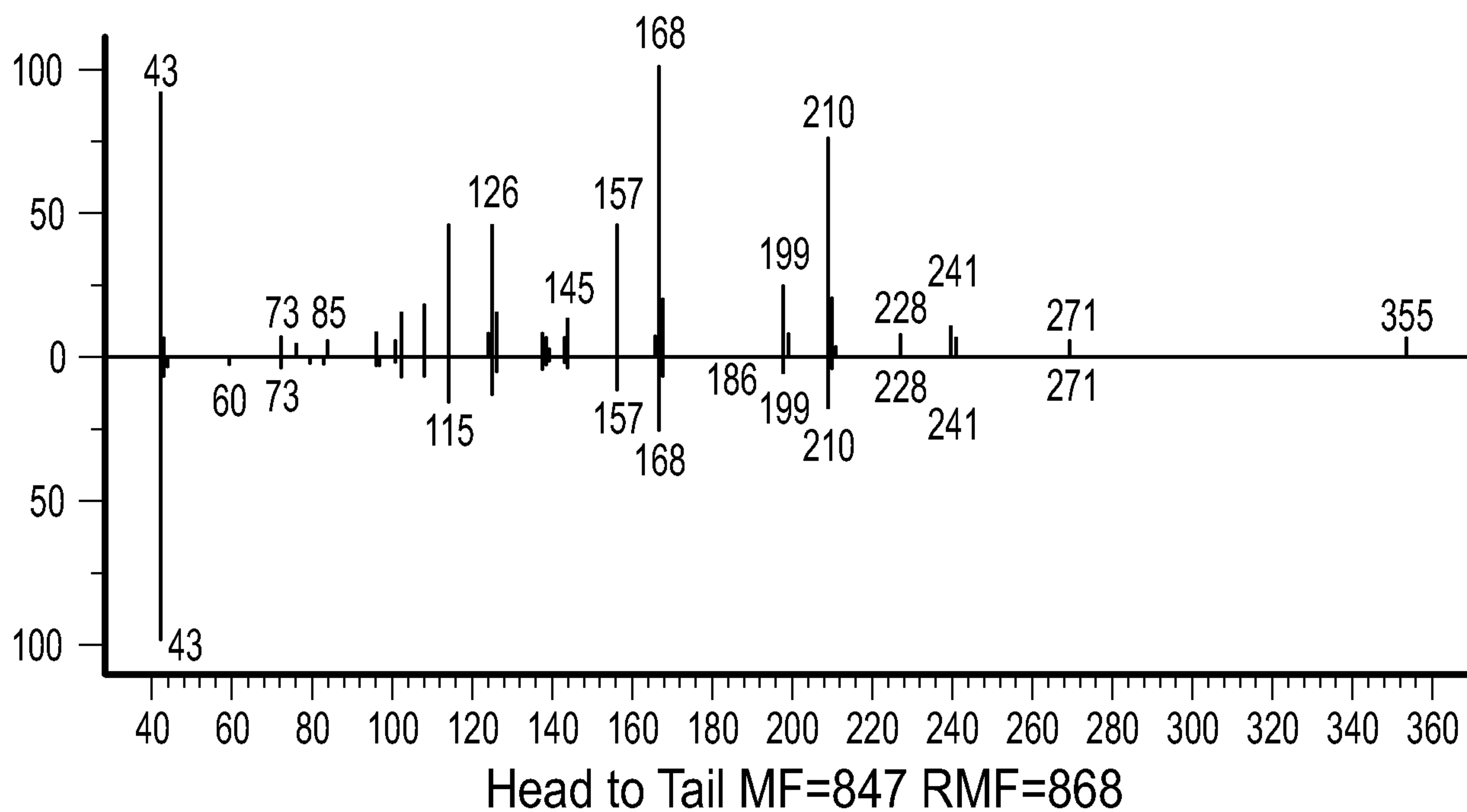
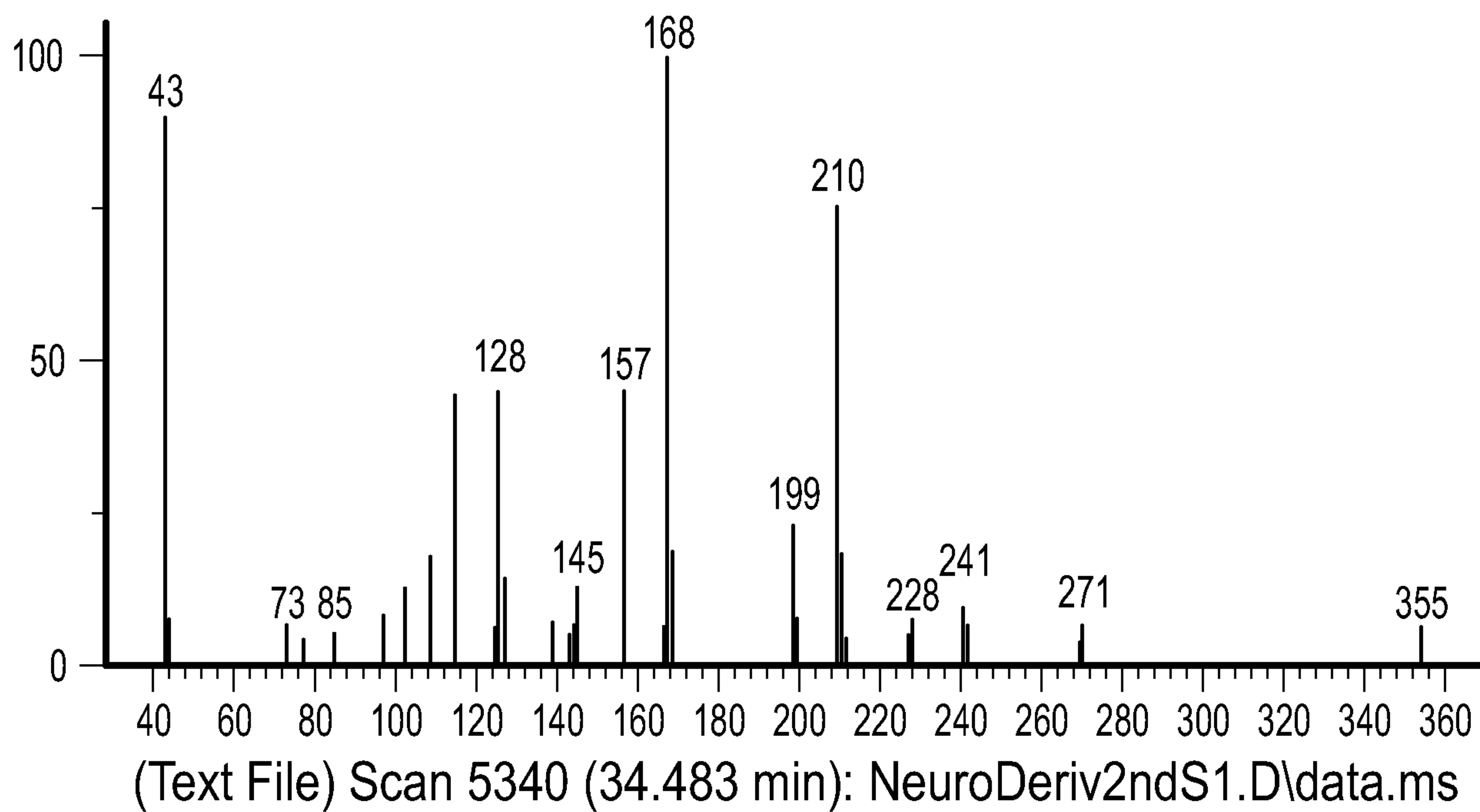


FIG. 27

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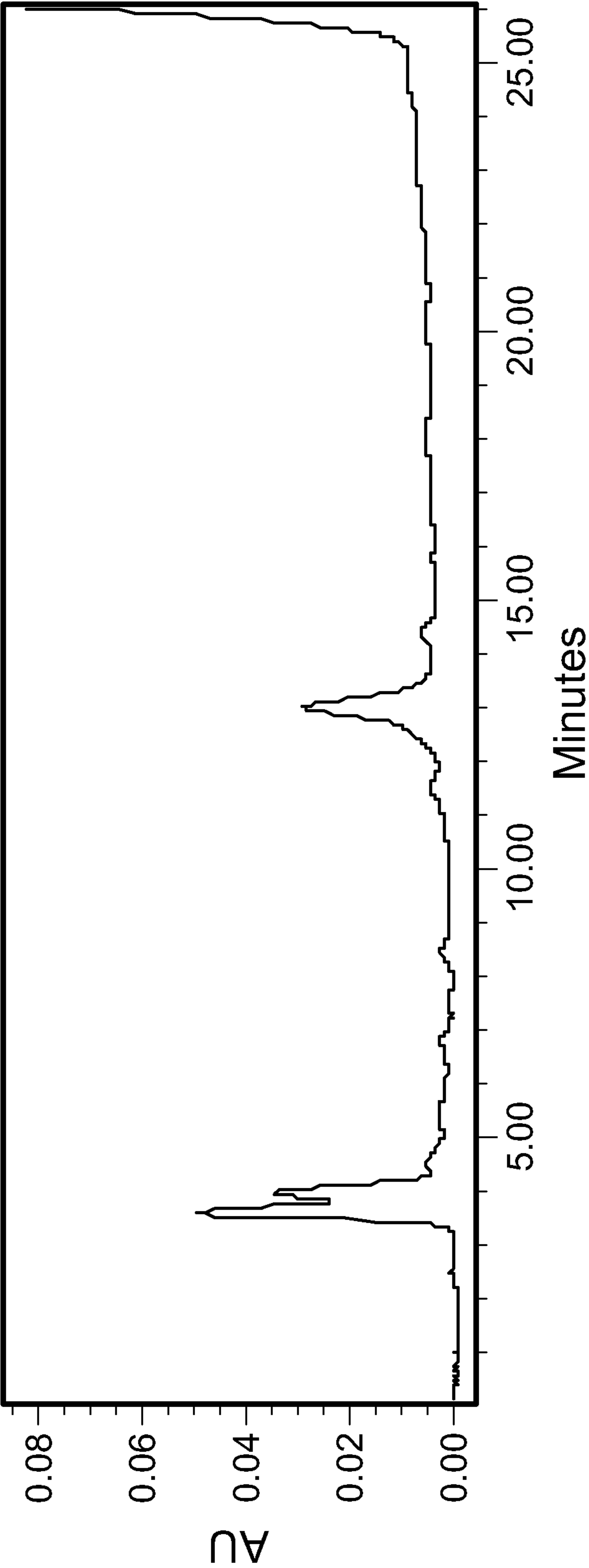


