TITLE OF THE INVENTION

MASS-BASED ENCODING AND QUALITATIVE ANALYSIS OF COMBINATORIAL LIBRARIES.

BACKGROUND OF THE INVENTION

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The present invention generally relates to the field of combinatorial chemistry and in particular relates to encoding the library products of combinatorial synthesis.

Recent trends in the area of research for novel chemical and especially pharmacological agents have been concentrated on the preparation of so-called "chemical libraries" as potential sources of new leads for drug discovery. Chemical libraries are intentionally created collections of differing molecules which can be prepared either synthetically or biosynthetically and screened for biological activity in a variety of different formats. One can have libraries of soluble molecules; libraries of compounds tethered to resin beads, silica chips or other solid supports; or recombinant peptide libraries displayed on bacteriaphage or other biological display vectors. Chemical libraries are advantageously made by using techniques from the field of combinatorial chemistry. The field of combinatorial chemistry is a synthetic strategy which leads to large chemical libraries. Combinatorial chemistry can be defined as the systematic and repetitive covalent connection of a set of different building blocks of varying

structures to each other to yield a large array of diverse molecular entitites.

Traditionally, new medicinal chemical lead structures have originated from the isolation of natural products from microbiological fermentations, plant extracts, and animal sources; from screening of pharmaceutical company compound databases; and more recently through the application of both mechanism-based and structure-based approaches to rational drug design. All of these methods are relatively expensive. Recent cost studies suggest that the average cost of creating a new molecular entity in a major pharmaceutical company is around $7,500 per compound, using the traditional chemical synthesis technology that requires more or less constant hands-on manipulation of reagents and apparatus and the attention of a chemist. Furthermore, the advent of high throughput automated techniques has made possible the robotized screening of in excess of hundreds of thousands of individual compounds per year, per drug target. The availability of this capability, combined with the relatively high cost of more traditional hand crafted chemistry has caused a global shift in emphasis toward the concept of mass production, which is an industrial concept that can be put into being using the approach of combinatorial chemistry.

The inefficiencies of hand crafted chemistry are thus largely addressed by a switch to the concept of using combinatorial chemical technologies for rapidly synthesizing compound collections. Thus, by employing a building block approach and by systematically assembling these blocks in many combinations using chemical procedures it is possible to create chemical libraries as vast populations of molecules. An essential starting point for the generation of molecular diversity is an assortment of small, reactive molecules which may be considered chemical building blocks. The universe of structural diversity accessible

through assembly of even a small set of building-block elements is potentially very large, and unleashing the power inherent in the building block approach is crucial to the success of the combinatorial method. The building block argument is easily illustrated as follows. Theoretically, the number of possible different individual compounds, N prepared by an ideal combinatorial synthesis is determined by two factors; the number of blocks available for each step "B" and the number of synthetic steps in the reaction scheme, s. If an equal number of building blocks are used in each reaction step, then $N = B^s$. If the number of blocks that one desires for each step varies (e.g. b, c, d in a three-step synthesis), then $N = bcd$.

From the above, it can be seen that a relatively conservative combinatorial synthesis procedure involving 20 blocks in a three step synthesis process will produce $20^3 = 8000$ compounds. This relatively generous production output then raises the next question, which is, how will the compounds be identified? For example, a typical combinatorial synthesis technique is that of the split synthesis. As an example of split synthesis in the solid state synthesis of peptides, a batch of resin support (typically small resin beads) is divided into n fractions, coupling a single monomer amino acid to each aliquot in a separate reaction, and then throroughly mixing all the resin particles together. Repeating this protocol for a total of x cycles can produce a stochastic collection of up to n^x different molecules, as governed by a hypergeometric distribution. To ensure representation of the majority of possible ligands one needs to begin with a multiplicity of beads. A typical value would be ten times as many beads as the desired number of ligands. Theoretically a set of every possible combination of the building blocks exists in the aliquots. In order to determine the composition of a particular compound which is found to be of interest, one could proceed with direct ligand structural analysis, preferably on a mass spectrometer, on a

species-by-species basis. A typical combinatorial synthesis now typically takes place on a reaction plate having from 96 to 2,304 reaction wells. One identifies the product compounds of true interest by a positive response in an appropriate assay. However, even after assays are run that will greatly reduce the number of compounds as having been non-active in the assay, the problem with a conventional mass spectrometer analytical approach is that many individual analysis trials are required, there may only be very small quantities of material available after running a combinatorial synthesis, and overall turn around time may be quite lengthy. A need exists, then to somehow label compounds as they are going through their combinatorial steps. Where compounds are, for example, tethered to resin beads, prior art solutions to the problem have included attaching chemical identifier tags to the beads coincident with each block coupling step in the synthesis. The different chemical properties of each tag would then convey which building block was coupled in a particular step of the synthesis, and the overall structure of a ligand on any bead could be deduced by "reading" the set of tags on that bead, in effect having encoded the bead.

Tags should ideally have a highly discrete information content, be amenable to very high sensitivity detection and decoding, and must be stable to reagents used in the ligand synthesis. Prior art tags attached onto beads have included nucleotides, peptides, or a combined series of hydrocarbon homologs and polychlorinated aromatics. Single stranded oligonucleotides are built on resin beads upon which peptide synthesis is being performed and which are subsequently amplified through polymerase chain reaction and sequenced. Another technique is one where orthogonally differentiated diamine linkers are used in the construction of soluble chimeric peptides comprising a "binding " strand and a "coding" strand. As amino acid monomer building blocks are coupled to the binding strand, this is recorded by building an

amino acid code onto the "coding " strand. The sequence of the coding strand is then resolved by Edman degradation. One problem with this approach is that it requires an extra chemical step for every step taken in the construction of the library. Another problem with this approach is that it requires requires orthogonal synthetic procedures for building up a tag in conjunction with synthesis of ligands, i.e., it requires the addition of like moieties, whereas there is very great interest in discovering methods for producing compounds which are not limited to sequential addition of like moieties. Such methods would find application, for example in the modification of steroids, antibiotics, sugars, coenzymes, enzyme inhibitors, ligands, and the like, which frequently involve a multi-stage synthesis in which one would wish to vary the reagents and/or reactions conditions to provide a variety of compounds. In such methods the reagents may be organic or inorganic reagents, where functionalities may be introduced or modified, side groups attached or removed, rings opened or closed, stereochemistry changed, and the like. For such a method to be viable, however, there needs to be a convenient way to identify the structures of the large number of compounds which result from a wide variety of different modifications.

A technique that is useful for the screening of nonsequenceable organic molecules prepared by multistep combinatorial synthesis uses a series of gas chromatographically resolvable halocarbon derivatives as molecular tags which, when appended to reactive groups on the bead surface, can constitute a binary code that reflects the chemical history of any member of a library. Instead of the oligonucleotide or peptide coding approaches where the order of assembly of the chemical building blocks for any library member is preserved in the sequence of a single cognate tagging molecule, the binary strategy uses a uniquely defined mixture of tags to represent each building block at each particular step of the

synthesis. Thus a set of N tags can be used to encode the combinatorial synthesis of a library of 2^N different members. After assembly, the tags are photolysed and analyzed by electron capture capillary gas chromatography.

In all cases, the use of reporter tags complicates synthetic strategies, increases the risk of side reactions and by-products, and yields only indirect evidence of structure. Thus, there is a need to find a way whereby a compound's reaction history may be recorded, and the structure of the resulting compound identified.

The use of ^{13}C site-specific labels on the ligand itself has also been used, in connection with ^{13}C NMR spectroscopy as a method of monitoring progress in solid state combinatorial synthesis.

Yet another method is that of using a chip which allows for separate analysis at physically separate sites on the surface of the chip. By knowing what reactant is added sequentially at each such site, one can record the sequence of events and thus the series of reactions. If one then subjects the chip to a screening method for a particular desired characteristic and detects the characteristic one can readily determine the compound synthesized at the site which demonstrates that characteristic.

A discrete sample-by-sample analysis will yield a great deal of extraneous information, as everything in the sample will be analyzed. However, in analyzing the results of a combinatorial synthesis, it is desirable to be able to track in linear terms, since all that is being tracked by a linear method is what is being added to the construct of interest in the synthesis, which will omit the presence of solvents, resin bits, side reactions and impurities.

In view of the above needs and shortcomings of the prior art, it is a primary object of the present invention to reduce the amount of time needed to read and de-code the products of a combinatorial

synthesis. It is another object of the present invention to provide a method of encoding combinatorial constructs that does not require orthogonal chemistry, that is, chemistry that has been carefully selected so as not to be interfering with the chemistry that is being executed as part of the combinatorial synthesis itself. Another object of the invention is to minimize the amount of capital investment needed to develop a coding strategy that requires no more than what is needed to initially develop a set of appropriate solid support links.

Unlike the methods of the prior art, the present invention embodies a method of isotopically rather than chemically encoding a monomer to read a synthetic history. Readable differences in the encoding moieties therefore rely on physical differentiation, rather than chemical differentiation. The isotopically encoded monomer is, however, chemically bonded to the ligand of interest during synthesis, in contrast to prior art identification methods in which differentiable isotopes are physically mixed into and interspersed with bulk chemicals or commodities to identify their manufacturing source. The invention likewise does not rely on tagging a molecule, like other prior art approaches.

DESCRIPTION OF THE FIGURES

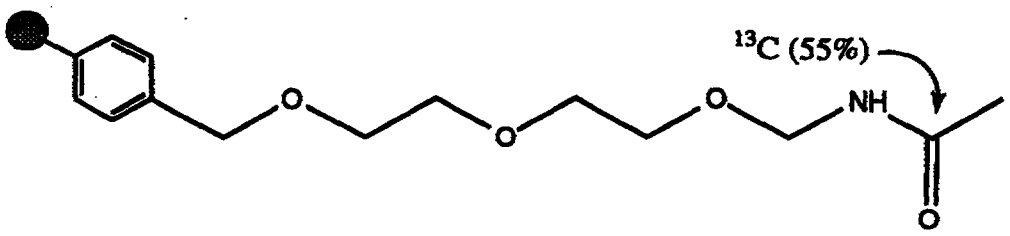
Figure 1 is an array of MS peaks that represent the observed peak signatures for the doped glycine code blocks described in the specification below.

Figure 2 is a graph that shows the observed correlation between number of carbon atoms present and the fraction of link content that has N^{15} present. The chart can be used to calculate equal intensity
peak signatures.

Figure 3 illustrates a two peak positional coding strategy for a molecule, featuring splitting MS peaks into doublets to enhance code recognition.

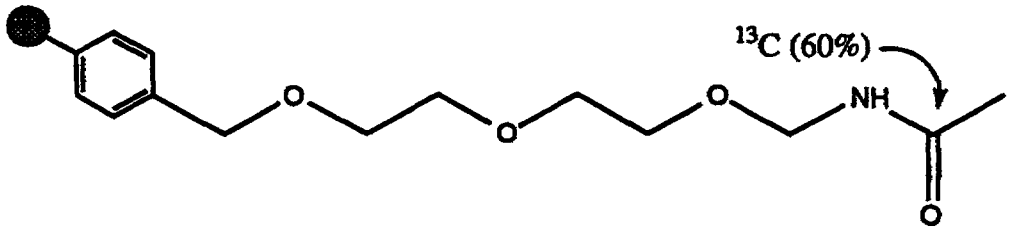
Figure 4 illustrates the observed correlation between MS peak area and ratio of N^{15} present in a code sample for a series of code samples differing in N^{15} content by 5% increments.

Figure 5 is an NMR peak pattern for the compound:



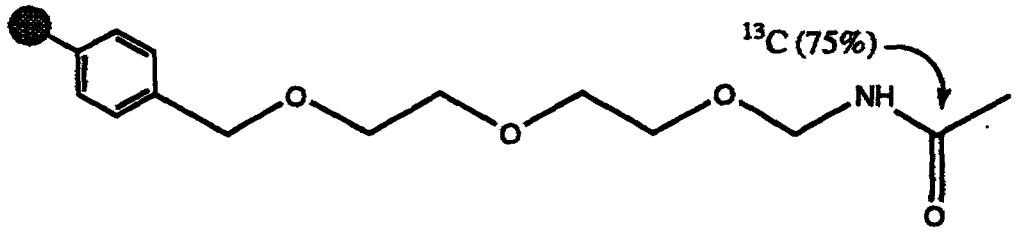
denoting that 55% of the carbon at the penultimate position was doped with C^{13}.

Figure 6 is an NMR peak pattern for the compound:



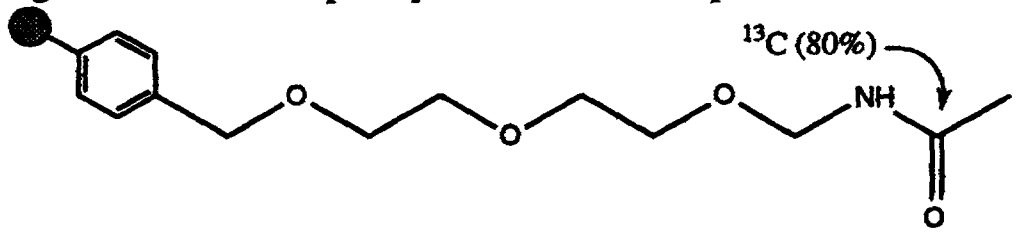
denoting that 60% of the carbon at the penultimate position was doped with C^{13}.

Figure 7 is an NMR peak pattern for the compound:



denoting that 75% of the carbon at the penultimate position was doped with C^{13}.

Figure 8 is an NMR peak pattern for the compound:



denoting that 80% of the carbon at the penultimate position was doped with C^{13}.

Figure 9 is a chart that correlates the observed ratio of C^{13} to C^{12} in the NMR spectra of Figures 5 through 8 with the % of C^{13} present in each.

Figures 10 through 12 show spectra observed in conjunction with the Example 23 procedure on the Reaction Screening embodiment of the invention.

Figures 13 through 17 show synthesis flow diagrams used in the Example 23 disclosure on the Reaction Screening embodiment of the invention.

Figures 18 through 51 show spectra observed in conjunction with the Example 24 disclosure of the Ratio Coding embodiment of the invention.

Figures 52 through 110 show spectra that are produced in conjunction the disclosure of Example 25 of encoding styrene and Example 26 disclosing copolymerization of styrene and F-styrene.

Figures 111 through 132 show spectra representing the decoding of a parallel synthesis of a library on encoded resin beads, using a dual linker approach in which a first linker was a photocleavable linker and a second linker was a Knorr linker.

Figures 133 to 286 are spectra that are produced by a set of code blocks organized in a type of ratio encoding designated as four peak ratio encoding, using four isotopically distinct F-moc protected versions of alanine

Figure 287 is a flow diagram for a computer program capable of automating the decoding of a set of code blocks and their associated spectra.

SUMMARY OF THE INVENTION

In brief summary, the invention is the application of mass or isotopic encoding in the imprinting of coded information into or in conjunction with materials or processes shch that the details of the components or process steps can be easily determined by one or more of the methods of mass spectrometry, nuclear megnetic resonance spectroscopy, or infrared spectroscopy, including the technique of Ramen spectroscopy. In a preferred embodiment, the invention is a method of encoding the products of combinatorial synthesis by isotopically doping a portion of a combinatorial chemistry construct and analyzing the combinatorial reaction products by mass spectrometry, nuclear magnetic resonance spectroscopy or infrared spectroscopy.

In overview, the invention comprises several embodiments. Firstly, the invention comprises a mass-based, non-chemical method for recording the reaction of at least a portion of a reaction series on each of a plurality of unique solid supports, the method comprising: preparing a plurality of agents each having a unique defined mass; preparing a group of unique solid supports; reacting each solid support group with a different chemical reagent under a controlled reaction condition; mixing these product groups together and then dividing the mixture of unique solid supports into a plurality of groups for a second intermediate or final stage; repeating the reacting stage with a chemical reagent under a controlled reaction condition at least once to provide a plurality of final products, having different products on the different individual unique solid supports; each of the unique defined mass agents being reacted with either: each of a group of unique solid supports; each of a group of first chemical reagents in a reaction series; each of a group of second chemical reagents in a reaction series; or each of a group of subsequently added chemical reagents in a reaction series; such that each of the group of unique solid supports, group of first chemical reagents, group of second chemical reagents or group of subsequent chemical reagents has been reacted with an agent having a defined mass that is different from any other defined mass agent reacted with any other of the aforesaid groups; the unique defined mass agents being capable of being analyzed and wherein such analysis defines the choice of a first chemical reagent, reaction condition under which the first chemical reagent was added, second chemical reagent, reaction condition under which the second chemical reagent was added, subsequent chemical reagent, or reaction condition under which the subsequent chemical reagent was added. The method is particularly preferred in performing an assay or using separation techniques including column or plate chromatography or fluorescence assistance cell scanning to find reaction products having a characteristic of interest and then

performing the identification analysis on such reaction products. This method is particularly preferred with respect to the determination of the first chemical reagent added to the reaction sequence. Reaction products can include a non-oligomer which is aliphatic, alicyclic, aromatic, or heterocyclic or an oligomer which is an oligopeptide, oligonucleotide, oligosaccharide, polylipid, polyester, polyamide, polyurethane, polyurea, polyether, polyphosphorus derivative where the phosporus is taken from the group consisting of phosphate, phosphonate, phosphoramide, phosphonamide, phosphite, or phosfinamide, or polysulfur derivative where the sulfur is taken from the group consisting of sulfone, sulfonate, sulfite, sulfinamide, or sulfenamide.

Preferred means of analysis are by mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, and infrared or Raman spectroscopy. These means of analysis produce distinctive peak patterns used in analysis, identification, coding and decoding strategies. The mass spectrometer in particular produces unique single mass peaks, unique double mass peaks, unique pairs of single mass peaks, unique pairs of double mass peaks and other unique multiple peak patterns, which are additionally capable of being translated into machine-readable patterns, including bar codes. The NMR, IR and Raman methods also produce useful unique peak patterns that can be transformed into machine-readable patterns, including bar codes. Such patterns, including machine-readable patterns, can be assigned in encoding strategies to represent discrete chemical reagents added in a chemical reaction series, or assigned to represent discrete chemical reaction conditions under which a chemical reagent was added in a reaction series, including, but not limited to, concentrations, temperatures, pressures, catalysts, enzymes, electromagnetic energy imparted to the system (visible light conditions, irradiation, etc.), and so on. This is done by initially

generating recognition patterns for unique mass defined agents which are either eye-readable or machine-readable. The patterns resulting from the analysis steps are then compared to the recognition patterns for identification and decoding, with or without the assistance of a machine. Recognition patterns and analysis patterns that are machine-readable are capable of being stored electronically in suitable computer storage and memory devices well known to those of ordinary skill in the art and such stored patterns form a readily retrievable database that also forms a claimed embodiment of the invention.

Mass agents used in these methods are preferably a molecular entity such as a solid state chemistry support resin bead linker which has had one or more of its atoms replaced by an isotope of that atom, thus altering the mass, but not the chemical properties of that chemical entity. Another alternative mass agent is to simply repeat the appearance of such a molecular entity an integral number of times in a linear chemical construct.

The method of the invention can be performed using solid state chemistry or solution chemistry. Reaction products can be cleaved off of a solid support for analysis, or the entire construct can be analyzed. Chemical reagents added to a reaction series can include one or more that can act as a substrate for the determination of binding specificity to a chemical compound of interest. Any or all of the steps of encoding, synthesis, analysis and decoding can be automated with the aid of suitable computer means and robotics means, all by methodologies well known to those of ordinary skill in the combinatorial chemistry, spectroscopy, computer science, robotics and optical scanning arts.

The invention also comprises a kit made up of a set of compounds prepared for the encoding, synthesis, analysis and

decoding methods described above of chemical reagents and reaction conditions in chemical reactions of interest in a combinatorial synthesis, where the compounds in the kit have different distinguishable masses, but the same chemical properties. Such kits can comprise solid state supports attached to isotopically doped linkers, series or combinations of isotope mixtures in readily identifiable ratios, or a variety of combinations of isotopically doped chemical moieties (also called code blocks herein) with covalent bonds or or other organic moieties as links or linkers.

The invention also comprises kits of solid state supports that have been prepared so as to bear unique defined mass agents on their surface. Solid supports can be resin beads in a wide range of sizes of from 1 to 10,000 μm in dimension. The support itself can be isotopically doped by incorporating an isotope into the chemical structure of the support. This differentiates the mass of the support from like supports, but does not change its chemical properties. Such solid supports would then be used in the methods of the invention. Groups of such uniquely mass-defined supports can comprise libraries, which are also an embodiment of the invention as claimed herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS AND BEST MODE OF THE INVENTION

The term "isotopic doping" or "isotopically doped" is used here to mean the introduction into a molecule of an isotope of one or more of the atoms normally appearing in that molecule.

A "link" is a covalent bond or a molecular moiety that is suitable for linking two portions of a construct together.

A "linker" is a moiety comprised of a code block, a first link for bonding the code block to a solid support or other moiety, and a second link for bonding the code block to a ligand or other moiety.

A "linker mix" is a mixture of two isotopically distinct but chemically identical molecules, the mix having a discrete ratio of first isotope to second isotope.

A "code block" is a molecule or series of molecules containing one or more isotopically doped atoms or having a repeating number of molecules in series, such that its mass can be discretely defined and differentiated from any other code block.

A "doped" atom, code block or moiety refers to an entity in which an atom in a molecule which has been replaced by one of its isotopes. Doped atoms as contemplated by this invention include all atoms found in organic chemistry having isotopes and in particular, hydrogen, carbon, nitrogen, fluorine and oxygen. Non-radioactive isotopes are generally preferred over radioactive ones.

The term "monomer" is used herein not only to denote subunits that make up a linear molecules such as amino

acids, but also to denote starting chemical materials and chemical reagents that are chemically reacted with one another in combinatorial chemistry organic synthesis to produce molecules that are not linear, such products including so-called "small molecules" which are organic molecules of 500 Daltons or less in molecular weight.. As used herein, the terms "monomer" and "chemical reagent" are interchangeable.

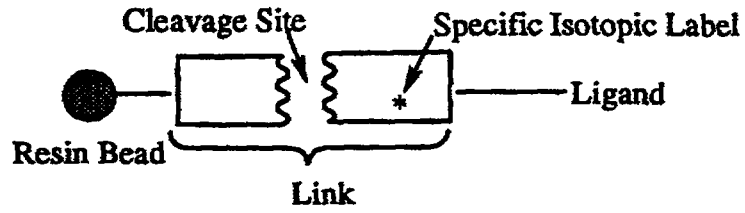
A "reaction series" as used herein refers to a series of steps in a chemical synthesis in a combinatorial synthesis format.

A "solid support" is one or materials upon which combinatorial chemistry syntheses can be performed, including beads, solid surfaces. solid substrates, particles, pellets, disks, capillaries, hollow fibers, needles, solid fibers, cellulose beads, pore-glass beads, silica gels, polystyrene beads optionally crosslinked with divinylbenzene, grafted co-polybeads, poly-acrylamide beads, latex beads, dimethylacrylamide beads optionally cross-linked with N,N'-bis-acryloyl ethylene diamine, glass particles coated with a hydrophobic polymer, fullerenes and soluble supports such as low molecular weight non-cross-linked polystyrene.

A "construct" is a covalently bonded entity comprising, in any combination, some type of solid support, one or more linkers, one or more code blocks, and one or more ligands.

A "ligand" is a chemical reaction product of interest. A ligand can be part of a larger construct, where the ultimate goal will be to identify and/or cleave the ligand apart from the rest of the construct.

In general, the methods of the invention make use of some variant of a construct of the non-limiting general formula:



Isotopes are inserted into such constructs via doped links. That is, after the determination has been made as to what will constitute a chemically suitable link, the link is synthesized using one or more atoms of the link that has been substituted by an isotopic form of that atom. The isotopic form is chemically indistinguishable from the non-isotopic form of the link. The isotopic form is, however physically distinguishable from other isotopic forms by MS or NMR analysis. This physical difference is manifested by differently appearing MS, IR, or NMR peak patterns. A wide variety of isotopic insertion or doping strategies are available, leading to a large number of physically distinguishable chemical moieties, each having its own distinctive peak pattern. The existence of such distinctive peak patterns means that the isotopic forms can be used to create a code that can be used in various encoding strategies to readily identify different chemical entities or conditions that can be used during a combinatorial synthesis. Several of such encoding strategies are given below.

Electrospray mass spectrometry provides mass and ionic charge intensity information for a given molecular entity. In general, smaller molecules only appear in the spectrum once as singly charged species, and the effect of isotopic compositional variation results in a very predictable quantum mass shift. Thus, for example, a molecule having a molecular weight of 304 will produce a peak at 305 (M + 1) on a mass spectrometer (MS) spectrum. If a nitrogen atom in such molecule having an atomic

weight of 14 (N^{14}) is replaced (by isotopic doping, as that term is used herein) by isotope N^{15}, then the MS peak will shift to the right precisely one unit to 306. Furthermore, such isotopic doping will not affect the ionization or chemical reactivity of the molecule. The ability to measure both of the properties of mass and ionic intensity with reasonable accuracy (i.e. mass to about 0.1 atomic mass units and relative intensity to about 3% provides the basis for a novel encoding strategy using isotopes to isotopically, rather than chemically, encode a monomer to read a synthetic history, instead of tagging a molecule itself. Using the methods of the invention, encoding strategies are devised from the use of the mass information alone, the relative intensity information in two or more mass peaks alone or a combination of the two. The basic methodology of the invention, which is to insert different isotopes into combinatorial constructs to identify addition of monomers or chemical conditions, gives rise to several alternative embodiments for encoding and decoding, which are capable of individual implementation or in selected combinations.

Multiple preferred coding approaches using defined mass agents will be discussed. These examples are non-limiting and other coding approaches are not meant to be excluded.

Example 1: Encoding Approaches

Encoding Example A: Ratio Coding Approach

In a most preferred embodiment of the invention, a series of isotopically doped linker mixes *n* is prepared, with each linker mix in the series comprising a discrete ratio of first isotope to second isotope, and with each mix in the series differing in ratio from the previous or subsequent mix in the series by an equal amount. Thus, for example, a series of 21 batches of doped

monomer can be prepared, with the first batch in the series having a ratio of 100% of first isotope to 0% of second isotope, the second batch having a ratio of 95% of first isotope to 5% of second isotope, and so on until the 21st batch, which will have 0% of first isotope and 100% of second isotope. Each linker is further characterized by being capable of being cleaved such that one cleavage portion will always contain the isotopically doped molecular moiety. Each linker mix is chemically reacted with a support means on one side of the linker to yield n batches of support-linker, again each having a discrete ratio of first to second isotope. Then a reagent of interest is added to each batch to yield n batches of support-linker-molecule, each likewise having the discrete ratios ot two isotopes. If, now for example, a split synthesis method is being pursued, then the n batches are combined into a single mixing vessel and the resulting mix is then divided into n aliquots, and to each aliquot is added a second reagent of interest, and the resultant reactions are allowed to proceed. The previous step of combining all aliquots and then splitting them out into n aliquots is repeated, and a third reagent of interest can be added. If all possible reactions have proceeded to completion, then there are now n^3 products. The linkers can be cleaved so that the isotopically labeled fragment stays with the chemical product, and the resulting isotope label-chemical product construct is analyzed by a mass spectrometer. The resulting mass spectrogram will display a peak pattern that mirrors the ratio of first isotope to second isotope present in the linker fragment, thus identifying what the first chemical reagent was that was added to that particular reaction well. Thus, for example, if the isotope ratio is 100% for first isotope to 0% for second isotope, then one relatively tall peak will appear on the spectrogram at the position on the spectrum occupied by the discrete atomic mass that that moiety has (as will be appreciated by those of ordinary skill in the art, other relatively small peaks, will, of course appear, but just one prominent peak that is characteristic of the molecule as used

in the identification method of the present invention appears.). If the isotope ratio is 95% of first isotope to 5% of second isotope, then there will be a first prominent peak and a second prominent peak, with the first prominent peak having about 95% of the total area under the combined prominent peaks, and the second prominent peak having the remaining approximately 5%, thus forming a distinct prominent peak pattern which serves to clearly identify the isotope ratio and therefore the chemical reagent. It is to be understood that another smaller peak not part of the patterns forming the codes of the invention will appear, by virtue of the natural abundance of C^{13}, and its relative size can be predicted using the following analysis. If a given moiety contains 24 carbons and nitrogen and it has been doped to a 50/50 ratio of N^{14}/N^{15}, then peak 1 will be calculated from the N^{14}/C^{12} present as $(0.898)^{24} \times 0.5 = 0.383$; peak 2 will be calculated from the N^{15}/C^{12} and N^{14}/C^{13} present as $(0.989)^{24} \times 0.5 + (0.989)^{23} (0.011) \times 24 \times 0.5 = 0.485$; and the third peak will be calculated from the N^{15}/C^{13} present as $(0.989)^{23} \times (0.011) \times 24 \times 0.5 = 0.102$, thus resulting in a distinctive pattern having two approximately equal prominent peaks, and the relatively small side peak. Ideally, the isotopically distinct species used should differ by two or more AMUs as this would produce well separated peaks that would not be affected by the natural presence of ^{13}C. To achieve this with the atoms that are most commonly used in such chemistry (C,H,N,O) typically requires that more than one atom be isotopically substituted, as available stable isotopes of C, H and N differ by only one mass unit.

Subsequently, in order to identify the third component in the combinatorial construct, the third component can be identified by its reaction well number. Now, with the identity of the first component known by virtue of the mass spectrograph and the third component known by virtue of the well number, their combined molecular weights are subtracted from the total

molecular weight of the construct to arrive at a residual mass which identifies the second component of the construct.

It should be appreciated that using the methods and constructs of the invention provide for an entire series of encoded linkers that provide great economic savings, since the only additional synthesis initially required is to isotopically dope a solid support linker that had to constructed in the first place. No other chemical modifications are needed to be made to the linkers that were initially chosen for the solid state combinatorial synthesis.

Encoding Example B: Dual Ratio Coding Approach

For syntheses having more than three steps, the procedure of Ratio Coding described above is followed in that a series of isotopically doped linker mixes *n* is prepared, with each linker mix in the series comprising a discrete ratio of first isotope to second isotope, and with each mix in the series differing in ratio from the previous or subsequent mix in the series by an equal amount. However, a second type of atom is also isotopically doped, so that there are two types of atomic isotopes present. For example a nitrogen position can be doped with a mix of N^{14} and N^{15}, while a carbon position can be doped with a mix of C^{12} and C^{13}. Again, this example will follow the progression of 5% increments, so that there are 21 possible nitrogen ratio combinations and 21 possible carbon ratio combinations. Furthermore, the carbon position is protected with a suitable protecting group, which can be deprotected to correlate to a reaction step in the combinatorial synthesis. Thus, the mass spectrograph peak pattern for the doped nitrogen identifies the first synthesis component, the mass spectrograph peak pattern for the doped carbon identifies the second synthesis component, an assay identifies the fourth component, and the third component is

identified by subtraction of the first, second and fourth components from the total weight of the product.

Occasionally, code degeneration may arise when using more than one type of isotope, as in the case where one moiety bore a N^{15}-C^{12} combination and another bore a N^{14}-C^{13} combination, both of which would have the same atomic weight and therefore give indistinguishable peak patterns in a mass spectrograph. This problem can be circumvented in one of two general ways. Firstly, by selecting C^{12} and C^{14} as the carbon isotope pair, this type of code degeneracy is avoided. Or, if radioactivity is to be avoided, C^{12} and C^{13} can still be used by the technique of combining mass spectrography with fragmentation. For example, an amide moiety of the structure

CH_3-NH--CO-CH_2-CH_3

can be doped in two ways that will yield the same atomic weight as follows:

I II

CH_3-$N^{14}H$-CO-CH_2-$C^{13}H_3$

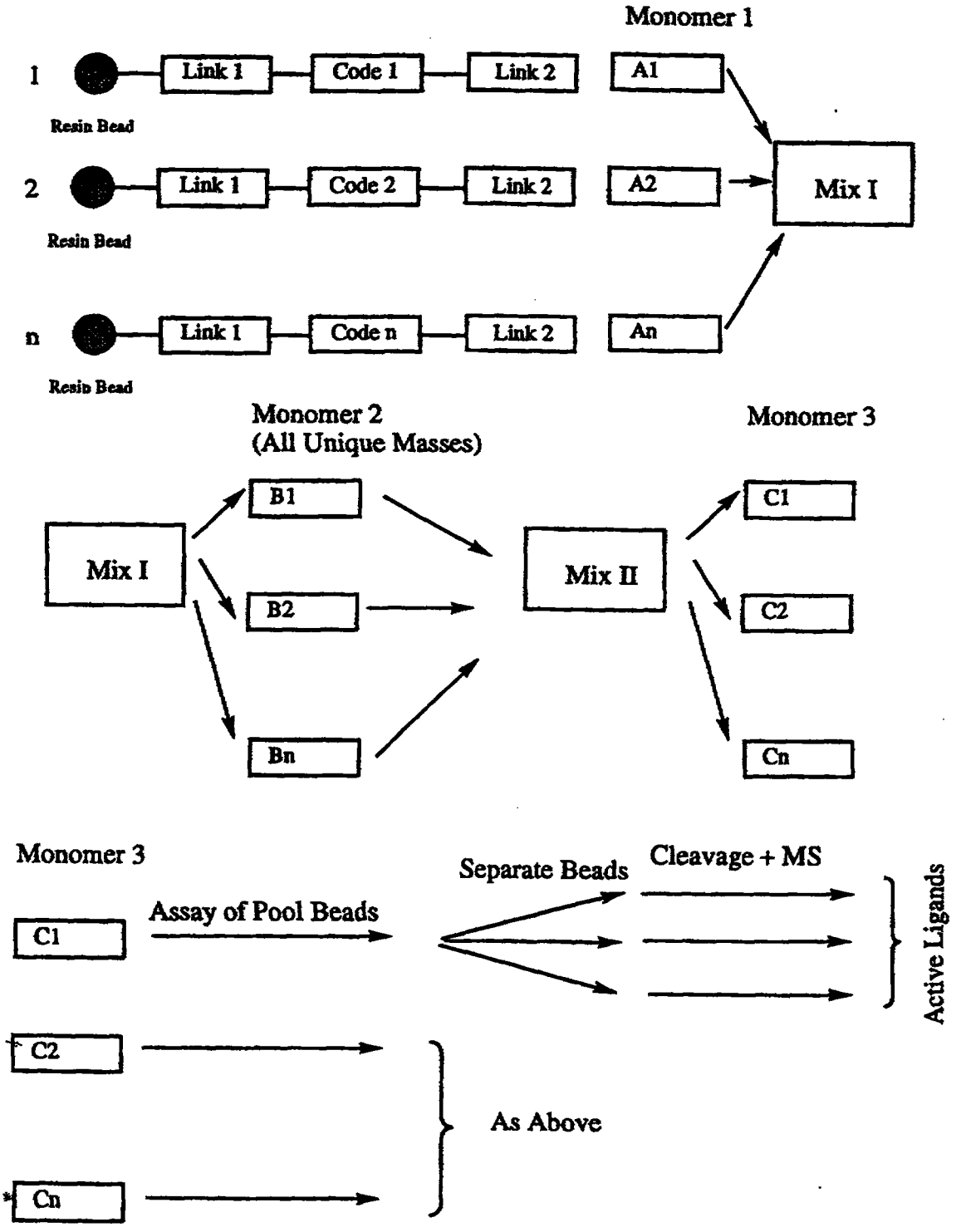
or

However, when they are fragmented along the indicated cleavage lines, moiety I will yield a fragment having a doped N and a normal C, while moiety II will yield a fragment having a doped C and a normal N, thereby yielding distinctive peak patterns in the MS.

The following scheme illustrates the Single Peak Positional Coding Approach

Encoding Example C: Single Peak Positional Coding

5


Monomer 1
1
Link 1
Code 1
Link 2
A1
Resin Bead
2
Link 1
Code 2
Link 2
A2
Mix I
Resin Bead
n
Link 1
Code n
Link 2
An
Resin Bead
Monomer 2
(All Unique Masses)
Monomer 3
Mix I
B1
B2
Bn
Mix II
C1
C2
Cn
Monomer 3
C1
Assay of Pool Beads
Separate Beads
Cleavage + MS
Active Ligands
C2
Cn
As Above

Scheme 2

Following the process in Scheme 2, another alternative embodiment of the invention of isotopic encoding can follow a single MS peak position approach. This approach generates a MS peak. In this format, the mass of the coding block is engineered such that it appears in a convenient part of the spectrum, and it is used to represent the first monomer or building block used in the synthesis of a particular compound. After the combinatorial synthesis is complete, Link 2 is cleaved in order to determine the molecular weight of the ligand. Then Link 1 is cleaved to enable identification of the Code block, which determines the identification of the first pool monomer.

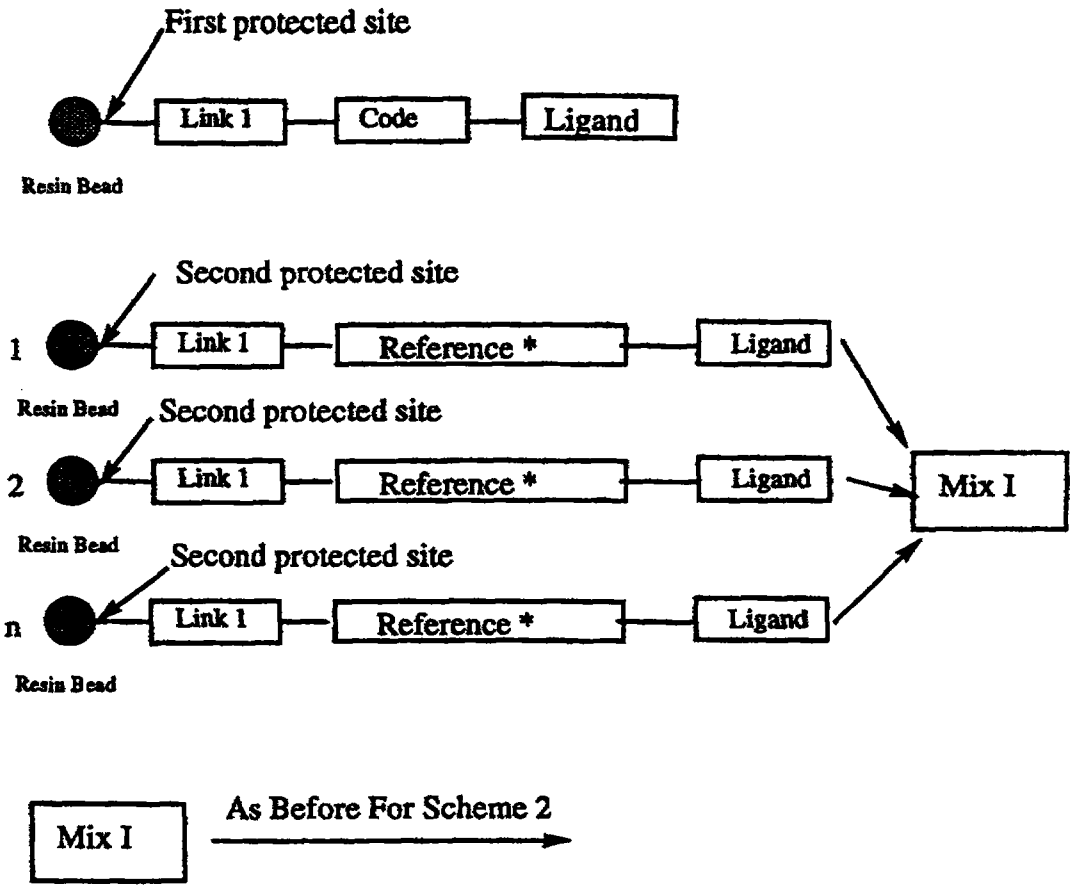
The first and second links in a linker scheme can be the same or different. The links can be the same when a direct binding assay is used, followed by removal of positive beads. When the links are different, this allows the assay to be either by direct binding or with cleaved ligand alone.

Decoding of a three monomer combinatorial library is achieved from three steps. The mass of the code block is determined, thus identifying the code, which identifies the first pool monomer. The pool number of the final monomer addition determines the final monomer, from which the mass of the final monomer is known. Then, the masses of the first and third pool monomers are subtracted from the total molecular weight of the entire construct, thus leaving the mass of the second pool monomer, from which the identity of the second pool monomer is inferred.

The Single Peak Positional encoding approach is especialy useful when active ligands are screened by use of a chromatography column, and the bound constructs are then eluted.

The following scheme illustrates the Double Peak Positional Coding Approach

Encoding Example D: Double Peak Positional Coding



Scheme 3

Following the process in Scheme 3, another alternative embodiment of the invention of isotopic encoding can follow a double MS peak position strategy. This approach yields two MS peaks. For example, a set of resin beads is prepared wherein the beads bear two protected sites, such as BOC and FMOC. A first protected site is de-protected. A number of isotopic code blocks *n* is prepared and each code is linked to a first de-protected site.

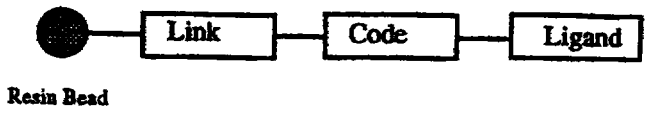
The second protected site is de-protected. A standard reference moiety having a different mass is linked to the second de-protected site. Upon MS, this will yield a peak for the standard reference and a second peak for the code, with the mass difference between the two peaks being the encoding unit. Decoding of a three monomer combinatorial library is achieved from three steps. The mass of the ligand plus code block is determined, thus identifying the code, which identifies the first pool monomer. The pool number of the final monomer addition determines the final monomer, from which the mass of the final monomer is known. Then, the masses of the first and third pool monomers are subtracted from the total molecular weight of the entire construct, thus leaving the mass of the second pool monomer, from which the identity of the second pool monomer is inferred.

In an alternative construct, the code block is prepared to contain two like species, one of which is constant and acts as a reference mass, while the other has variable mass blocks similar to those described for the single peak positional encoding scheme. After cleavage of the link to the resin, ligand is generated with an attached variable code increment. The encoded information is now determined from the difference in mass of the coding unit and the reference mass unit. The advantage of this is that the code can be left attached to the ligand and read at the same time as the mass of the whole construct is determined by MS. This strategy gives two mass peaks that represent the ligand attached to either the reference code or the variable code. The difference in mass is used to determine the identity of monomer 1, while monomer 3 known from the corresponding pool and therefore monomer 2 is inferred as described above.

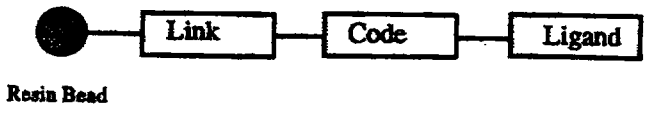
The invention also makes possible an alternative embodiment that in effect creates a bar coding mechanism. Several non-limiting exemplary versions of solid state constructs are possible as follows.

Encoding Example E: The Bar Coding Approach

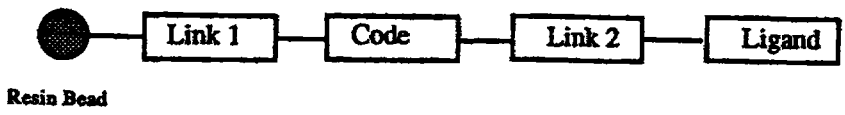
Version 1: Mass only:



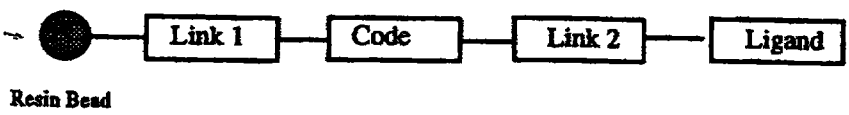
Version 2: Mass and Intensity:



Version 3: Mass only:



Version 4: Mass and Intensity:



In this approach and its variations, a code block most advantageously consists of a dimer, each of which unit has one, two or three discrete masses. For example a construct of the structure:

contains a code block having two mass blocks, M_1 and M_2, which in this example will be comprised of one, two or three amino acids. The amino acids are doped to give three discrete masses yielding, for example, Glycine (G^0), with a mass of 57, Glycine bearing N^{15} (G^1) with a mass of 58 and Glycine bearing two Deuterium atoms (G^2) at carbon 2 with a mass of 59. Assembling these three moieties into 7 possible mass sets yields the following codes and their fractions of the total:

Composition	Relative Presence
G^0	100%
G^1	100%
G^2	100%
G^0G^1	50% and 50%
G^0G^2	50% and 50%
G^1G^2	50% and 50%
$G^0G^1G^2$	33.3%, 33.3% and 33.3%

It is now possible to assemble these mass sets into blocks M_1 and M_2 and to predict what the characteristic MS peak pattern will be for each code block. For this group of mass sets in Version 1 of the Bar Coding Approach, the following MS peak pattern is predicted:

Code Sample	M1	M2	Predicted Peak Pattern, (AMU) 114	115	116	117	118
1	57 (G^0)	57 (G^0)	▮				
2	57 (G^0)	57,58 (G^0),(G^1)	▮	▮			
3	57 (G^0)	57,59 (G^0),(G^2)	▮		▮		
4	57 (G^0)	57,58,59 (G^0),(G^1),(G^2)	▮	▮	▮		
5	57,58 (G^0),(G^1)	57.59 (G^0),(G^2)	▮	▮	▮	▮	
6	57,59 (G^0),(G^2)	57,59 (G^0),(G^2)	▮		▮		▮
7	57,59 (G^0),(G^2)	57,58,59 (G^0),(G^1),(G^2)	▮	▮	▮	▮	▮

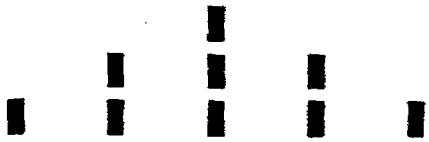
In this table, for code sample 1 a single peak is predicted at 114, since the combined masses of each G^0 are 57 + 57 = 114. For code sample 2, two equal peaks are predicted at 114 and 115, since G^0 in M_1 plus G^0 in M_2 adds up to 114, and G^0 in M_1 plus G^1 in M_2 adds up to 115. In code sample 6, two single peaks are predicted at 114 and 118 and a redundancy is predicted at 116 to yield a peak approximately two times as tall as the peaks at 114 and 118.

In the following table, predicted MS peak patterns are shown for 25 code samples. The actual MS peak patterns are shown below

the predicted peak pattern table, and it can be seen that there is excellent correlation between observed and predicted peak patterns. References to G^0, G^1 and G^2 are omitted although the same three isotopically doped versions of Glycine described above are still being used in this table (Note that the numerical values for the MS in Figure 1 are for the total mass of the entire construct, including a Lysine residue and the linkers, which fall into a range of 300 to 309 mass units)

Code Sample	M1	M2	Predicted Peak Pattern (AMU)				
			1 1 4	1 1 5	1 1 6	1 1 7	1 1 8
1	57	57	▮				
2	57	58		▮			
3	57	57,58	▮	▮			
4	57	59			▮		
5	57	57,59	▮		▮		
6	57	58,59		▮	▮		
7	57	57,58,59	▮	▮	▮		
8	58	59				▮	
9	58	57, 59		▮		▮	

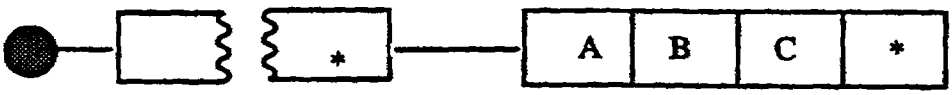
10	59	57, 58	
11	58	57, 58,59	
12	57, 58	57, 58	
13	57, 58	57, 59	
14	57, 58	58, 59	
15	57, 58	57, 58, 59	
16	59	59	
17	59	57, 59	
18	57, 59	57, 59	
19	59	58, 59	
20	59	57,58,59	
21	57, 59	58, 59	
22	57, 59	57, 58, 59	
23	58, 59	58, 59	

24	58, 59	57, 58, 59	
25	57, 58, 59	57, 58, 59	

Once the MS is run on a completed combinatorial synthesis sample, the pattern is compared to a predicted pattern, which in turn identifies the code, which in turn identifies the first pool monomer. The predicted patterns can form a type of machine readable bar code, which, using methods well known to those of ordinary skill in the optical scanning art, enables rapid data inputing, decoding and interpretation.

Other Encoding Strategies

It is possible to combine elements of one or all of the ratio, single peak, double peak or bar code methods to give code constructs. Code blocks don't have to be added into the front end of a construct-they can be added in at any point, assuming a suitable reagent is available, for example:



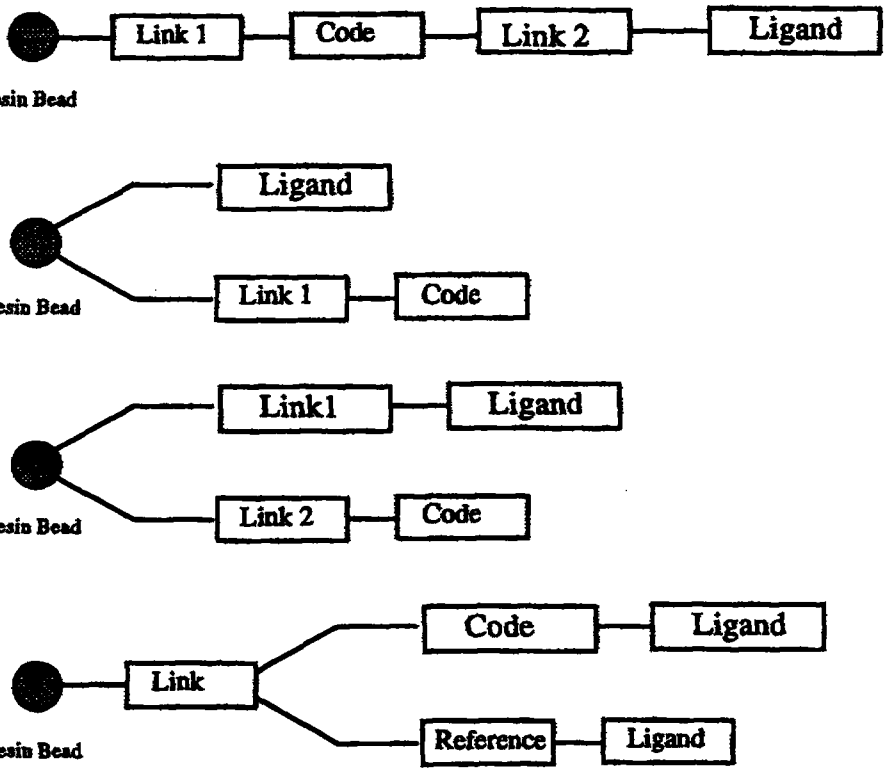
Link

where isotope doping occurs at the bead link and attached to the end of a three monomer ligand, as indicated by the asterisk. Isotope doping could also be performed at the other end of the ligand as well.

In another alternative embodiment of the invention, since isotopes can be readily read by nuclear magnetic resonance

(NMR), this can be used instead of, or in conjunction with, MS spectroscopy. NMR offers the advantages of greater accuracy (one can run ratio pools in increments of down to 1%), the bead does not have to be cleaved off of the construct prior to analysis, and that NMR, unlike MS, is non-destructive.

Other constructs can take the general non-limiting exemplary formulae:



Figures 133 to 286 display spectragrams associated with another variation of ratio encoding, which is a four peak ratio encoding scheme. In the following table, the first column represents the code block, the second column is an internal reference number, and the third, fourth, fifth and sixth columns represent the respective mole fractions of FMOC-protected alanines with different integral masses using isotope doping, i.e.

A^0, A^3, A^2, and A^1 (A is reference alanine, A^3 is alanine plus 3 atomic mass units, A^2 is alanine plus two atomic mass units, etc.).

1	,111,	0.56,	0.16,	0.16,	0.16
2	,112,	0.56,	0.16,	0.16,	0.21
3	,113,	0.51,	0.11,	0.11,	0.26
4	,114,	0.46,	0.11,	0.11,	0.31
5	,115,	0.46,	0.11,	0.11,	0.36
6	,116,	0.41,	0.11,	0.11,	0.41
7	,121,	0.56,	0.16,	0.21,	0.16
8	,122,	0.51,	0.11,	0.21,	0.21
9	,123,	0.46,	0.11,	0.21,	0.26
10	,124,	0.46,	0.11,	0.16,	0.31
11	,125,	0.41,	0.11,	0.16,	0.36
12	,126,	0.41,	0.11,	0.16,	0.41
13	,131,	0.51,	0.11,	0.26,	0.11
14	,132,	0.46,	0.11,	0.26,	0.21
15	,133,	0.46,	0.11,	0.26,	0.26
16	,134,	0.41,	0.11,	0.21,	0.31
17	,135,	0.41,	0.11,	0.21,	0.31
18	,136,	0.36,	0.11,	0.21,	0.36
19	,141,	0.46,	0.11,	0.31,	0.11
20	,142,	0.46,	0.11,	0.31,	0.16
21	,143,	0.41,	0.11,	0.31,	0.21
22	,144,	0.41,	0.11,	0.26,	0.26
23	,145,	0.36,	0.11,	0.26,	0.31
24	,146,	0.36,	0.11,	0.26,	0.36
25	,151,	0.46,	0.11,	0.36,	0.11
26	,152,	0.41,	0.11,	0.36,	0.16
27	,153,	0.41,	0.11,	0.31,	0.21
28	,154,	0.36,	0.11,	0.31,	0.26
29	,155,	0.36,	0.11,	0.31,	0.31
30	,156,	0.31,	0.11,	0.26,	0.31
31	,161,	0.41,	0.11,	0.41,	0.11
32	,162,	0.41,	0.11,	0.41,	0.16
33	,163,	0.36,	0.11,	0.36,	0.21
34	,164,	0.36,	0.11,	0.36,	0.26
35	,165,	0.31,	0.11,	0.31,	0.26
36	,166,	0.31,	0.11,	0.31,	0.31
37	,211,	0.56,	0.21,	0.16,	0.16
38	,212,	0.51,	0.21,	0.11,	0.21
39	,213,	0.46,	0.21,	0.11,	0.26
40	,214,	0.46,	0.16,	0.11,	0.31
41	,215,	0.41,	0.16,	0.11,	0.36
42	,216,	0.41,	0.16,	0.11,	0.41
43	,221,	0.51,	0.21,	0.21,	0.11
44	,222,	0.46,	0.21,	0.21,	0.21
45	,223,	0.46,	0.16,	0.16,	0.26
46	,224,	0.41,	0.16,	0.16,	0.31
47	,225,	0.41,	0.16,	0.16,	0.31
48	,226,	0.36,	0.16,	0.16,	0.36
49	,231,	0.46,	0.21,	0.26,	0.11
50	,232,	0.46,	0.16,	0.26,	0.16

51 ,233, 0.41, 0.16, 0.21, 0.21
52 ,234, 0.41, 0.16, 0.21, 0.26
53 ,235, 0.36, 0.16, 0.21, 0.31
54 ,236, 0.36, 0.16, 0.21, 0.36
55 ,241, 0.46, 0.16, 0.31, 0.11
56 ,242, 0.41, 0.16, 0.31, 0.16
57 ,243, 0.41, 0.16, 0.26, 0.21
58 ,244, 0.36, 0.16, 0.26, 0.26
59 ,245, 0.36, 0.16, 0.26, 0.31
60 ,246, 0.31, 0.16, 0.26, 0.31

61 ,251, 0.41, 0.16, 0.36, 0.11
62 ,252, 0.41, 0.16, 0.31, 0.16
63 ,253, 0.36, 0.16, 0.31, 0.21
64 ,254, 0.36, 0.16, 0.31, 0.26
65 ,255, 0.31, 0.16, 0.26, 0.26
66 ,256, 0.31, 0.11, 0.26, 0.31
67 ,261, 0.41, 0.16, 0.41, 0.11
68 ,262, 0.36, 0.16, 0.36, 0.16
69 ,263, 0.36, 0.16, 0.36, 0.21
70 ,264, 0.31, 0.16, 0.31, 0.26
71 ,265, 0.31, 0.11, 0.31, 0.26
72 ,266, 0.31, 0.11, 0.31, 0.31
73 ,311, 0.51, 0.26, 0.11, 0.11
74 ,312, 0.46, 0.26, 0.11, 0.21
75 ,313, 0.46, 0.26, 0.11, 0.26
76 ,314, 0.41, 0.21, 0.11, 0.31
77 ,315, 0.41, 0.21, 0.11, 0.31
78 ,316, 0.36, 0.21, 0.11, 0.36
79 ,321, 0.46, 0.26, 0.21, 0.11
80 ,322, 0.46, 0.26, 0.16, 0.16
81 ,323, 0.41, 0.21, 0.16, 0.21
82 ,324, 0.41, 0.21, 0.16, 0.26
83 ,325, 0.36, 0.21, 0.16, 0.31
84 ,326, 0.36, 0.21, 0.16, 0.36
85 ,331, 0.46, 0.26, 0.26, 0.11
86 ,332, 0.41, 0.21, 0.21, 0.16
87 ,333, 0.41, 0.21, 0.21, 0.21
88 ,334, 0.36, 0.21, 0.21, 0.26
89 ,335, 0.36, 0.21, 0.21, 0.31
90 ,336, 0.31, 0.21, 0.21, 0.31
91 ,341, 0.41, 0.21, 0.31, 0.11
92 ,342, 0.41, 0.21, 0.26, 0.16
93 ,343, 0.36, 0.21, 0.26, 0.21
94 ,344, 0.36, 0.21, 0.26, 0.26
95 ,345, 0.31, 0.21, 0.26, 0.26
96 ,346, 0.31, 0.16, 0.21, 0.31
97 ,351, 0.41, 0.21, 0.31, 0.11
98 ,352, 0.36, 0.21, 0.31, 0.16
99 ,353, 0.36, 0.21, 0.31, 0.21
100 ,354, 0.31, 0.21, 0.26, 0.26

101 ,355, 0.31, 0.16, 0.26, 0.26
102 ,356, 0.31, 0.16, 0.26, 0.31
103 ,361, 0.36, 0.21, 0.36, 0.11
104 ,362, 0.36, 0.21, 0.36, 0.16
105 ,363, 0.31, 0.21, 0.31, 0.21
106 ,364, 0.31, 0.16, 0.31, 0.21
107 ,365, 0.31, 0.16, 0.31, 0.26
108 ,366, 0.31, 0.16, 0.31, 0.31
109 ,411, 0.46, 0.31, 0.11, 0.11
110 ,412, 0.46, 0.31, 0.11, 0.16
111 ,413, 0.41, 0.31, 0.11, 0.21
112 ,414, 0.41, 0.26, 0.11, 0.26
113 ,415, 0.36, 0.26, 0.11, 0.31
114 ,416, 0.36, 0.26, 0.11, 0.36
115 ,421, 0.46, 0.31, 0.16, 0.11
116 ,422, 0.41, 0.31, 0.16, 0.16
117 ,423, 0.41, 0.26, 0.16, 0.21
118 ,424, 0.36, 0.26, 0.16, 0.26
119 ,425, 0.36, 0.26, 0.16, 0.31
120 ,426, 0.31, 0.26, 0.16, 0.31

121 ,431, 0.41, 0.31, 0.21, 0.11
122 ,432, 0.41, 0.26, 0.21, 0.16
123 ,433, 0.36, 0.26, 0.21, 0.21
124 ,434, 0.36, 0.26, 0.21, 0.26
125 ,435, 0.31, 0.26, 0.21, 0.26
126 ,436, 0.31, 0.21, 0.16, 0.31
127 ,441, 0.41, 0.26, 0.26, 0.11
128 ,442, 0.36, 0.26, [illegible], 0.16
129 ,443, 0.36, [illegible], 0.26, 0.21
130 ,444, 0.31, 0.26, 0.26, 0.26
131 ,445, 0.31, 0.21, 0.21, 0.26
132 ,446, 0.31, 0.21, 0.21, 0.31
133 ,451, 0.36, 0.26, 0.31, 0.11
134 ,452, 0.36, 0.26, 0.31, 0.16
135 ,453, 0.31, 0.26, 0.26, 0.21
136 ,454, 0.31, 0.21, 0.26, 0.21
137 ,455, 0.31, 0.21, 0.26, 0.26
138 ,456, 0.31, 0.21, 0.26, 0.31
139 ,461, 0.36, 0.26, 0.36, 0.11
140 ,462, 0.31, 0.26, 0.31, 0.16
141 ,463, 0.31, 0.21, 0.31, 0.16
142 ,464, 0.31, 0.21, 0.31, 0.21
143 ,465, 0.31, 0.21, 0.31, 0.26
144 ,466, 0.26, 0.21, 0.26, 0.26

In the following table, each of the enumerated code blocks listed immediately above is correlated with a spectragram number identified in the second column and shown on the face of each respective spectra in the figures.

Code Block	Spectra Identifying Number
1	ASA008683
2	ASA 008684
3	ASA 008685
4	ASA 008686
5	ASA 008687
6	ASA 008688
7	ASA 008689
8	ASA 008690
9	ASA 008691
10	ASA 008692
11	ASA 008693
12	ASA 008694
13	ASA 008695
14	ASA 008696
15	ASA 008697
16	ASA 008698
17	ASA 008699
18	ASA 008700
19	ASA 008701
20	ASA 008702
21	ASA 008703
22	ASA 008704
23	ASA 008705
24	ASA 008706
25	ASA 008707
26	ASA 008708

27	ASA 008709
28	ASA 008710
29	ASA 008711
30	ASA 008712
31	ASA 008713
32	ASA 008714
33	ASA 008715
34	ASA 008716
35	ASA 008717
36	ASA 008718
37	ASA 008719
38	ASA 008720
39	ASA 008721
40	ASA 008722
41	ASA 008723
42	ASA 008724
43	ASA 008725
44	ASA 008726
45	ASA 008727
46	ASA 008728
47	ASA 008729
48	ASA 008730
49	ASA 008731
50	ASA 008732
51	ASA 008733
52	ASA 008734
53	ASA 008735
54	ASA 008736
55	ASA 008737
56	ASA 008738
57	ASA 008739
58	ASA 008740
59	ASA 008741
60	ASA 008742

61	ASA 008743
62	ASA 008744
63	ASA 008745
64	ASA 008746
65	ASA 008747
66	ASA 008748
67	ASA 008749
68	ASA 008750
69	ASA 008751
70	ASA 008752
71	ASA 008753
72	ASA 008754
73	ASA 008755
74	ASA 008756
75	ASA 008757
76	ASA 008758
77	ASA 008759
78	ASA 008760
79	ASA 008761
80	ASA 008762
81	ASA 008763
82	ASA 008764
83	ASA 008765
84	ASA 008766
85	ASA 008767
86	ASA 008768
87	ASA 008769
88	ASA 008770
89	ASA 008771
90	ASA 008772
91	ASA 008773
92	ASA 008774
93	ASA 008775
94	ASA 008776

95	ASA 008777
96	ASA 008778
97	ASA 008779
98	ASA 008780
99	ASA 008781
100	ASA 008782
101	ASA 008783
102	ASA 008784
103	ASA 008785
104	ASA 008786
105	ASA 008787
106	ASA 008788
107	ASA 008789
108	ASA 008790
109	ASA 008791
110	ASA 008792
111	ASA 008793
112	ASA 008794
113	ASA 008795
114	ASA 008796
115	ASA 008797
116	ASA 008798
117	ASA 008799
118	ASA 008800
119	ASA 008801
120	ASA 008802
121	ASA 008803
122	ASA 008804
123	ASA 008805
124	ASA 008806
125	ASA 008807
126	ASA 008808
127	ASA 008809
128	ASA 008810

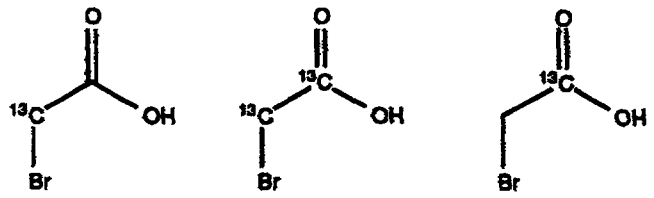
129	ASA 008811
130	ASA 008812
131	ASA 008813
132	ASA 008814
133	ASA 008815
134	ASA 008816
135	ASA 008817
136	ASA 008818
137	ASA 008819
138	ASA 008820
139	ASA 008821
140	ASA 008822
141	ASA 008823
142	ASA 008824
143	ASA 008825
144	ASA 008826

While in principle any number of codes can be generated, the greatest utility is achieved by minimizing the size of the encoding unit, which will likewise minimize the chemical investment in it.

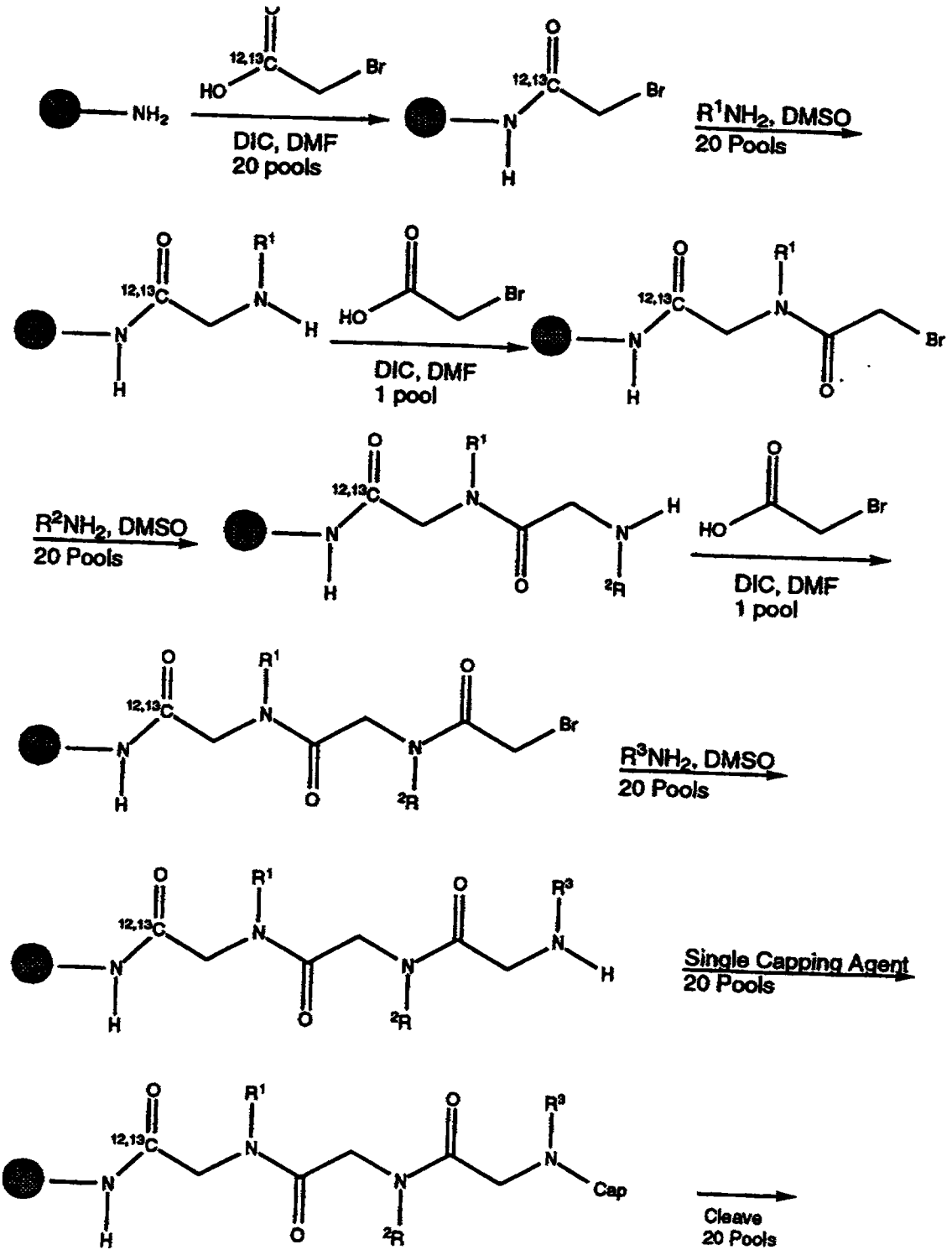
The disclosure of the following references is incorporated in their entirety herein by reference: Atherton,E. and Sheppard,R.C. (1989) *Solid Phase Peptide Synthesis: A Practical Approach.* IRL Press, Oxford. Bodanszky,A. and Bodanszky,M. (1984) *The Practice of Peptide Synthesis.* Springer-Verlag, Berlin.

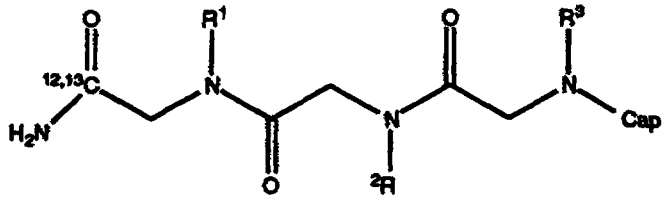
Example 2

Three commercially available (isotopically doped bromoacetic acids provide three encoding moieties



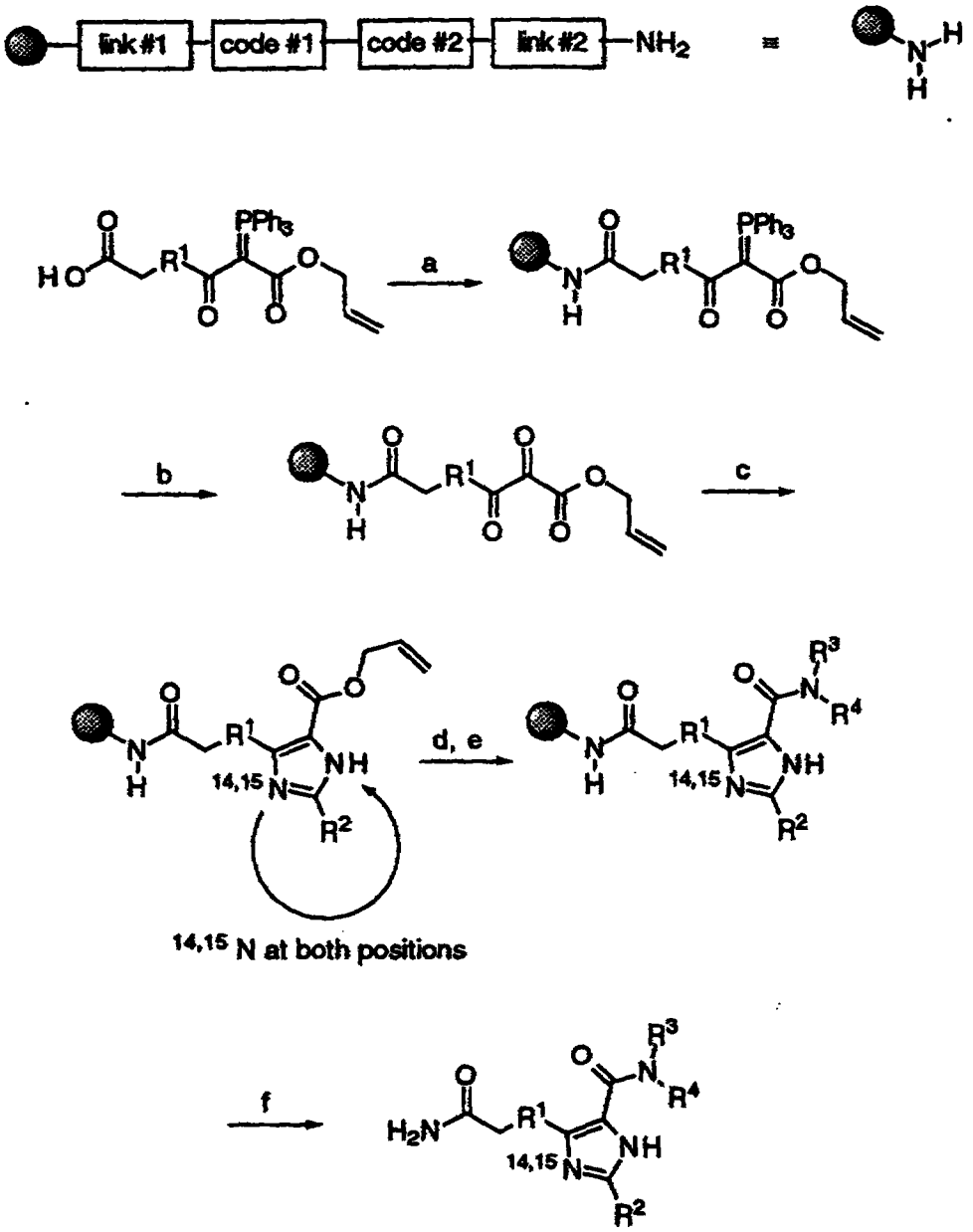
The following synthesis scheme illustrates one variant of the ratio approach. 21 Pools of bromoacetic acid, each having ratios of C^{12} to C^{13} that progress in 5% increments of from 0% to 100% of each are prepared, in this case with the isotope doping occuring at the number one carbon only.


DIC, DMF
20 pools
R1NH2, DMSO
20 Pools
DIC, DMF
1 pool
R2NH2, DMSO
20 Pools
DIC, DMF
1 pool
R3NH2, DMSO
20 Pools
Single Capping Agent
20 Pools
Cap
Cleave
20 Pools



The R^1 moiety is encoded by the C^{12} to C^{13} ratio sample, the R^3 is encoded by the pool number from R^3 was taken, and the R^2 moiety is encoded by subtraction of the known R^1 and R^3 masses from the total construct mass.

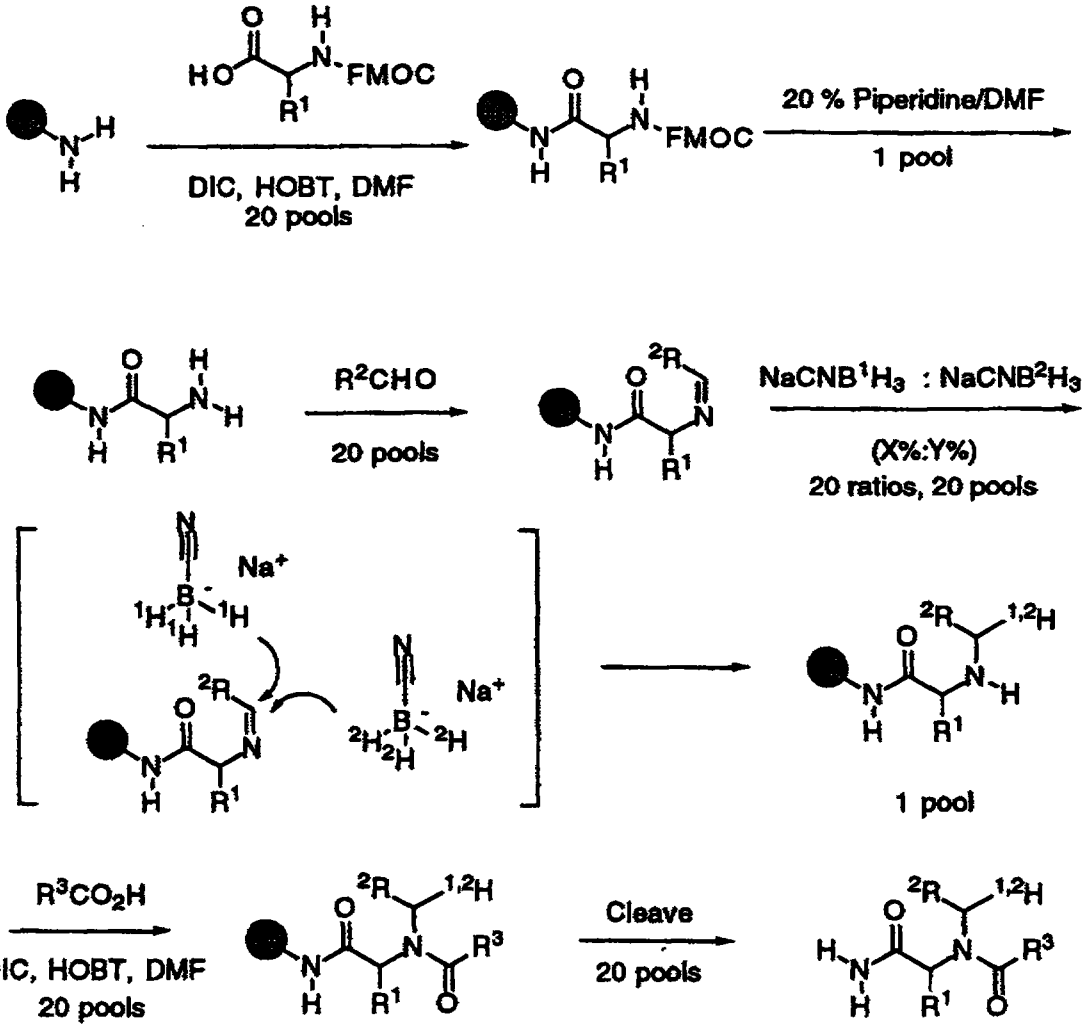
Example 3: An Example of Isotope Encoding Using the $N^{14,15}$ Isotope Ratio in the Form of a Reagent - $N^{14,15}H_4OAc$



(a) Encoded resin, 1-hydroxy-7-azabenzotriazole, diisopropylcarbodiimide, DMF; (b) trans-(±)-3-phenyl-2-(phenylsulfonyl)-oxaziridine, $CHCl_3$; (c) Aldehyde, (X%:Y%) $^{14}NH_4OAc$:$^{15}NH_4OAc$, AcOH/$CHCl_3$ (50:50); (d) (i) $Pd(PPh_3)_4$, $CHCl_3$/4-methylmorphline/AcOH (90:5:5), (ii) sodium diethyldithiocarbamate/diisopropylethylamine/DMF (99:0.5:0.5); (e) Amine, PyBOP, diisopropylethylamine, DMF; (f) TFA/H_2O (95:5)

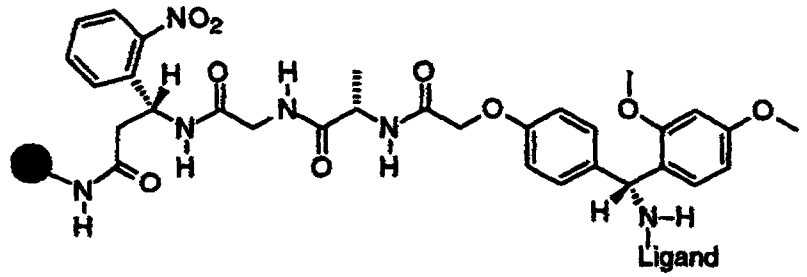
Example 4: An Example of Isotope Encoding Using the $^{1,2}H$ Isotope Ratio in the Form of a Reagent - $NaCNBD_4$

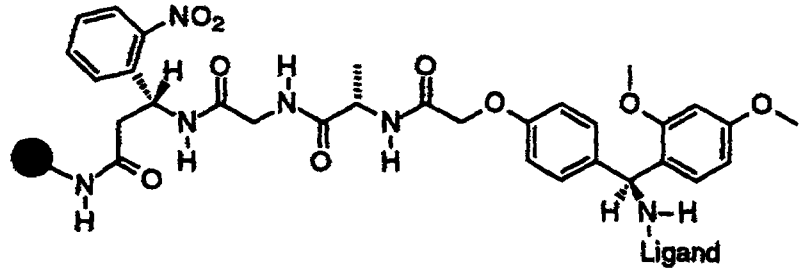
This example incorporates by reference the disclosure of Lebl, M. et al., *Drug Development and Research* 1994,*33*,146-156)

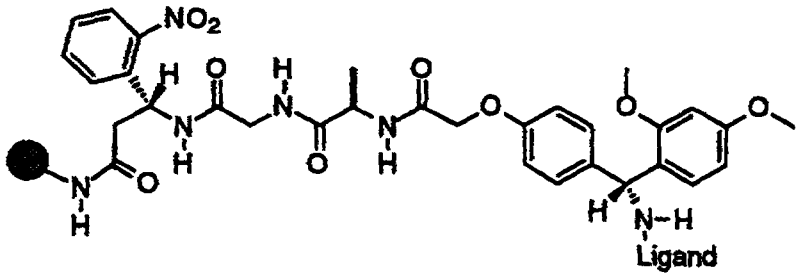


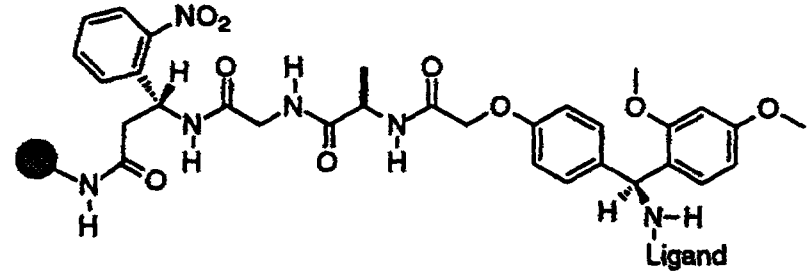
First reagent mass encodes R^1
^{1,2} H ratio encodes R^2
Pool number encodes R^3

Example 5: Encoding Using Four Possible Diastereomers of Link 1, Code 2, and Link 2

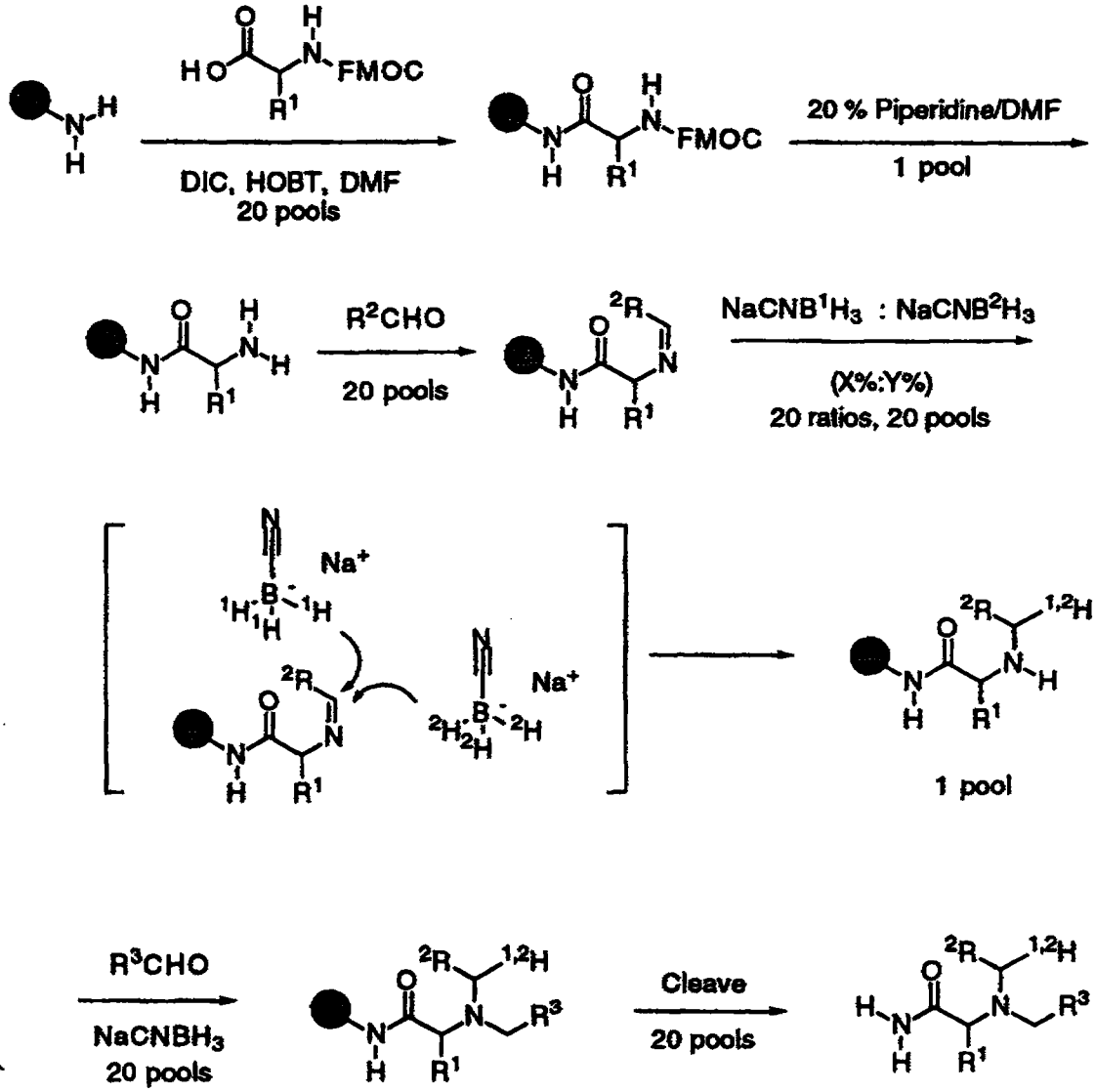






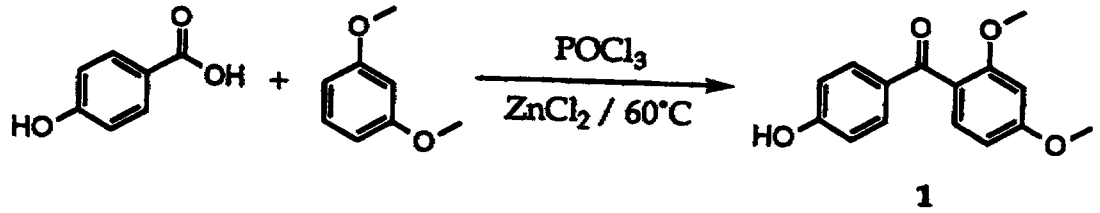


Example 6: An Example of Isotope Encoding Using the $H^{1,2}$ Isotope Ratio in the Form of a Reagent - $NaCNBD_4$

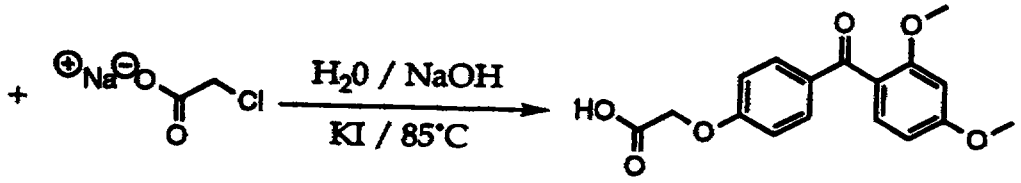


Monomer mass encodes R^1
$^{1,2}H$ ratio encodes R^2
Pool number encodes R^3

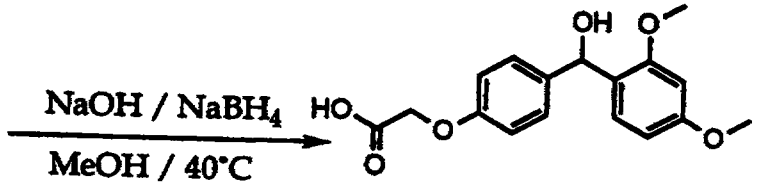
Scheme for Examples 7 through 13


HO
OH
+
POCl3
ZnCl2 / 60°C
HO

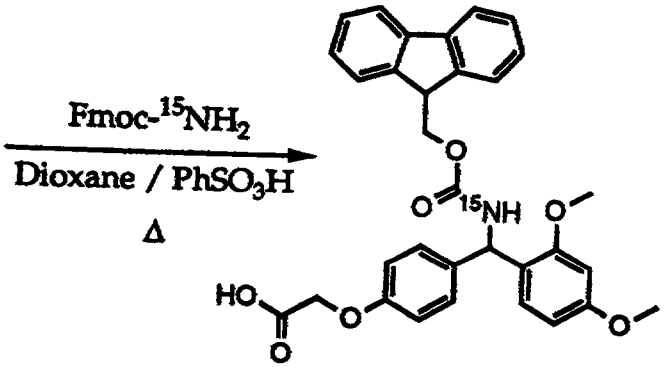
1


+
Na
Cl
H20 / NaOH
KI / 85°C
HO

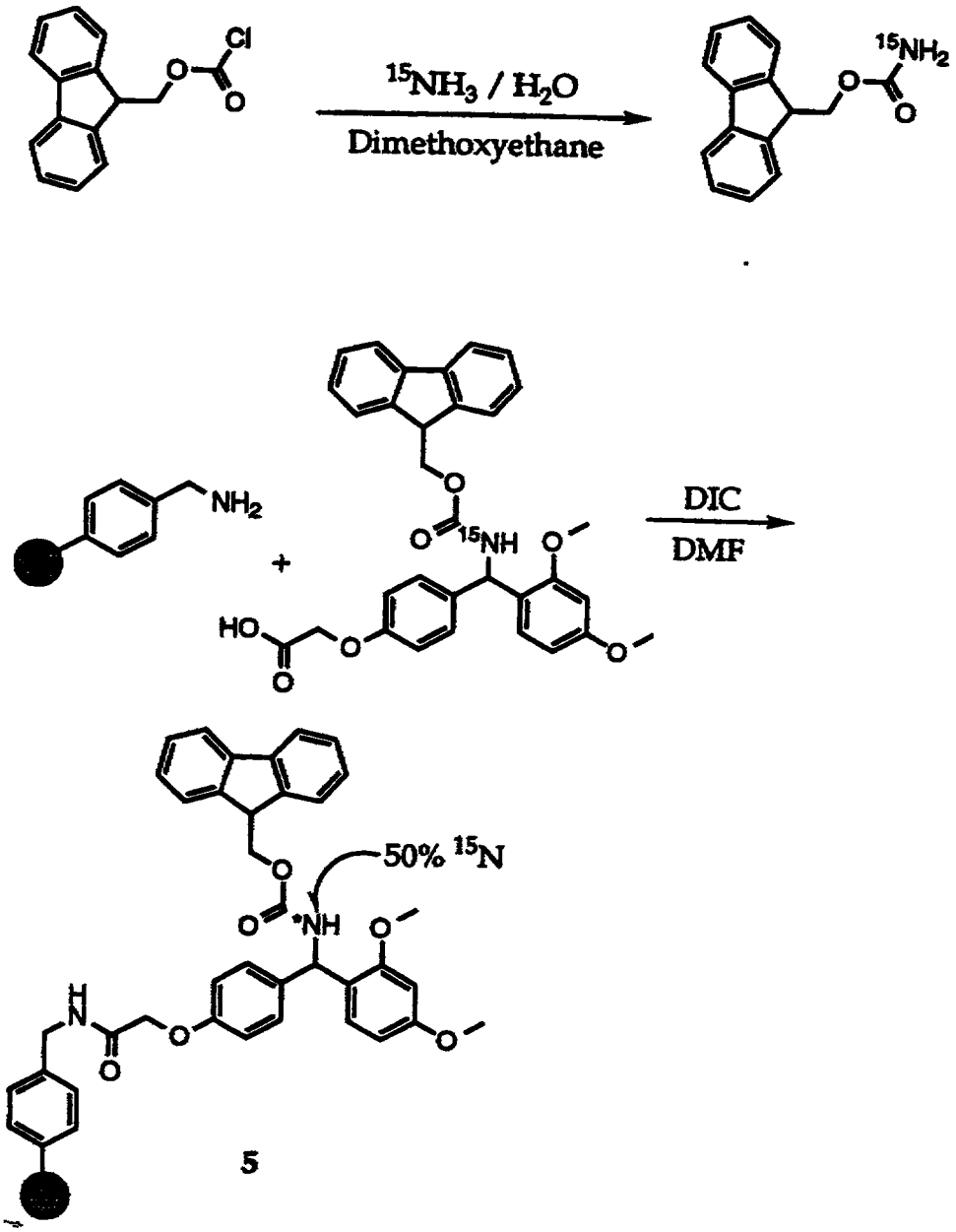
2


NaOH / NaBH4
MeOH / 40°C
HO
OH

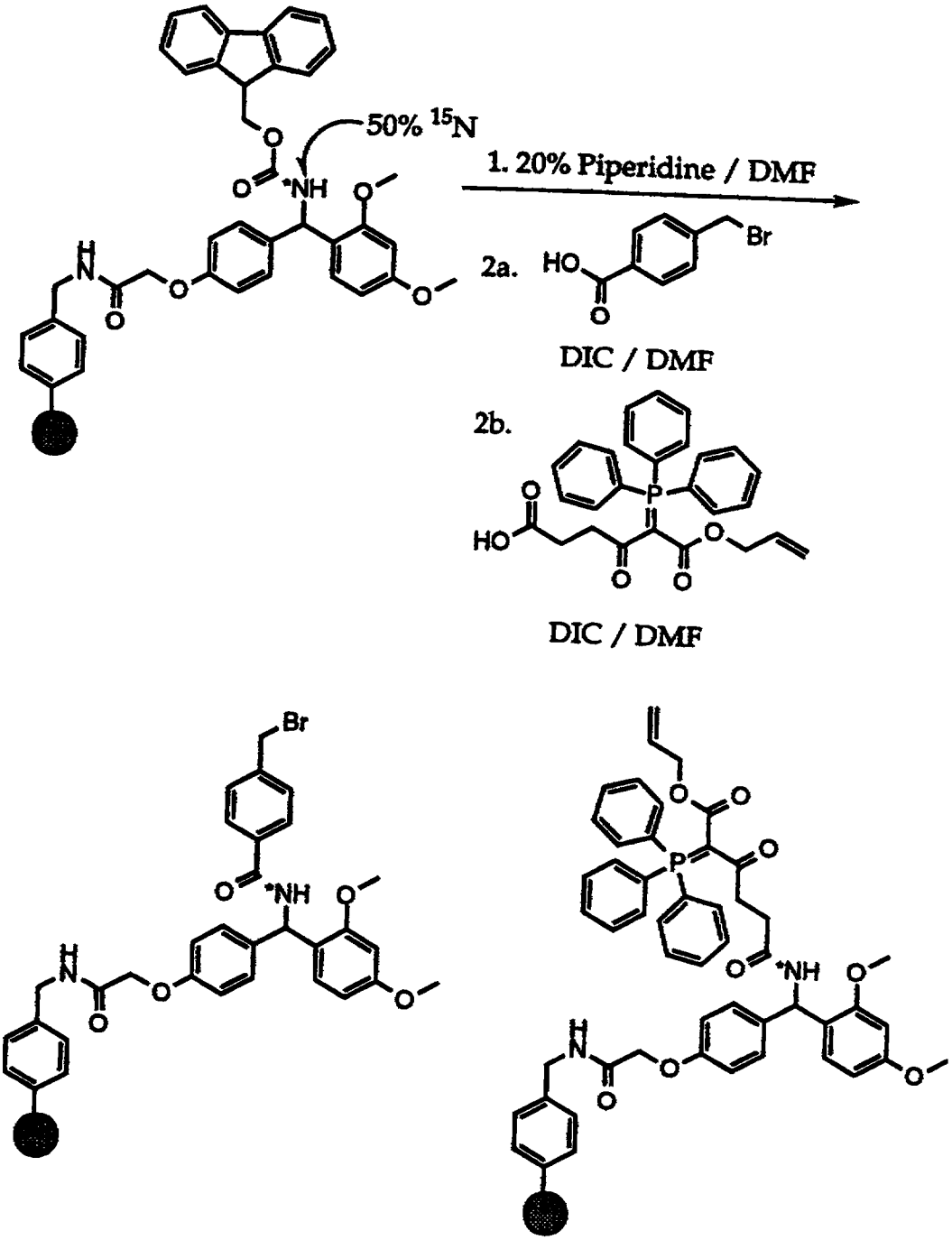
3

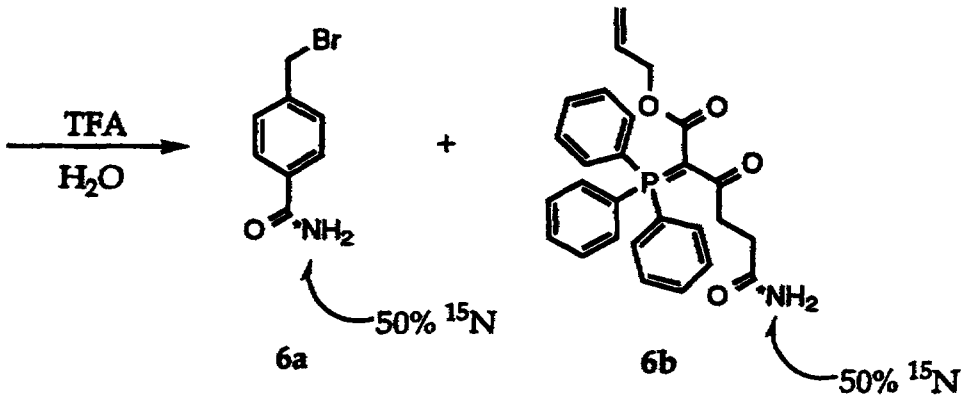

Fmoc-15NH2
Dioxane / PhSO3H
Δ
15NH
HO

4

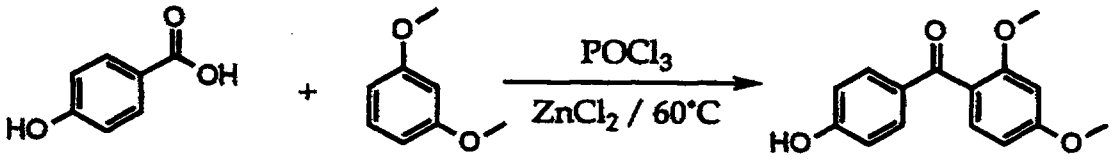

Cl
O
O
$^{15}NH_3$ / H_2O
Dimethoxyethane
$^{15}NH_2$
O
O
NH2
+
HO
O
O
^{15}NH
O
O
DIC
DMF
50% ^{15}N
*NH
O
O
O
H
N
O
O

5


50% 15N
1. 20% Piperidine / DMF
2a.
DIC / DMF
2b.
DIC / DMF



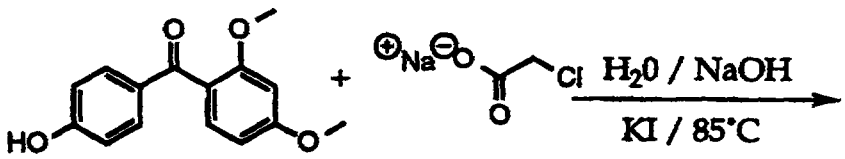
Example 7

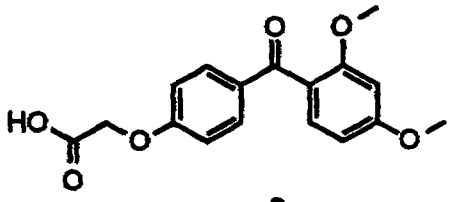


1

1 - In a 500 ml three-neck round-bottom flask, charged with a stir bar, fitted with a reflux condenser, and 60 ml addition funnel (under nitrogen), was placed 50.5 g 4-hydroxybenzoic acid, and 95 ml 1,3-dimethoxybenzene. 123.33 g zinc chloride was added and the mixture was heated to 60° with an oil bath. 126 ml phosphorus oxychloride was added drop-wise over aprox. 30 min. After addition, the reaction ran for 90 min at 60°. The dark red mixture was poured over 1.5 L of ice (under heavy mixing), and to this was added 276 g sodium carbonate, in small portions (significant gas evolution was observed). 400 ml ethyl acetate was added and the aqueous was extracted with another 500 ml ethyl acetate. The organics were combined and washed twice with brine and dried over mag. sulfate, filtered, and concentrated in vacuo at 40°, and further dried under vacuum to give 142.2 g of a redish-pink solid. The solid was tritrated with 400 ml hot hexane, filtered, and dried to give 63.3 g of a pink solid. Recrystalization from 75ml hot methanol gave a first crop yield of pure 2,4-dimethoxy-4-hydroxy-benzophenone (1) as a light-pink solid (21.9%).

Example 8

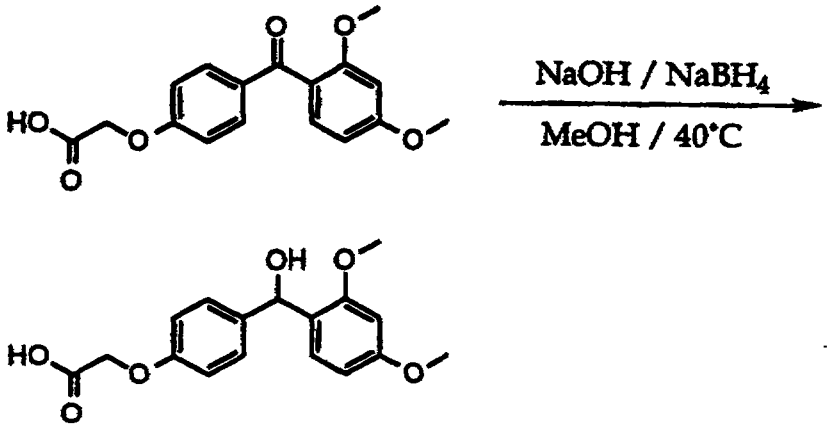




2

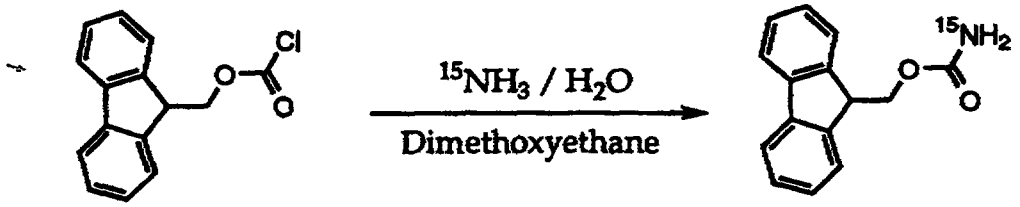
2 - In a 500 ml recovery flask was added 20.043 g of 2,4-dimethoxy-4-hydroxy-benzophenone, 150 ml water, 0.75 g potassium iodide, and 82.5 g sodium chloroacetate. The mixture was then heated to 85° in an oil bath. To the mixture was added 50% NaOH (w/v) in small amounts, to maintain the pH at 11-14. The reaction was followed by TLC (2/5 methanol/methylene chloride) until the reaction was complete (3 hrs). The reaction solution was transfered to a 500 ml erlenmyer flask, while still hot, and cooled to room temp. 150 ml ethyl acetate was added and the solution was acidified to pH 2 with conc. HCl. The solution mixed overnight. The large amount of white precipitate was filtered and washed 3 x 50 ml water. The off-white solid was dried under vacuum to give a first crop yield of 16.17 g pure **2** (66%)

Example 9



3 - In a 100 ml recovery flask was placed 1.00 g of 2, 32 ml methanol, and 3.2 ml 1N NaOH. This clear solution was warmed to 50° in an oil bath. To the solution was added 0.18 g sodium borohydride in small amounts. The reaction was allowed to proceed for 2.5 hrs. The reaction was then cooled to room temp. and the solution was concentrated to a small volume. The mixture was acidified with 2N HCl and the solution was concentrated further to remove the methanol. The solution was extracted with ethyl acetate. The organics were washed with brine, dried over sodium sulfate, filtered, concentrated, and dried under vacuum to give 0.98 g of a light pink foam 3 (97.5%). The product was used immediately for the next step.

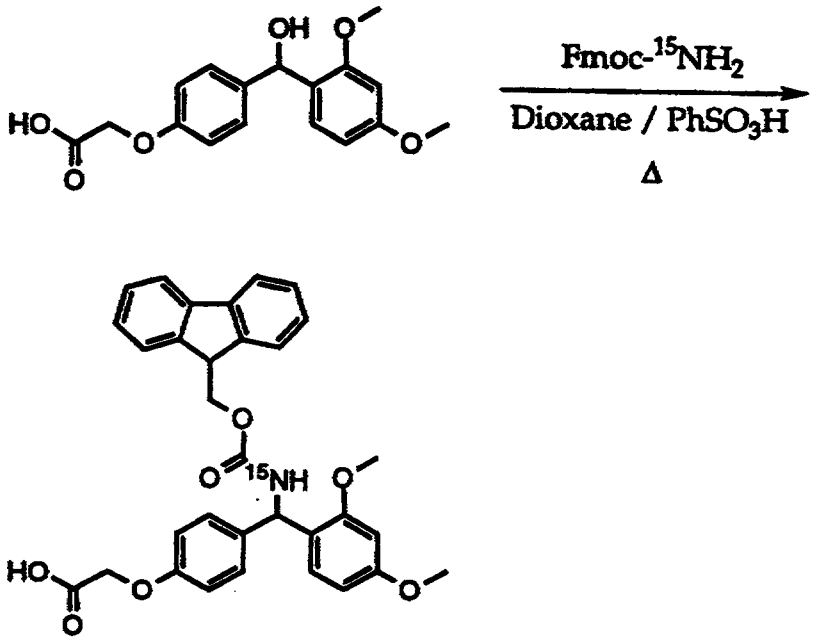
Example 10



In a 200 ml recovery flask was placed 10.0 g of Fmoc-Cl, which was disolved in 100 ml of 80% dimethoxyethane. To this mixture was added approx. 35 ml of 10% ^{15}N-ammonia in water. A white precipitate began to form. The pH of the mixture was brought to 7-9. The reaction was allowed to proceed for 30 min.

The reaction was acidified with 12N HCl and the white solid was filtered off and air dried. Further drying under vacuum gave a first crop yield of 8.072 g pure Fmoc-$^{15}NH_2$ as a white crystaline solid.

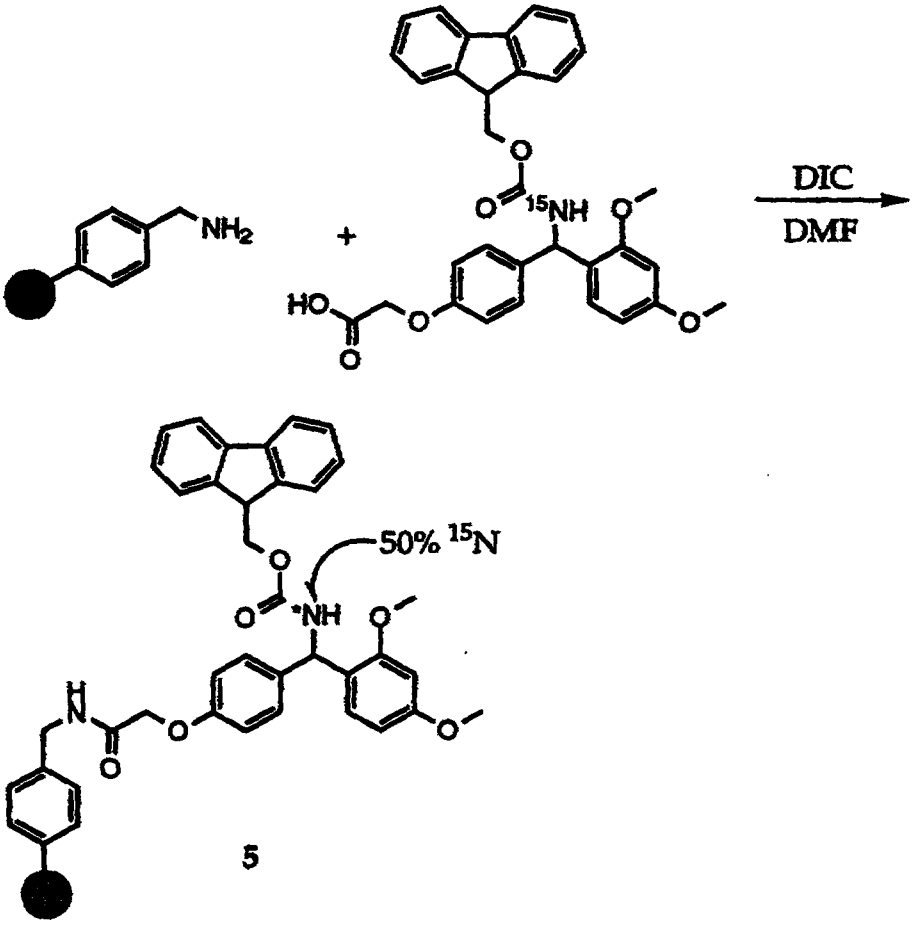
Example 11



4

4 - In the 100 ml recovery flask used to dry 3 was added 20 ml dioxane, 0.75 g Fmoc-$^{15}NH_2$ and 0.25 g benzenesulfonic acid. The reaction was heated to 40°C for 18 hrs. A large amount of light gray precipitate was noted. The mixture was added to water and the light brown solid was filtered and purified by flash col. chromatography (100% ethyl acetate, then 98% ethyl acetate/acetic acid) to give 0.37 g of pure 4 as a light-brown oil.

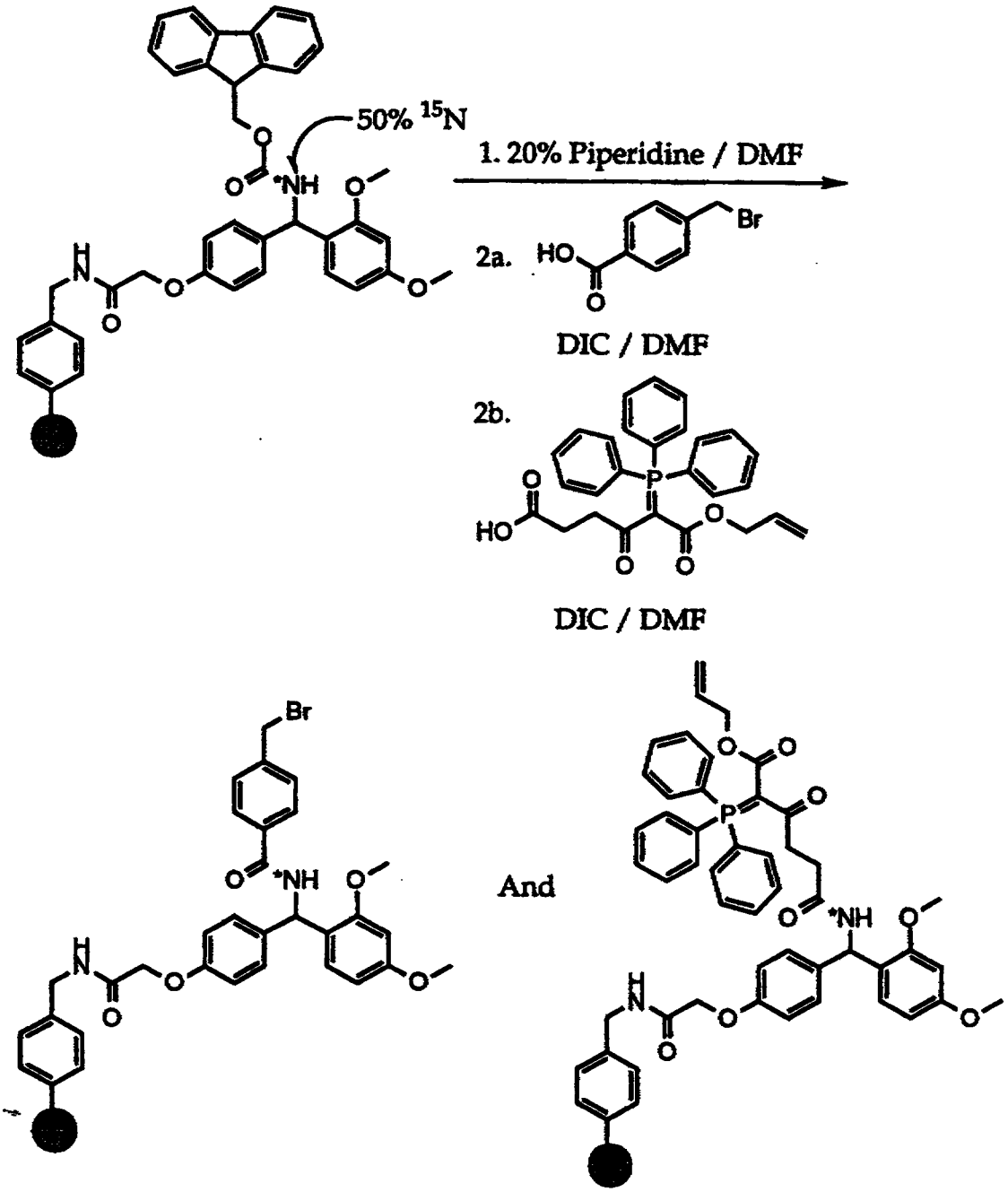
Example 12

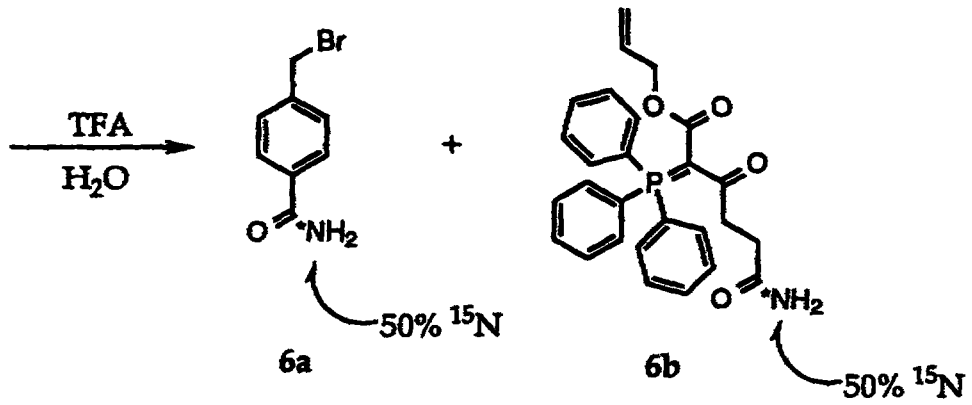


5

5 - In a 10 ml shaker tube was placed 0.50 g of aminomethylated polystyrene (0.21 mmol/g). To the resin was added a solution of 0.1845 g 4 ^{15}N-Knorr linker and 0.184 g commercial ^{14}N-Knorr linker in 5 ml DMF, and 0.164 ml diisopropylcarbodiimide. The coupling ran on a shaker for 5 hrs. The coupling solution was filtered off, and the resin was washed with DMF and CH2Cl2, and dried under vacuum (ninhydrin negative) to provide 5.

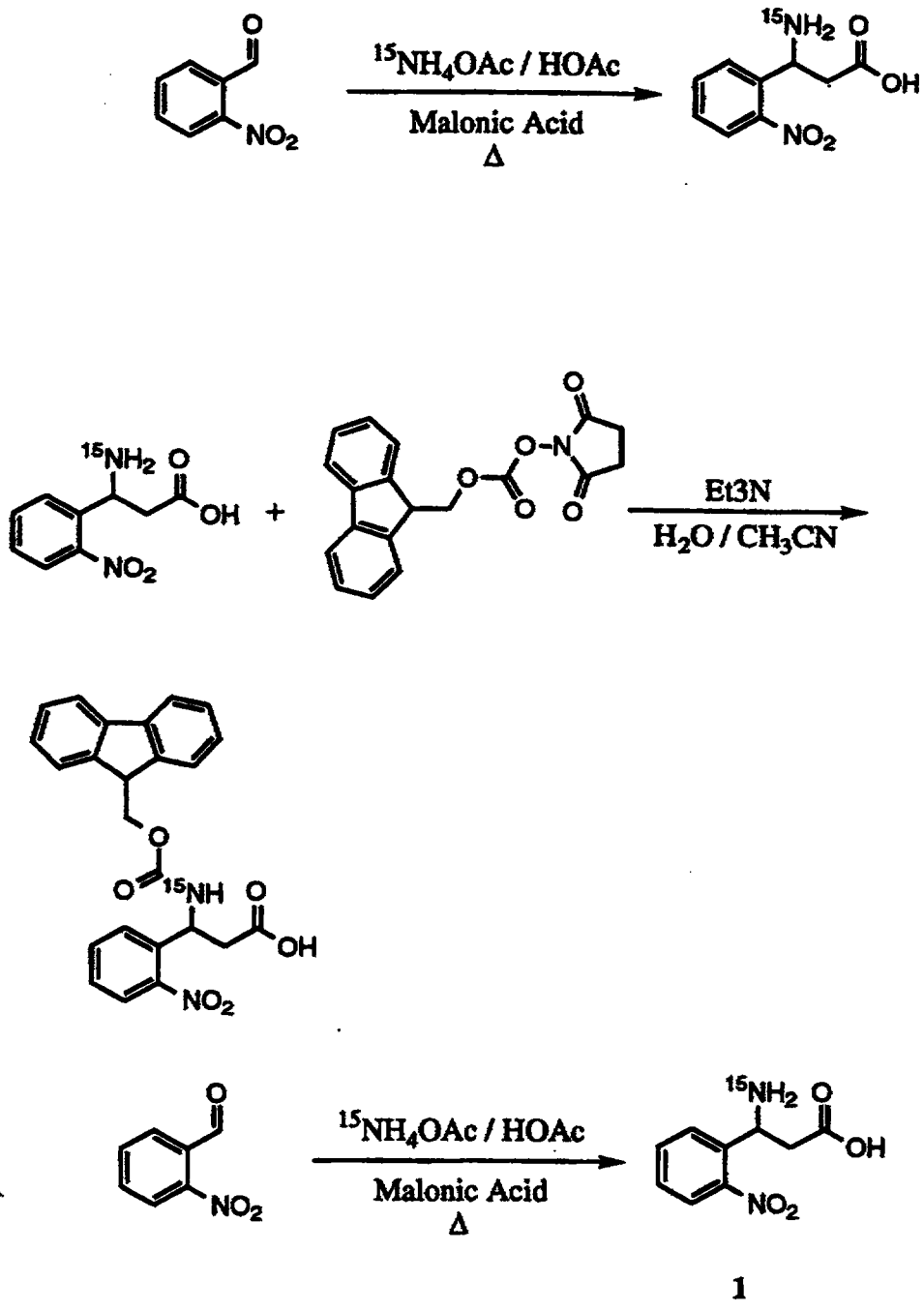
Example 13


50% 15N
1. 20% Piperidine / DMF
2a.
DIC / DMF
2b.
DIC / DMF
And



6a & 6b - In two 5 ml shaker tubes, each with approx 10 mg of resin 5, 2 x 4 ml of 20% piperidine/DMF was added to both. Both were then washed with DMF (ninhydrin pos). To the first shaker was added 0.0246 g of 4-bromomethyl benzoicacid, 0.05 ml DIC, in 1.0 ml DMF. To the second was added 0.0168 of the ylide-acid, 0.05 ml DIC, in 1.0 ml DMF. Each reaction ran on a shaker overnight. The resins were washed with DMF, methylene chloride, and dried under vacuum (ninhydrin negative). To the dry resins was added 1.0 ml of 95% TFA/water and the cleavage ran for 1 hr. Filtered the solutions and concentrated to give **6a** and **6b**. ESI-MS showed an aprox. 46% ^{15}N ratio.

Example 14-Preparation of Mass-labeled photocleavable linkers

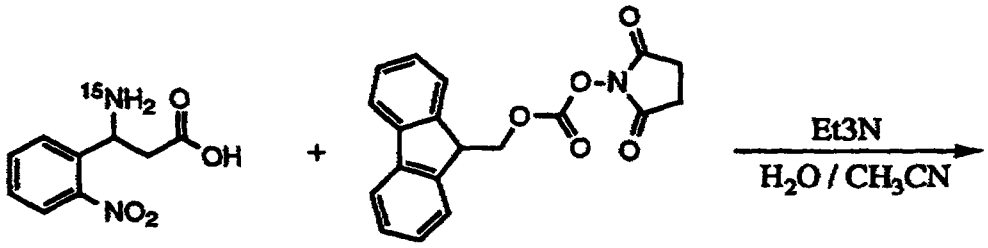


1

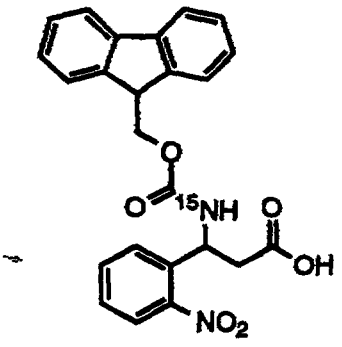
Example 15-Ratio Codes

1 - A solution of 1.511 g 2-Nitrobenzaldehyde (10.0 mmol), 1.563 g malonic acid (15.0 mmol), 2.00g 15N(98%)-ammonium acetate (25.6 mmol), in 5.0 ml acetic acid (99.999%) was heated to 100° with an oil bath. As noted in the Oelschläger

experimental, during heating there was a temporary, almost colorless precipitate (ammonium salt of the benzyliden compound). After 5 hours of heating, 8.0 ml of 25% HCl was added and heating continued for another 5 hours. To this mixture was added 12.0 ml of water and the reaction was cooled to room temperature. A light brown precipitate was filtered off and the filtrate was evaporated to almost dryness. The solution was then briefly boiled with activated carbon and filtered. The filtrate was made basic with the addition of concentrated ammonium hydroxide. 1 precipitated as a yellowish solid. The solid was then washed twice with water, once with 50% methanol in water, once with 1:1 methanol-ether, and three times with ether. The solid was then dried under vacuum to yield 0.8 g pure product 1 (38%).



1

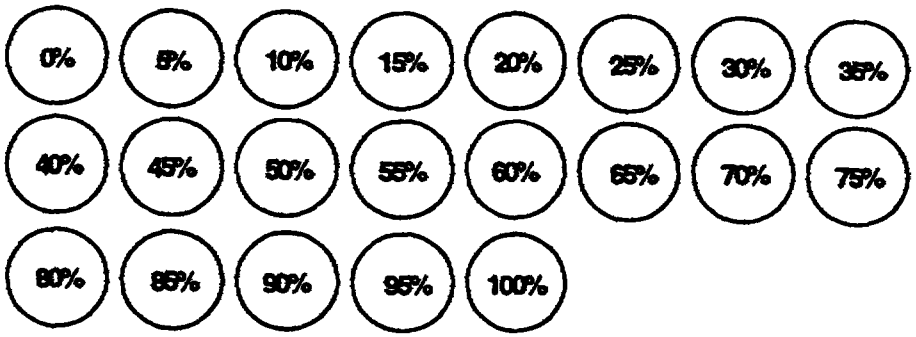


2

0.470 g (2.22 mmol) of 1 was suspended in 5.0 ml water, and subsaquently dissolved by the addition of 0.299 (2.13 mmol) ml triethylamine. To this solution was added 0.757 g Fmoc-OSU (2.25 mmol) in 5.0 ml acetonitrile. The reation then ran for 30

min. (pH ≈ 10). The slurry was evaporated and diluted with 5.0 ml water and 10.0 ml ethyl acetate. The pH was adjusted to 2 with 12N HCl. A white solid precipitated. Filtered and extracted with ethyl acetate. The organics were washed with 2N HCl, H2O, and brine, dried over mag. sulfate, filtered and evaporated to give a white solid which upon tritration with ethyl acetate and hexane gave 0.36 g pure **2** (0.37%).

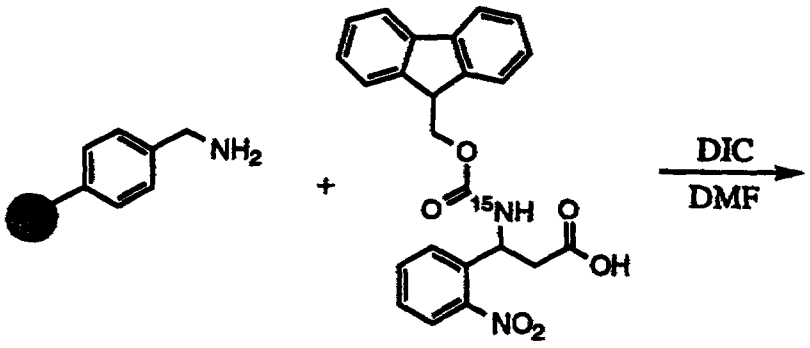
Well array:



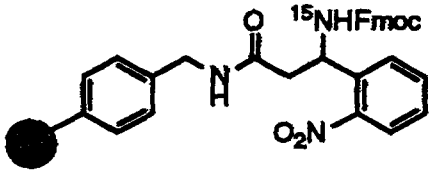
Percentage/ratio solutions of $^{14}N/^{15}N$-photolinker were generated in the following manner (from 10.5 ml stock solutions DMF of each photolinker).

0% = 20 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 0 x 0.050 ml of 10.5 ml ^{15}N-photo
5% = 19 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 1 x 0.050 ml of 10.5 ml ^{15}N-photo
10% = 18 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 2 x 0.050 ml of 10.5 ml ^{15}N-photo
15% = 17 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 3 x 0.050 ml of 10.5 ml ^{15}N-photo
20% = 16 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 4 x 0.050 ml of 10.5 ml ^{15}N-photo
25% = 15 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 5 x 0.050 ml of 10.5 ml ^{15}N-photo
30% = 14 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 6 x 0.050 ml of 10.5 ml ^{15}N-photo

35% = 13 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 7 x 0.050 ml of 10.5 ml ^{15}N-photo
40% = 12 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 8 x 0.050 ml of 10.5 ml ^{15}N-photo
45% = 11 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 9 x 0.050 ml of 10.5 ml ^{15}N-photo
50% = 10 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 10 x 0.050 ml of 10.5 ml ^{15}N-photo
55% = 9 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 11 x 0.050 ml of 10.5 ml ^{15}N-photo
60% = 8 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 12 x 0.050 ml of 10.5 ml ^{15}N-photo
65% = 7 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 13 x 0.050 ml of 10.5 ml ^{15}N-photo
70% = 6 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 14 x 0.050 ml of 10.5 ml ^{15}N-photo
75% = 5 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 15 x 0.050 ml of 10.5 ml ^{15}N-photo
80% = 4 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 16 x 0.050 ml of 10.5 ml ^{15}N-photo
85% = 3 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 17 x 0.050 ml of 10.5 ml ^{15}N-photo
90% = 2 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 18 x 0.050 ml of 10.5 ml ^{15}N-photo
95% = 1 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 19 x 0.050 ml of 10.5 ml ^{15}N-photo
100% = 0 x 0.050 ml of 10.5 ml ^{14}N-photolinker, and 20 x 0.050 ml of 10.5 ml ^{15}N-photo



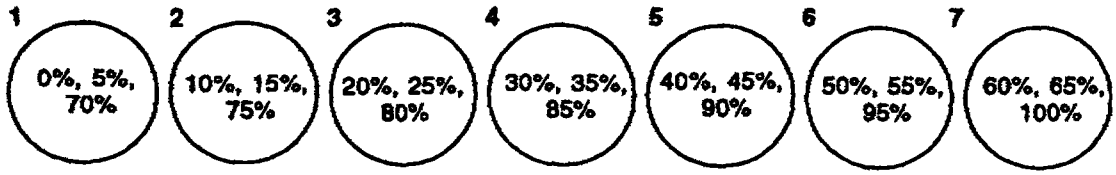
2

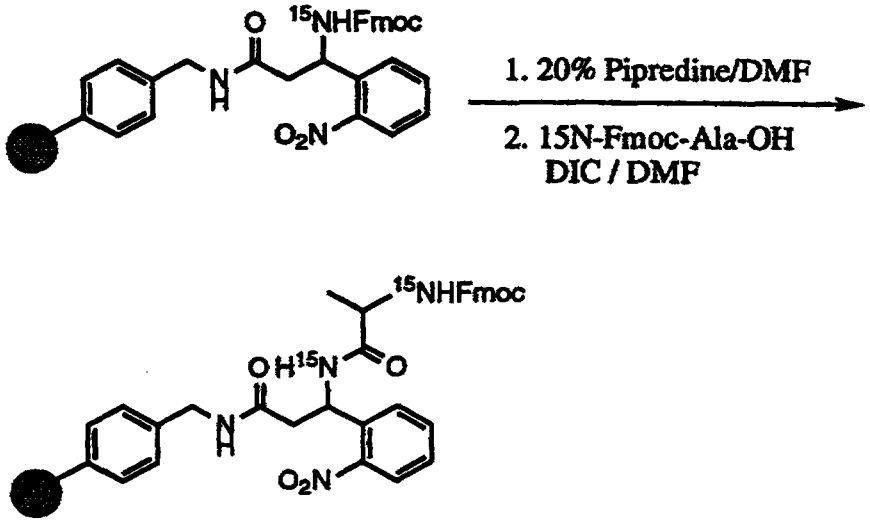


Starting with 6.3 g of aminomethyl polystyrene (0.21 mmol/g), divided into 21 equal lots of 0.300 grams each, were added the 1.0 ml solutions of varying ratios of ^{15}N-2 and ^{14}N-2, in 5% increments (0%, 5%, 10%, to 100% ^{15}N-2 photolinker) (see CDW fig. 1). These solutions were generated by disolving 0.4988 g ^{14}N-2 photolinker and 0.500 g ^{15}N-2 photolinker, and using 0.050 ml aloquats of each (20:0, 19:1, 18:2, to 0:20). To the mixture was then added 0.169 ml diisopropylcarbodiimide. The samples were then mixed and the coupling ran overnight (approx. 16 hours). The resins were washed 8 times with 1.5 ml DMF, and then with copious amounts of methanol.

Approx. 0.1 g of each lot was combined into 7 lots consisting of the following ratios per lot (see CDW fig. 2). These 7 resin lots were used in the Tertiary Amine Library Study.

Well array:



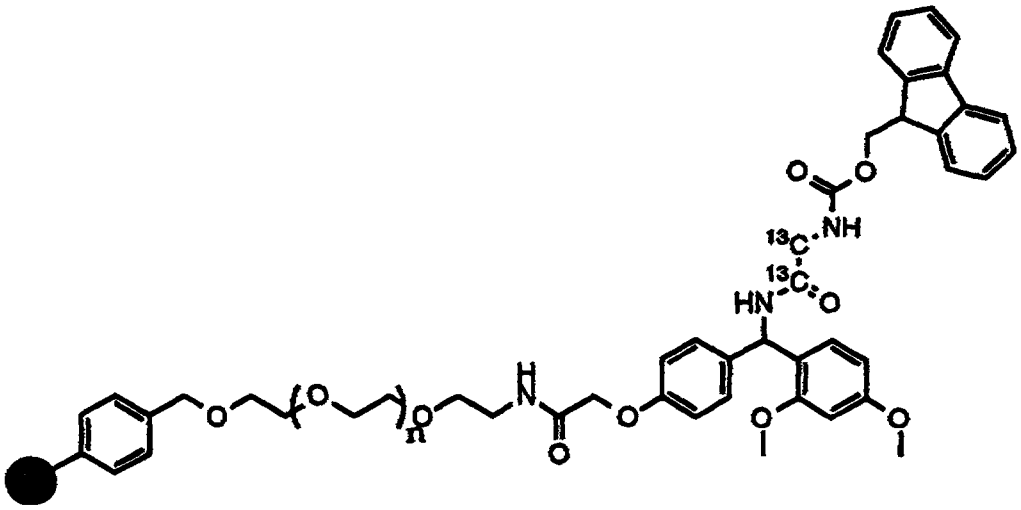


Approx. 0.1 g of each resin lot ratio was coupled with 0.50 ml of a 10.5 ml, 0.55 g 15N-Fmoc-Alanine-OH in DMF solution, followed by the addition of 0.169 ml DIC. The coupling then ran overnight. The resins were washed with copious amounts of methanol and dried under vacuum (ninhydrin negative).

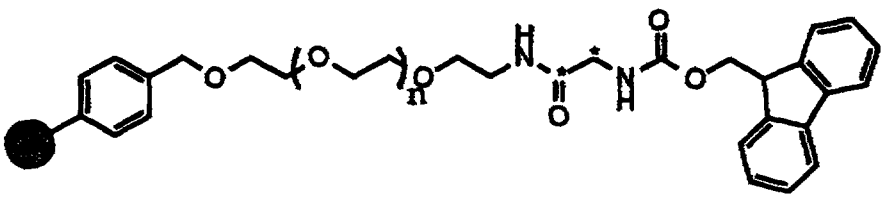
A small amout of each resin lot, approx 0.01 g, was photo-cleaved for 4hrs in 0.200 ml 3:1 water/THF. MS was subsequently performed.

Example 16-Preparation of mass-based codes distinguishable by NMR

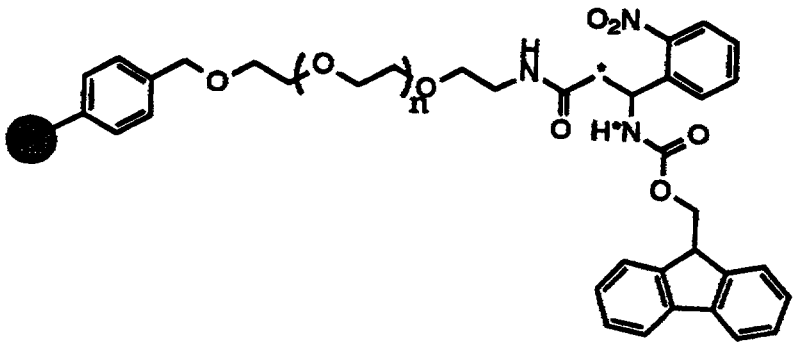
Novabiochem TGR resin coupled with $^{13}C_2$-Fmoc-gly-OH. Both the carbonyl carbon and methylene carbon of glycine were evident by ^{13}C NMR of the resin in $CDCl_3$. Additionally, these carbons could be integrated against the standard PEG signal that would remain constant throughout & the Ratios of ^{13}C linker/ligand could be varied and subsequently determined (ligand resolution) by this non-destructive method.



Novabiochem TG resin coupled with $^{13}C_2$-Fmoc-gly-OH

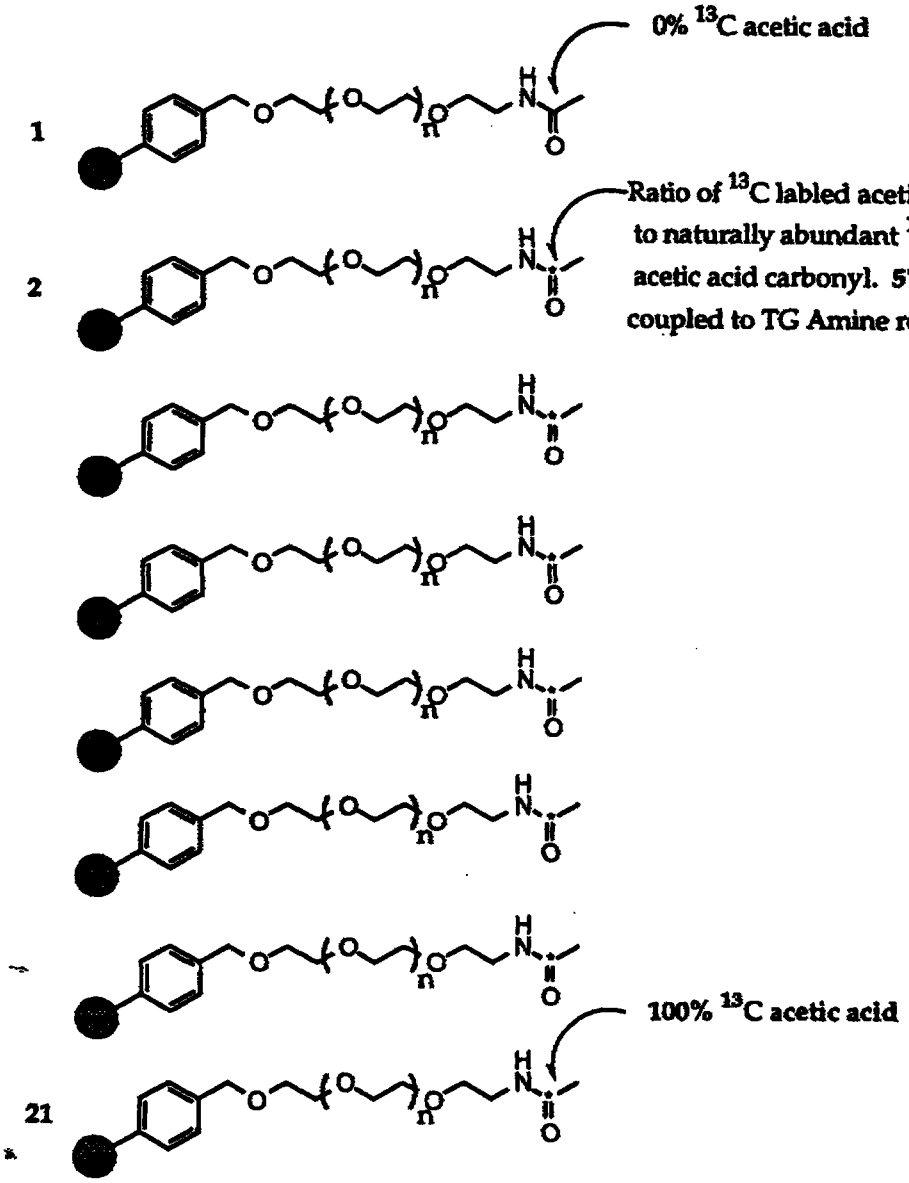


Novabiochem TG resin coupled with ^{13}C, ^{15}N-Photolinker. This linker could have a hard ratio ^{13}C to ^{13}C tag, as well as a cleavable ^{15}N tag.



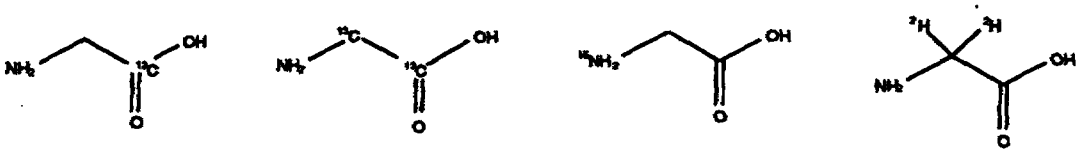
Example 17-NMR Ratio Coding Approach

^{13}C NMR quantitation study on a ratio of ^{13}C labled acetic acid to non-labled acetic acid bound to Tenta-Gel-NH_2 resin. The ^{13}C acetic acid carbonyl can be integrated against naturally occuring ^{13}C in the PEG portion of the TG-NH_2 resin. A differentiation of 5% increments is observed.

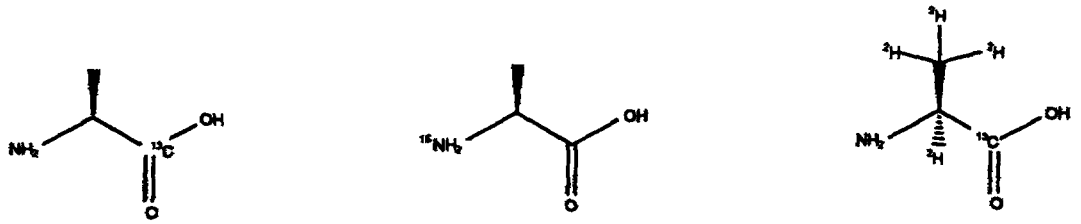


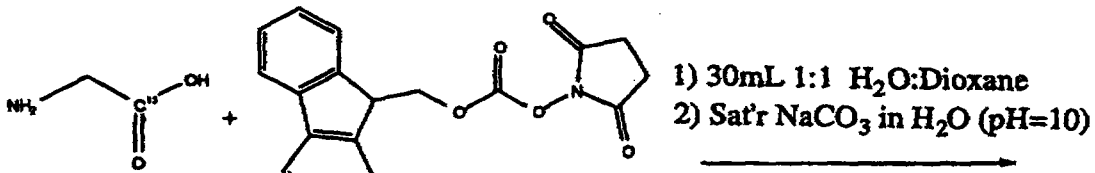
Example 18-Preparation of FMOC-protected isotopically doped code blocks

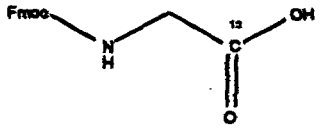
Isotope Labeled Glycine from Cambridge Isotope Laboratories



Isotope Labeled Alanine from Cambridge Isotope Laboratories







N-Fmoc-L-glycine

1 g of each isotope labeled glycine (13.3 mmol) were dissolved in 15 mL of purified water and 1.4 g of sodium carbonate (see Figure GP1). 15 mL of 1,4-Dioxane was added slowly to each and stirred. Over the period of two hours, 4.5 g of Fmoc-OSu (9-Fluorenylmethyl-N-hydroxysuccinimide) was added to each

(see Figure GP3 for scheme). Additional saturated sodium carbonate in water was added to maintain a pH=10. Solutions were allowed to stir overnight. 6M HCl was slowly added to the solution until the pH was approximately 2. Extraction of the compound was completed using 50 mL of ethyl acetate, washing four times with 50 mL of acidified/purified water. Aqueous portions were washed with 50 mL of ethyl acetate. Both portions of ethyl acetate were combined. Magnesium sulfate was added to remove any excess water. Samples were filtered and concentrated using a RotoVap until the final volume was approximately one-third the original volume. Crystallization was completed using Hexane. Hexane was decanted and compound allowed to dry.

N-Fmoc-L-alanine

1 g of each isotope labeled alanine (11.2 mmol) were dissolved in 15 mL of purified water and 1.2 g of sodium carbonate (see Figure GP2). 15 mL of 1,4-Dioxane was added slowly to each and stirred. Over the period of two and a half hours, 3.8 g of Fmoc-OSu (9-Fluorenylmethyl-N-hydroxysuccinimide) was added to each (see Figure GP3 for scheme). Additional saturated sodium carbonate in water was added to maintain a pH=10. Solutions were allowed to stir overnight. 6M HCl was slowly added to the solution until the pH was approximately 2. Extraction of the compound was completed using two times 150 mL of ethyl acetate, washing four times with 300 mL of acidified/purified water. Magnesium sulfate was added to remove any excess water. Samples were filtered and concentrated using a RotoVap until the final volume was approximately one-third the original volume. Crystallization was completed using Hexane. Hexane was decanted and compound allowed to dry.

The disclosure of the following references is incorporated in their entirety herein by reference: Atherton,E. and Sheppard,R.C. (1989) *Solid Phase Peptide Synthesis: A Practical Approach.* IRL Press, Oxford. Bodanszky,A. and Bodanszky,M. (1984) *The Practice of Peptide Synthesis.* Springer-Verlag, Berlin.

Example 18-Synthesis of Isotopically Labeled Peptides for Mass Spectral Analysis, Showing Their Use in Four Encoding Approaches

Fmoc-protected alanine, serine and lysine were purchased from Bachem Bioscience. Fmoc-glycine was purchased from Novabiochem. Isotopically labeled amino acids were purchased from Cambridge Isotope Laboratories and were Fmoc protected in house (GP). Fmoc Knorr linker was purchased from Novabiochem. Fmoc-3-(2-nitrophenyl)-3-aminopropionic acid (a photolabile linkage agent) was purchased from Universal Organics. Aminomethyl polystyrene resin (0.81 mmol/gram) was purchased from Advanced ChemTech.

Linkers were attached to solid support manually in reaction shakers (CM). Resin was split to 85 reaction vessels on an Advanced ChemTech ACT496 MBS. Resin was deprotected with 25% piperidine/dimethylformamide twice for 10 minutes, then washed thoroughly with dimethylformamide. The first amino acids were coupled as 0.142 M solutions in N-methyl-pyrolidone, with PyBOP/Diisopropylethylamine in situ activation for 1.5 hours at room temperature. Boc deprotection was performed with 25 % trifluoroacetic acid in dichloromethane for 30 minutes. Acetylations were performed with 33 % acetic anhydride in dimethyl formamide for 30 minutes. All couplings were verified by ninhydrin color tests. Cleavage from the knorr linker was accomplished in 90% trifluoroacetic acid, 3% each water, phenol and thioanisole for 1.5 hours. Samples were dried under a nitrogen stream, then dissolved in water and lyophilized twice. Photocleavage was performed in 2:1 water:tetrahydrofuran under uv lamp for 12 hours. Samples were lyophiliized once.

Single Peak Positional Code

This array was designed to produce 20 samples with singlet, unique molecular weights for positive identification by mass spectroscopy. The samples were assembled in duplicate, one set of twenty on a chemically cleavable solid support, and the second set of twenty on a photocleavable support. By using a combination of one or two amino acids, a "coding region" was generated before addition of the synthetic ligand (in this case

Acetyl-lysine). The twenty codes were constructed from the following amino acids :

Glycine
Glycine (15N)
Glycine (2,2-D2)
Alanine
Alanine (15N)
Alanine (1-13C)
Serine

After the coding region had been assembled, lysine was coupled as a test ligand as well as to generate a free amino side chain for ease of observation by mass spectroscopy. The a-amino group of the lysine was then acetylated.

The codes and ligand were assembled on polystyrene resin functionalized with either Fmoc-Knorr or Fmoc-3-(2-nitrophenyl)-3-aminopropionic acid linkers.

The array for the single peak positional code is shown below :

Figure 1

	Position 1	Position 2	Position 3	Total MW
1	Ac-Lys-	X	X	187
2	Ac-Lys-	X	-Gly0-	244
3	Ac-Lys-	X	-Gly1-	245
4	Ac-Lys-	X	-Gly2-	246
5	Ac-Lys-	X	-Ala0-	258
6	Ac-Lys-	X	-Ala1-	259
7	Ac-Lys-	X	-Ala4-	262

8	Ac-Lys-	X	-Ser-	274
9	Ac-Lys-	-Gly0-	-Gly0-	301
10	Ac-Lys-	-Gly0-	-Gly1-	302
11	Ac-Lys-	-Gly1-	-Gly1-	303
12	Ac-Lys-	-Gly2-	-Gly1-	304
13	Ac-Lys-	-Gly2-	-Gly2-	305
14	Ac-Lys-	-Ala0-	-Gly0-	315
15	Ac-Lys-	-Ala1-	-Gly0-	316
16	Ac-Lys-	-Ala0-	-Gly2-	317
17	Ac-Lys-	-Ala1-	-Gly2-	318
18	Ac-Lys-	-Ala4-	-Gly2-	321
19	Ac-Lys-	-Ser-	-Gly0-	331
20	Ac-Lys-	-Ser-	-Gly1-	332

Double Peak Positional Code

This array was designed to produce 20 samples with doublet peaks by mass spectroscopy; one peak arising from the ligand attached to a unique code, with a second peak resulting from a simultaneously assembled reference peak (ligand plus a fixed residue). As described in the SPPC above, by using a combination of one and two amino acids, a "coding region" was generated before addition of the synthetic ligand (in this case Acetyl-lysine). The twenty codes were also constructed from the following amino acids :

Glycine

Glycine (15N)
Glycine (2,2-D2)
Alanine
Alanine (15N)
Alanine (1-13C)
Serine

The codes and ligand were assembled on polystyrene resin functionalized with Fmoc-Knorr of Fmoc-3-(2-nitrophenyl)-3-aminopropionic acid linkers.

The array for the double peak positional code is shown below :

Figure 2

	Position 1	Position 2	Position 3	Mwt
1	Ac-Lys-	X	X	187
2	Ac-Lys-	X	-Gly0-	244
3	Ac-Lys-	X	-Gly1-	245
4	Ac-Lys-	X	-Gly2-	246
5	Ac-Lys-	X	-Ala0-	258
6	Ac-Lys-	X	-Ala1-	259
7	Ac-Lys-	X	-Ala4-	262
8	Ac-Lys-	X	-Ser-	274
9	Ac-Lys-	-Gly0-	-Gly0-	301
10	Ac-Lys-	-Gly0-	-Gly1-	302
11	Ac-Lys-	-Gly1-	-Gly1-	303

1 2	Ac-Lys-	-Gly2-	-Gly1-	304
1 3	Ac-Lys-	-Gly2-	-Gly2-	305
1 4	Ac-Lys-	-Ala0-	-Gly0-	315
1 5	Ac-Lys-	-Ala1-	-Gly0-	316
1 6	Ac-Lys-	-Ala0-	-Gly2-	317
1 7	Ac-Lys-	-Ala1-	-Gly2-	318
1 8	Ac-Lys-	-Ala4-	-Gly2-	321
1 9	Ac-Lys-	-Ser-	-Gly0-	331
2 0	Ac-Lys-	-Ser-	-Gly1-	332

In each of the samples produced in this experiment, the peptide molecular weight shown above will appear superimposed with the reference peak generated by Ac-Lys-Gly-NH_2. This is to demonstrate the ability to identify both the first pooling lot and the molecular ion generated by the unknown ligand.

To produce samples displaying the coded double peak, an orthogonal protection scheme was used. The first Fmoc-protected amino acid of the coding region was coupled simultaneously with an equimolar amount of Boc-glycine. The coding region was assembled using Fmoc chemistry, then the Boc protecting group was removed with trifluoroacetic acid. After a final removal of the code Fmoc protecting group with piperidine (which concommittentley neutralized TFA salts on the exposed amine of glycine), the ligand (acetyl llysine) was coupled. Upon photocleavage, two compounds were liberated in equimolar amounts : the ligand linked to a reference amino acid (glycine) and the ligand linked to a unique code. The mass difference between the two peaks indicates the identity of the code, and hence the identity of the first monomer of the ligand coupled.

Mass Spectral Barcode

This array will produce twenty five samples, each dislying a unique molecular ion or peak pattern by mass spectroscopy. By using only combinations of isotopically labeled glycine at only two positions, twenty five unique "barcodes" are produced. In this manner the first pooled lot of any single bead derived from a split-combine library can be readily identified.

In this experiment Fmoc-protected amino acids were coupled either as discretes or equimolar mixtures of two or three amino acids.

The array for the mass spectral barcode is shown below :

Figure 3

	Position 1	Position 2	Position 3	Peak Pattern
1	Ac-Lys-	-G0-	-G0-	1
2	Ac-Lys-	-G1-	-G0-	1
3	Ac-Lys-	-G0/G1-	-G0-	1:1
4	Ac-Lys-	-G2-	-G0-	1
5	Ac-Lys-	-G0/G2-	-G0-	1:1
6	Ac-Lys-	-G1/G2-	-G0-	1:1
7	Ac-Lys-	-G0/G1/G2-	-G0-	1:1:1
8	Ac-Lys-	-G2-	-G1-	1
9	Ac-Lys-	-G0/G2-	-G1-	1:1
10	Ac-Lys-	-G0/G1-	-G2-	1:1
11	Ac-Lys-	-G0/G1/G2-	-G1-	1:1:1
12	Ac-Lys-	-G0/G1-	-G0/G1-	1:2:1
13	Ac-Lys-	-G0/G2-	-G0/G1-	1:1:1

1	Ac-	-G1/G2-	-G0/G1-	1:2:1
4	Lys-			
1	Ac-	-	-G0/G1-	1:2:2:1
5	Lys-	G0/G1/G2-		
1	Ac-	-G2-	-G2-	1
6	Lys-			
1	Ac-	-G0/G2-	-G2-	1:1
7	Lys-			
1	Ac-	-G0/G2-	-G0/G2-	1:2:1
8	Lys-			
1	Ac-	-G1/G2-	-G2-	1:1
9	Lys-			
2	Ac-	-	-G2-	1:1:1
0	Lys-	G0/G1/G2-		
2	Ac-	-G1/G2-	-G0/G2-	1:1:1:1
1	Lys-			
2	Ac-	-	-G0/G2-	1:1:2:1:
2	Lys-	G0/G1/G2-		1
2	Ac-	-G1/G2-	-G1/G2-	1:2:1
3	Lys-			
2	Ac-	-	-G1/G2-	1:2:2:1
4	Lys-	G0/G1/G2-		
2	Ac-	-	-	1:2:3:2:
5	Lys-	G0/G1/G2-	G0/G1/G2-	1

Example 19

4 g of aminomethylated polystyrene (0.81 mmol/g) was put into each of 2-250 mL shakers. The resin was swelled with dimethylformamide (DMF) and drained. The resin was then washed with 20% piperidine/DMF for ~3 minutes and drained. The resin was washed three times with DMF, once with dichloromethane (DCM):DMF 1:1, and twice more with DMF.

To the first shaker was added 3.5 equivalents of Knorr linker (6.12g, 11.34 mmol) and 3.5 equivalents of PyBop (5.9g, 11.34 mmol). Enough DMF was added to cover the resin bed. The solution was then activated with 10.5 equivalents of DIEA (5.93 mL, 34.02 mmol). The reaction ran for 1 hour with manual shaking every 5-10 min.

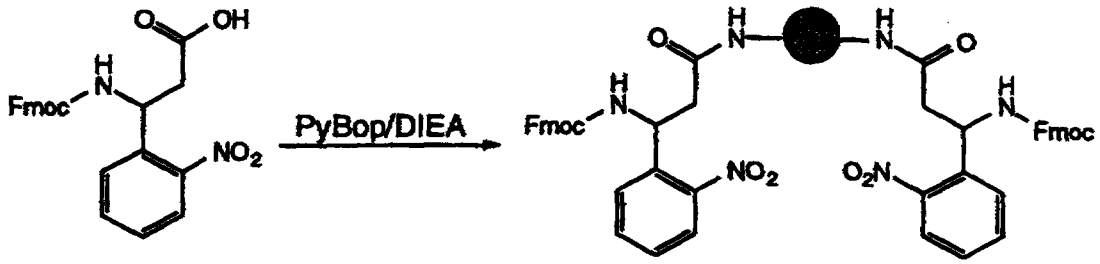
To the second shaker was added 3.5 equivalents of photo linker (4.89g, 11.34 mmol) and 3.5 equivalents of PyBop (5.9g,

11.34 mmol). Enough DMF was added to cover the resin bed. The solution was then activated with 10.5 equivalents of DIEA (5.93 mL, 34.02 mmol). The reaction ran for 1 hour with manual shaking every 5-10 min.

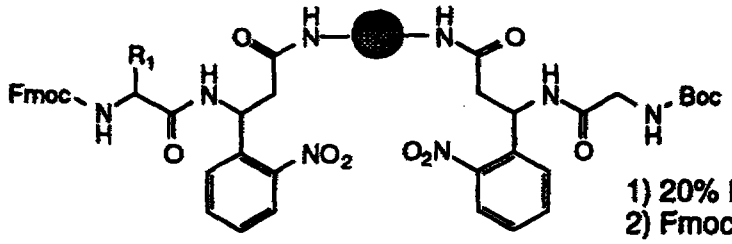
After 1 hour both shakers were drained. Ninhydrin tests indicated complete coupling for both linkers. The resin was washed four times with DMF, once with dichloromethane (DCM):DMF 1:1, and two more times with DMF.

The resin was split to a 96 well ACT 496 Teflon reaction block.

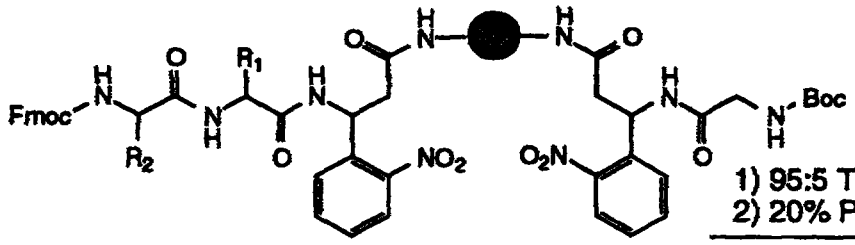
Example 20-Double Peak Positional Code



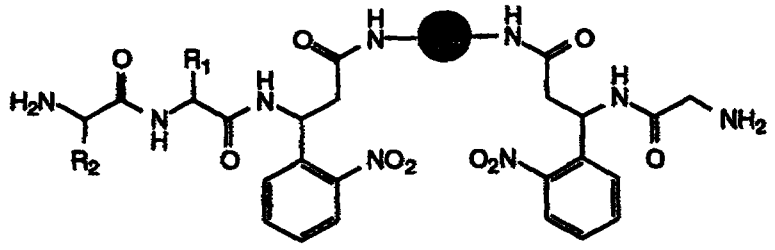
1) 20% Piperidine / DMF
2) 1:1 Boc-Gly-OH : Fmoc-R_1-OH / PyBop / DIEA



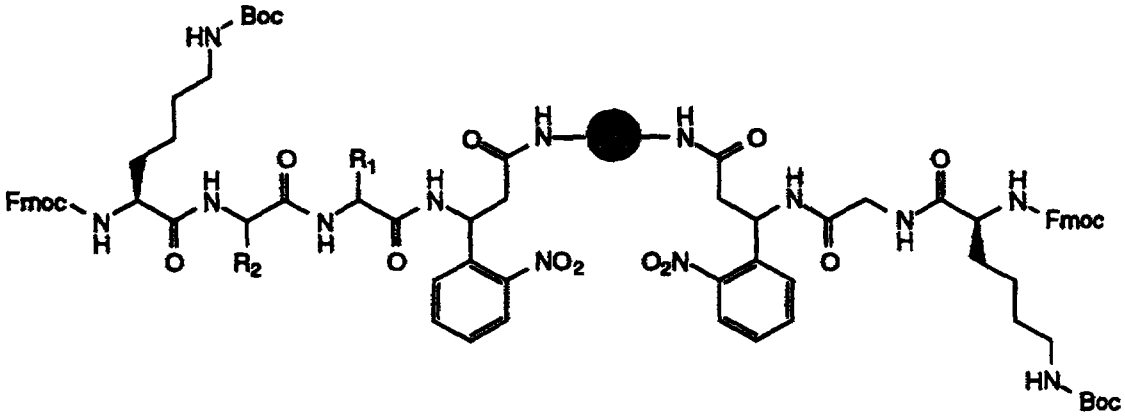
1) 20% Piperidine / DMF
2) Fmoc-R_2-OH / PyBop / DIEA



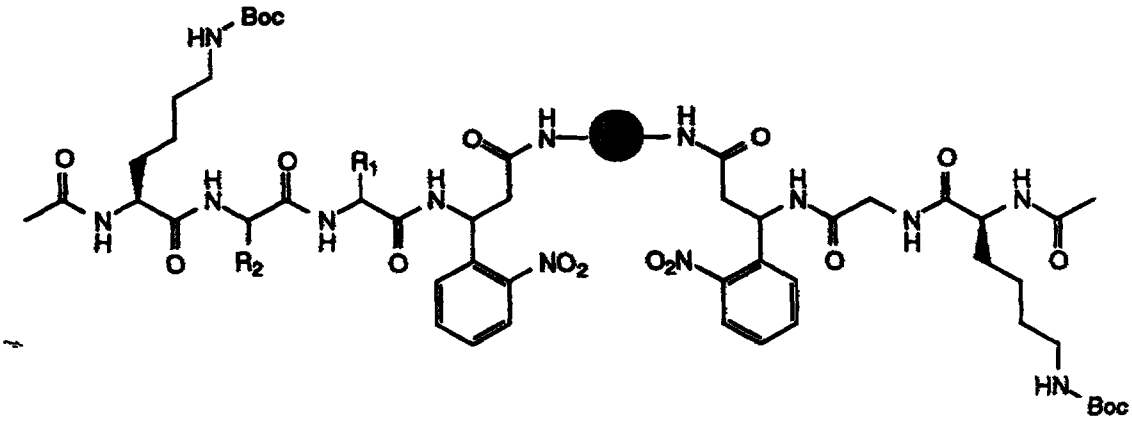
1) 95:5 TFA:Water
2) 20% Piperidine / DMF



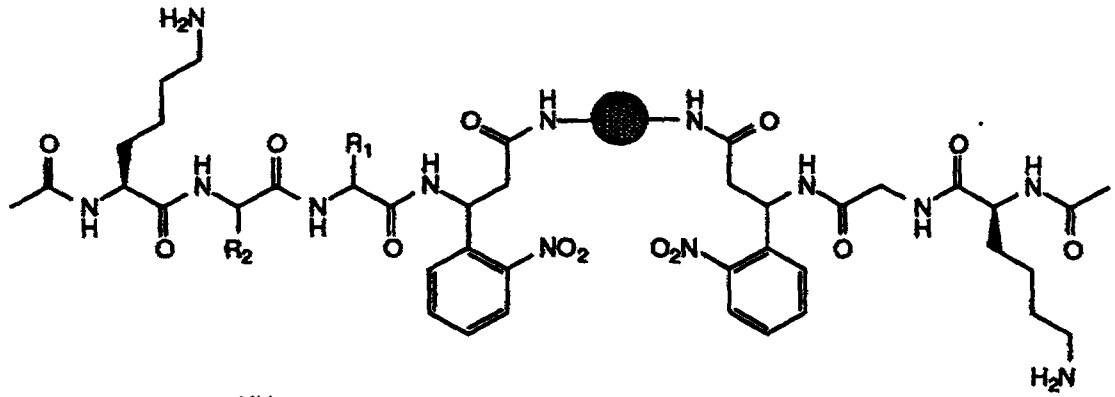
Fmoc-L-Lys(Boc)-OH / PyBop / DIEA



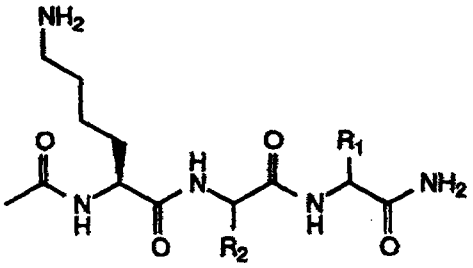
1) 20% Piperidine / DMF
2) 30% Acetic Anhydride / DMF



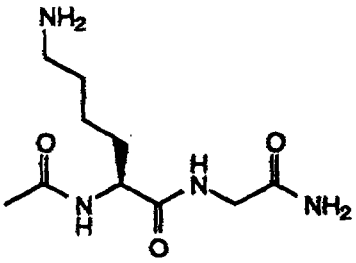
95:5 TFA:Water



hv



Code



Reference

Example 21-Ratio Code Using Tertiary Amine

The seven lots of resin (CDW Fig. 2) were transferred to 10 mL shakers using dimethylformamide (DMF). The shakers were then covered with aluminum foil. The linker was Fmoc deprotected twice for 5 minutes each using 20% piperidine/DMF. The resin was washed four times with DMF, once with dichloromethane (DCM):DMF 1:1, and twice with DMF.

0.315 mmol of each of seven halo acids were weighed in separate vials and an equimolar amount of PyBop was added to each. The halo acids were then dissolved in 2 mL of DMF. Each solution was then added to the respective lot of resin and activated

with 165 µL of diisopropylethylamine (DIEA). The coupling ran for 1 hour. After coupling the resins were drained and washed four times with DMF, once with DCM:DMF 1:1, and twice with DCM to dry the resin.

0.315 mmol of each of seven halo acids were weighed in separate vials and an equimolar amount of HBTU was added to each. The halo acids were then dissolved in 2 mL of DMF. Each solution was then added to the respective lot of resin and activated with 165 µL of DIEA. The coupling ran for 1 hour. After coupling the resins were drained and washed four times with DMF, once with DCM:DMF 1:1, and twice with DMF. Coupling was complete by ninhydrin.

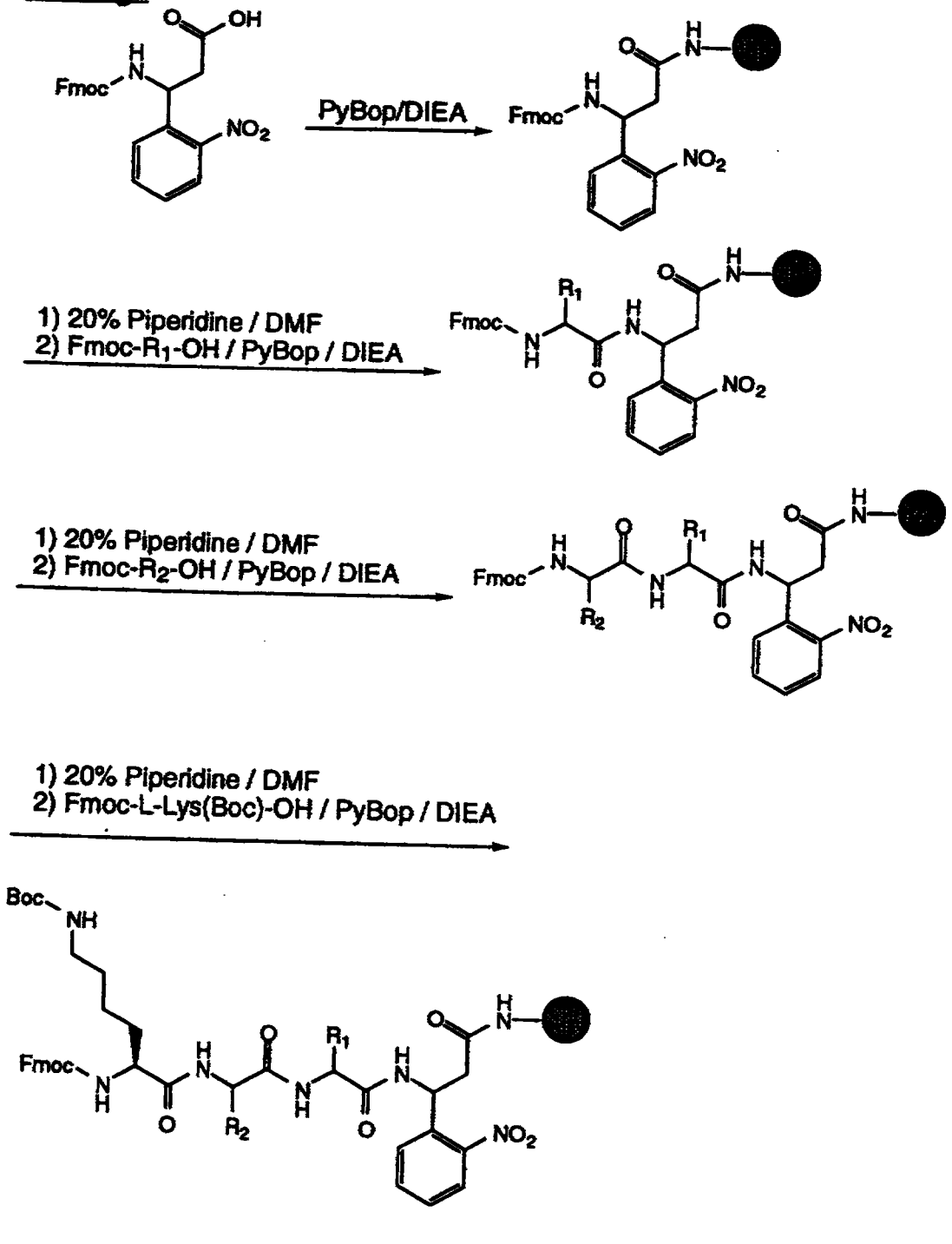
The resin lots were combined and split to 24 wells of a 96 well ACT 396 polypropylene reaction block. The resin was washed twice with DCM and dried.

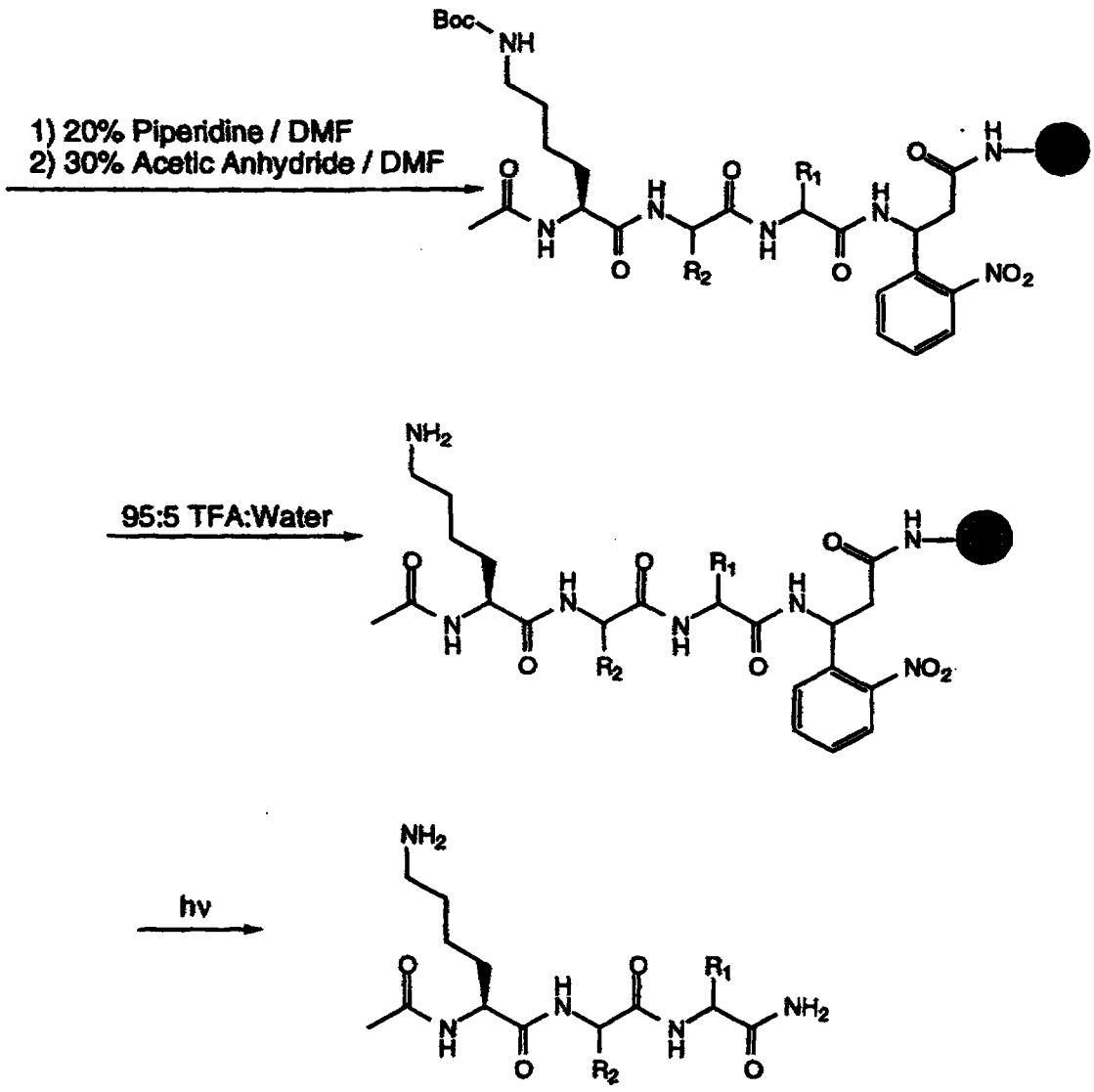
The resin was swelled with DMF and drained. 1 mL of 1.0 M amine solution in dimethylsulfoxide (DMSO) was added to each well. The reaction ran overnight. The resin was drained and washed twice with DMF, once with DMF:methanol:water (1:1:1), and washed three more times with DMF. The 24 lots of resin were then combined and split back to 24 wells.

350µL of aldehyde solution (3.0 M / DMF) was added to each well and mixed for 2 minutes. An additional 250µL of trimethylorthoformate was added to each well and mixed for 1 minute followed by 100 µL of 3% acetic acid in DMF. The reaction mixed for 15 minutes before a final addition of 1mL of 1.5 M $NaBH_3CN$. The reductive amination reaction ran for 3 hours. The resin was drained and washed twice with DMF.

A second reductive amination was run using sodium triacetoxyborohydride. 350µL of aldehyde solution (3.0 M / DMF) was added to each well and mixed for 2 minutes. An additional 250µL of trimethylorthoformate was added to each well and mixed for 1 minute followed by 100 µL of 3% acetic acid in DMF. The reaction mixed for 15 minutes before a final addition of 1mL of 1.5 M $NaBH(O_2CCH_3)$. The reaction ran overnight. The resin was drained and washed twice with DMF, three times with DMF:methanol:water, three times with DCM, and three final times with methanol.

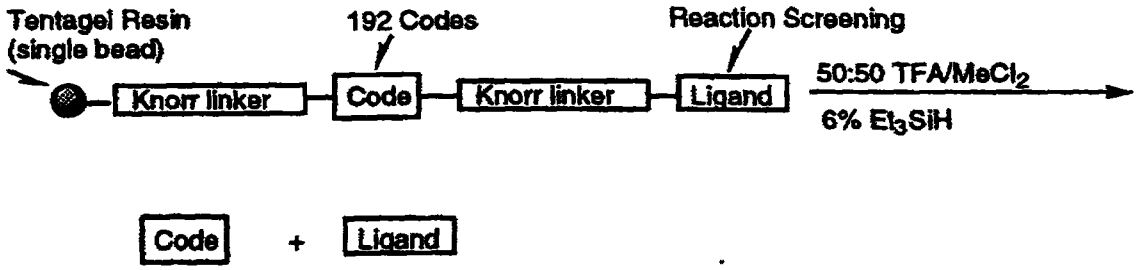
Example 22-Single Peak Positional Code With Photolabile Cleavage





Example 23-Reaction Screening

The synthesis of a set of serially encoded resins contained 192 combinations of of isotopically labeled amino acids (glycine G^0, G^1, G^2 G^3 and alanine: A^0, A^1, A^2, and A^3) and were separated by Knorr linkers as shown below:

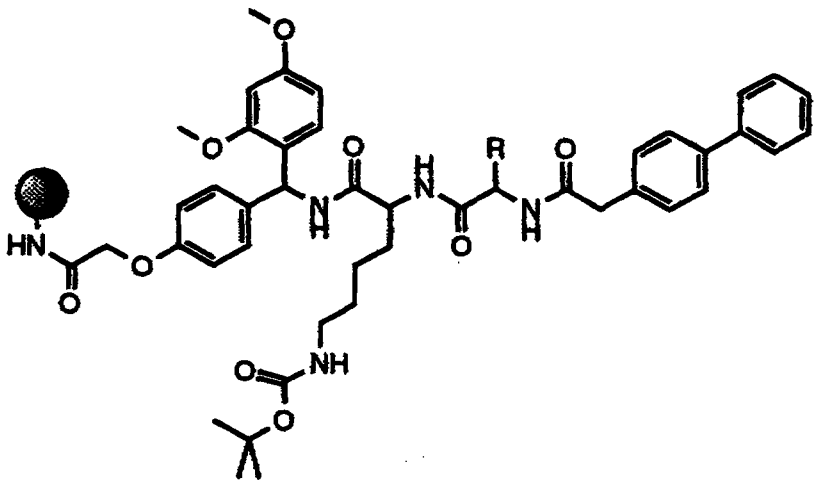


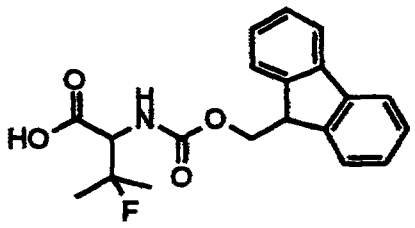
The reaction screening is performed on the ligand portion of the molecule where 3 different monomers were used for the coupling of primary amines to allylic bromides as well as 4 different reaction conditions to give a total of 12 combinations. The acylation of secondary amines with carboxylic acids involved 4 different acids and 4 different reaction conditions to give another 16 combinations. The resin was pooled and treated with 36 different conditions for the final intramolecular Heck reaction to give over 6900 potential compounds that contains different monomers and reaction conditions. Upon single bead cleavage with TFA/$MeCl_2$ and 6% triethylene both the encoded portion and the ligand are liberated as outlined above. The ligand is also encoded by the incorporation of glycine(0) and glycine(2) to help identify the ligand peaks in the mass spectrum.

The mass spectra that are shown in Figures 10 through 12 contain both the code (544-562) and the ligand (462 and 464), (504 and 506), (478 and 480). The monomers and conditions that were run for that particular mass spectrum are listed on the spectrum.

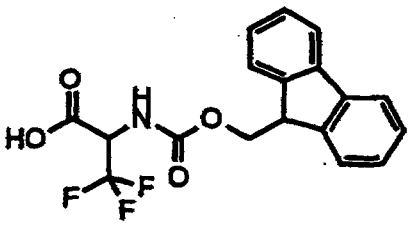
From these results one can use the combinatorial approach to look at various reaction conditions and monomers on a single bead and read both the code and the ligand when the material is cleaved off of the bead.

Example 24-Ratio Code: IR, NMR and MS analysis

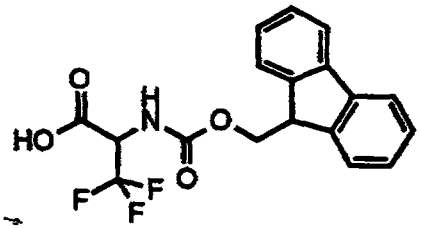




Monomer 1 (R1)



Monomer 2 (R2)



Monomer 3 (R3)

16 resin samples were synthesized where R was defined by a simultaneous coupling of monomers 1 through 3 in different ratio patterns (ratios noted below). These resing could then be analysed by several analytical techniques to elucidate their ratio identity. The beads were analysed by IR, mass spec, NMR, and Amino Acid analysis. The ratios generated for the simultaneous coupling are

defined R1:R2:R3 and were as follows for the 16 samples: #1-1:1:5; Sample #2-1:2:5; Sample #3-1:3:5; Sample #4-1:4:5; Sample #5-2:1:5; Sample #6-2:2:5; Sample #7-2:3:5; Sample #8-2:4:5; Sample #9-3:1:5; Sample #10-3:2:5; Sample #11-3:3:5; Sample #12-3:4:5-Sample #13-4:1:5; Sample #14-4:2:5; Sample #15-4:3:5; Sample #16-4:4:5. Spectra for these ratios is shown in the accompanying Figures 18 through 51 as follows:

Sample	IR Spectra Number	Mass Spec. Number
1	u7125-86-1	CW-001
2	u7125-86-2	CW-002
3	u7125-86-3	CW-003
4	u7125-86-4	CW-004
5	u7125-86-5	CW-005
6	u7125-86-6	CW-006
7	u7125-86-7	CW-007
8	u7125-86-8	CW-008
9	u7125-86-9	CW-009
10	u7125-86-10	CW-0010
11	u7125-86-11	CW-0011
12	u7125-86-12	CW-0012
13	u7125-86-13	CW-0013
14	u7125-86-14	CW-0014
15	u7125-86-15	CW-0015
16	u7125-86-16	CW-0016

Example 25-Encoding Styrene

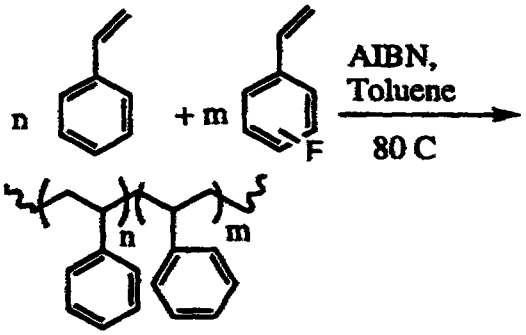
The beads themselves generally used as solid supports in solid state synthesis can be isotopically doped. Styrene beads comprised of styrene can readily by doped with C^{13}, F^{20} or H^{2}. Additionally, it is possible to combine isotopically doped constructs with beads that have themselves been coded or tagged with one or more of a series of monomers.

Styrene (M_s), 2-Fluorostyrene (M_1), 3-Fluorosytrene, (M_2) and 4-Fluorostyrene (M_3) were deinhibited prior to polymerization by passing through an alumina adsorption column.

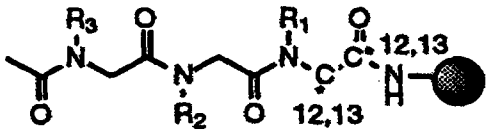
The initiator 2,2-azobisisobutyronitrile (AIBN) was purified by crystallization from methanol Specral grade toluene was used as solvent in a free radical polymerization without further purification.

Run	M_1(%)	M_2(%)	M_3(%)	M_s(%)
YL4001	100	0	0	0
YL4002	0	100	0	0
YL4003	0	0	100	0
YL4004	0	0	0	100
YL4005	0	0	50	50
YL4006	0	10	40	50
YL4007	0	20	30	50
YL4008	0	20	30	50
YL4009	0	40	10	50
YL4010	0	50	0	50
YL4011	50	0	0	50
YL4012	40	10	0	50
YL4013	30	20	0	50
YL4014	20	30	0	50
YL4015	10	40	0	50
YL4016	40	0	10	50
YL4017	30	0	20	50
YL4018	20	0	30	50
YL4019	10	0	40	50

Copolymerization of Styrene and F-Styrene



Example 26-Encoding a Peptoid Library



A 1000 component library consisting of three monomer positions was designed to demonstrate the utility of the encoding strategy. The library was synthesized using the split-mix methodology to create a 10 x 10 x 10 library. Since the split mix method yields one compound per bead and the beads are mixed twice during the synthesis, the chemistry or monomer addition at each step must be recorded on the bead in order to decode the compound.

The first position is encoded by controlling the ratio of ^{12}C:$^{13}C_2$ incorporated with bromoacetic acid in the first synthetic step. Ten unique ratios were employed with nine percent increments ranging from 9:91 to 90:10. The use of nine percent increments avoided the endpoints of either 0:100 or 100:0 while allowing a total of ten codes. The third monomer was alreacy known because the library was not recombined after addition of the final monomer (only one monomer from set three was present

in each pool.) This position was therefore pool or spatially encoded.

The second position was encoded by the molecular weight of the compound. Since monomer one is known by the isotopic reaction and monomer three by the final pool, monomer two can be calculated using the molecular weight determined by the mass spectrometer. This imposes one constraint for any library: the monomers in the second position must have different molecular weights. The other monomers have no restrictions. For this test example, the final pools were composed of compounds having unique molecular weights in order to facilitate decoding.

Twenty single beads from each of the 10 pools were individually cleaved. The compounds were then analyzed by mass spectrometry and identified by the isotope ratio and molecular weight of the analyzed peaks. The peak resulting from the protonated monoisotopic ion was designated M_oH^+ while that resulting from the diisotopic ion $(M_0H+2)^+$ was designated M_2H^+ . The deliberate doping with $^{13}C_2$ controlled the intensity of the M_2H^+ peak relative to the M_0H^+ peak.

Mass spectral data from a single bead in pool 3 showed that M_0H^+ and M_2H^+ were 552 and 554, respectively. The M_0H^+:M_2H^+ ratio was calculated to be 10:90, which was quite close to the actual ratio for ion 552, which was 9:91. Using M_0H^+ as 550 and M_2H^+ as 552, the calculated M_0H^+ to M_2H^+ ratio was 56:44. The compound having a M_0H^+ ion in pool 2 had a theoretical of 54:46, again in very close agreement to the calculated ratio. In some cases, side-reactions involved in the addition of monomers may complicate the spectra. Spectra 2C below shows the mass spectrum of a single bead from pool 1. The most intense ion in the spectrum is at m/z 586. However, the calculated M_0H^+:M_2H^+ ratio (65:35) does no agree with known ration for the compound in pool 1 with M_0H^+ of 586. This apparent discrepancy is due to the addition of the third monomer for pool 1, a

nitrile. It is known that under acidic conditions (cleavage conditions) nitriles can be hydrated to an amide. With the addition of water, the peaks for the M_0H^+ ion at 586 shift to 586 (M_0H^++18). Thus, the M_0H^+:M_2H^+ ratio for the peaks at 586 and 588 verifies the encode for the ion at 568 (which has its own, weaker set of peaks having the same ratio.). The known ration for the compound in pool 1 with a M_0H^+ ion of 568 is 63:37, which corresponds to the calculated value. This particular hydration reaction was observed for all compounds in pool 1. This example demonstrates the ability to decode compounds and determine side reactions, a powerful enhancement over other encoding methodologies which would be very useful during solid phase chemistry development.

Example 27-Pseudo-Code Program Listing for Computer-Assisted Detection of Isotope Encoded Compounds in a Mass Spectrum

1. Input the molecular formula and isotope ratios of an encoded compound.

2. Calculate the monoisotopic molecular weight from step 1.

3. Calculate the theoretical isotope distribution from step 1.

4. Open the mass spectrum output file.

5. Locate the monoisotopic molecular weight in the mass spectrum output file to within +/- 0.3 amu and check for corresponding isotope peaks.

6. If step 5 was successful compare the theoretical distribution from step 3 with the measured values in the mass spectrum using a Chi-Square test. The outcome of the Chi-Square determines the presence or absence of the encoded compound.

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This invention is executable on a MacIntosh computer or a IBM-PC compatible computer, running the Windows 95, Windows NT or Macintosh OS operating system, which includes a CPU, main storage, I/O resources, and a user interface including a manually operated keyboard and mouse.

While the invention has been described and illustrated with reference to certain alternative embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow, and that such claims be interpreted as broadly as possible.

CLAIMS

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What is claimed is:

1. A mass-based, non-chemical method for recording the reaction of at least a portion of a reaction series on each of a plurality of unique solid supports, said method comprising:

(a) preparing a plurality of agents each having a unique defined mass;

(b) preparing a group of solid supports;

(c) reacting each solid support group with a different chemical reagent under a controlled reaction condition;

(d) mixing the product groups of step (c) together and then dividing said mixture of unique solid supports into a plurality of groups for a second intermediate or final stage;

(e) repeating said reacting with a chemical reagent under a controlled reaction condition at least once to provide a plurality of final products, having different products on the different individual unique solid supports;

each of said unique defined mass agents being reacted with either: each of a group of unique solid supports; each of a group of first chemical reagents in a reaction series; each of a group of second chemical reagents in a reaction series; or each of a group of subsequently added chemical reagents in a reaction series; such that each of said group of unique solid supports, group of first chemical reagents, group of second chemical reagents or group of subsequent chemical reagents has been reacted with an agent

having a defined mass that is different from any other defined mass agent reacted with any other of said groups;

said unique defined mass agents being capable of being analyzed and wherein said analysis defines the choice of a first chemical reagent, reaction condition under which said first chemical reagent was added, second chemical reagent, reaction condition under which said second chemical reagent was added, subsequent chemical reagent, or reaction condition under which said subsequent chemical reagent was added.

2. A mass-based, non-chemical method for recording the reaction history of a reaction series on each of a plurality of unique solid supports, said method comprising:

(a) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports;

(b) reacting each solid support group having a different defined mass agent with a different chemical reagent;

(c) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage;

(d) repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports;

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said unique defined mass agents being capable of being analyzed and wherein said analysis defines the choice of a first chemical reagent.

3. The method as claimed in claim 1, wherein said defined mass agents are analyzed by mass spectroscopy.

4. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique single mass peak when analyzed by mass spectroscopy.

5. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique double mass peak when analyzed by mass spectroscopy.

6. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique pair of single mass peaks when analyzed by mass spectroscopy.

7. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique pair of double mass peaks when analyzed by mass spectroscopy.

8. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique pattern of one or more mass peaks.

9. The method as claimed in claim 8, wherein said unique peak patterns for each of said defined mass agents can be expressed as a machine-readable pattern.

10. The method as claimed in claim 9, wherein said machine readable patterns are bar codes.

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11. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each independantly generate a unique mass spectrometry mass peak pattern selected from the group consisting of unique single mass peaks, unique double mass peaks, unique pairs of single mass peaks, unique pairs of double mass peaks, and unique peak patterns that are capable of being expressed as machine-readable patterns.

12. The method as claimed in claim 1, wherein said defined mass agent is analyzed by nuclear magnetic resonance spectroscopy.

13. The method as claimed in claim 12, wherein said defined mass agents are selected so as to each generate a unique pattern of one or more nuclear magnetic resonance peaks.

14. The method as claimed in claim 13, wherein said unique peak patterns for each of said defined mass agents can be expressed as a machine-readable pattern.

15. The method as claimed in claim 14, wherein said machine readable patterns are bar codes.

16. The method as claimed in claim 1, wherein said defined mass agent is analyzed by infrared spectroscopy or by Raman spectroscopy.

17. The method as claimed in claim 16, wherein said defined mass agents are selected so as to each generate a unique pattern of one or more infrared spectroscopy or Raman spectroscopy peaks.

18. The method as claimed in claim 17, wherein said unique peak patterns for each of said defined mass agents can be expressed as a machine-readable pattern.

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19. The method as claimed in claim 18, wherein said machine readable patterns are bar codes.

20. The method as claimed in claim 1, wherein said first, second or subsequent reagent is a substrate for the determination of binding specificity to a chemical compound of interest.

21. The method as claimed in claim 3, wherein said mass spectroscopy analysis provides mass peaks capable of being recognized as representing encoded reagents.

22. The method as claimed in claim 1, wherein additional mass peaks are generated that serve as signature peaks for positive identification of relevant mass peaks.

23. The method as claimed in claim 1, wherein said plurality of defined mass agents are molecular entities that differ from one another by having at least one of their atoms substituted by a different isotope of that atom, provided that the chemical structural formula of said defined mass agents is the same.

24. The method as claimed in claim 23, wherein said plurality of defined mass agents are molecular entities that differ from one another by having at least one isotopic substitution at different atomic positions within the molecule provided that the chemical structural formula of said defined mass agents is the same.

25. The method as claimed in claim 1, wherein said plurality of defined mass agents are regularly repeating molecular entities that differ from one another by an integral number of said repeating molecular entities.

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26. The method as claimed in claim 1, whrein at least two groups of said unique solid supposts are employed in each said reacting.

27. The method as claimed in claim 1, comprising the additional step of screening said final products on said unique solid supports for a characteristic of interest and identifying the reaction history of at least one final product having said characteristic of interest.

28. The method as claimed in claim 1, comprising the additional step of cleaving said final products from said solid supports and screening said final products.

29. The method as claimed in claim 1, wherein said analysis is automated.

30. The method as claimed in claim 10, wherein said reaction steps are automated.

31. A kit for encoding the reaction history of a plurality of reaction series, comprising a plurality of different isotopically distinguishable organic compounds, each of the compounds characterized by having distinguishable masses but having the same chemical composition and the same chemical properties, each compound encoding at least one bit of different physical information which can be determined by a physical measurement.

32. A kit as claimed in claim 31, wherein said compounds are mixed with one another in a plurality of discrete ratios to produce a plurality of isotope mixtures that are physically distinguishable from each other.

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33. A kit as claimed in claim 32, wherein said compounds are mixed with one another in a series of regularly repeating increasing increments.

34. A kit as claimed in claim 31, wherein said compounds are of the formula:

R-C

where R is a suitable solid support which allows for attachment and detachment of a molecular moiety of choice; and C is an isotopically doped linker which allows for attachment and detachment from said solid supprt.

35. A kit as claimed in claim 31, wherein said compounds are of the formula:

L^1-C-L^2

where L^1 is a covalent bond or an organic moiety; C is an isotopically doped linker; and L^2 is a covalent bond or an organic moiety.

36. A kit as claimed in claim 35, wherein L^1 and L^2 are the same.

37. A kit as claimed in claim 31, wherein said compounds are of the formula

R-L^1-C-L^2

where R is a suitable solid support which allows for attachment and detachment of a molecular moiety of choice; L^1 is a covalent

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bond or an organic moiety; C is an isotopically doped linker; and L^2 is a covalent bond or an organic moiety.

38. A kit as claimed in claim 31, wherein said compounds are of the formula

$(L)_{n1}$-$(C)_{n2}$

where n1 is an integer of from one to ten, n2 is an integer of from one to ten, L an organic moiety or a covalent bond when n1 is one, and C is an isotopically doped linker.

39. A kit as claimed in claim 31, wherein said compounds are of the formula

R-L-C

where R is a suitable solid support which allows for attachment and detachment of a plurality of molecular moiety of choice; L is a covalent bond or an organic moiety; and C is an isotopically doped linker.

40. A kit as claimed in claim 31, wherein said compounds are of the formula

L-C^1-A-B-D-C^2

L is a covalent bond or an organic moiety; C^1 is an isotopically doped linker; A is a first monomer in a reaction series, B is a second monomer in a reaction series, and D is a third monomer in a reaction series; and C^2 is a second isotopically doped linker that can physically be the same as or different from C^1.

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41. A kit as claimed in claim 31, wherein said compounds are of the formula

$L\text{-}C^1\text{-}A\text{-}B\text{-}C^2$

L is a covalent bond or an organic moiety; C^1 is an isotopically doped linker; A is a first monomer in a reaction series, B is a second monomer in a reaction series; and C^2 is a second isotopically doped linker that can physically be the same as or different from C^1.

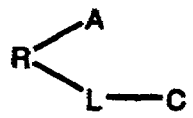
42. A kit as claimed in claim 31, wherein said compounds are of the formula

$L\text{-}C^1\text{-}A\text{-}C^2$

L is a covalent bond or an organic moiety; C^1 is an isotopically doped linker; A is a first monomer in a reaction series; and C^2 is a second isotopically doped linker that can physically be the same as or different from C^1.

43. A kit as claimed in claim 31, wherin said componsnts are isotopically doped suitable solid supports.

44. A kit as claimed in claim 31, wherein said components are of the formula

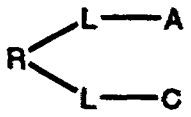


where R is a suitable solid support; L is a covalent bond or an organic moiety; C is an isotopically doped moiety; and A is a first chemical reagent in a reaction series.

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45. A kit as claimed in claim 31, where said components are of the formula



where R is a suitable solid support; L is a covalent bond or an organic moiety; C is an isotopically doped moiety; and A is a first chemical reagent in a reaction series.

46. A solid support characterized by having a unique defined mass agent and a ligand bound to the surface of said solid support.

47. A solid support characterized by having up to 20 discrete unique defined mass agents bound to the surface of said solid support.

48. A solid support as claimed in claim 46, wherein said ligand is an organic moiety.

49. A solid support as claimed in claim 46, wherein said ligand is bound to said unique defined mass agent.

50. A solid supoport as claimed in claim 46, wherein said ligand is a non-oligomer which is aliphatic, alicyclic, aromatic, heterocyclic or a combination therof.

51. A solid support as claimed in claim 46, wherein said ligand is an oligomer which is an oligopeptide, oligonucleotide, oligosaccharide, polylipid, polyester, polyamide, polyurethane, polyurea, polyether, polyphosphorus where phosphorus is a derivative taken from the group consisting of phosphate, phosphonate, phosphoramide, phosphonamide, phosphite, or phosfinamide, or polysulfur where sulfur is a derivative taken

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from the group consisting of sulfone, sulfonate, sulfite, sulfinamide, or sulfenamide.

52. A solid support as claimed in claim 46, wherein said support is a resin bead of about 1 to 10000 μm in diameter.

53. A solid support as claimed in claim 46, wherein said support is a polystyrene resin bead of about 1 to 10000 μm in diameter.

54. A solid support characterized by being isotopically doped.

55. A solid support as claimed in claim 54, wherein said support is an isotopically doped resin bead.

56. A solid support as claimed in claim 55, wherein said support is an isotopically doped polystyrene resin bead of about 10 to 2000 μm in diameter.