FIG. 28

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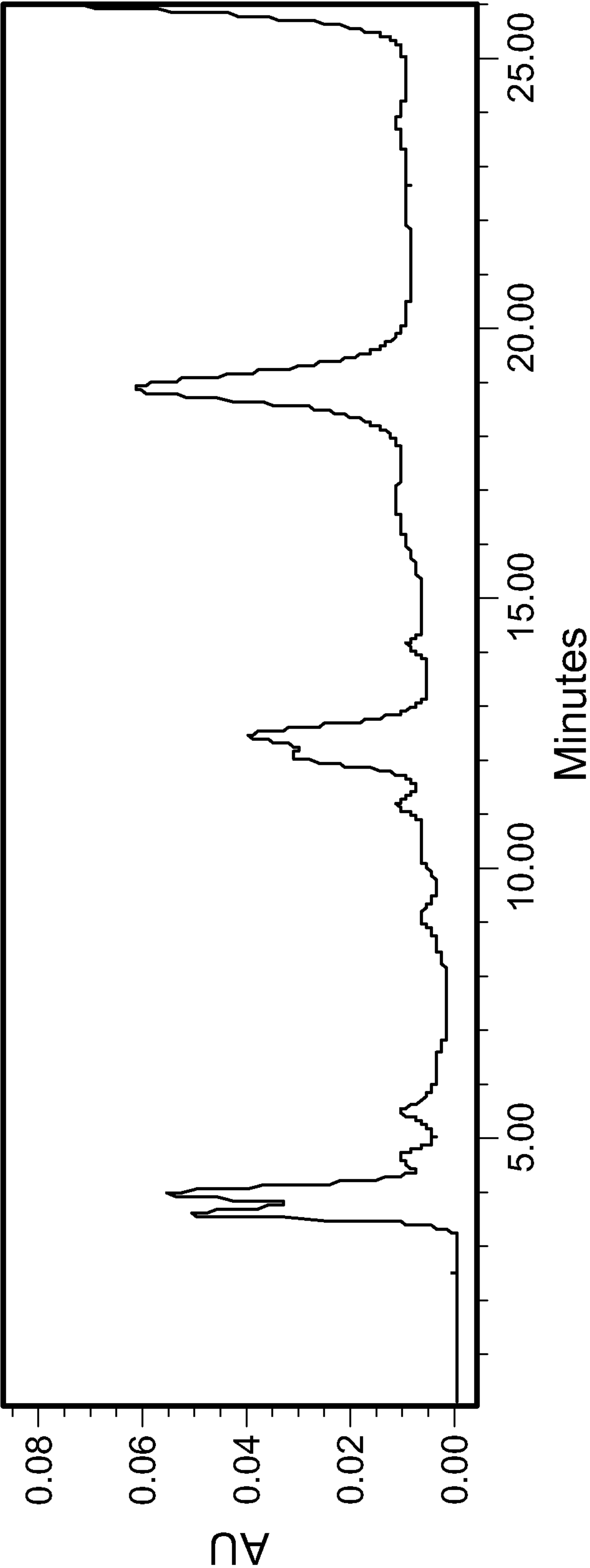


FIG. 29

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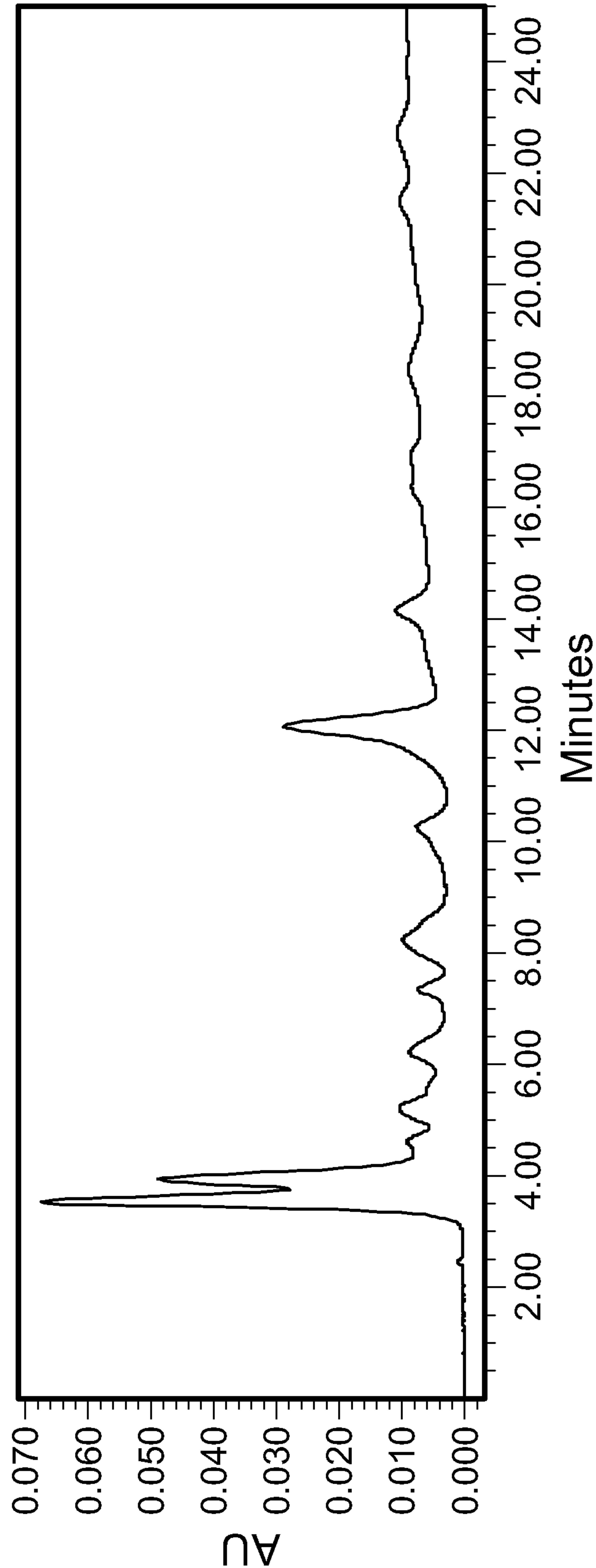


FIG. 30

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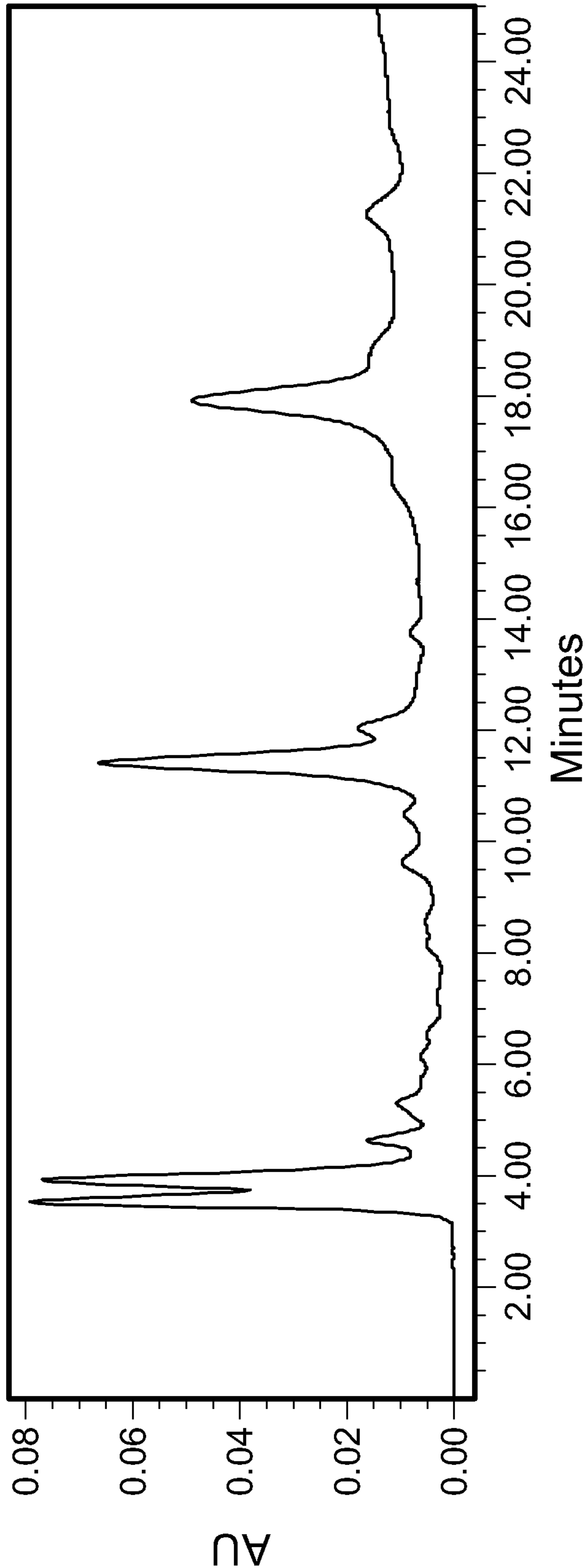