57. A library comprising a plurality of solid supports as claimed in claim 46.

58. A library comprising a plurality of solid supports as claimed in claim 46, wherein said final products have been cleaved from said solid supports.

59. A process for identifying compounds having a characteristic of interest, which comprises screening a library as claimed in claim 57.

60. A process as claimed in claim 59, wherein the compounds have been cleaved from the solid support.

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61. A process as claimed in claim 60, wherein said cleavage is between said solid support and said unique defined mass agent.

62. A mass-based, non-chemical method for generating machine or human-recognizable patterns to record the reaction history of a reaction series on each of a plurality of unique solid supports, said method comprising:

(a) generating a set of agents each having a unique defined mass such that each agent differs from any other agent in the set by having a defined mass that is different from any other agent in the set;

(b) generating a recognition pattern for each agent in said set;

(c) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports;

(d) reacting each solid support group having a different defined mass agent with a different first chemical reagent;

(e) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage;

(f) optionallly repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports;

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(g) analyzing said products for a characteristic of interest;

(h) further analyzing products found to have a characteristic of interest in step (g) by an analytical method that generates a like type of patterns as that type generated for the recognition patterns in step (b); and

(i) comparing the analytical patterns generated in step (h) to said recognition patterns.

63. A mass-based, non-chemical method for generating machine-recognizable patterns to record the reaction history of a reaction series on each of a plurality of unique solid supports, said method comprising:

(a) generating a set of agents each having a unique defined mass such that each agent differs from any other agent in the set by having a defined mass that is different from any other agent in the set;

(b) generating a machine-recognizable recognition pattern for each agent in said set;

(c) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports;

(d) reacting each solid support group having a different defined mass agent with a different first chemical reagent;

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(e) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage;

(f) optionallly repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports;

(g) analyzing said products for a characteristic of interest through the use of an analysis device;

(h) further analyzing products found to have a characteristic of interest in step (g) by an analytical method that generates a like type of patterns as that type generated for the recognition patterns in step (b); and

(i) comparing the analytical patterns generated in step (h) to said recognition patterns such that said unique defined mass agents are capable of being analyzed and identified.

64. The method as claimed in claim 63, wherein said identification in step (i) leads to the ready identification of said first chemical reagent.

65. The method as claimed in claim 63, wherein said method steps are executed by suitable automation apparatus means and under the control of a suitable computer means.

66. The method as claimed in claim 63, wherein said analysis device is selected from the group consisting of a flourescence activation cell scanner, a chromatography column or a chromatography plate.

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67. The method as claimed in claim 63, wherein said analytical method is selected from the group consisting of mass spectrometry, nuclear magnetic resonance spectroscopy, infrared spectroscopy or Raman spectroscopy.

68. The method as claimed in claim 63 wherein said analysis device is close coupled to said automation apparatus used in the method so as to be automated and under the control of a computer.

69. The method as claimed in claim 63, wherein said analytical method is executed by a corresponding device that is close coupled to said automation apparatus used in the method so as to be automated and under the control of a computer.

70. A database readily retrievable from a suitable data storage means comprised of the set of machine-readable patterns generated by the method as claimed in claim 63.

71. A mass-based, non-chemical method for generating machine or human-recognizable patterns to record the reaction history of a reaction sequence of interest selected from a reaction series on each of a plurality of unique solid supports, said method comprising:

(a) generating a set of agents each having a unique defined mass such that each agent differs from any other agent in the set by having a defined mass that is different from any other agent in the set;

(b) generating a recognition pattern for each agent in said set;

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(c) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports;

(d) reacting each solid support group having a different defined mass agent with a different first chemical reagent;

(e) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage;

(f) optionallly repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports;

(g) analyzing said products for a characteristic of interest;

(h) further analyzing products found to have a characteristic of interest in step (g) by an analytical method that generates a like type of patterns as that type generated for the recognition patterns in step (b);

(i) comparing the analytical patterns generated in step (h) to said recognition patterns;

(j) evaluating said analytical patterns to arrive at a qualitative and quantitative assessment of the output of a reaction sequence of interest, thereby identifying all products, quantities

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and yields of each of incomplete reactions, side reactions and previously unknown reactions in said sequence of interest.

72. A mass-based, non-chemical method for recording the reaction history of a reaction series in solution, said method comprising:

(a) preparing, a plurality of agents each having a unique defined mass within each of a group of solution reaction wells, such that each of said group of reaction wells contains an agent having a defined mass that is different from any other agent within any other of said reaction wells;

(b) reacting each different defined mass agent with a different first chemical reagent in each well;

(c) mixing said groups together in to a resulting batch and then dividing said batch into a plurality of wells for a second intermediate or final stage;

(d) repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products within said wells;

said unique defined mass agents being capable of being analyzed and wherein said analysis defines the choice of said first chemical reagent.

73. A programmed computer system for executing a mass-based method for recording the reaction history of at least a portion of a reaction series of interest on each of a plurality of solid supports or in each or a plurality of reaction vessels, wherein one or more chemical reagents or chemical conditions are discretely identifiable by one or more recognition patterns

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and wherein said reaction series' chemical products are subjected to analytical means that generate analytical patterns for each of said products; comprising:

first input means for introducing unique recognition patterns into the computer system, each pattern representing one of a plurality of agents each having a unique defined mass;

memory means for storing said recognition pattern;

second input means for introducing said resultant analytical patterns; and

means for comparing said resulting analytical patterns to said recognition patterns in order to generate an output which is the identity of one or more of said chemical reagents or chemical conditions.

74. The programmed computer system as claimed in claim 73, additionally comprising means for controlling a robot means for performing one or more steps of said reaction series of interest.

75. The programmed computer system as claimed in claim 73, additionally comprising means for generating said unique recognition patterns.

76. The programmed computer system as claimed in claim 73, additionally comprising means for subjecting said reaction products to analytical means and generating analytical patterns.

77. A mass-based, non-chemical method for identifying different chemical compounds in a mixture of said chemical compounds, said method comprising:

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(a) preparing a plurality of chemical agents each having a unique defined mass;

(b) preparing a group of chemical compounds to be identified;

each of said unique defined mass agents being chemically linked or reacted with each of said chemical compounds to be identified to form a plurality of unique covalently bound one-to-one pairs of unique defined mass agents with compounds to be identified;

said unique defined mass agents being capable of being analyzed on the basis of its mass, and wherein said analysis thus identifies the chemical compound reacted with said analyzed mass agent.

78. A mass-based, non-chemical method for identifying a chemical compound, said method comprising:

(a) preparing a chemical agent having a unique defined mass;

(b) preparing a chemical compound to be identified;

said unique defined mass agent being chemically linked or reacted with said chemical compound to be identified to form a unique covalently bound one-to-one pairing of unique defined mass agent with compound to be identified;

said unique defined mass agent being capable of being analyzed on the basis of its mass, and wherein said analysis thus identifies the chemical compound reacted with said analyzed mass agent.

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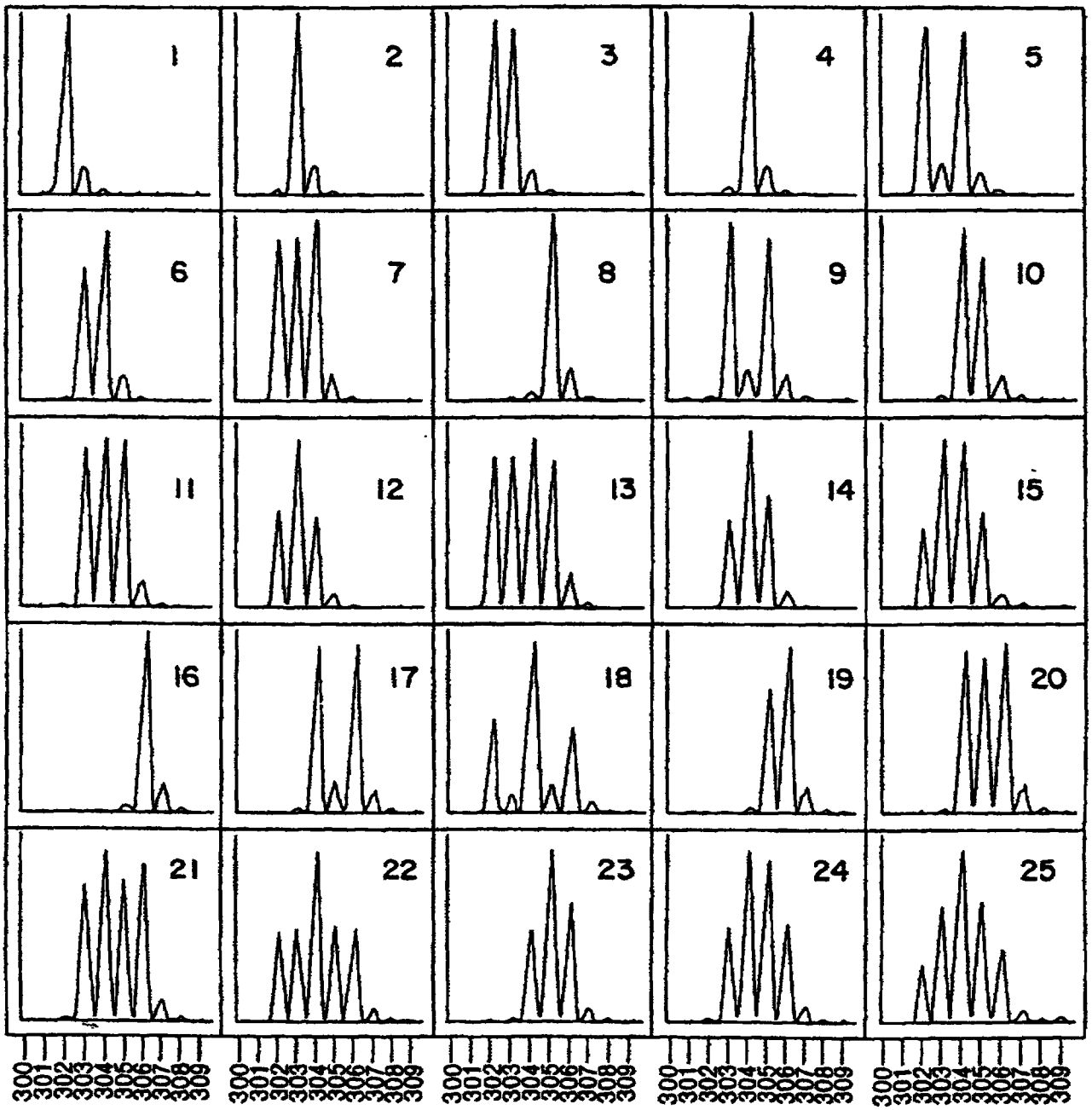


FIG 1

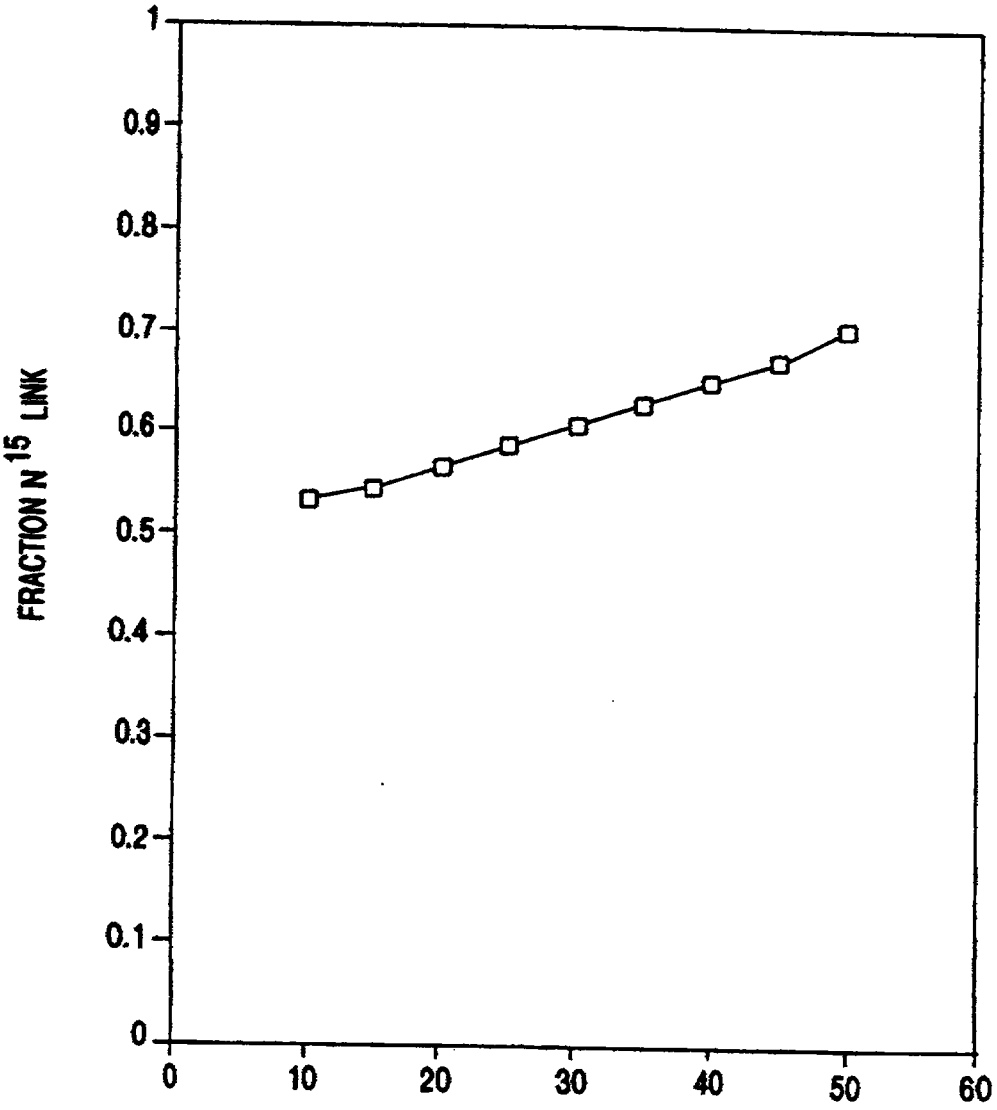


FIG. 2

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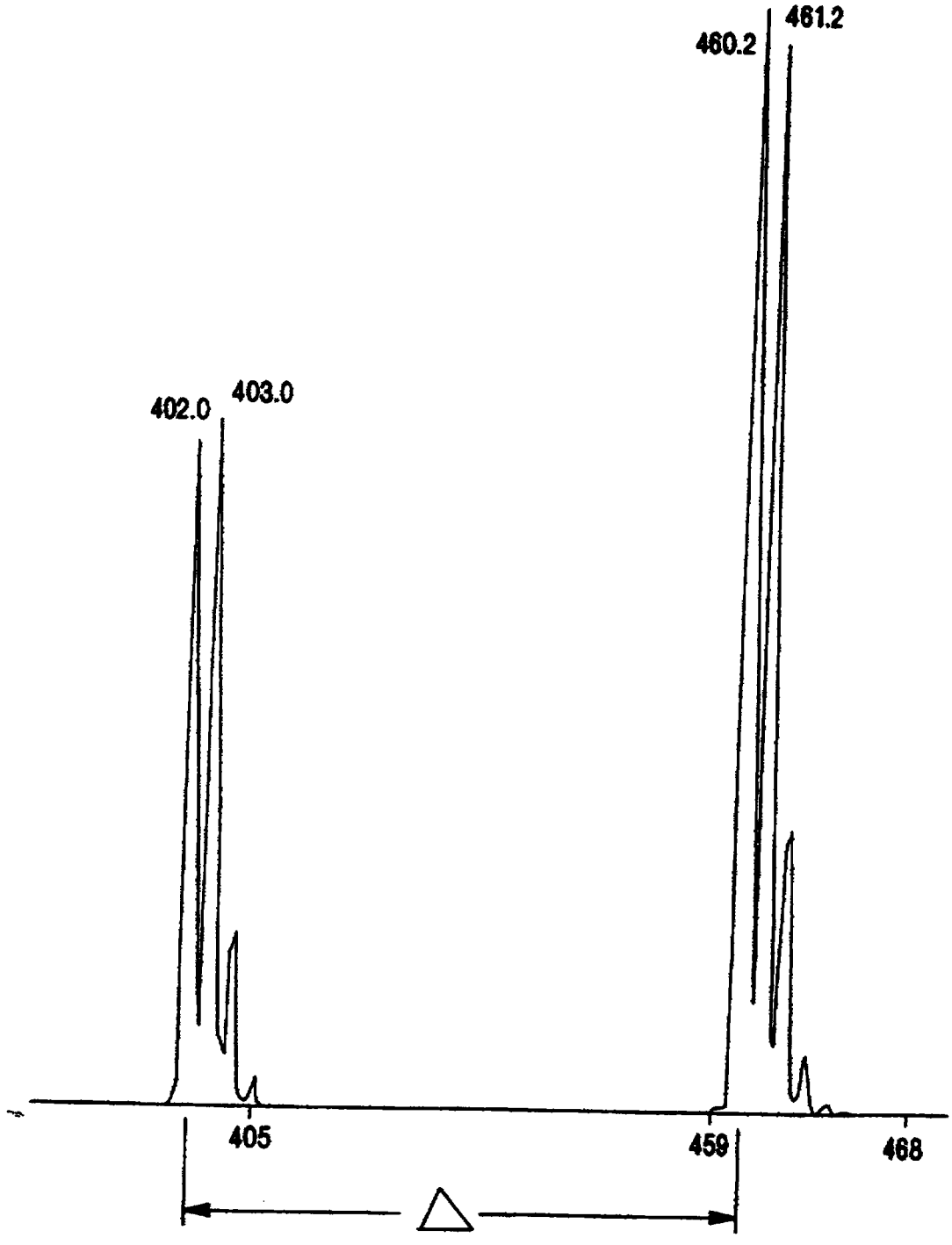


FIG. 3

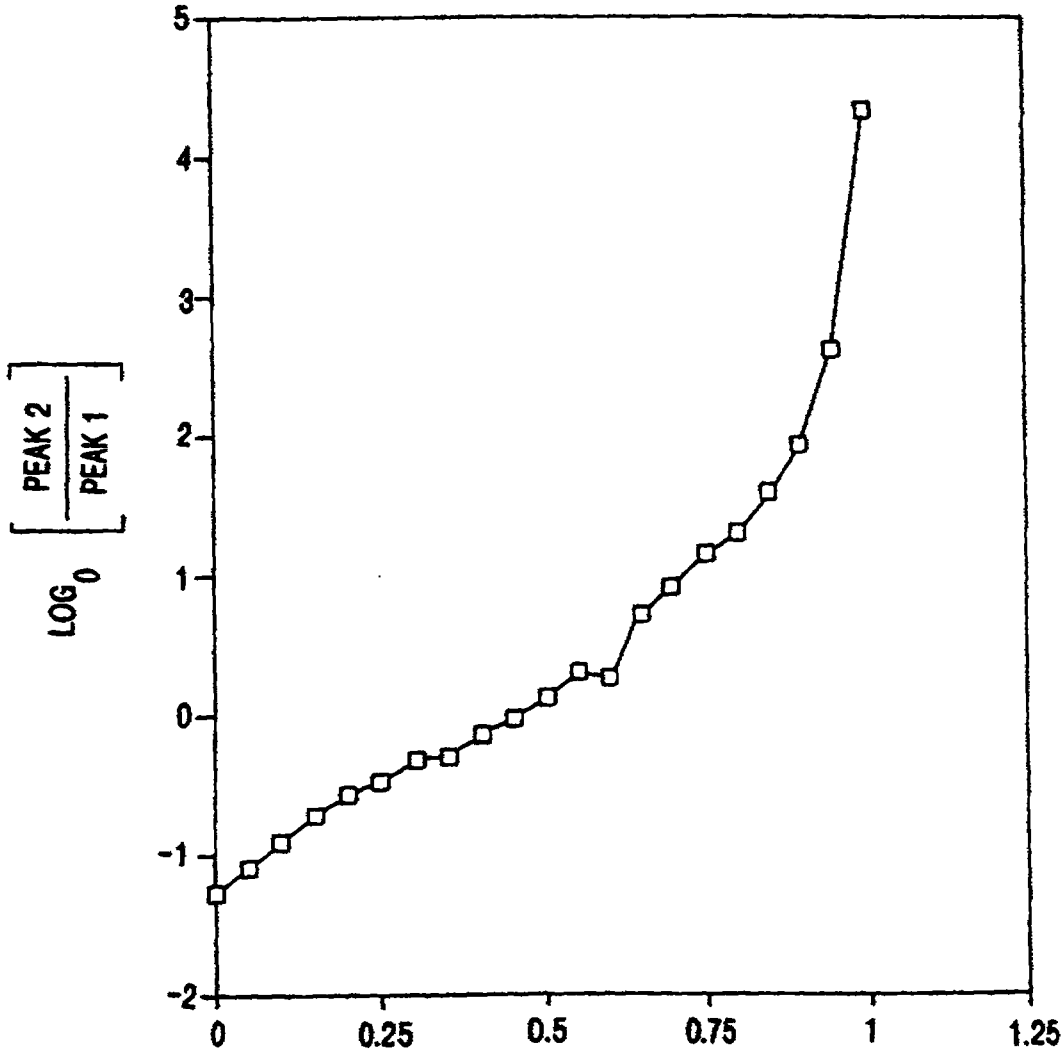


FIG. 4

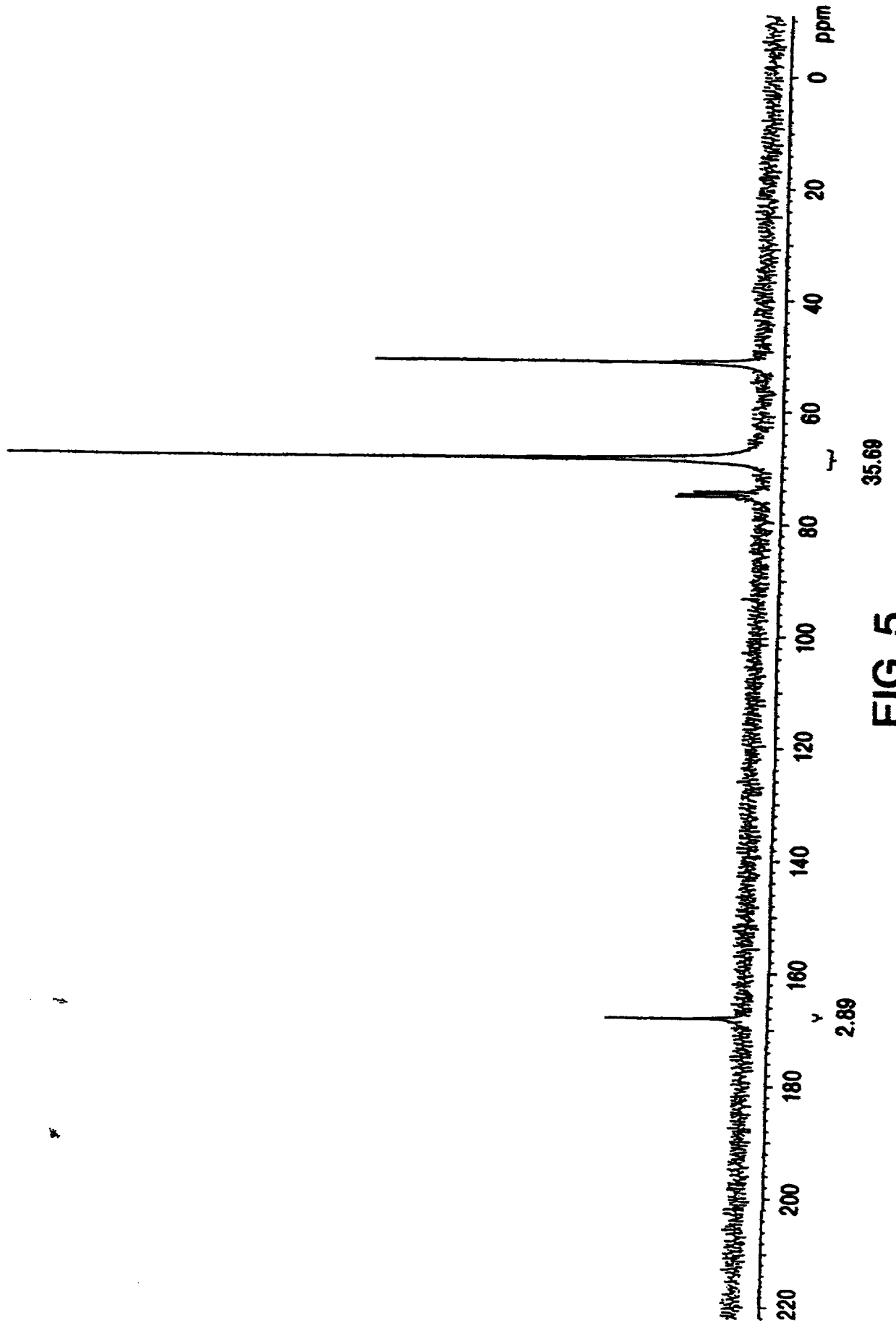


FIG. 5

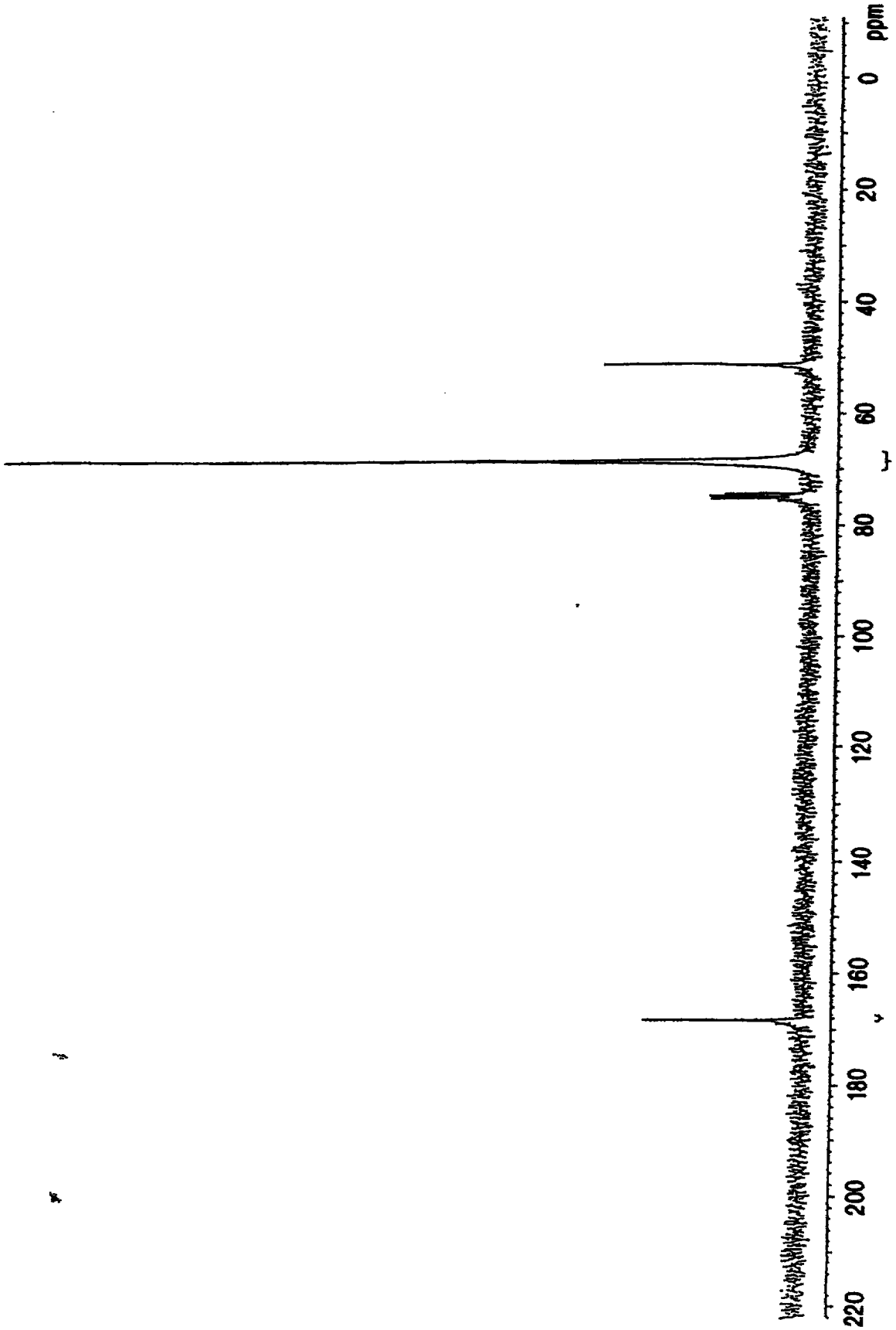


FIG. 6

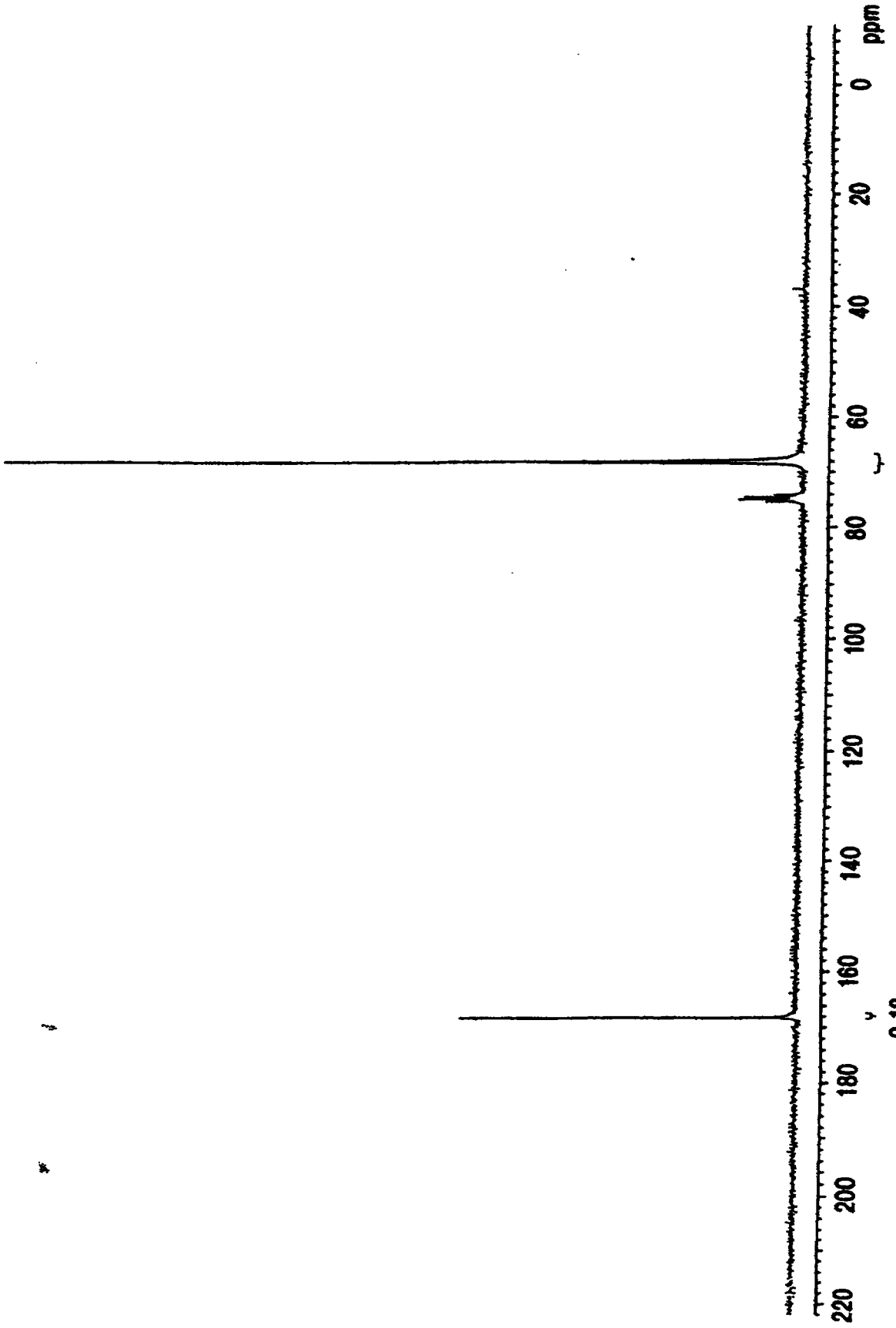


FIG. 7

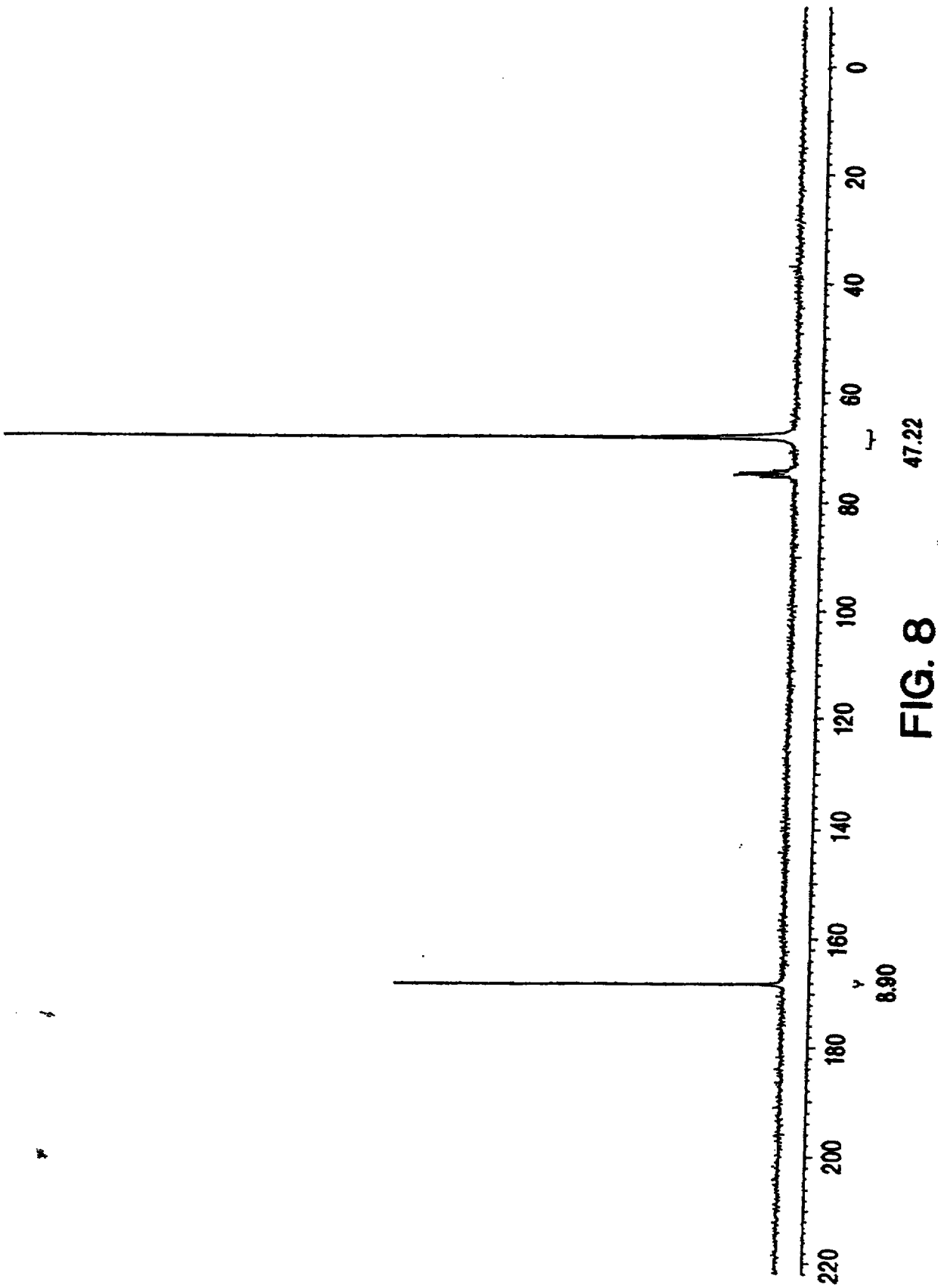


FIG. 8

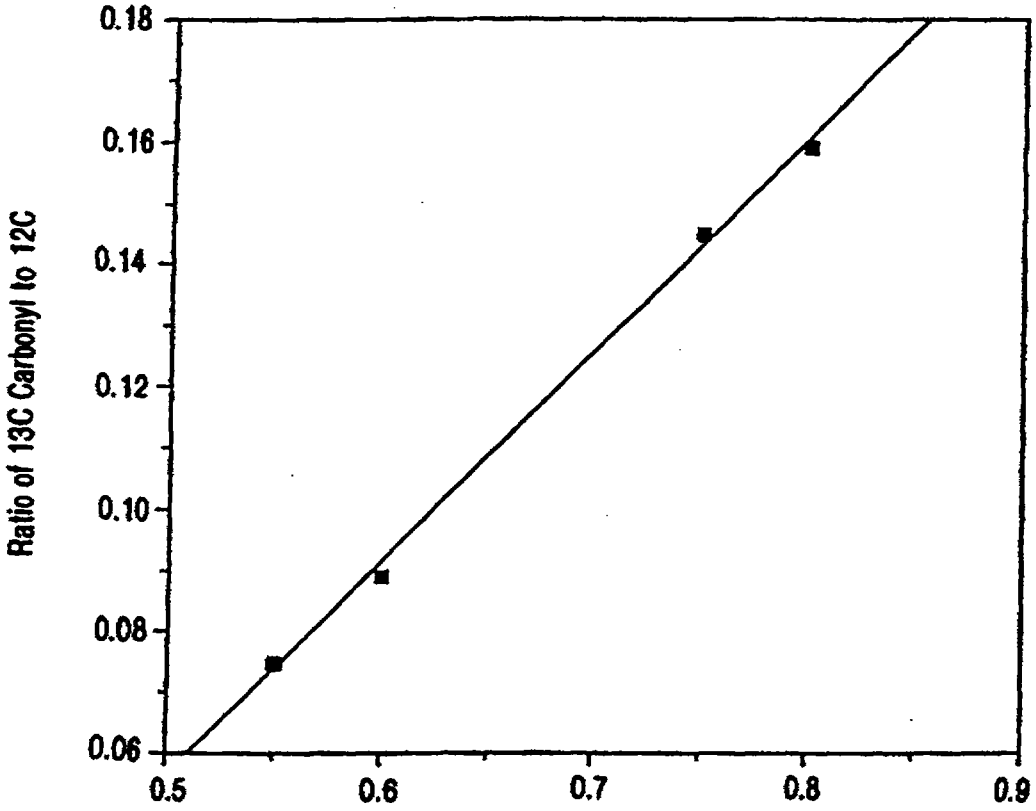

0.18
0.16
0.14
0.12
0.10
0.08
0.06
Ratio of 13C Carbonyl to 12C
0.5
0.6
0.7
0.8
0.9
% 13C Acetic Acid

FIG. 9

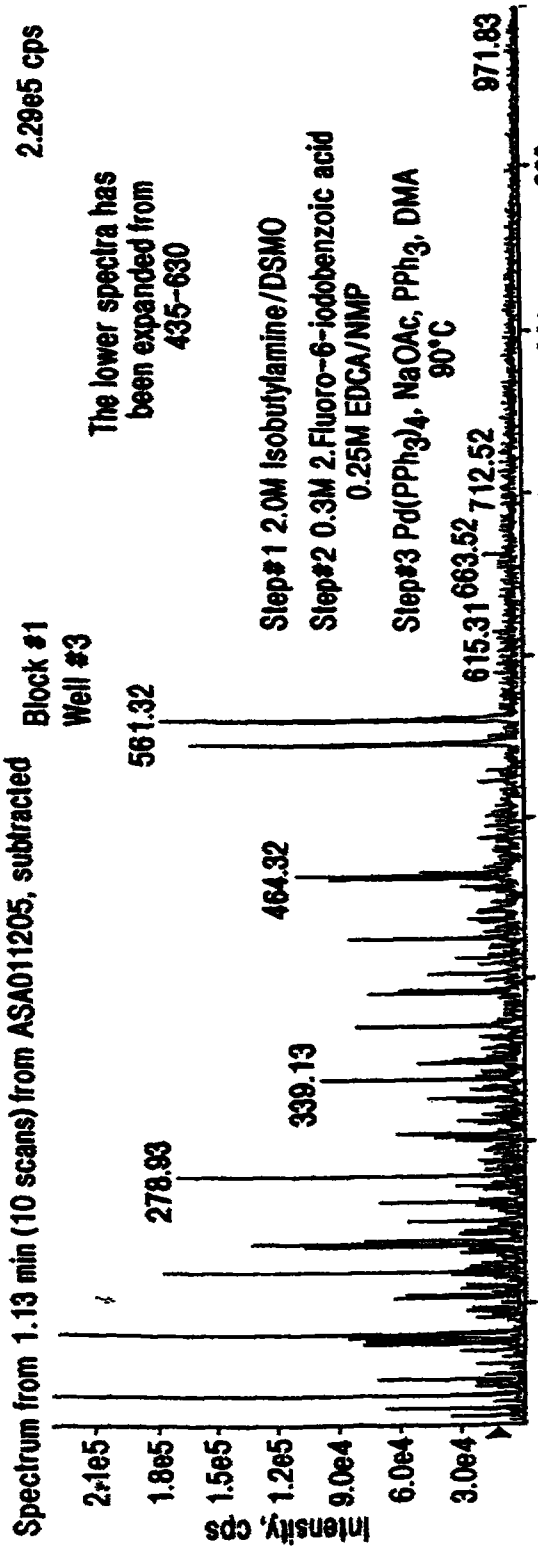


FIG. 10A

FIG. 10B

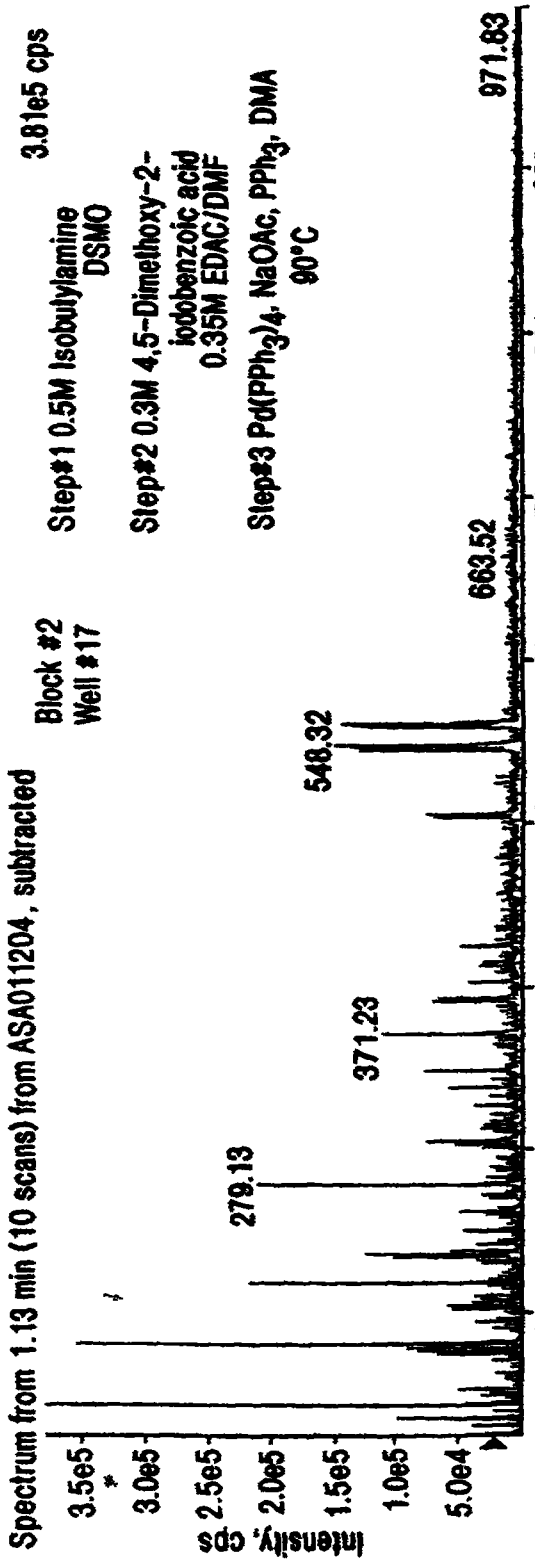


FIG. 11A

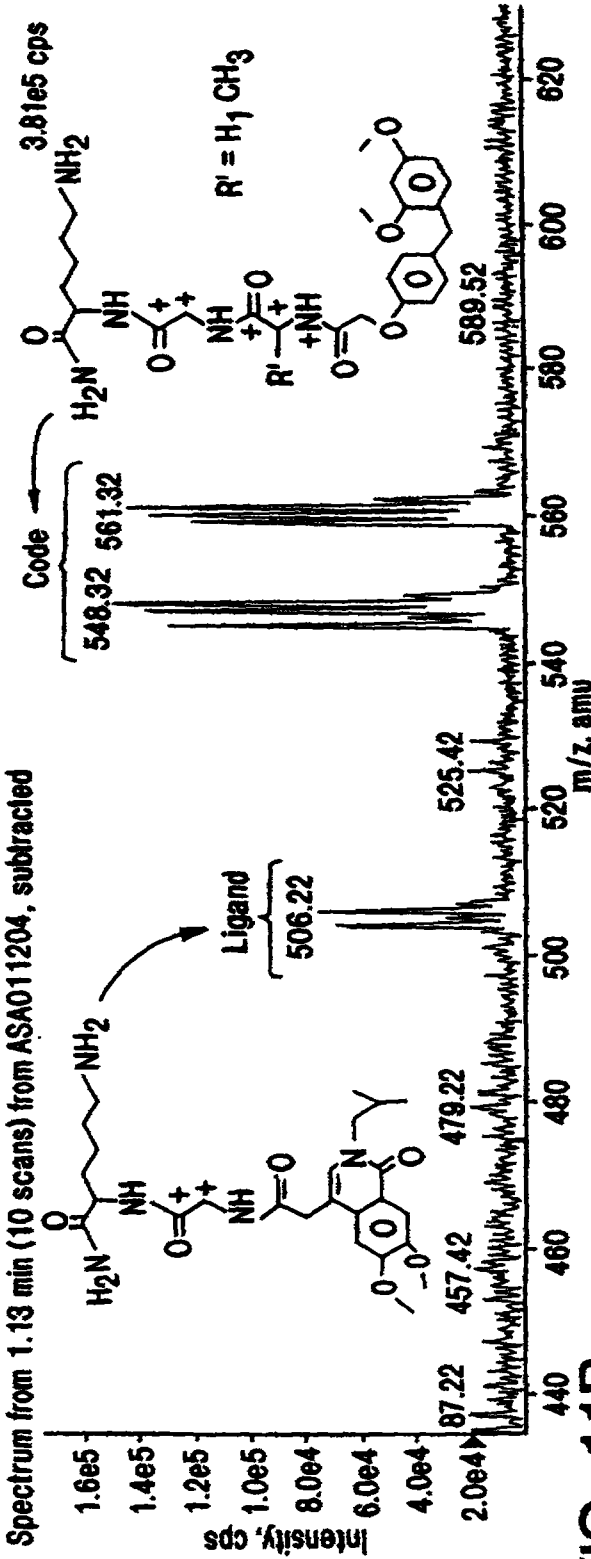


FIG. 11B

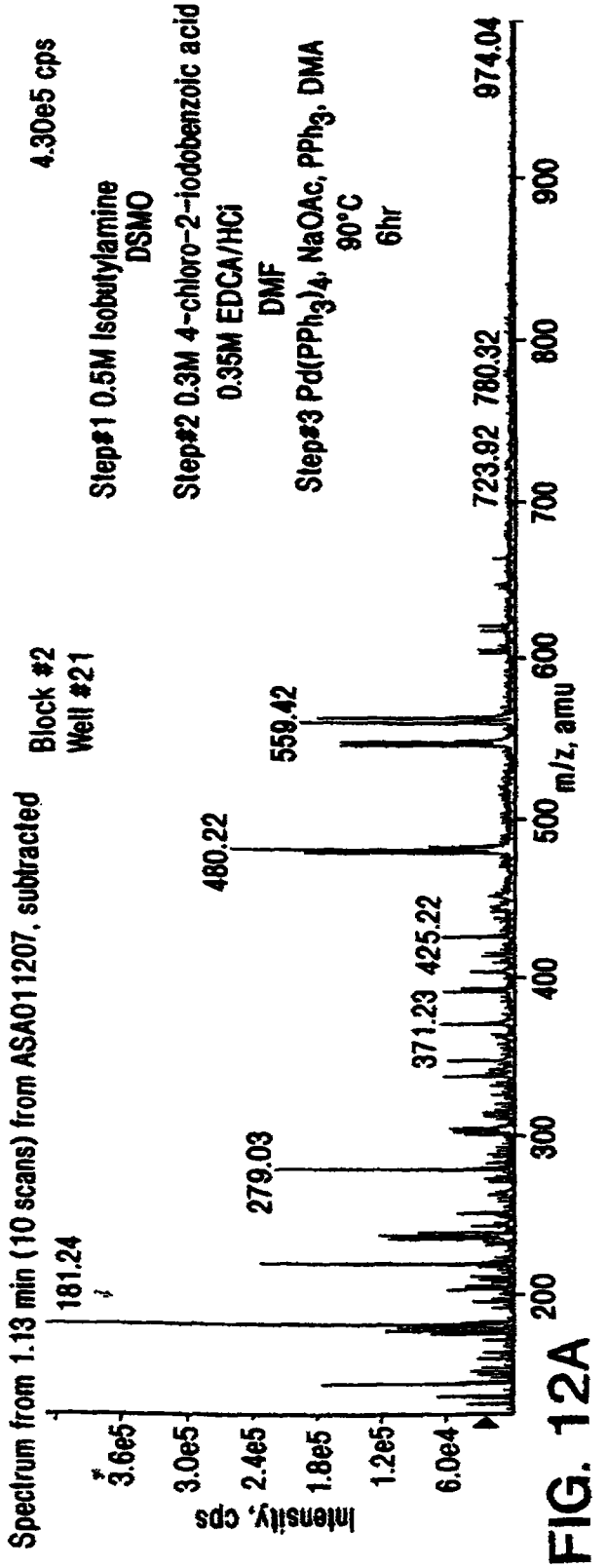


FIG. 12A

FIG. 12B

I. Systhesis of serially encoded tentagel resin.

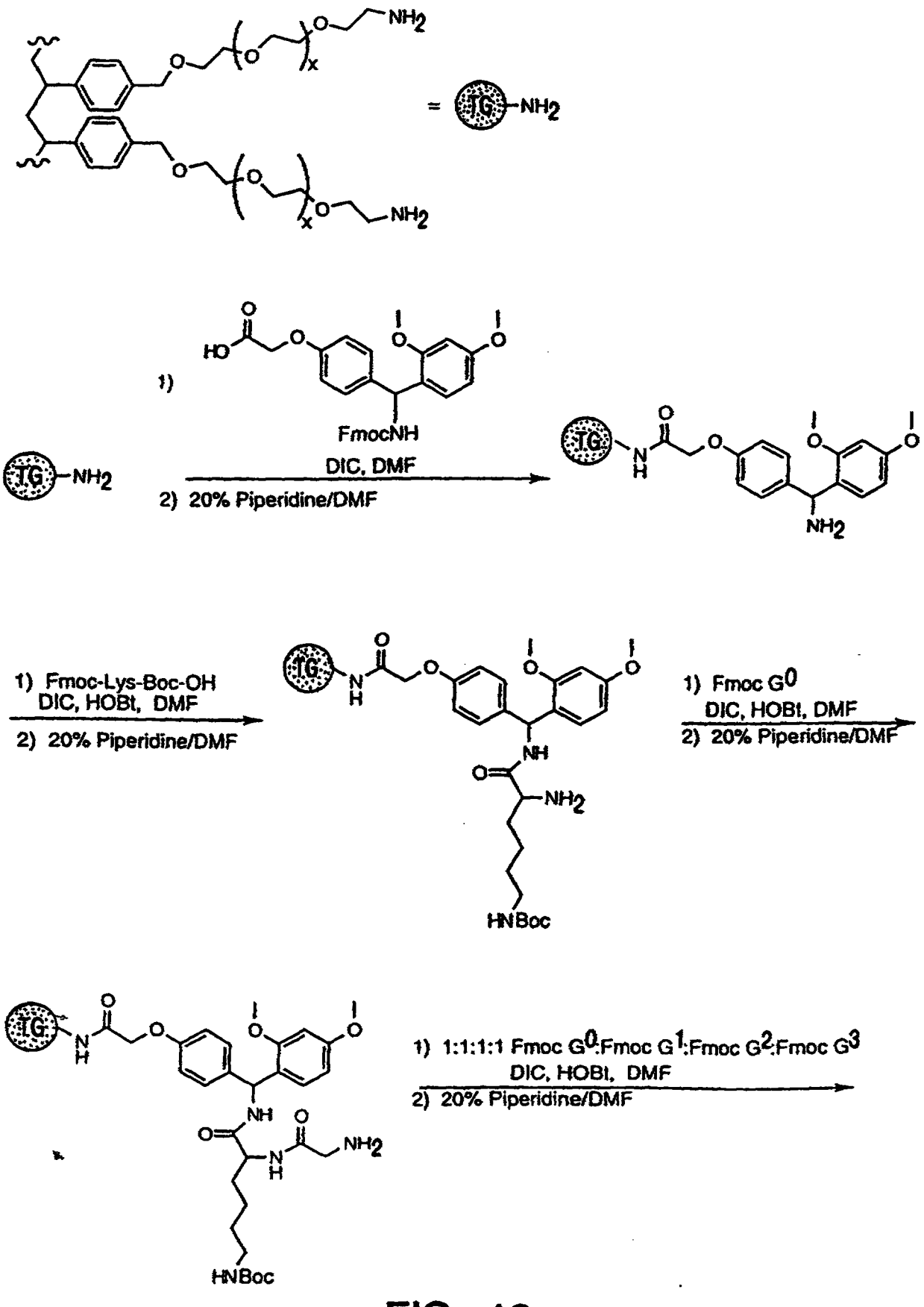


FIG. 13

1. Synthesis of serially encoded tentagel resin.

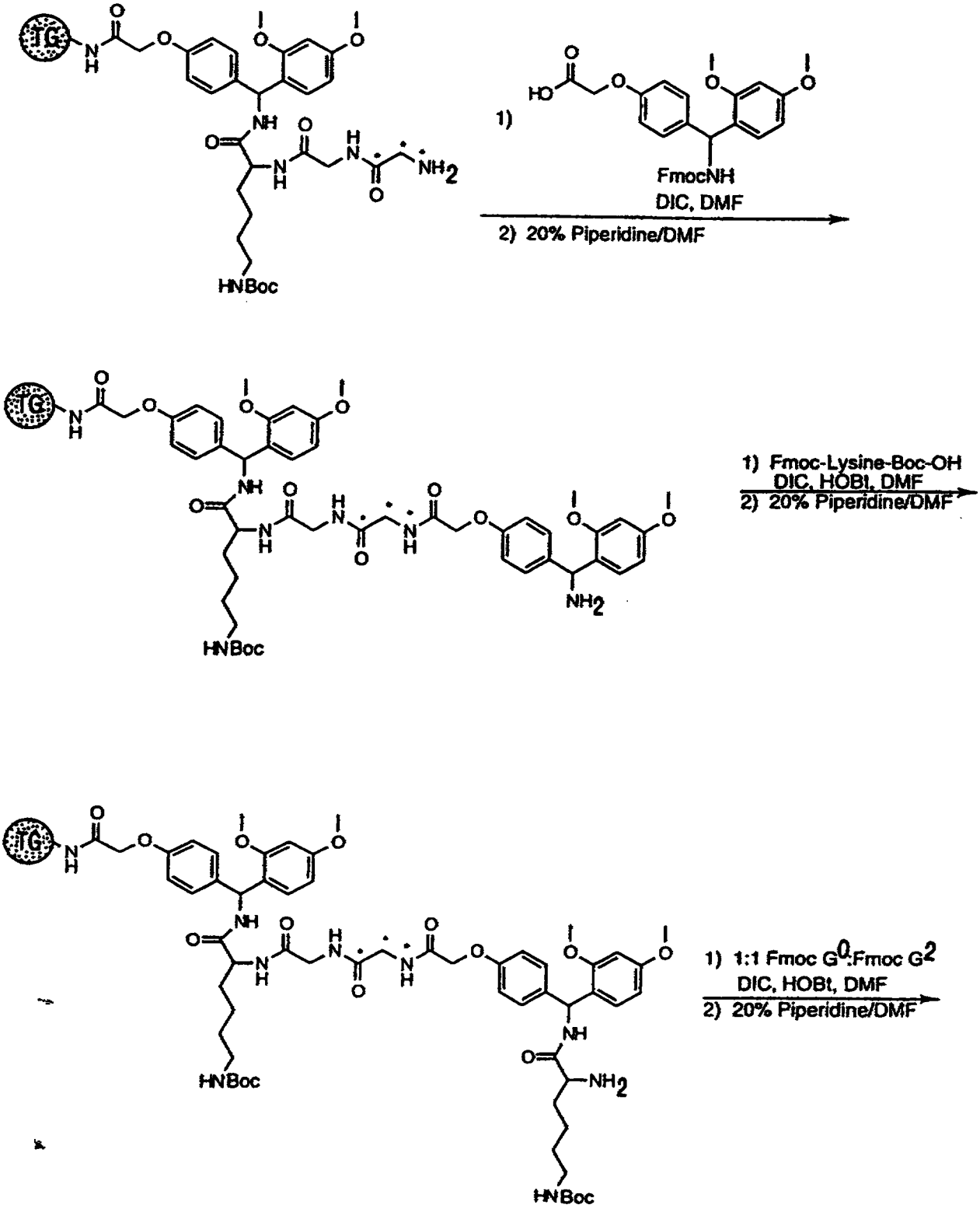


FIG. 14

II. Reaction Screening of 1(2H)-Isoquinolinones with serially encoded lentagel resin.

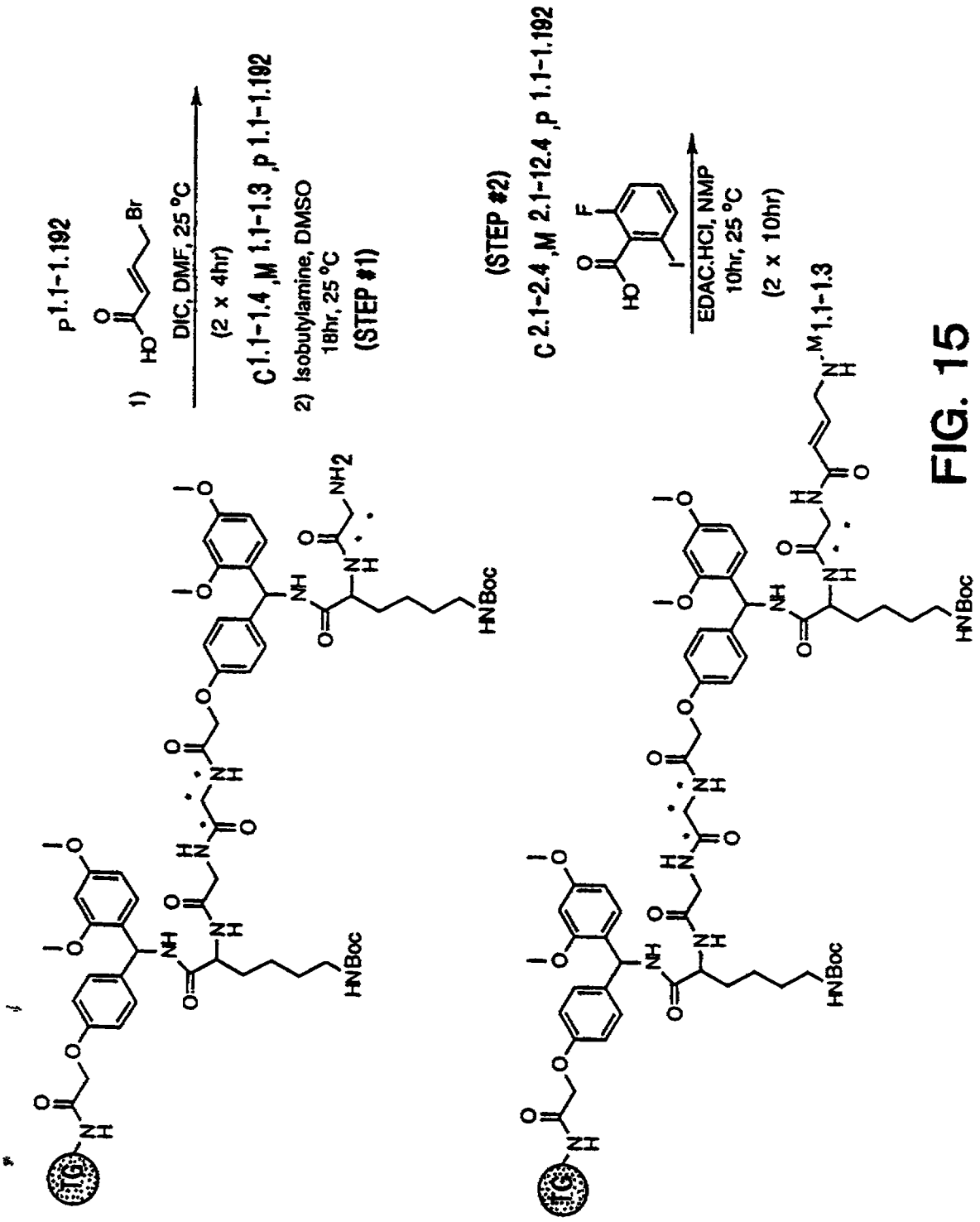


FIG. 15

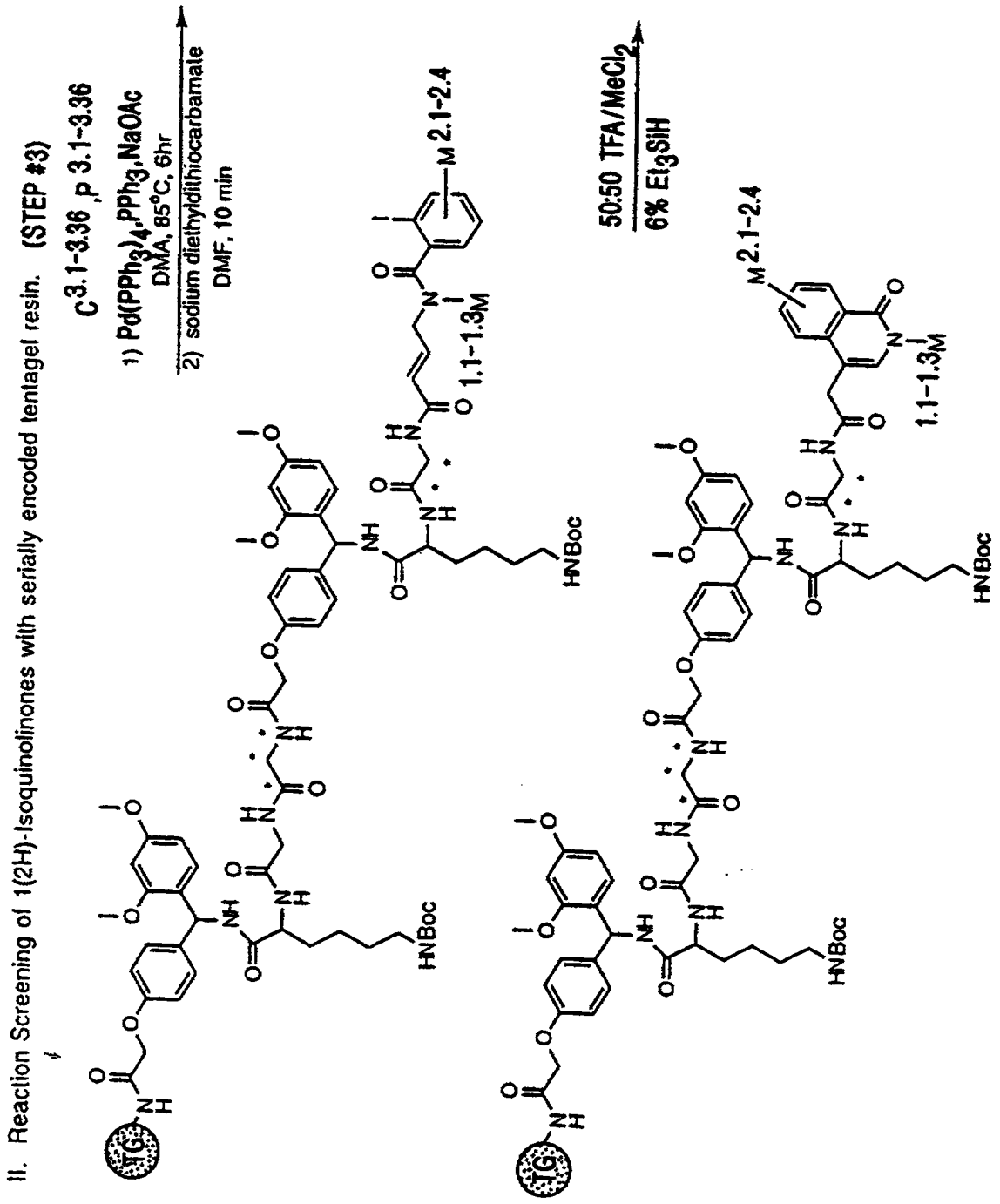
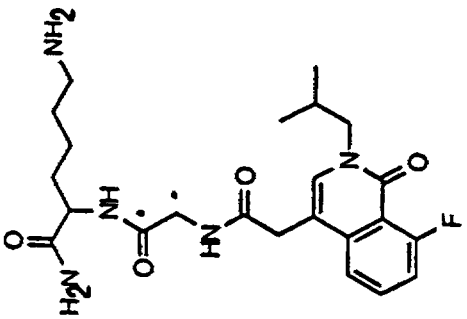

II. Reaction Screening of 1(2H)-Isoquinolinones with serially encoded lentagel resin. (STEP #3)
C 3.1-3.36 , p 3.1-3.36
1) Pd(PPh3)4,PPh3,NaOAc
DMA, 85°C, 6hr
2) sodium diethyldithiocarbamate
DMF, 10 min
M 2.1-2.4
1.1-1.3M
HNBoc
50:50 TFA/MeCl2
6% Et3SiH

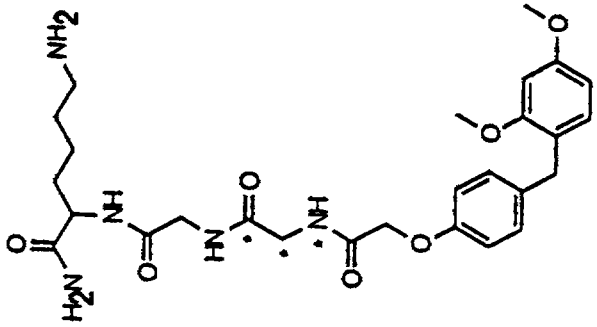
FIG. 16

II. Reaction Screening of 1(2H)-Isoquinolinones with serially encoded tentagel resin.



$C_{23}H_{32}FN_5O_4$
Exact Mass: 461.24
Mol. Wt.: 461.54
C, 59.86; H, 6.99; F, 4.12; N, 15.17; O, 13.87

+



$C_{27}H_{37}N_5O_7$
Exact Mass: 543.27
Mol. Wt.: 543.62
C, 59.66; H, 6.86; N, 12.88; O, 20.60

FIG. 17

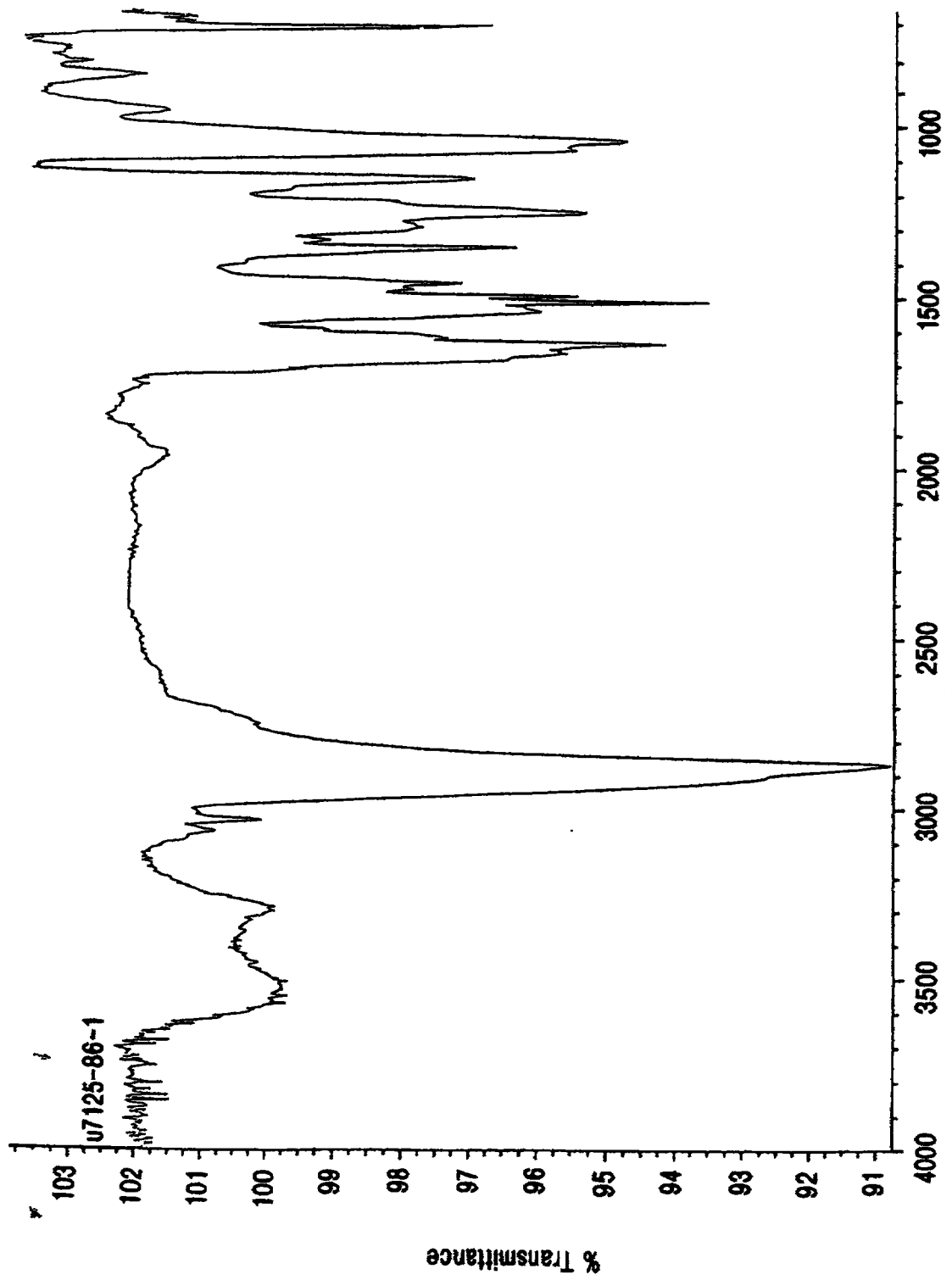

u7125-86-1
% Transmittance
103
102
101
100
99
98
97
96
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94
93
92
91
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 18

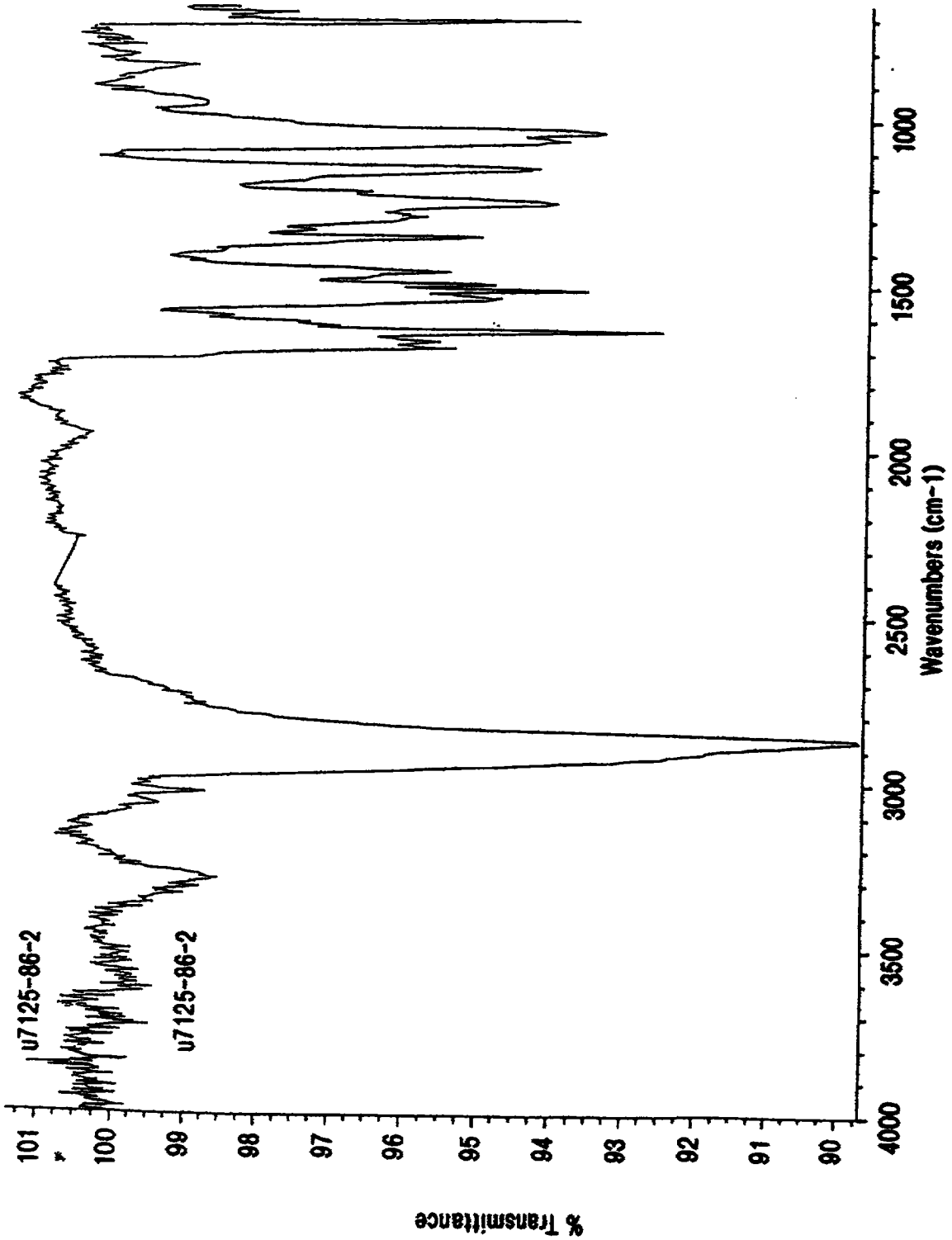

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91
90
% Transmittance
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2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 19

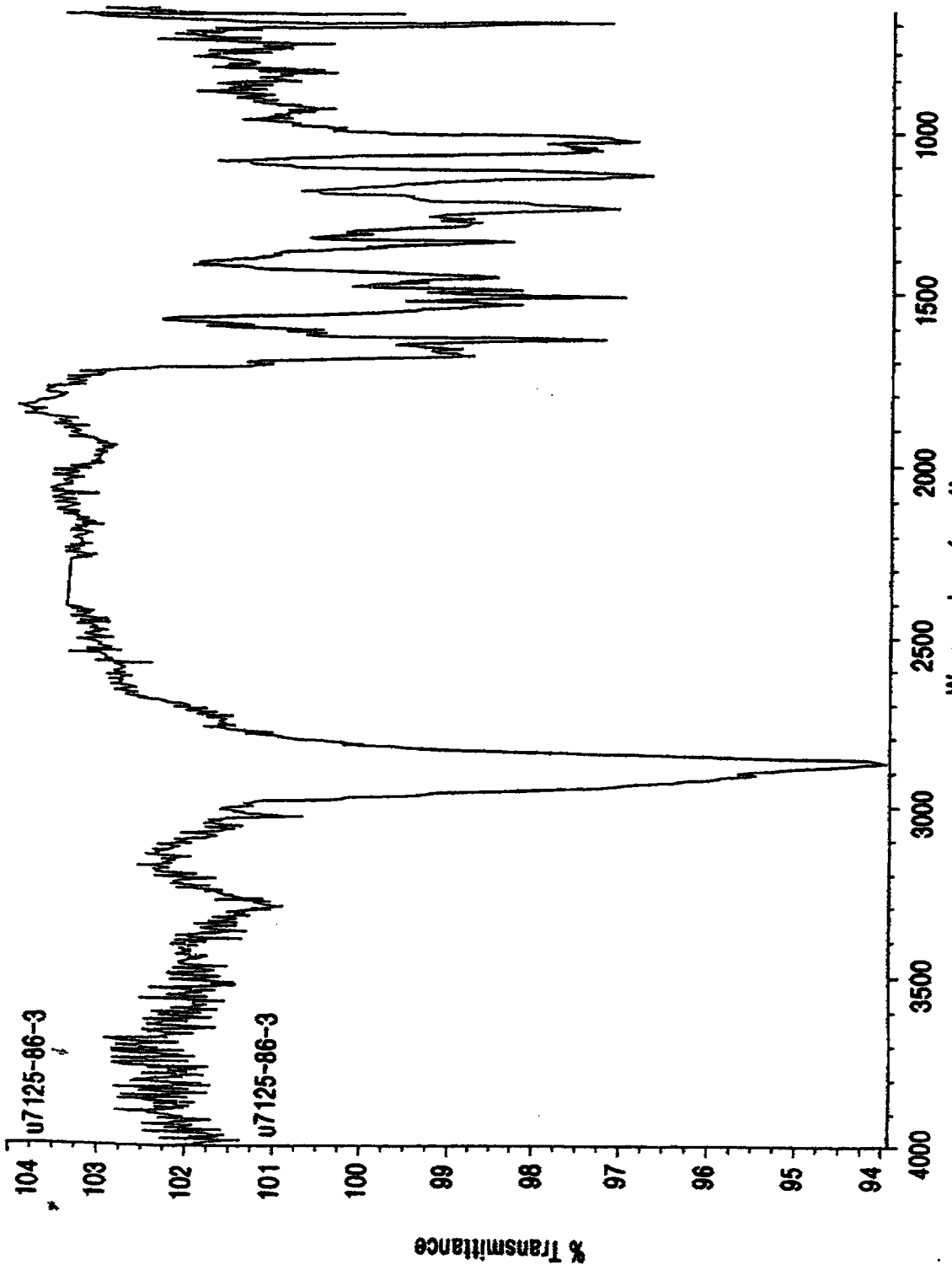

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101
100
99
98
97
96
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94
% Transmittance
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2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 20

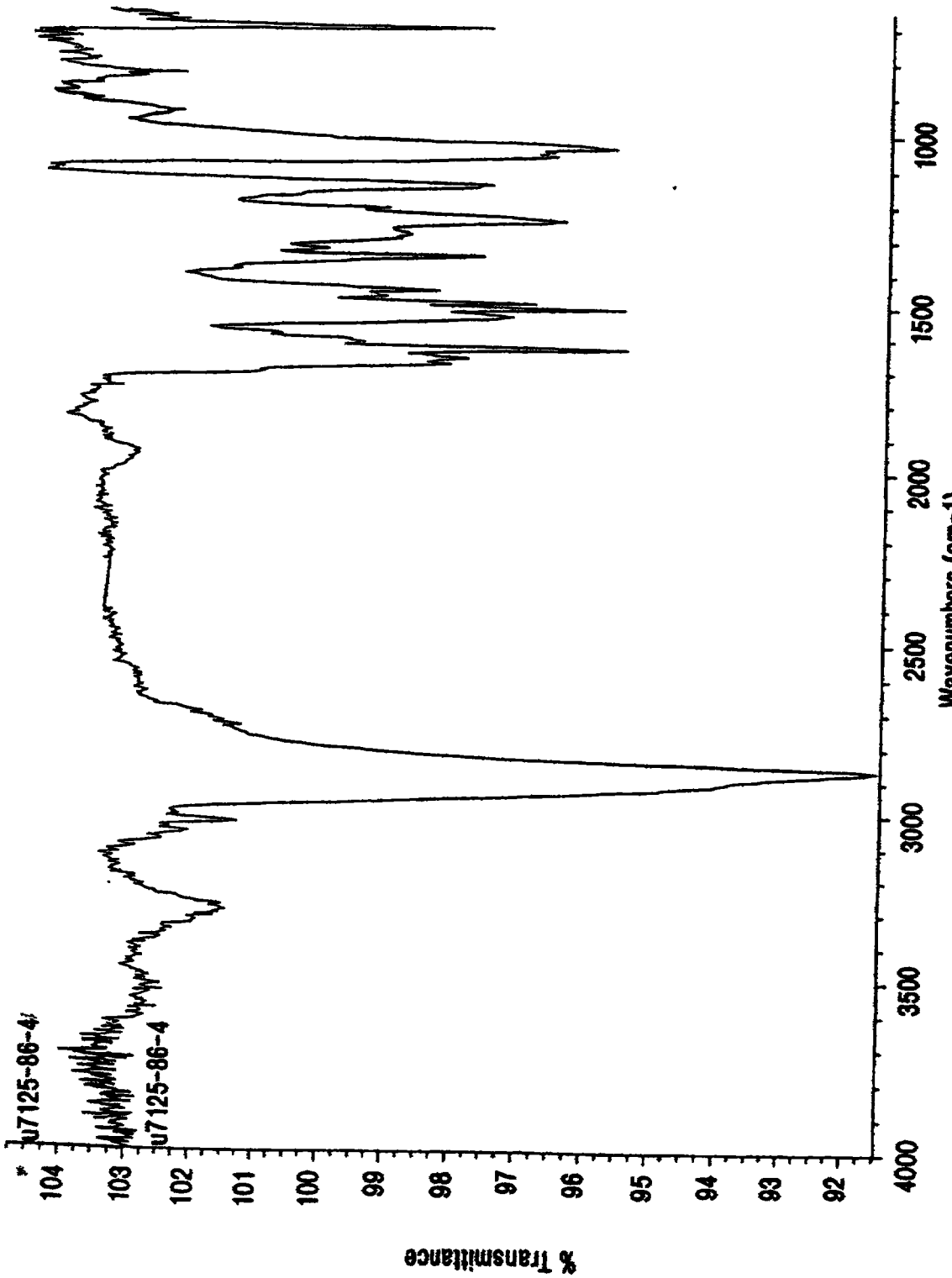

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u7125-86-4
% Transmittance
Wavenumbers (cm-1)
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2500
2000
1500
1000
104
103
102
101
100
99
98
97
96
95
94
93
92

FIG. 21

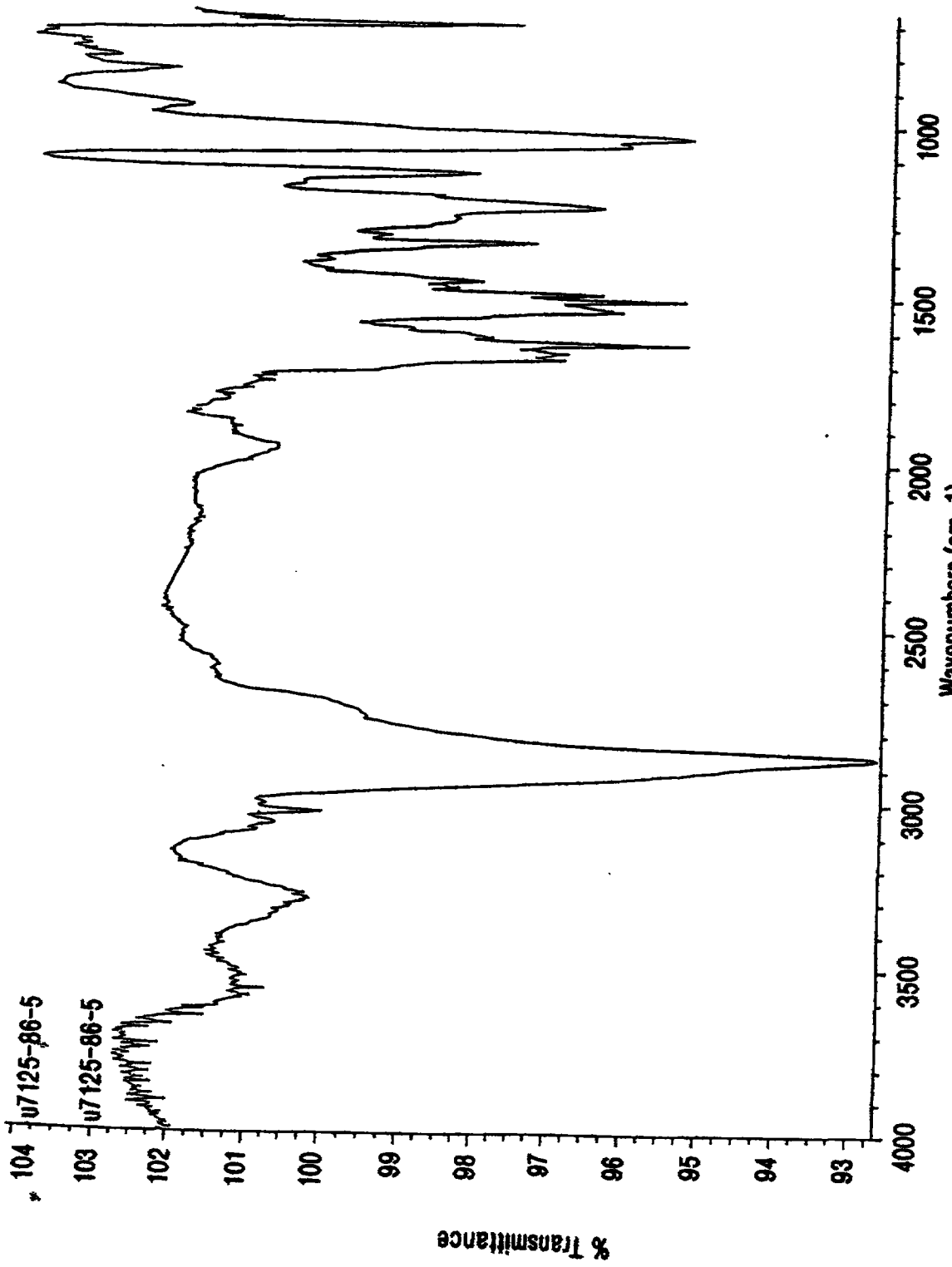

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u7125-86-5
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99
98
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96
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93
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 22

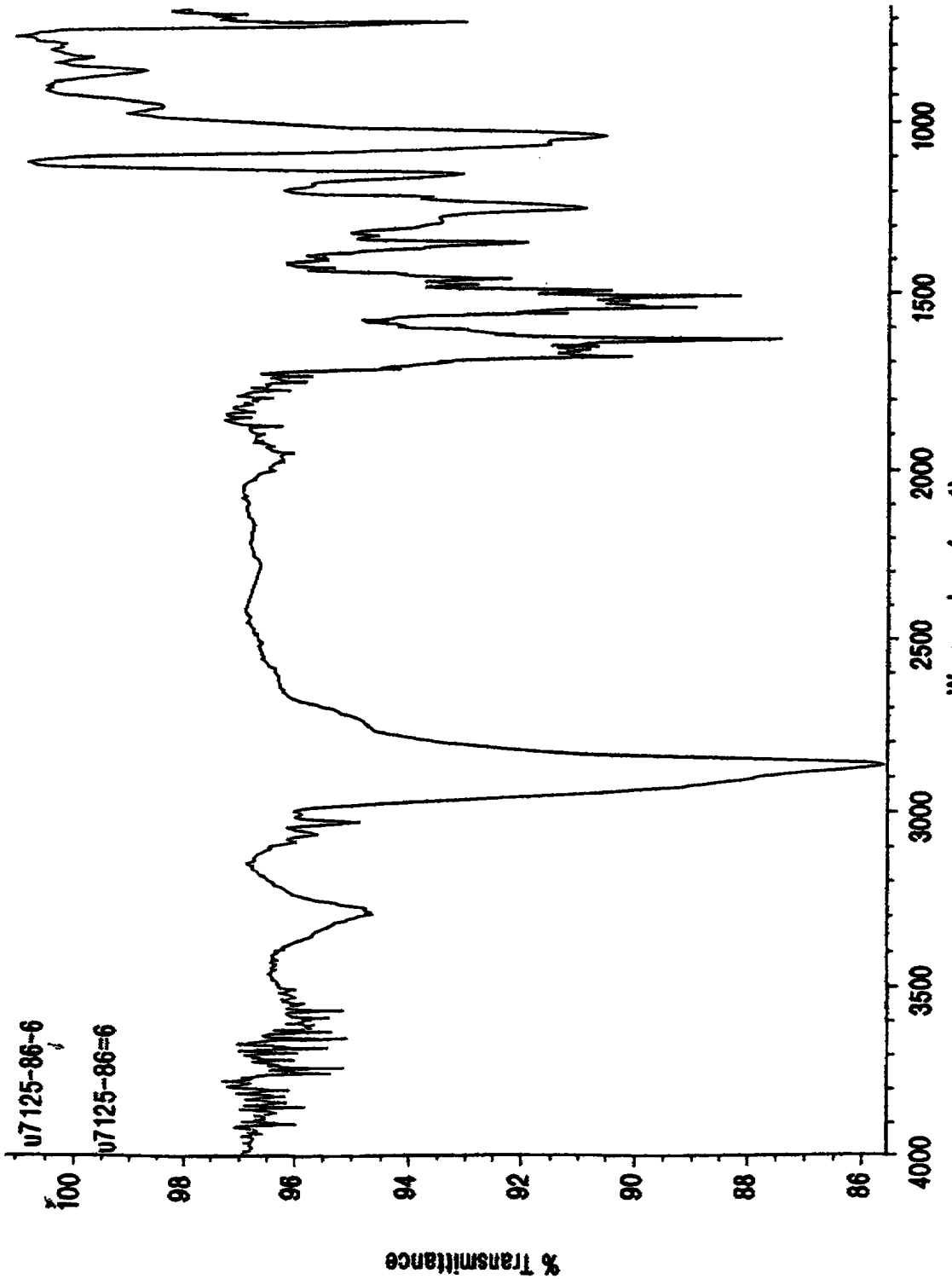

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u7125-86=6
% Transmittance
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2000
1500
1000
Wavenumbers (cm-1)

FIG. 23

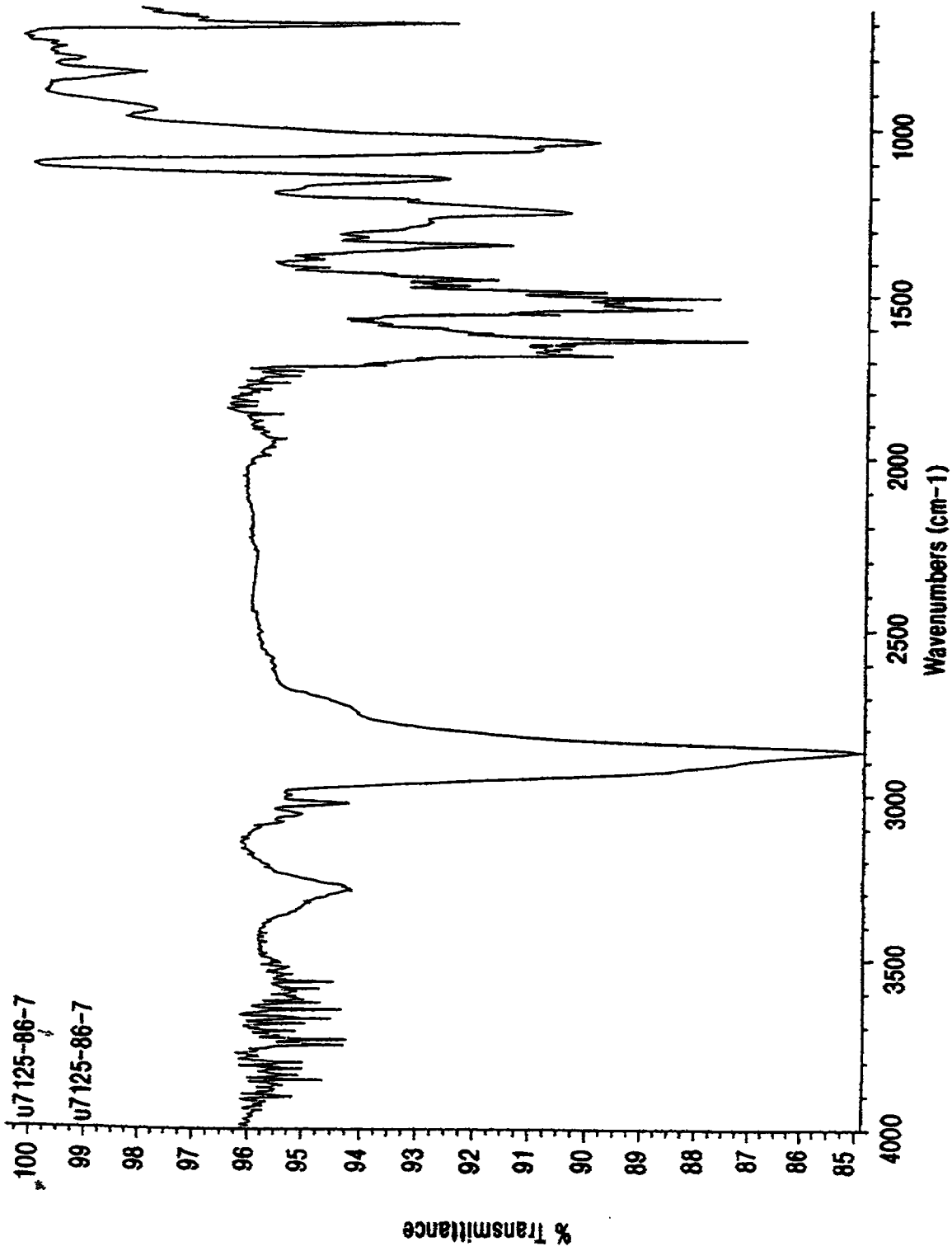

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u7125-86-7
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94
93
92
91
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89
88
87
86
85
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 24

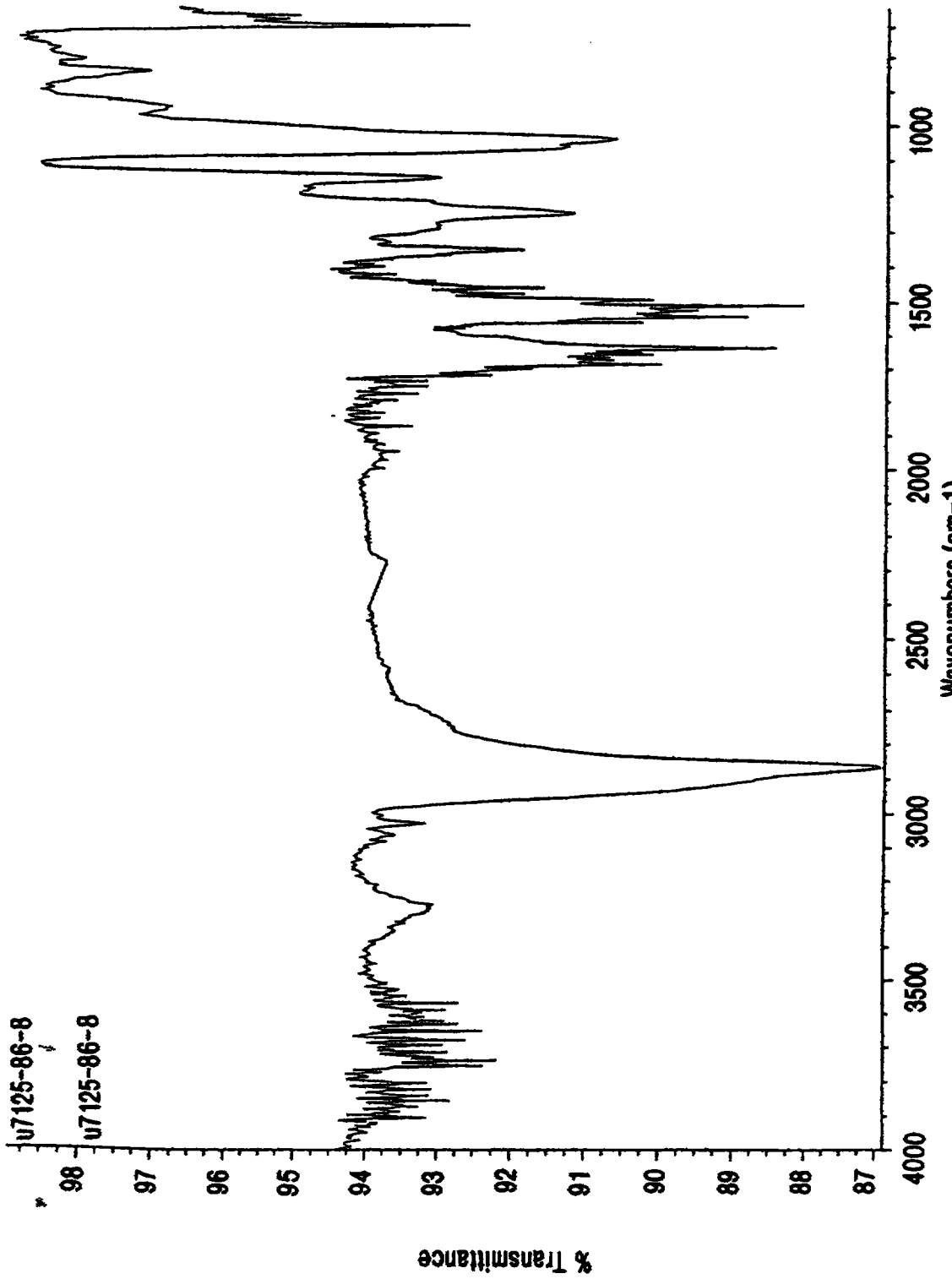

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% Transmittance
4000
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2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 25