FIG. 31

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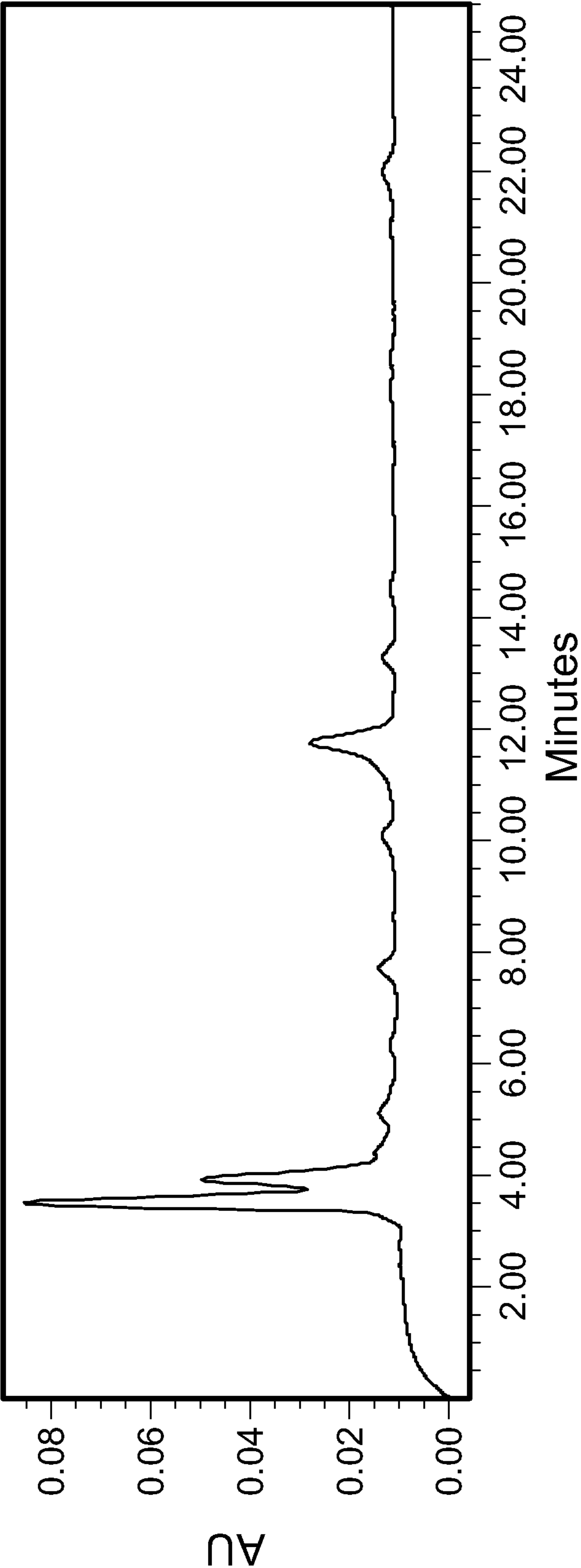


FIG. 32

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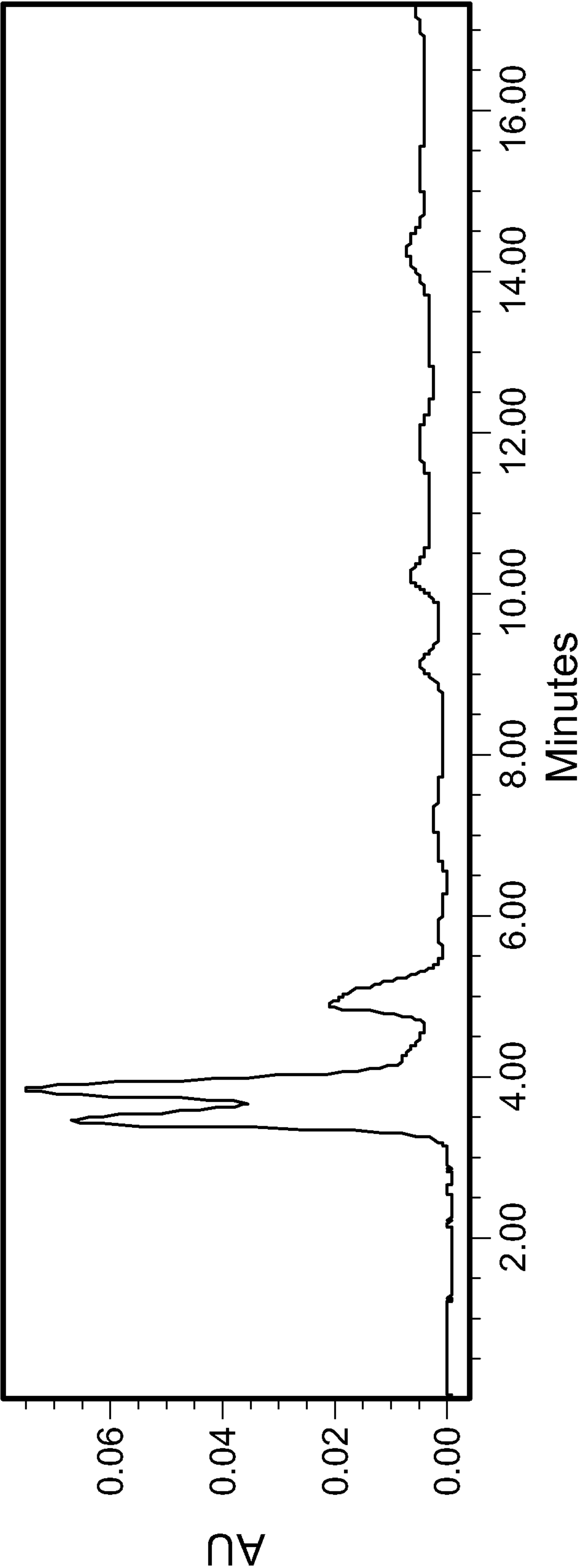


FIG. 33

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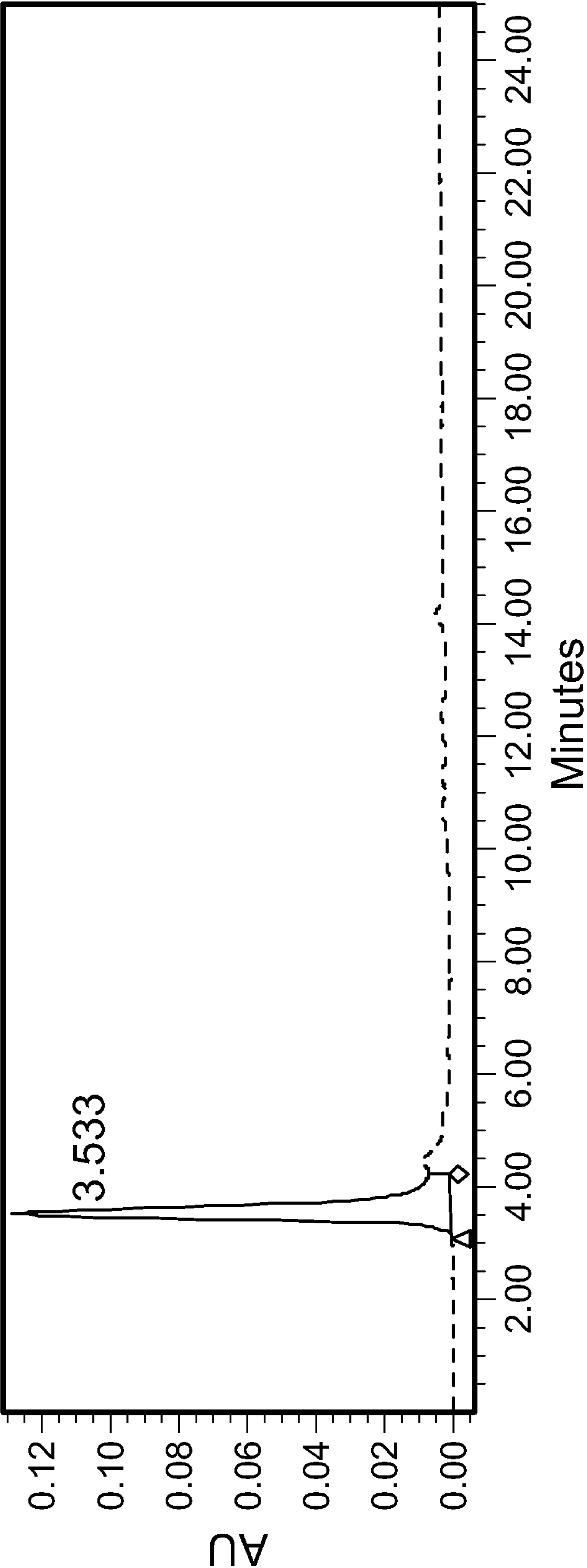


FIG. 34

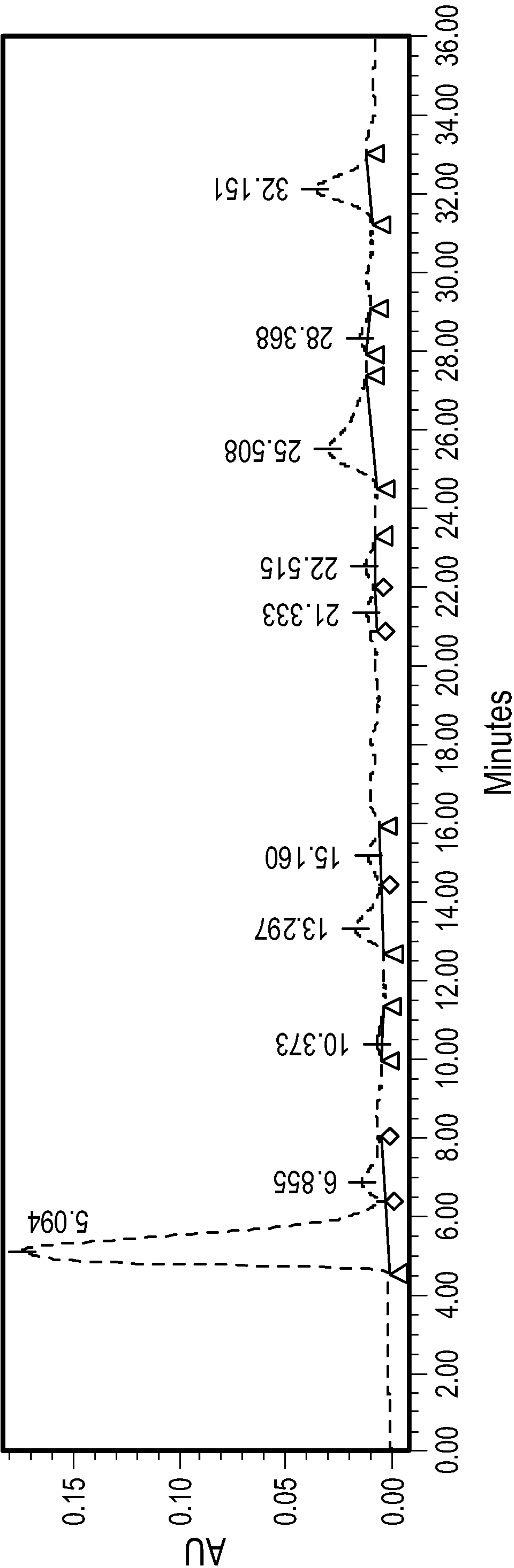


FIG. 35

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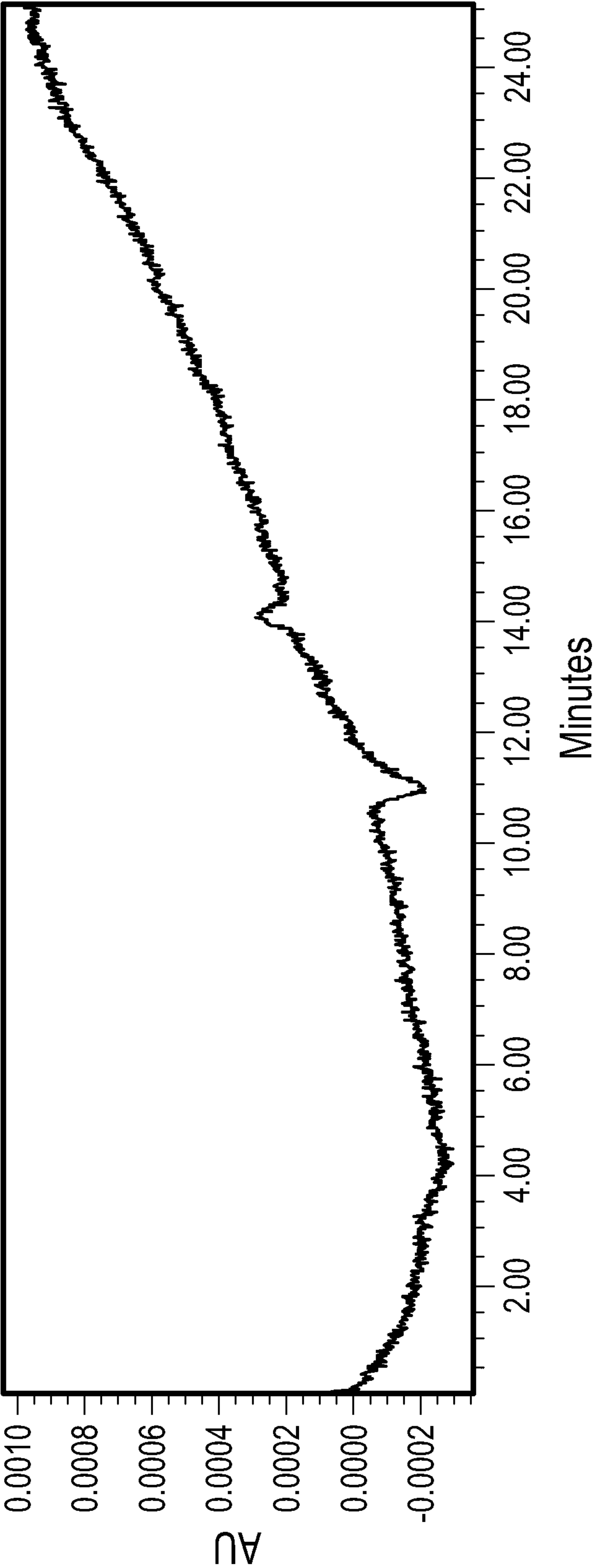
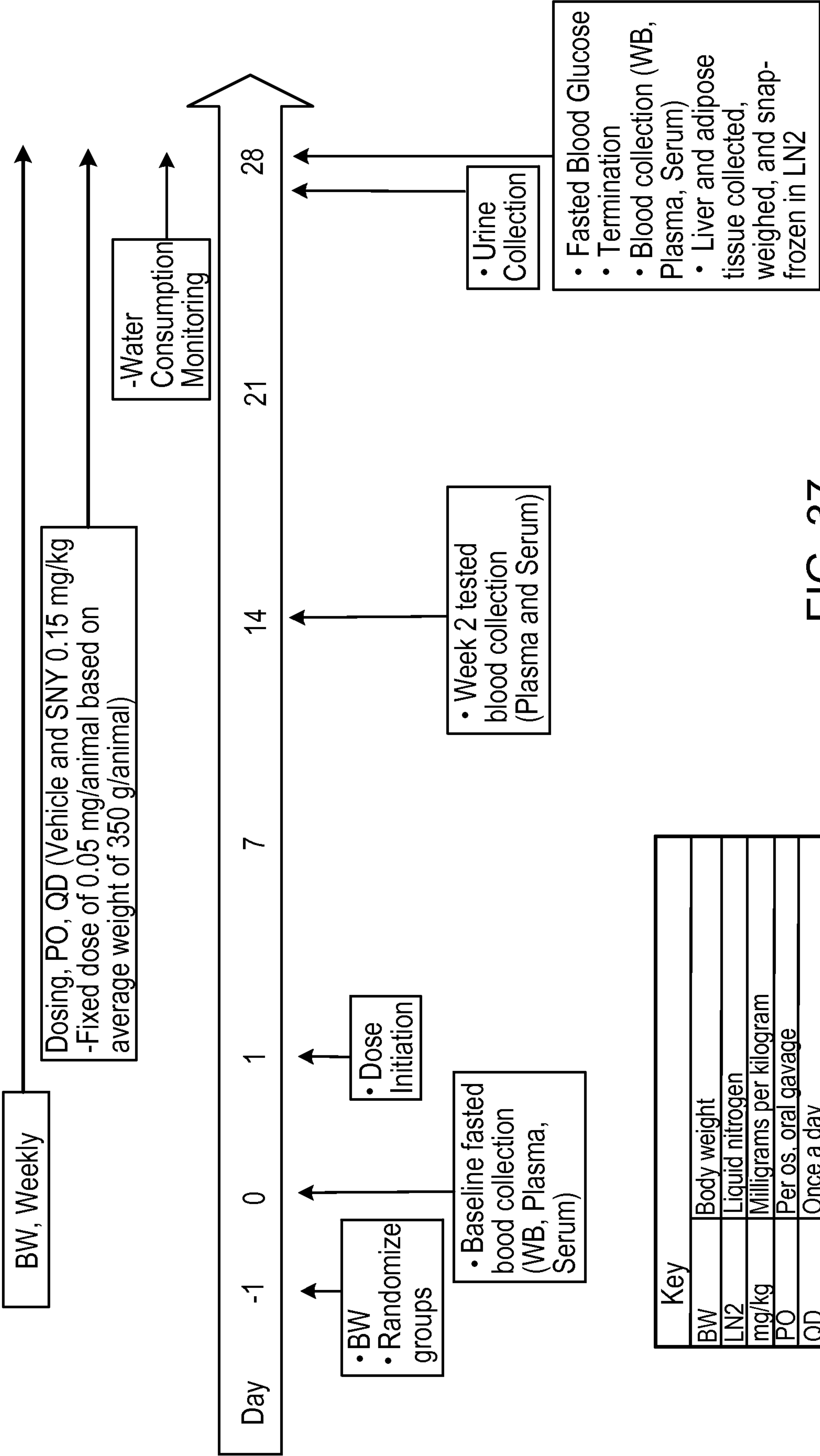


FIG. 36



Key	
BW	Body weight
LN2	Liquid nitrogen
mg/kg	Milligrams per kilogram
PO	Per os, oral gavage
QD	Once a day
WB	Whole blood

FIG. 37

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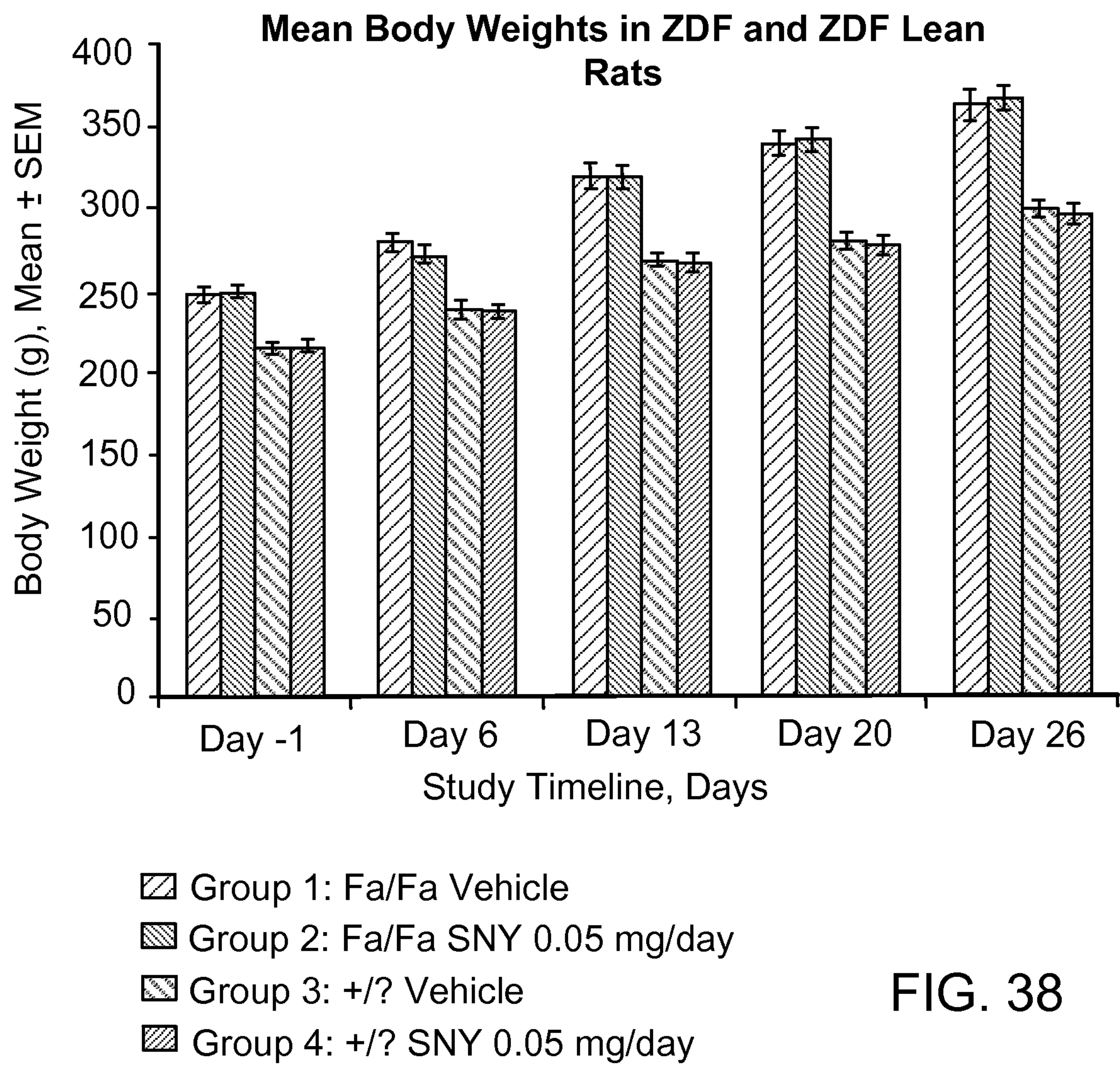
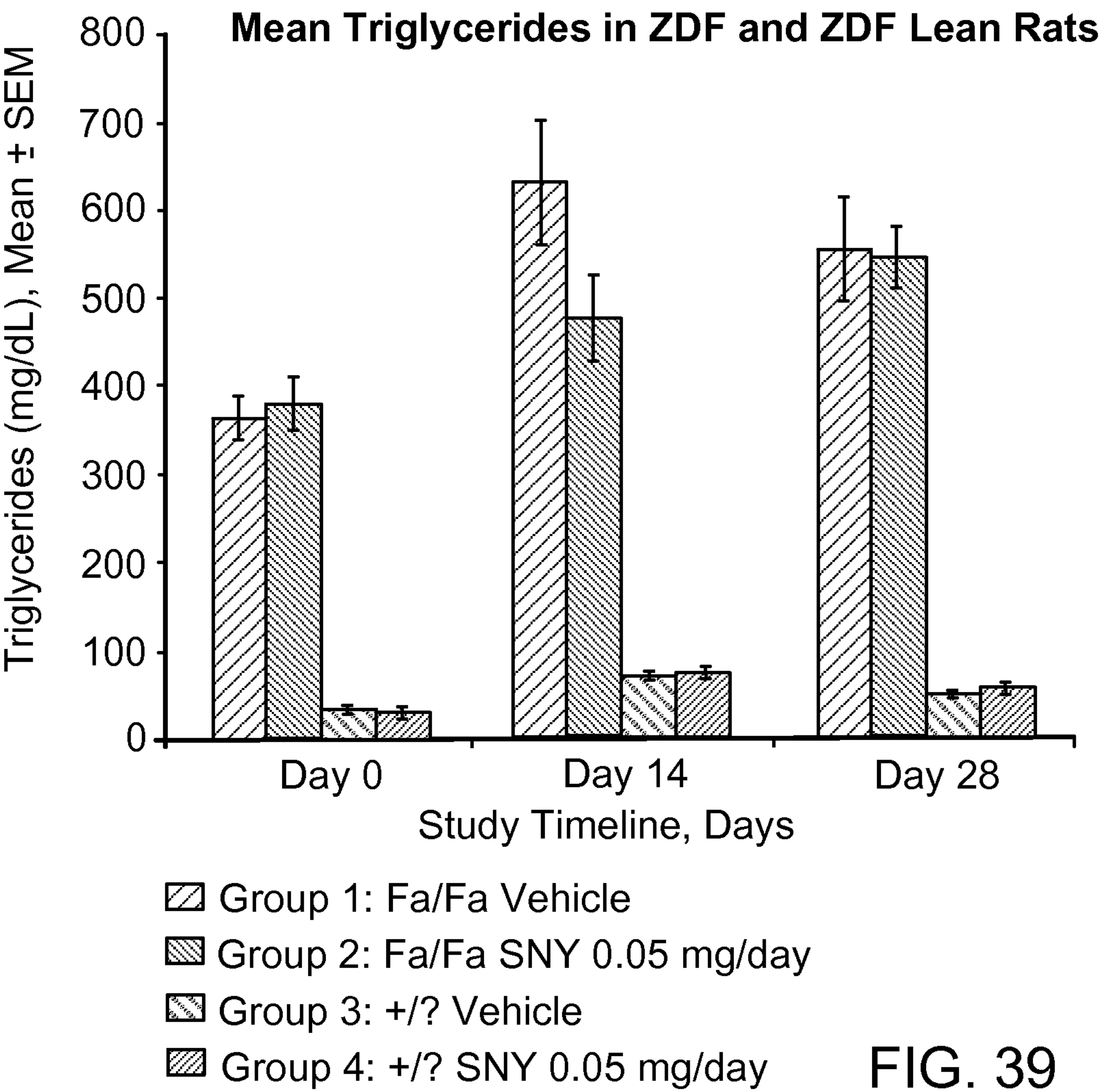