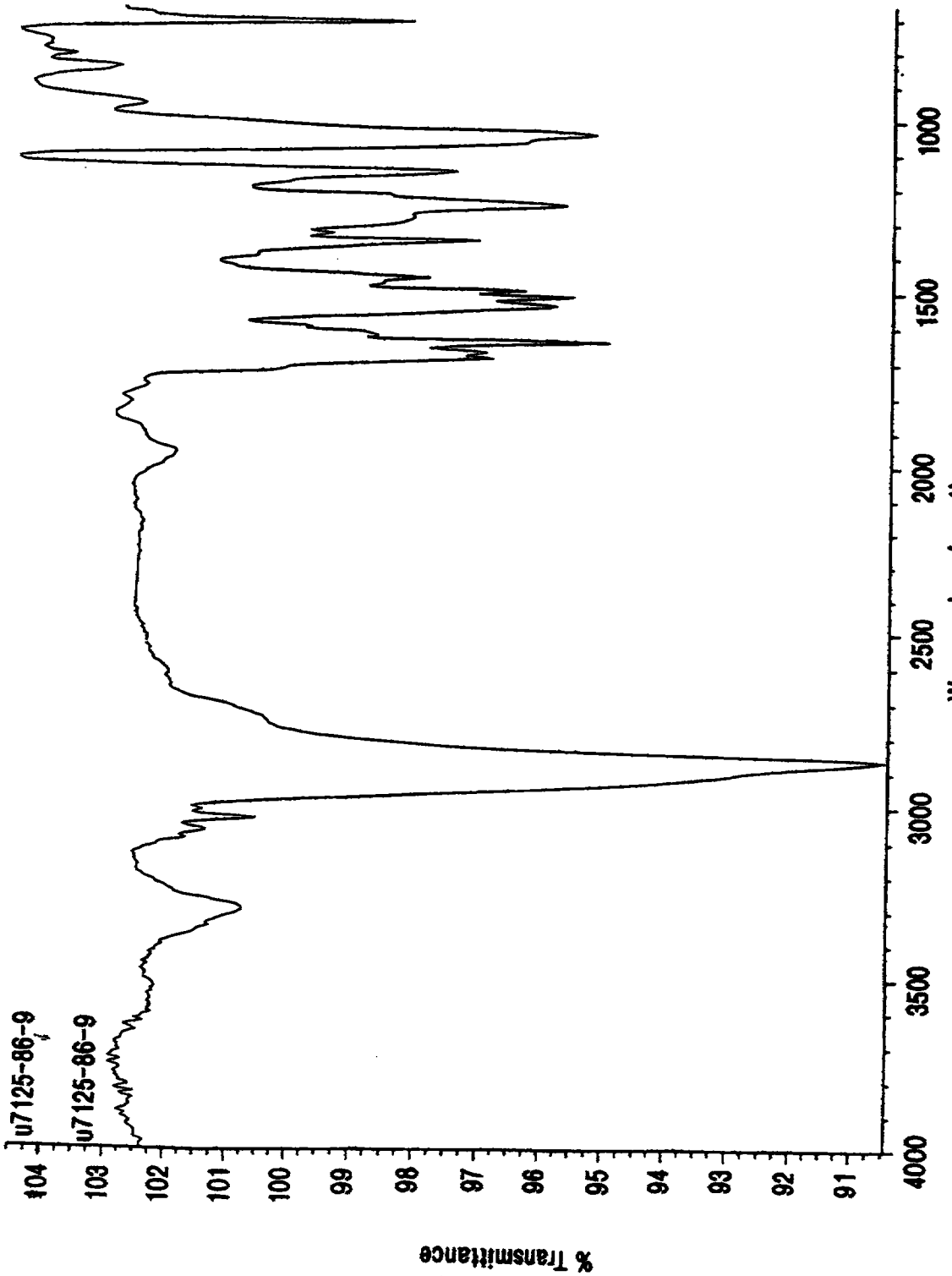

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2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 26

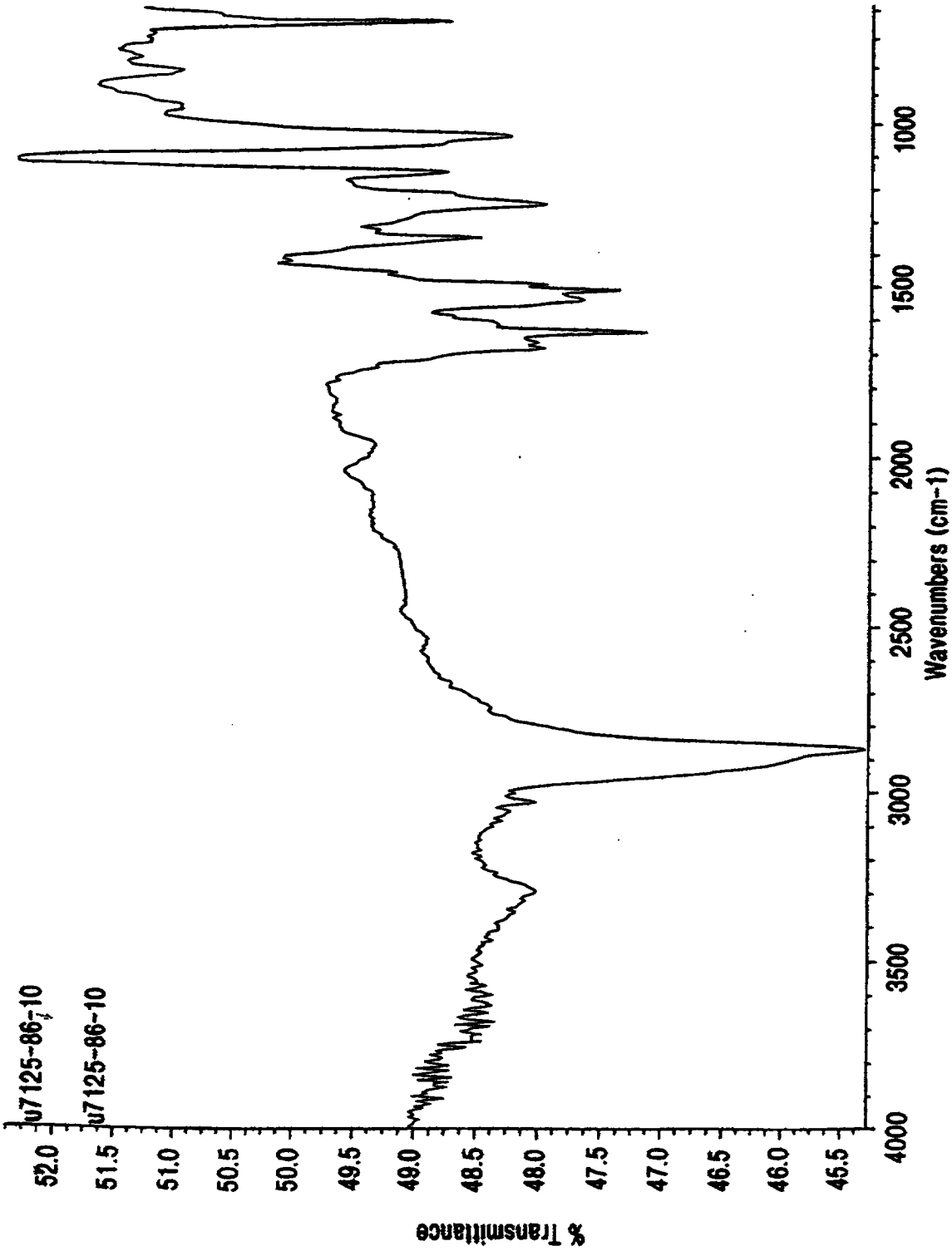

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48.0
47.5
47.0
46.5
46.0
45.5
% Transmittance
4000
3500
3000
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2000
1500
1000
Wavenumbers (cm-1)

FIG. 27

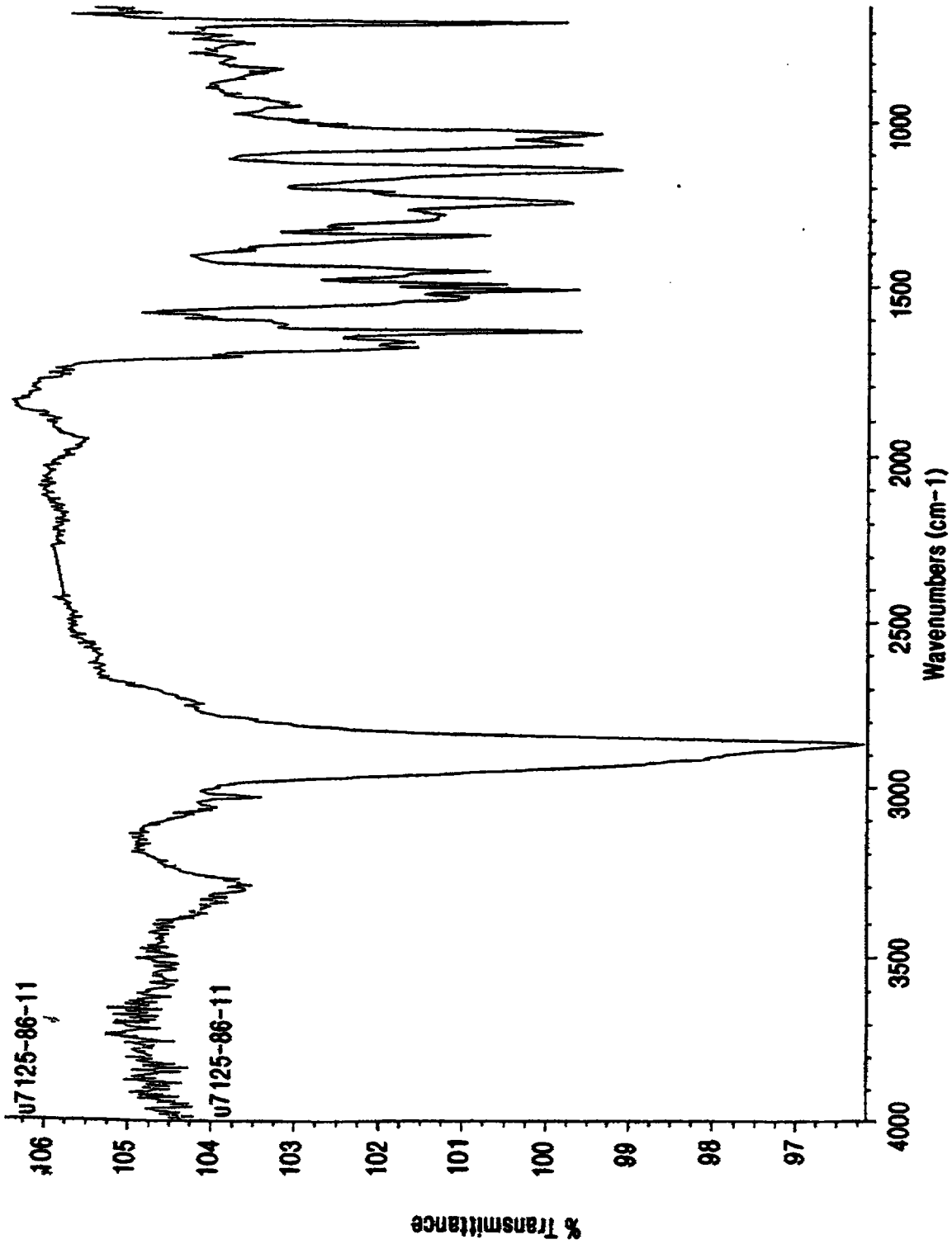

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1500
1000
Wavenumbers (cm-1)

FIG. 28

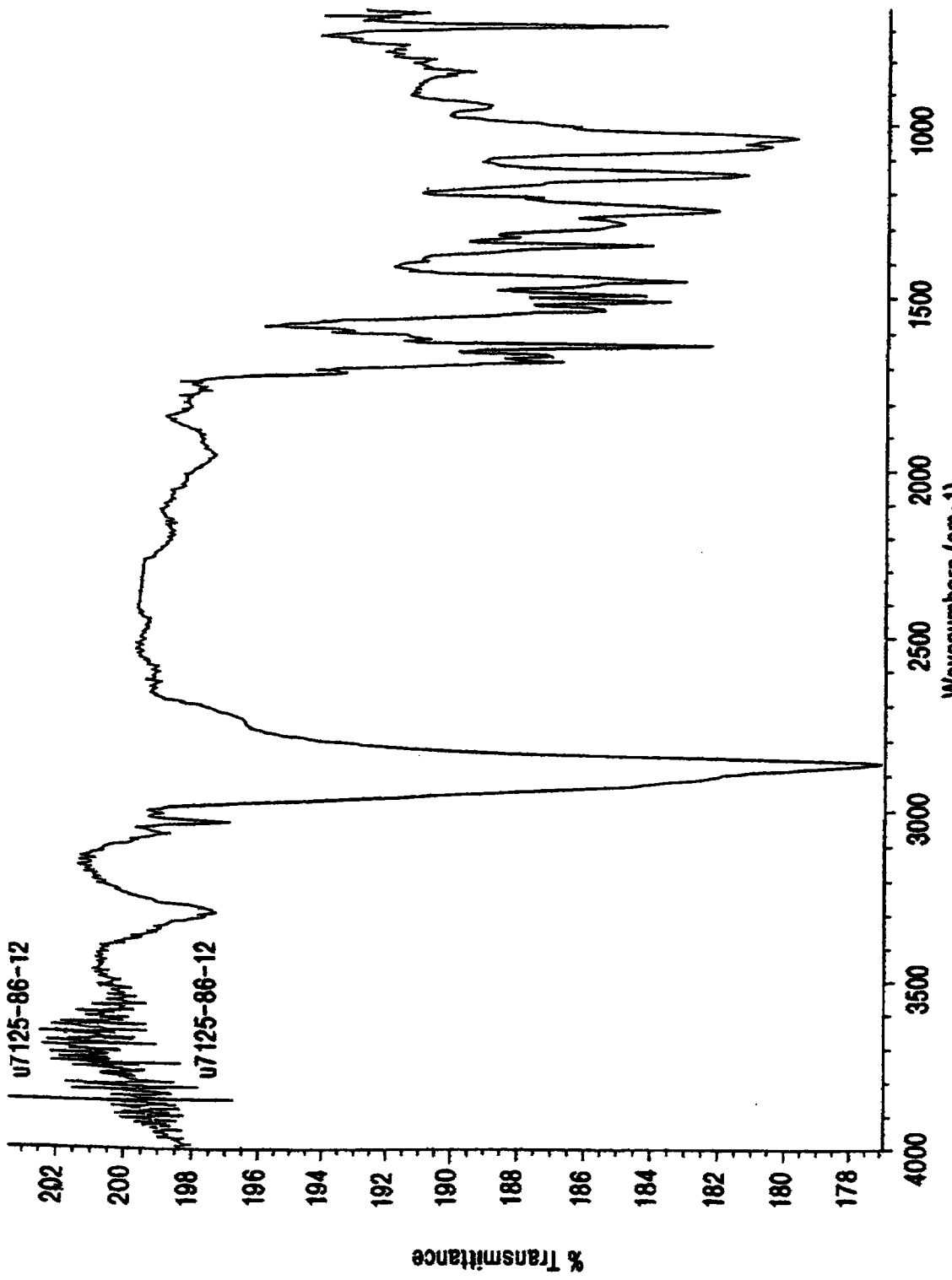

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4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 29

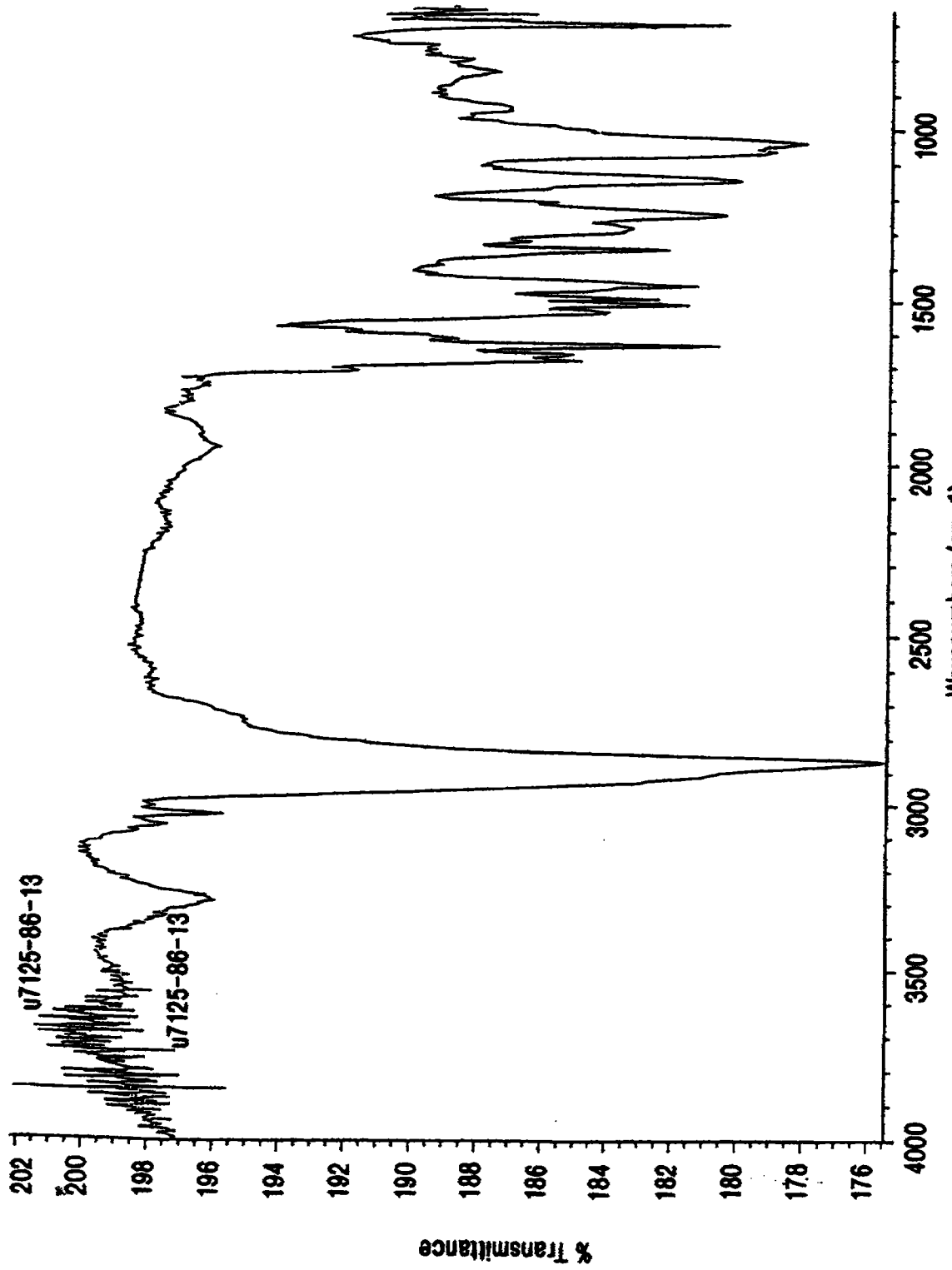

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4000
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1000
Wavenumbers (cm-1)

FIG. 30

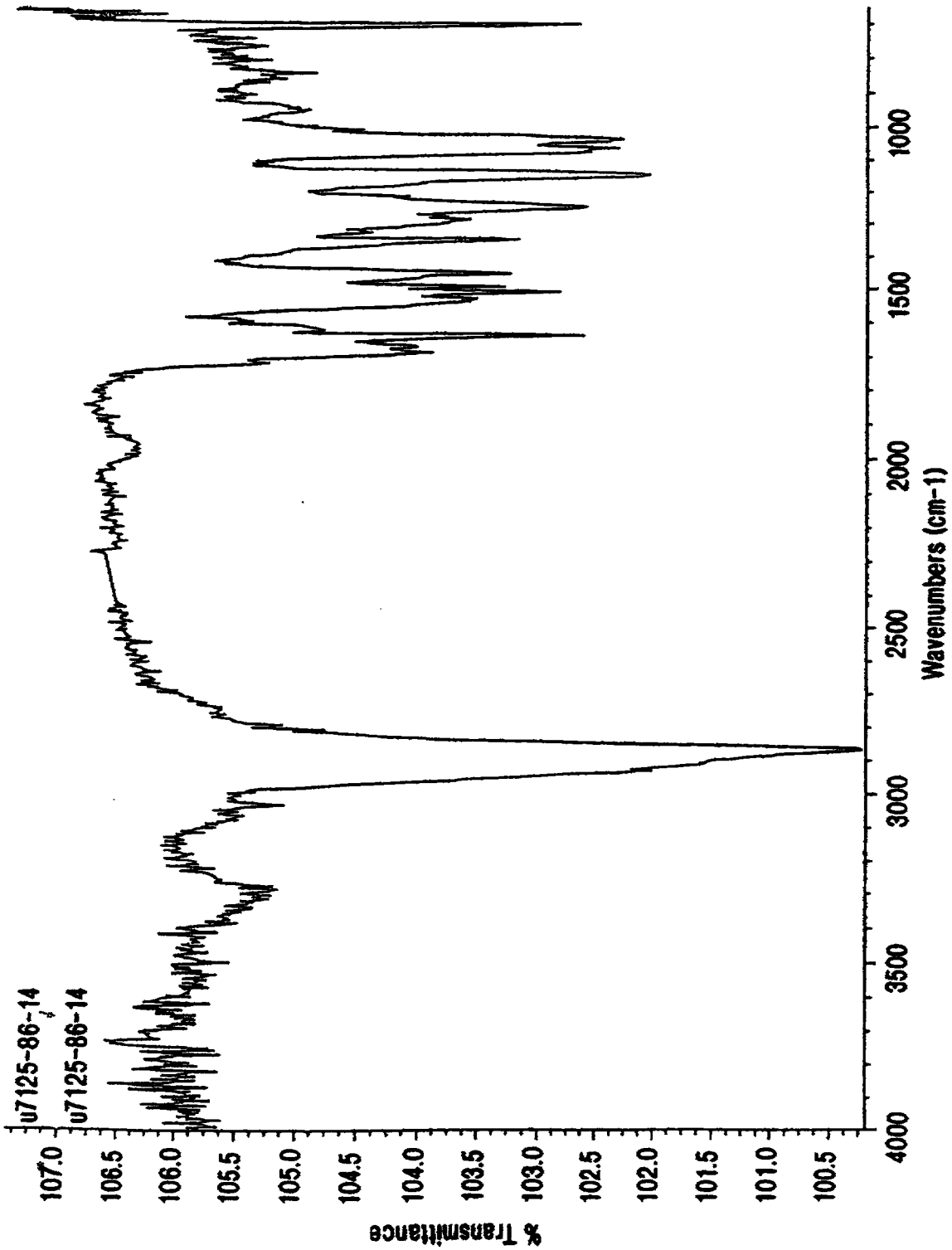

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102.0
101.5
101.0
100.5
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3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 31

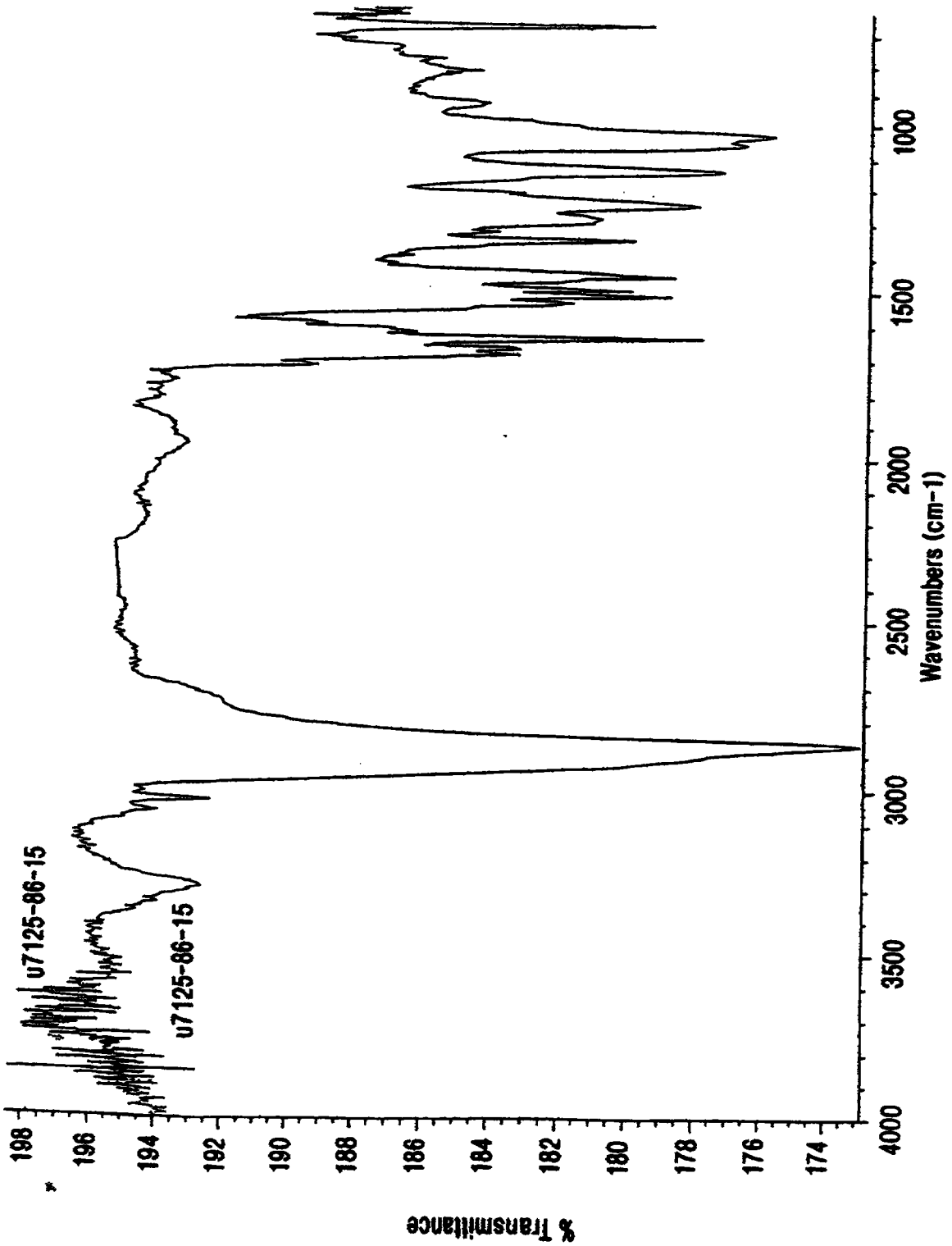

u7125-86-15
u7125-86-15
% Transmittance
198
196
194
192
190
188
186
184
182
180
178
176
174
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 32

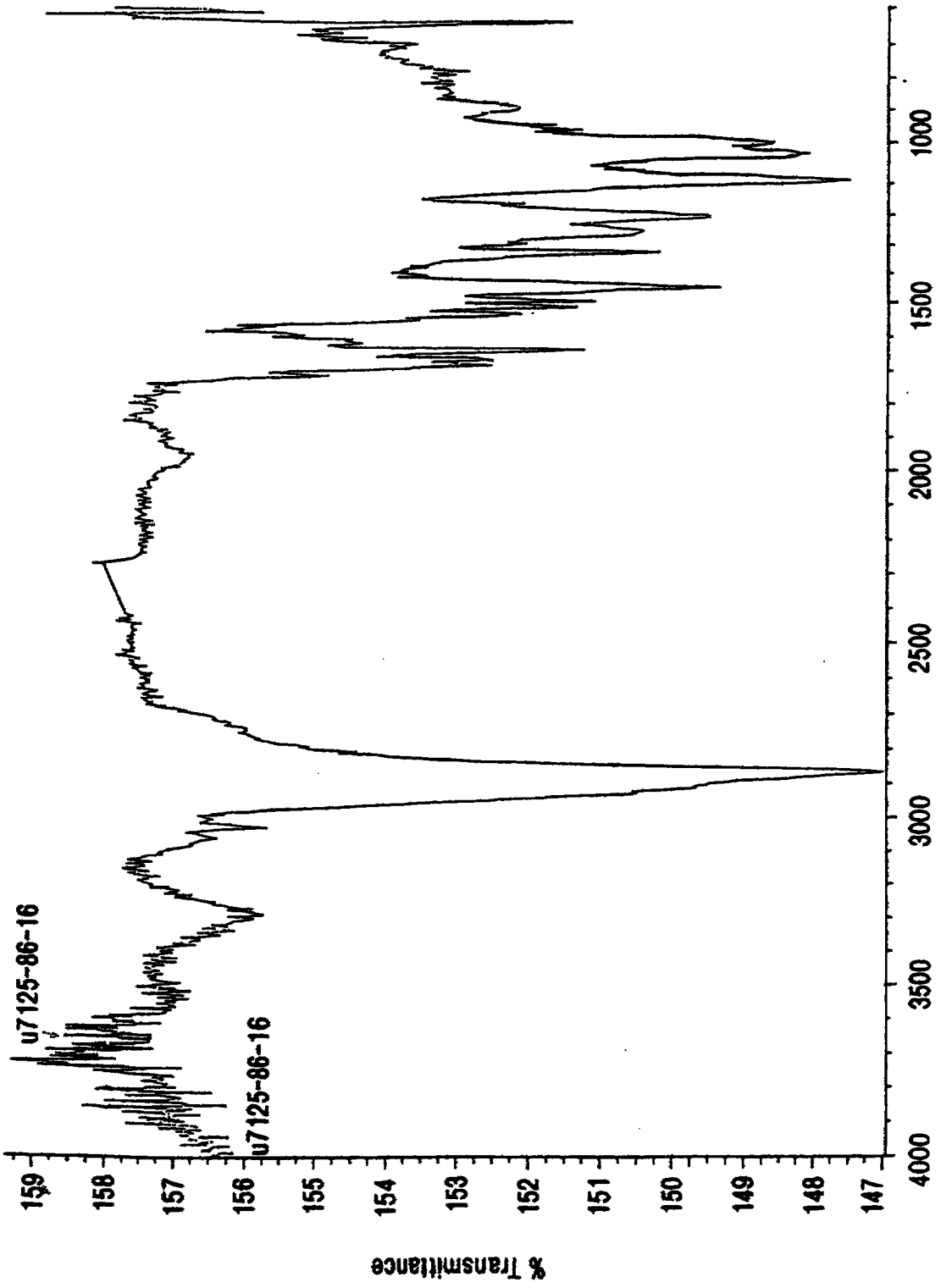

u7125-86-16
u7125-86-16
% Transmittance
159
158
157
156
155
154
153
152
151
150
149
148
147
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 33

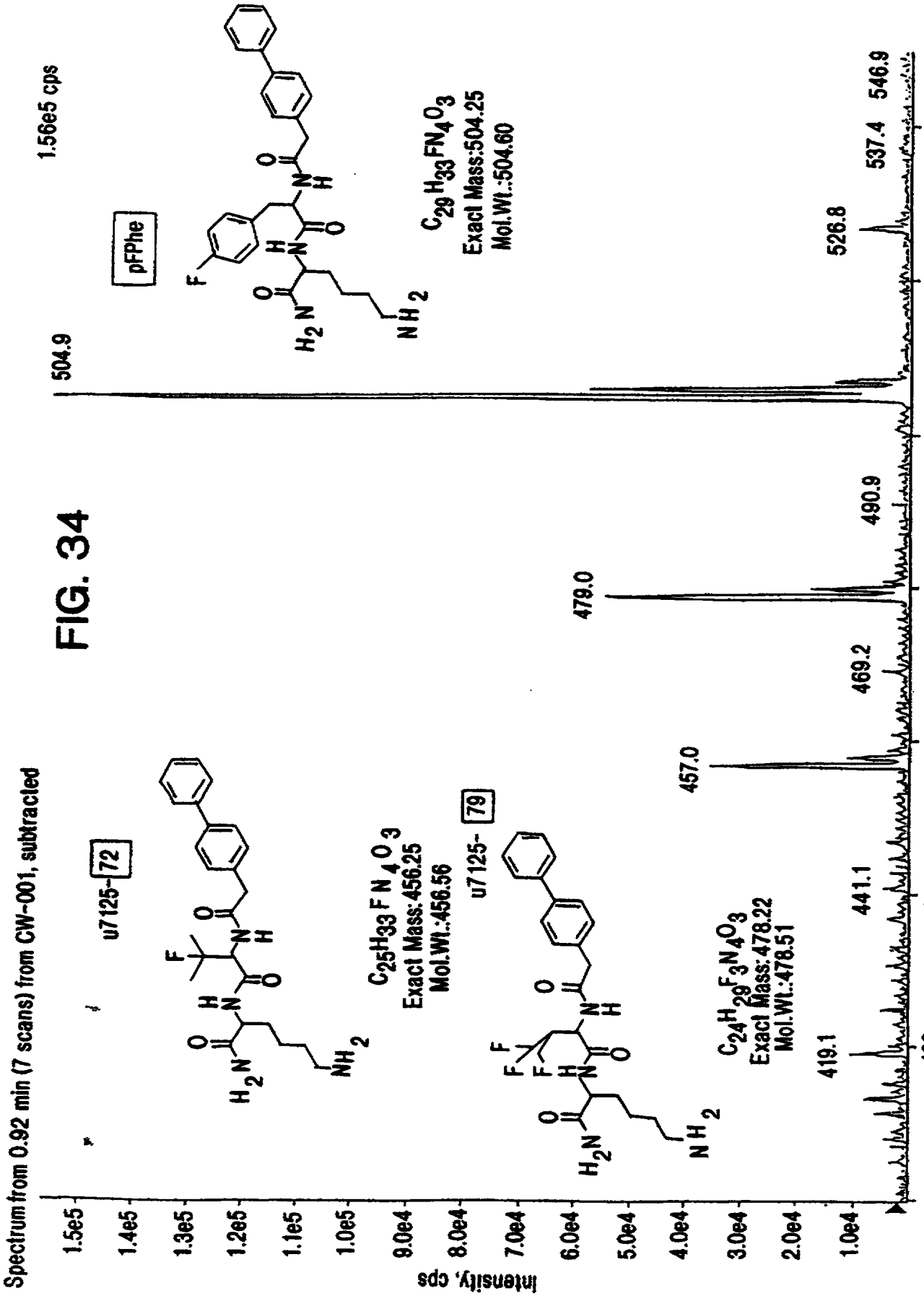

Spectrum from 0.92 min (7 scans) from CW-001, subtracted
u7125-72
u7125-79
pFPhe
1.56e5 cps
C25H33FN4O3
Exact Mass:456.25
Mol.Wt.:456.56
C29H33FN4O3
Exact Mass:504.25
Mol.Wt.:504.60
C24H29F3N4O3
Exact Mass:478.22
Mol.Wt.:478.51
Intensity, cps
m/z, amu
504.9
526.8
537.4
546.9
490.9
479.0
469.2
457.0
441.1
419.1

FIG. 34

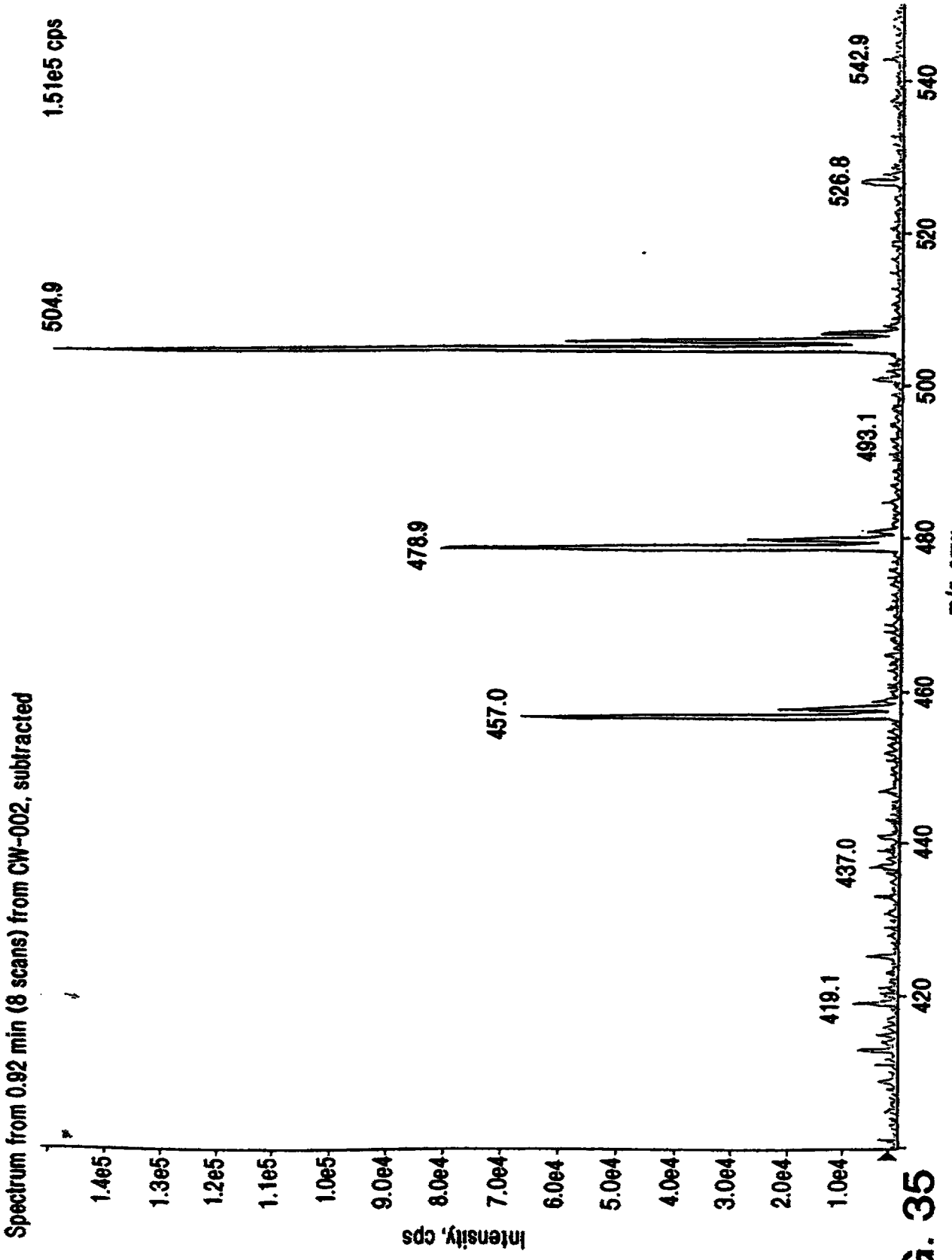

Spectrum from 0.92 min (8 scans) from CW-002, subtracted
1.51e5 cps
Intensity, cps
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
504.9
478.9
457.0
493.1
526.8
542.9
419.1
437.0
420
440
460
480
500
520
540
m/z, amu

FIG. 35

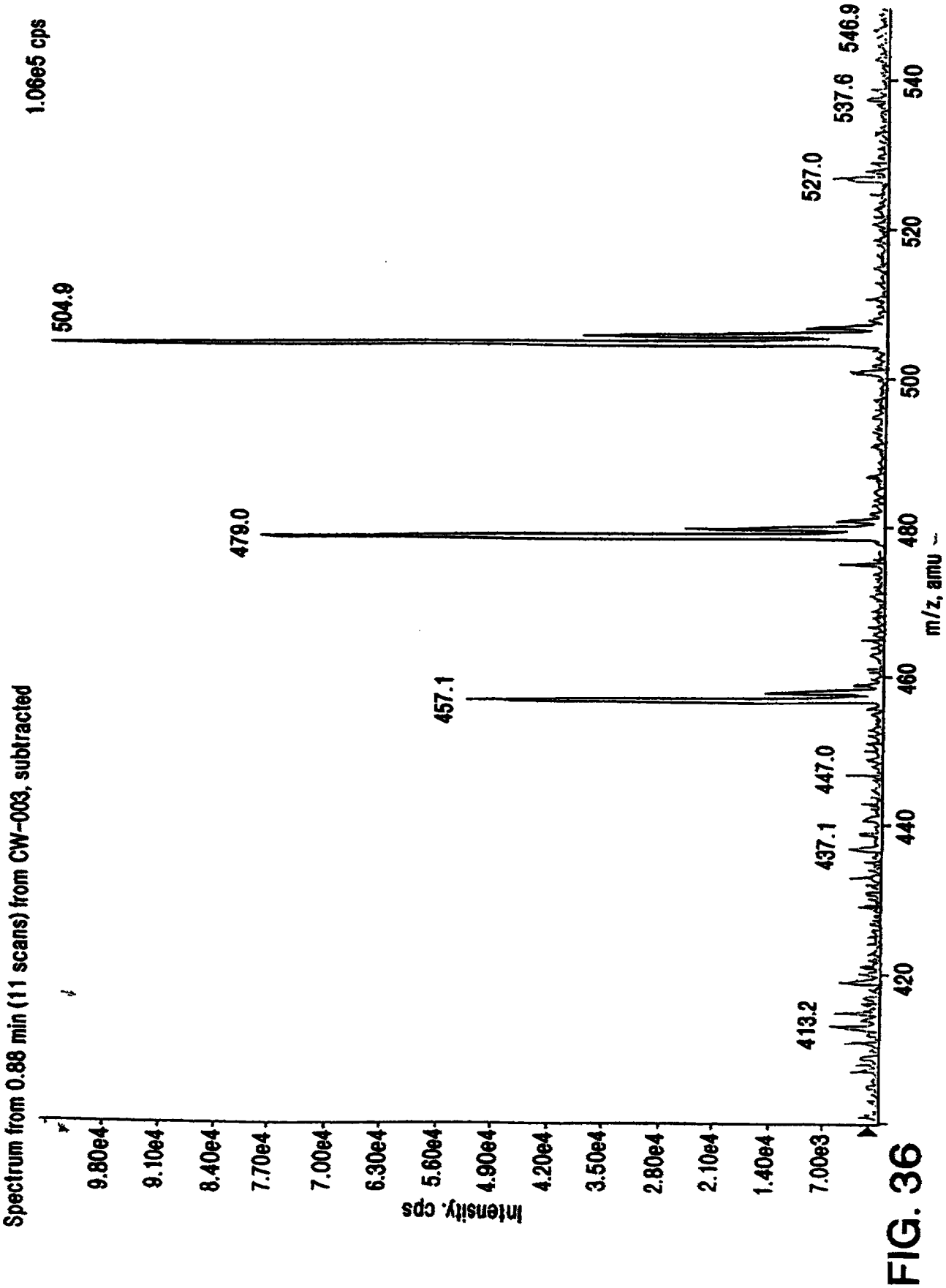

Spectrum from 0.88 min (11 scans) from CW-003, subtracted
1.06e5 cps
Intensity, cps
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
504.9
479.0
457.1
527.0
537.6
546.9
413.2
437.1
447.0
420
440
460
480
500
520
540
m/z, amu

FIG. 36

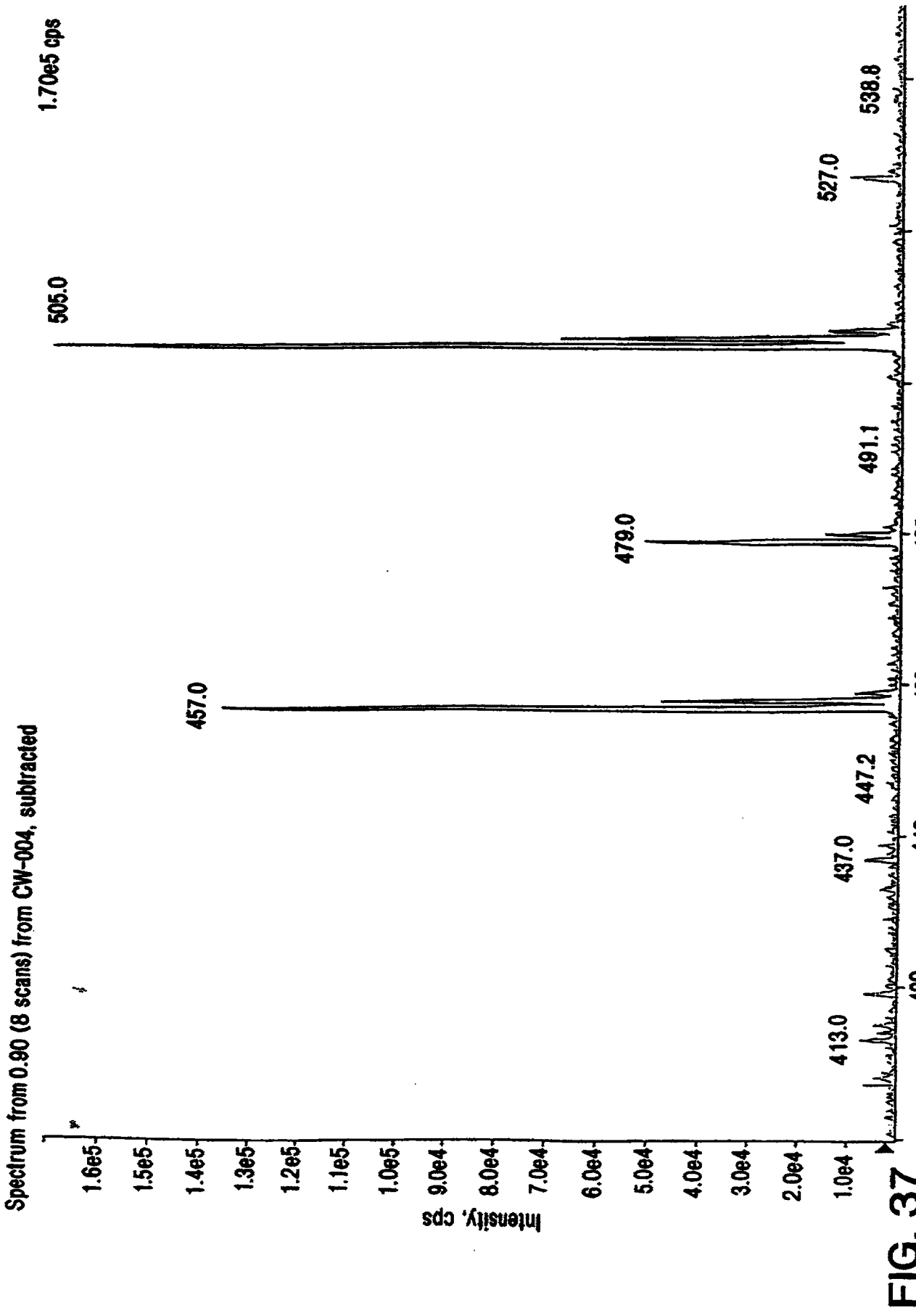

Spectrum from 0.80 (8 scans) from CW-004, subtracted
1.70e5 cps
Intensity, cps
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
505.0
457.0
479.0
491.1
527.0
538.8
413.0
437.0
447.2
420
440
460
480
500
520
540
m/z, amu

FIG. 37

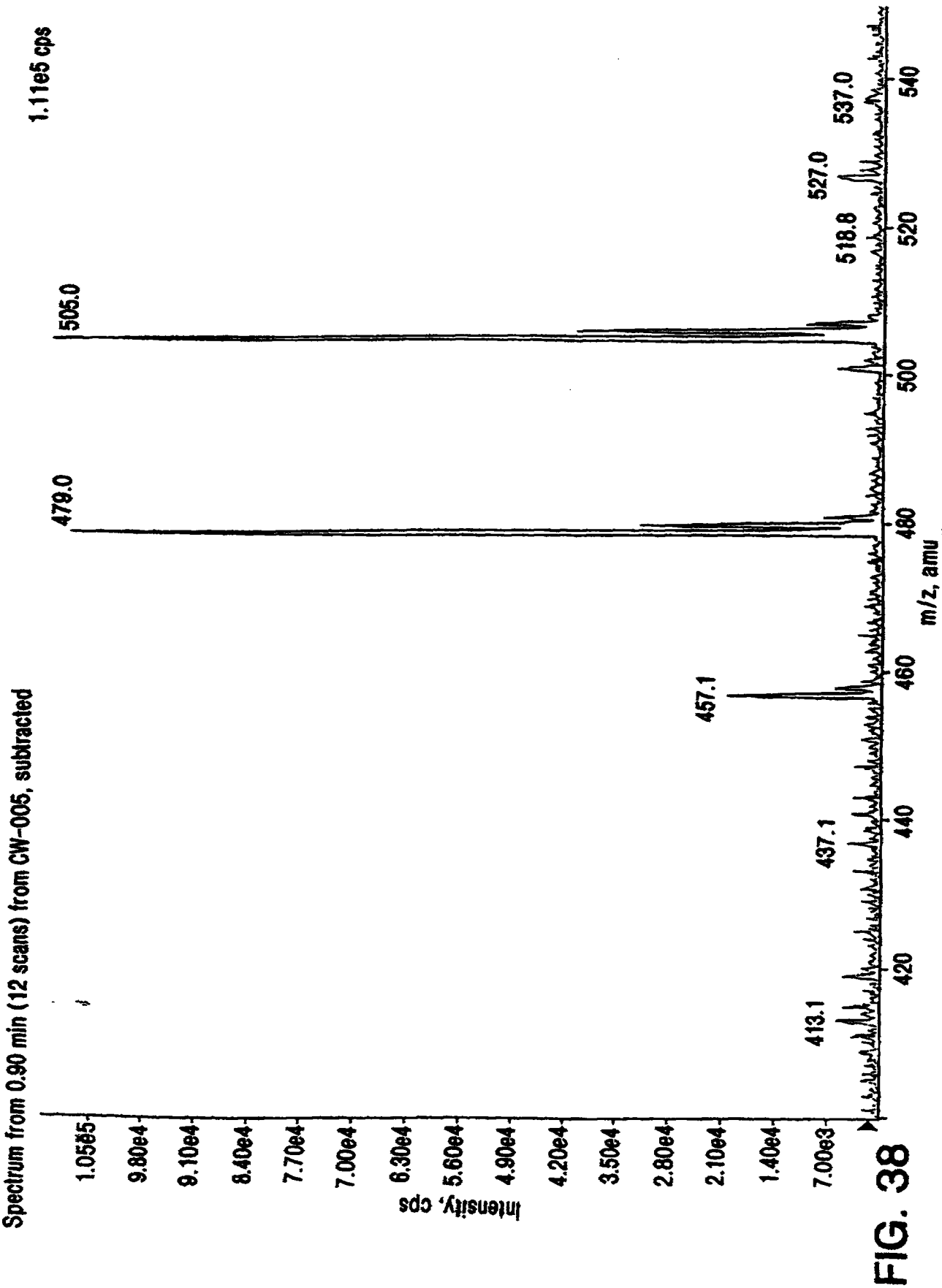

Spectrum from 0.90 min (12 scans) from CW-005, subtracted
1.11e5 cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
Intensity, cps
413.1
437.1
457.1
479.0
505.0
518.8
527.0
537.0
420
440
460
480
500
520
540
m/z, amu

FIG. 38

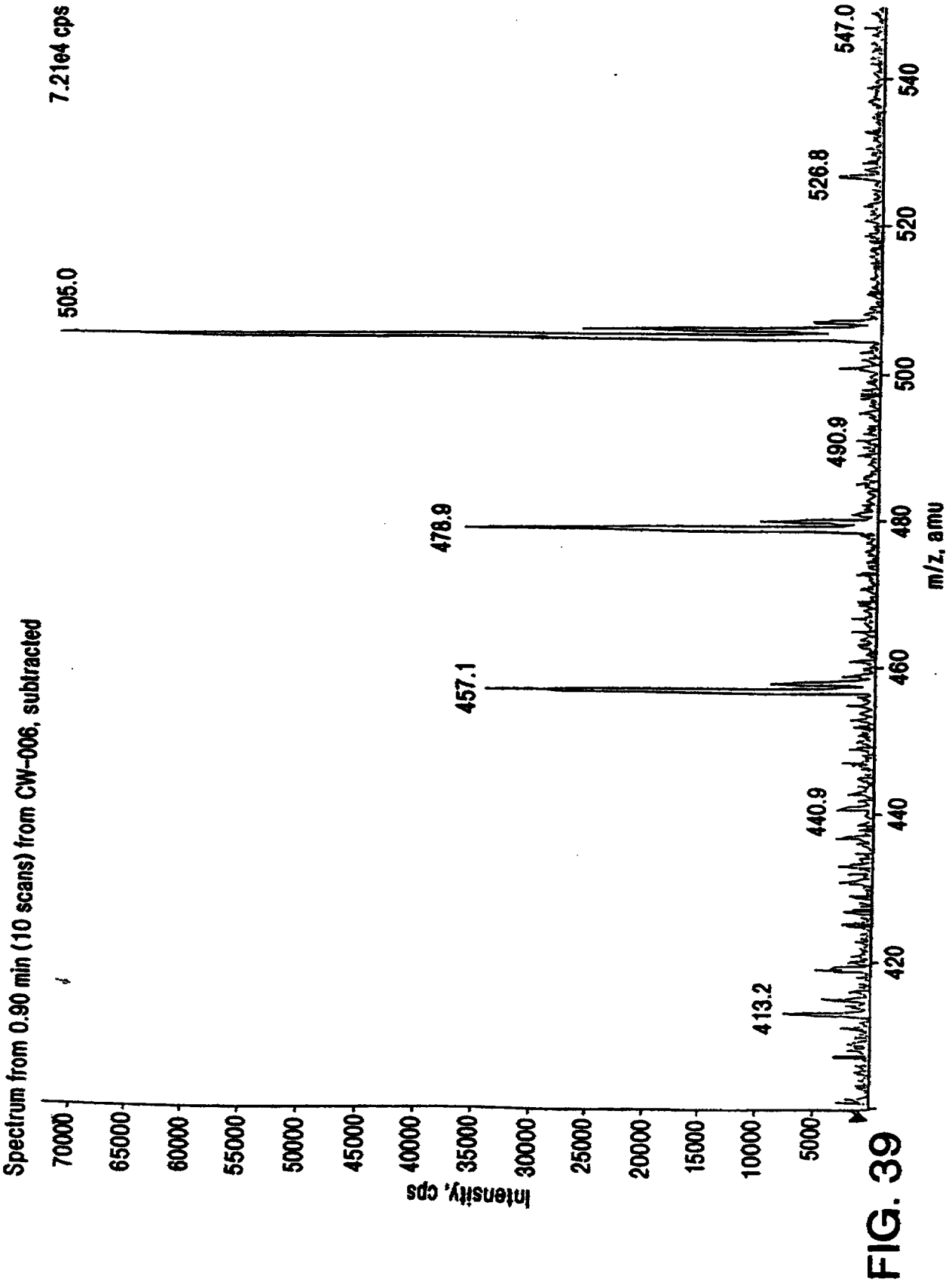

Spectrum from 0.90 min (10 scans) from CW-006, subtracted
7.21e4 cps
Intensity, cps
m/z, amu
505.0
478.9
457.1
526.8
490.9
547.0
440.9
413.2

FIG. 39

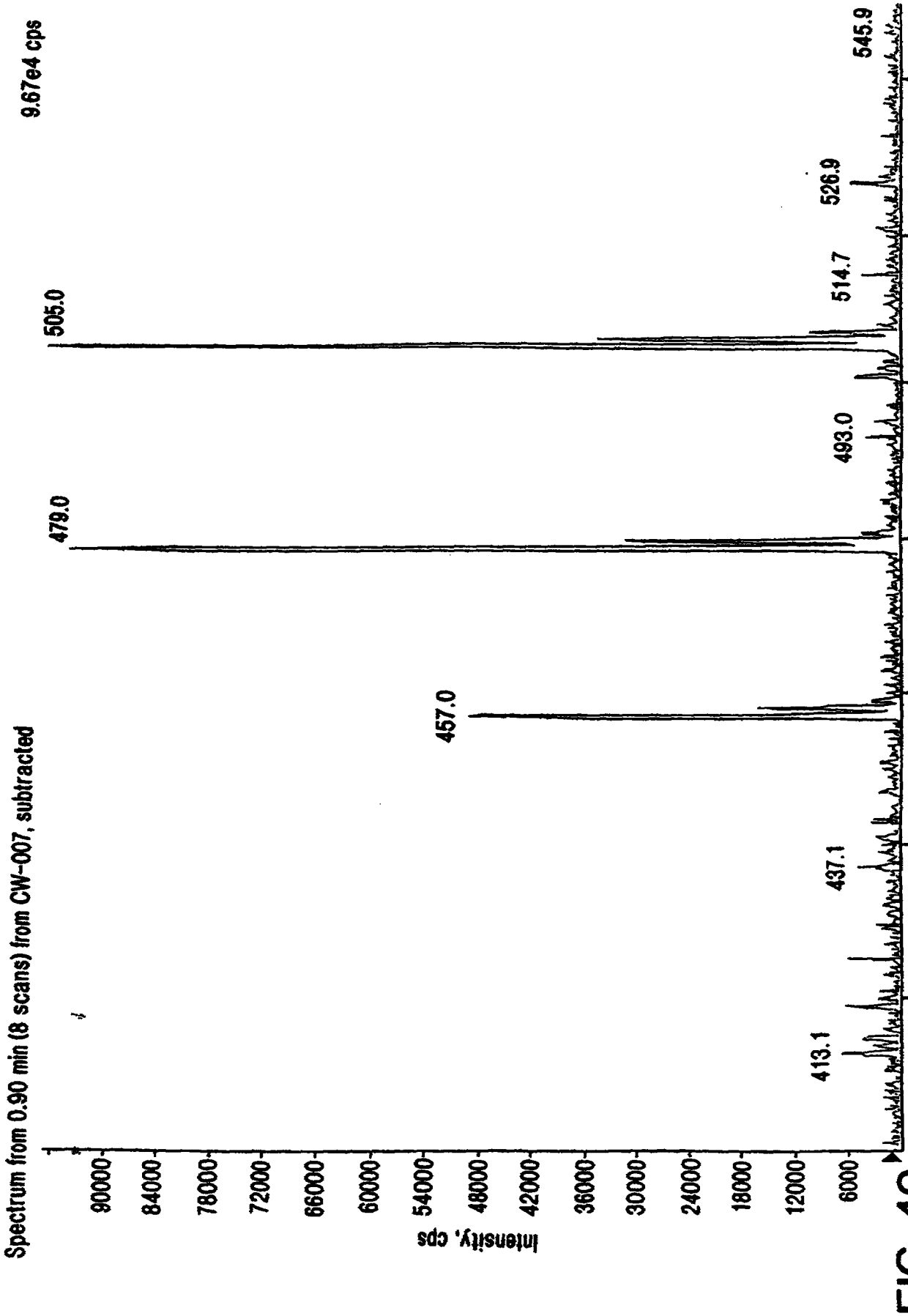

Spectrum from 0.90 min (8 scans) from CW-007, subtracted
9.67e4 cps
Intensity, cps
m/z, amu
505.0
479.0
457.0
437.1
413.1
526.9
514.7
493.0
545.9

FIG. 40

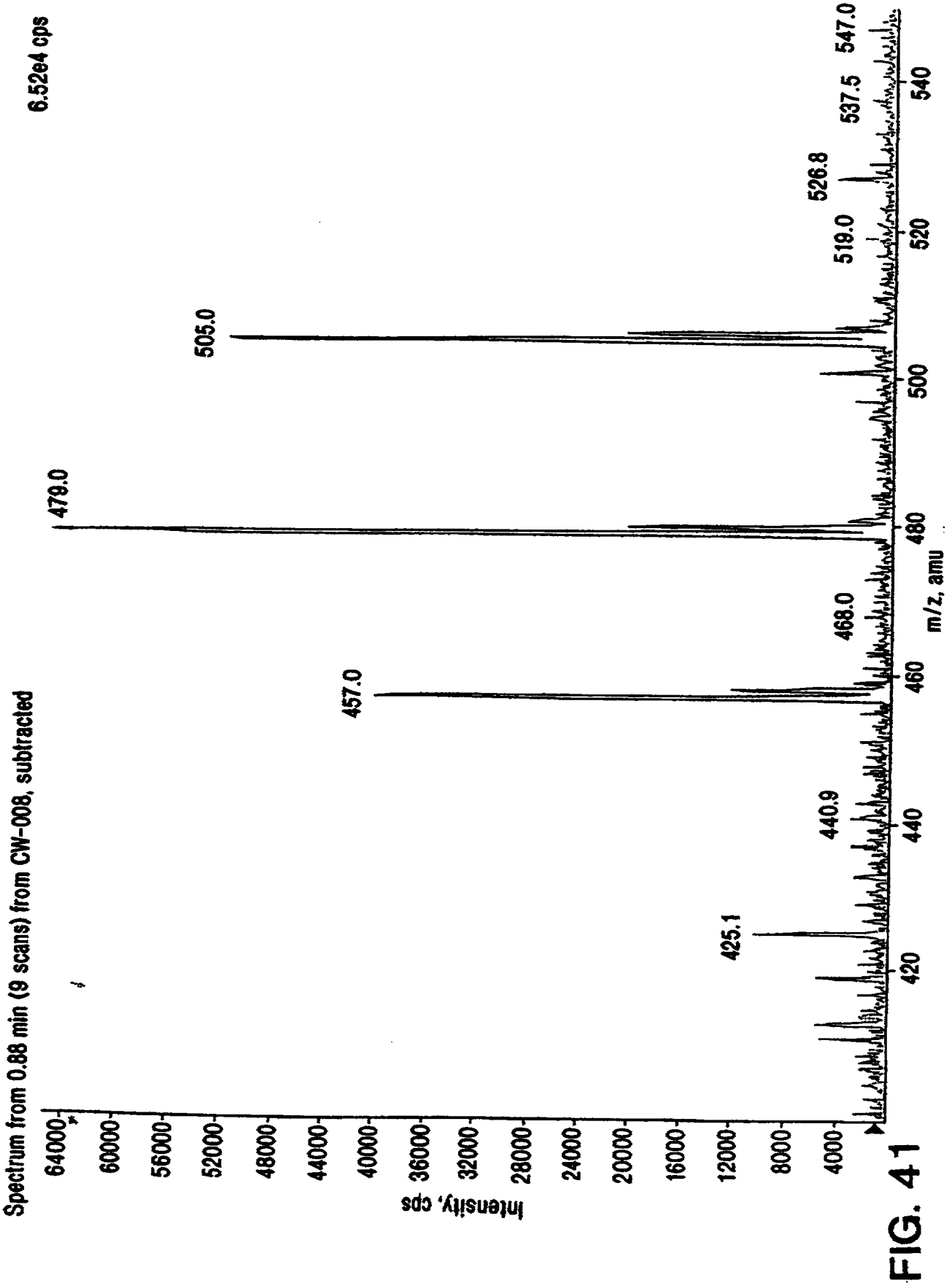

Spectrum from 0.88 min (9 scans) from CW-008, subtracted
6.52e4 cps
Intensity, cps
m/z, amu
64000
60000
56000
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
420
440
460
480
500
520
540
425.1
440.9
457.0
468.0
479.0
505.0
519.0
526.8
537.5
547.0

FIG. 41

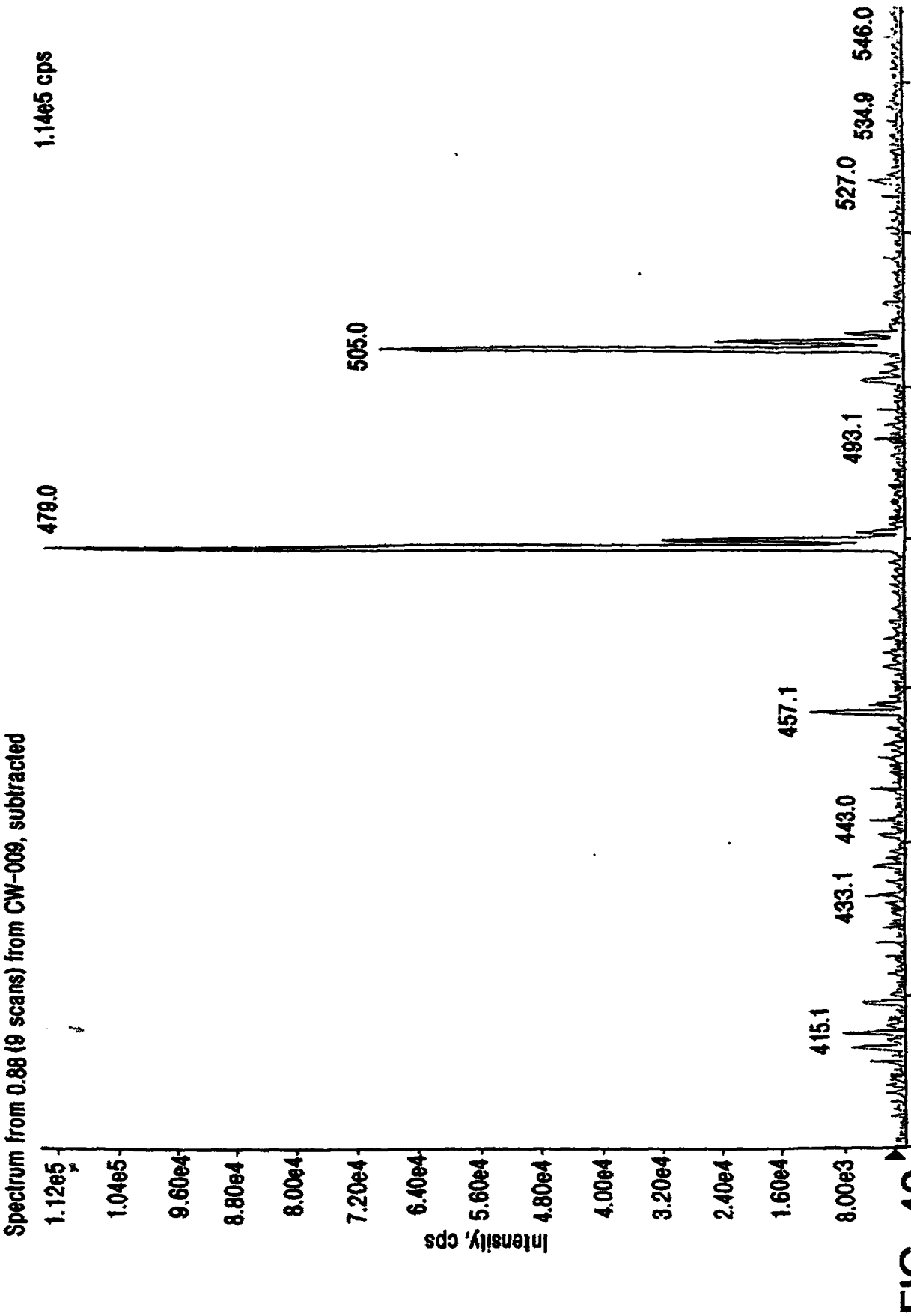

Spectrum from 0.88 (9 scans) from CW-009, subtracted
1.14e5 cps
Intensity, cps
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
420
440
460
480
500
520
540
415.1
433.1
443.0
457.1
479.0
493.1
505.0
527.0
534.9
546.0

FIG. 42

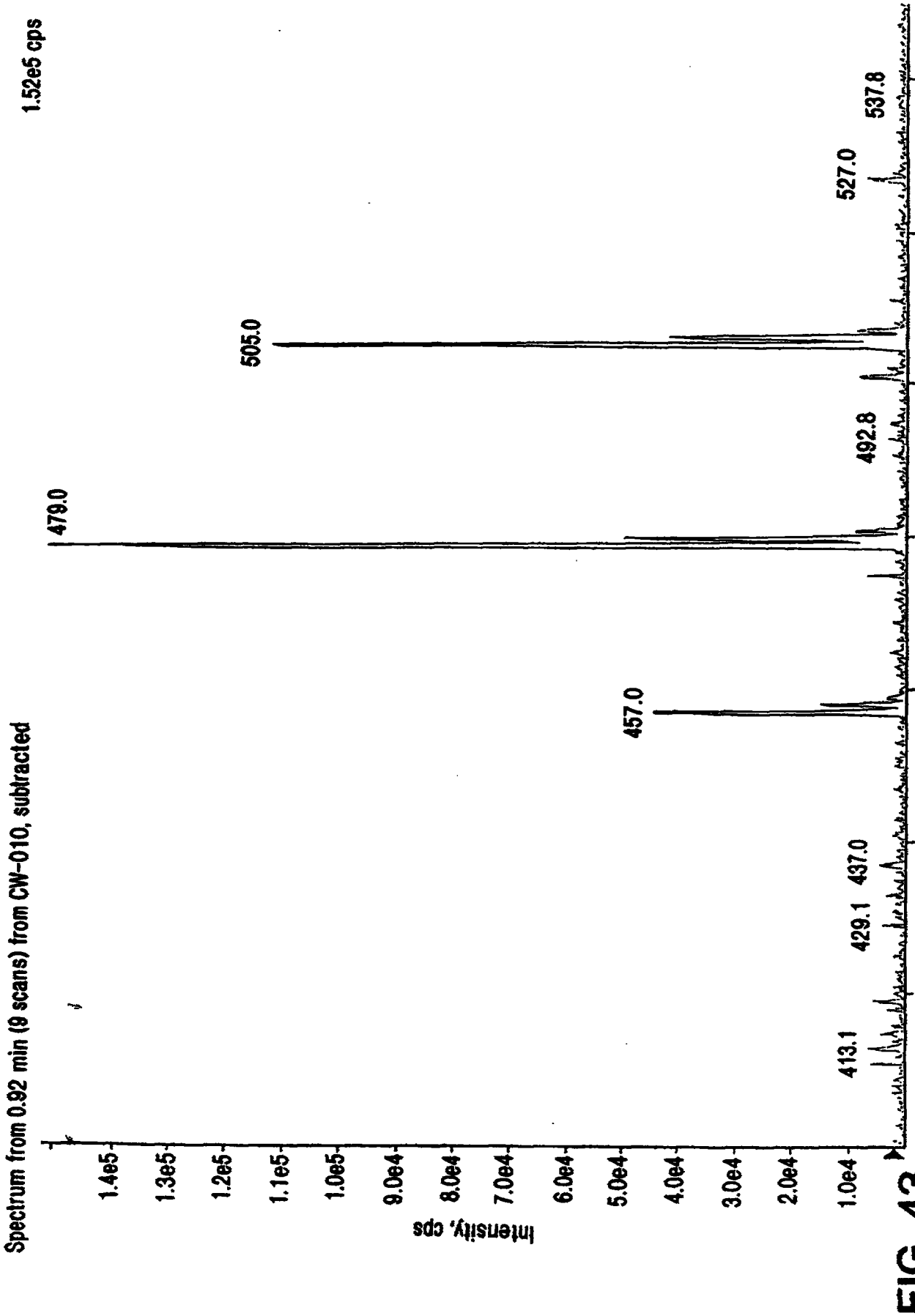

Spectrum from 0.92 min (9 scans) from CW-010, subtracted
1.52e5 cps
Intensity, cps
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
413.1
429.1
437.0
457.0
479.0
505.0
492.8
527.0
537.8
420
440
460
480
500
520
540
m/z, amu

FIG. 43

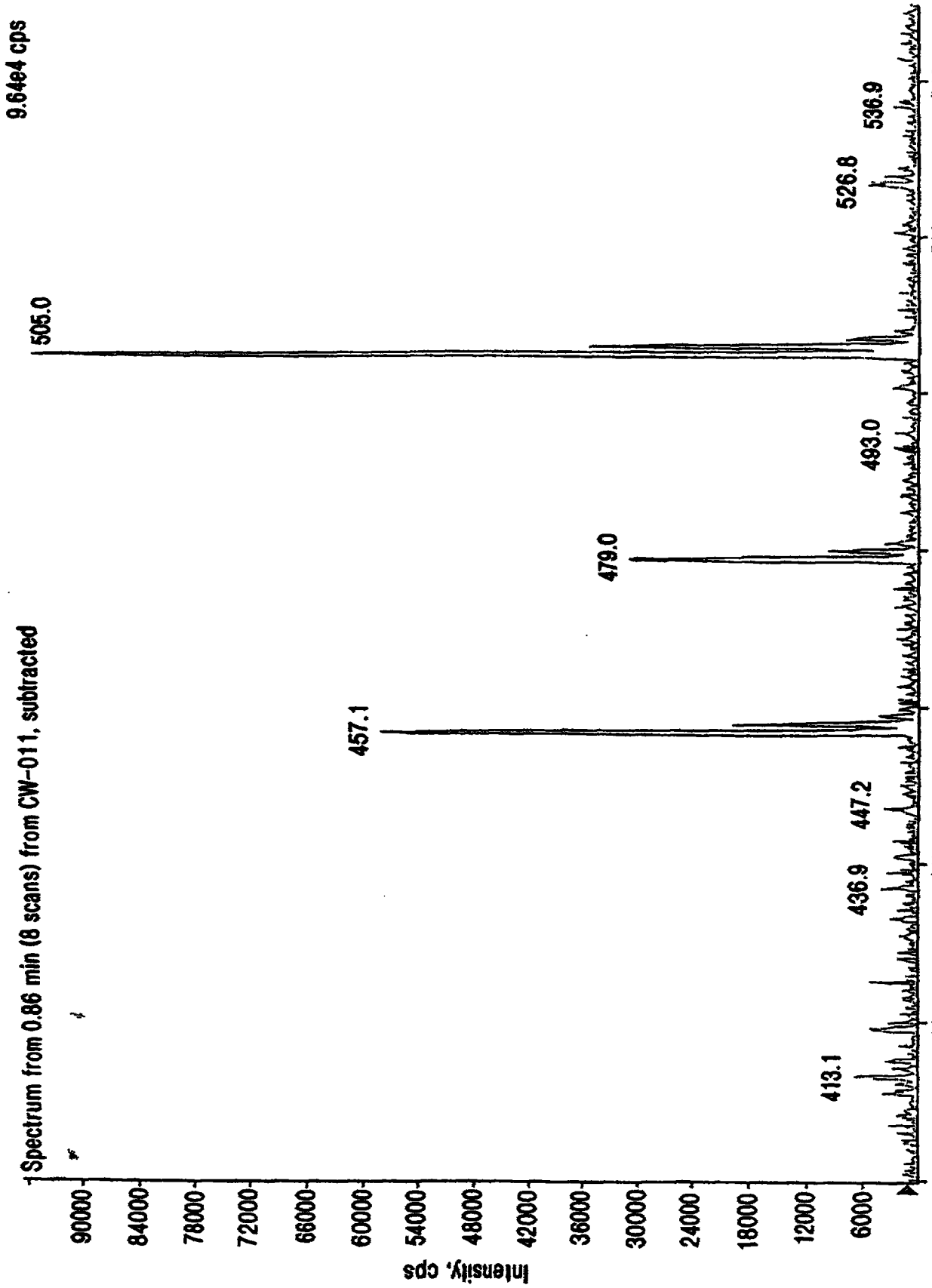

9.64e4 cps
Spectrum from 0.86 min (8 scans) from CW-011, subtracted
505.0
526.8
536.9
493.0
479.0
457.1
447.2
436.9
413.1
Intensity, cps
m/z, amu
90000
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
420
440
460
480
500
520
540

FIG. 44

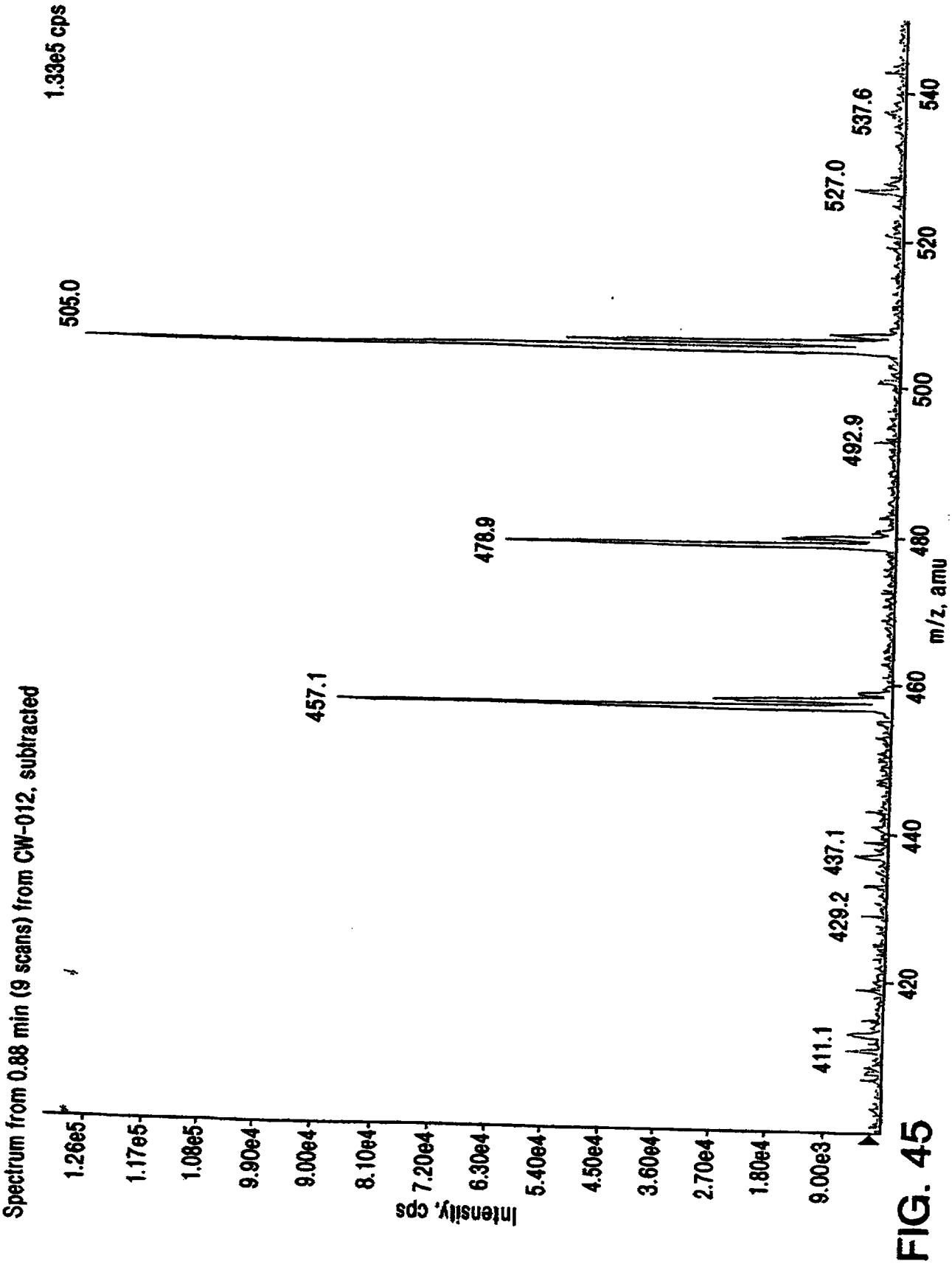

Spectrum from 0.88 min (9 scans) from CW-012, subtracted
1.33e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.1
429.2
437.1
457.1
478.9
492.9
505.0
527.0
537.6
420
440
460
480
500
520
540
m/z, amu

FIG. 45

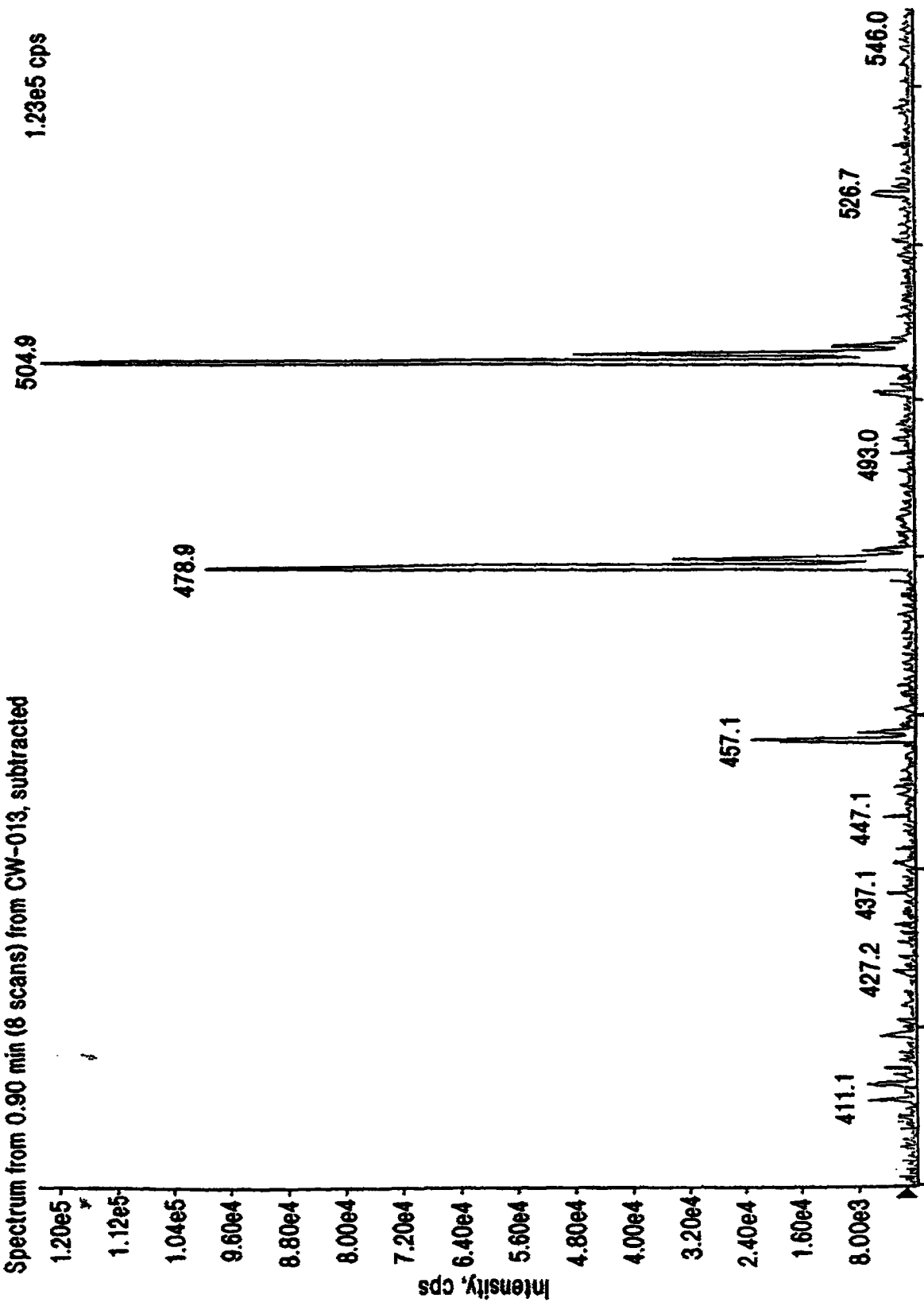

Spectrum from 0.90 min (8 scans) from CW-013, subtracted
1.23e5 cps
Intensity, cps
1.20e5
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
411.1
427.2
437.1
447.1
457.1
478.9
493.0
504.9
526.7
546.0
420
440
460
480
500
520
540
m/z, amu

FIG. 46

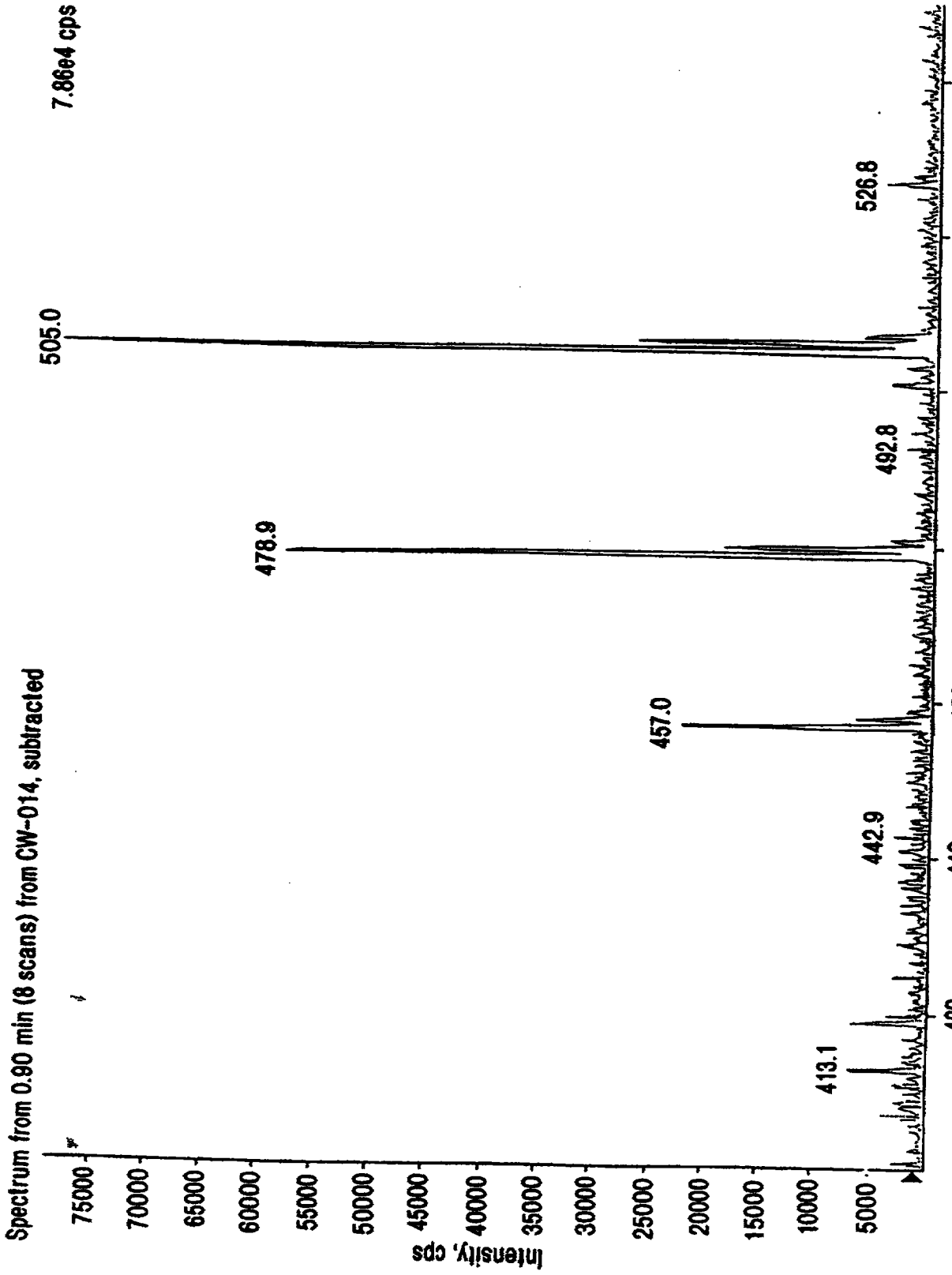

Spectrum from 0.90 min (8 scans) from CW-014, subtracted
7.86e4 cps
Intensity, cps
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
505.0
478.9
457.0
413.1
442.9
492.8
526.8
420
440
460
480
500
520
540
m/z, amu

FIG. 47

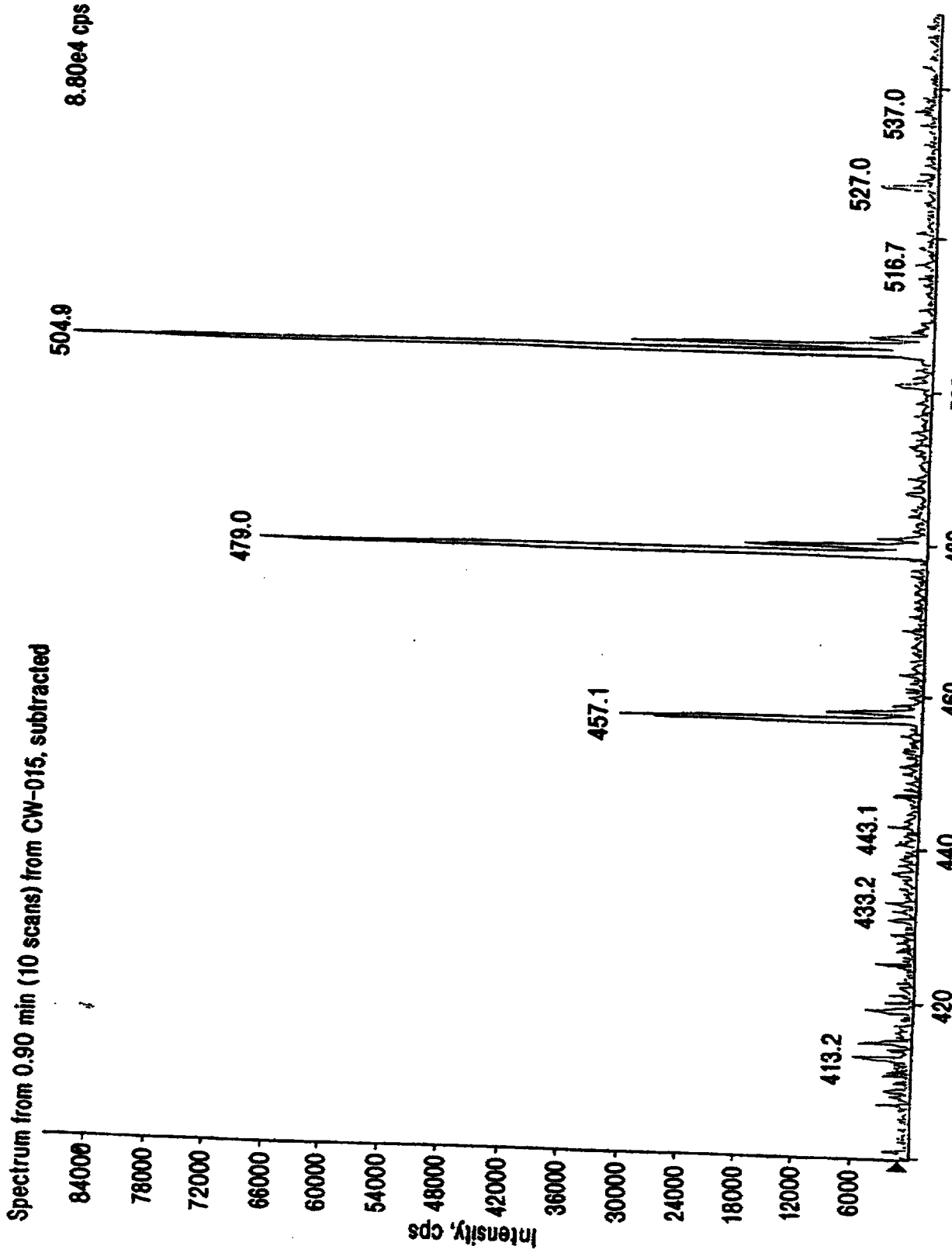

Spectrum from 0.90 min (10 scans) from CW-015, subtracted
8.80e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
504.9
479.0
457.1
443.1
433.2
413.2
527.0
537.0
516.7
420
440
460
480
500
520
540
m/z, amu

FIG. 48

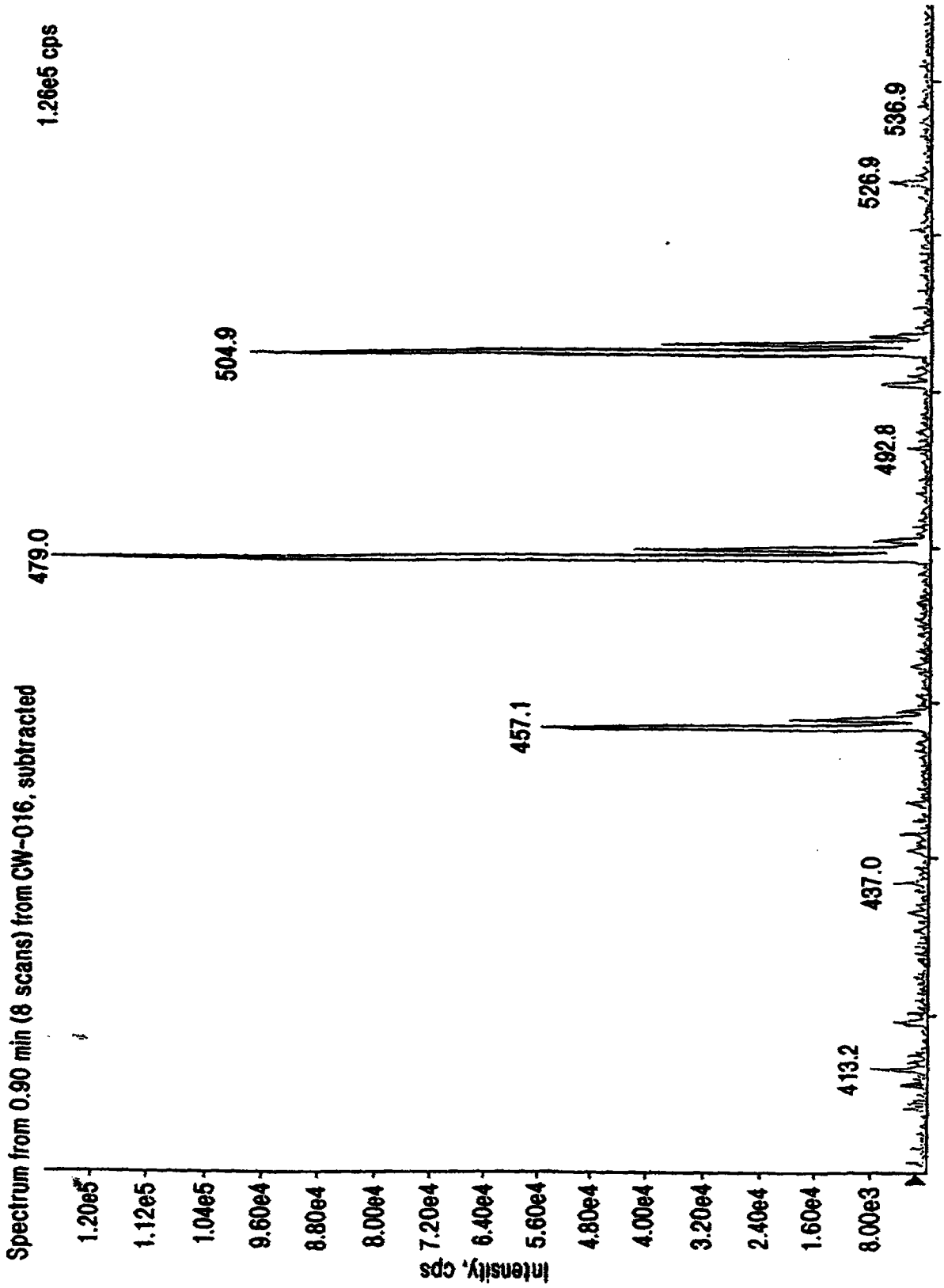

Spectrum from 0.90 min (8 scans) from CW-016, subtracted
1.26e5 cps
Intensity, cps
1.20e5
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
420
440
460
480
500
520
540
413.2
437.0
457.1
479.0
492.8
504.9
526.9
536.9