FIG. 38

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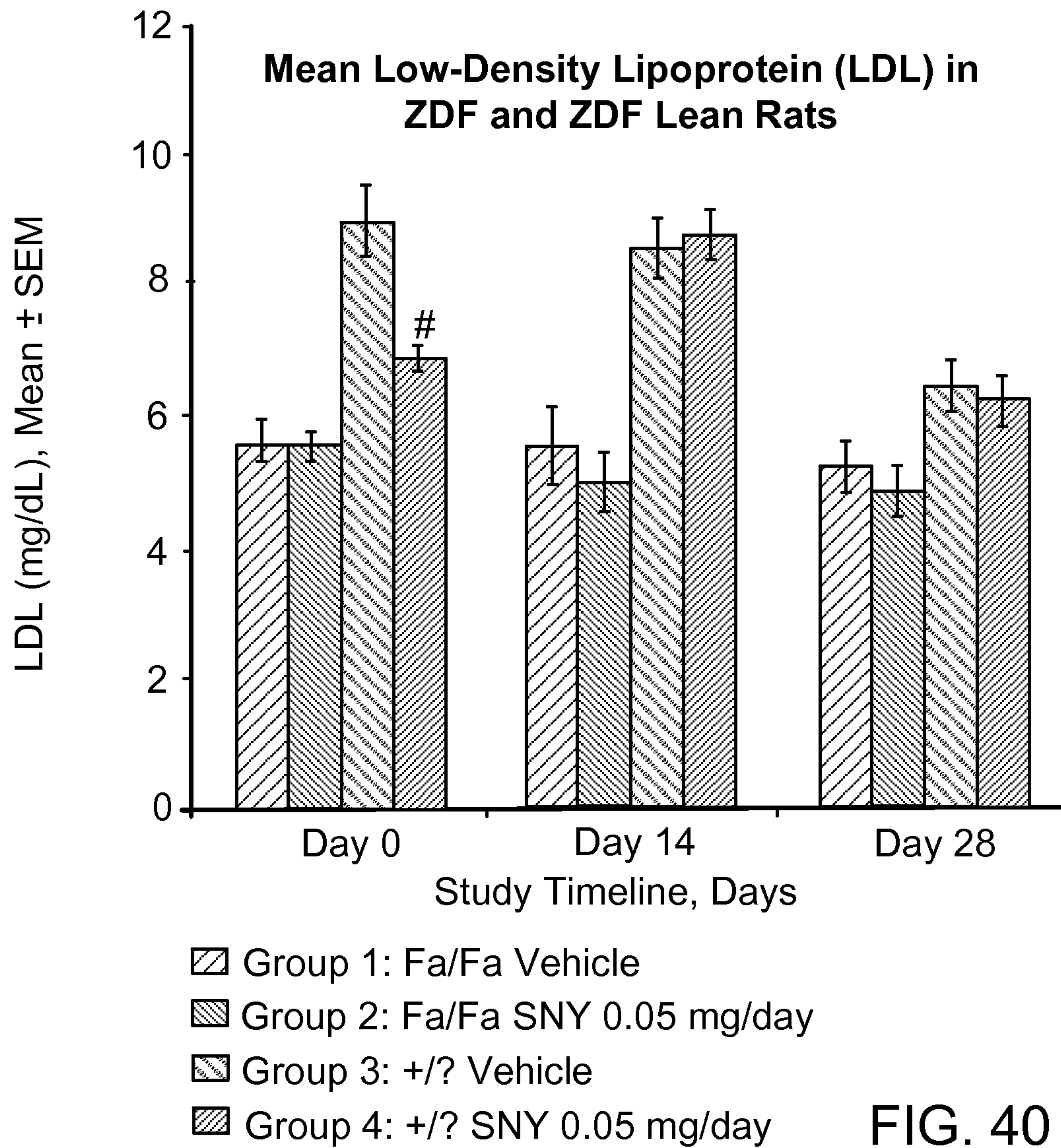
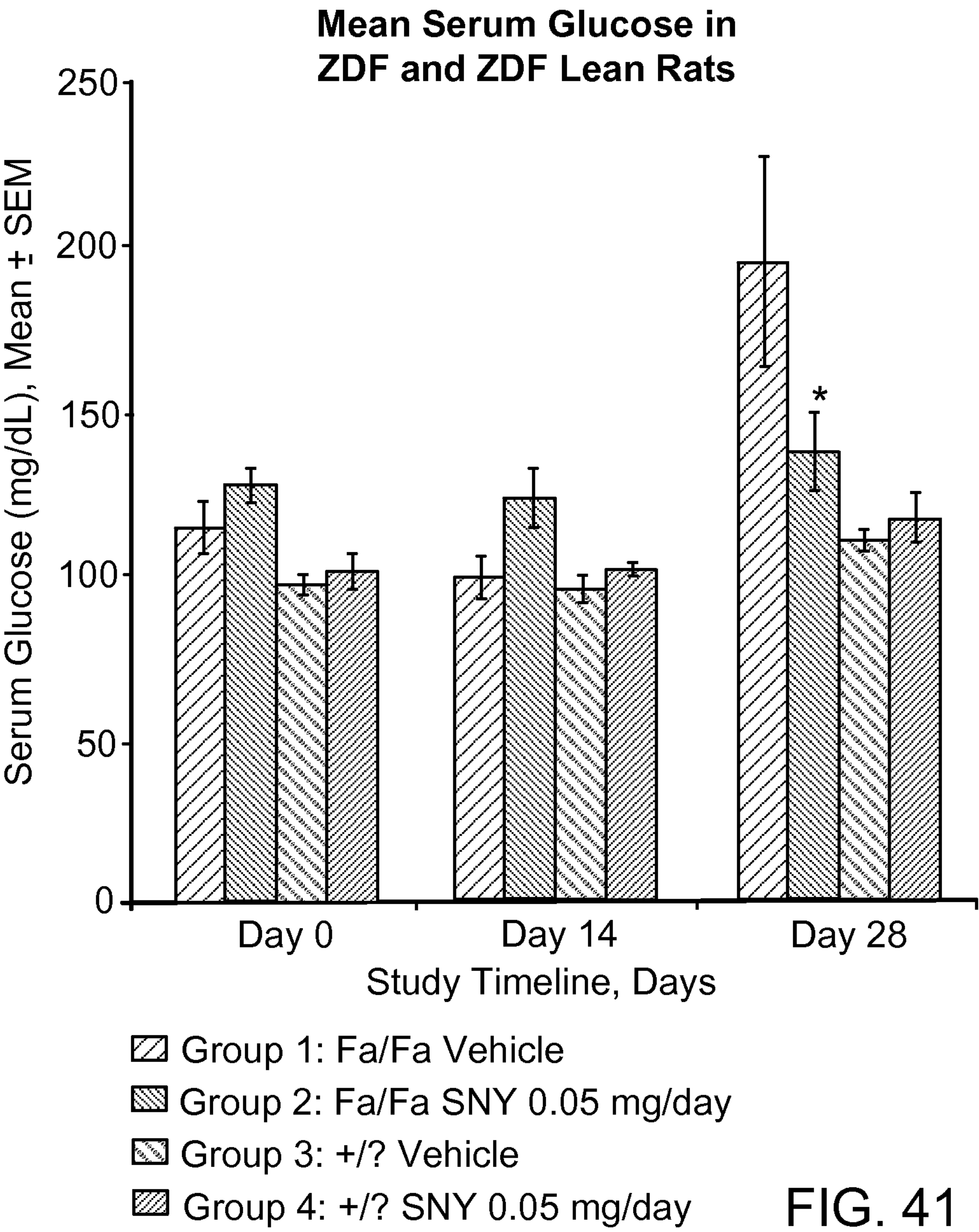