FIG. 49

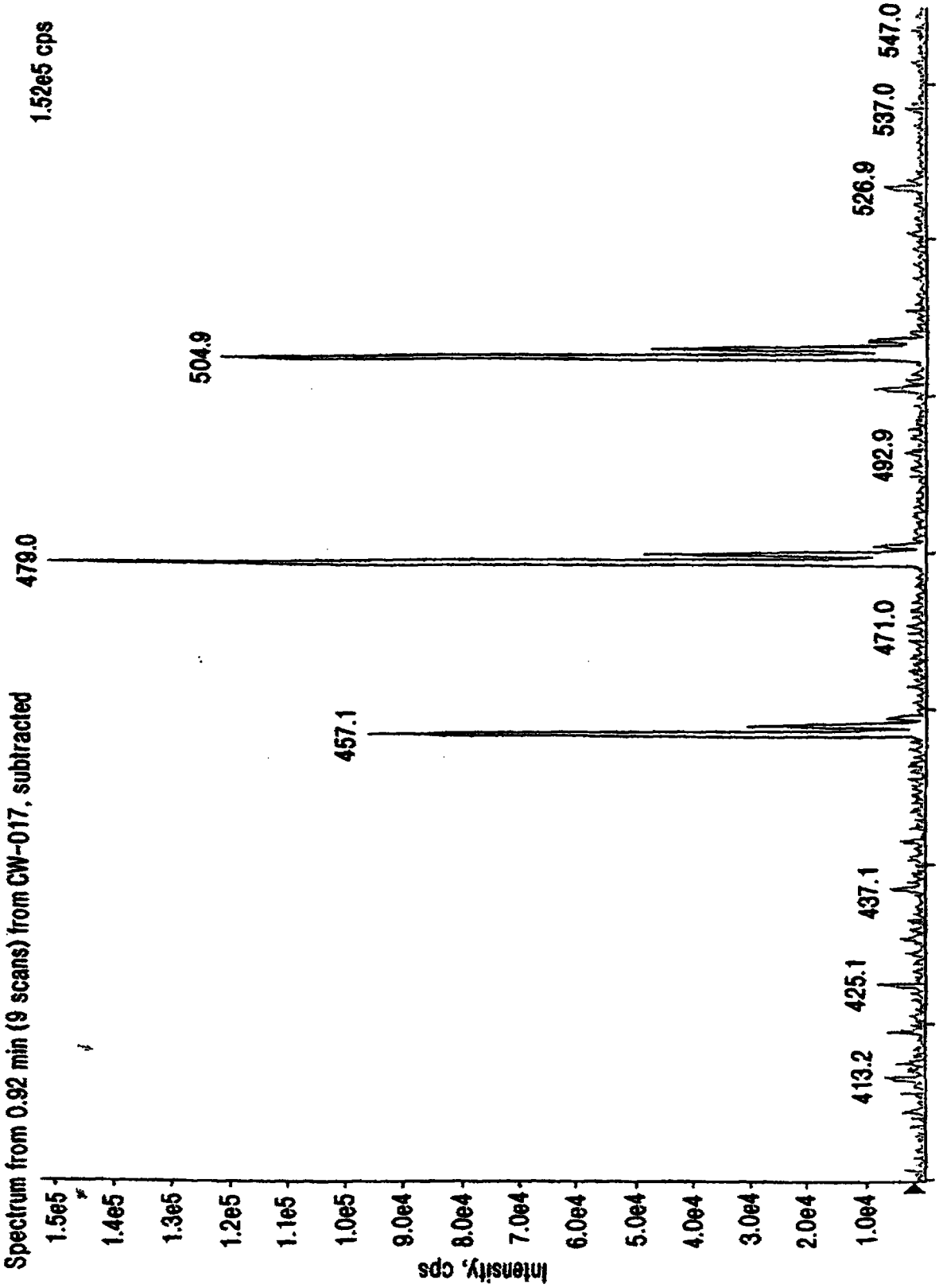

Spectrum from 0.92 min (9 scans) from CW-017, subtracted
1.52e5 cps
Intensity, cps
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
413.2
425.1
437.1
457.1
471.0
479.0
492.9
504.9
526.9
537.0
547.0
420
440
460
480
500
520
540
m/z, amu

FIG. 50

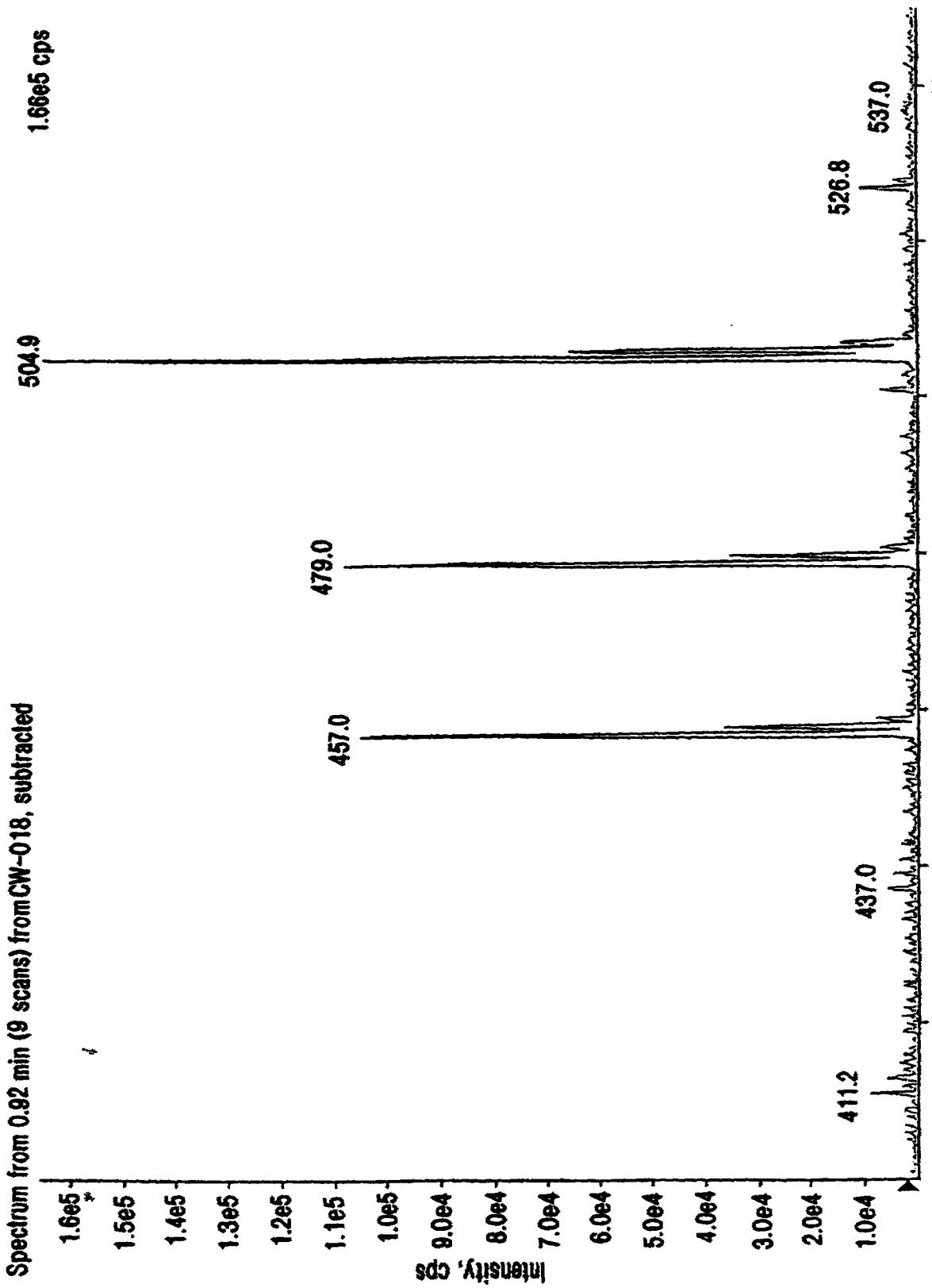

Spectrum from 0.92 min (9 scans) from CW-018, subtracted
1.66e5 cps
Intensity, cps
m/z, amu
504.9
479.0
457.0
437.0
411.2
526.8
537.0

FIG. 51

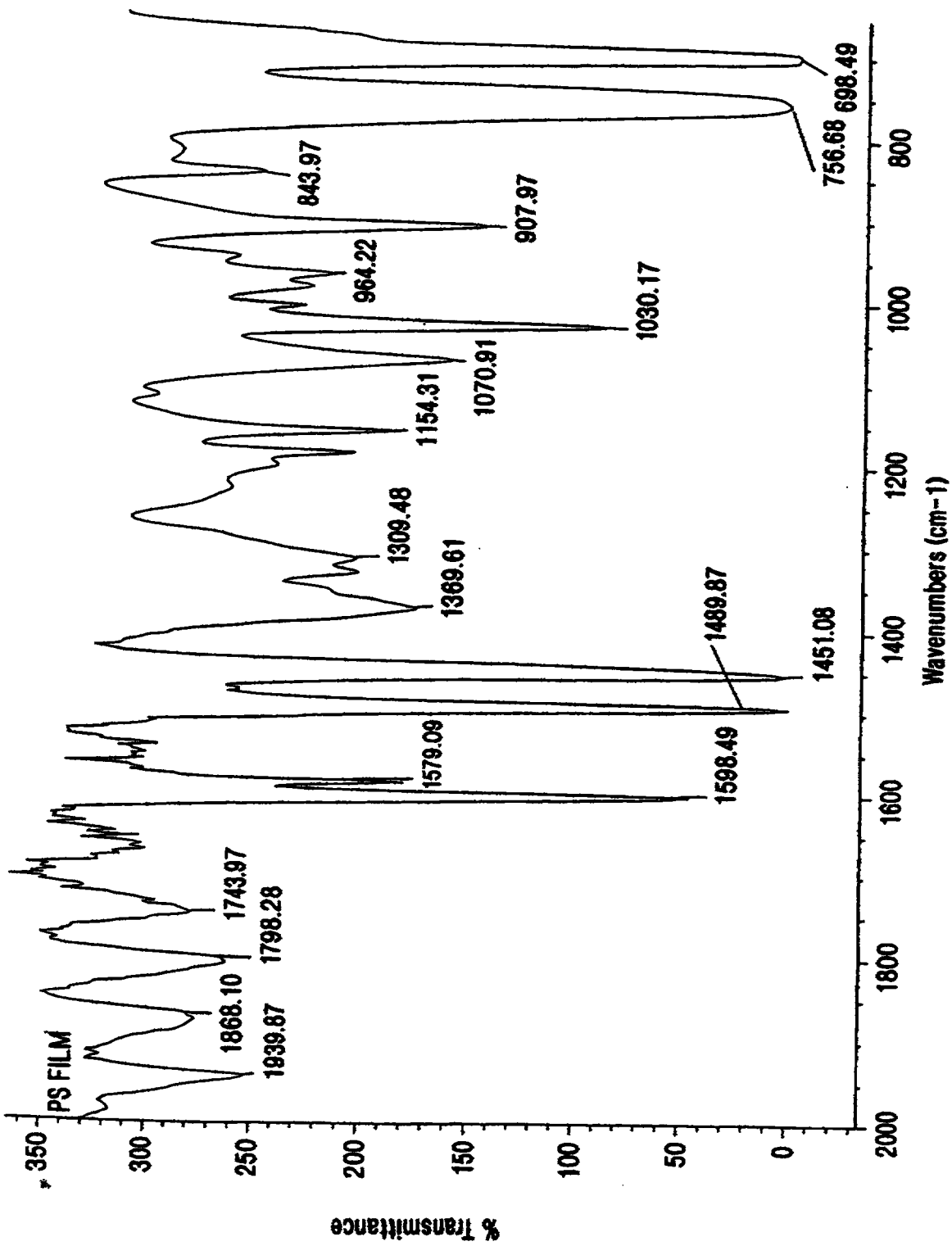

% Transmittance
350
300
250
200
150
100
50
0
2000
1800
1600
1400
1200
1000
800
Wavenumbers (cm-1)
PS FILM
1939.87
1868.10
1798.28
1743.97
1598.49
1579.09
1489.87
1451.08
1369.61
1309.48
1154.31
1070.91
1030.17
964.22
907.97
843.97
756.68
698.49

FIG. 52

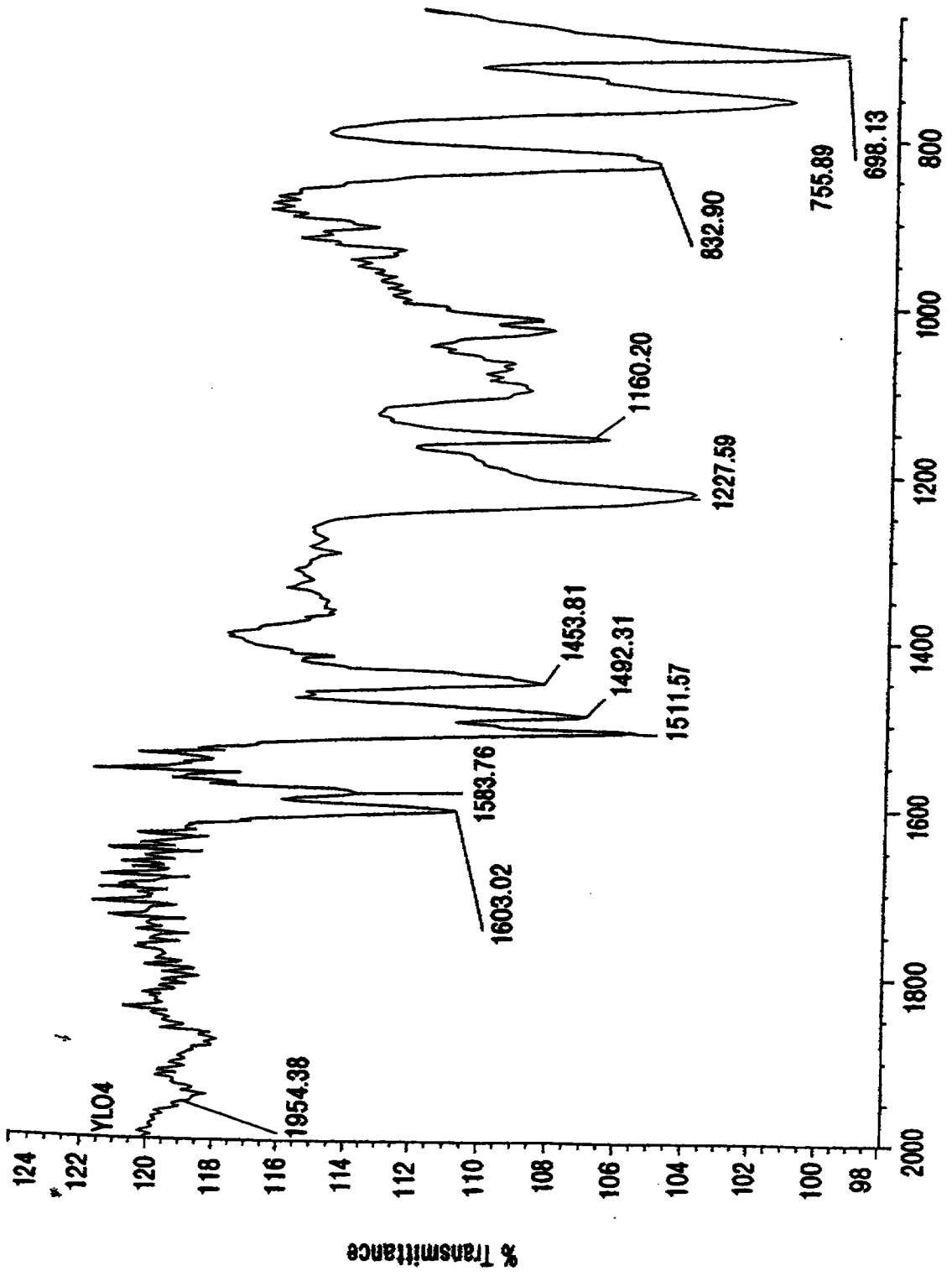

YLO4
1954.38
1603.02
1583.76
1511.57
1492.31
1453.81
1227.59
1160.20
832.90
755.89
698.13
% Transmittance
Wavenumbers (cm-1)
124
122
120
118
116
114
112
110
108
106
104
102
100
98
2000
1800
1600
1400
1200
1000
800

FIG. 53

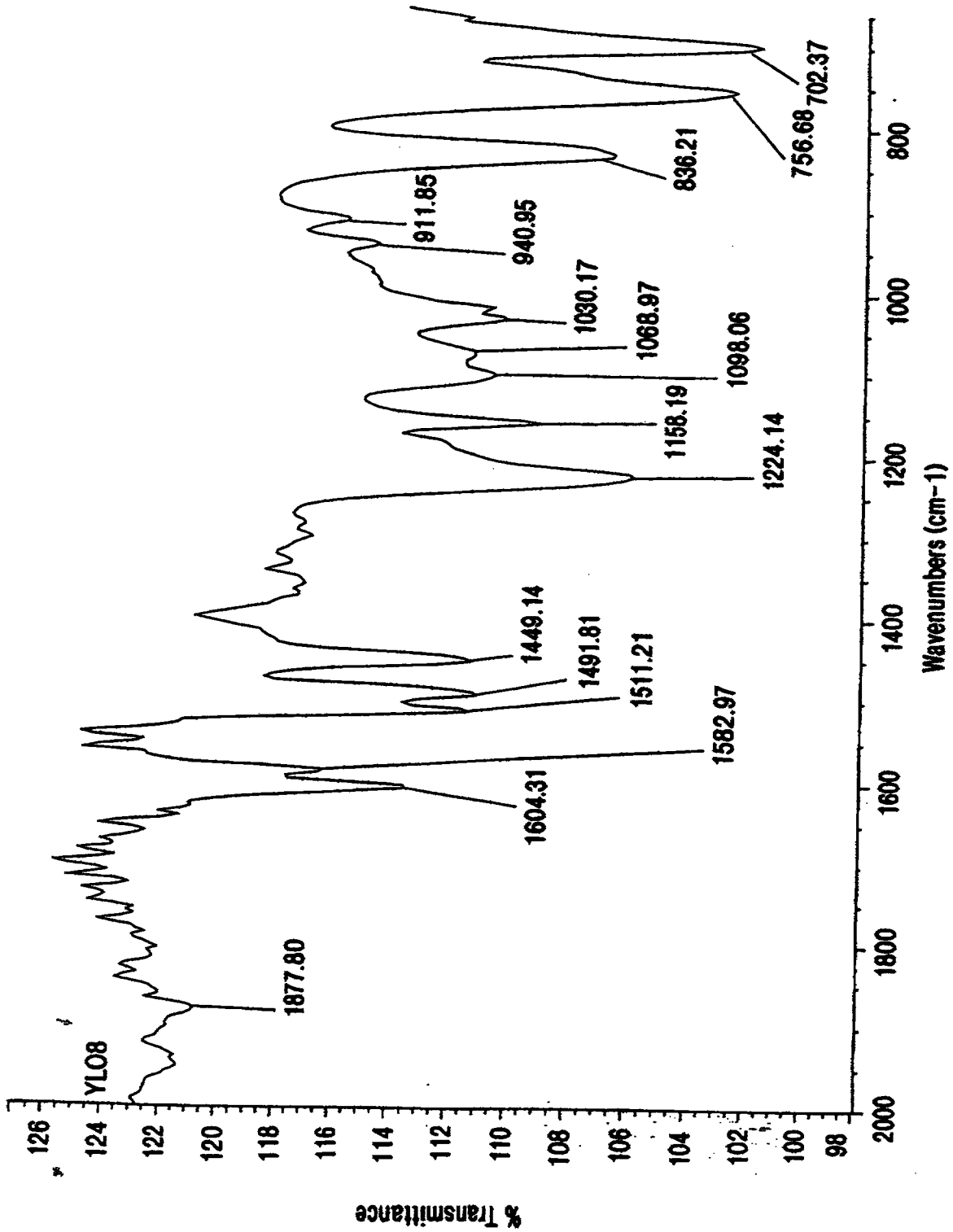

YLO8
1877.80
1604.31
1582.97
1511.21
1491.81
1449.14
1224.14
1158.19
1098.06
1068.97
1030.17
940.95
911.85
836.21
756.68
702.37
% Transmittance
Wavenumbers (cm-1)

FIG. 54

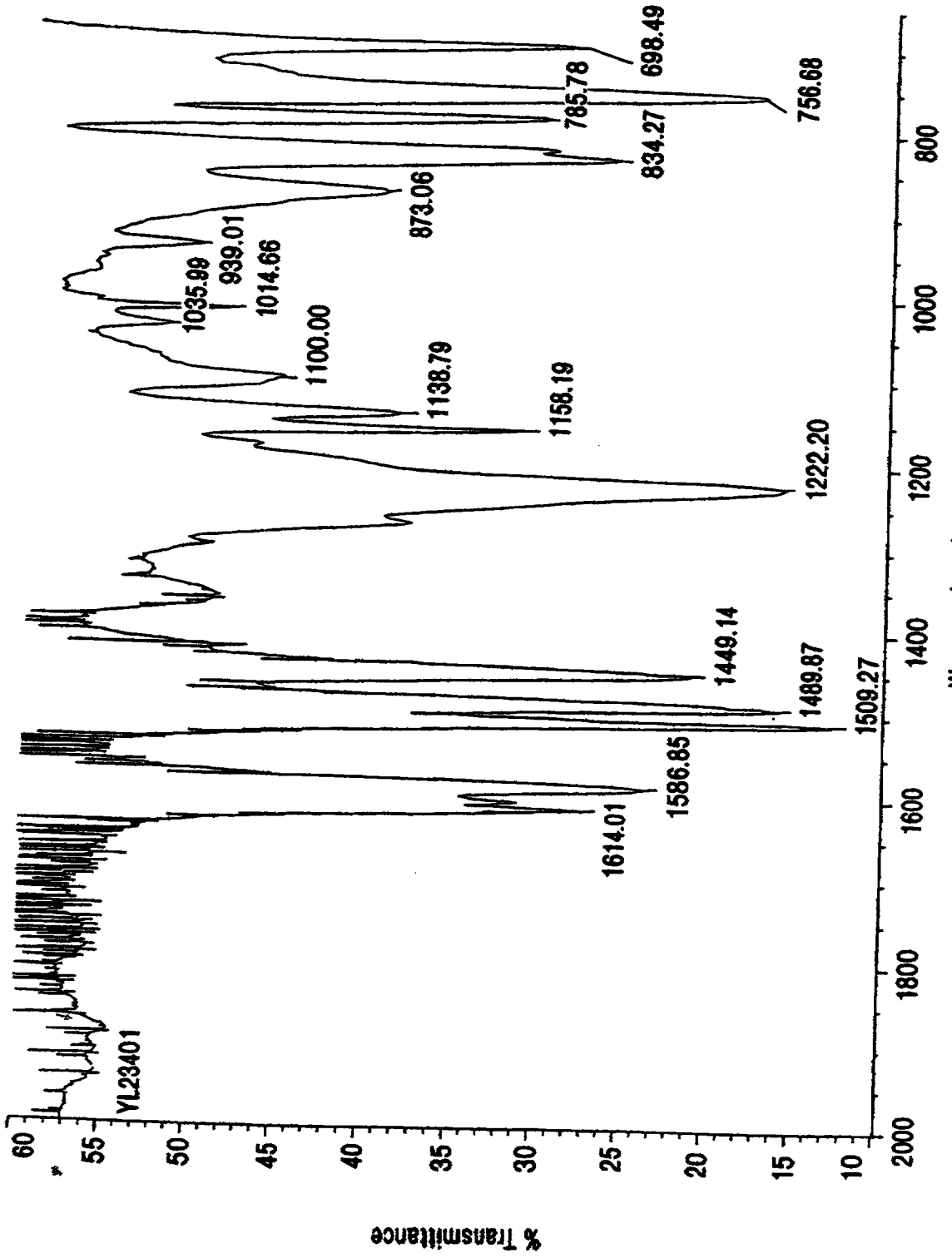

YL23401
% Transmittance
Wavenumbers (cm-1)
60
55
50
45
40
35
30
25
20
15
10
2000
1800
1600
1400
1200
1000
800
1614.01
1586.85
1509.27
1489.87
1449.14
1222.20
1158.19
1138.79
1100.00
1035.99
1014.66
939.01
873.06
834.27
785.78
756.68
698.49

FIG. 55

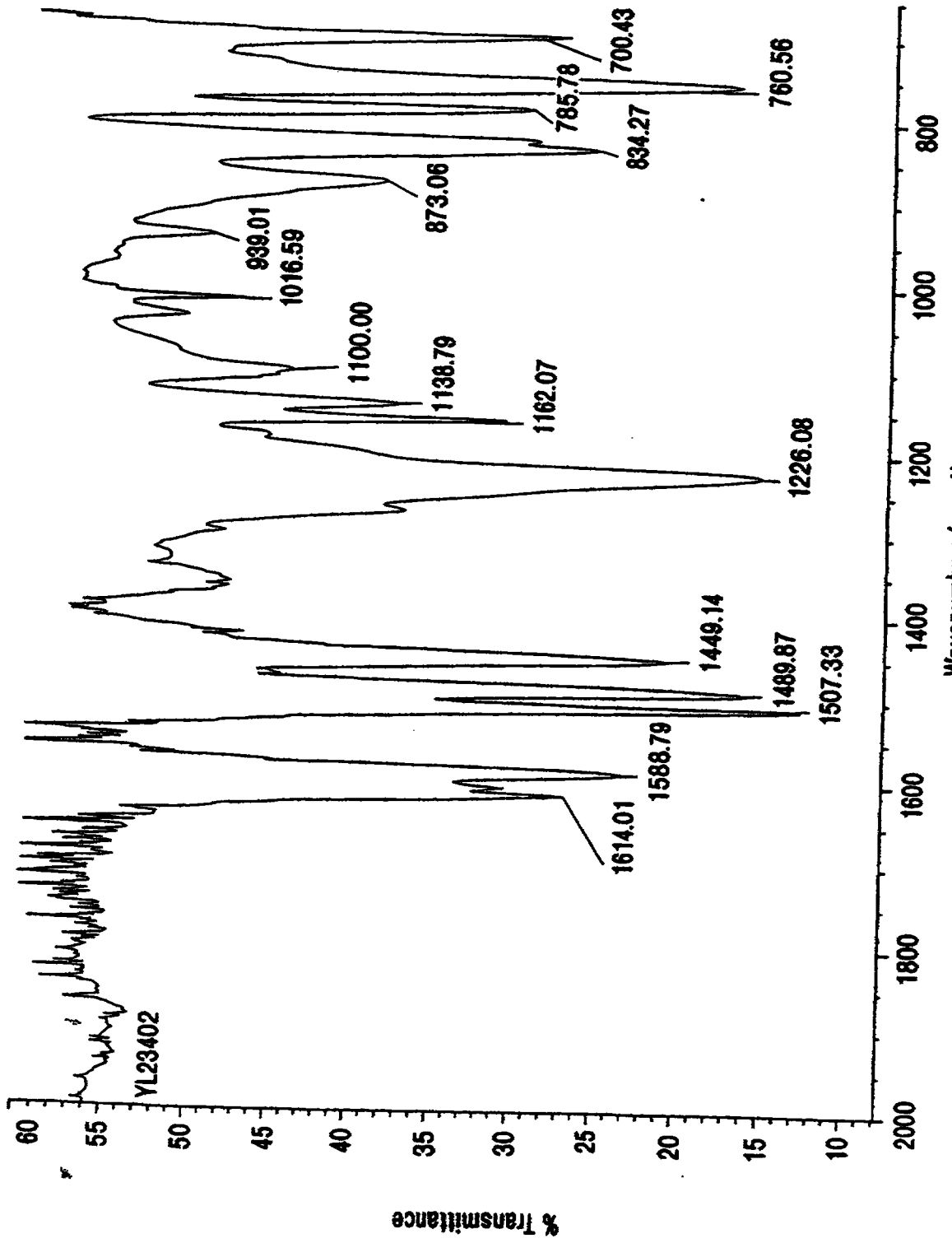

YL23402
% Transmittance
Wavenumbers (cm-1)
700.43
760.56
785.78
834.27
873.06
939.01
1016.59
1100.00
1138.79
1162.07
1226.08
1449.14
1489.87
1507.33
1588.79
1614.01

FIG. 56

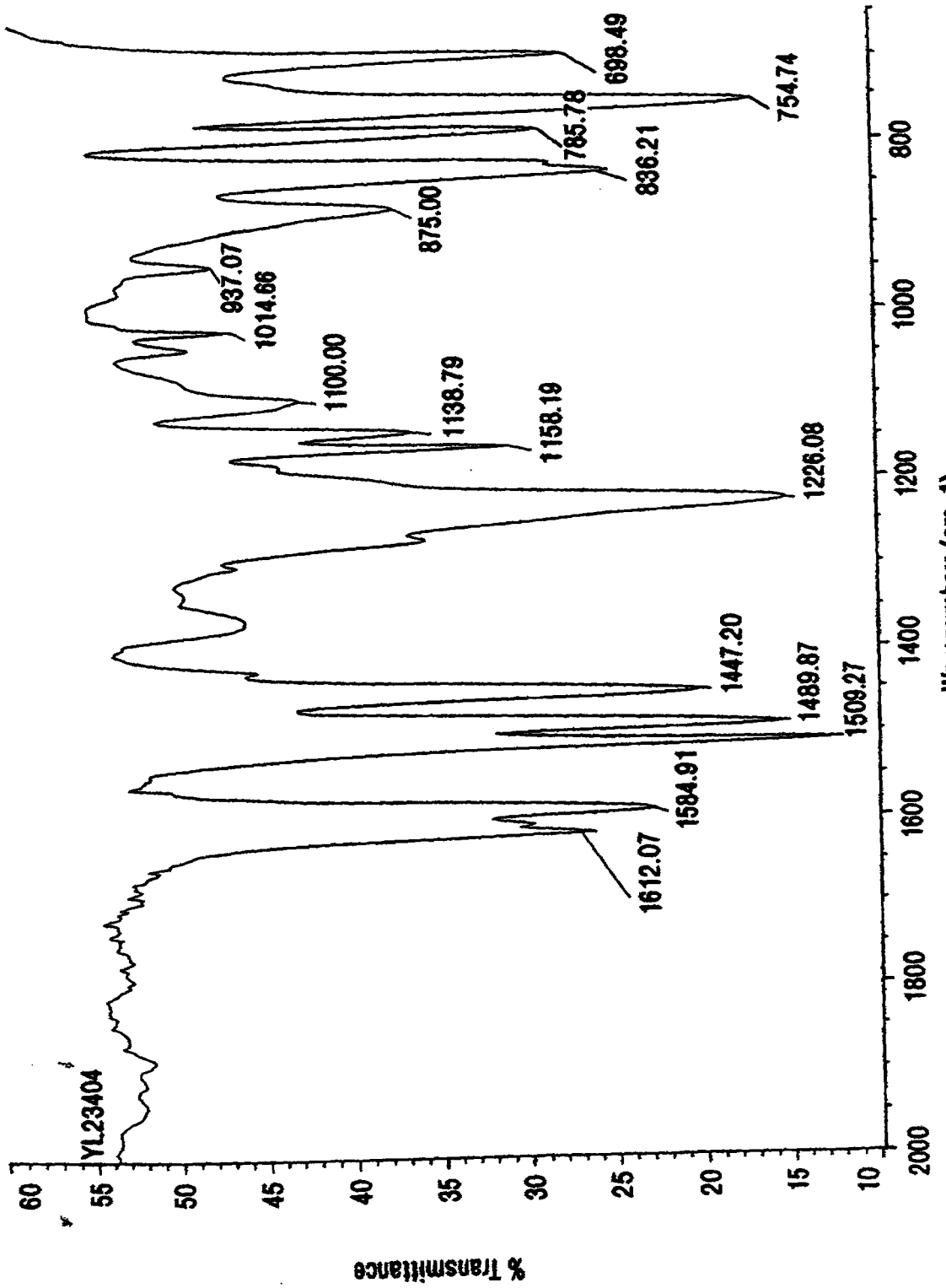

YL2304
% Transmittance
60
55
50
45
40
35
30
25
20
15
10
2000
1800
1600
1400
1200
1000
800
Wavenumbers (cm-1)
1612.07
1584.91
1509.27
1489.87
1447.20
1226.08
1158.19
1138.79
1100.00
1014.66
937.07
875.00
836.21
785.78
754.74
698.49

FIG. 57

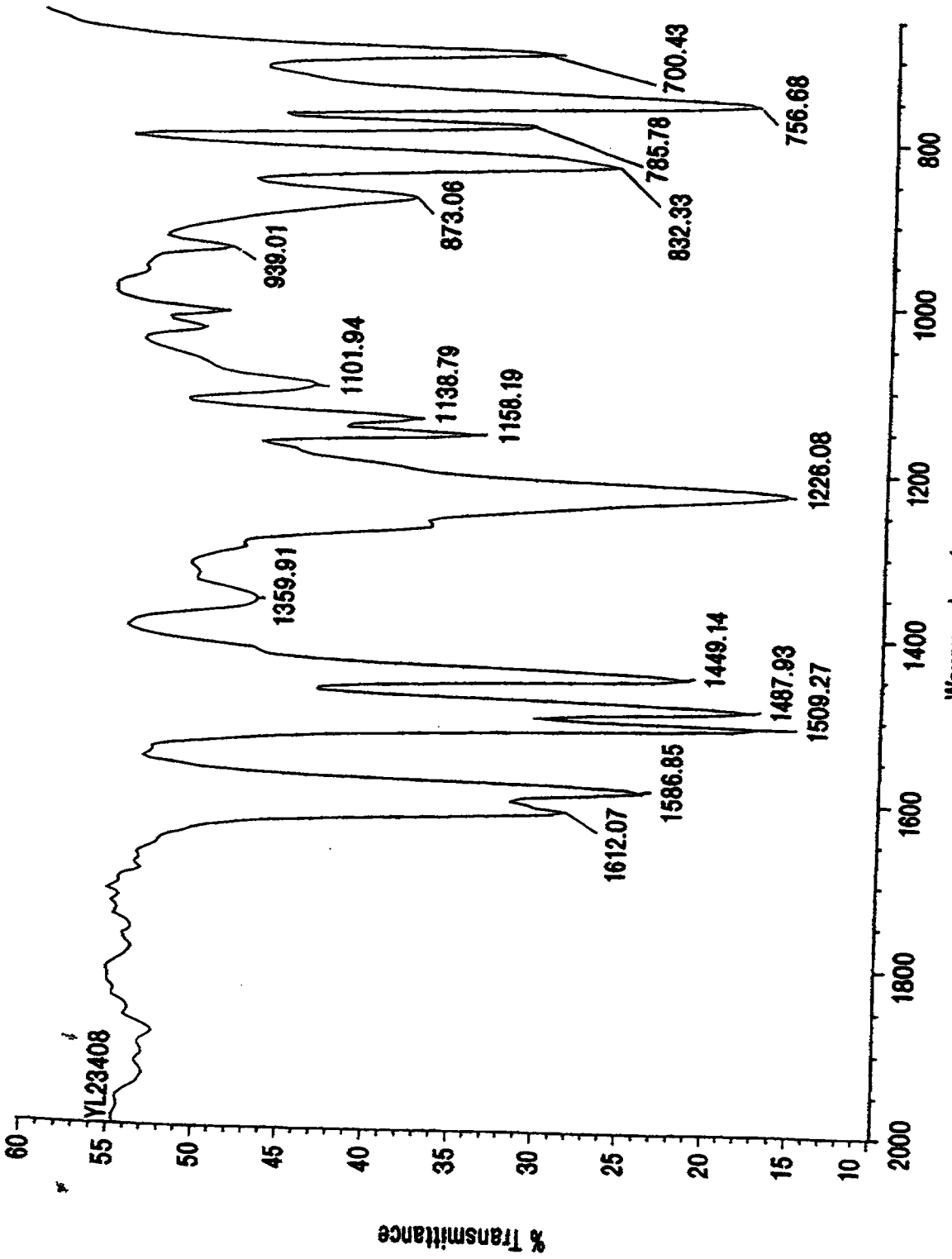

YL23408
700.43
756.68
785.78
832.33
873.06
939.01
1101.94
1138.79
1158.19
1226.08
1359.91
1449.14
1487.93
1509.27
1586.85
1612.07
% Transmittance
Wavenumbers (cm-1)
60
55
50
45
40
35
30
25
20
15
10
2000
1800
1600
1400
1200
1000
800

FIG. 58

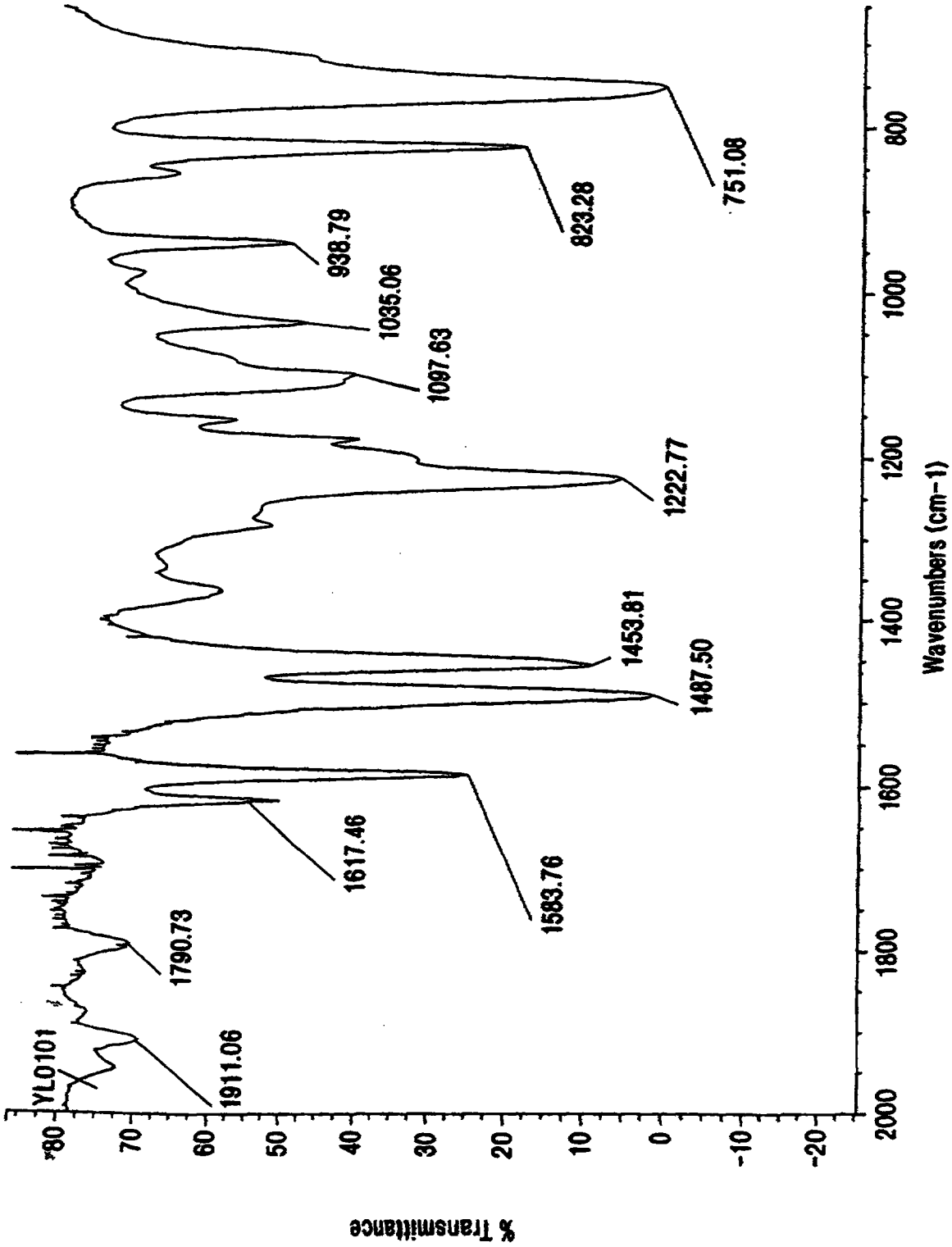

YL0101
1911.06
1790.73
1617.46
1583.76
1487.50
1453.81
1222.77
1097.63
1035.06
938.79
823.28
751.08
% Transmittance
Wavenumbers (cm-1)

FIG. 59

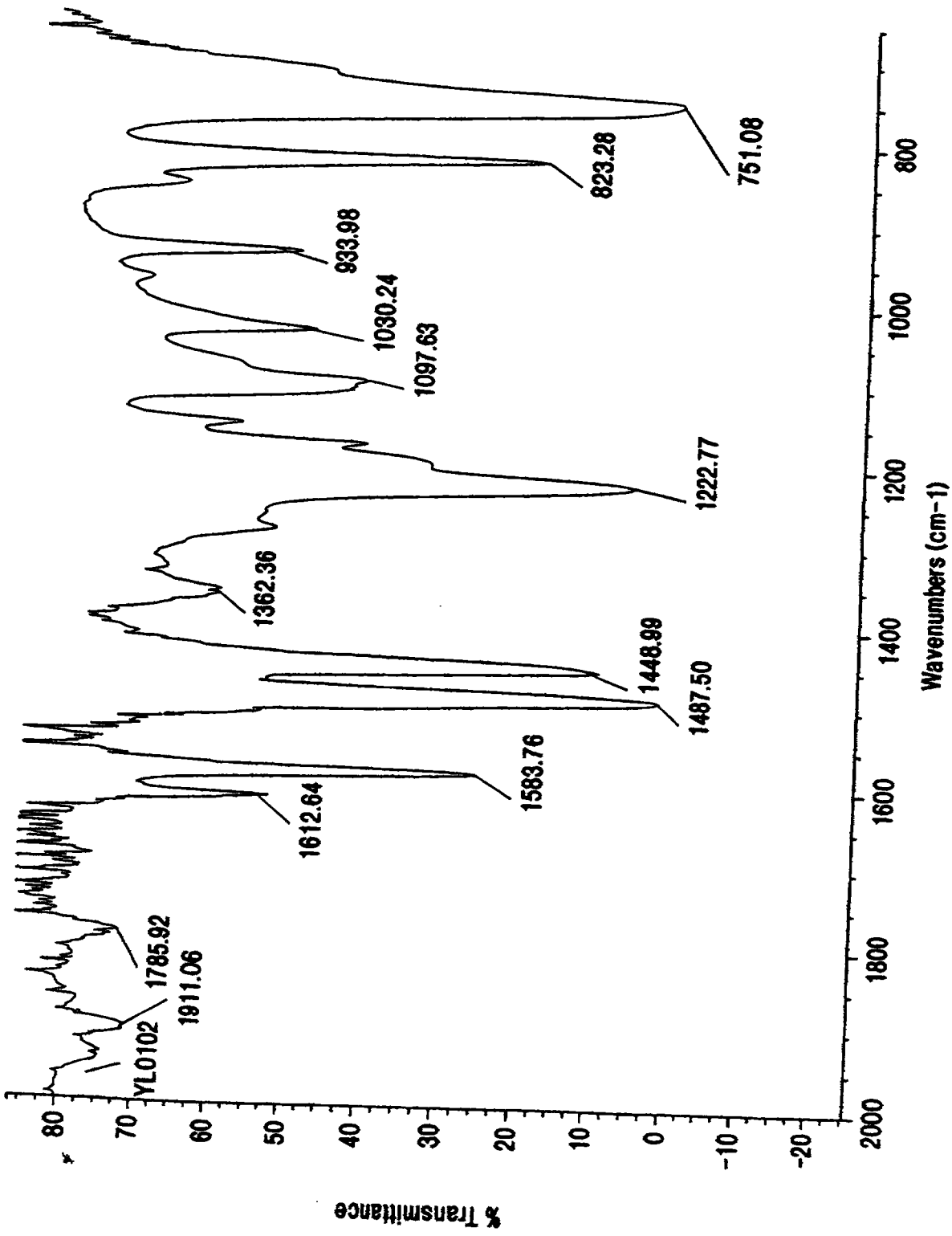

YL0102
1785.92
1911.06
1612.64
1583.76
1487.50
1448.99
1362.36
1222.77
1097.63
1030.24
933.98
823.28
751.08
% Transmittance
Wavenumbers (cm-1)

FIG. 60

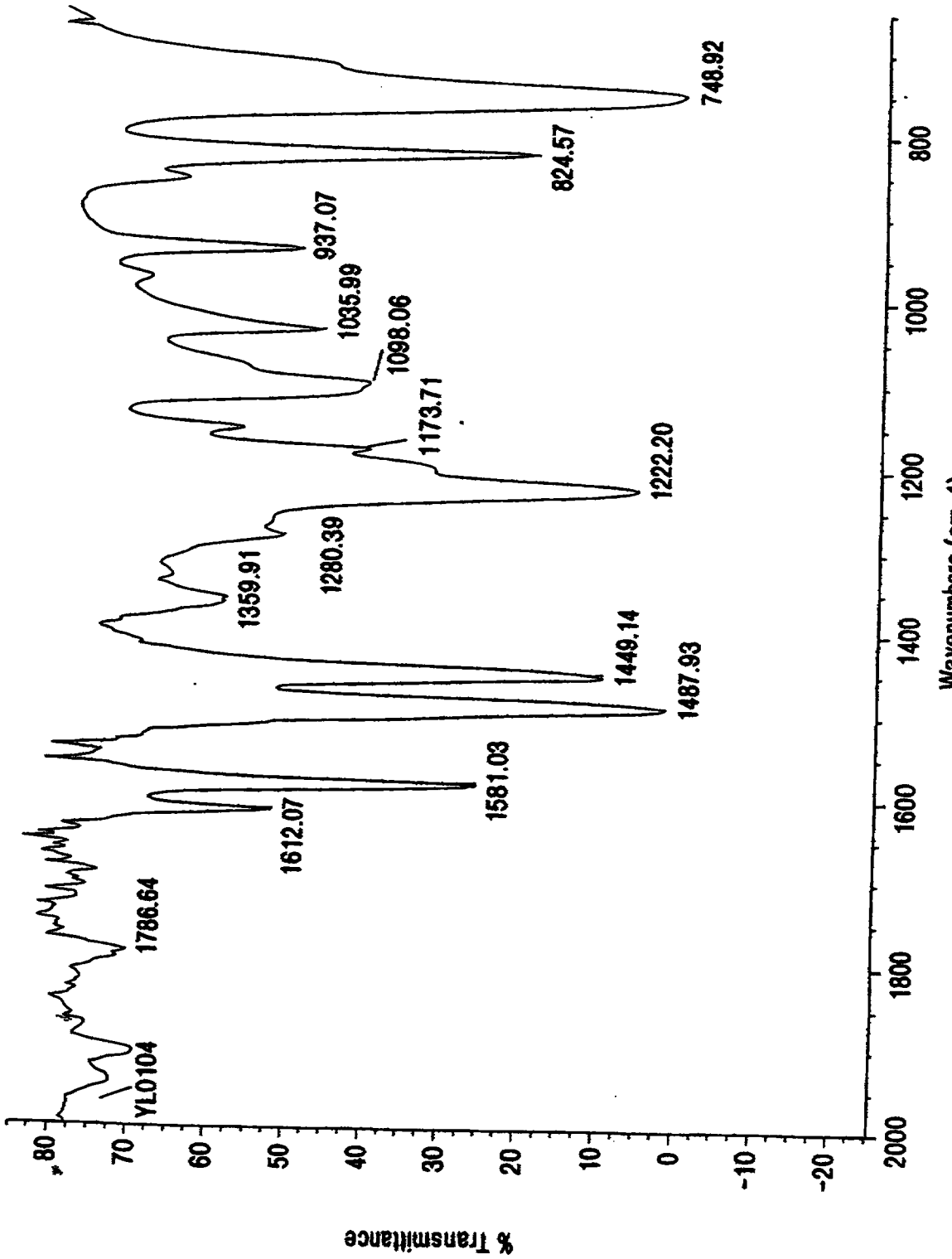

YL0104
1786.64
1612.07
1581.03
1487.93
1449.14
1359.91
1280.39
1222.20
1173.71
1098.06
1035.99
937.07
824.57
748.92
% Transmittance
Wavenumbers (cm-1)

FIG. 61

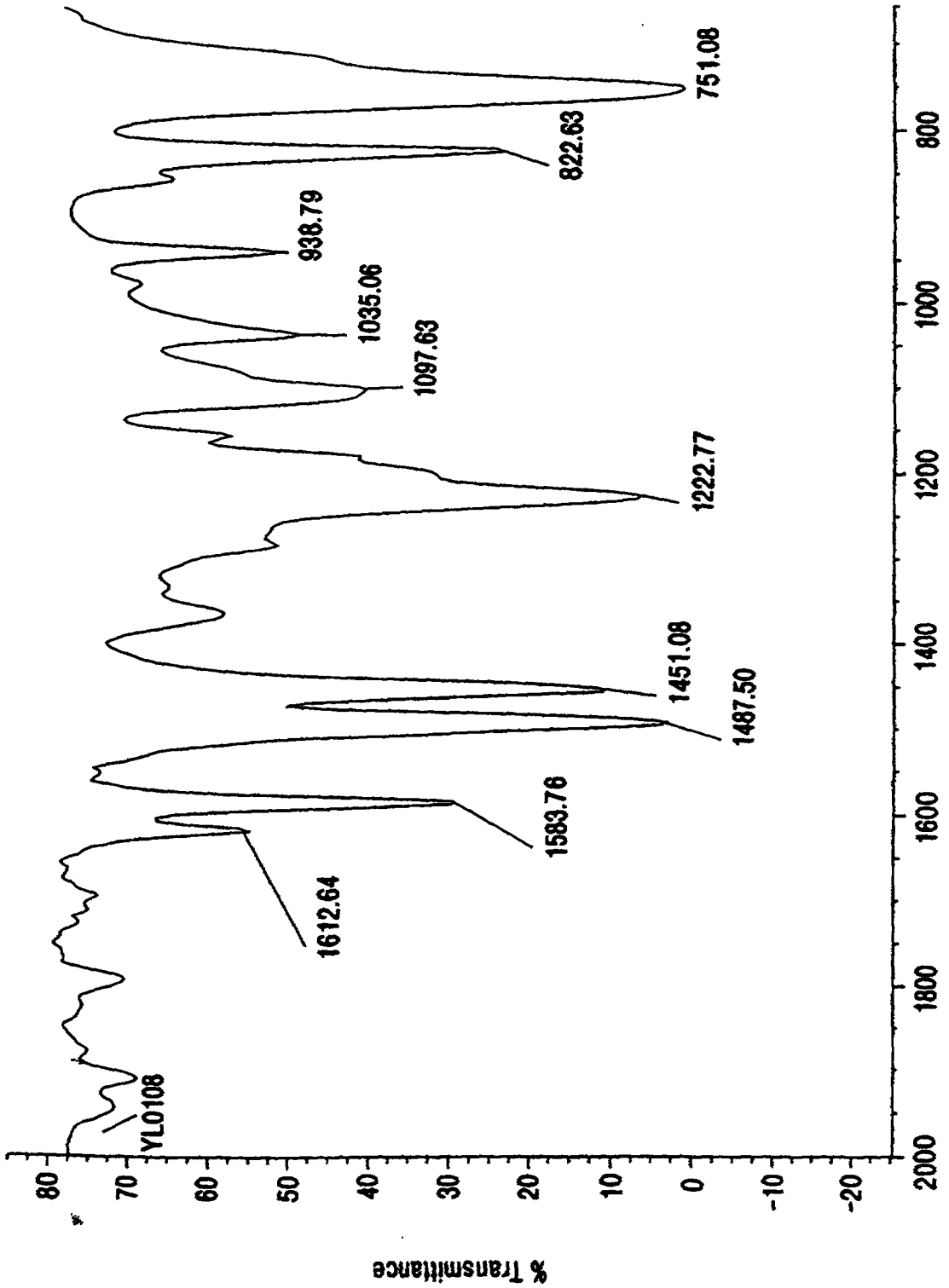

YL0108
1612.64
1583.76
1487.50
1451.08
1222.77
1097.63
1035.06
938.79
822.63
751.08
% Transmittance
Wavenumbers (cm-1)

FIG. 62

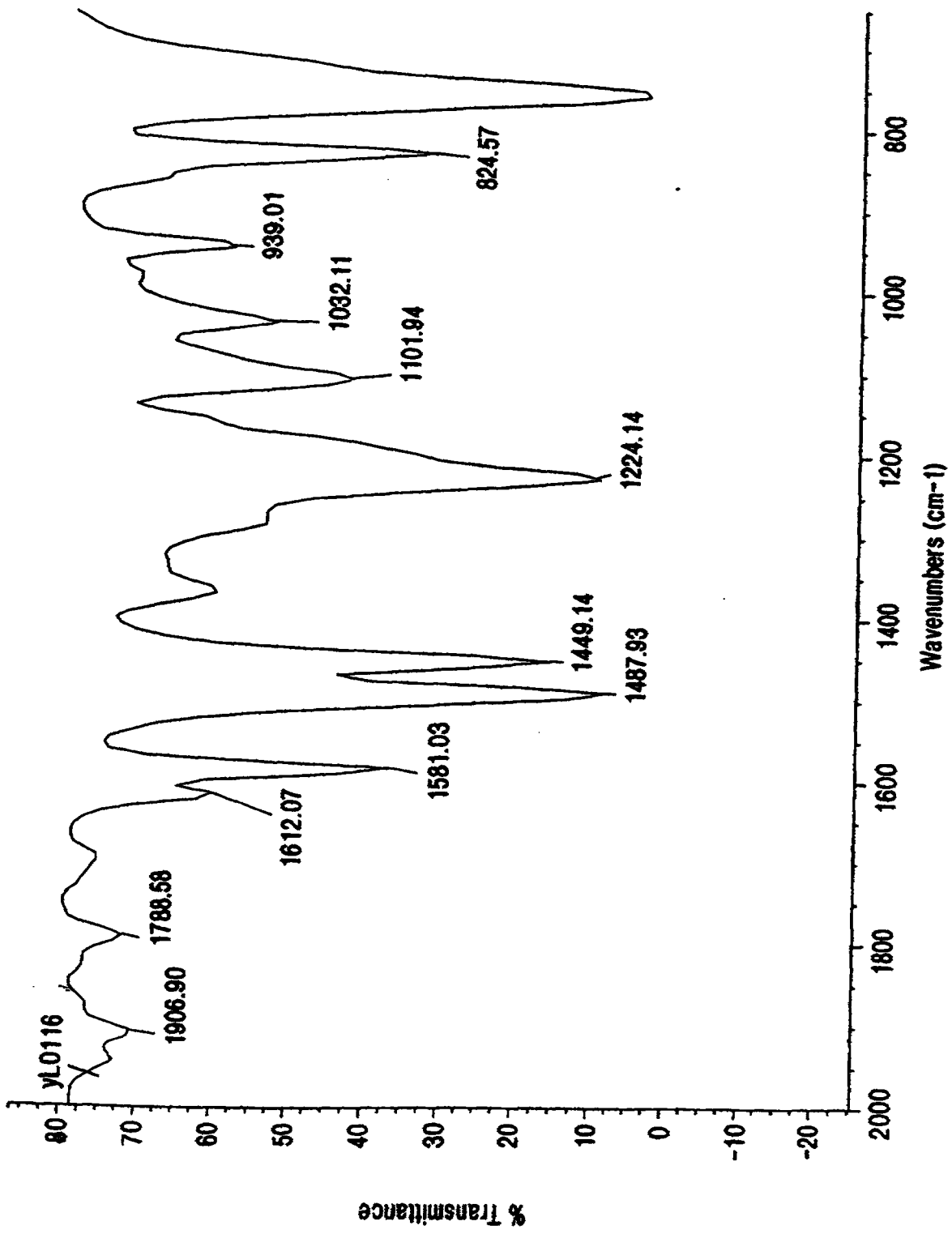

yL0116
1906.90
1788.58
1612.07
1581.03
1487.93
1449.14
1224.14
1101.94
1032.11
939.01
824.57
% Transmittance
80
70
60
50
40
30
20
10
0
-10
-20
2000
1800
1600
1400
1200
1000
800
Wavenumbers (cm-1)

FIG. 63

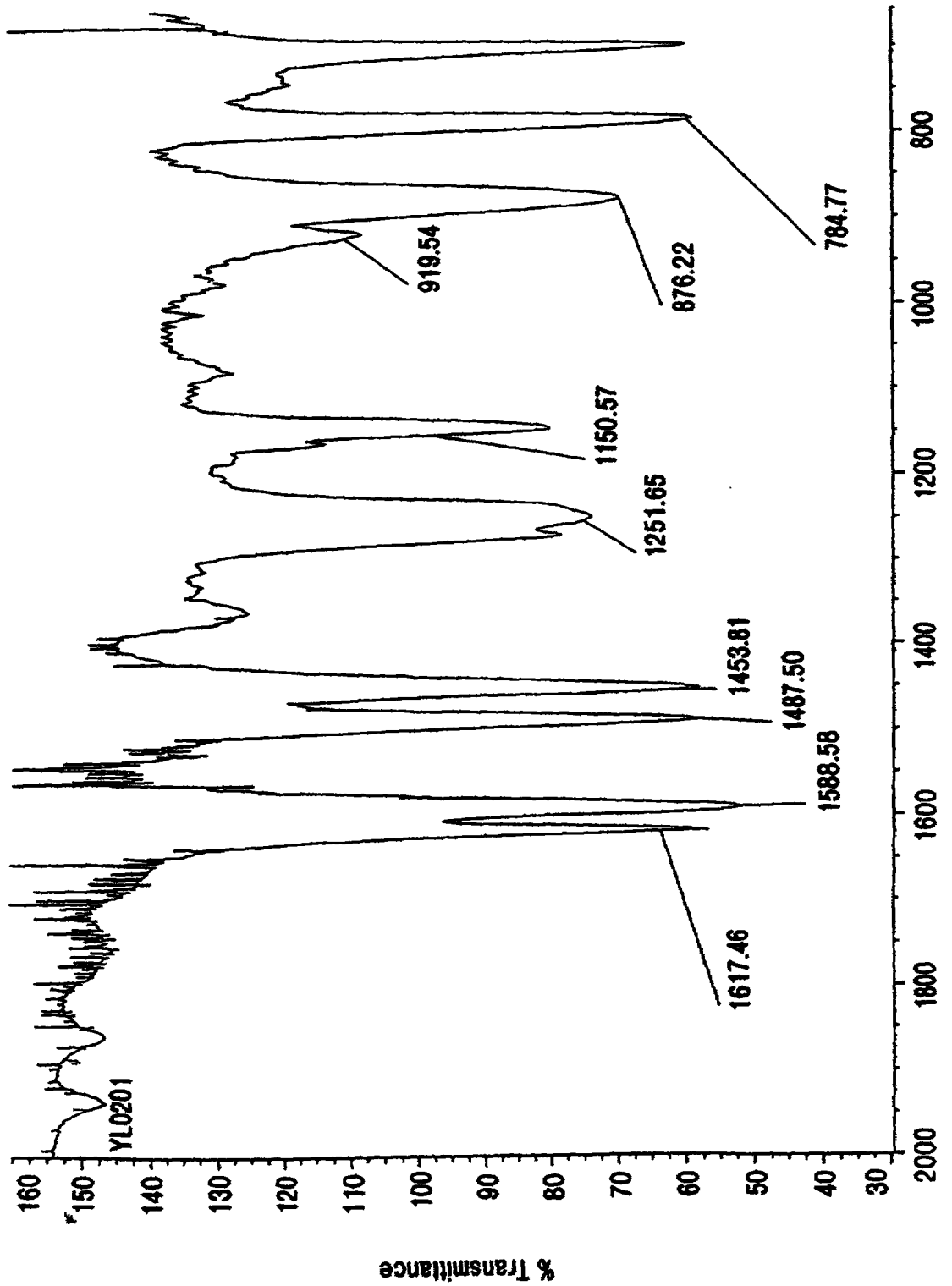

YL0201
1617.46
1588.58
1487.50
1453.81
1251.65
1150.57
919.54
876.22
784.77
% Transmittance
Wavenumbers (cm-1)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
2000
1800
1600
1400
1200
1000
800

FIG. 64

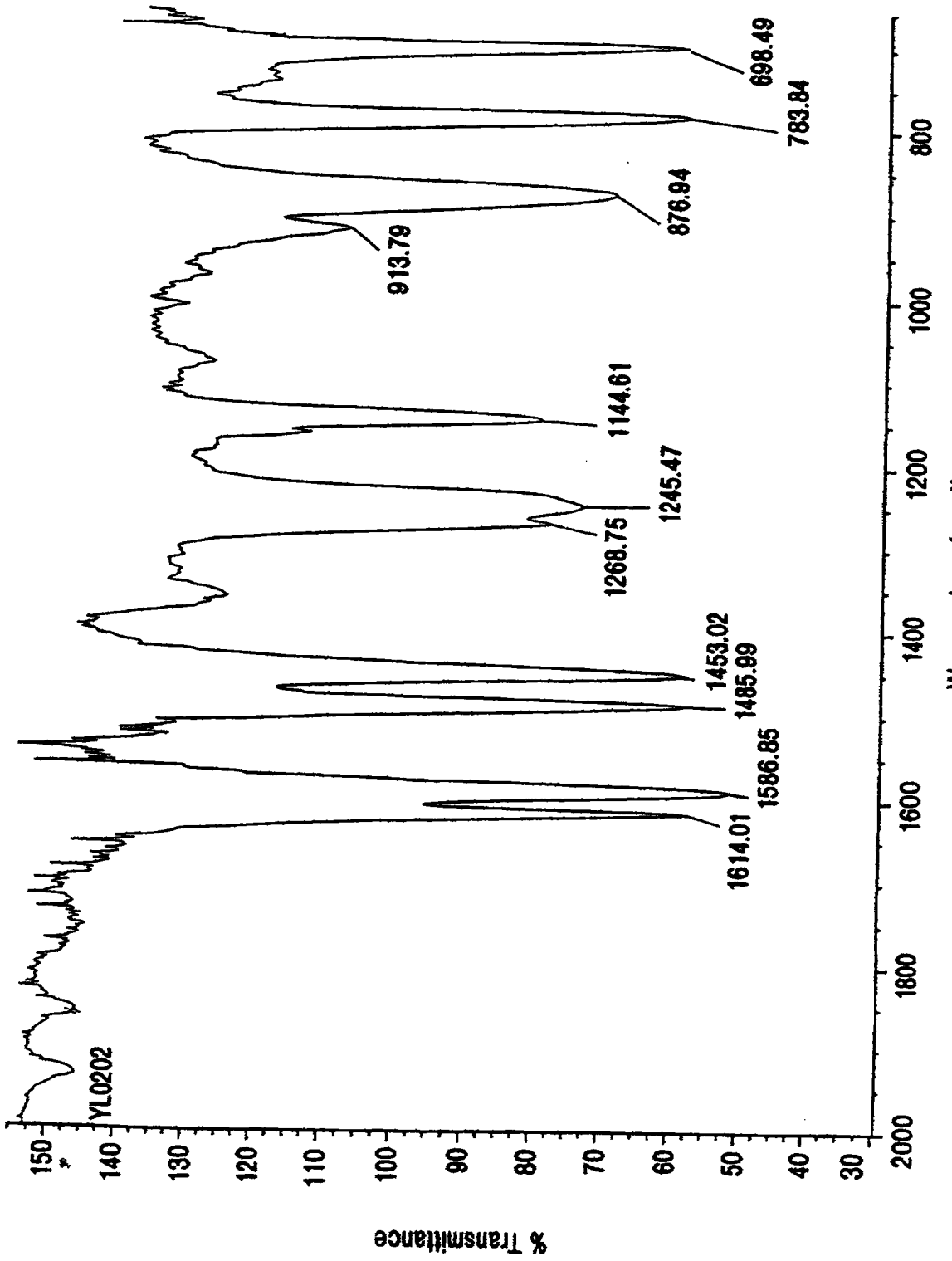

YL0202
% Transmittance
Wavenumbers (cm-1)
150
140
130
120
110
100
90
80
70
60
50
40
30
2000
1800
1600
1400
1200
1000
800
1614.01
1586.85
1485.99
1453.02
1268.75
1245.47
1144.61
913.79
876.94
783.84
698.49

FIG. 65

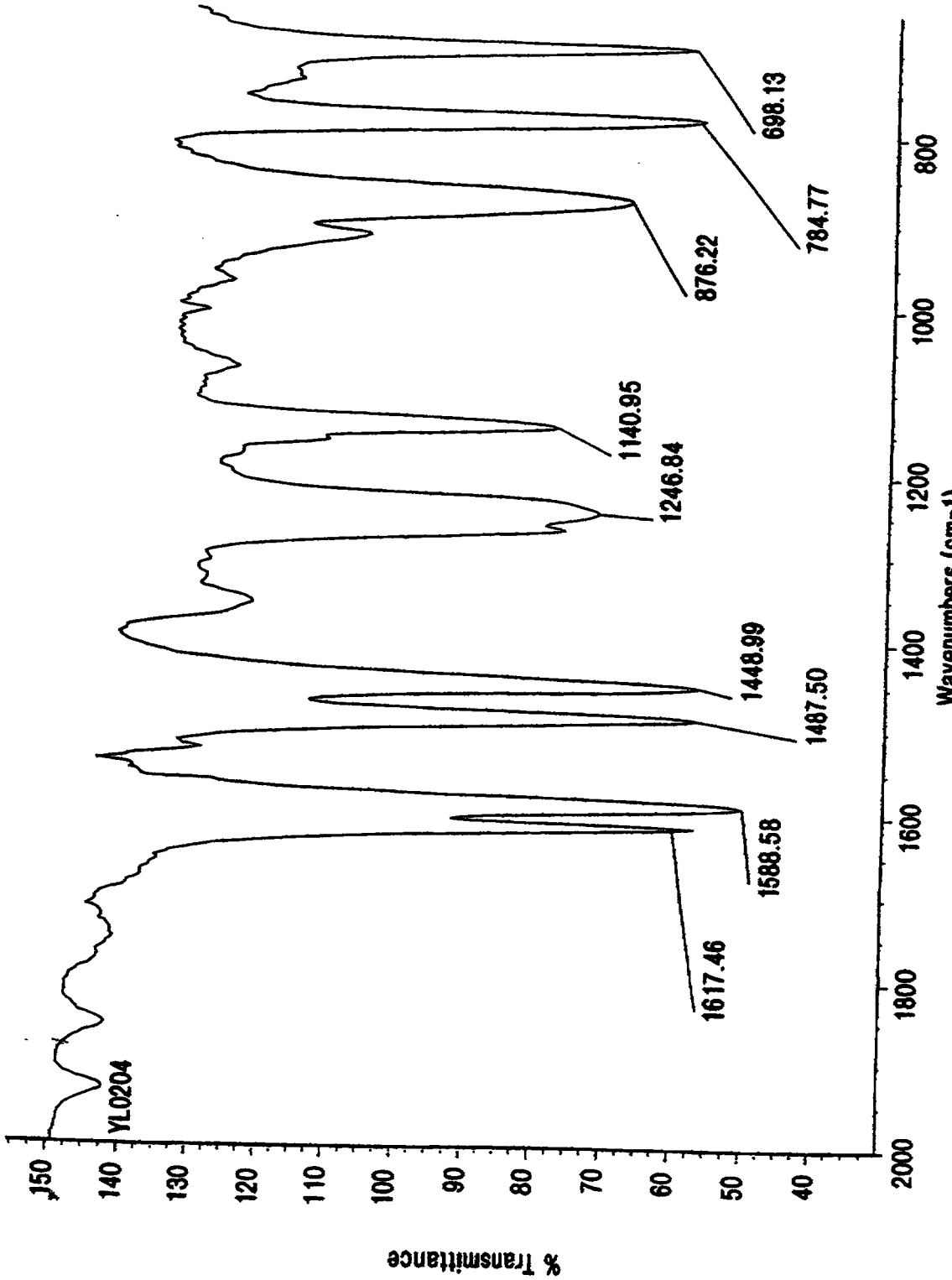

YL0204
698.13
784.77
876.22
1140.95
1246.84
1448.99
1487.50
1588.58
1617.46
% Transmittance
Wavenumbers (cm-1)
150
140
130
120
110
100
90
80
70
60
50
40
2000
1800
1600
1400
1200
1000
800

FIG. 66

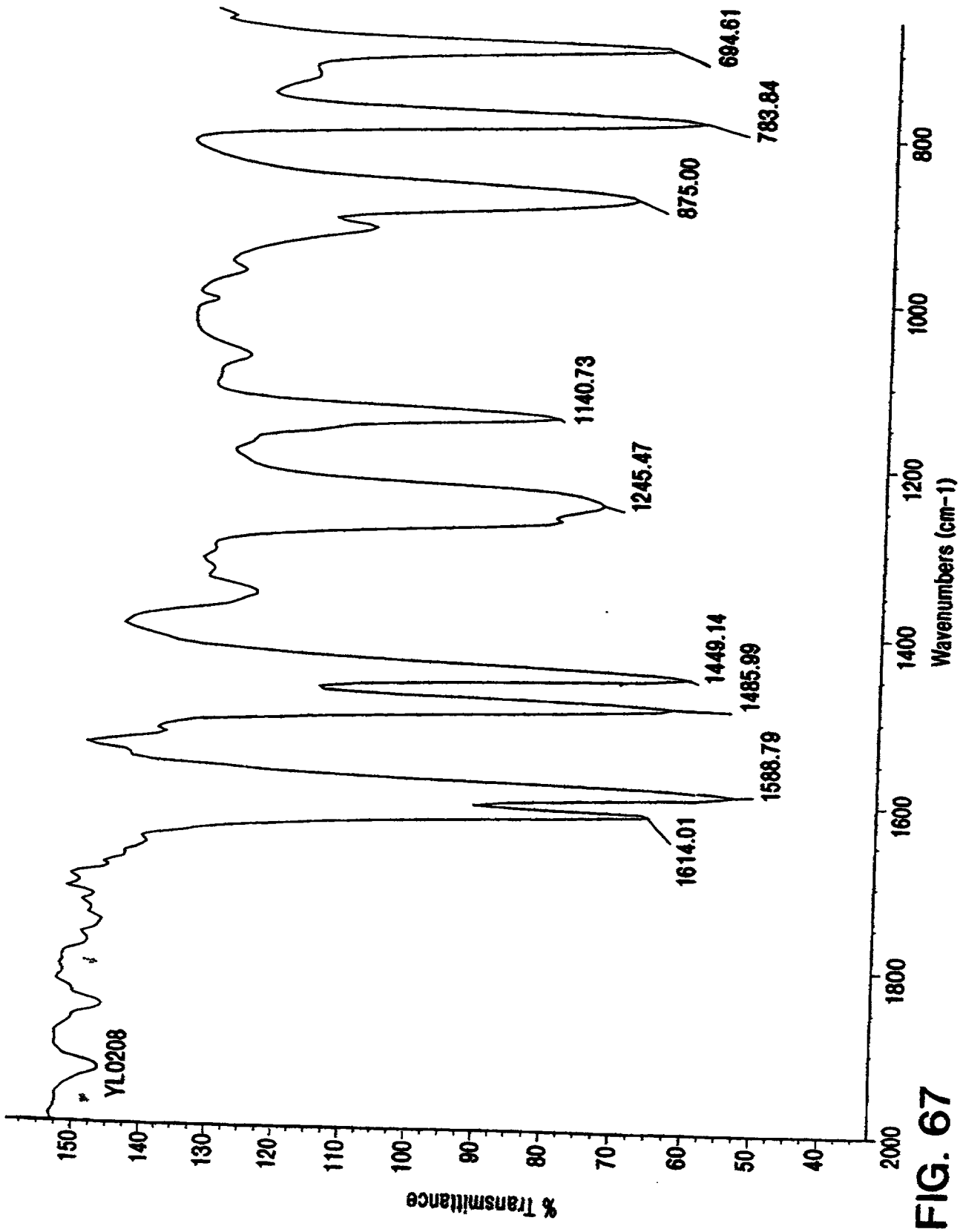

YL0208
% Transmittance
Wavenumbers (cm-1)
150
140
130
120
110
100
90
80
70
60
50
40
2000
1800
1600
1400
1200
1000
800
1614.01
1588.79
1485.99
1449.14
1245.47
1140.73
875.00
783.84
694.61

FIG. 67

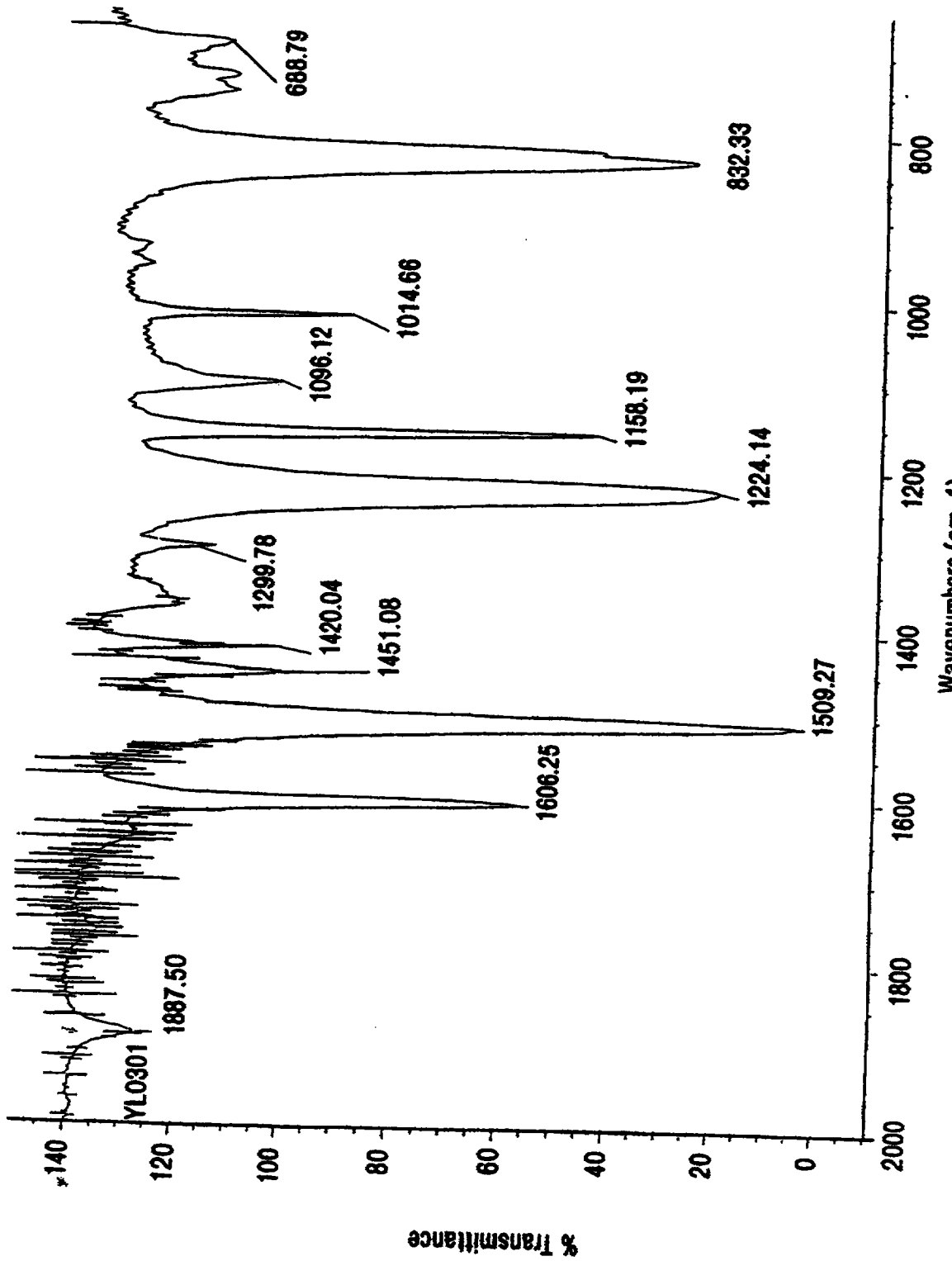

YL0301
1887.50
1606.25
1509.27
1451.08
1420.04
1299.78
1224.14
1158.19
1096.12
1014.66
832.33
688.79
% Transmittance
Wavenumbers (cm-1)

FIG. 68

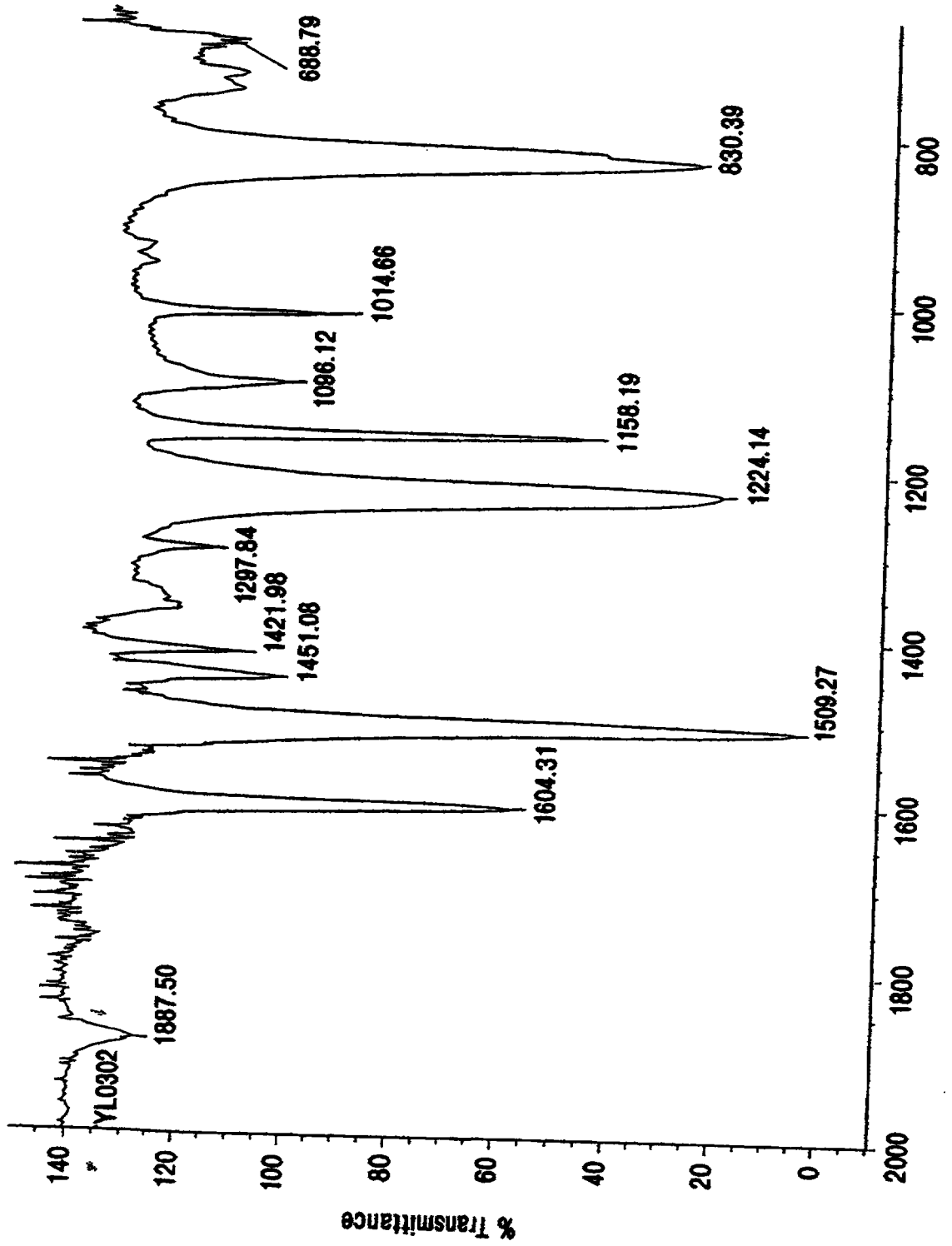

YL0302
1887.50
1604.31
1509.27
1451.08
1421.98
1297.84
1224.14
1158.19
1096.12
1014.66
830.39
688.79
% Transmittance
Wavenumbers (cm-1)
140
120
100
80
60
40
20
0
2000
1800
1600
1400
1200
1000
800

FIG. 69

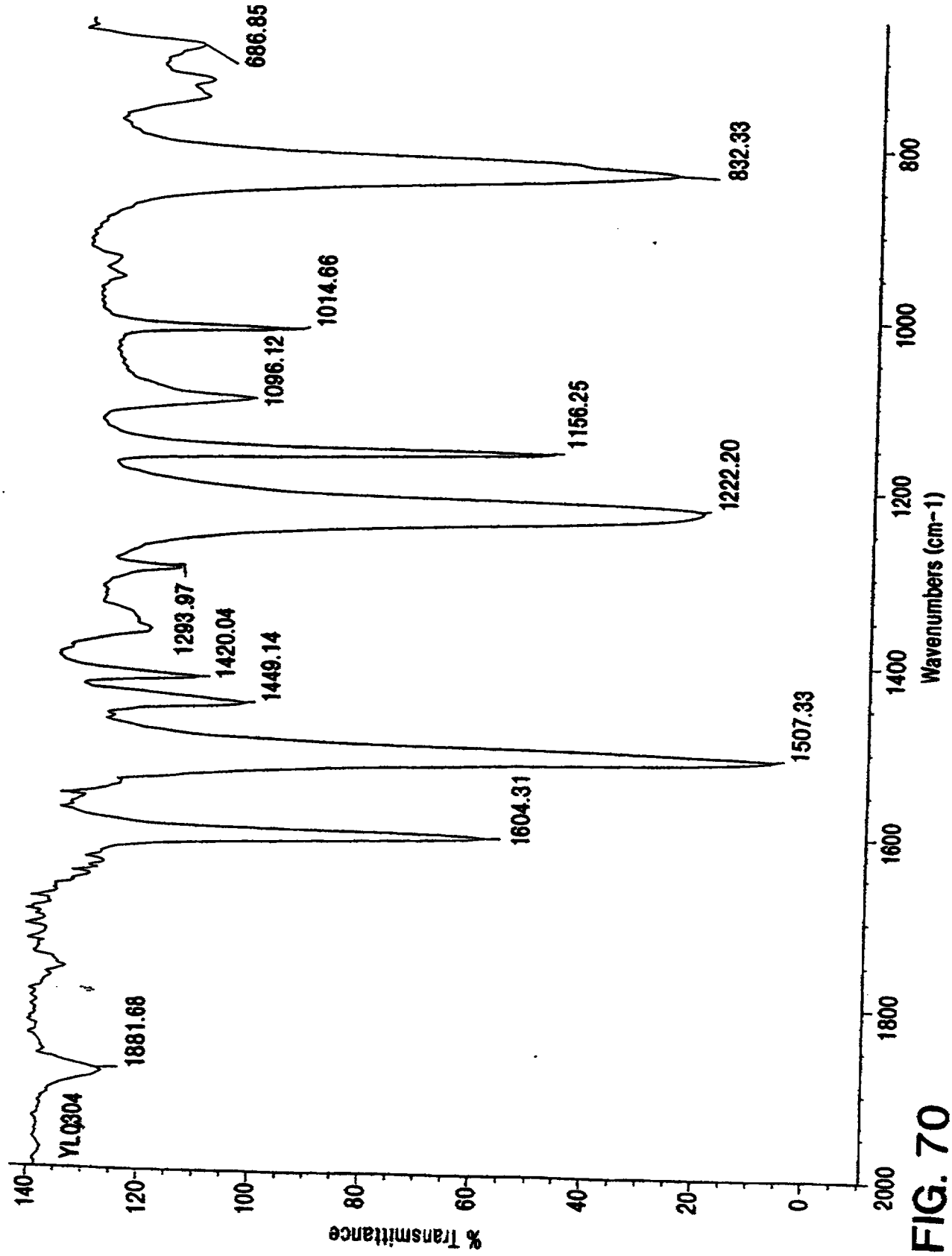

YL0304
1881.68
1604.31
1507.33
1449.14
1420.04
1293.97
1222.20
1156.25
1096.12
1014.66
832.33
686.85
% Transmittance
Wavenumbers (cm-1)
140
120
100
80
60
40
20
0
2000
1800
1600
1400
1200
1000
800

FIG. 70

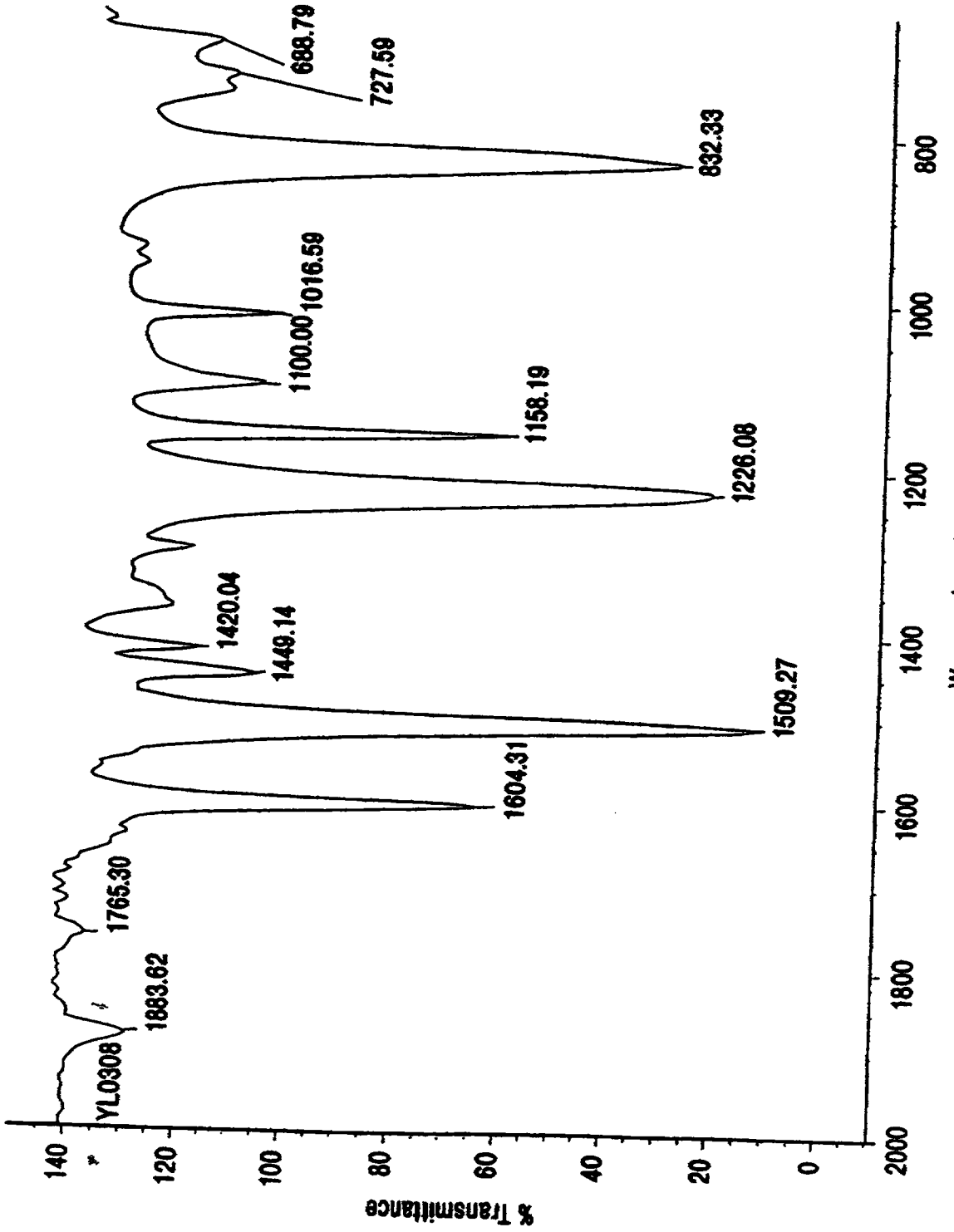

YL0308
1883.62
1765.30
1604.31
1509.27
1449.14
1420.04
1226.08
1158.19
1100.00
1016.59
832.33
727.59
688.79
% Transmittance
Wavenumbers (cm-1)
140
120
100
80
60
40
20
0
2000
1800
1600
1400
1200
1000
800

FIG. 71

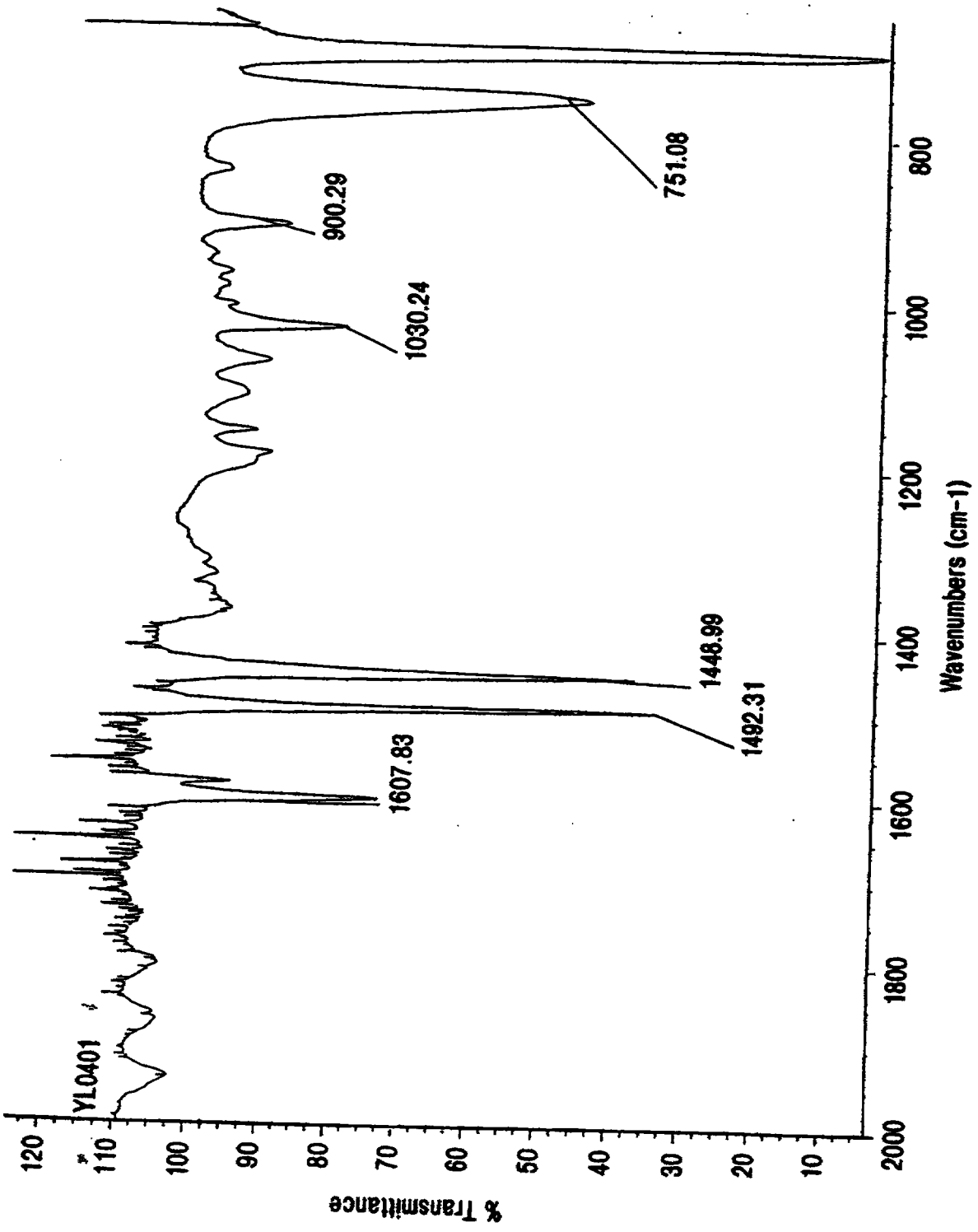

YL0401
751.08
900.29
1030.24
1448.99
1492.31
1607.83
% Transmittance
Wavenumbers (cm-1)
120
110
100
90
80
70
60
50
40
30
20
10
800
1000
1200
1400
1600
1800
2000

FIG. 72

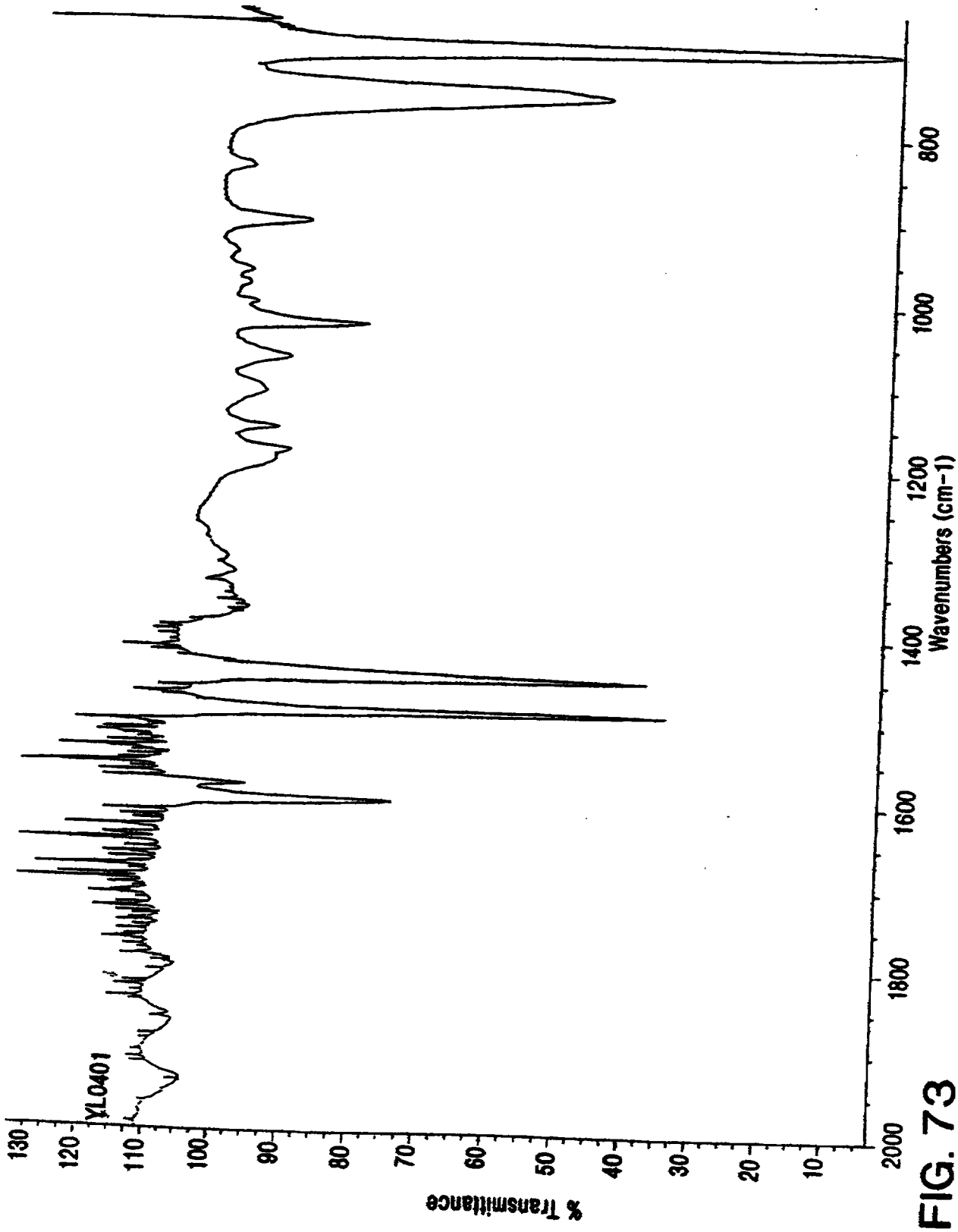

YL0401
% Transmittance
130
120
110
100
90
80
70
60
50
40
30
20
10
2000
1800
1600
1400
1200
1000
800
Wavenumbers (cm-1)

FIG. 73

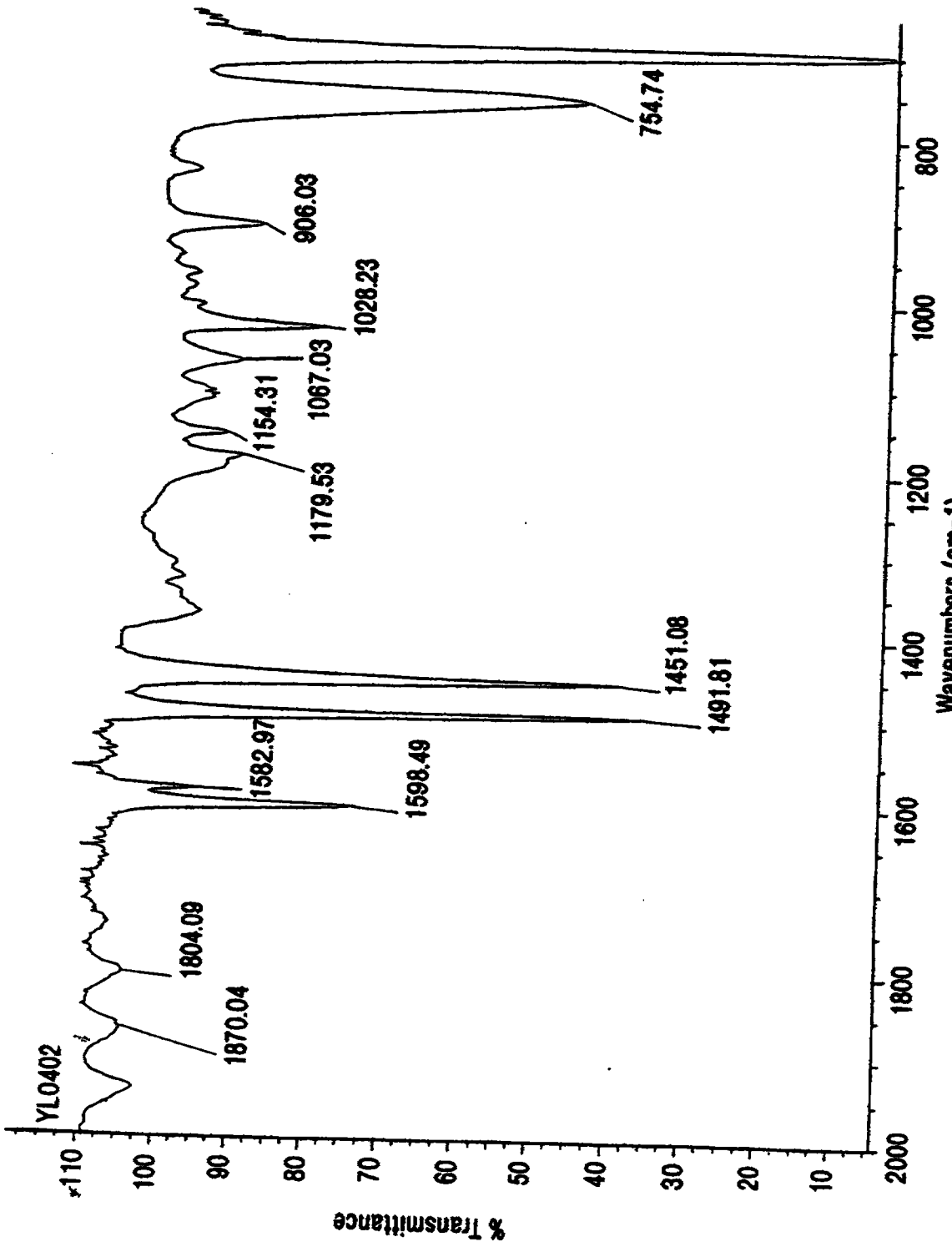

YL0402
x110
100
90
80
70
60
50
40
30
20
10
% Transmittance
2000
1800
1600
1400
1200
1000
800
Wavenumbers (cm-1)
1870.04
1804.09
1582.97
1598.49
1451.08
1491.81
1179.53
1154.31
1067.03
1028.23
906.03
754.74