FIG. 40

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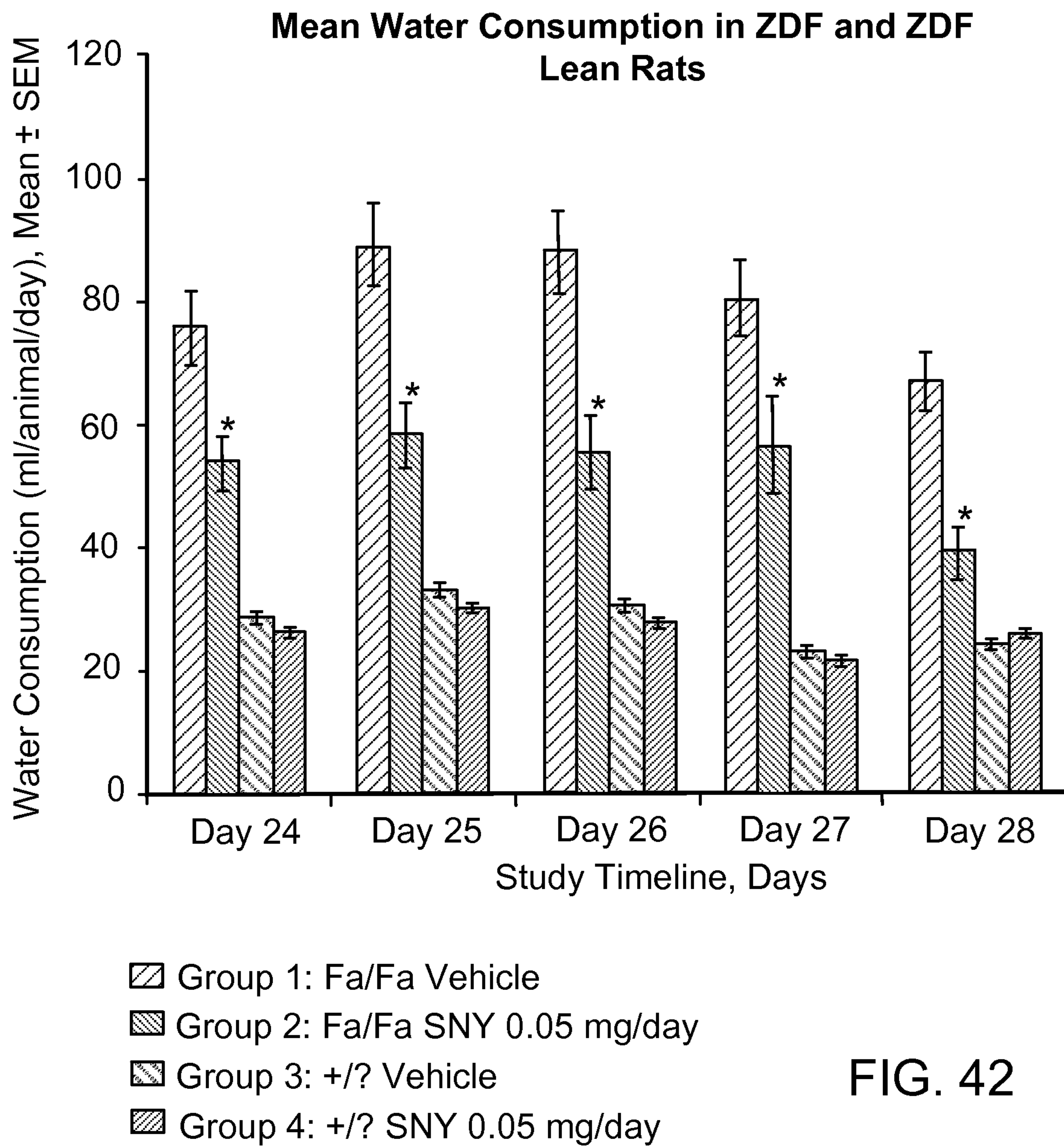


FIG. 42

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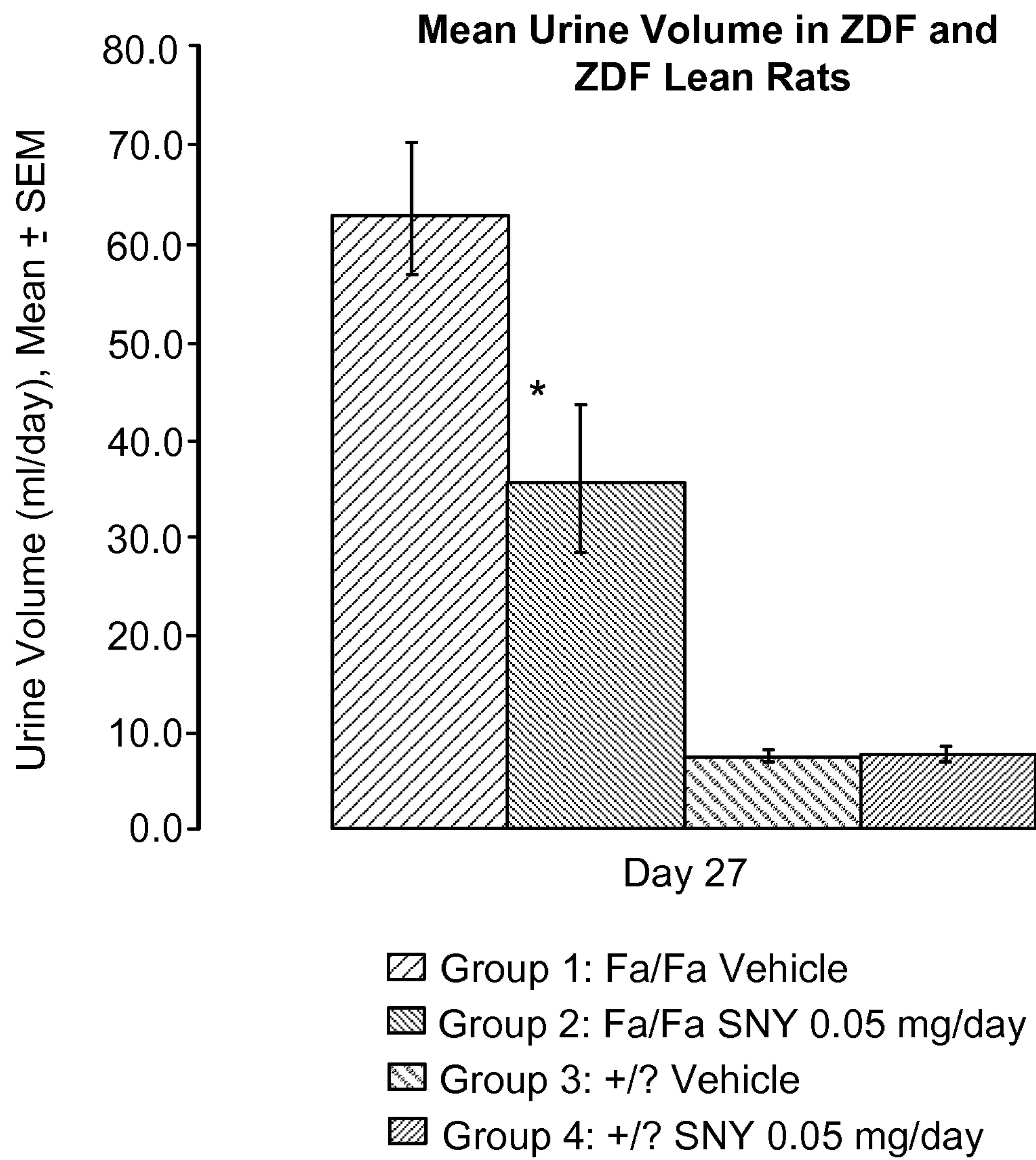


FIG. 43

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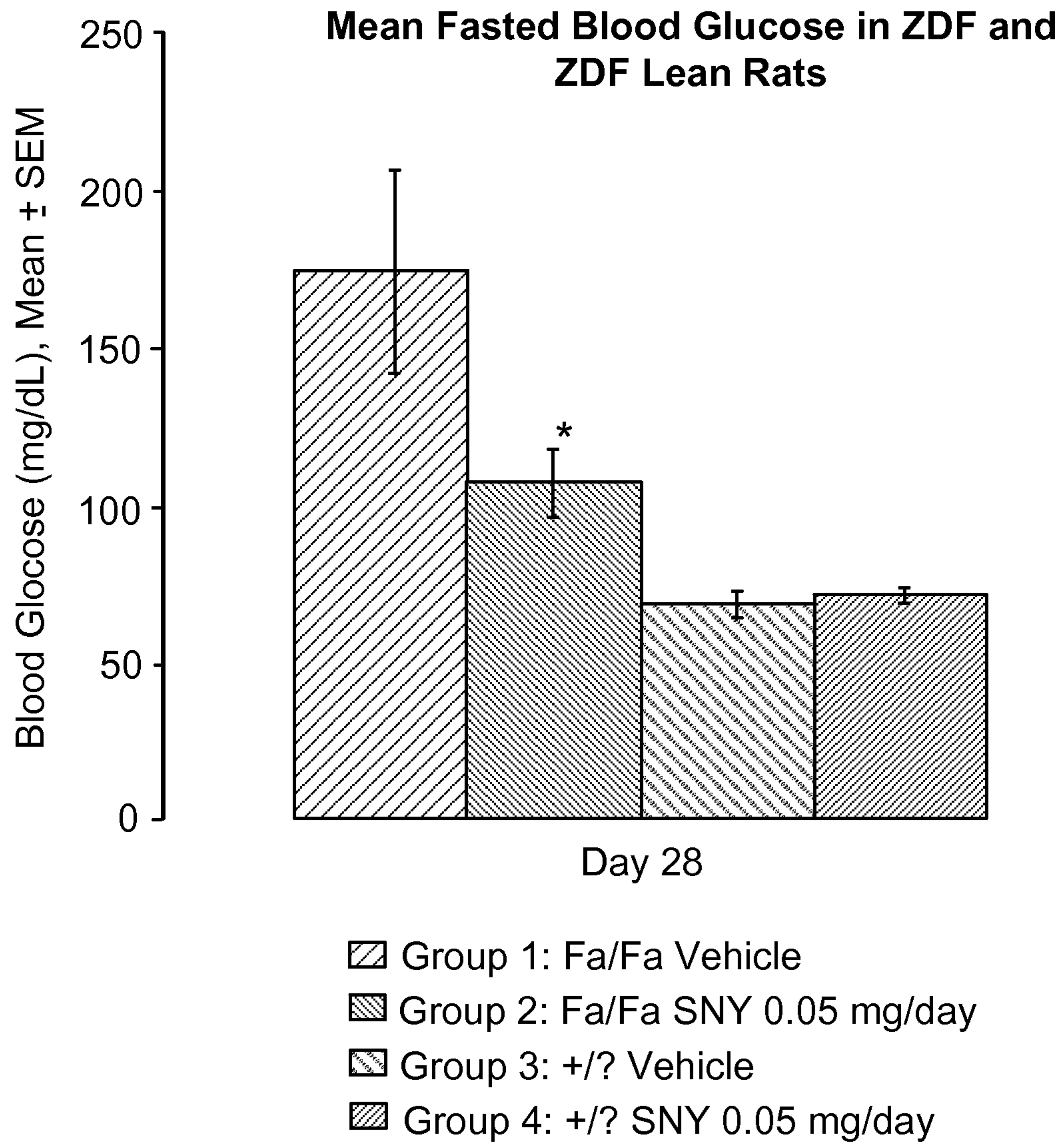


FIG. 44

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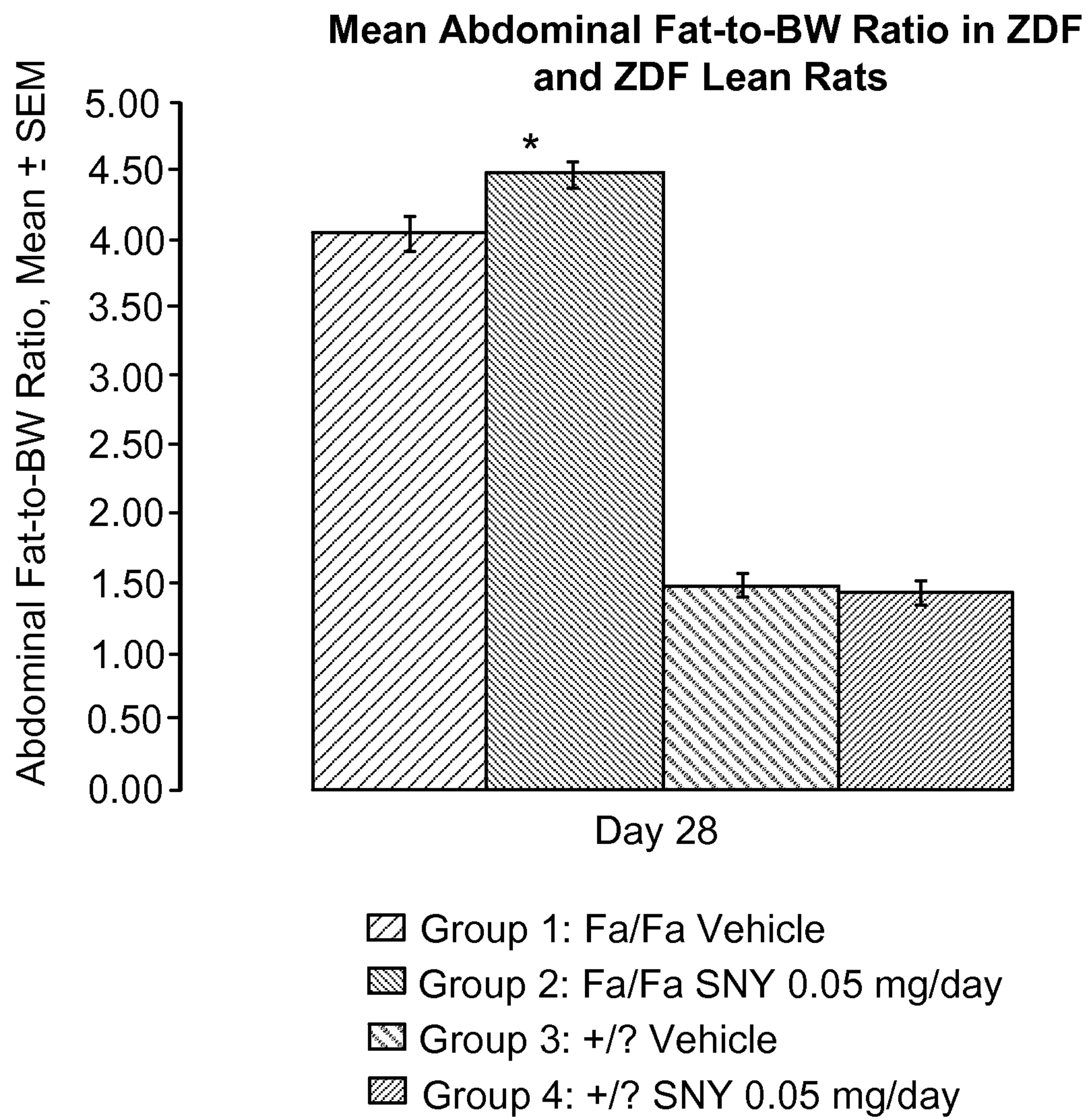


FIG. 45

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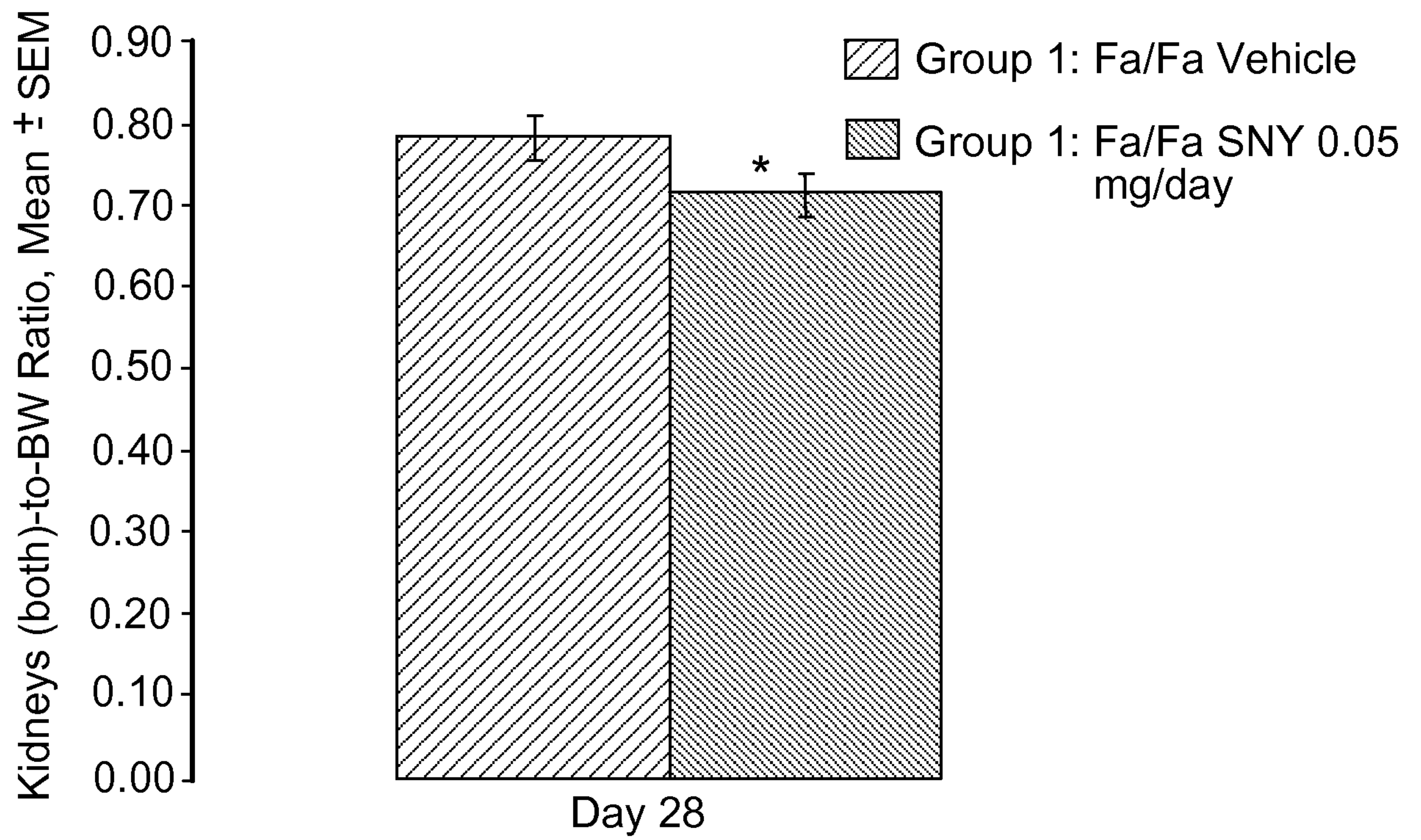
Mean Kidneys-to-BW Ratio in ZDF Rats