FIG. 74

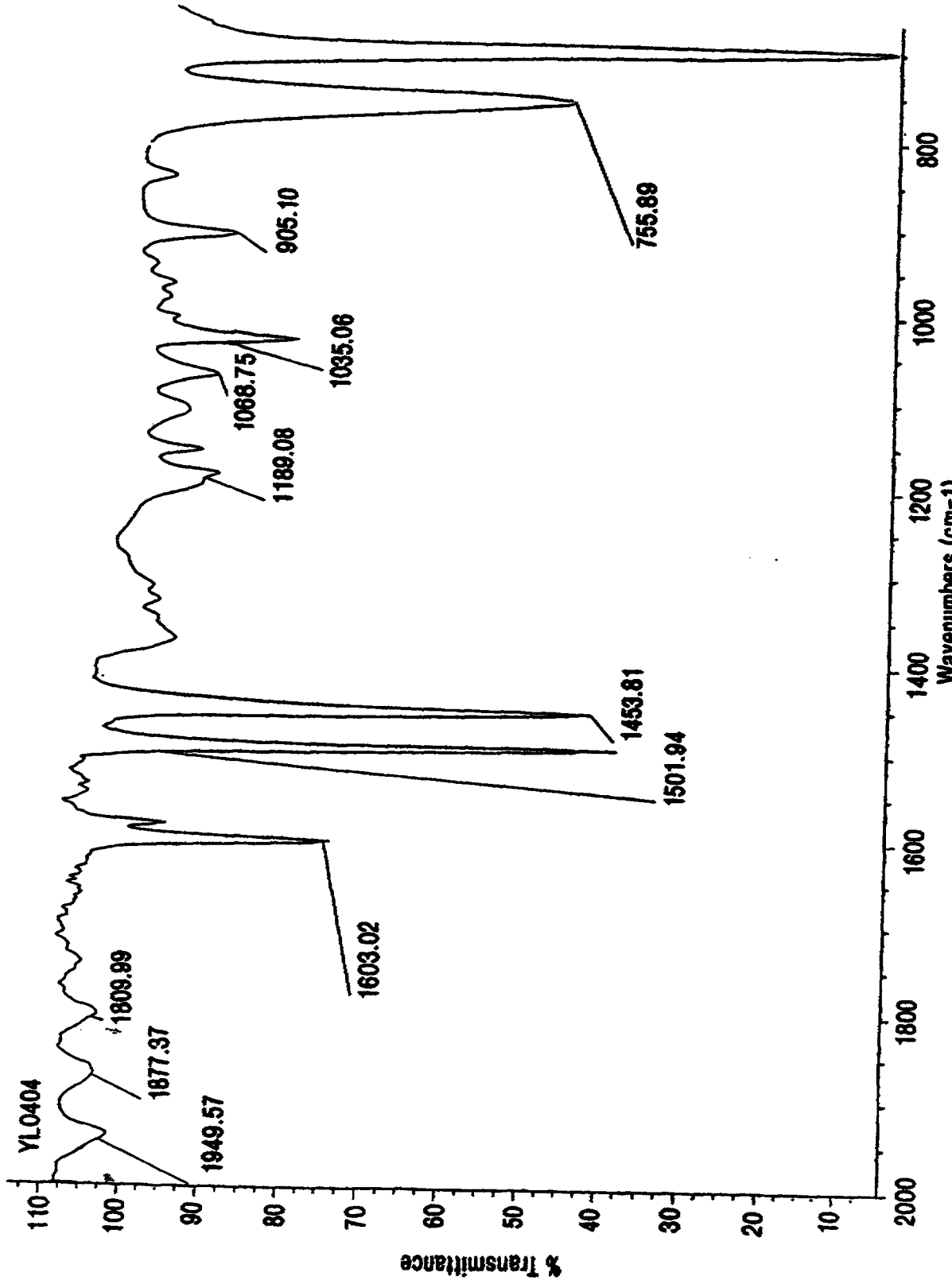

YL0404
1949.57
1877.37
1809.99
1603.02
1501.94
1453.81
1189.08
1068.75
1035.06
905.10
755.89
% Transmittance
Wavenumbers (cm-1)
110
100
90
80
70
60
50
40
30
20
10
2000
1800
1600
1400
1200
1000
800

FIG. 75

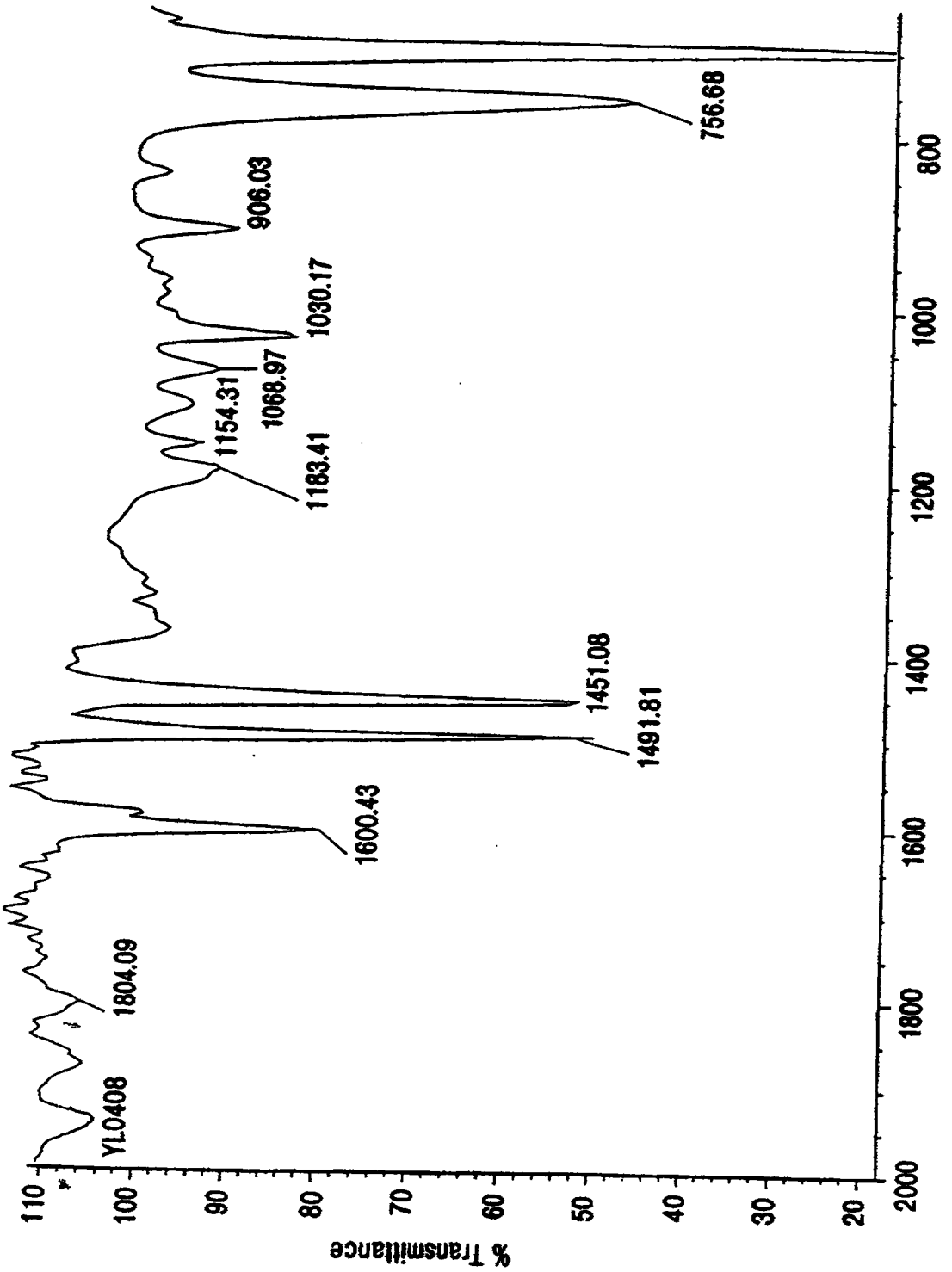

YL0408
1804.09
1600.43
1491.81
1451.08
1183.41
1154.31
1068.97
1030.17
906.03
756.68
% Transmittance
Wavenumbers (cm-1)
110
100
90
80
70
60
50
40
30
20
2000
1800
1600
1400
1200
1000
800

FIG. 76

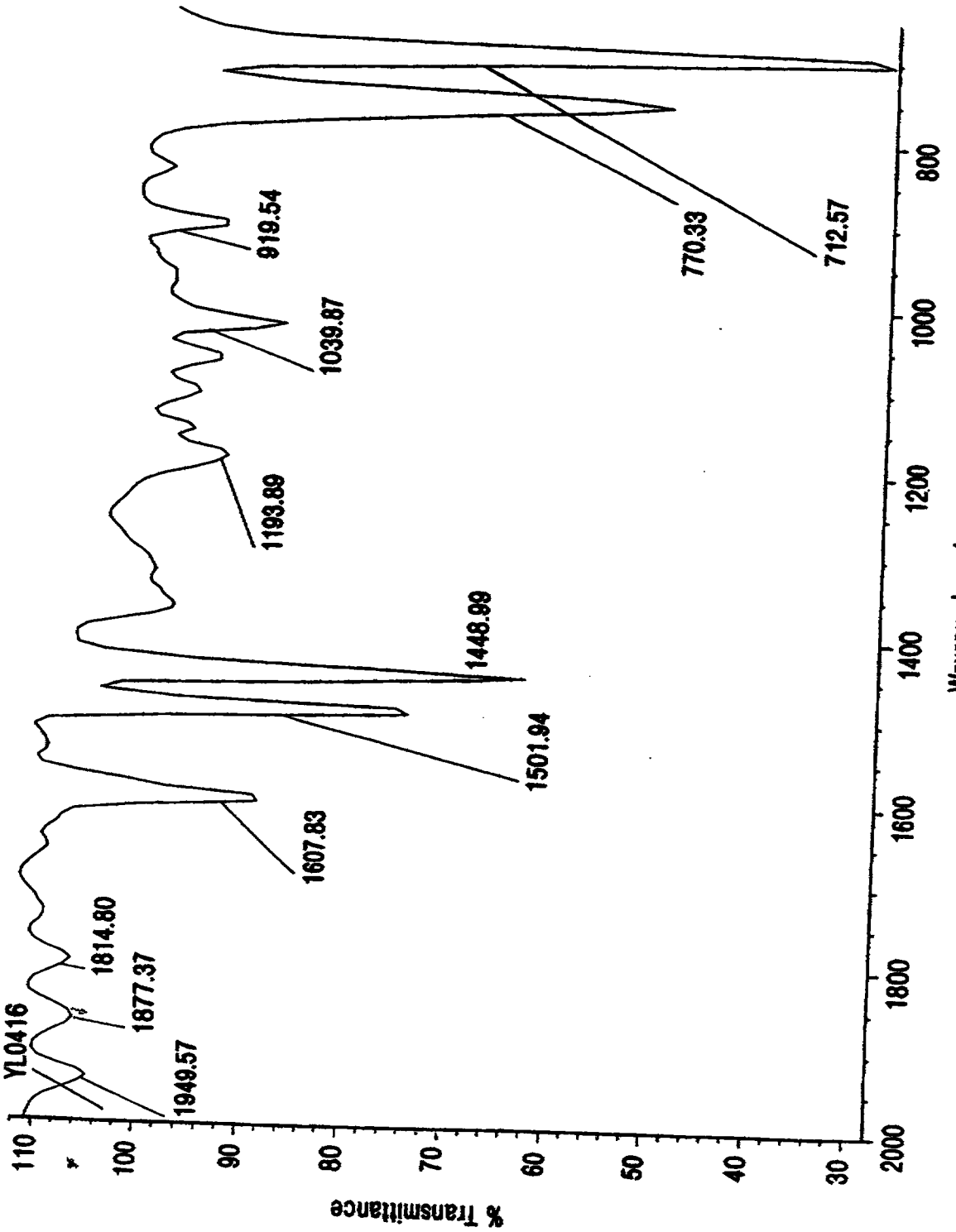

YL0416
1949.57
1877.37
1814.80
1607.83
1501.94
1448.99
1193.89
1039.87
919.54
770.33
712.57
% Transmittance
Wavenumbers (cm-1)
110
100
90
80
70
60
50
40
30
2000
1800
1600
1400
1200
1000
800

FIG. 77

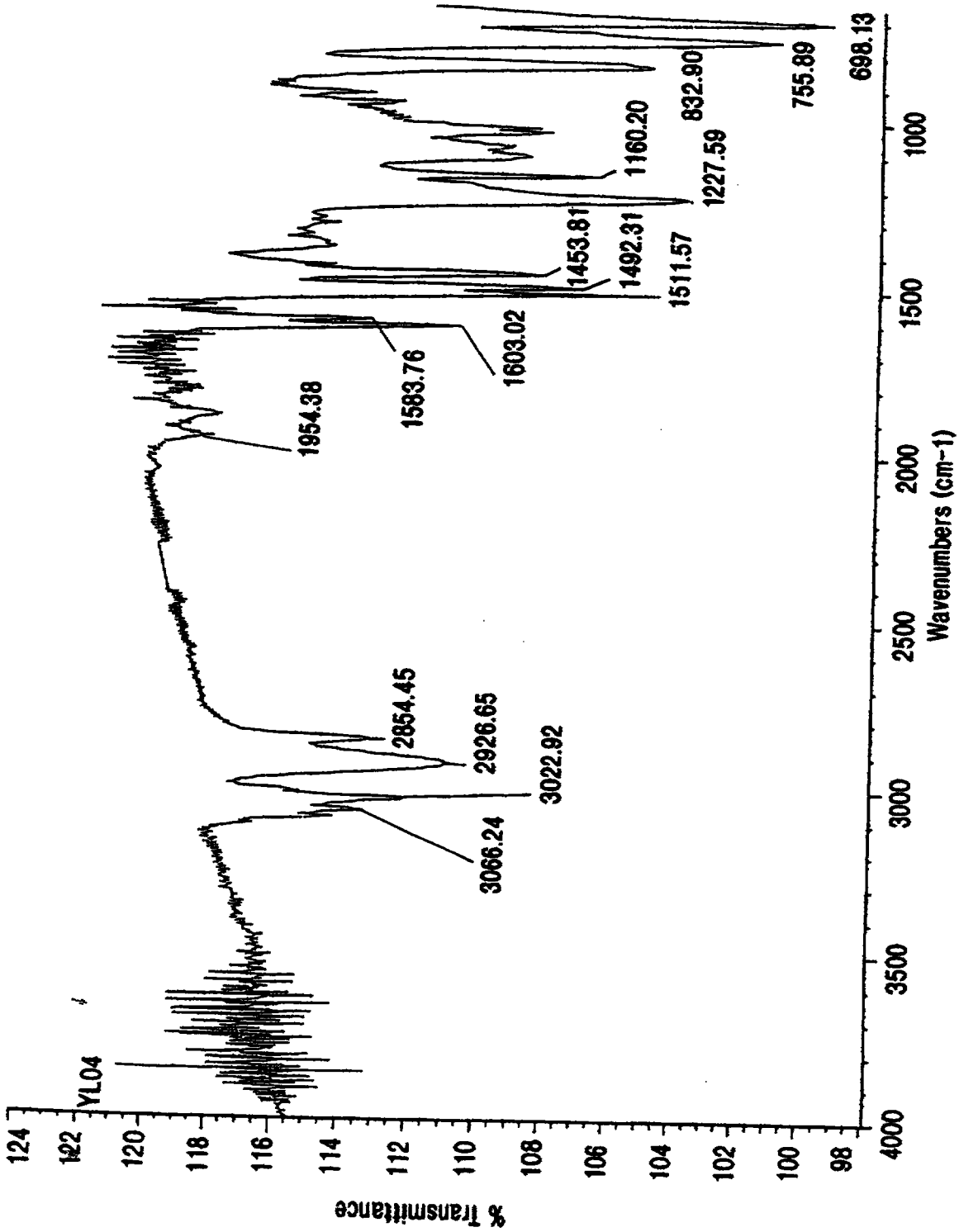

YL04
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
124
122
120
118
116
114
112
110
108
106
104
102
100
98
3066.24
3022.92
2926.65
2854.45
1954.38
1603.02
1583.76
1511.57
1492.31
1453.81
1227.59
1160.20
832.90
755.89
698.13

FIG. 78

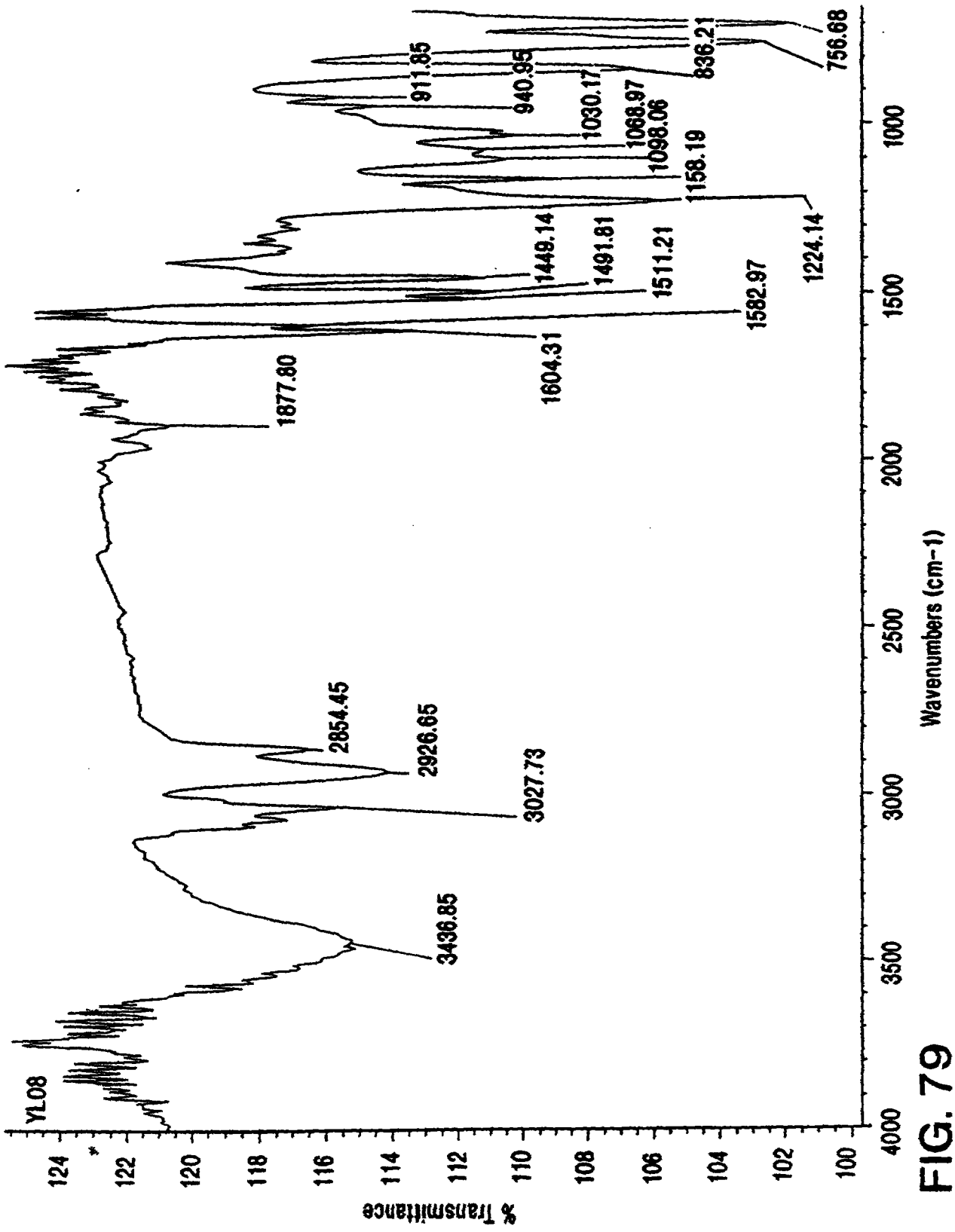

YL08
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
102
104
106
108
110
112
114
116
118
120
122
124
3436.85
3027.73
2926.65
2854.45
1877.80
1604.14
1582.97
1511.21
1491.81
1449.14
1224.14
1158.19
1098.06
1068.97
1030.17
940.95
911.85
836.21
756.68

FIG. 79

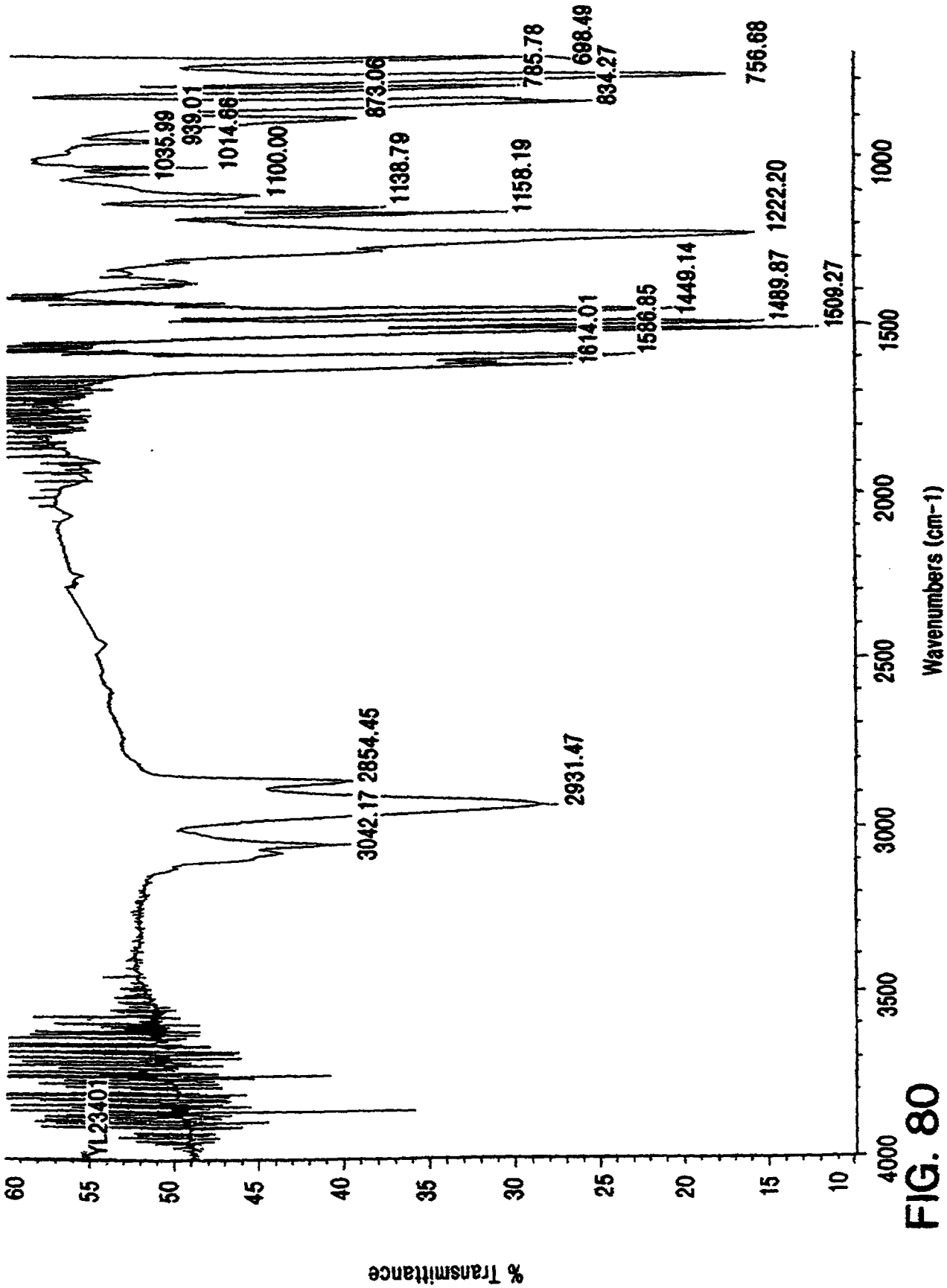

% Transmittance
Wavenumbers (cm-1)
YL2340 1
3042.17
2854.45
2931.47
1614.01
1586.85
1449.14
1489.87
1509.27
1222.20
1158.19
1138.79
1100.00
1035.99
939.01
1014.86
873.06
785.78
756.68
698.49
834.27

FIG. 80

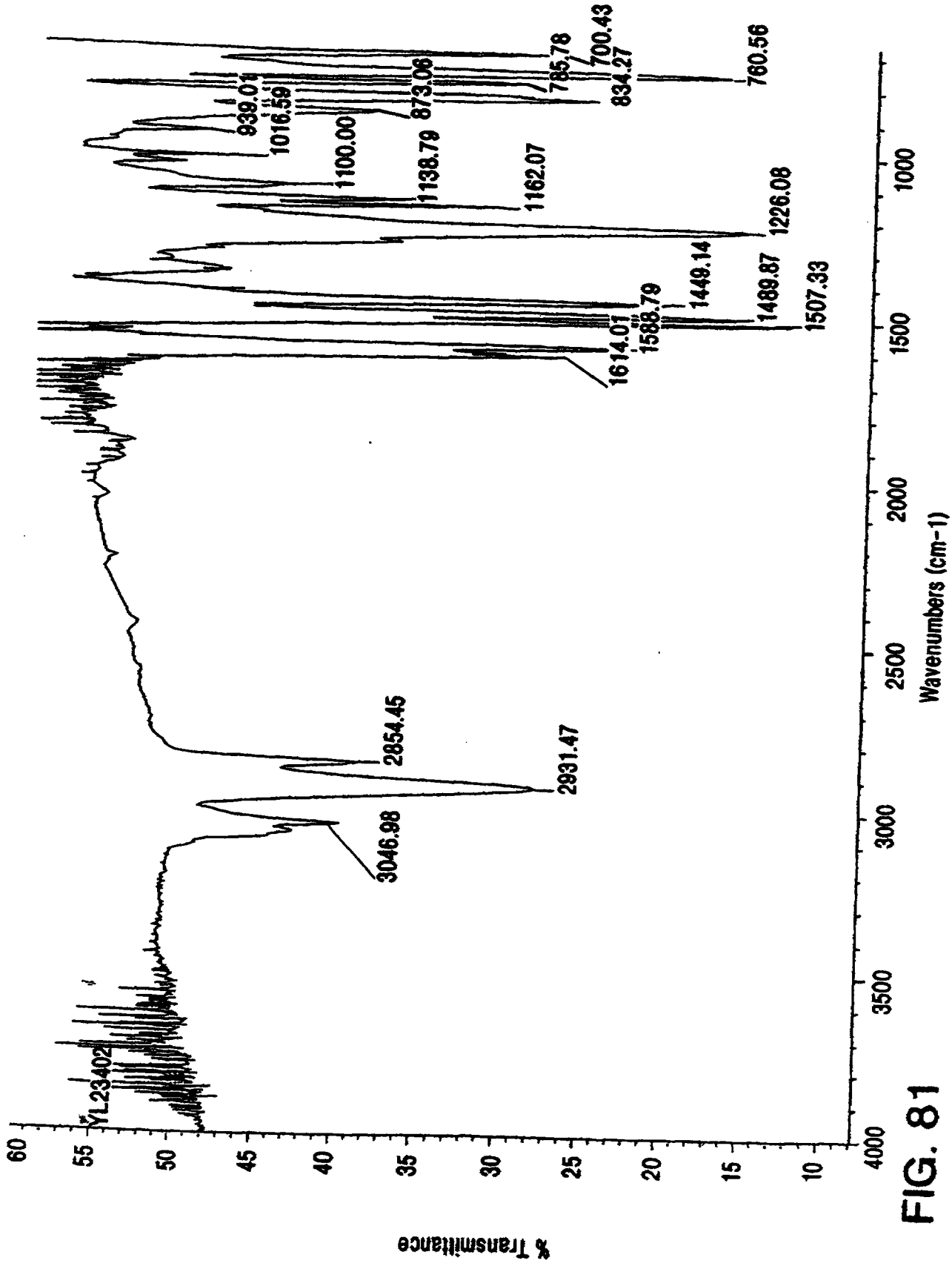

% Transmittance
Wavenumbers (cm-1)
YL23402
3046.98
2931.47
2854.45
1614.01
1588.79
1507.33
1489.87
1449.14
1226.08
1162.07
1138.79
1100.00
1016.59
939.01
873.06
834.27
785.78
760.56
700.43

FIG. 81

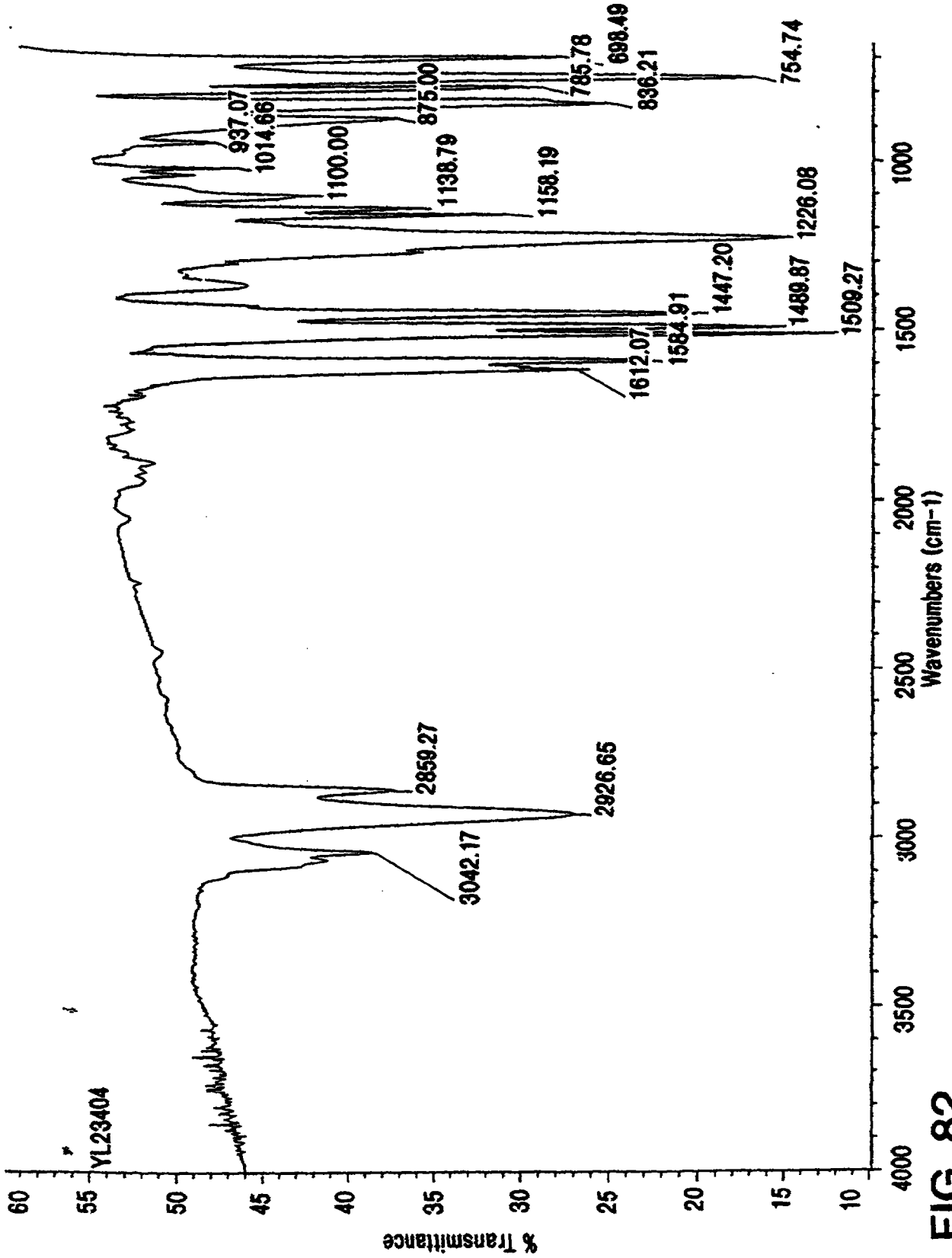

YL23404
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
60
55
50
45
40
35
30
25
20
15
10
3042.17
2926.65
2859.27
1612.07
1584.91
1509.27
1489.87
1447.20
1226.08
1158.19
1138.79
1100.00
1014.66
937.07
875.00
836.21
785.78
754.74
698.49

FIG. 82

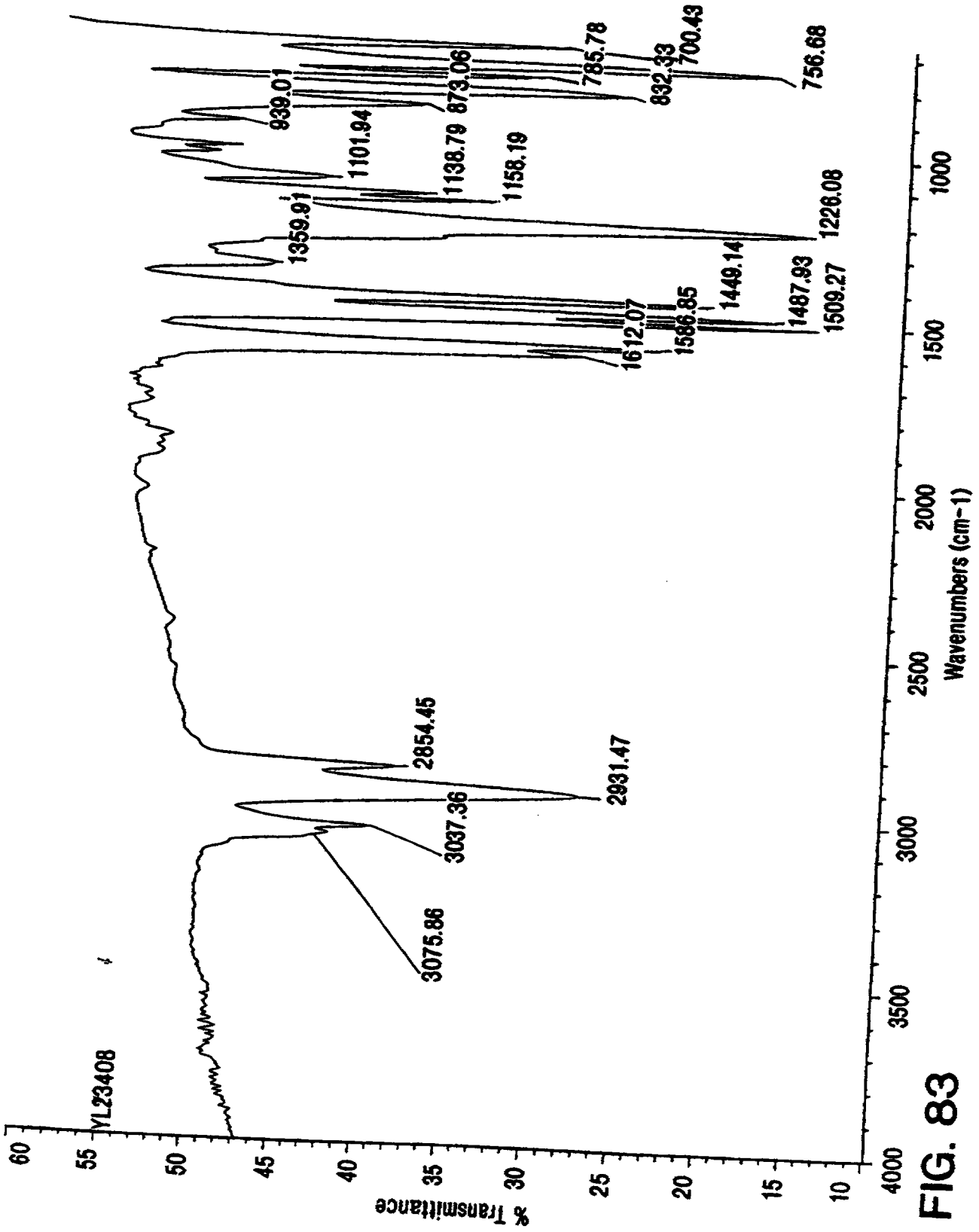

YL23408
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
60
55
50
45
40
35
30
25
20
15
10
3075.86
3037.36
2931.47
2854.45
1612.07
1586.85
1509.27
1487.93
1449.14
1359.91
1226.08
1158.19
1138.79
1101.94
939.01
873.06
832.33
785.78
756.68
700.43

FIG. 83

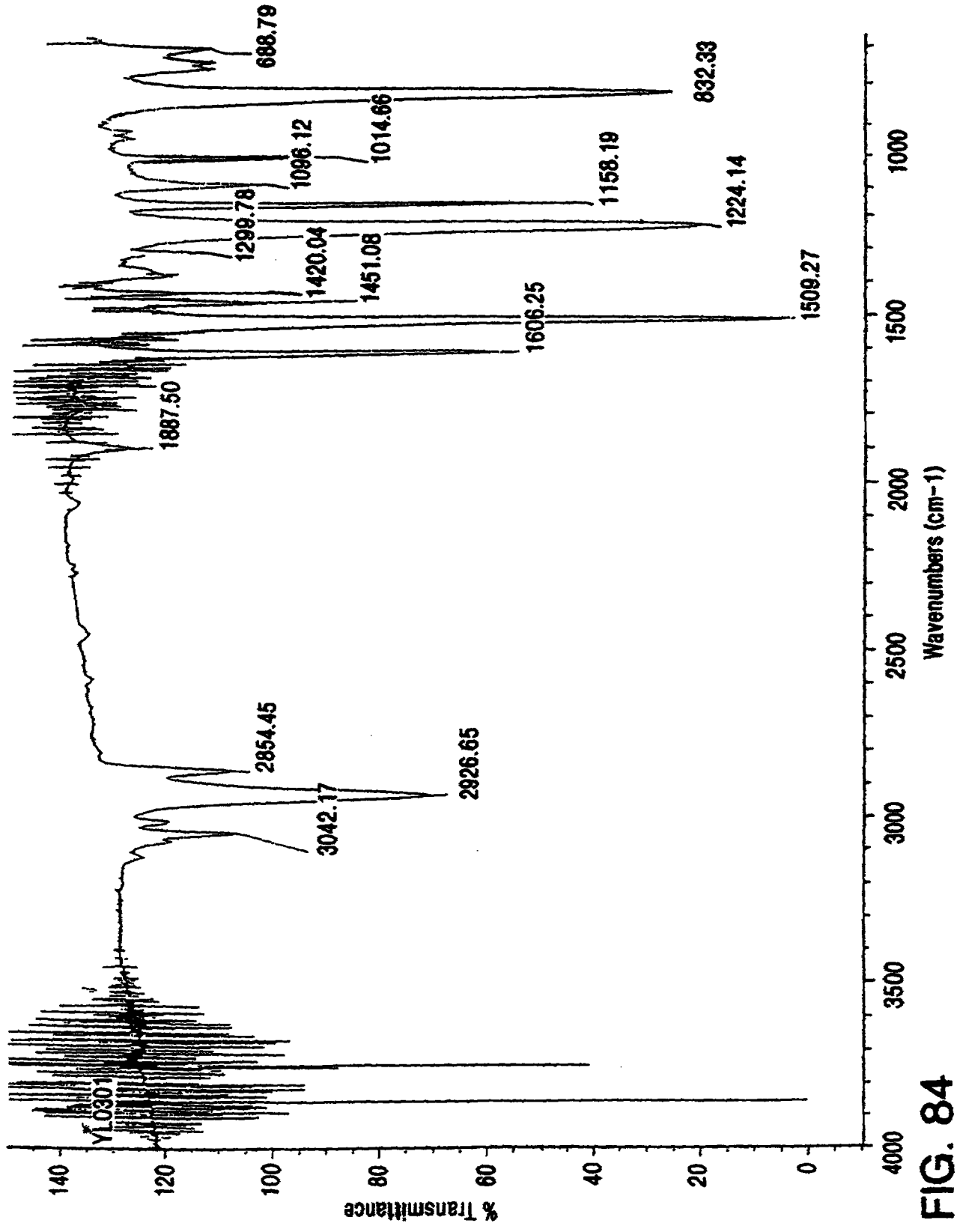

YL0301
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
0
20
40
60
80
100
120
140
688.79
832.33
1014.66
1096.12
1158.19
1224.14
1298.78
1420.04
1451.08
1509.27
1606.25
1887.50
2854.45
2926.65
3042.17

FIG. 84

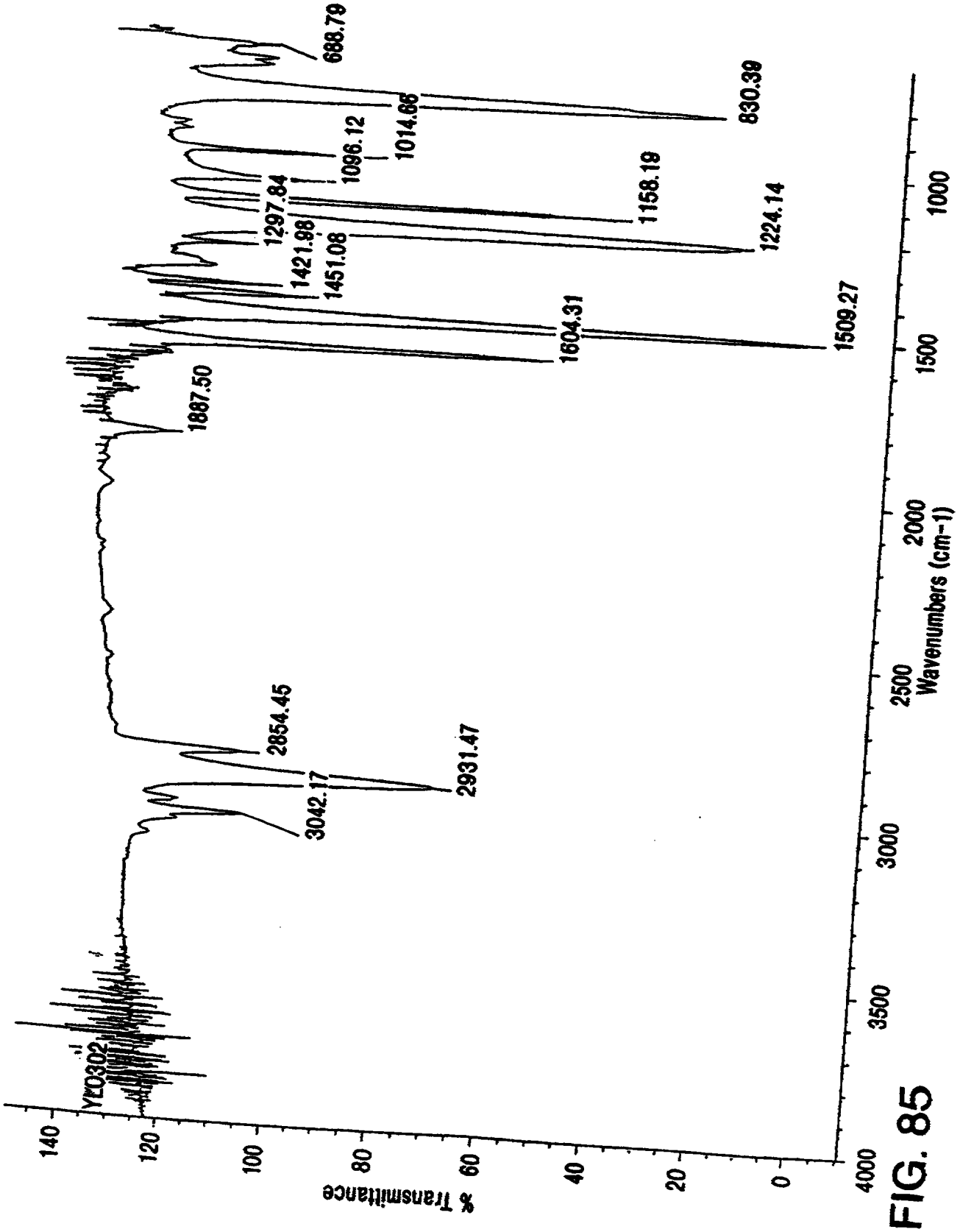

YEO302
% Transmittance
Wavenumbers (cm-1)
140
120
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
688.79
830.39
1014.66
1096.12
1158.19
1224.14
1297.84
1421.98
1451.08
1509.27
1604.31
1887.50
2854.45
2931.47
3042.17

FIG. 85

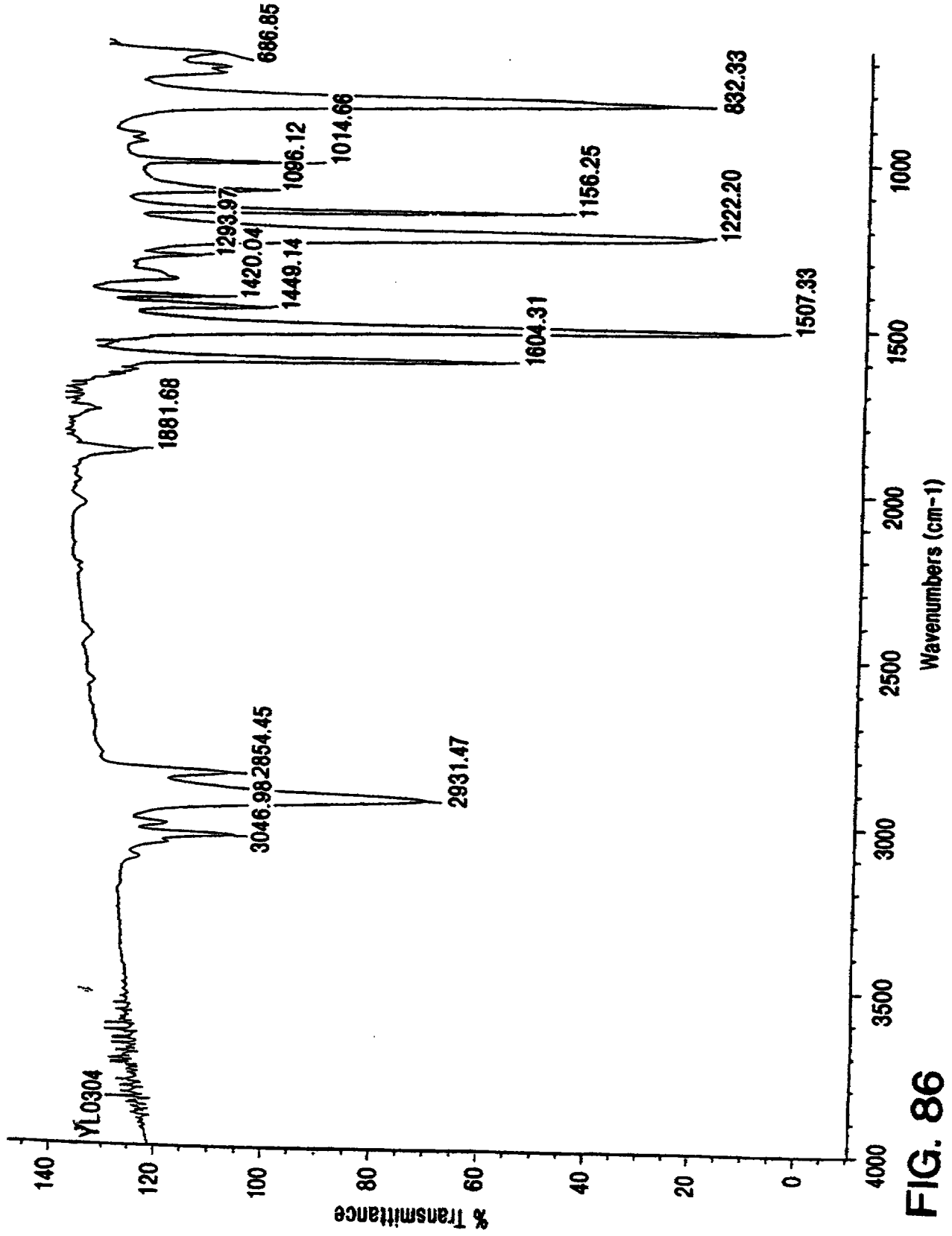

YL0304
% Transmittance
Wavenumbers (cm-1)
140
120
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
686.85
832.33
1014.66
1096.12
1156.25
1222.20
1293.97
1420.04
1449.14
1507.33
1604.31
1881.68
2854.45
2931.47
3046.98

FIG. 86

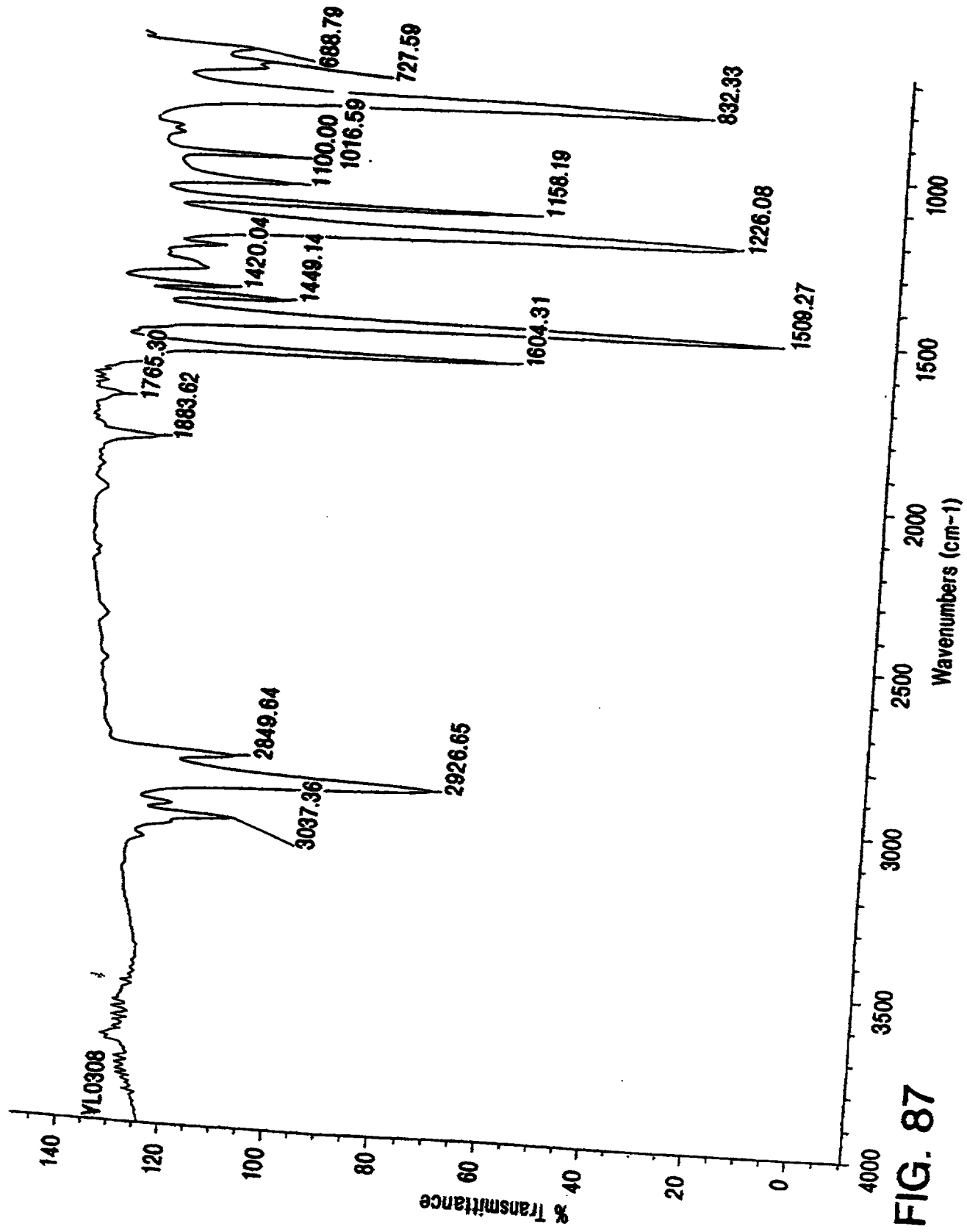

¥L0308
688.79
727.59
832.33
1016.59
1100.00
1158.19
1226.08
1420.04
1449.14
1509.27
1604.31
1765.30
1883.62
2849.64
2926.65
3037.36
% Transmittance
Wavenumbers (cm-1)
140
120
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000

FIG. 87

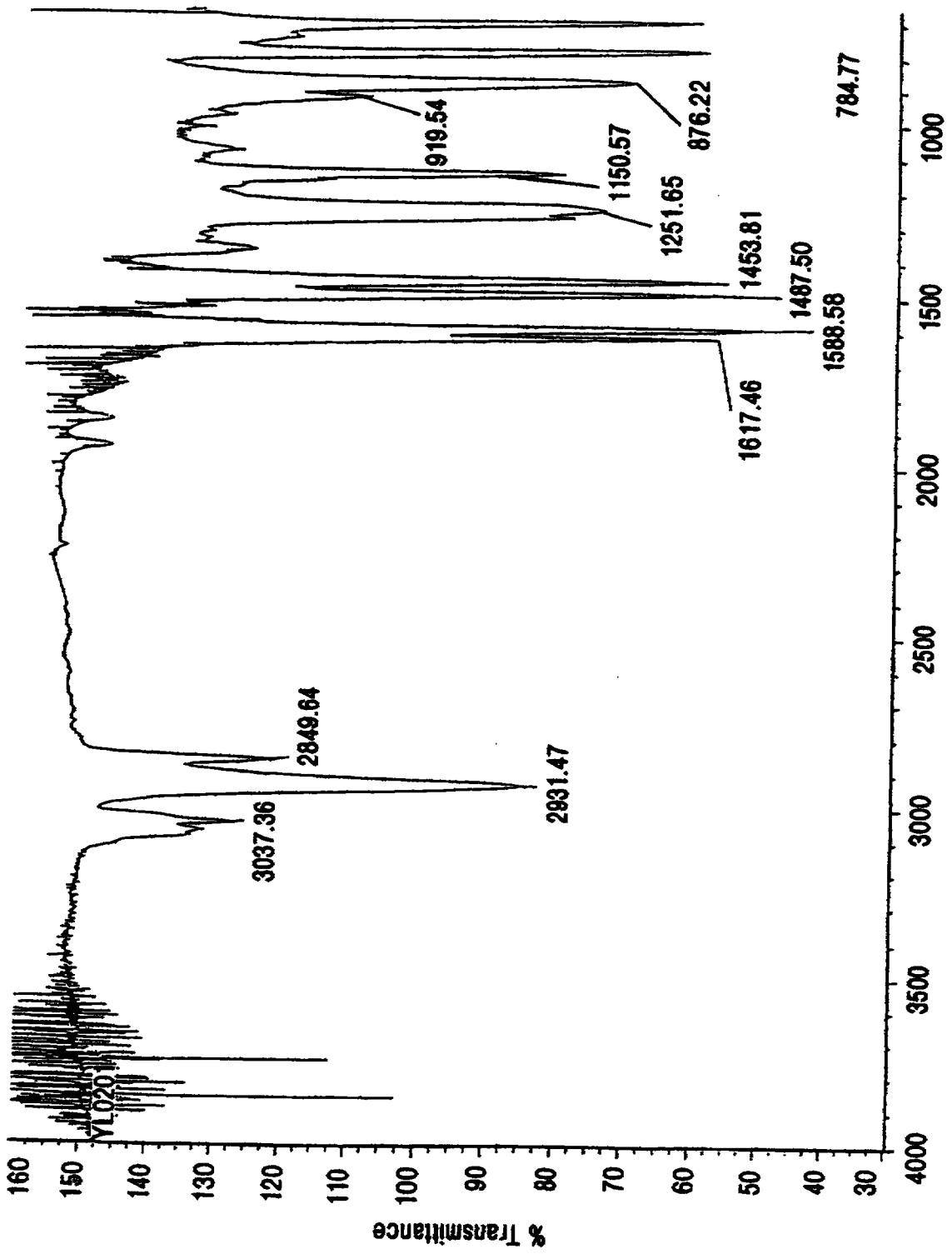

% Transmittance
Wavenumbers (cm-1)
YL020
2931.47
2849.64
3037.36
1617.46
1588.58
1487.50
1453.81
1251.65
1150.57
919.54
876.22
784.77

FIG. 88

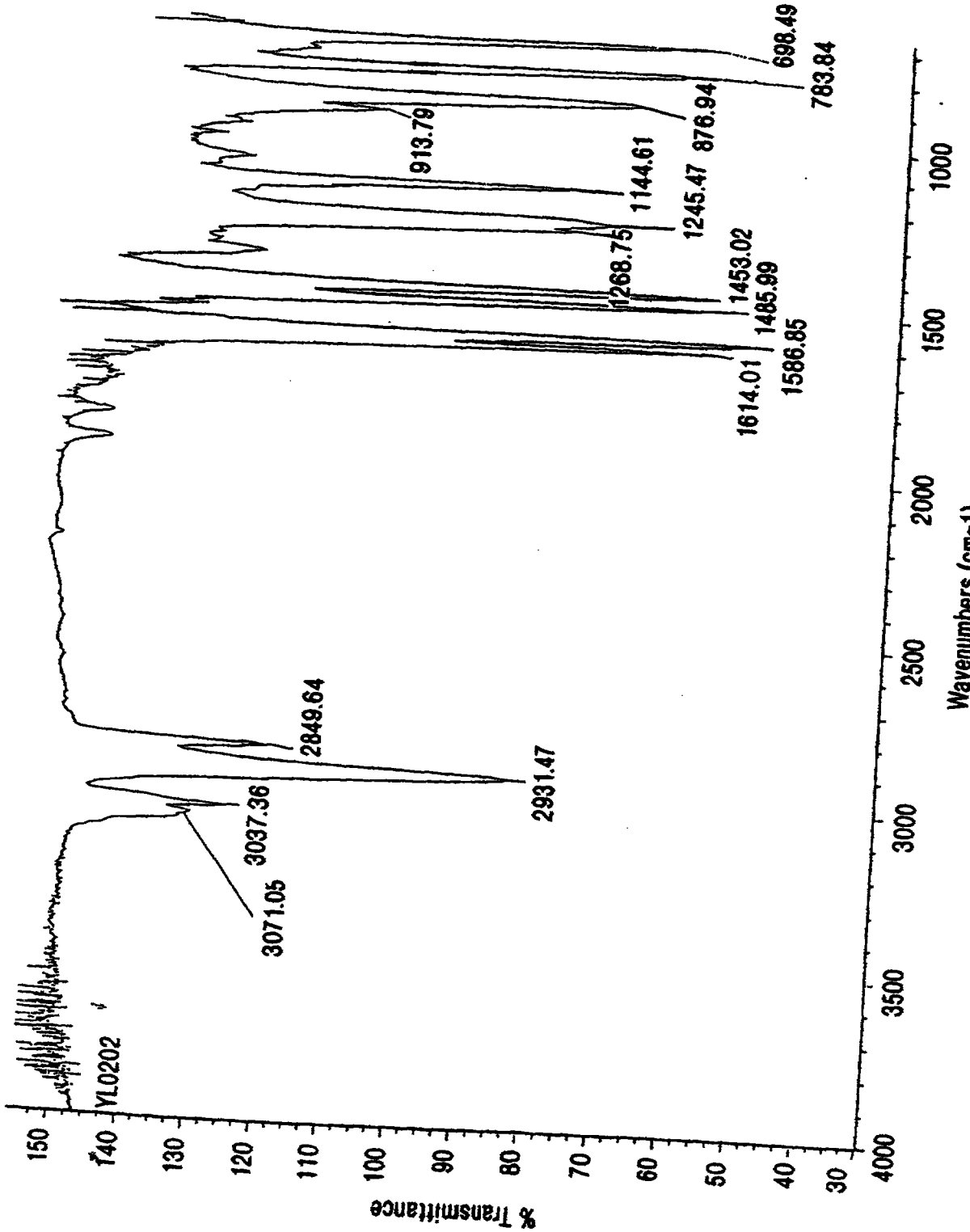

YL0202
% Transmittance
Wavenumbers (cm-1)
150
140
130
120
110
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
3071.05
3037.36
2931.47
2849.64
1614.01
1586.85
1485.99
1453.02
1268.75
1245.47
1144.61
913.79
876.94
783.84
698.49

FIG. 89

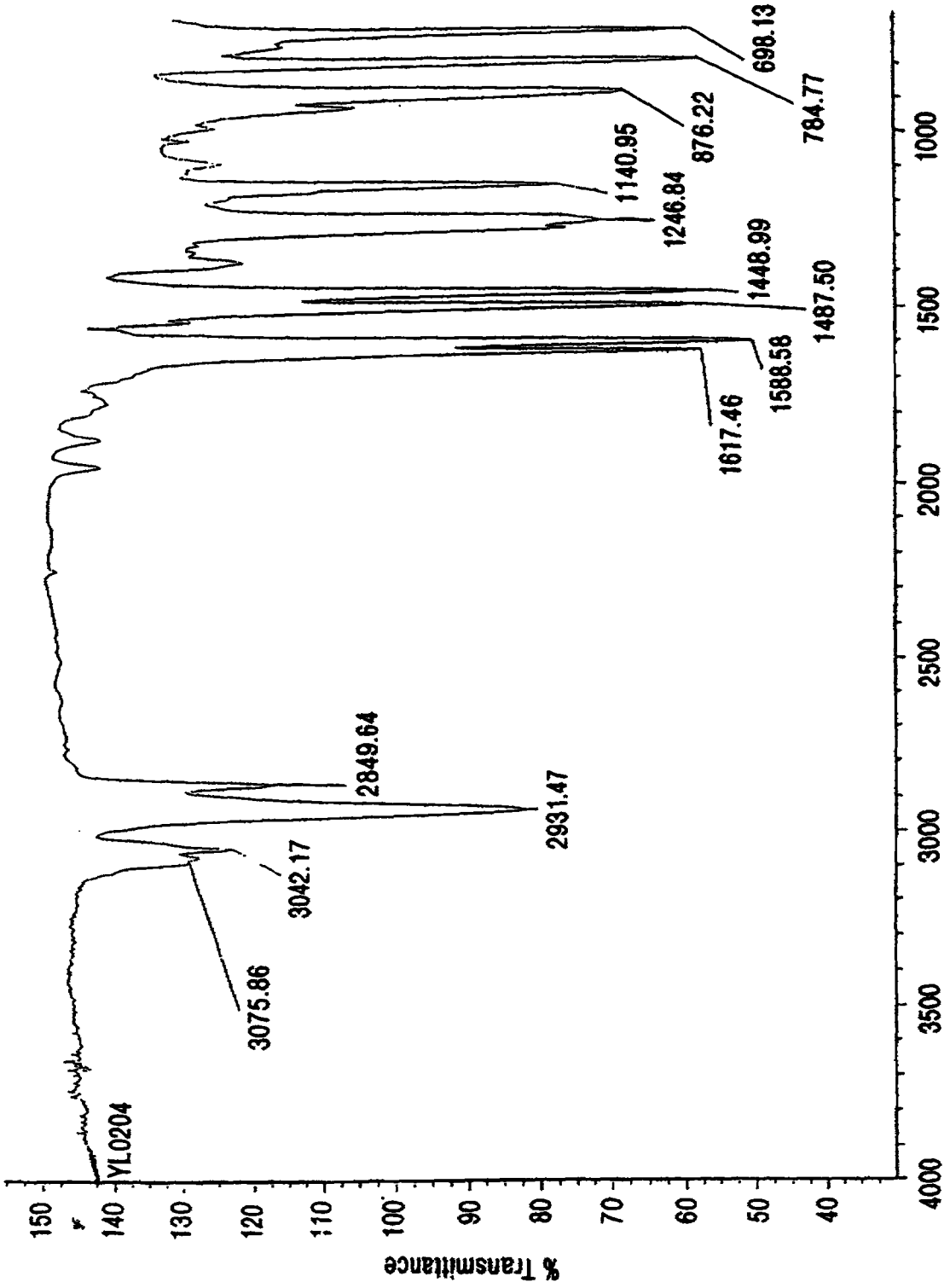

YL0204
3075.86
3042.17
2931.47
2849.64
1617.46
1588.58
1487.50
1448.99
1246.84
1140.95
876.22
784.77
698.13
% Transmittance
Wavenumbers (cm-1)
150
140
130
120
110
100
90
80
70
60
50
40
4000
3500
3000
2500
2000
1500
1000

FIG. 90

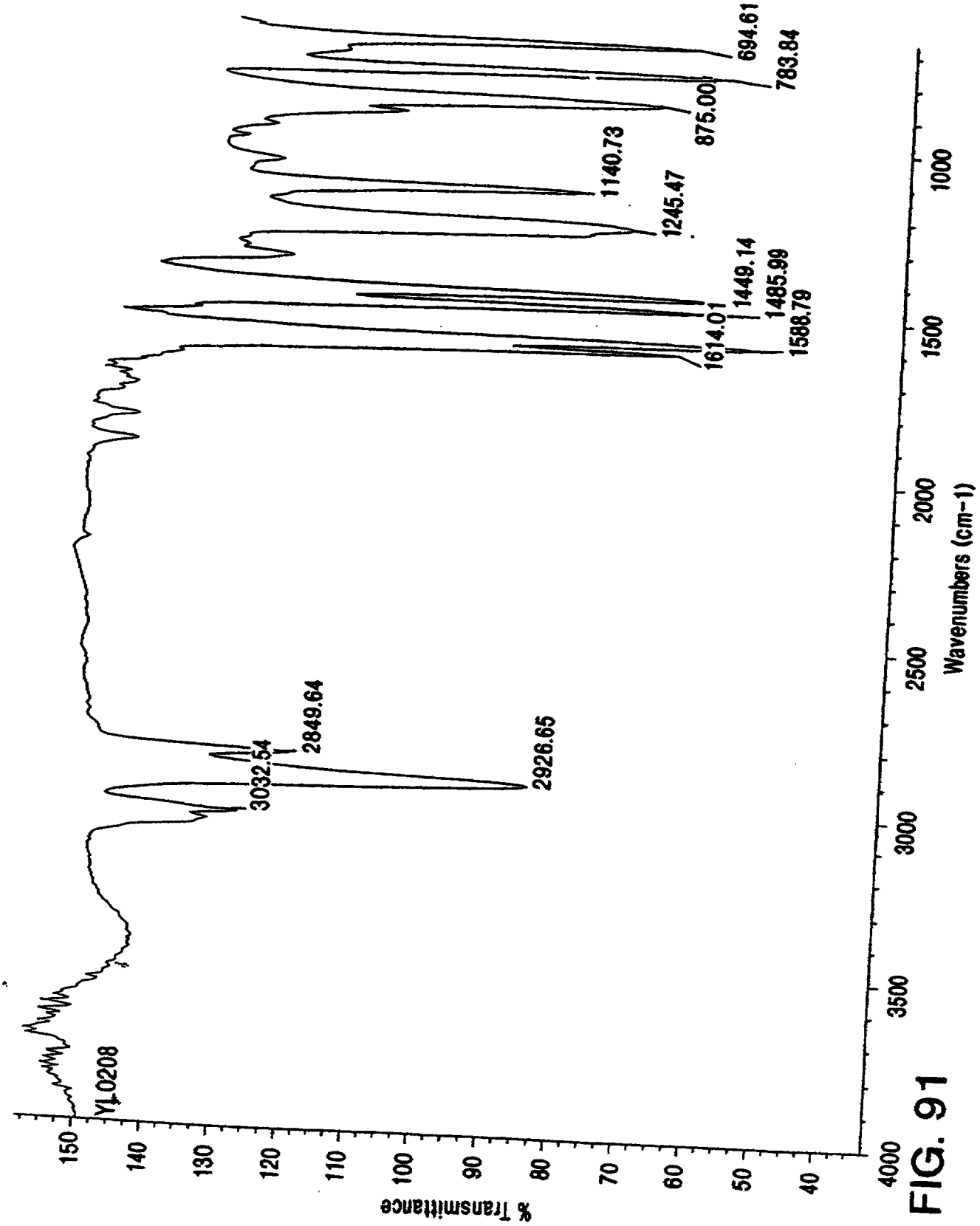

694.61
783.84
875.00
1140.73
1245.47
1449.14
1485.99
1588.79
1614.01
2849.64
3032.54
2926.65
Y1.0208
% Transmittance
Wavenumbers (cm-1)
150
140
130
120
110
100
90
80
70
60
50
40
4000
3500
3000
2500
2000
1500
1000

FIG. 91

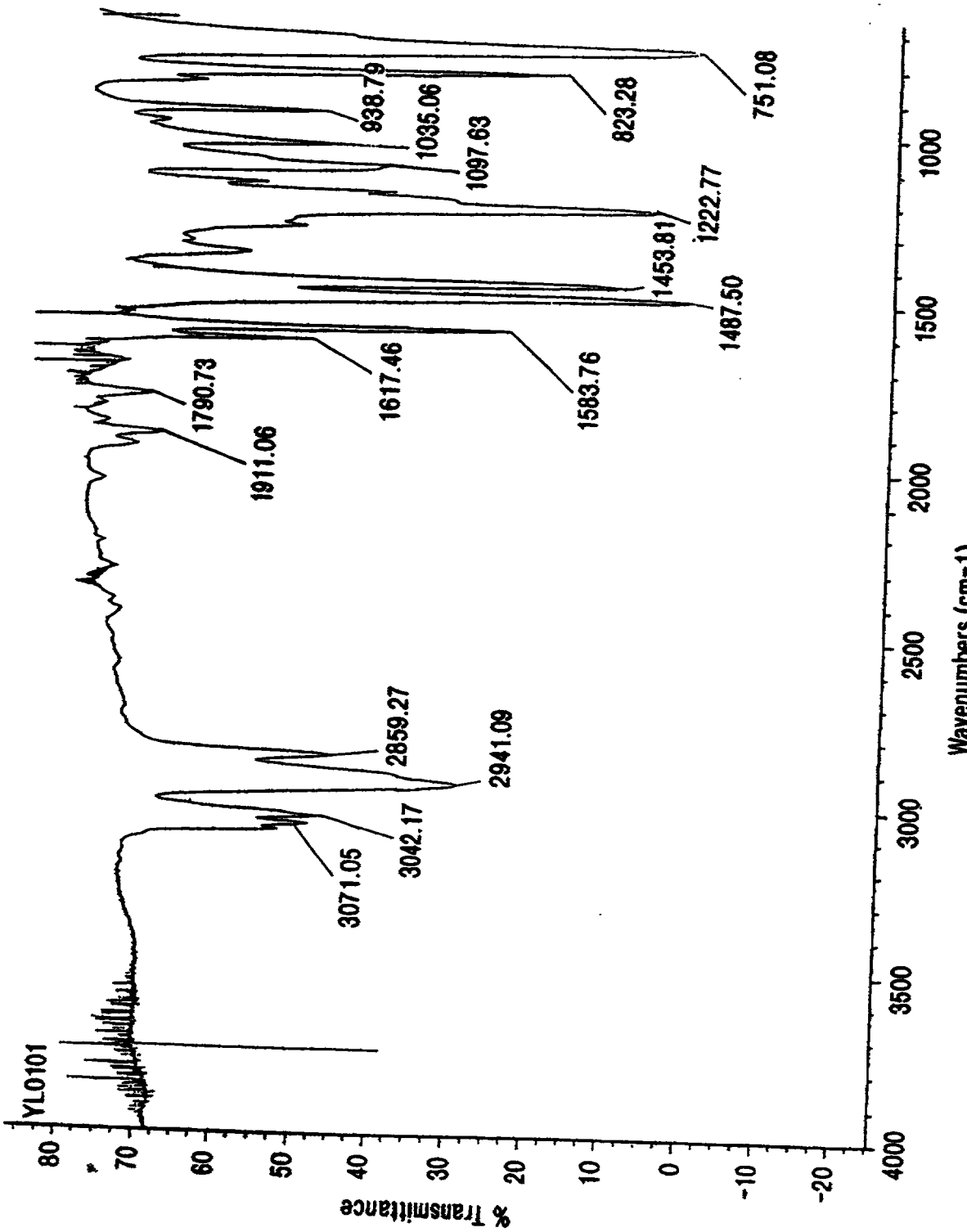

YL0101
% Transmittance
Wavenumbers (cm-1)
751.08
823.28
938.79
1035.06
1097.63
1222.77
1453.81
1487.50
1583.76
1617.46
1790.73
1911.06
2859.27
2941.09
3042.17
3071.05

FIG. 92

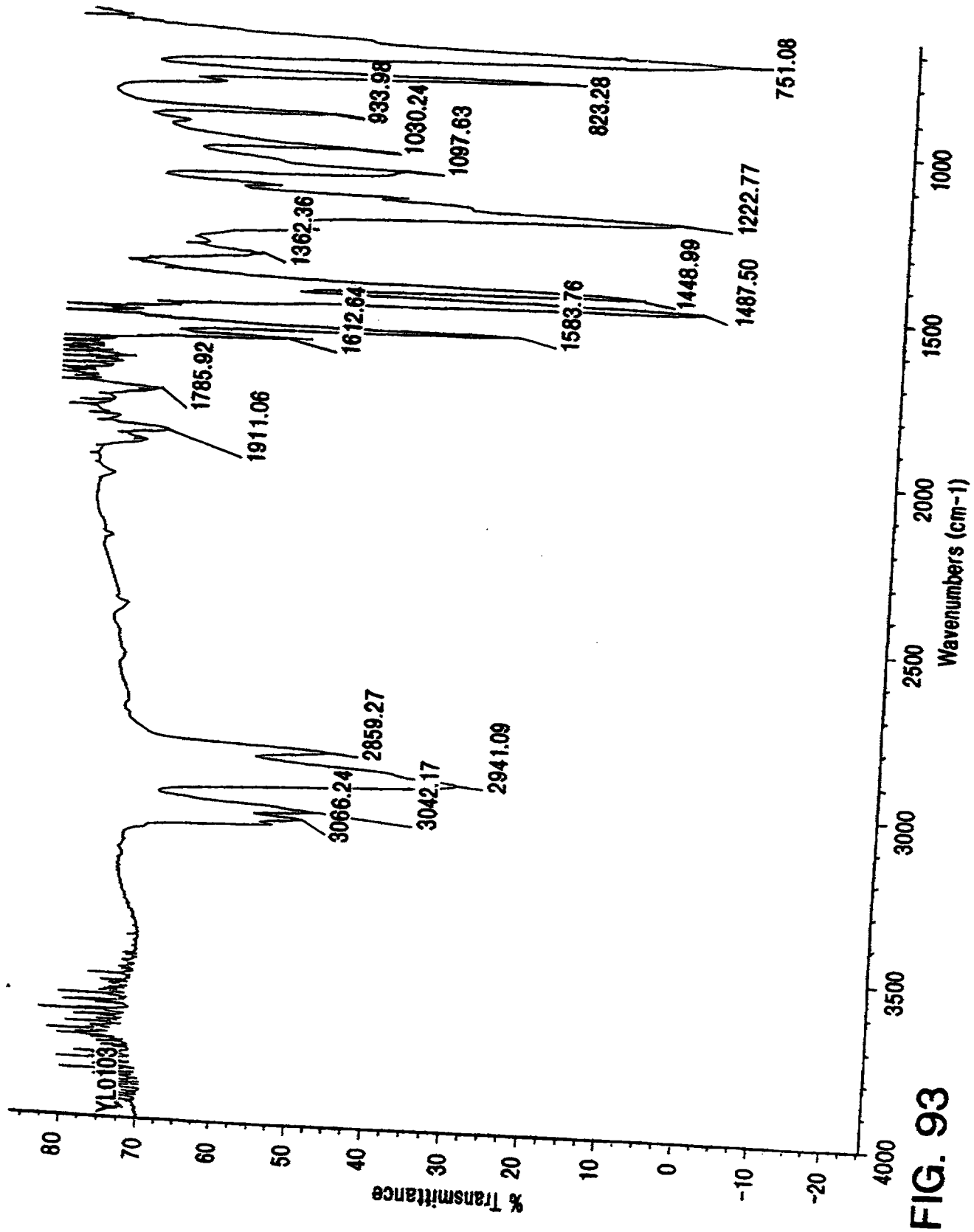

YL0103
% Transmittance
Wavenumbers (cm-1)
751.08
823.28
933.98
1030.24
1097.63
1222.77
1362.36
1448.99
1487.50
1583.76
1612.64
1785.92
1911.06
2859.27
2941.09
3042.17
3066.24

FIG. 93

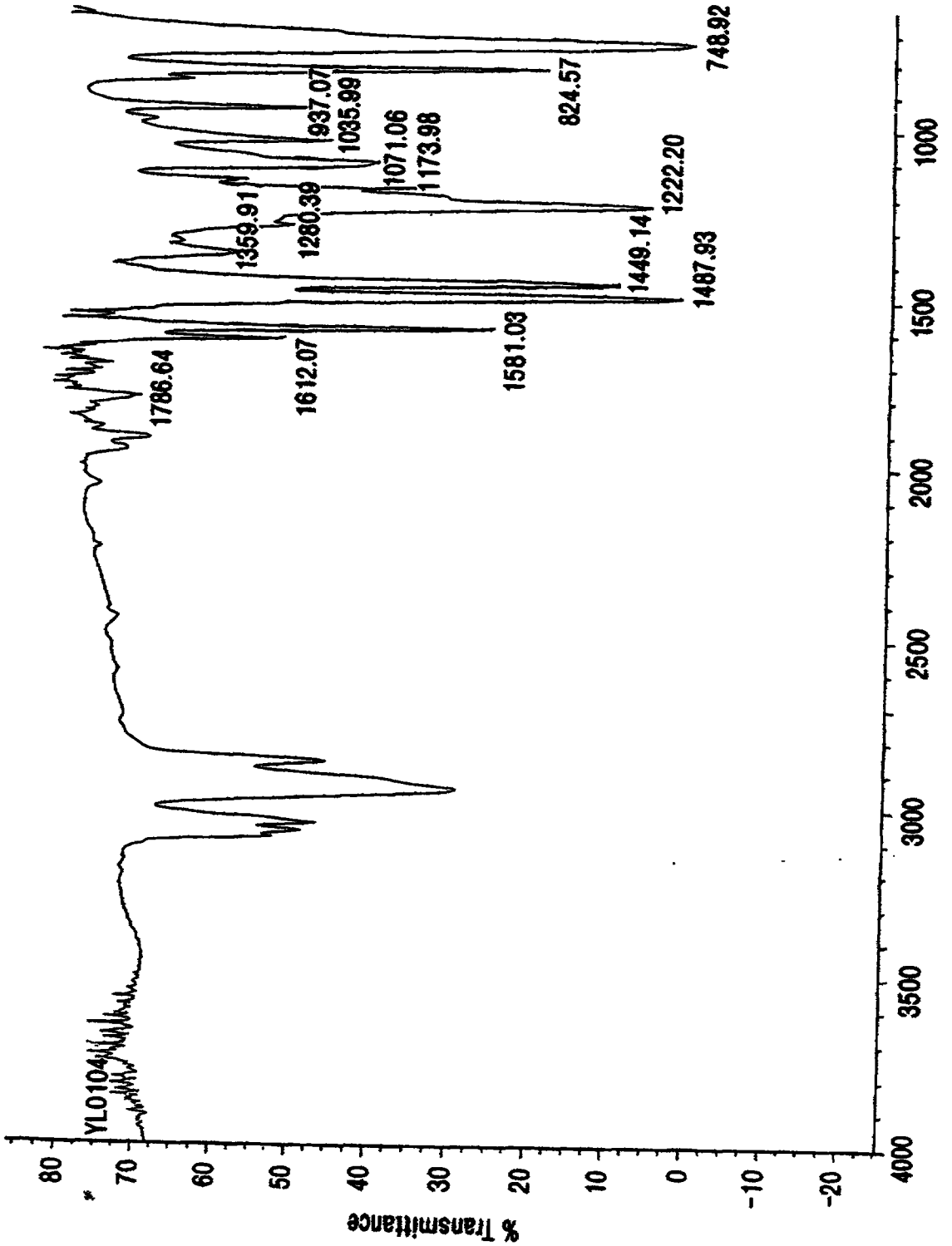

YL0104
% Transmittance
Wavenumbers (cm-1)
1786.64
1612.07
1581.03
1487.93
1449.14
1359.91
1280.39
1222.20
1173.98
1071.06
1035.99
937.07
824.57
748.92

FIG. 94

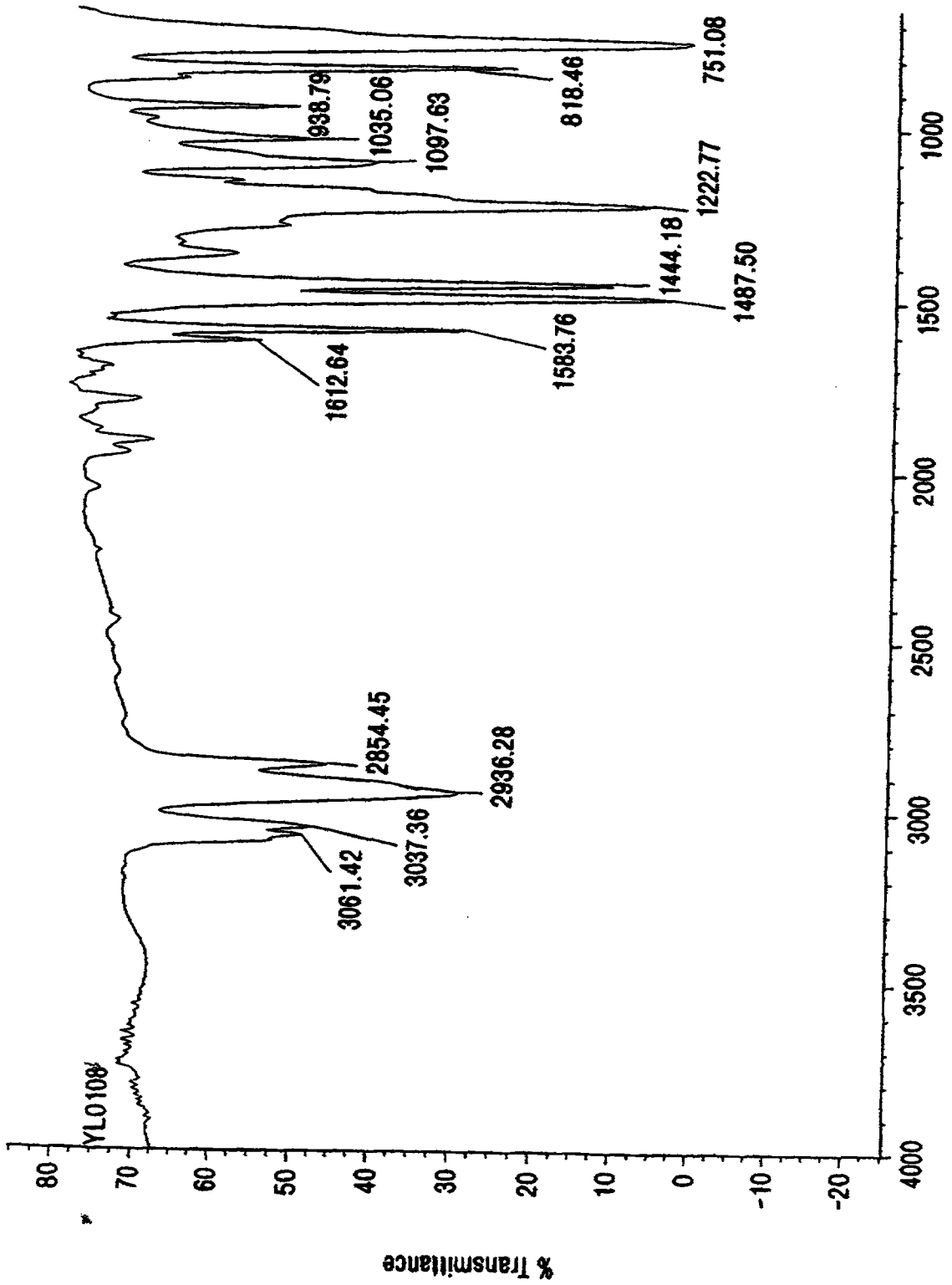

YL0108
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
80
70
60
50
40
30
20
10
0
-10
-20
3061.42
3037.36
2936.28
2854.45
1612.64
1583.76
1487.50
1444.18
1222.77
1097.63
1035.06
938.79
818.46
751.08

FIG. 95

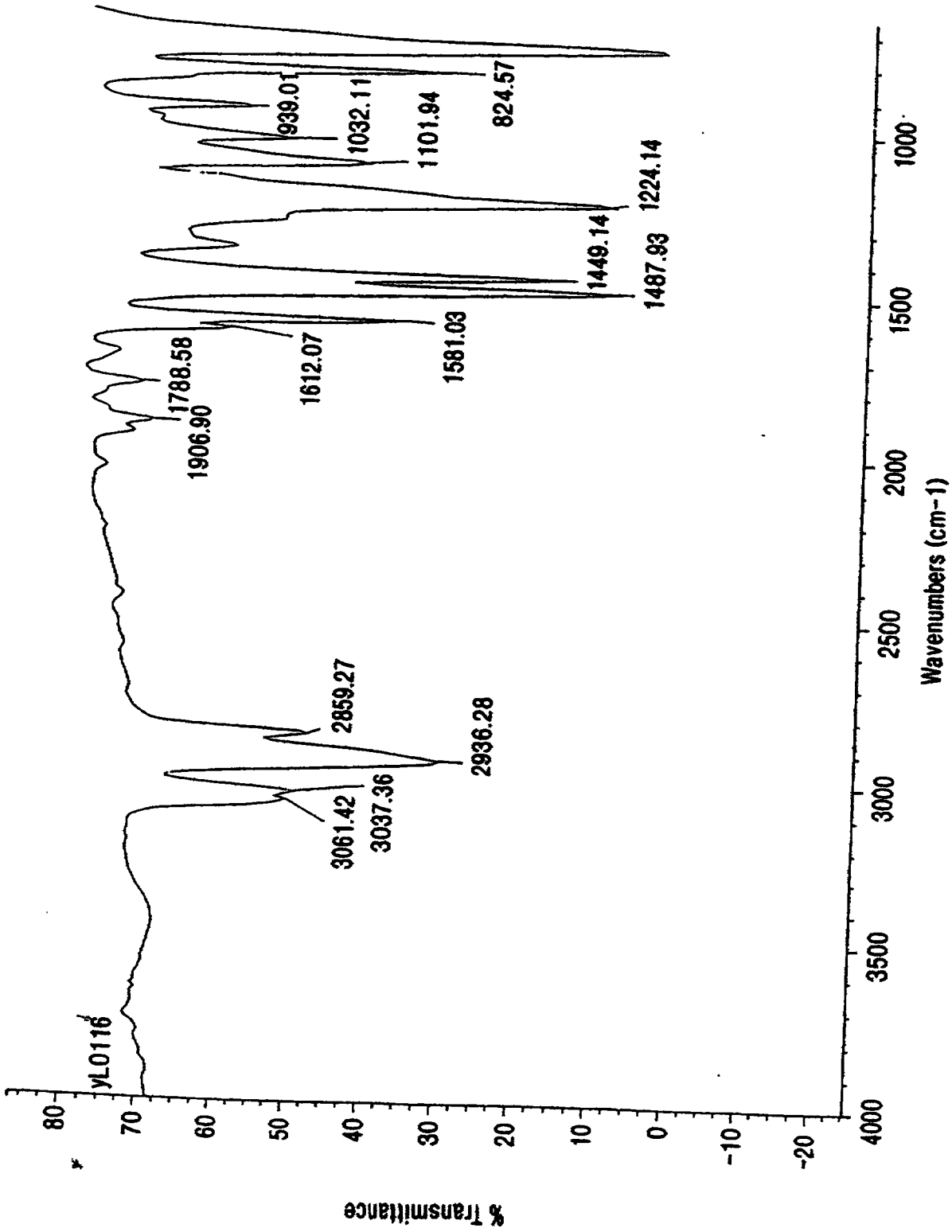

yL0116
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
80
70
60
50
40
30
20
10
0
-10
-20
3061.42
3037.36
2936.28
2859.27
1906.90
1788.58
1612.07
1581.03
1487.93
1449.14
1224.14
1101.94
1032.11
939.01
824.57

FIG. 96

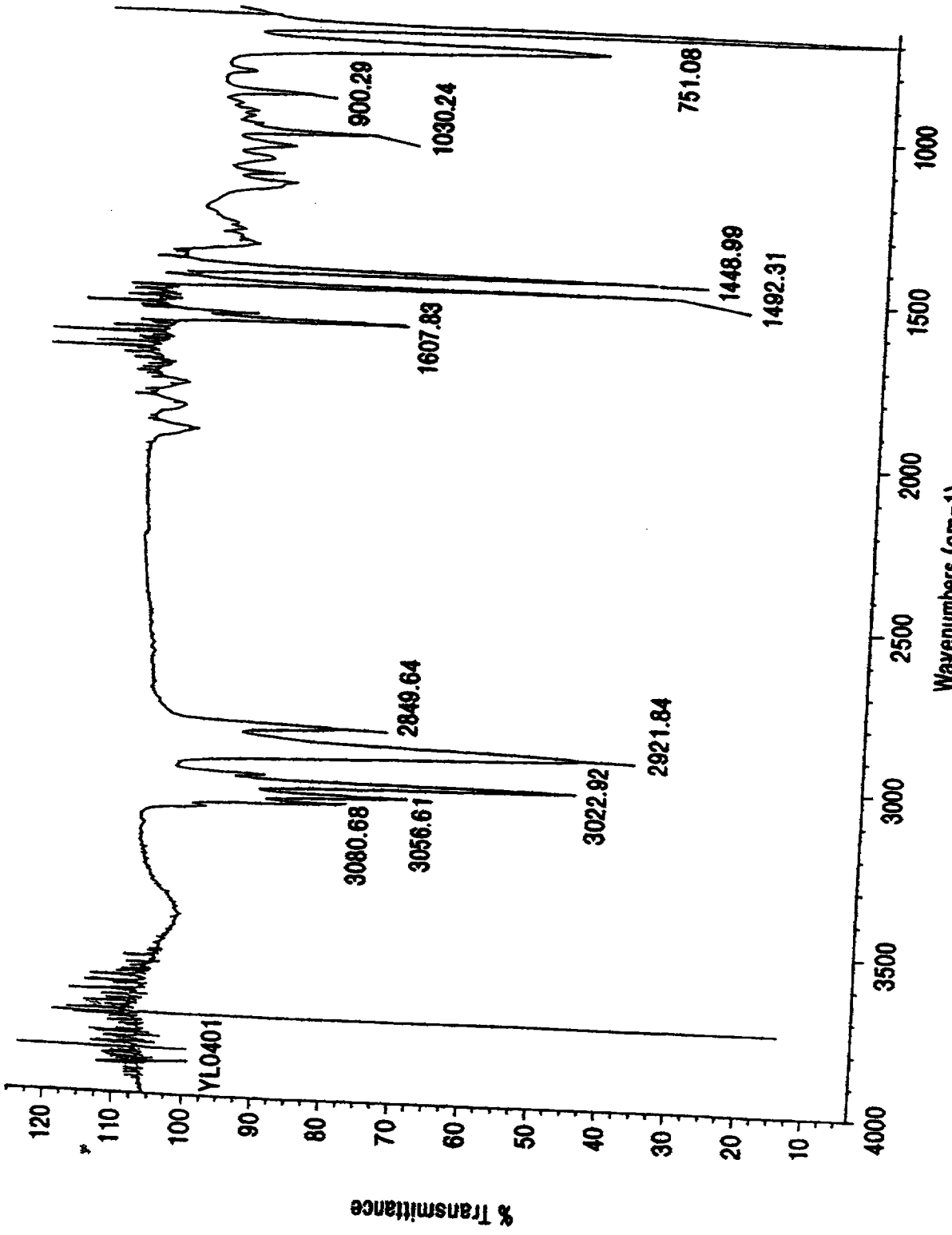

YL0401
751.08
900.29
1030.24
1448.99
1492.31
1607.83
2849.64
2921.84
3022.92
3056.61
3080.68
% Transmittance
Wavenumbers (cm-1)
120
110
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000

FIG. 97

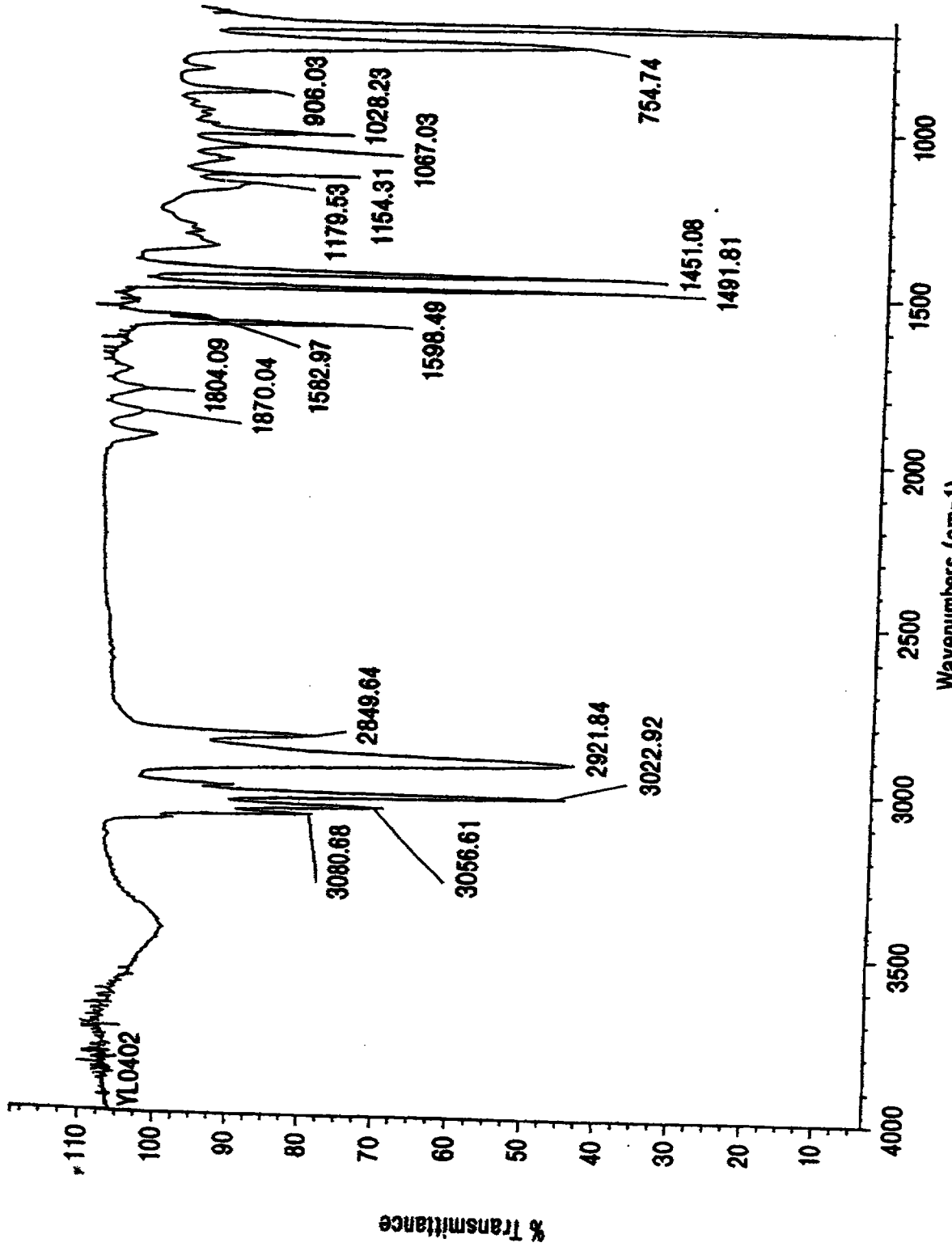

YL0402
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
110
100
90
80
70
60
50
40
30
20
10
3080.68
3056.61
2921.84
3022.92
2849.64
1804.09
1870.04
1582.97
1598.49
1451.08
1491.81
1179.53
1154.31
1067.03
1028.23
906.03
754.74

FIG. 98

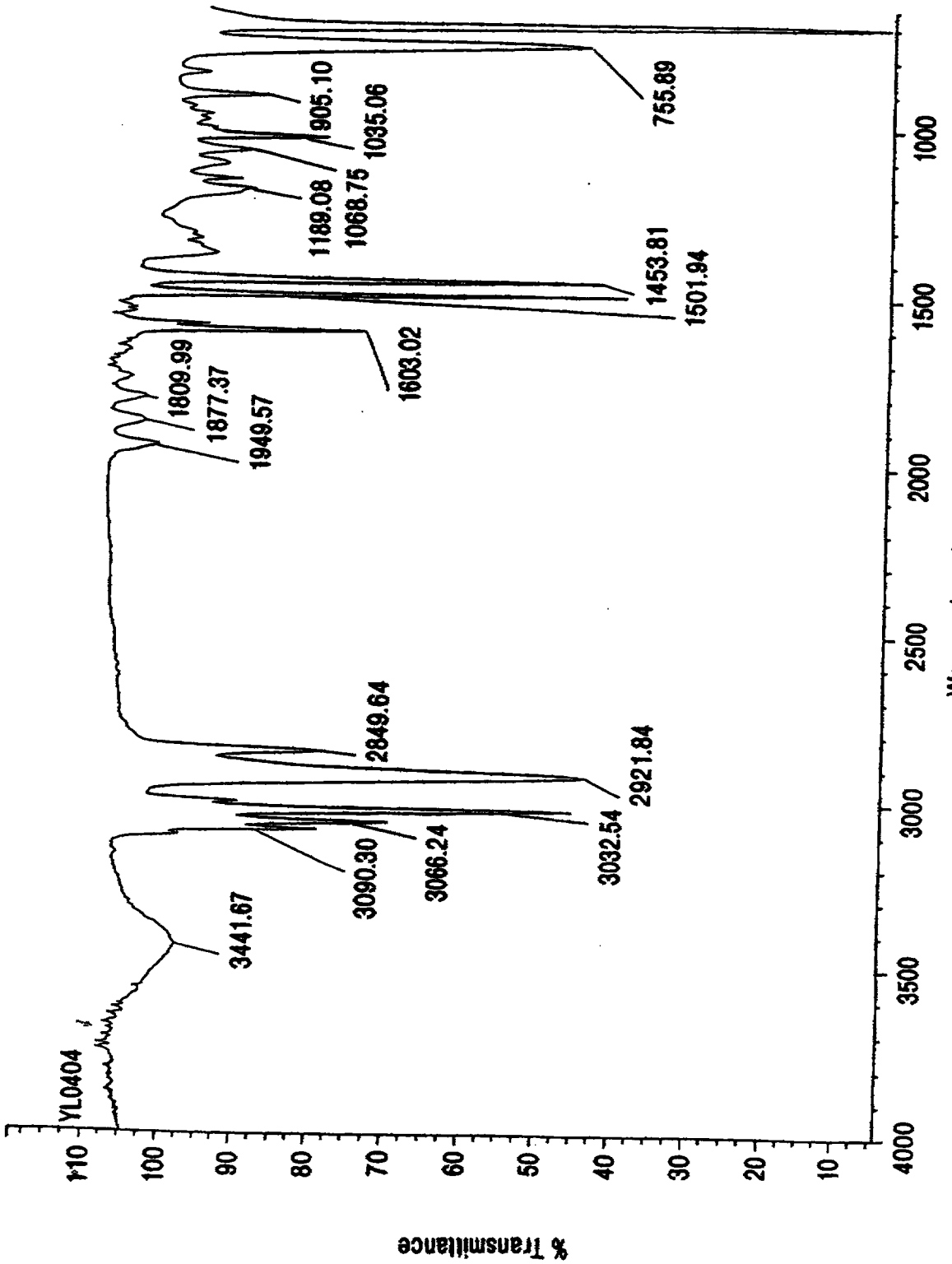

YL0404
3441.67
3090.30
3066.24
3032.54
2921.84
2849.64
1949.57
1877.37
1809.99
1603.02
1501.94
1453.81
1189.08
1068.75
1035.06
905.10
755.89
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
10
20
30
40
50
60
70
80
90
100
110

FIG. 99

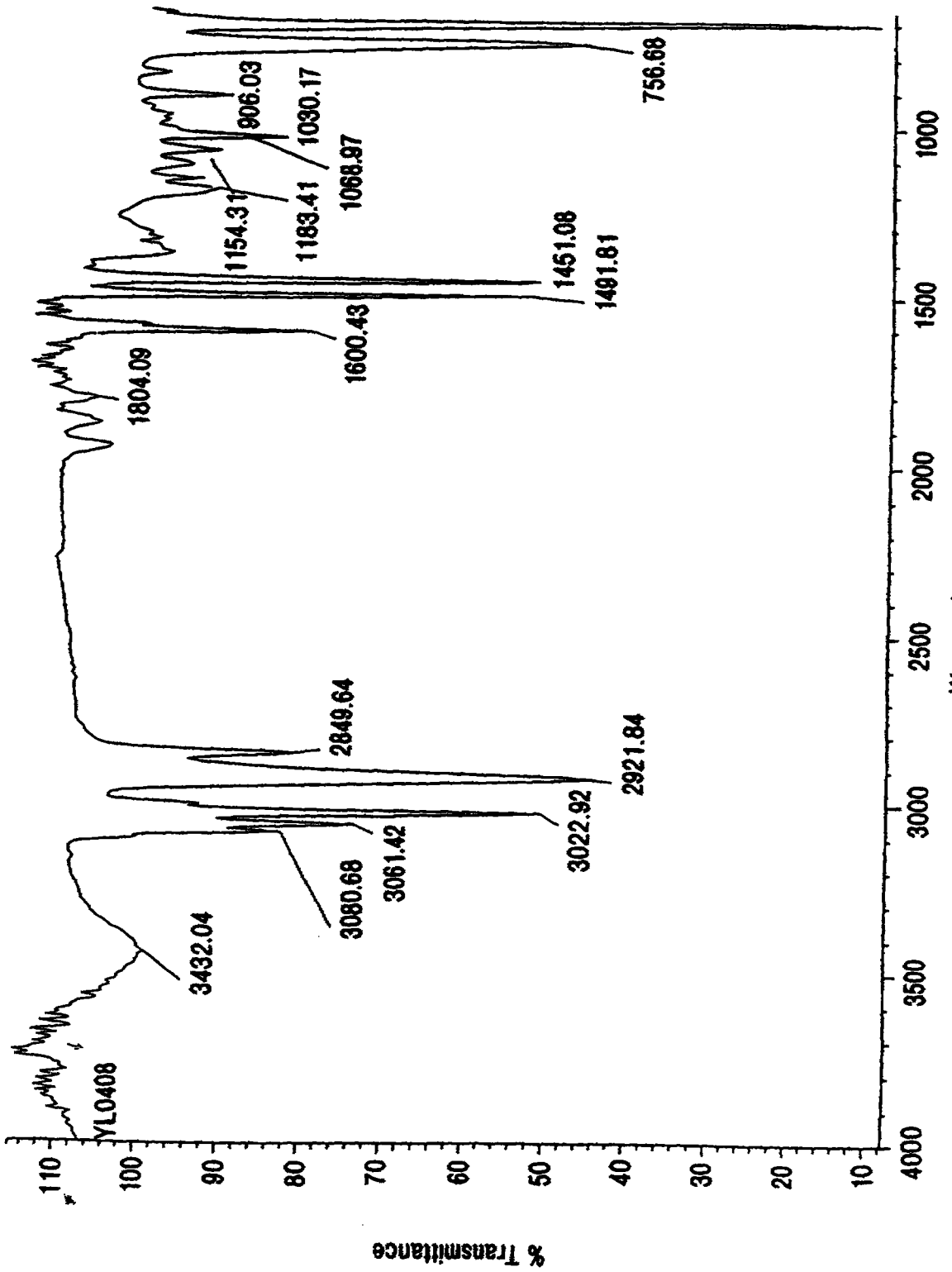

YL0408
3432.04
3080.68
3061.42
3022.92
2921.84
2849.64
1804.09
1600.43
1491.81
1451.08
1183.41
1154.31
1068.97
1030.17
906.03
756.68
% Transmittance
Wavenumbers (cm-1)
110
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000

FIG. 100

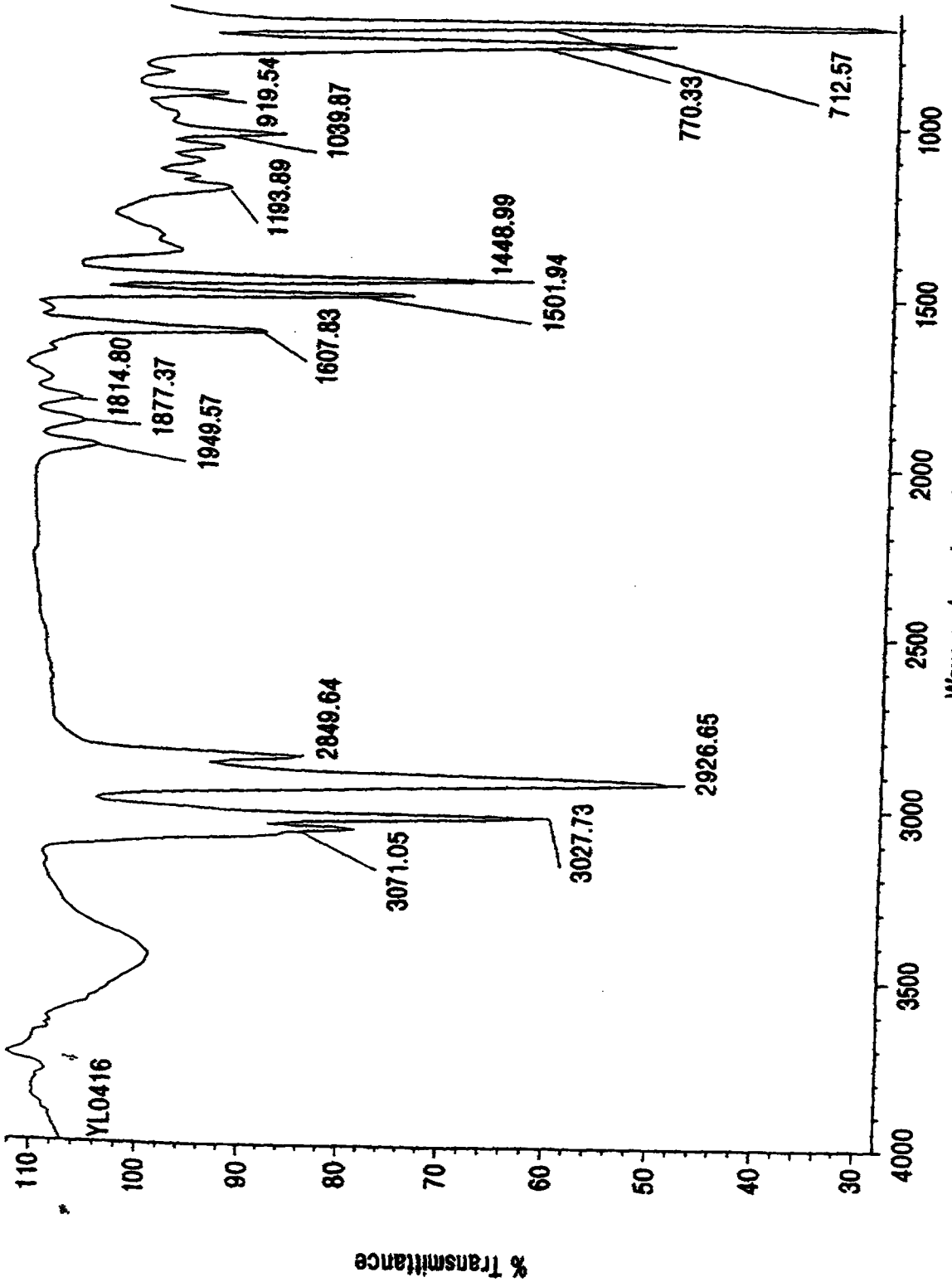

YL0416
% Transmittance
110
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
3071.05
3027.73
2926.65
2849.64
1949.57
1877.37
1814.80
1607.83
1501.94
1448.99
1193.89
1039.87
919.54
770.33
712.57

FIG. 101

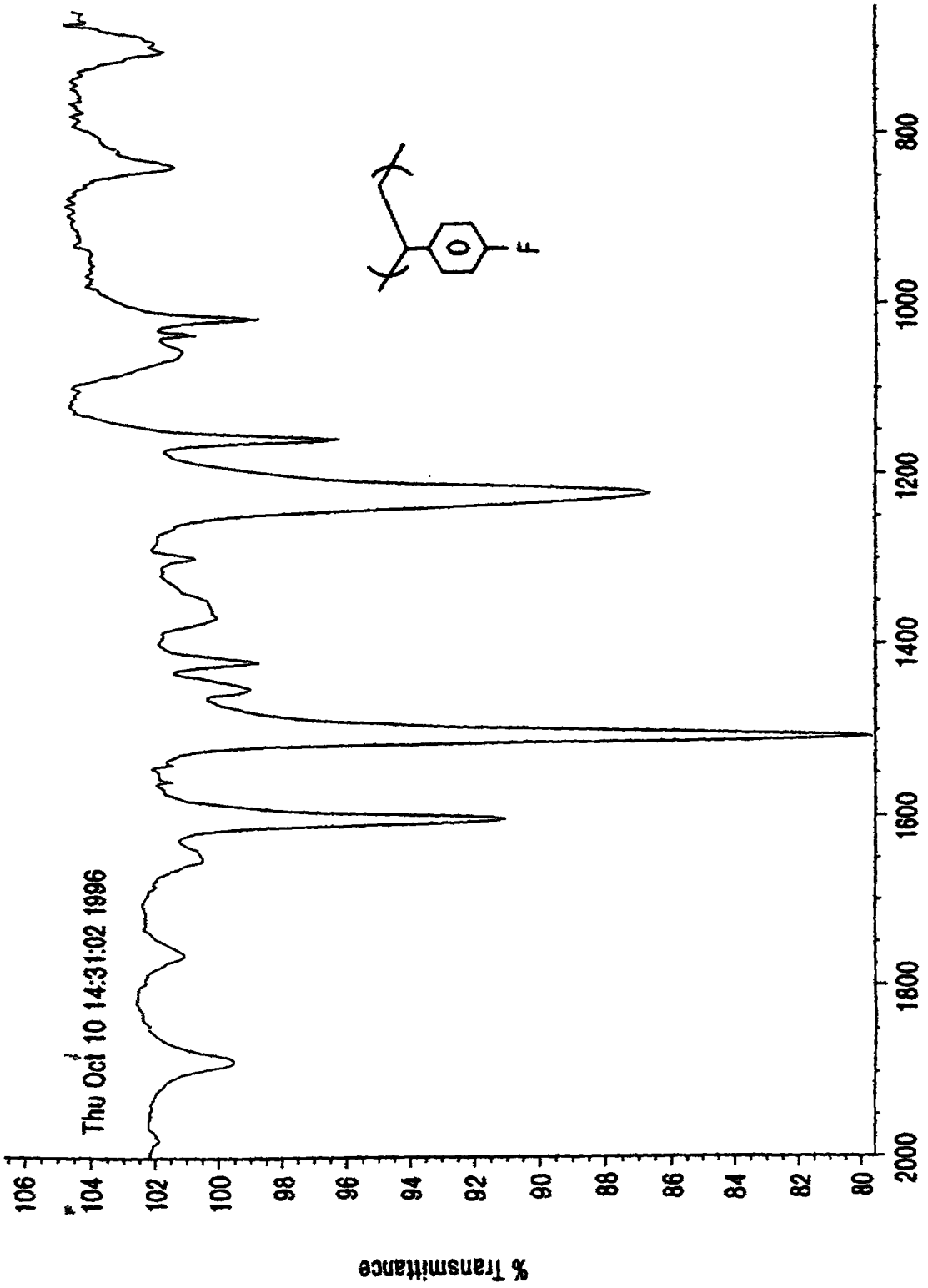

Thu Oct 10 14:31:02 1996
% Transmittance
Wavenumbers (cm-1)
106
104
102
100
98
96
94
92
90
88
86
84
82
80
2000
1800
1600
1400
1200
1000
800
F

FIG. 102

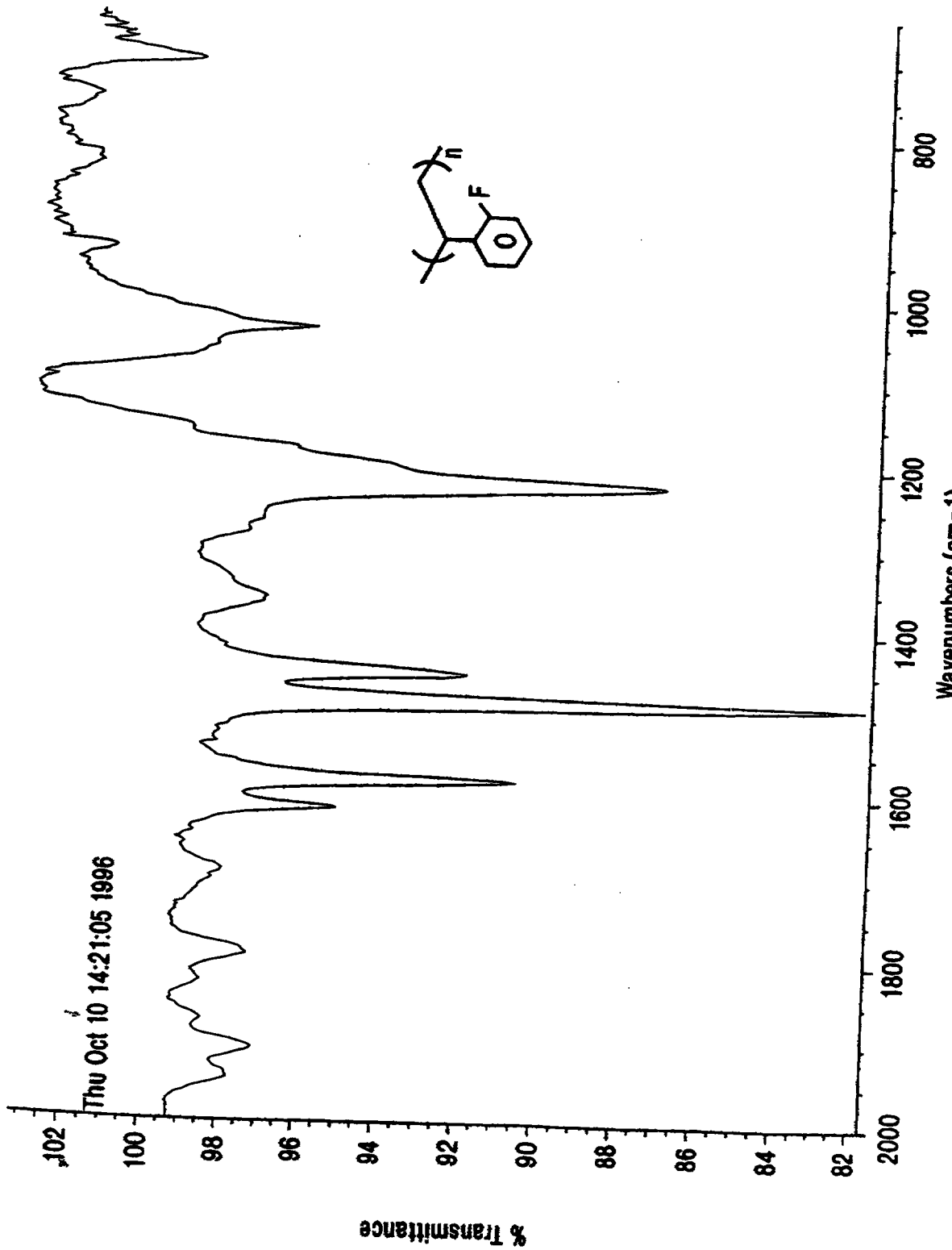


FIG. 103

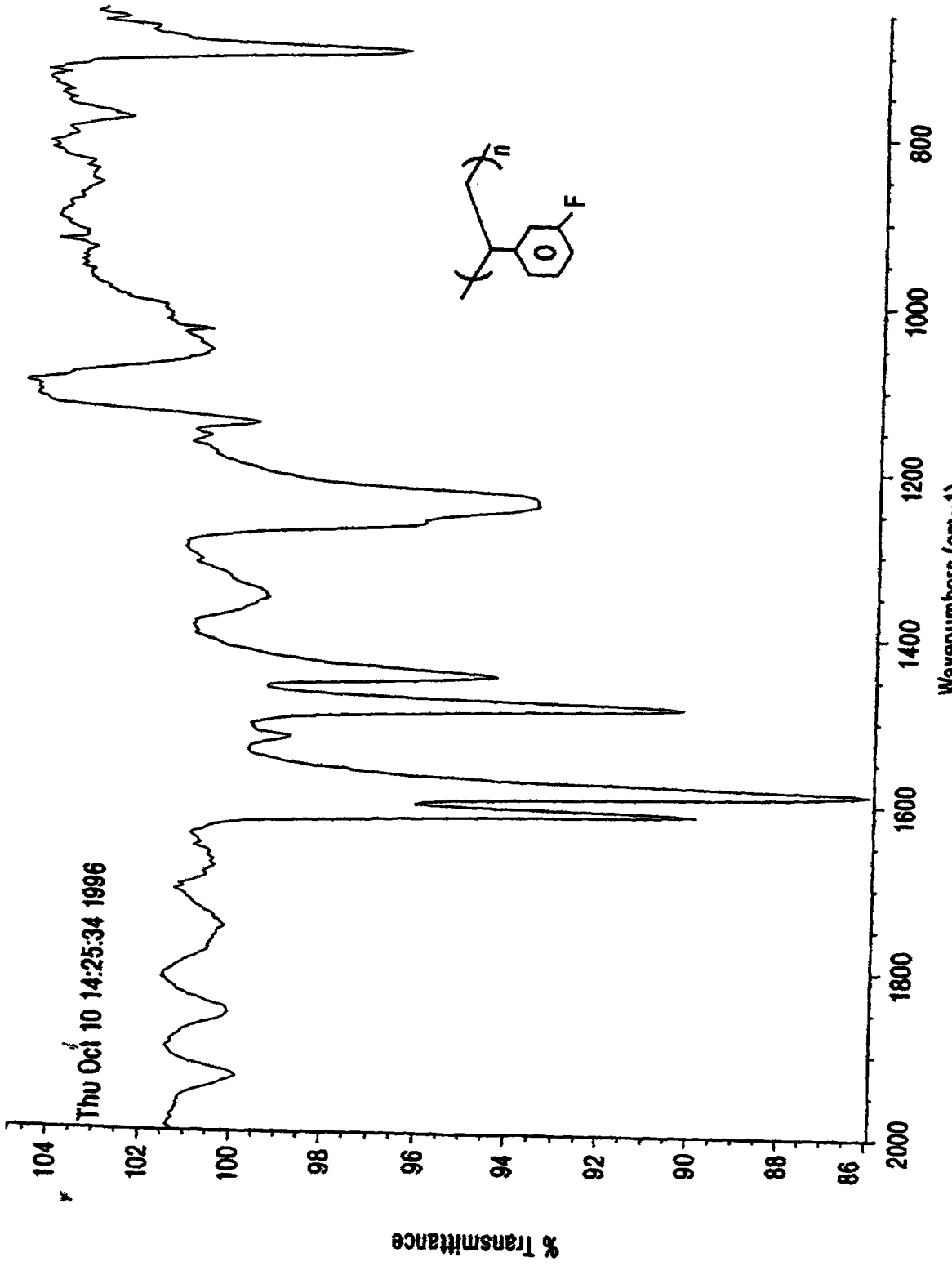

Thu Oct 10 14:25:34 1996
% Transmittance
Wavenumbers (cm-1)
104
102
100
98
96
94
92
90
88
86
2000
1800
1600
1400
1200
1000
800
n
F
O

FIG. 104

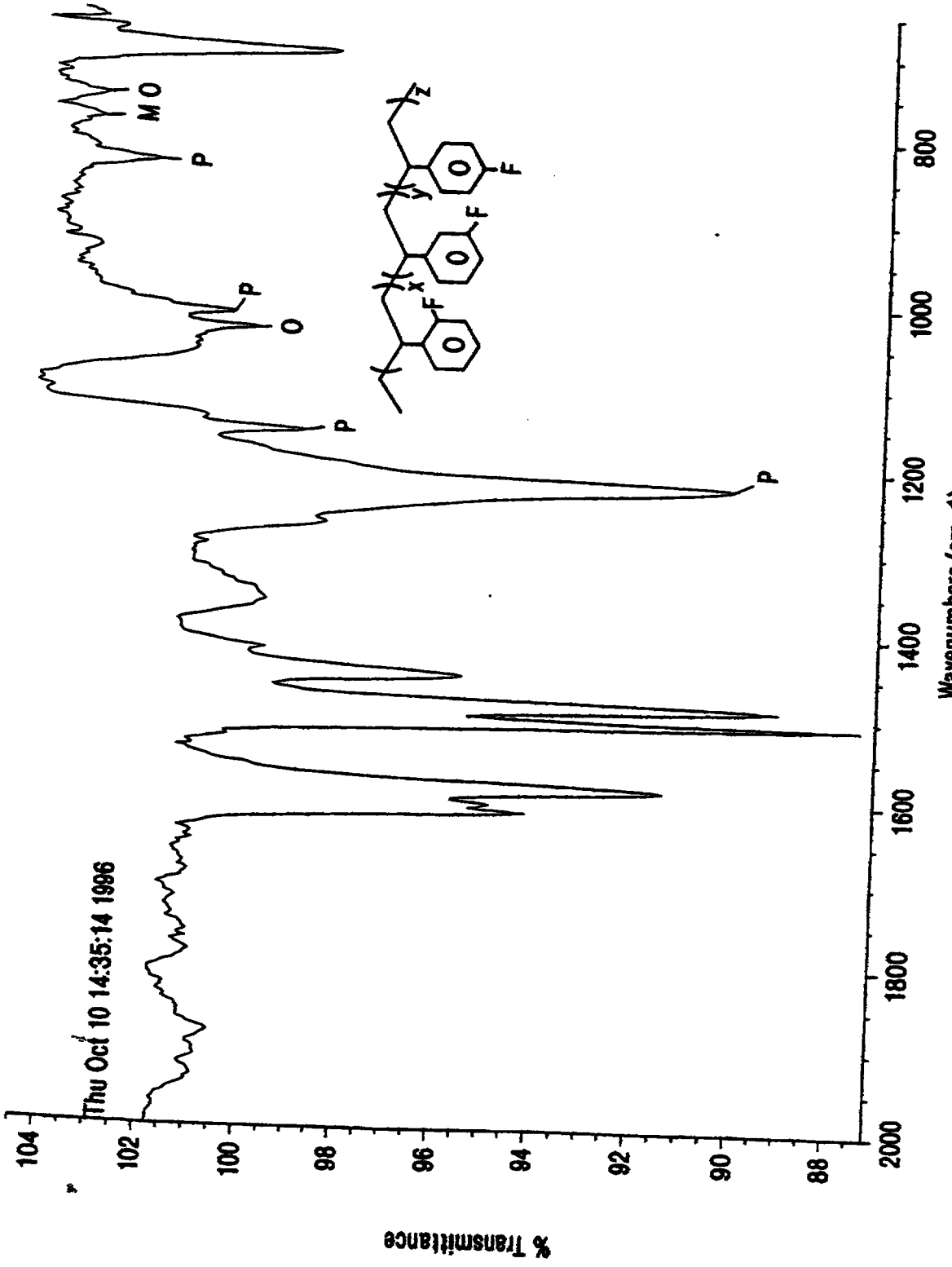

Thu Oct 10 14:35:14 1996
% Transmittance
Wavenumbers (cm-1)
104
102
100
98
96
94
92
90
88
2000
1800
1600
1400
1200
1000
800
M O
P
O
F
x
y
z

FIG. 105

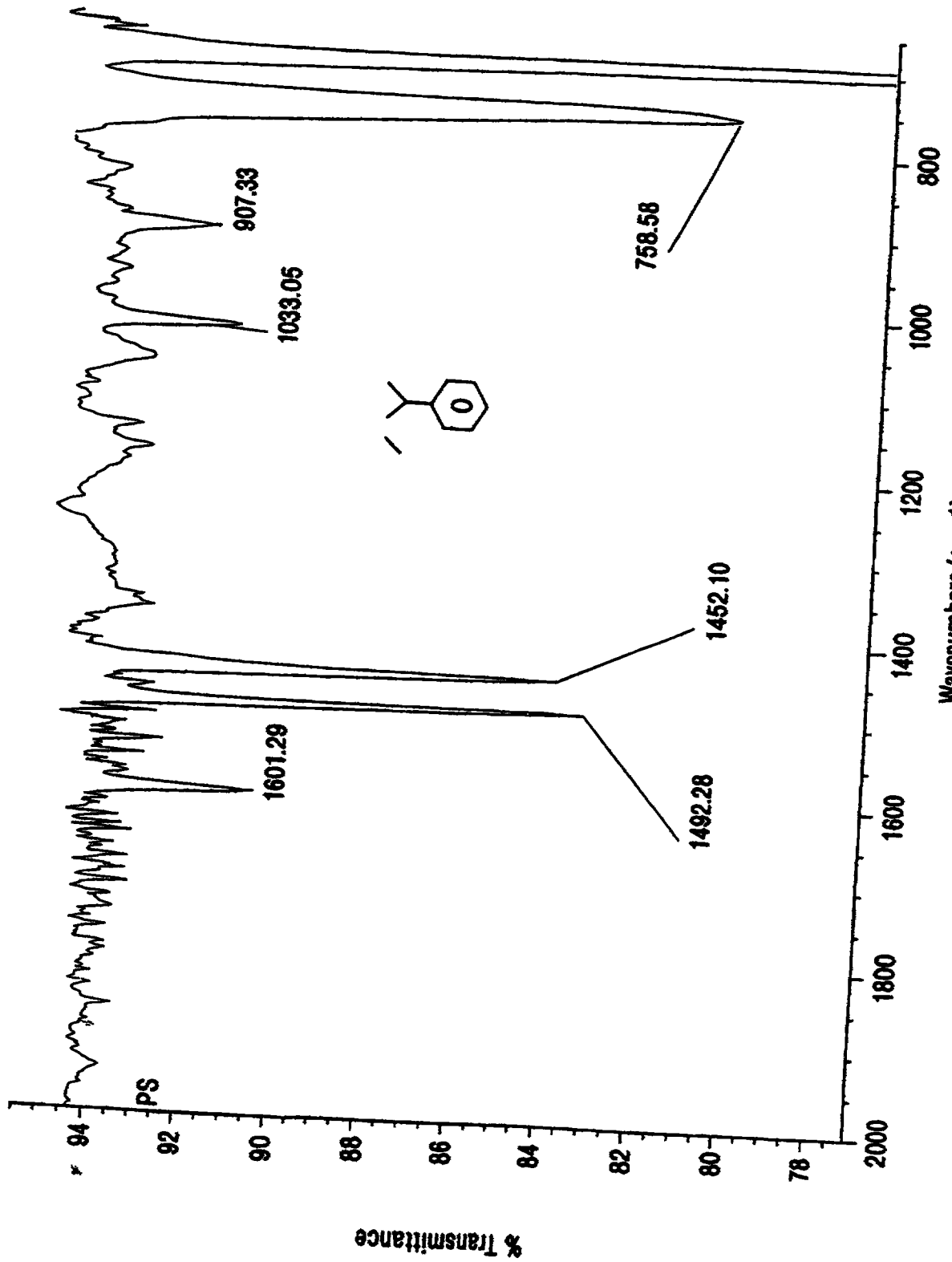
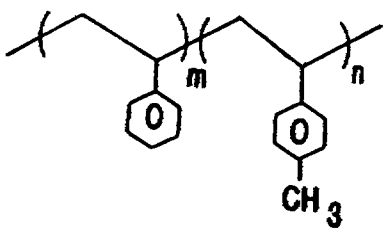
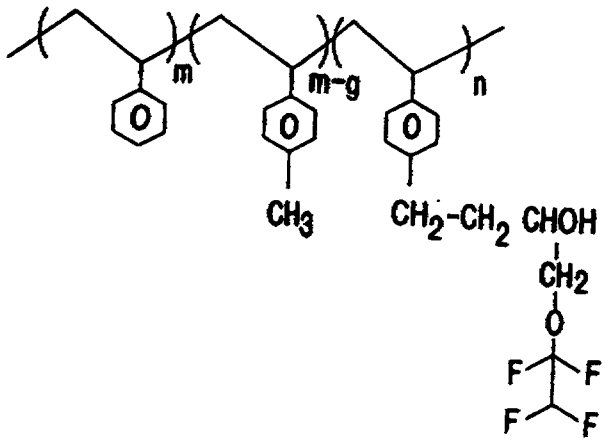

PS
907.33
1033.05
758.58
1452.10
1601.29
1492.28
% Transmittance
Wavenumbers (cm-1)
94
92
90
88
86
84
82
80
78
2000
1800
1600
1400
1200
1000
800

FIG.106

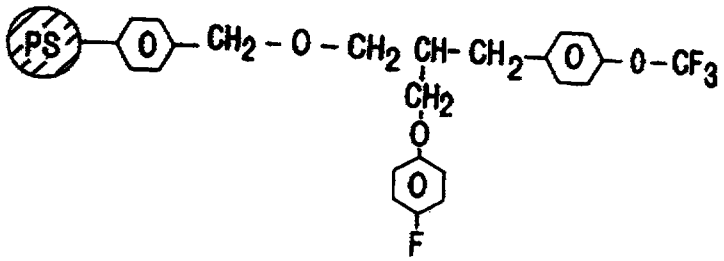
P (S-co-MS)



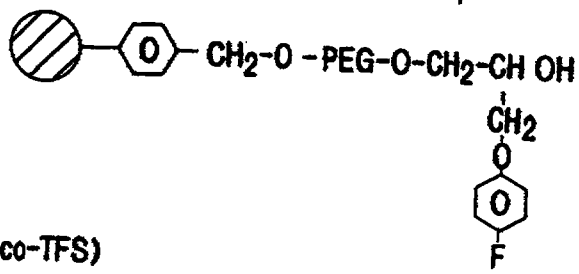
P(S-co-MS)-Rf_1



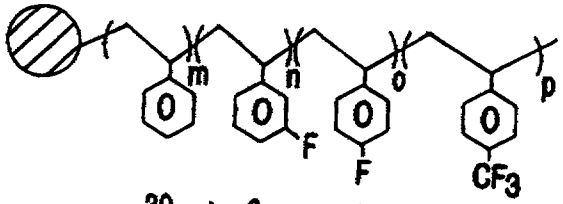
PS-BOH-Rf_1-Rf_2



PS-PEG-Rf_1



Poly(S-co-FS-co-TFS)



30 : 2 : 1 : 0.8

FIG. 107

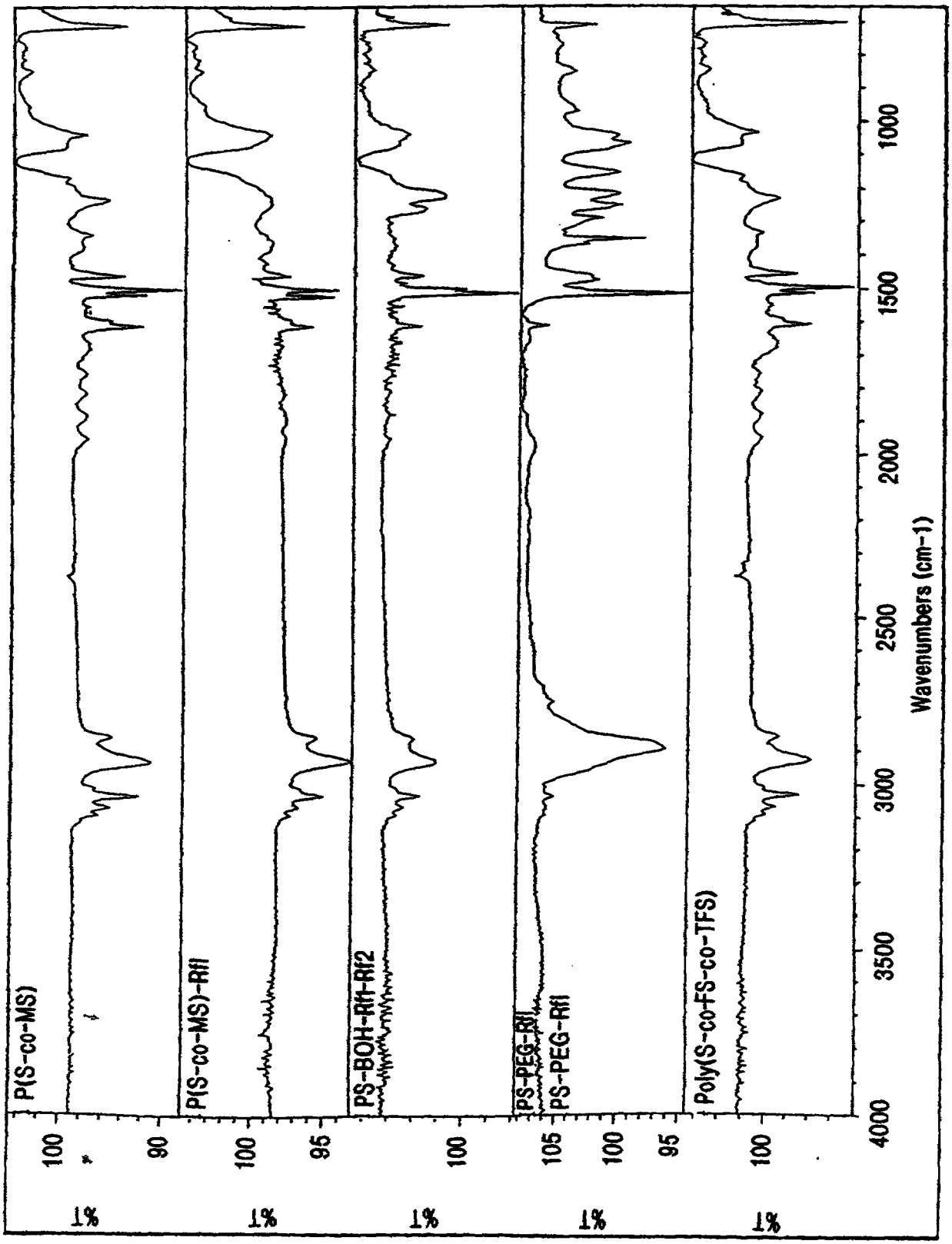

P(S-co-MS)
P(S-co-MS)-Rf1
PS-BOH-Rf1-Rf2
PS-PEG-Rf1
PS-PEG-Rf1
Poly(S-co-FS-co-TFS)
%T
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000

FIG. 108

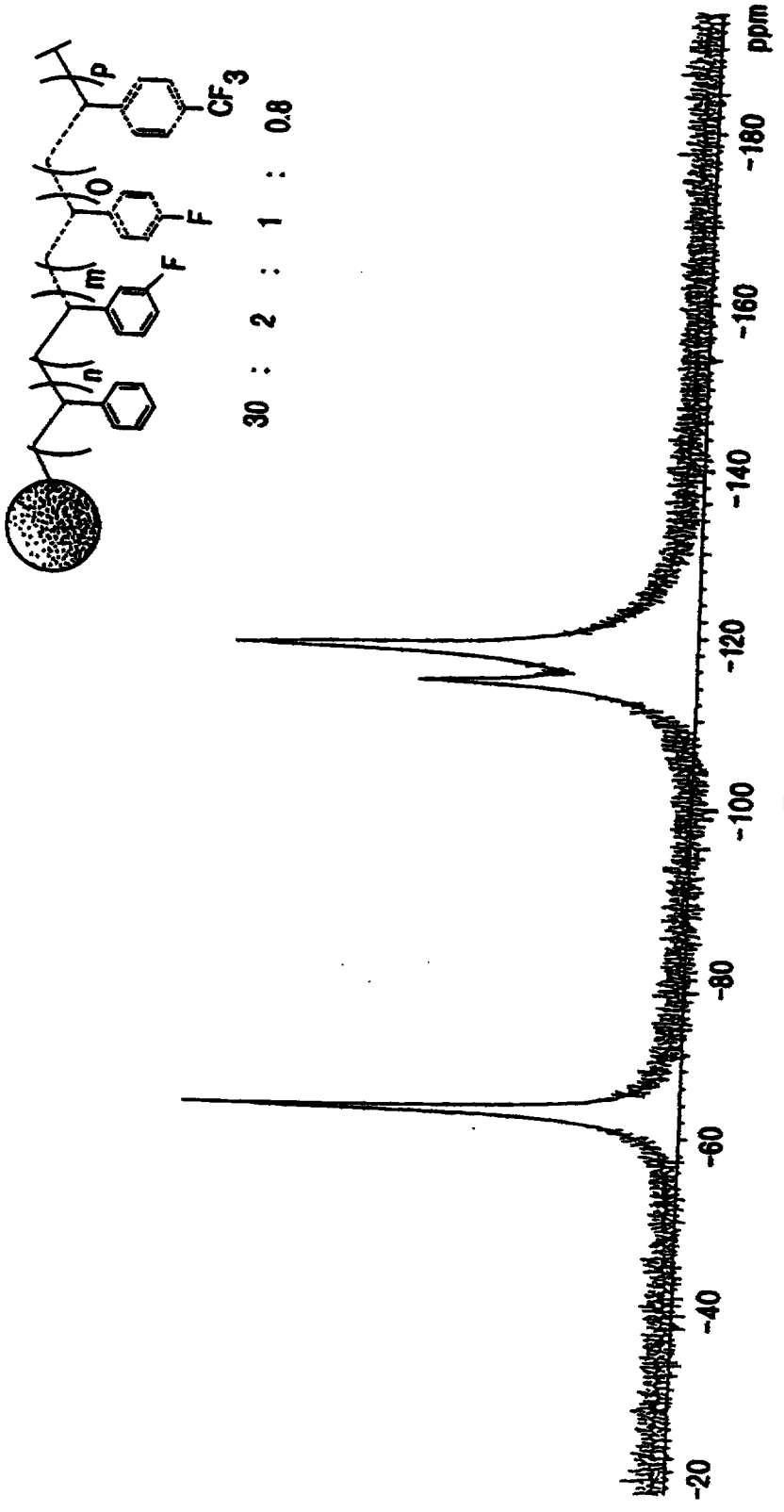


FIG. 109

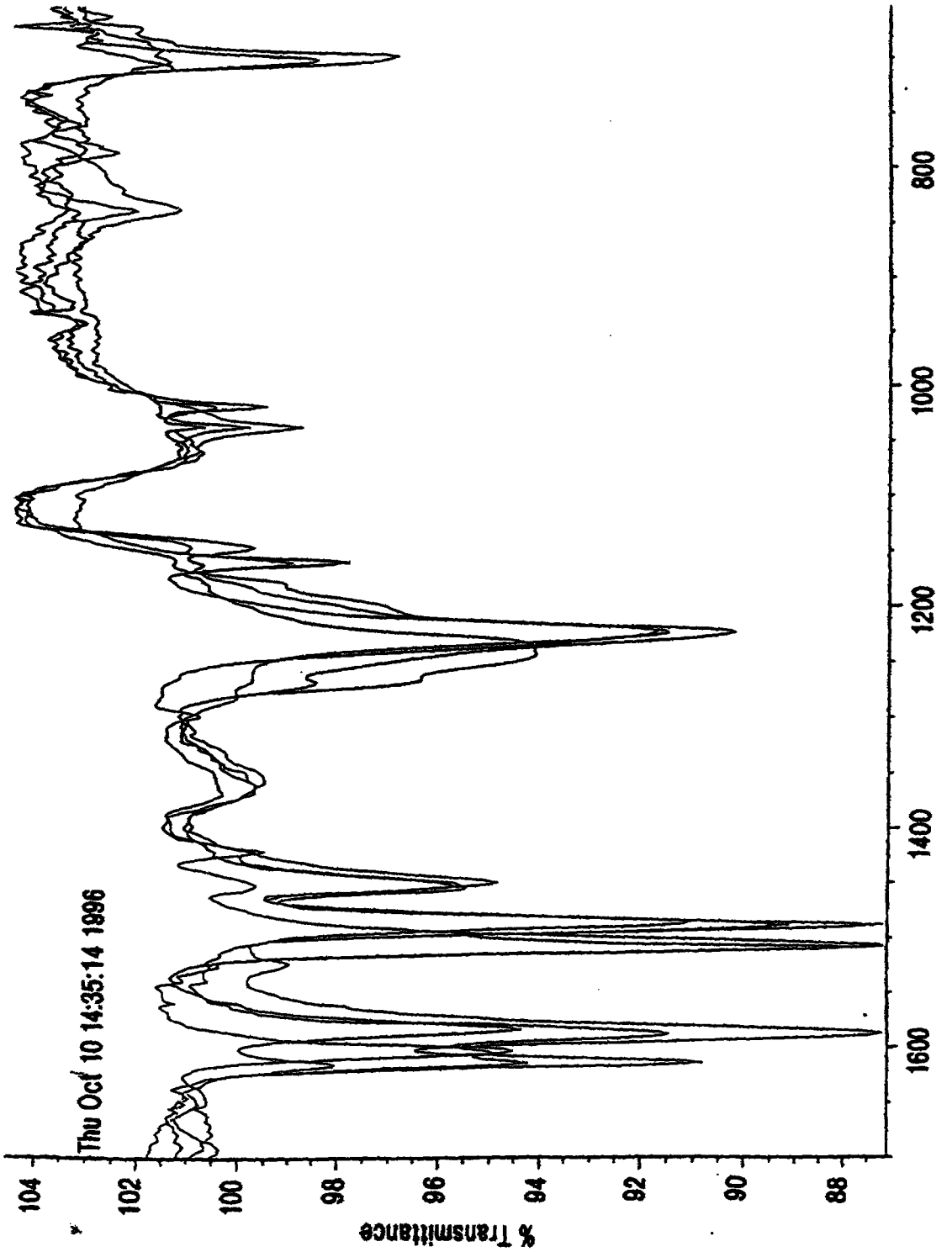

Thu Oct 10 14:35:14 1996
% Transmittance
104
102
100
98
96
94
92
90
88
1600
1400
1200
1000
800
Wavenumbers(cm-1)

FIG. 11O

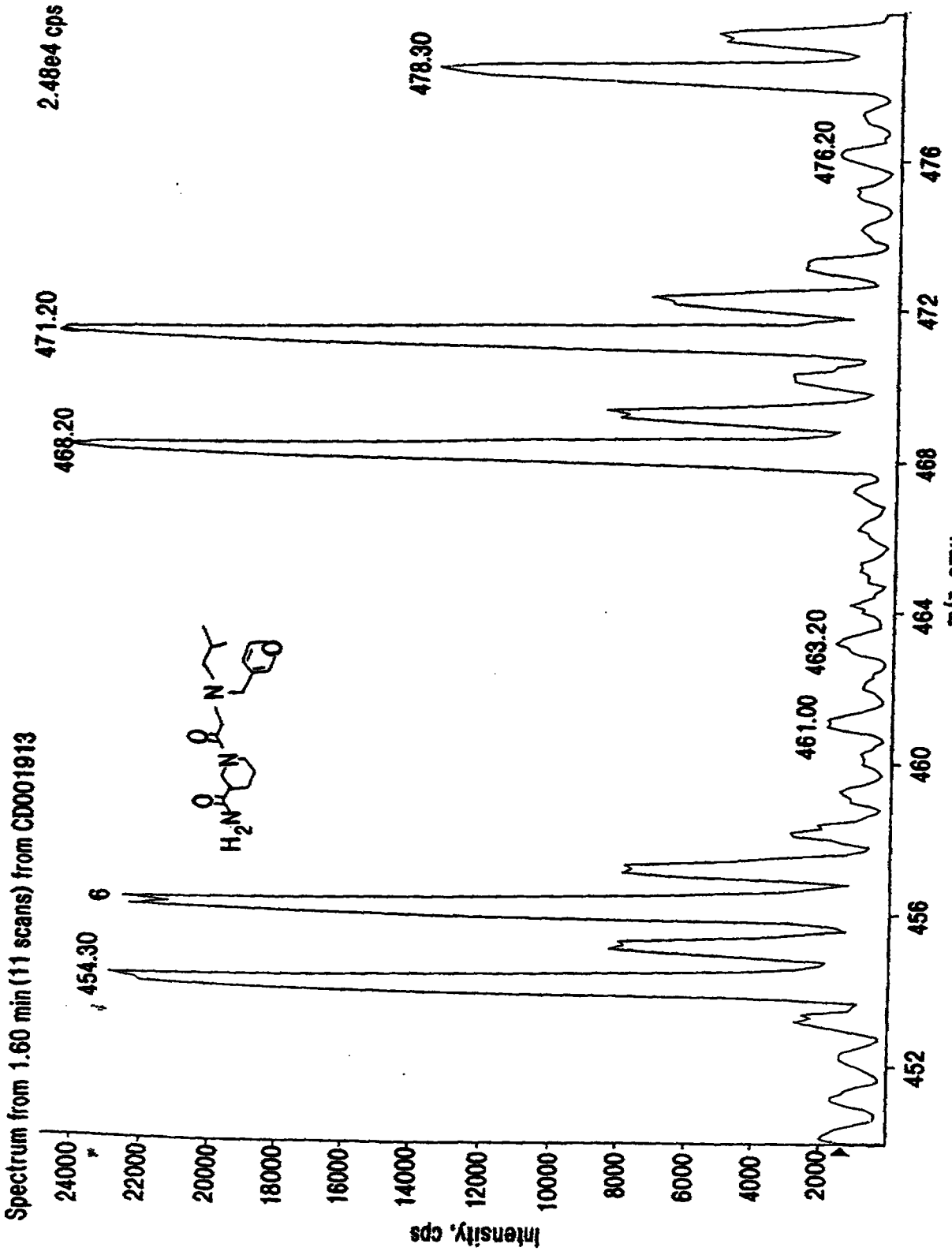

Spectrum from 1.60 min (11 scans) from CD001913
Intensity, cps
m/z, amu
2.48e4 cps
454.30
6
468.20
471.20
461.00
463.20
478.30
476.20
H_2N

FIG. 111

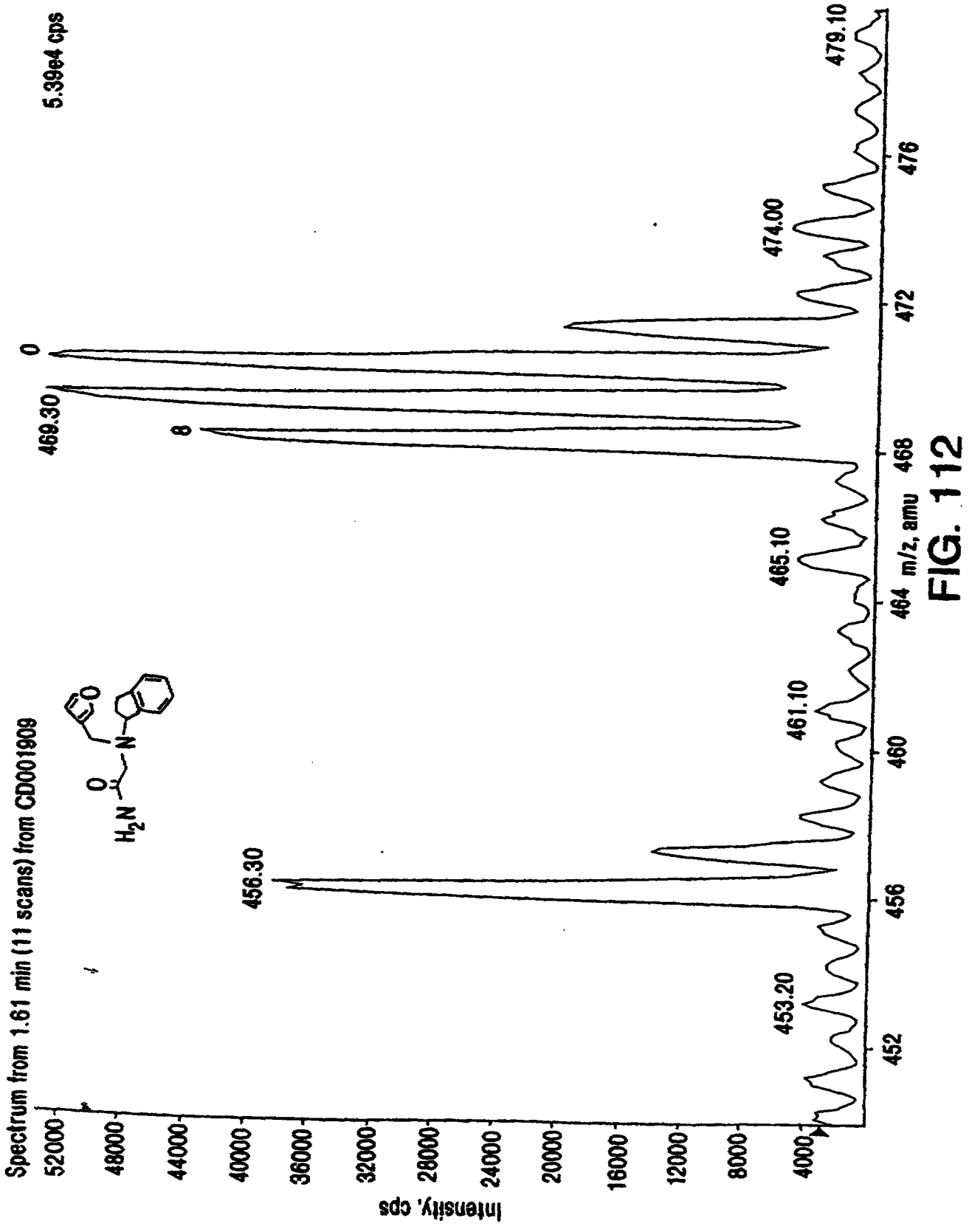

Spectrum from 1.61 min (11 scans) from CD001909
5.39e4 cps
0
8
469.30
456.30
453.20
461.10
465.10
474.00
479.10
Intensity, cps
m/z, amu
H_2N

FIG. 112

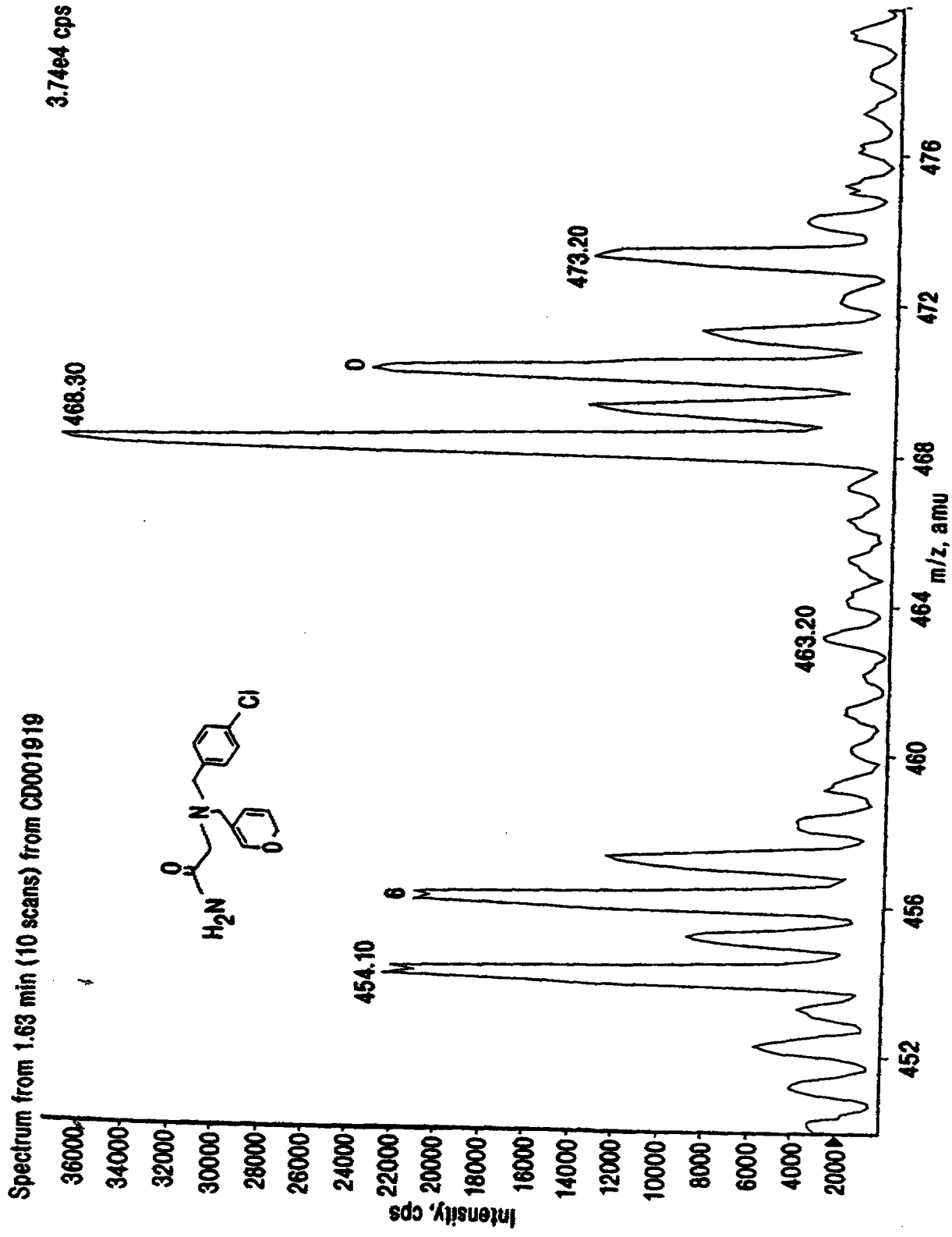

Spectrum from 1.63 min (10 scans) from CD001919
3.74e4 cps
Intensity, cps
m/z, amu
468.30
473.20
463.20
454.10
Cl
O
N
H_2N

FIG. 113

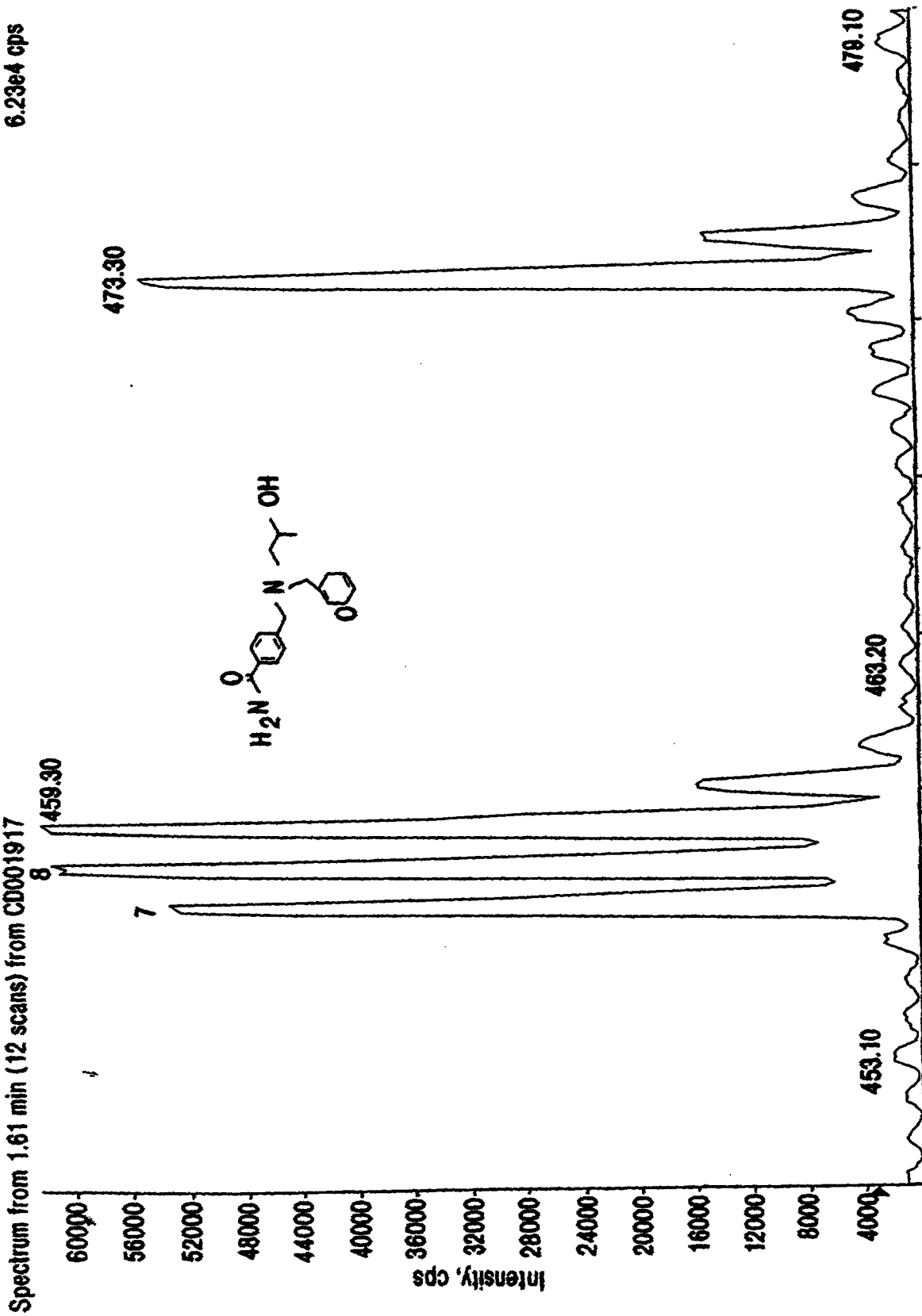

6.23e4 cps
Spectrum from 1.61 min (12 scans) from CD001917
Intensity, cps
60000
56000
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
452
456
460
464
468
472
476
m/z, amu
453.10
459.30
463.20
473.30
478.10
8
7
OH
N
O
H_2N

FIG. 114

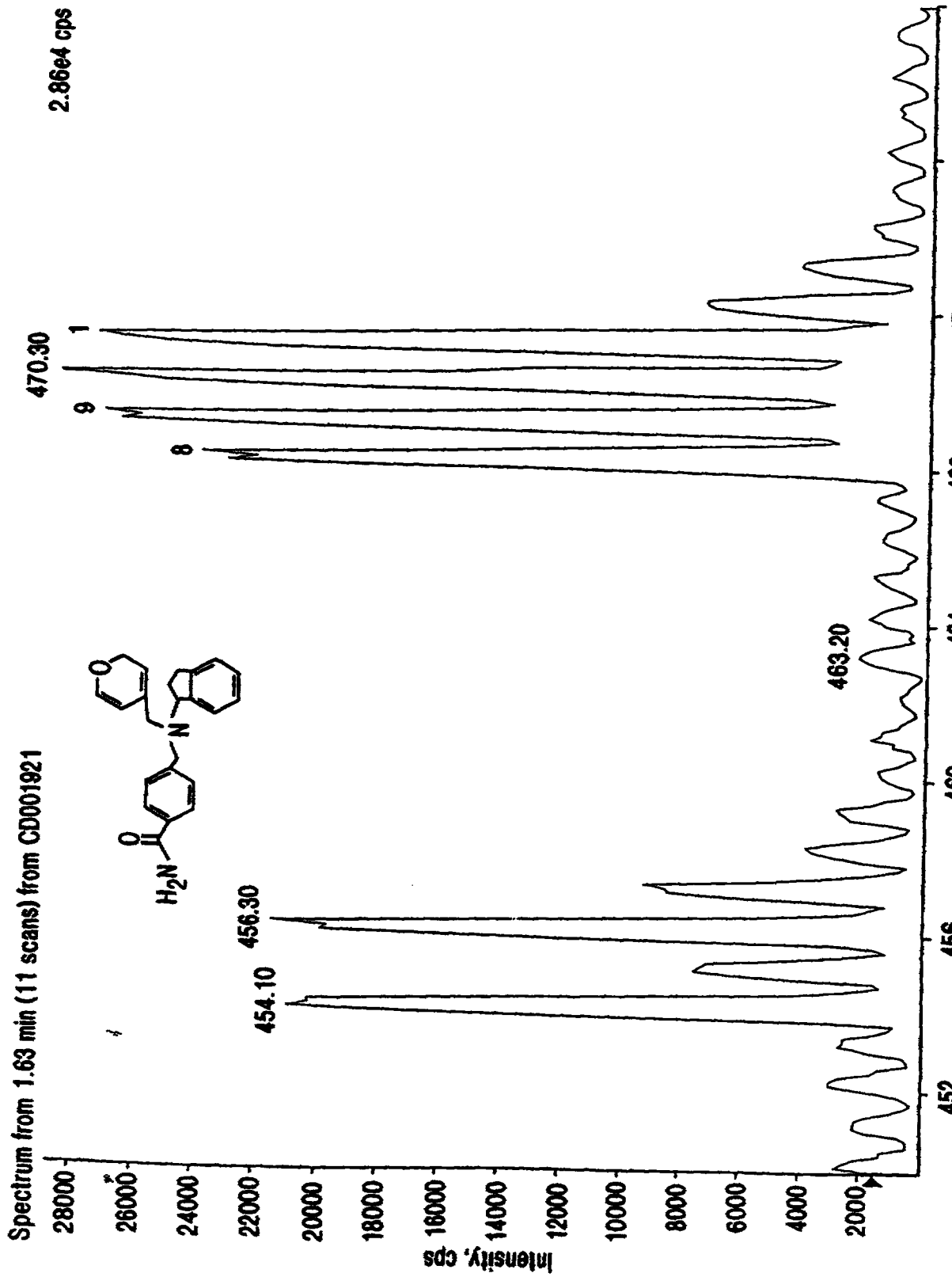

Spectrum from 1.63 min (11 scans) from CD001921
2.86e4 cps
Intensity, cps
m/z, amu
454.10
456.30
463.20
470.30
1
9
8
H_2N
O
N

FIG. 115

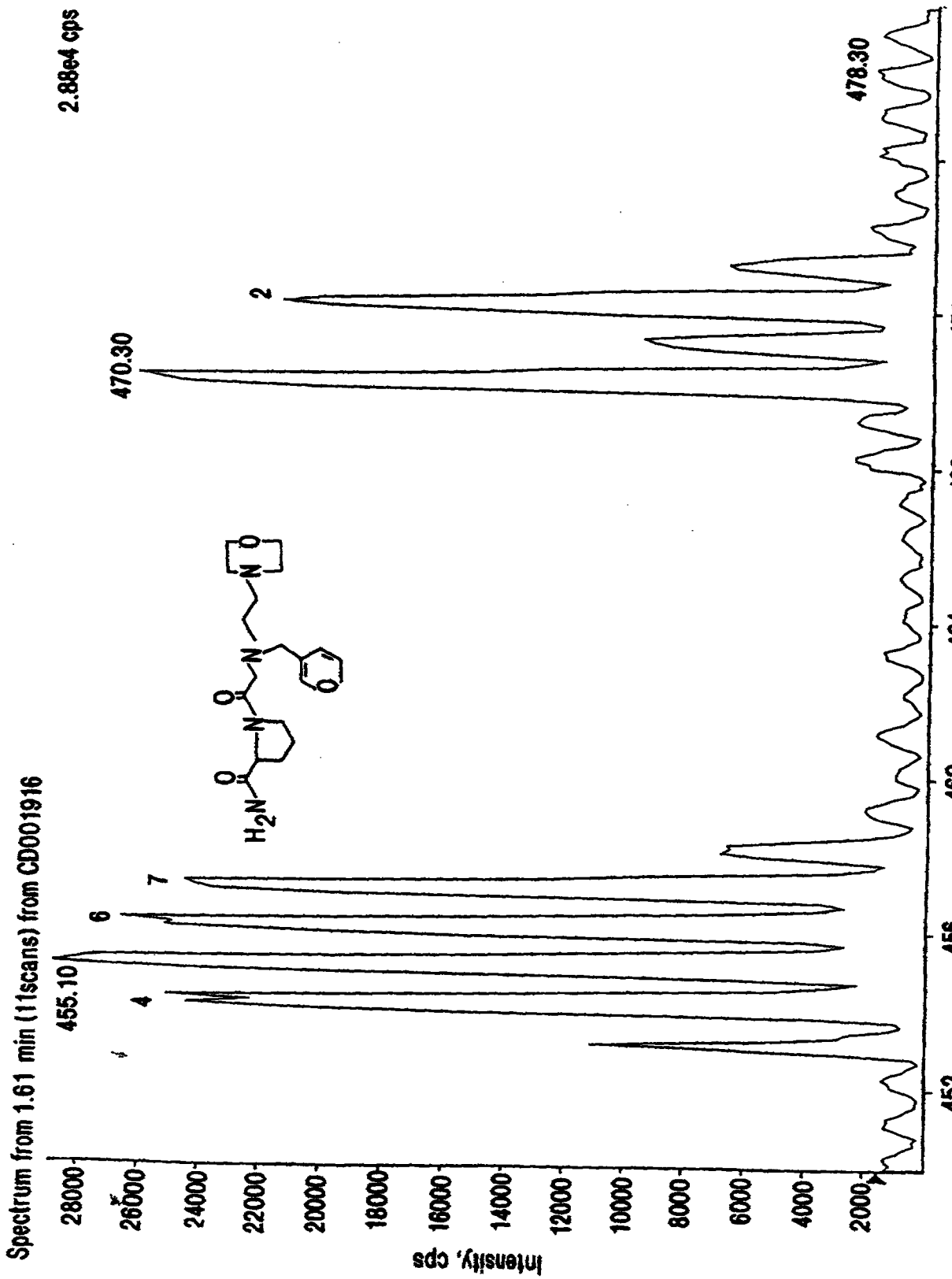

Spectrum from 1.61 min (11scans) from CD001916
2.88e4 cps
Intensity, cps
m/z, amu
455.10
470.30
478.30
4
6
7
2
H_2N

FIG. 116

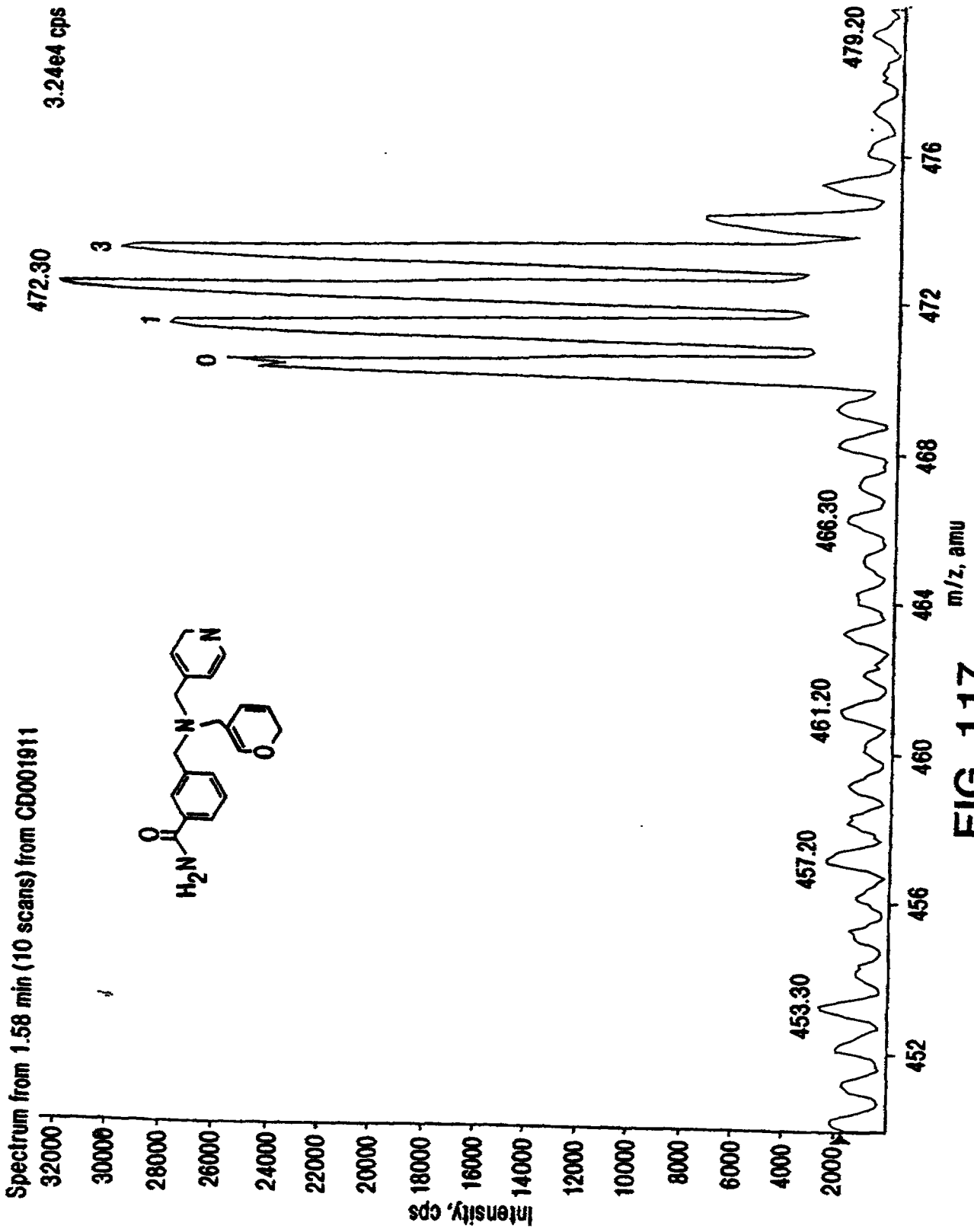

Spectrum from 1.58 min (10 scans) from CD001911
3.24e4 cps
Intensity, cps
m/z, amu
472.30
453.30
457.20
461.20
466.30
479.20
0
1
3
H_2N
O
N
N
O

FIG. 117

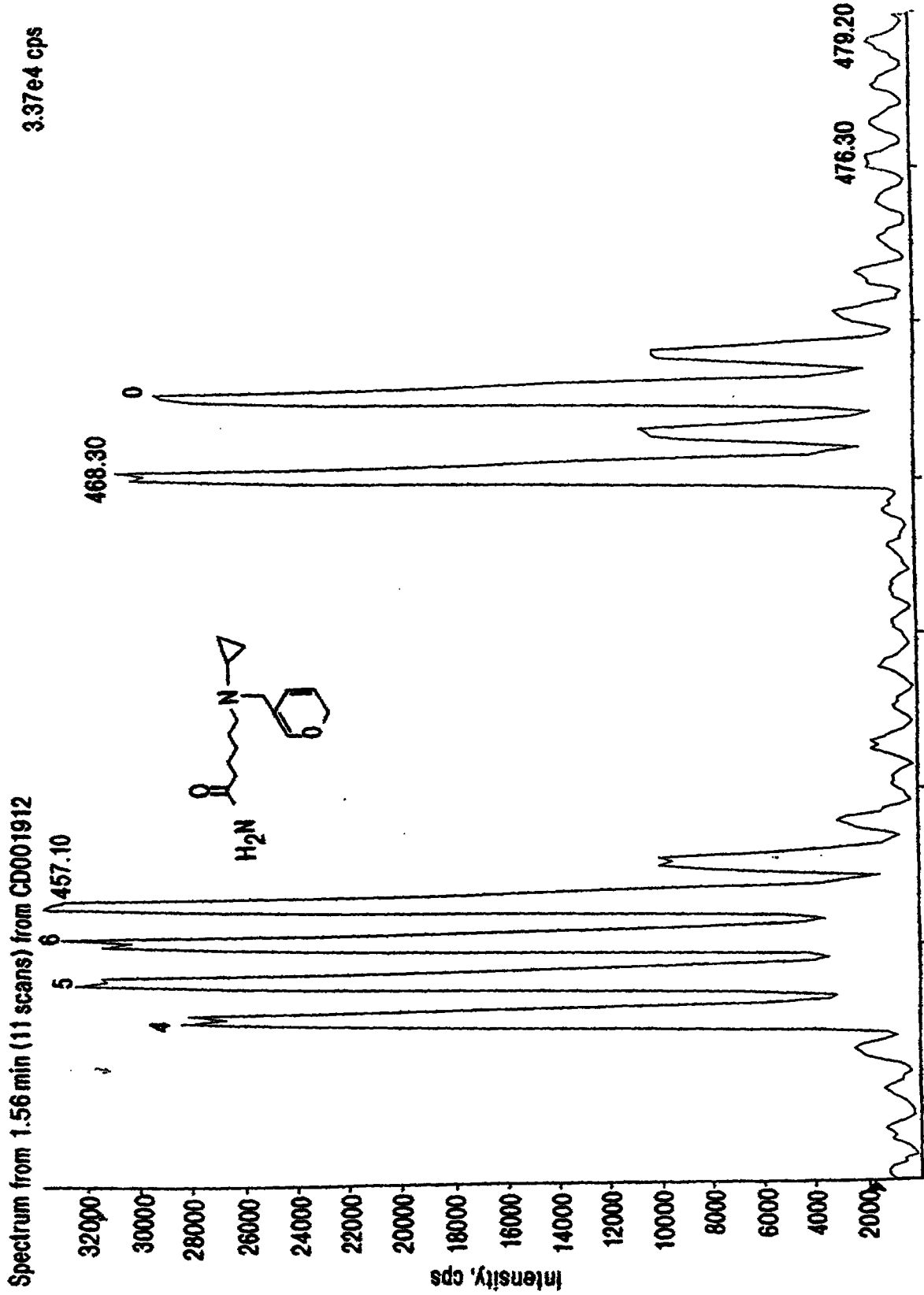

Spectrum from 1.56 min (11 scans) from CD001912
3.37e4 cps
Intensity, cps
m/z, amu
457.10
468.30
476.30
479.20
4
5
6
0
H_2N
N
O

FIG. 118

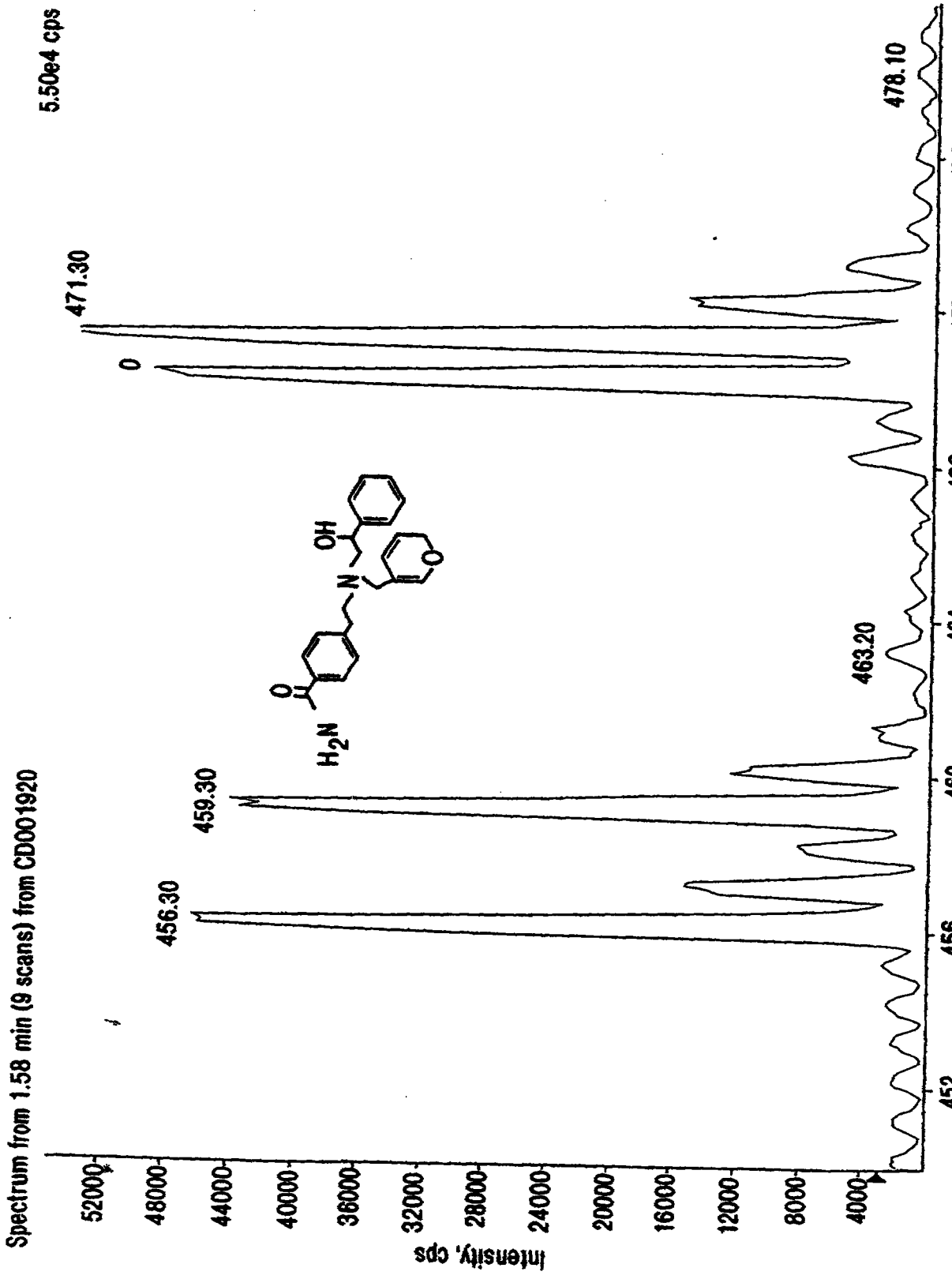

Spectrum from 1.58 min (9 scans) from CD001920
5.50e4 cps
Intensity, cps
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
452
456
460
464
468
472
476
m/z, amu
456.30
459.30
463.20
471.30
478.10
OH
N
O
O
H_2N

FIG. 119

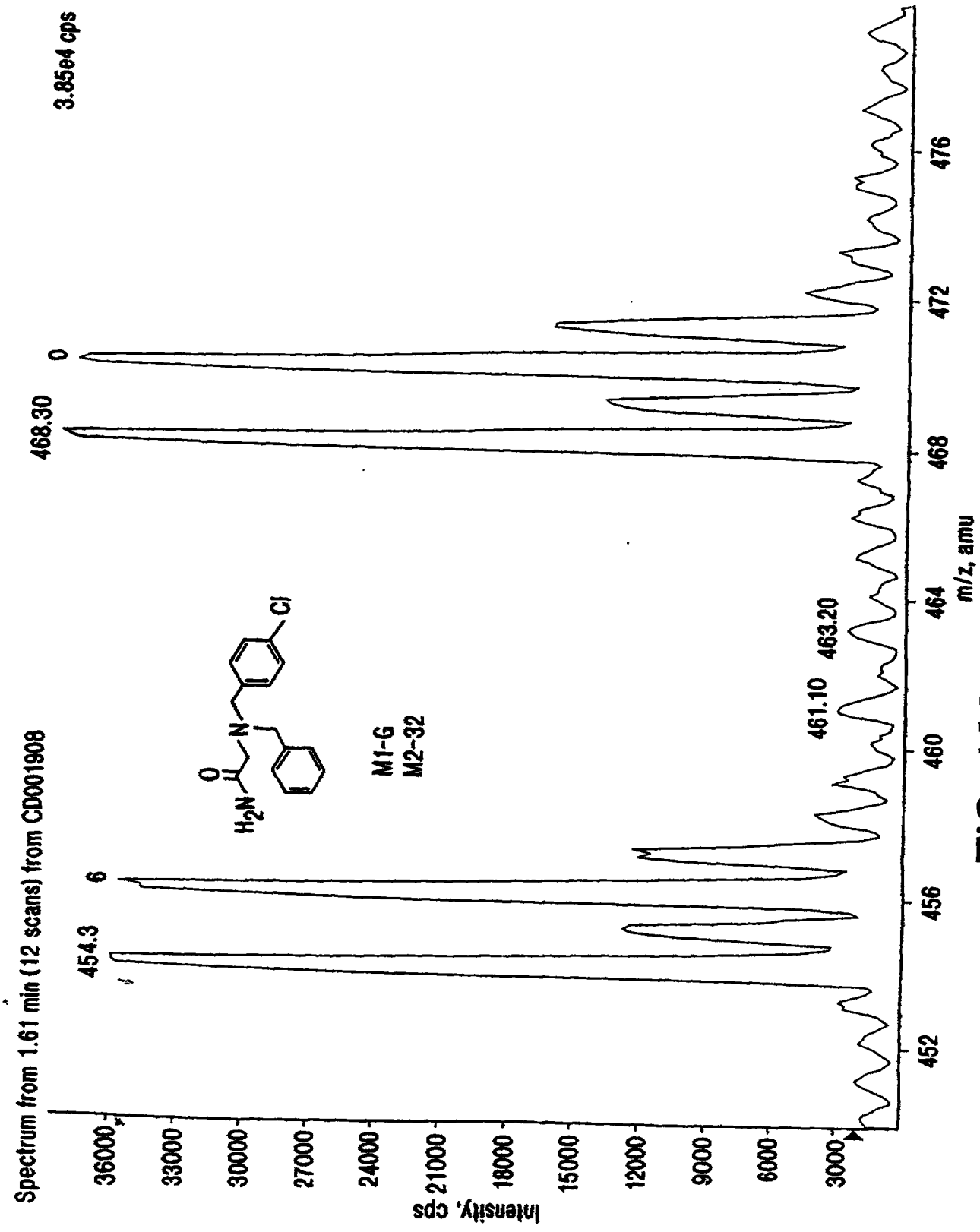

Spectrum from 1.61 min (12 scans) from CD001908
3.85e4 cps
468.30
0
454.3
6
461.10
463.20
M1-G
M2-32
Intensity, cps
m/z, amu
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
452
456
460
464
468
472
476

FIG. 120

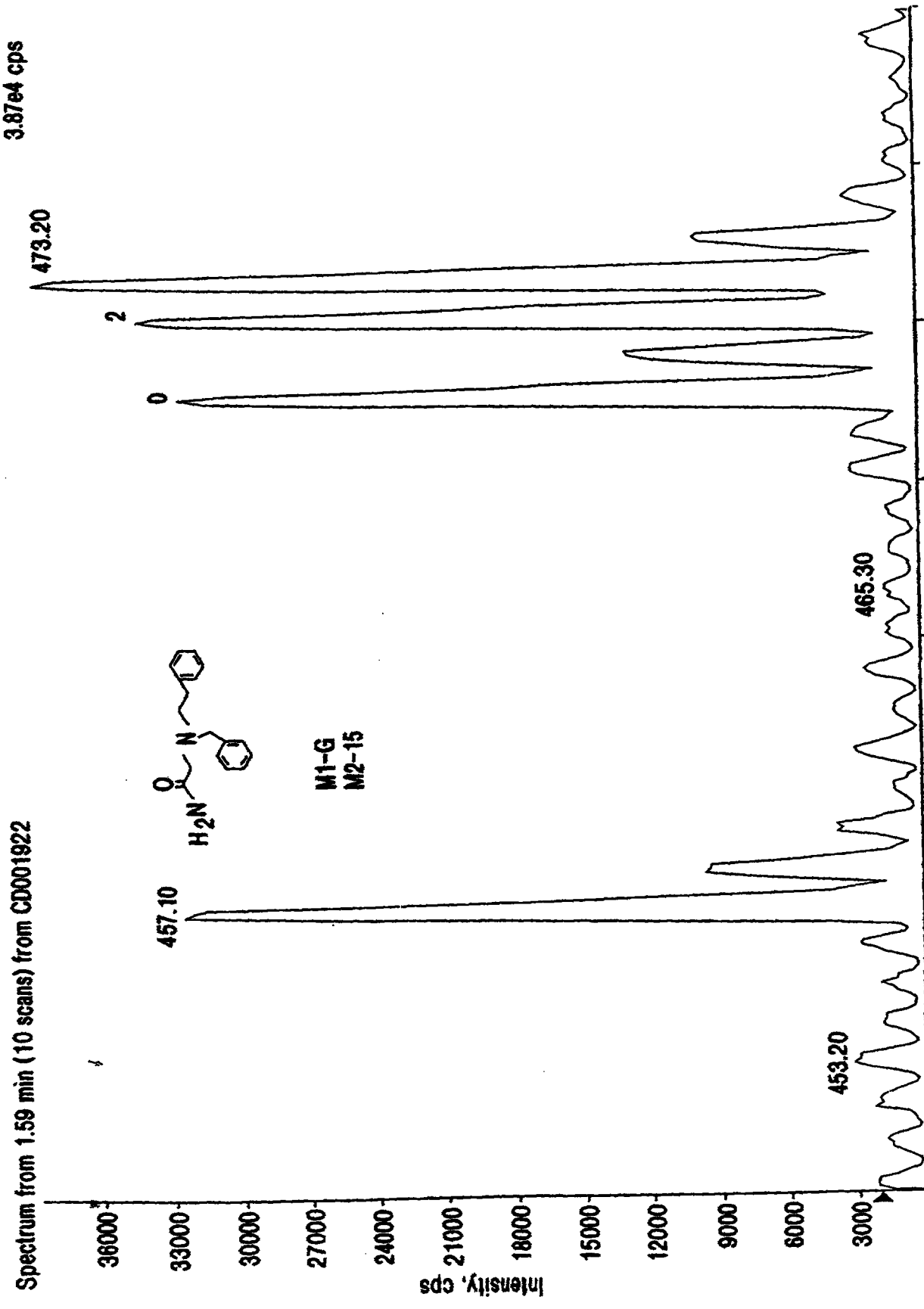

Spectrum from 1.59 min (10 scans) from CD001922
3.87e4 cps
Intensity, cps
m/z, amu
457.10
473.20
453.20
465.30
M1-G
M2-15
H2N
O
N
2
0

FIG. 121

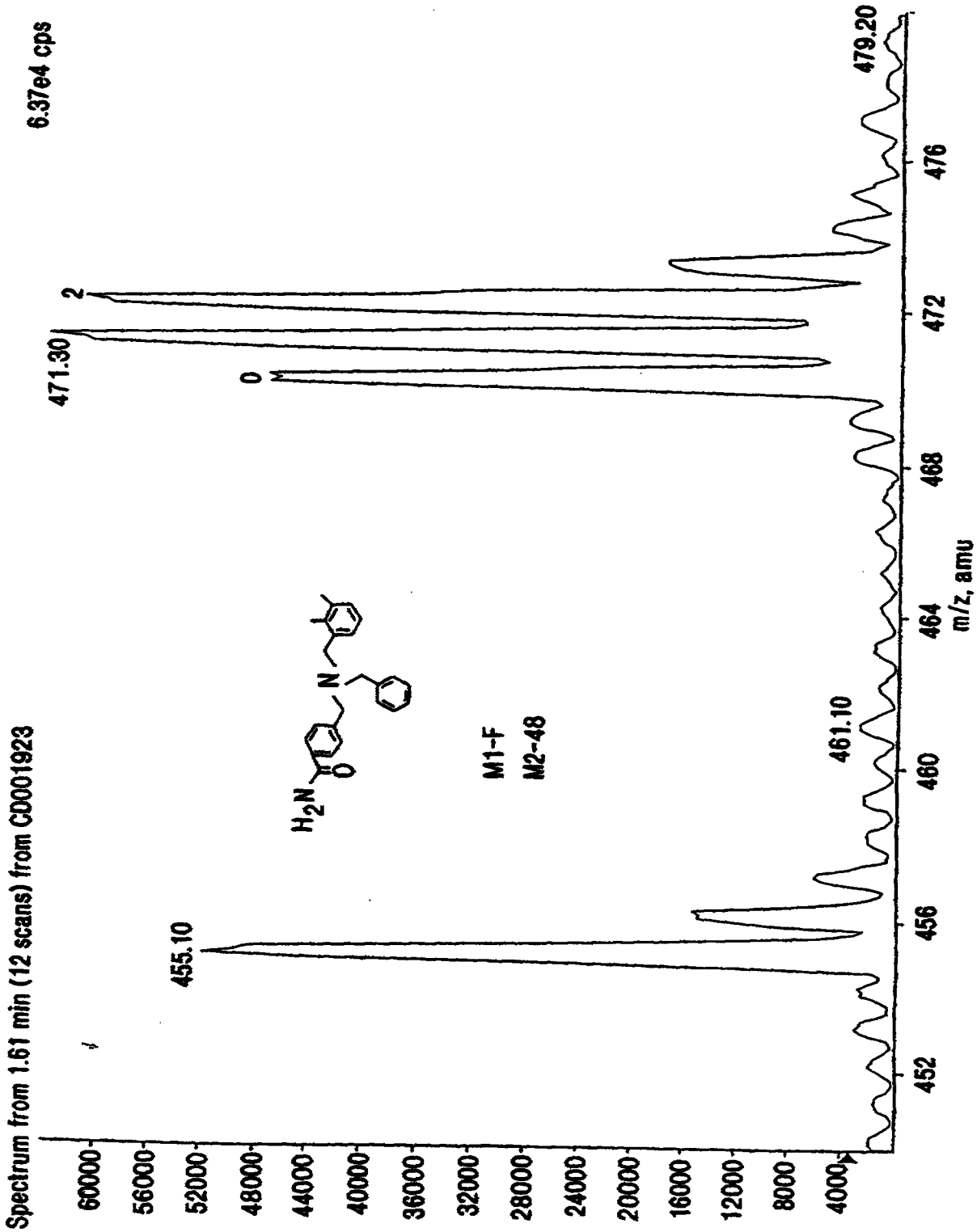

Spectrum from 1.61 min (12 scans) from C0001923
6.37e4 cps
455.10
461.10
471.30
479.20
M1-F
M2-48
m/z, amu
452
456
460
464
468
472
476
60000
56000
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000

FIG. 122

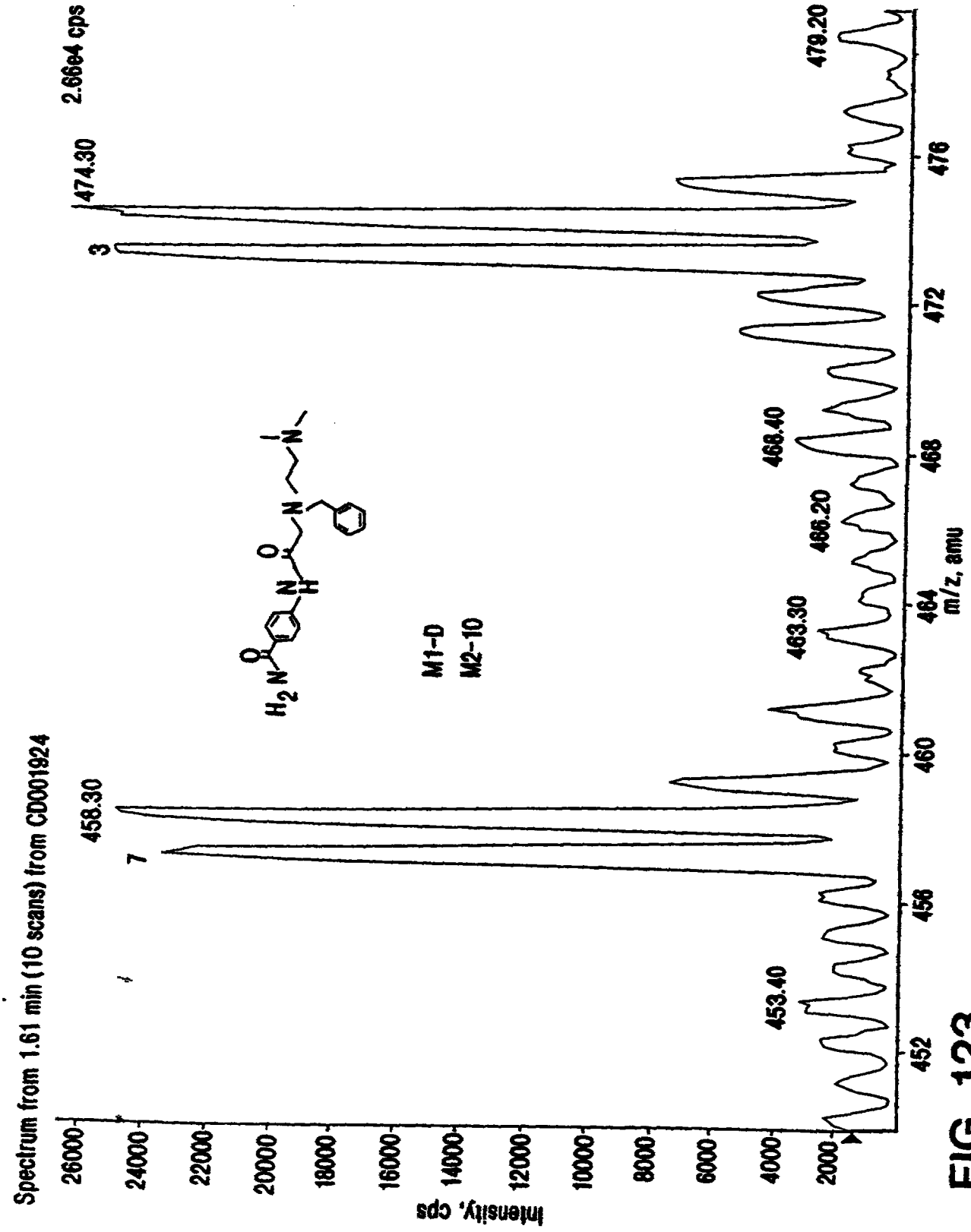

Spectrum from 1.61 min (10 scans) from CD001924
Intensity, cps
m/z, amu
458.30
7
453.40
463.30
468.40
466.20
474.30
3
479.20
2.66e4 cps
M1-D
M2-10