FIG. 46

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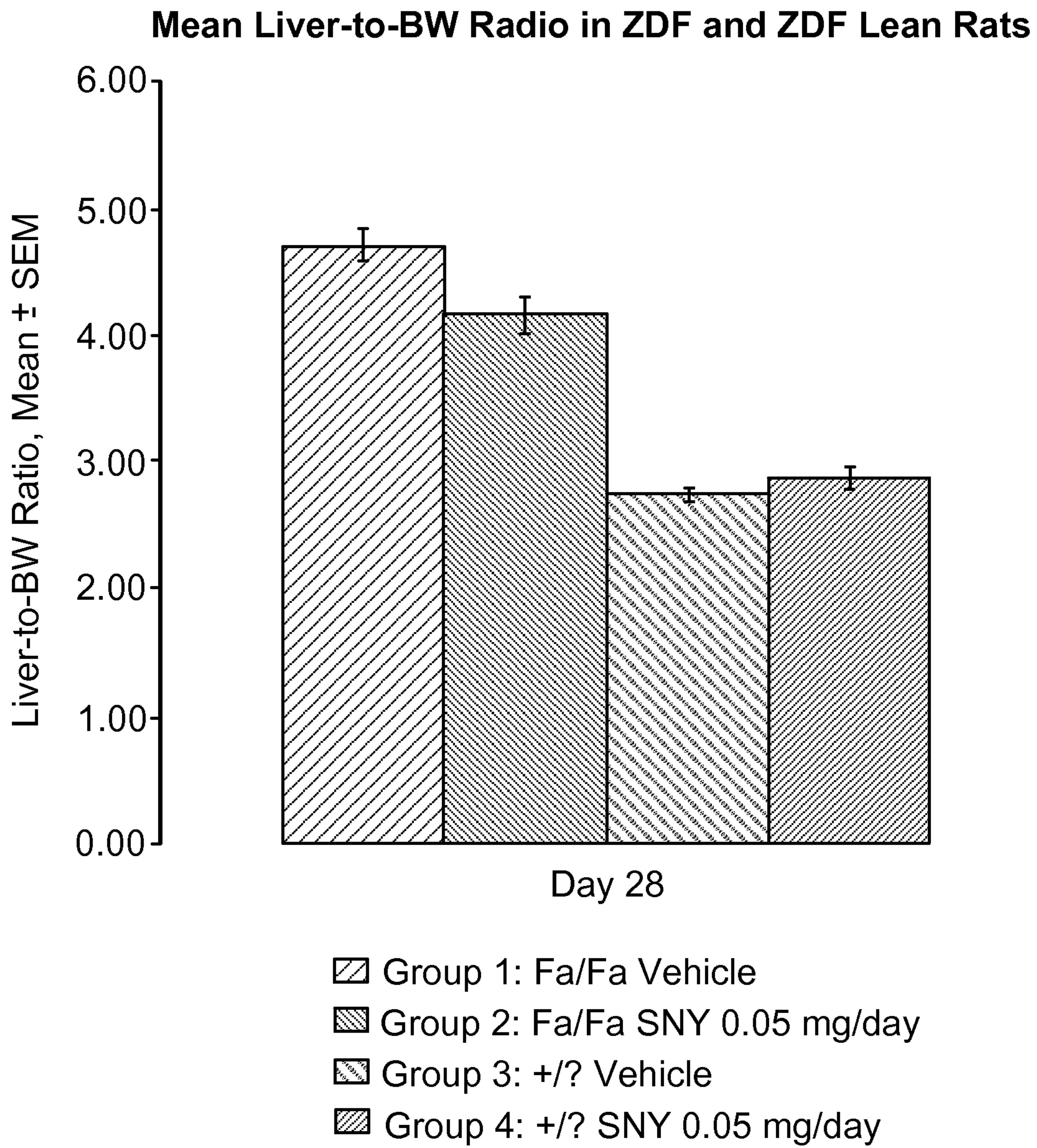


FIG. 47

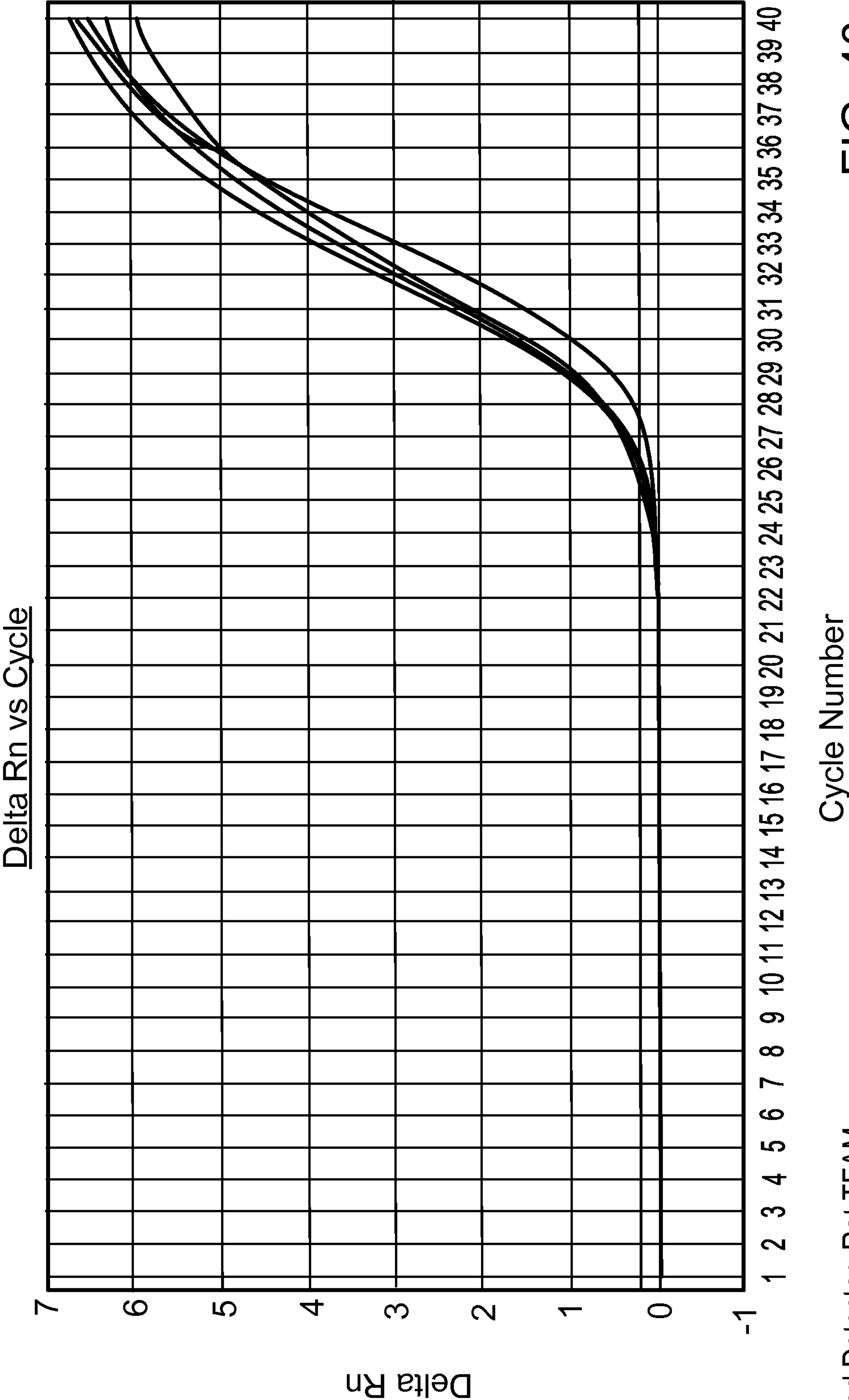


FIG. 48

Selected Detector: Rat TFAM

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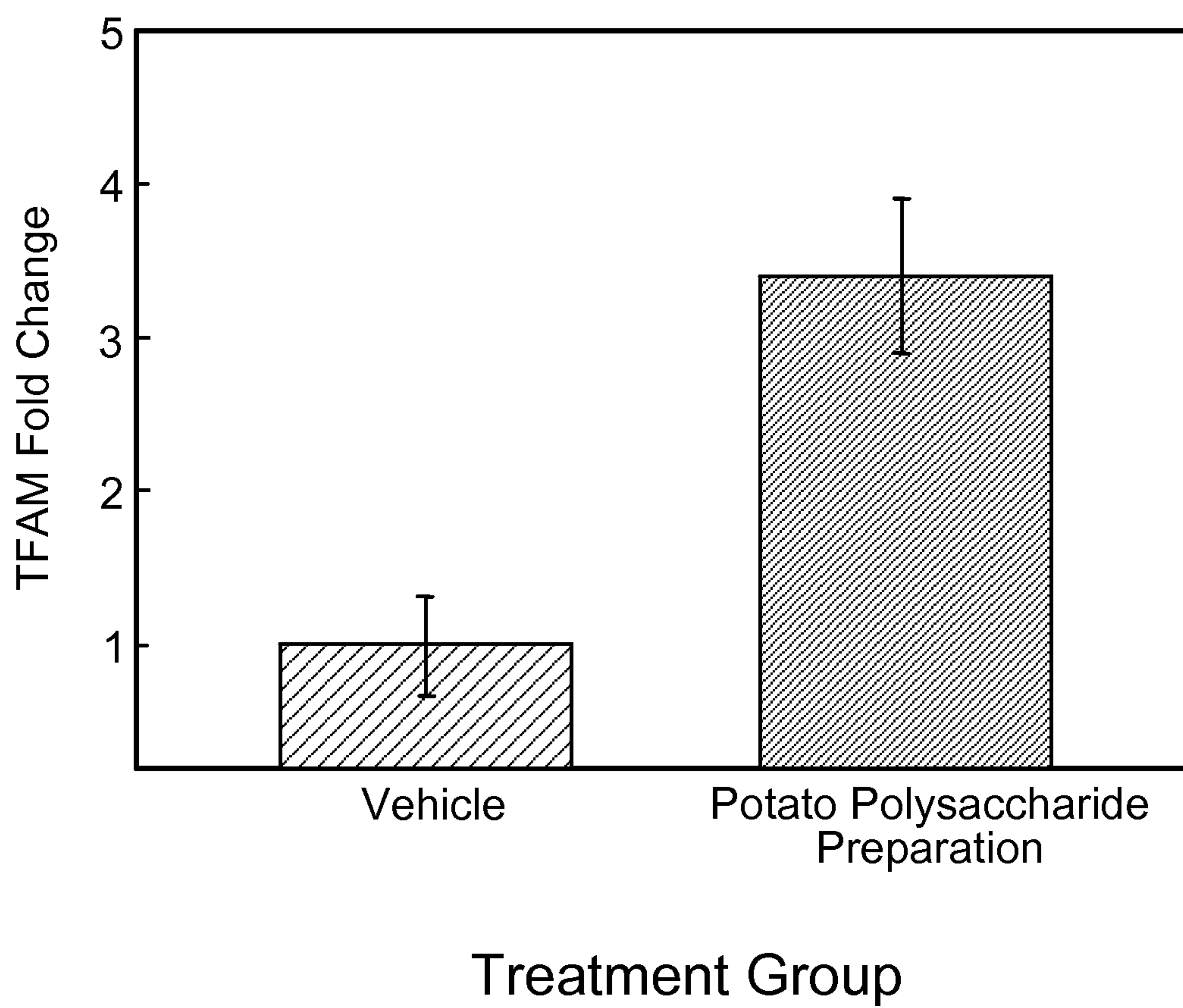


FIG. 49