FIG. 123

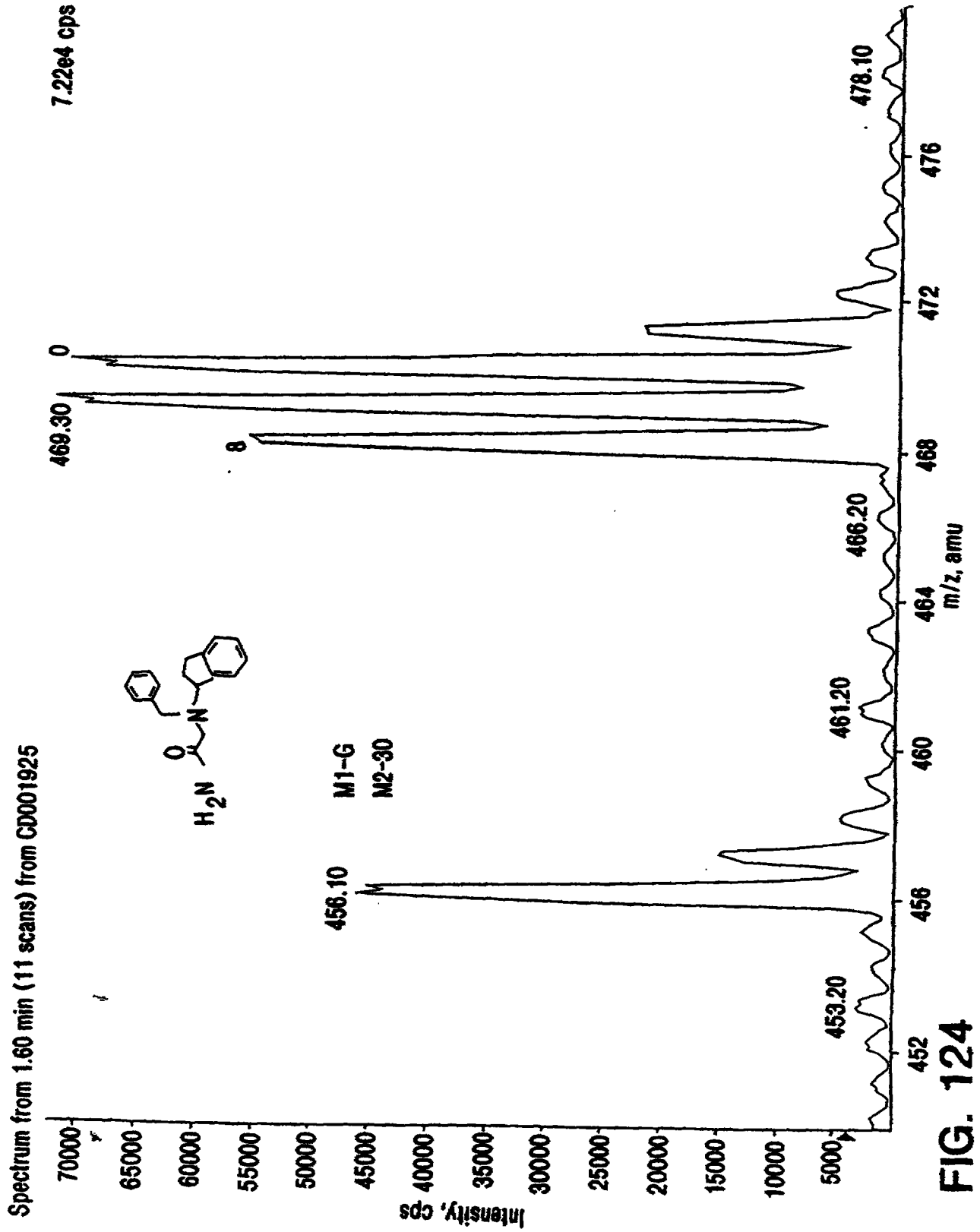

Spectrum from 1.60 min (11 scans) from CD001925
Intensity, cps
m/z, amu
7.22e4 cps
469.30
456.10
453.20
461.20
466.20
478.10
M1-G
M2-30
H_2N
O
N

FIG. 124

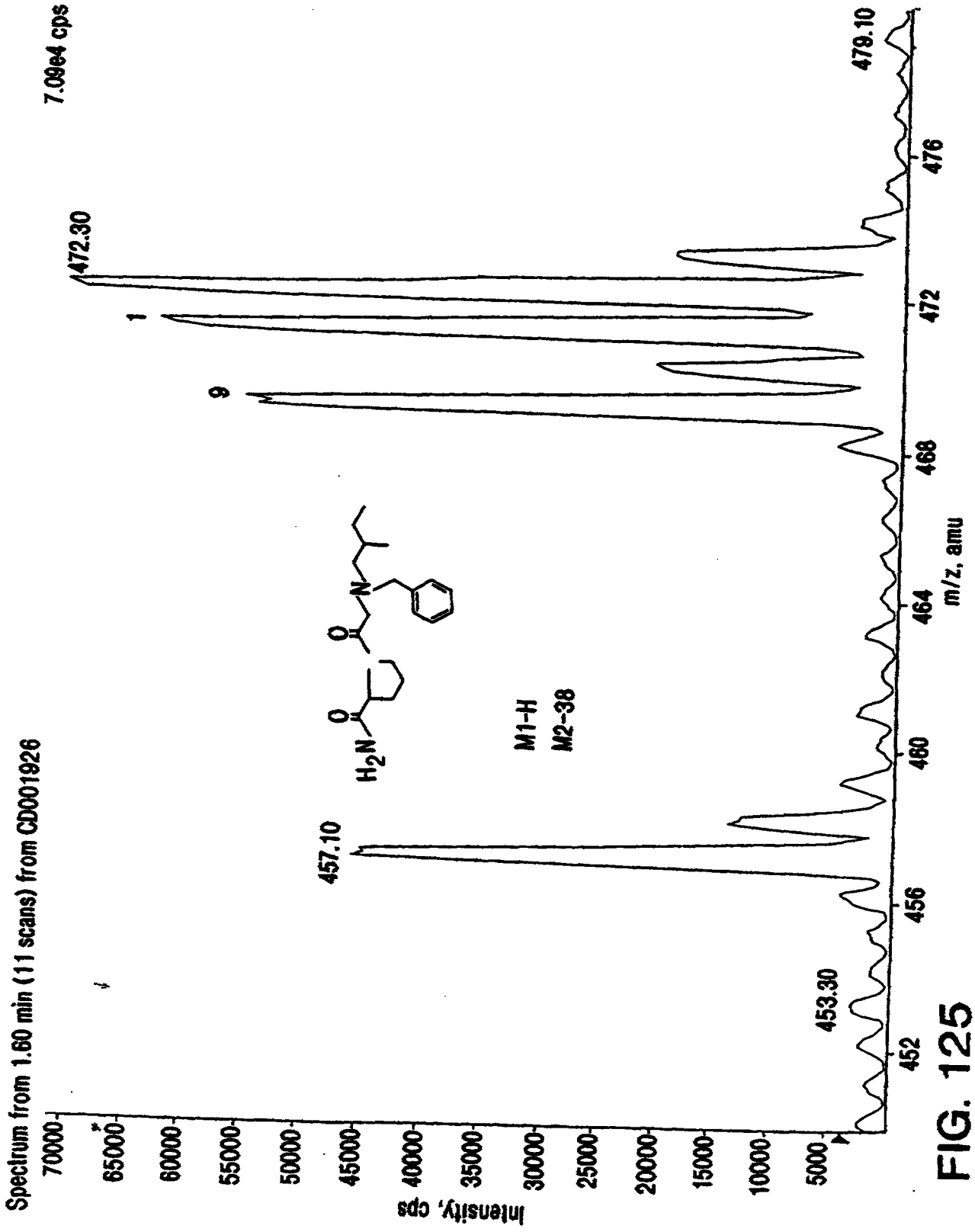

Spectrum from 1.60 min (11 scans) from CD001926
7.0964 cps
Intensity, cps
m/z, amu
457.10
472.30
479.10
453.30
M1-H
M2-38
H2N

FIG. 125

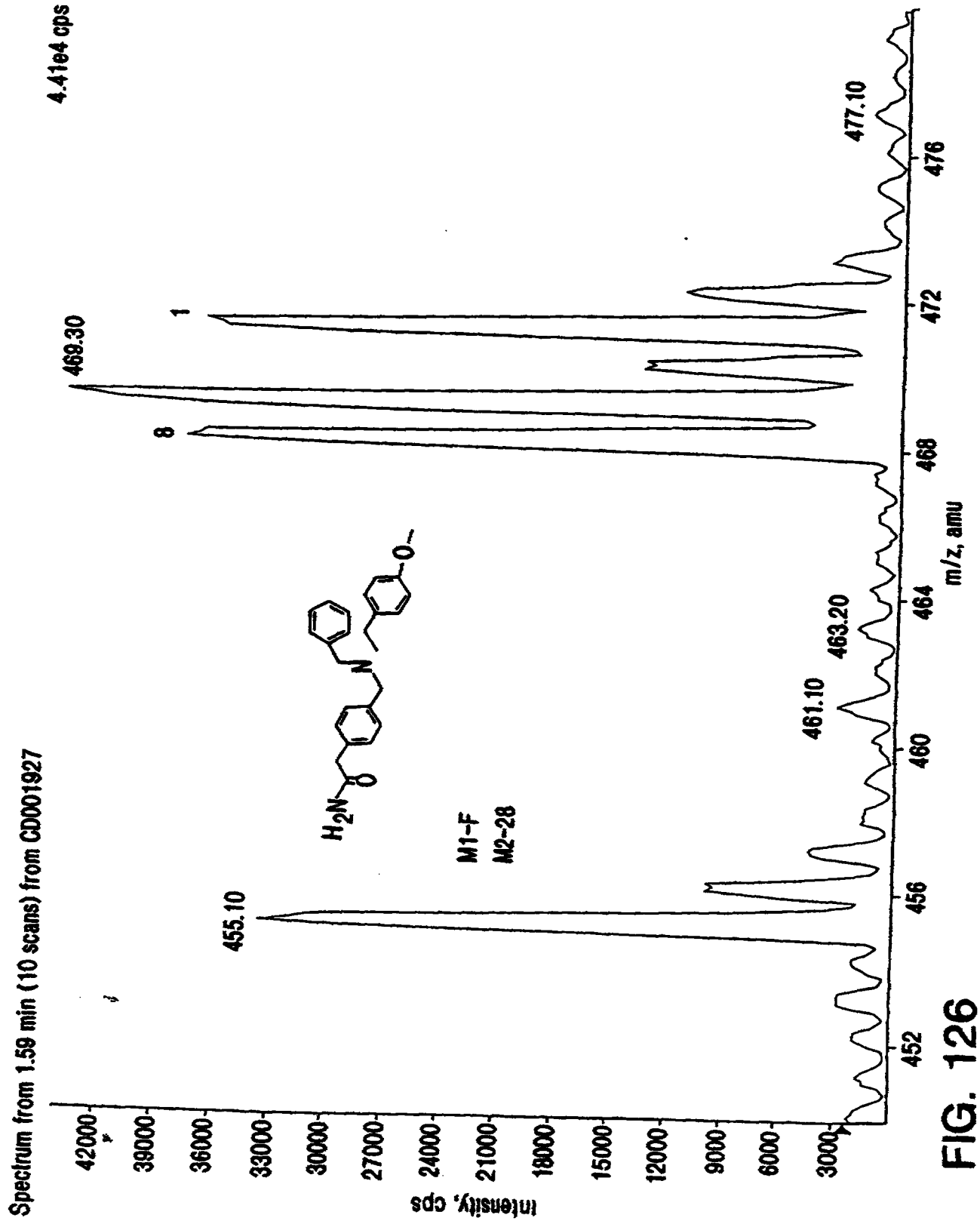

Spectrum from 1.59 min (10 scans) from CD001927
4.41e4 cps
Intensity, cps
m/z, amu
455.10
461.10
463.20
469.30
477.10
M1-F
M2-28
8
1

FIG. 126

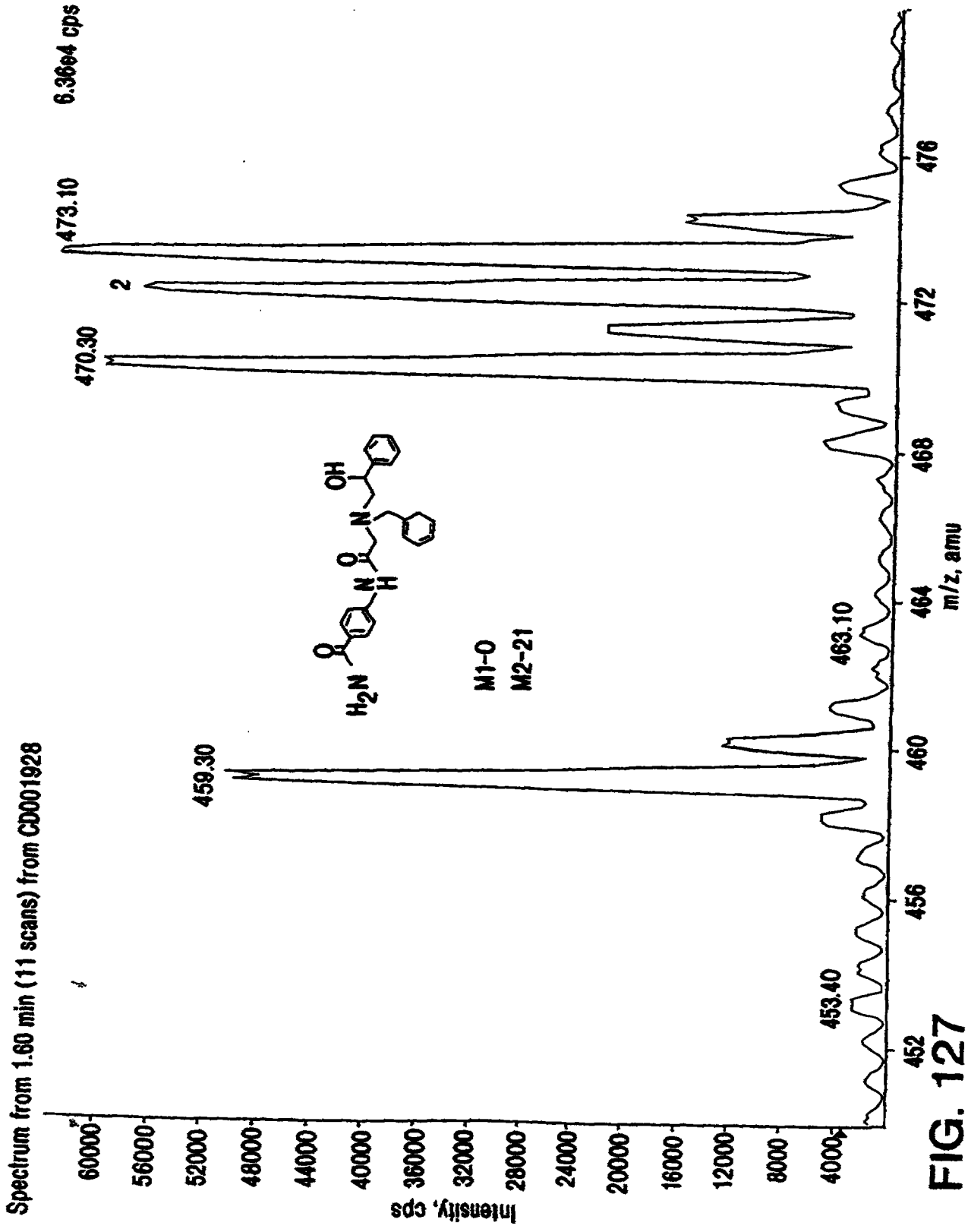

Spectrum from 1.60 min (11 scans) from CD001928
Intensity, cps
60000
56000
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
m/z, amu
452
456
460
464
468
472
476
453.40
459.30
463.10
470.30
473.10
6.36e4 cps
2
M1-O
M2-21
OH
N
O
H
H_2N

FIG. 127

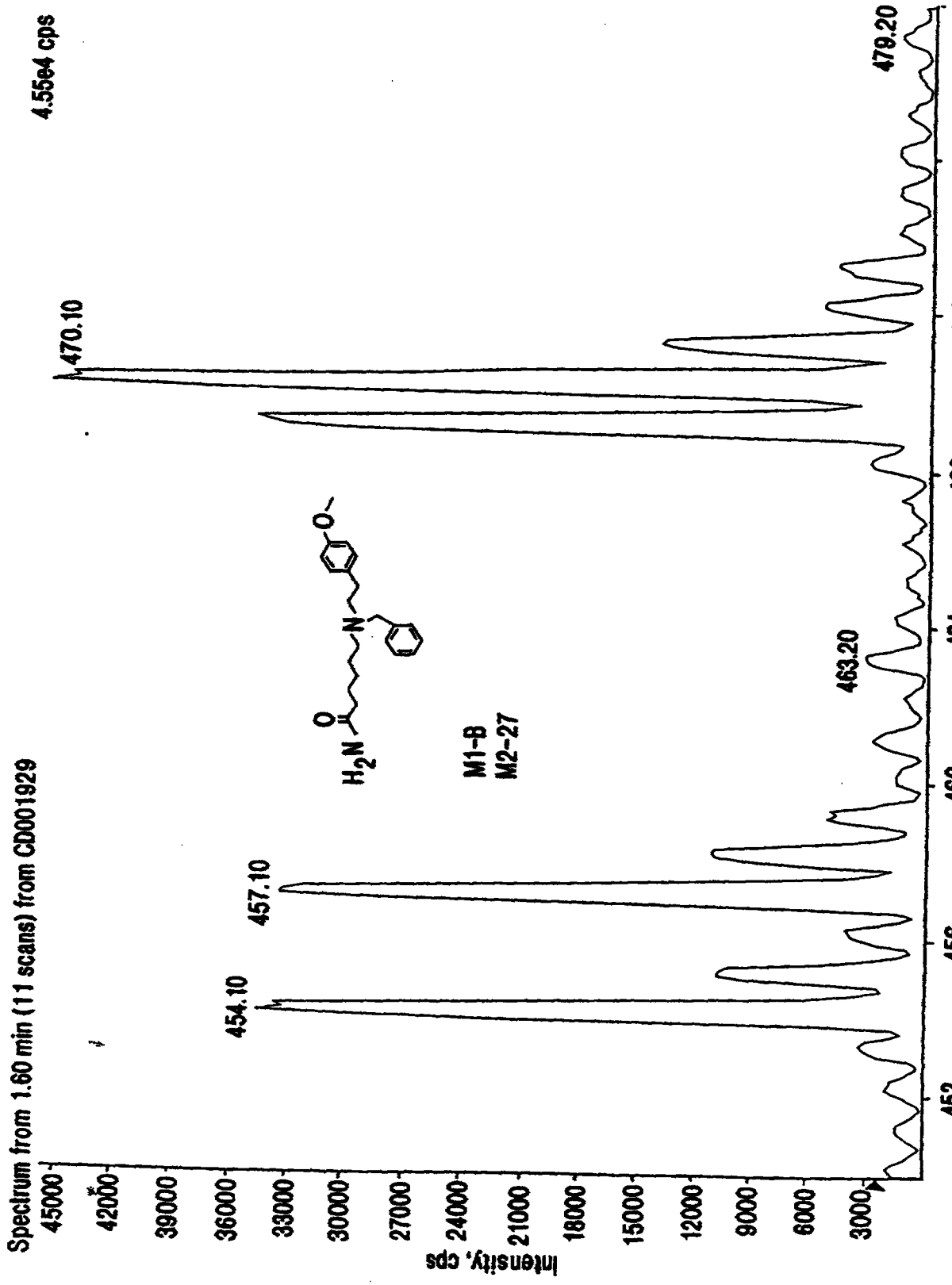

Spectrum from 1.60 min (11 scans) from CD001929
4.55e4 cps
Intensity, cps
m/z, amu
454.10
457.10
463.20
470.10
479.20
M1-B
M2-27

FIG. 128

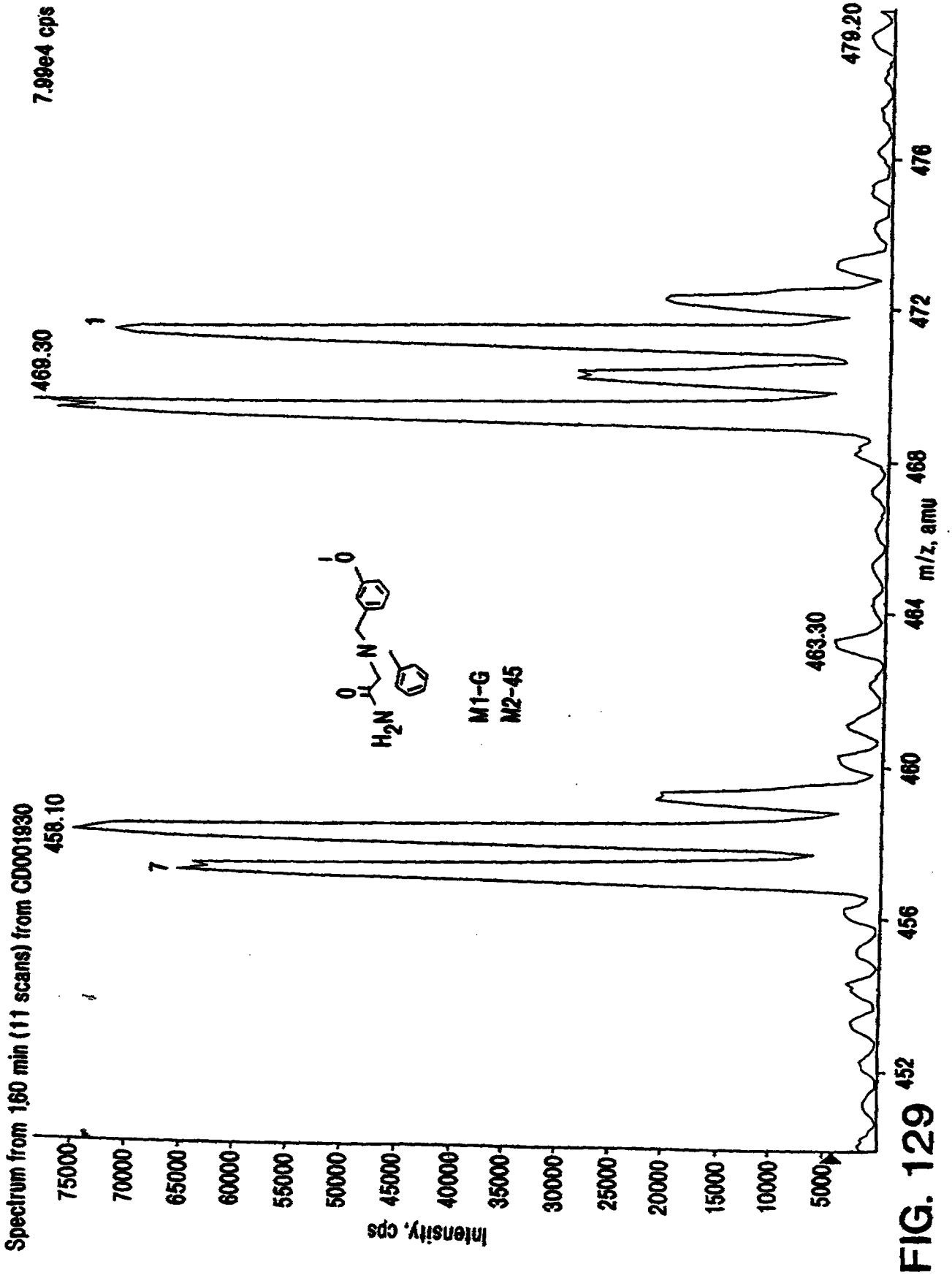

Spectrum from 160 min (11 scans) from CD001930
7.99e4 cps
458.10
469.30
479.20
463.30
7
1
M1-G
M2-45
Intensity, cps
m/z, amu
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
452
456
460
464
468
472
476

FIG. 129

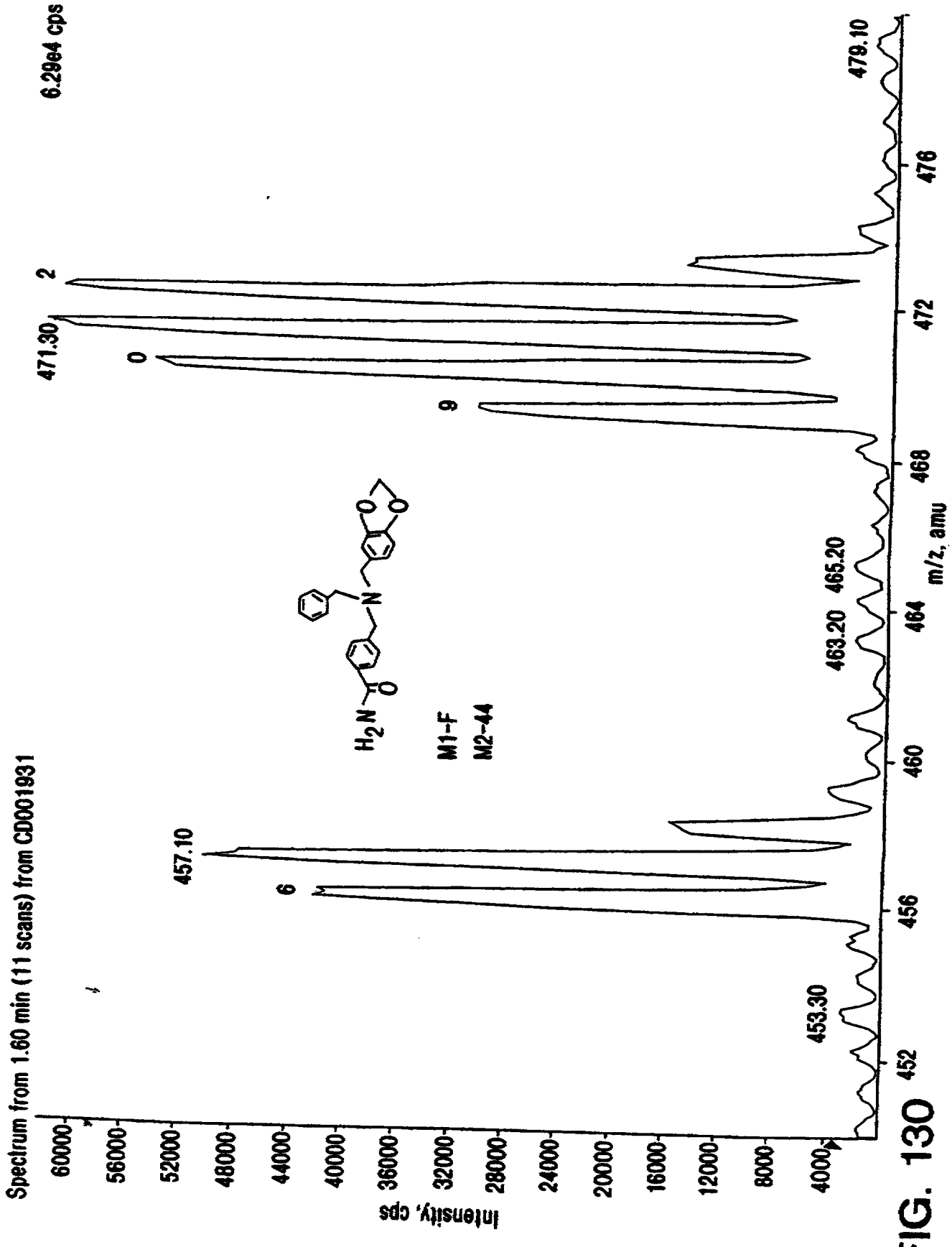

Spectrum from 1.60 min (11 scans) from CD001931
6.29e4 cps
Intensity, cps
m/z, amu
457.10
471.30
479.10
453.30
463.20
465.20
M1-F
M2-44

FIG. 130

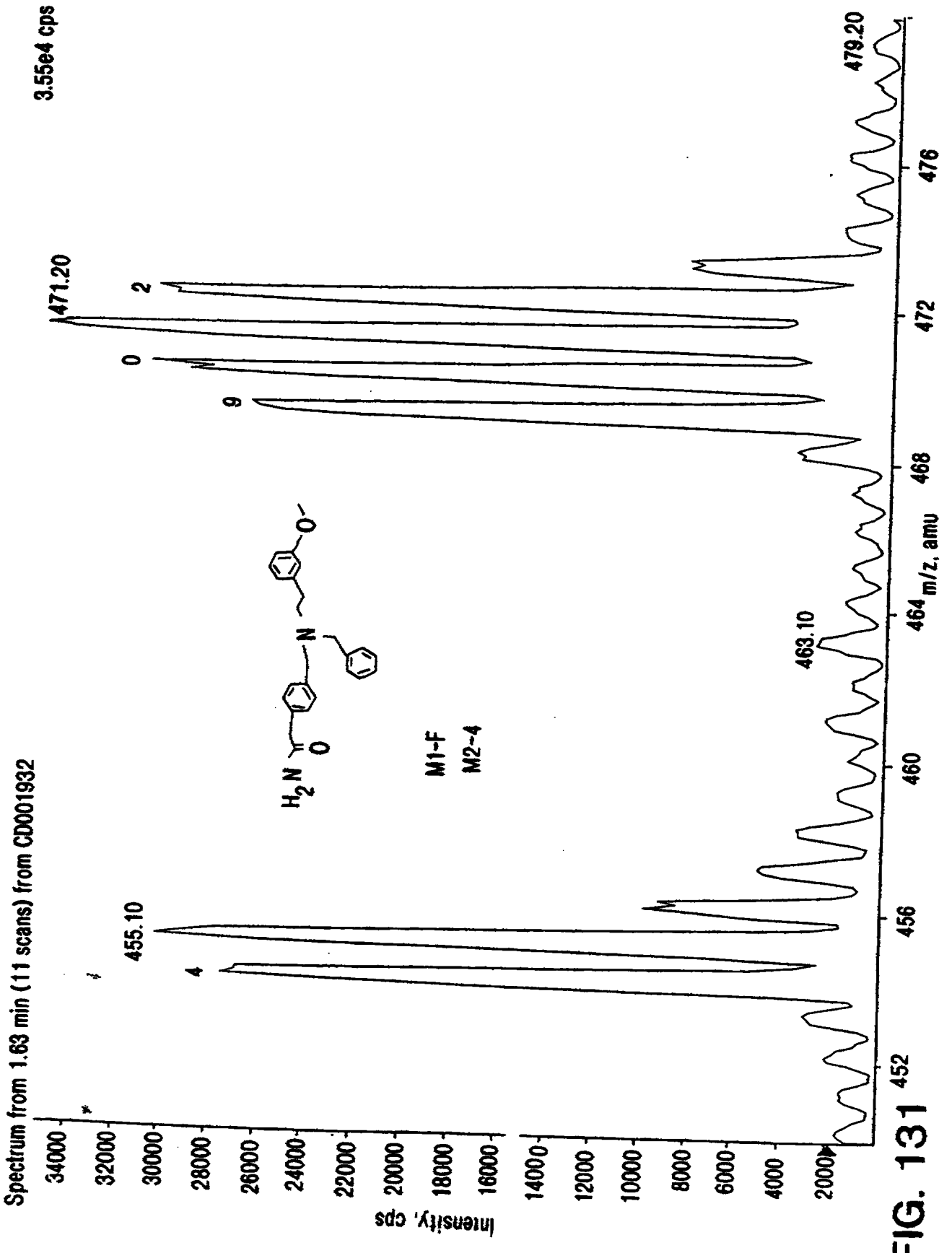

Spectrum from 1.63 min (11 scans) from CD001932
3.55e4 cps
Intensity, cps
m/z, amu
455.10
463.10
471.20
479.20
M1-F
M2-4

FIG. 131

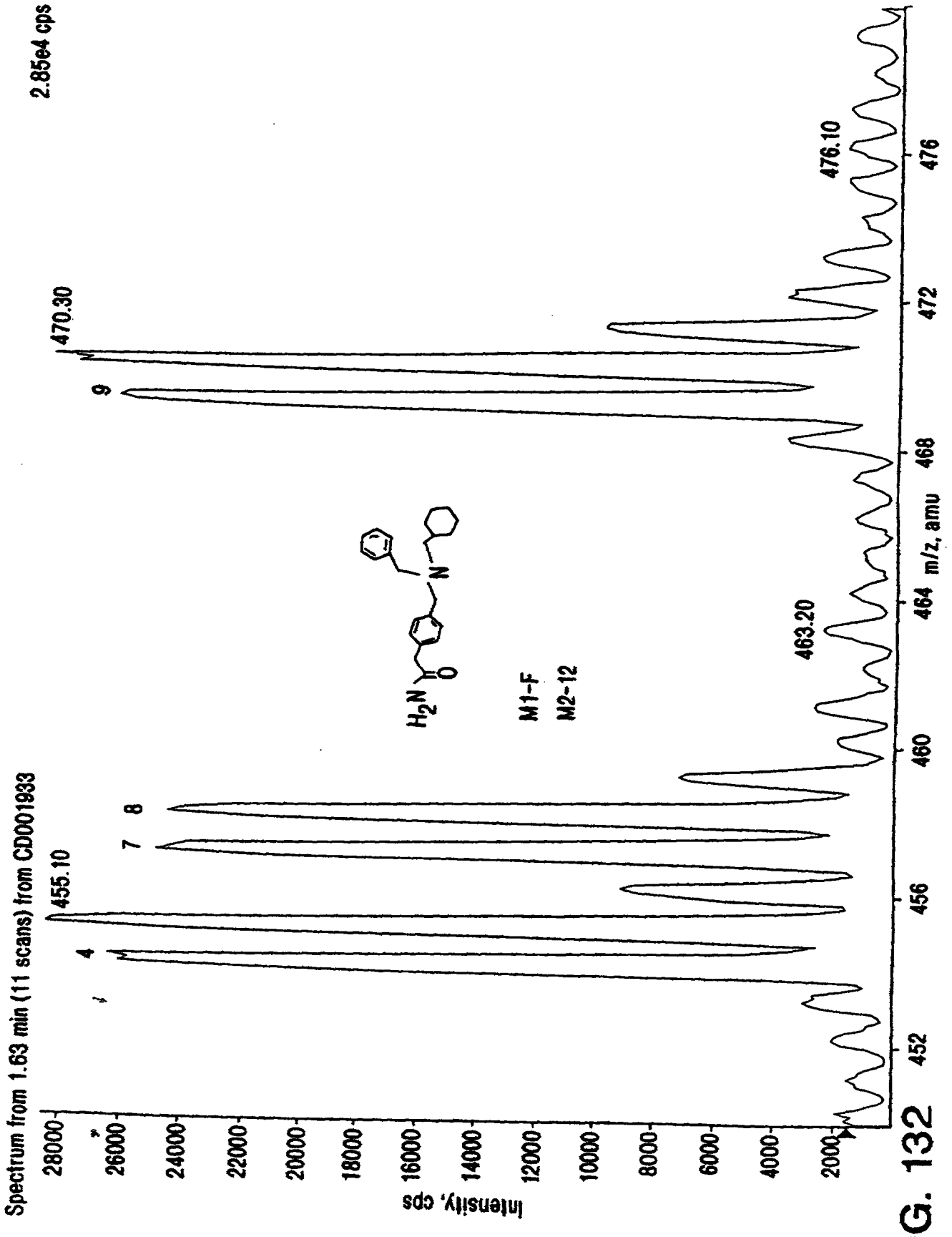

Spectrum from 1.63 min (11 scans) from CD001933
2.85e4 cps
Intensity, cps
m/z, amu
455.10
463.20
470.30
476.10
4
7
8
9
M1-F
M2-12

FIG. 132

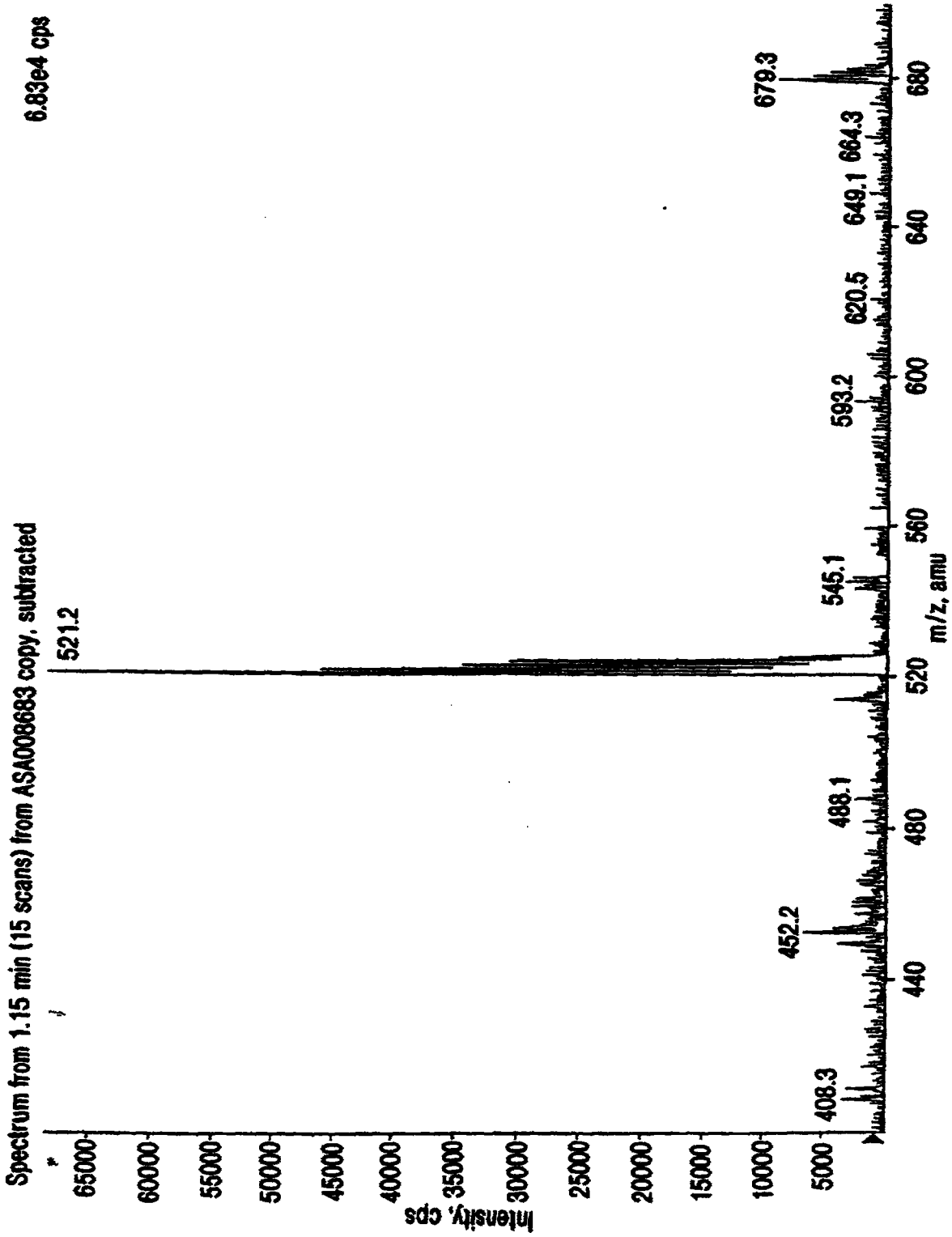

Spectrum from 1.15 min (15 scans) from ASA008683 copy, subtracted
6.83e4 cps
Intensity, cps
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
m/z, amu
440
480
520
560
600
640
680
408.3
452.2
488.1
521.2
545.1
593.2
620.5
649.1
664.3
679.3

FIG. 133

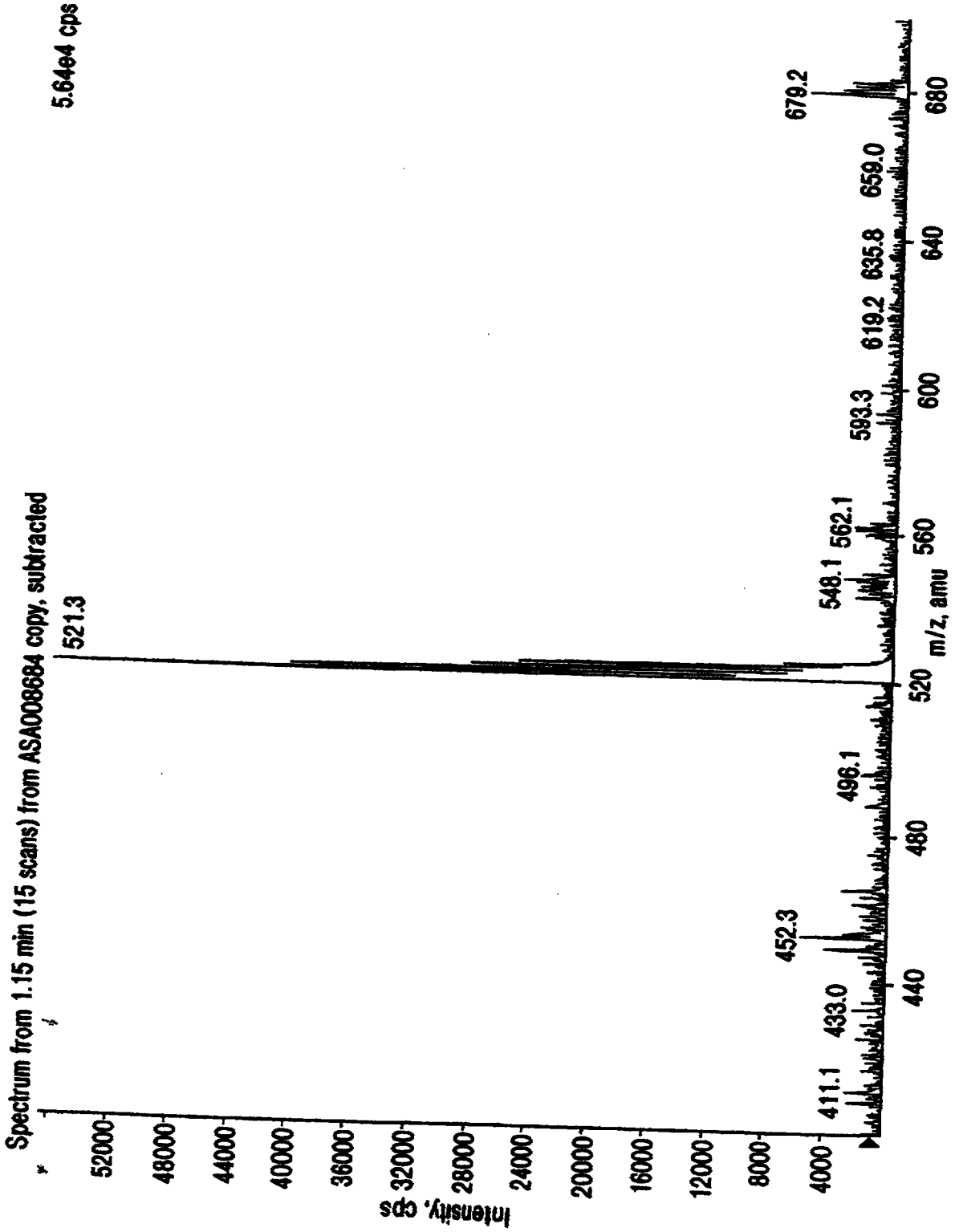

Spectrum from 1.15 min (15 scans) from ASA008684 copy, subtracted
5.64e4 cps
Intensity, cps
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
m/z, amu
411.1
433.0
452.3
496.1
521.3
548.1
562.1
593.3
619.2
635.8
659.0
679.2
440
480
520
560
600
640
680

FIG. 134

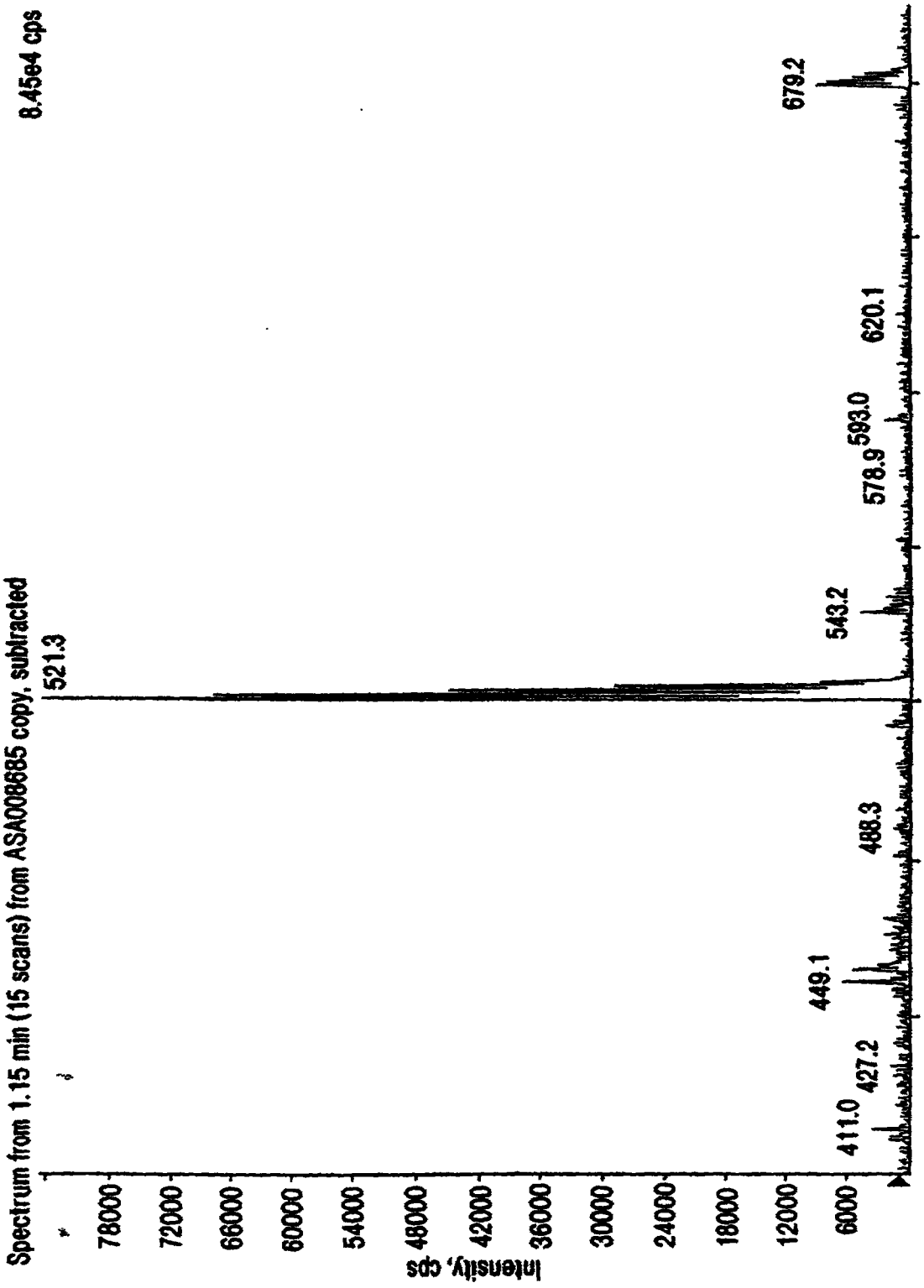

Spectrum from 1.15 min (15 scans) from ASA008685 copy, subtracted
8.45e4 cps
Intensity, cps
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
m/z, amu
440
480
520
560
600
640
680
411.0
427.2
449.1
488.3
521.3
543.2
578.9
583.0
620.1
679.2

FIG. 135

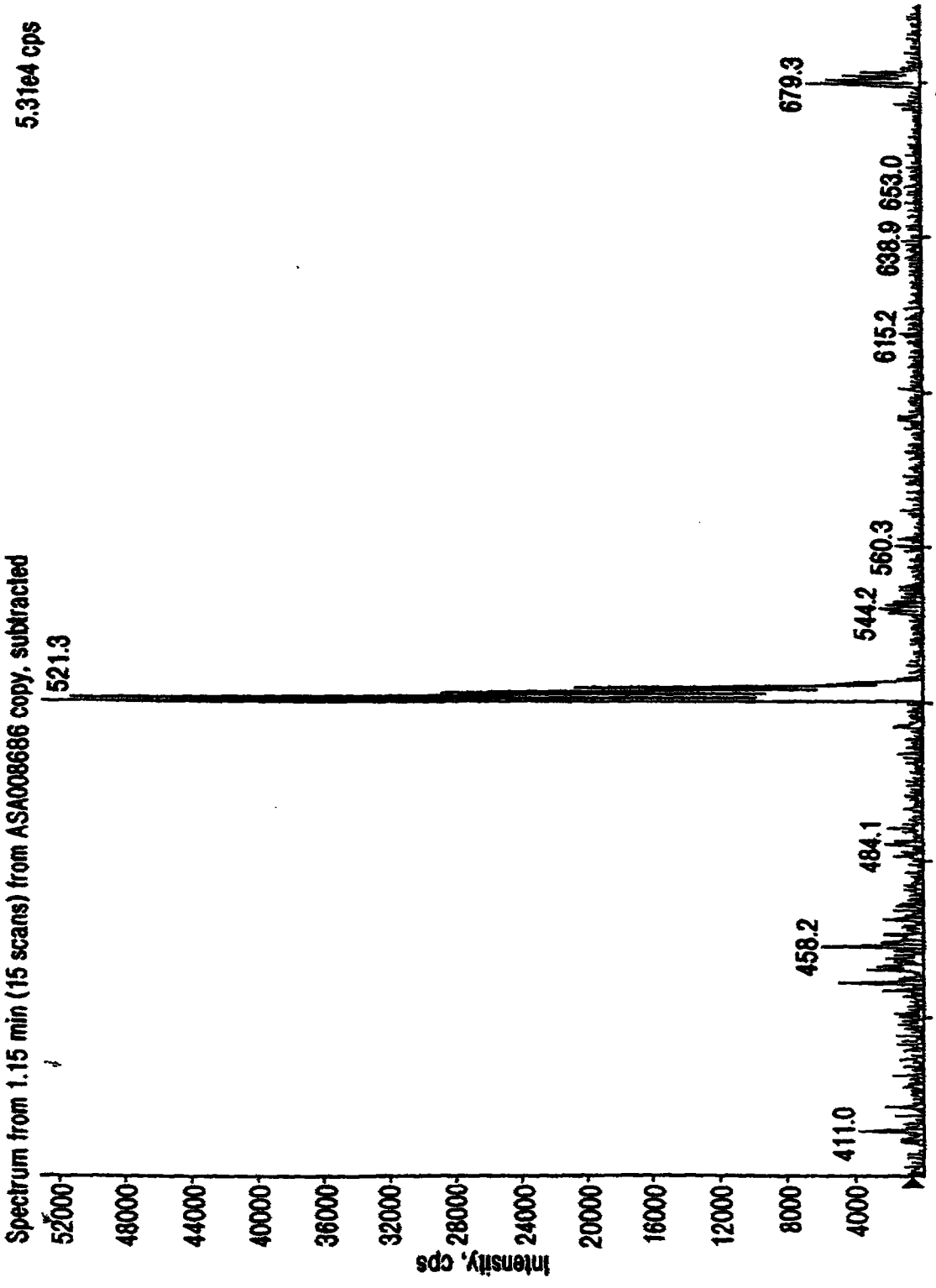

Spectrum from 1.15 min (15 scans) from ASA008686 copy, subtracted
5.31e4 cps
Intensity, cps
m/z, amu
521.3
544.2
560.3
615.2
638.9
653.0
679.3
458.2
484.1
411.0

FIG. 136

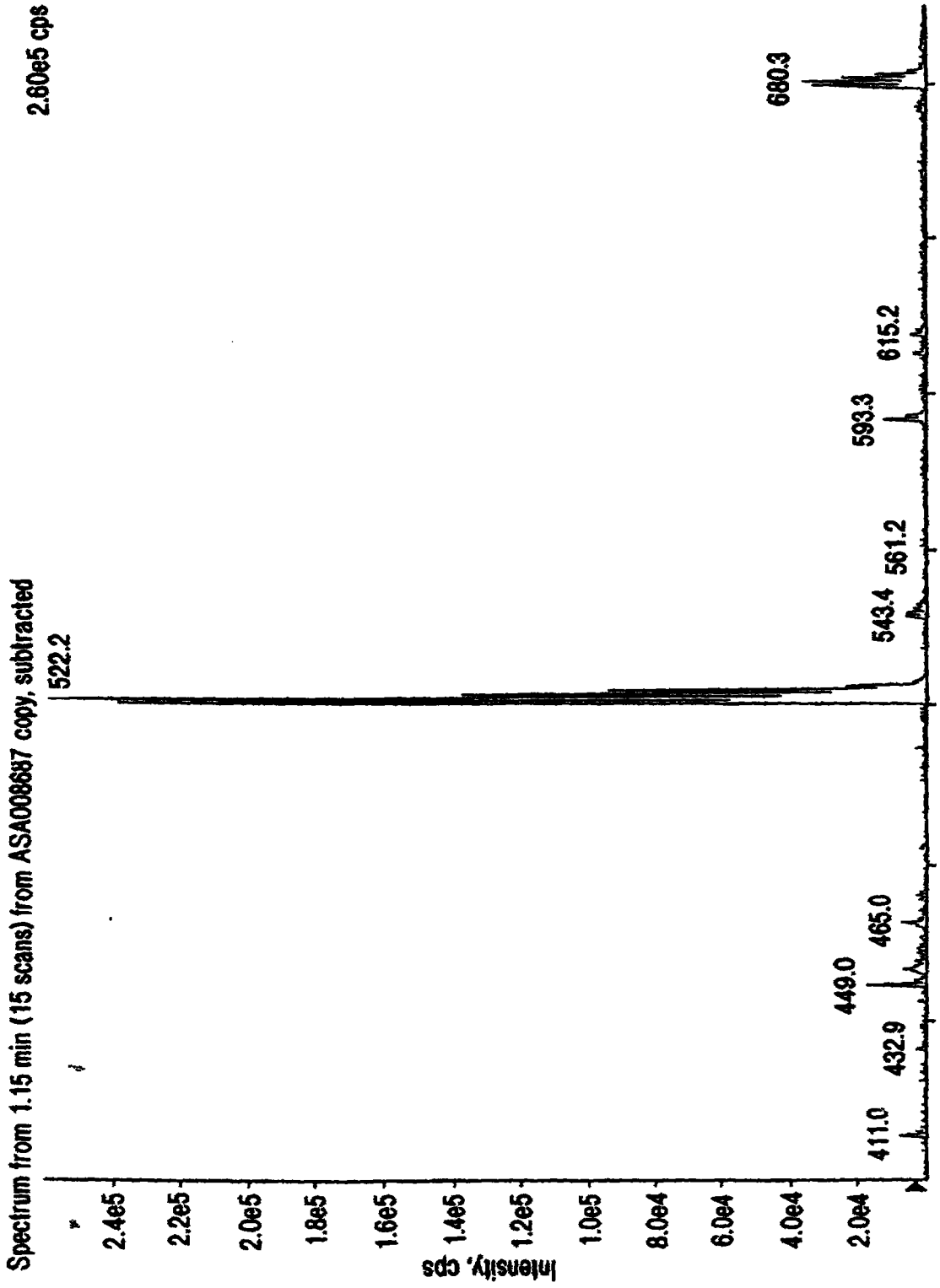

Spectrum from 1.15 min (15 scans) from ASA008687 copy, subtracted
2.80e5 cps
Intensity, cps
2.4e5
2.2e5
2.0e5
1.8e5
1.6e5
1.4e5
1.2e5
1.0e5
8.0e4
6.0e4
4.0e4
2.0e4
411.0
432.9
449.0
465.0
522.2
543.4
561.2
593.3
615.2
680.3
440
480
520
560
600
640
680
m/z, amu

FIG. 137

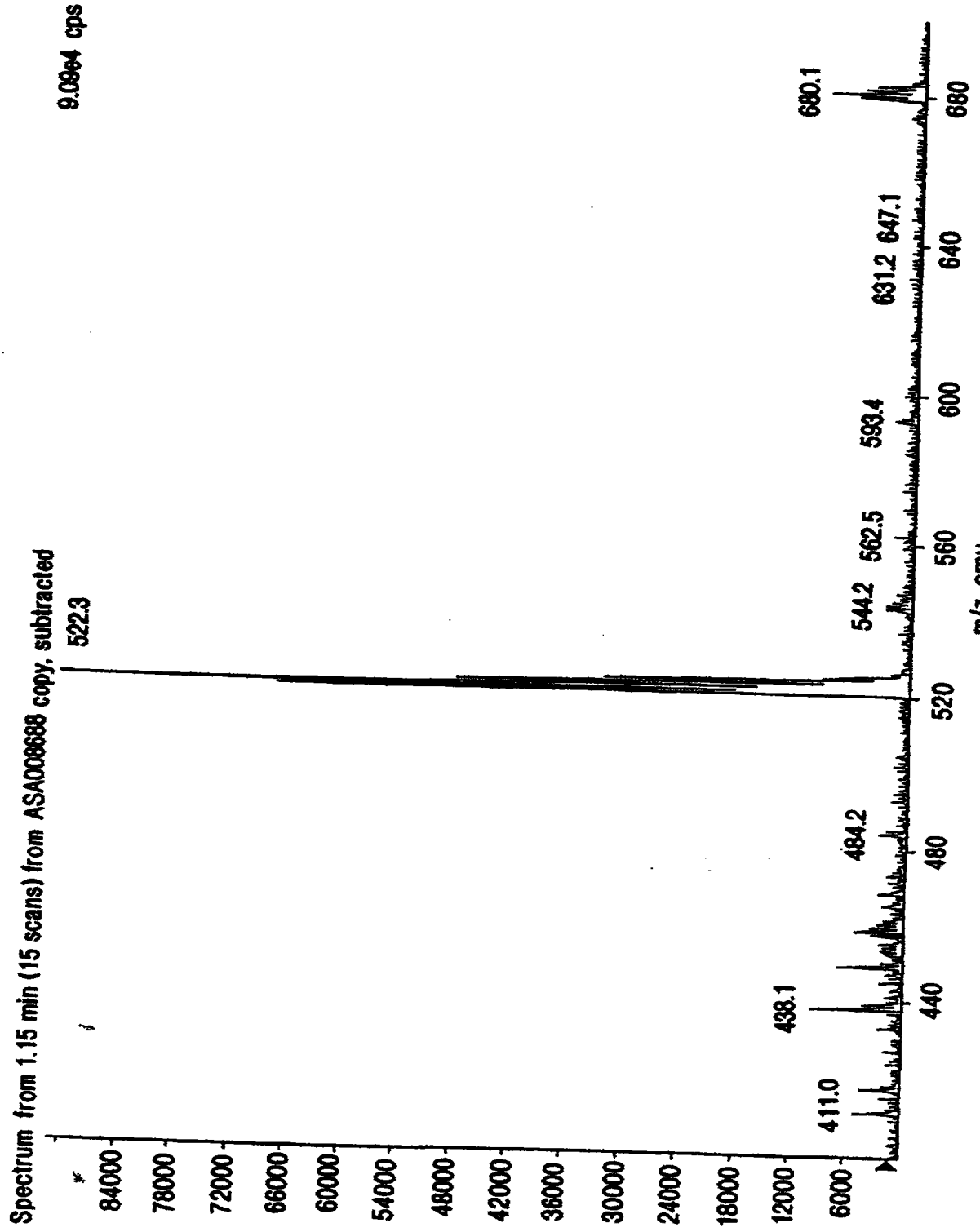

Spectrum from 1.15 min (15 scans) from ASA008688 copy, subtracted
9.0e4 cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.0
438.1
484.2
522.3
544.2
562.5
593.4
631.2
647.1
680.1
440
480
520
560
600
640
680
m/z, amu

FIG. 138

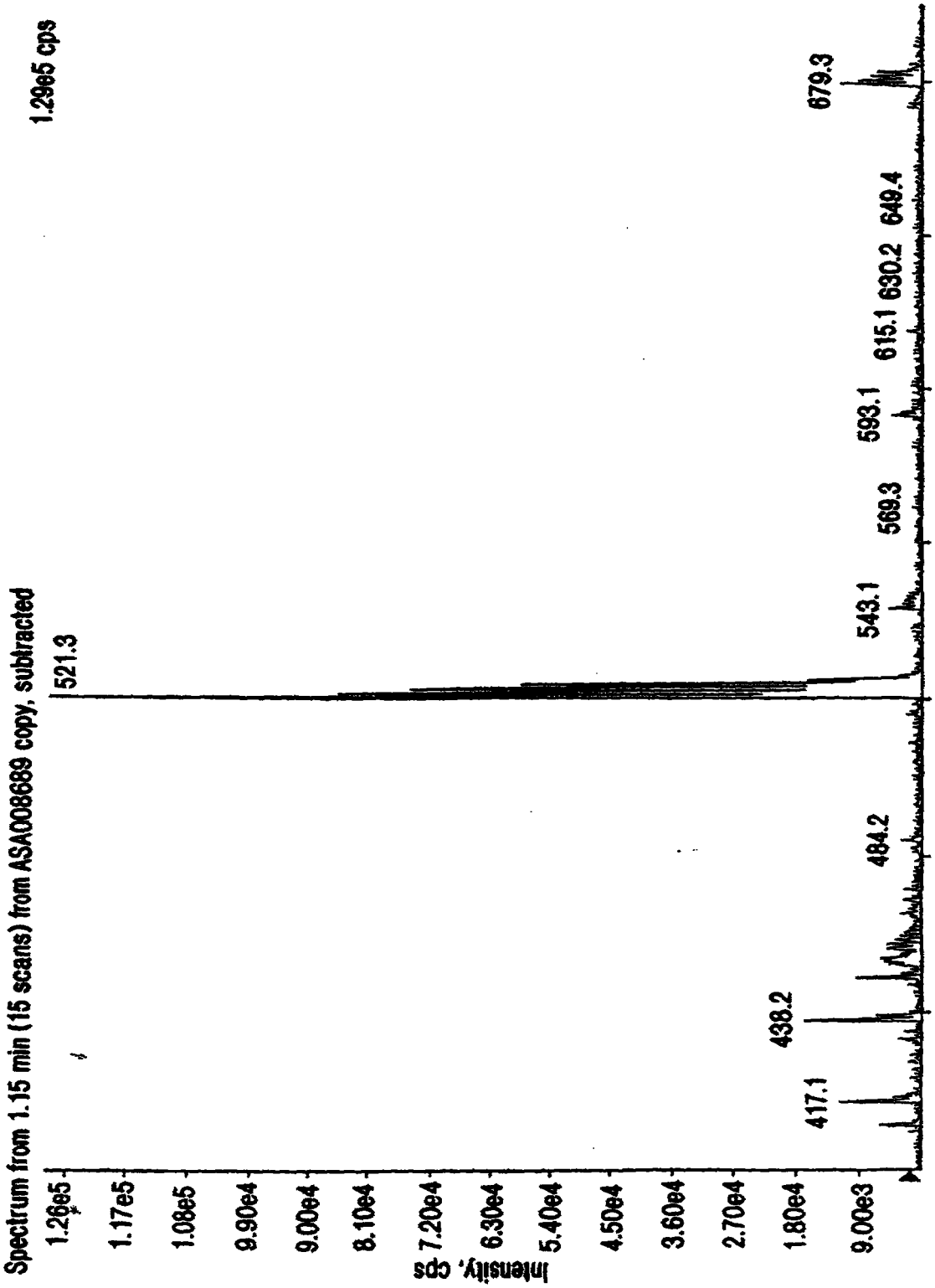

Spectrum from 1.15 min (15 scans) from ASA008689 copy, subtracted
1.29e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
m/z, amu
440
480
520
560
600
640
680
417.1
438.2
484.2
521.3
543.1
569.3
593.1
615.1
630.2
649.4
679.3

FIG. 139

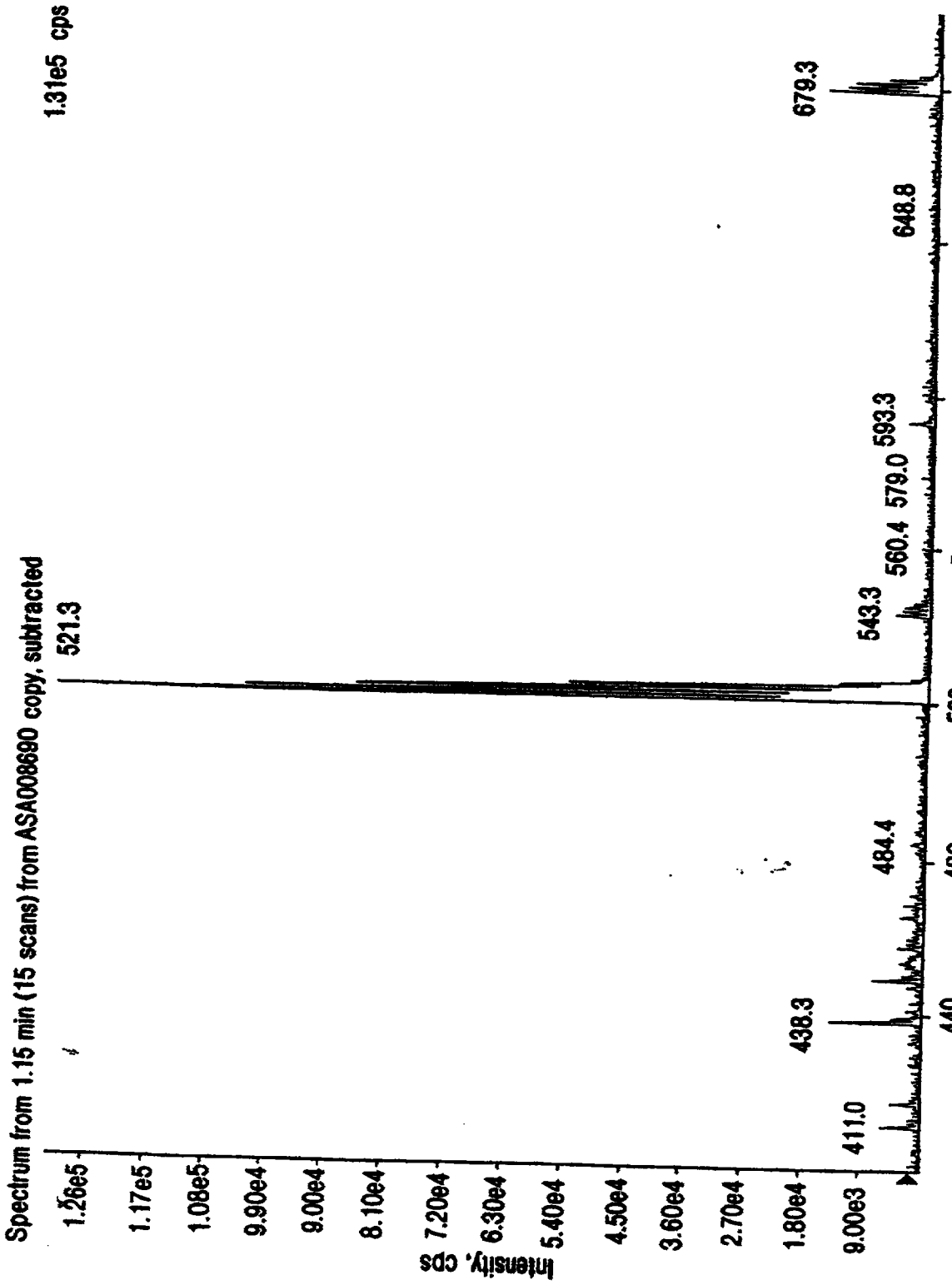

Spectrum from 1.15 min (15 scans) from ASA008690 copy, subtracted
1.31e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.0
438.3
484.4
521.3
543.3
560.4
579.0
593.3
648.8
679.3
440
480
520
560
600
640
680
m/z, amu

FIG. 140

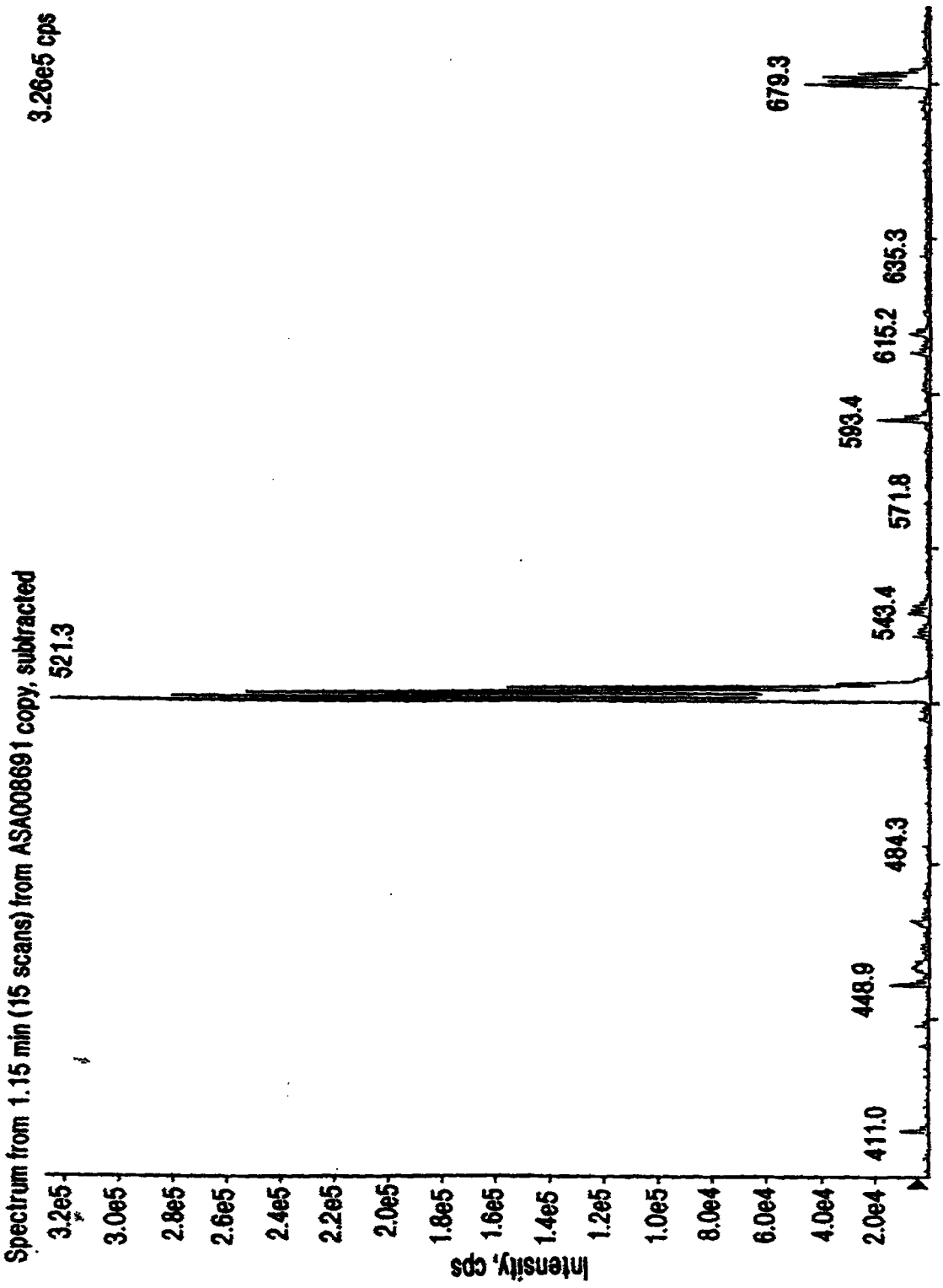

Spectrum from 1.15 min (15 scans) from ASA008691 copy, subtracted
3.26e5 cps
Intensity, cps
m/z, amu
521.3
543.4
571.8
593.4
615.2
635.3
679.3
484.3
448.9
411.0

FIG. 141

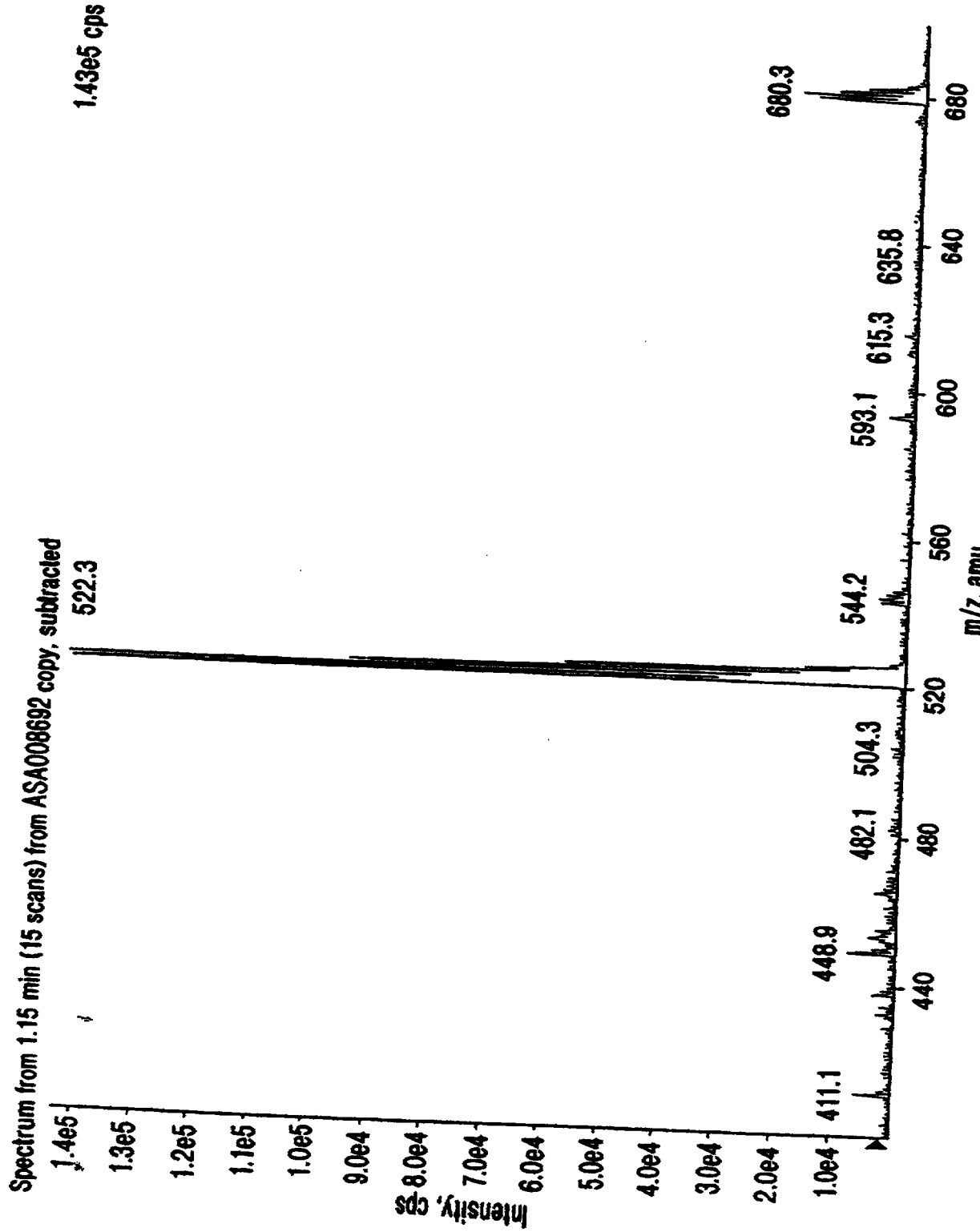

Spectrum from 1.15 min (15 scans) from ASA008692 copy, subtracted
1.43e5 cps
Intensity, cps
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
448.9
482.1
504.3
522.3
544.2
593.1
615.3
635.8
680.3
440
480
520
560
600
640
680
m/z, amu

FIG. 142

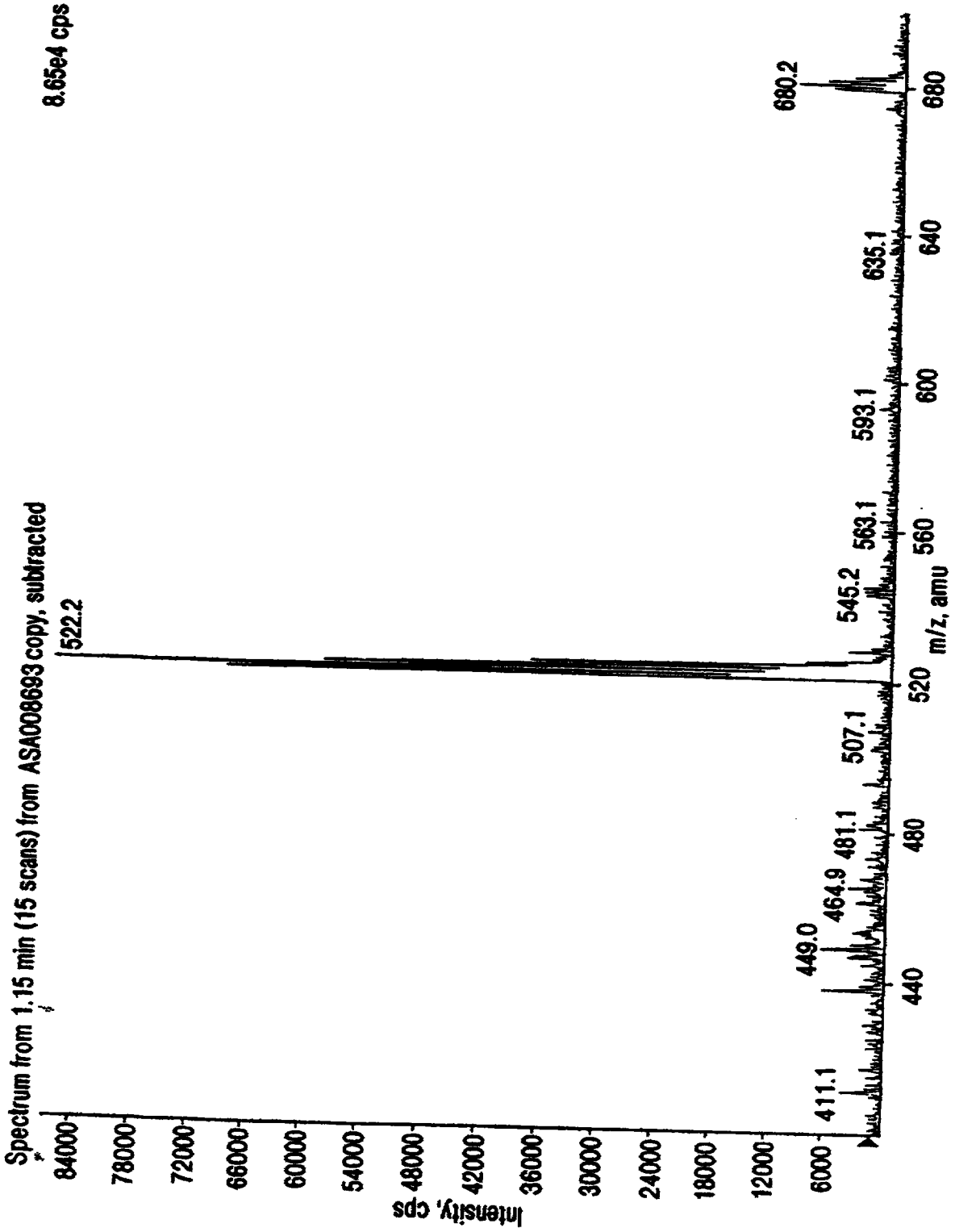

Spectrum from 1.15 min (15 scans) from ASA008693 copy, subtracted
8.65e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.1
449.0
464.9
481.1
507.1
522.2
545.2
563.1
593.1
635.1
680.2
440
480
520
560
600
640
680
m/z, amu

FIG. 143

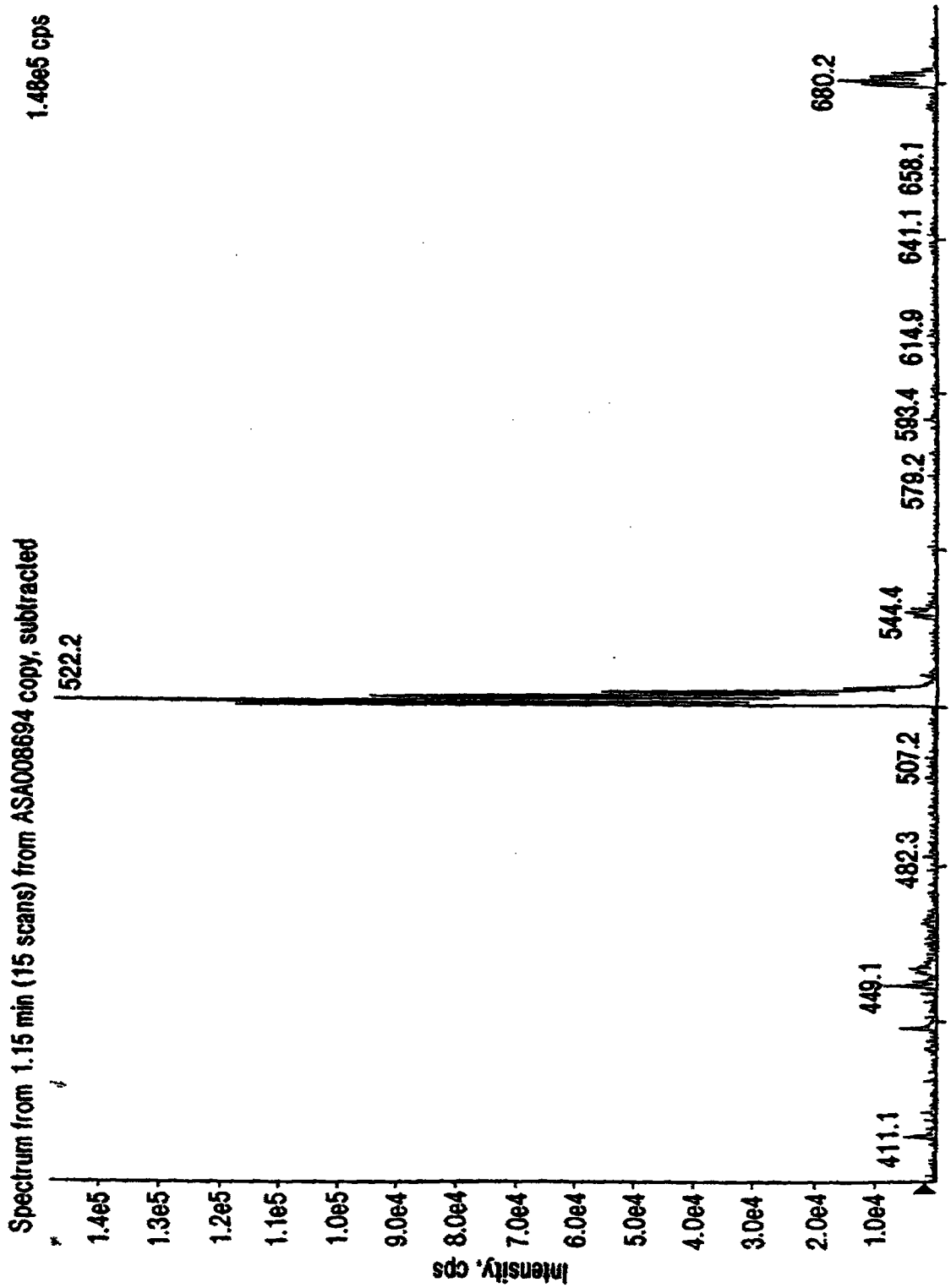

Spectrum from 1.15 min (15 scans) from ASA008694 copy, subtracted
1.48e5 cps
Intensity, cps
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
449.1
482.3
507.2
522.2
544.4
578.2
593.4
614.9
641.1
658.1
680.2
440
480
520
560
600
640
680
m/z, amu

FIG. 144

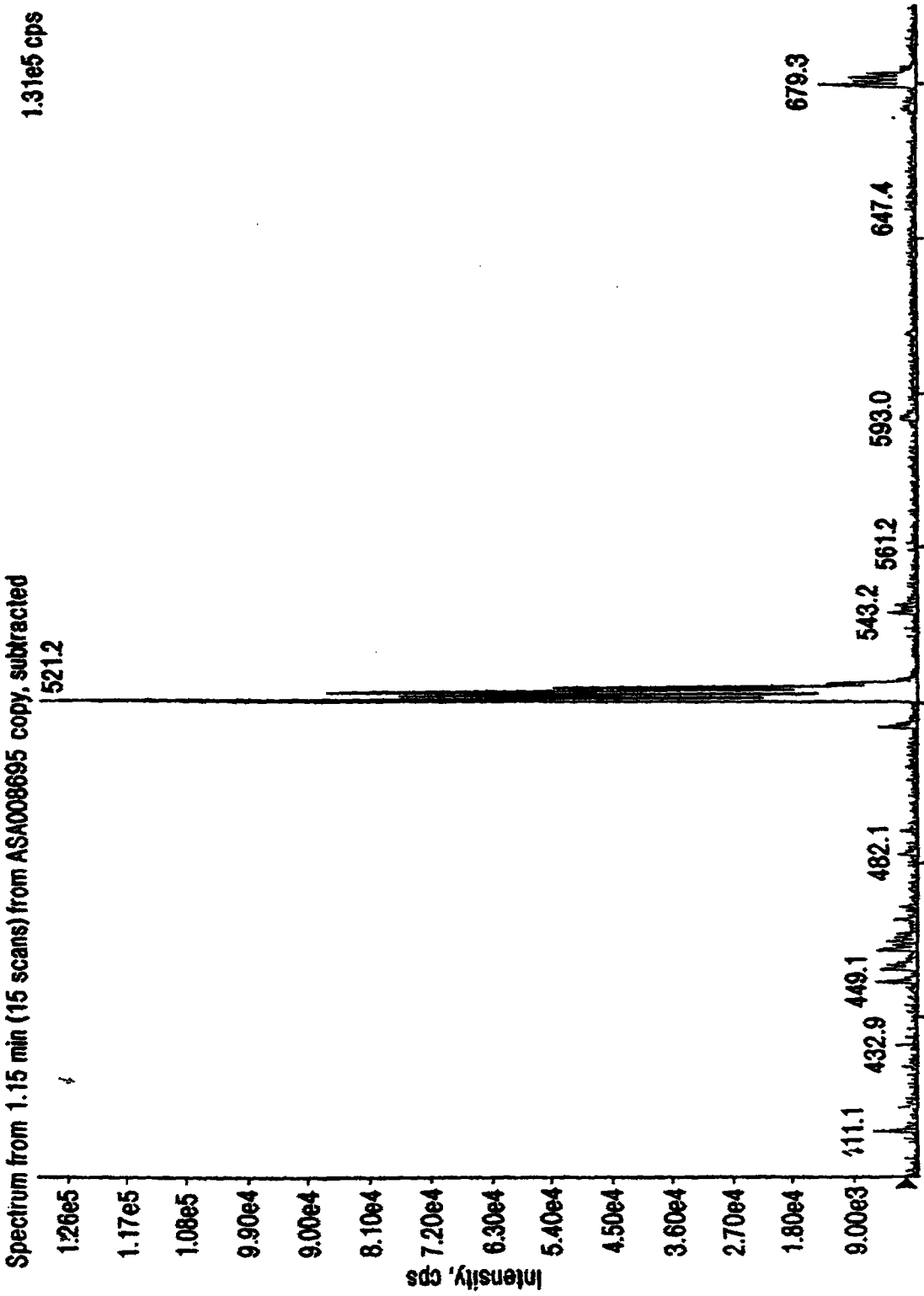

Spectrum from 1.15 min (15 scans) from ASA008695 copy, subtracted
1.31e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
111.1
432.9
449.1
482.1
521.2
543.2
561.2
593.0
647.4
679.3
440
480
520
560
600
640
680
m/z, amu

FIG. 145

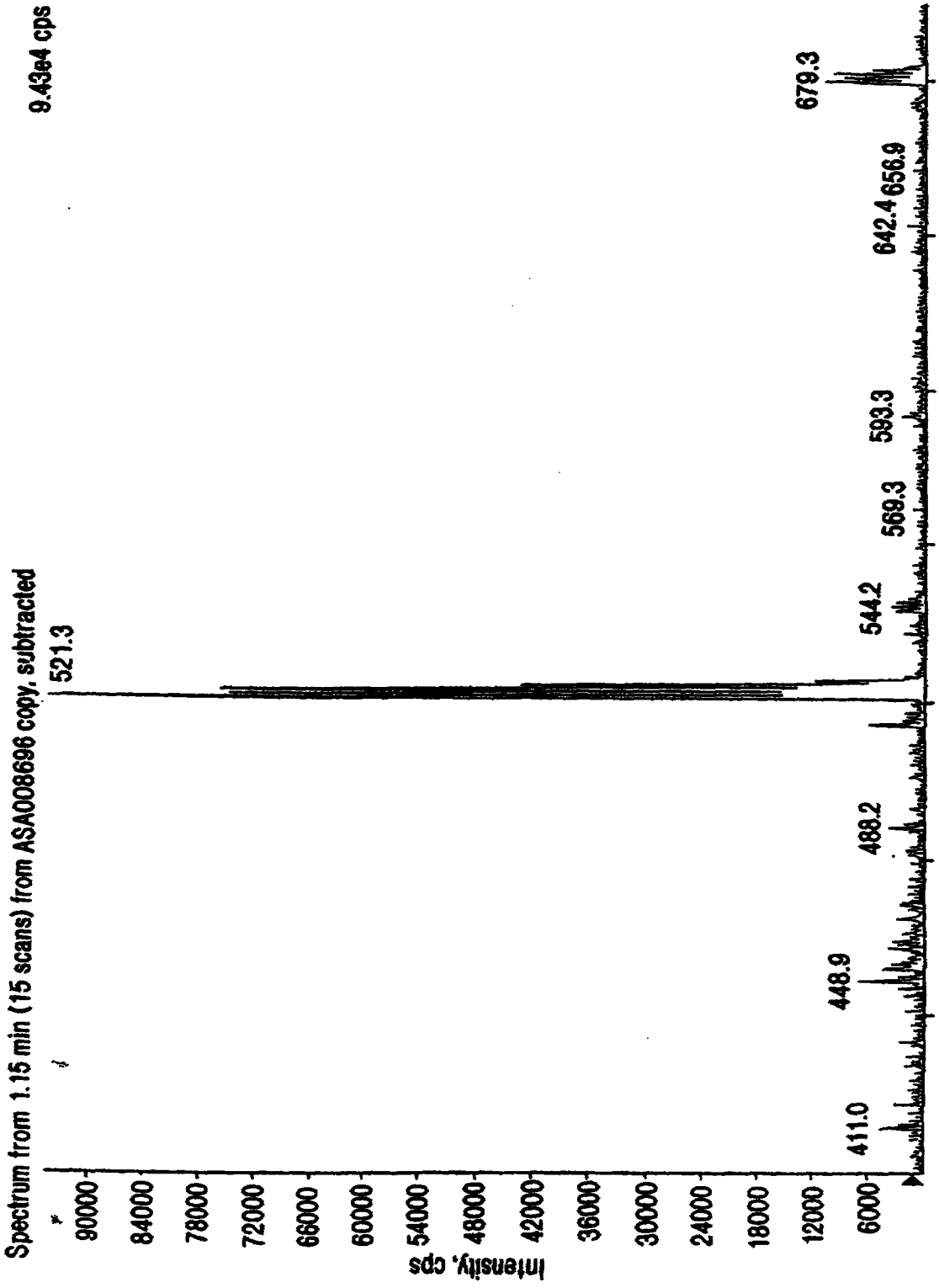

Spectrum from 1.15 min (15 scans) from ASA008696 copy, subtracted
9.43e4 cps
Intensity, cps
m/z, amu
521.3
544.2
569.3
583.3
642.4
656.9
679.3
488.2
448.9
411.0

FIG. 146

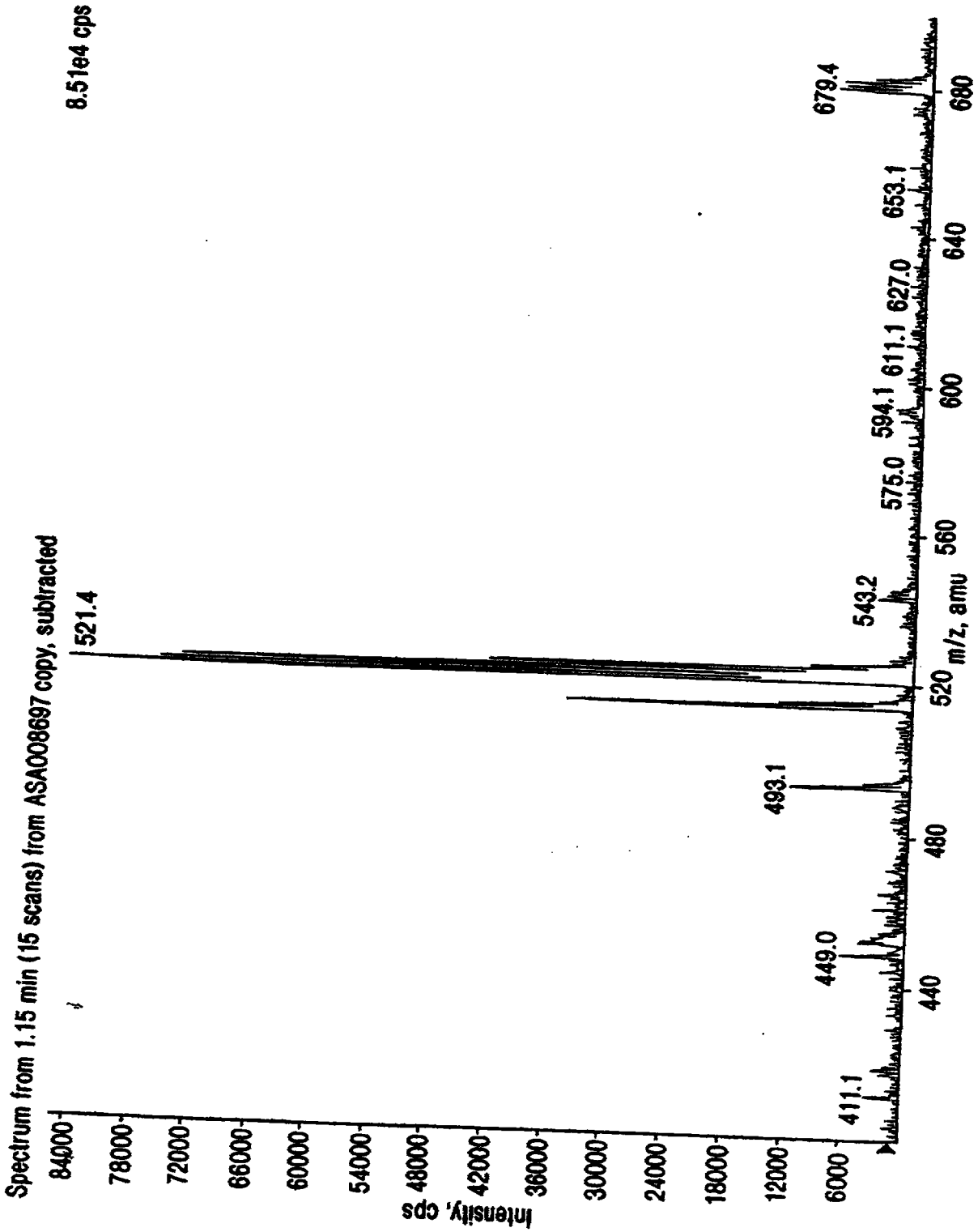

Spectrum from 1.15 min (15 scans) from ASA008697 copy, subtracted
8.51e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.1
449.0
493.1
521.4
543.2
575.0
594.1
611.1
627.0
653.1
679.4
440
480
520
560
600
640
680
m/z, amu

FIG. 147

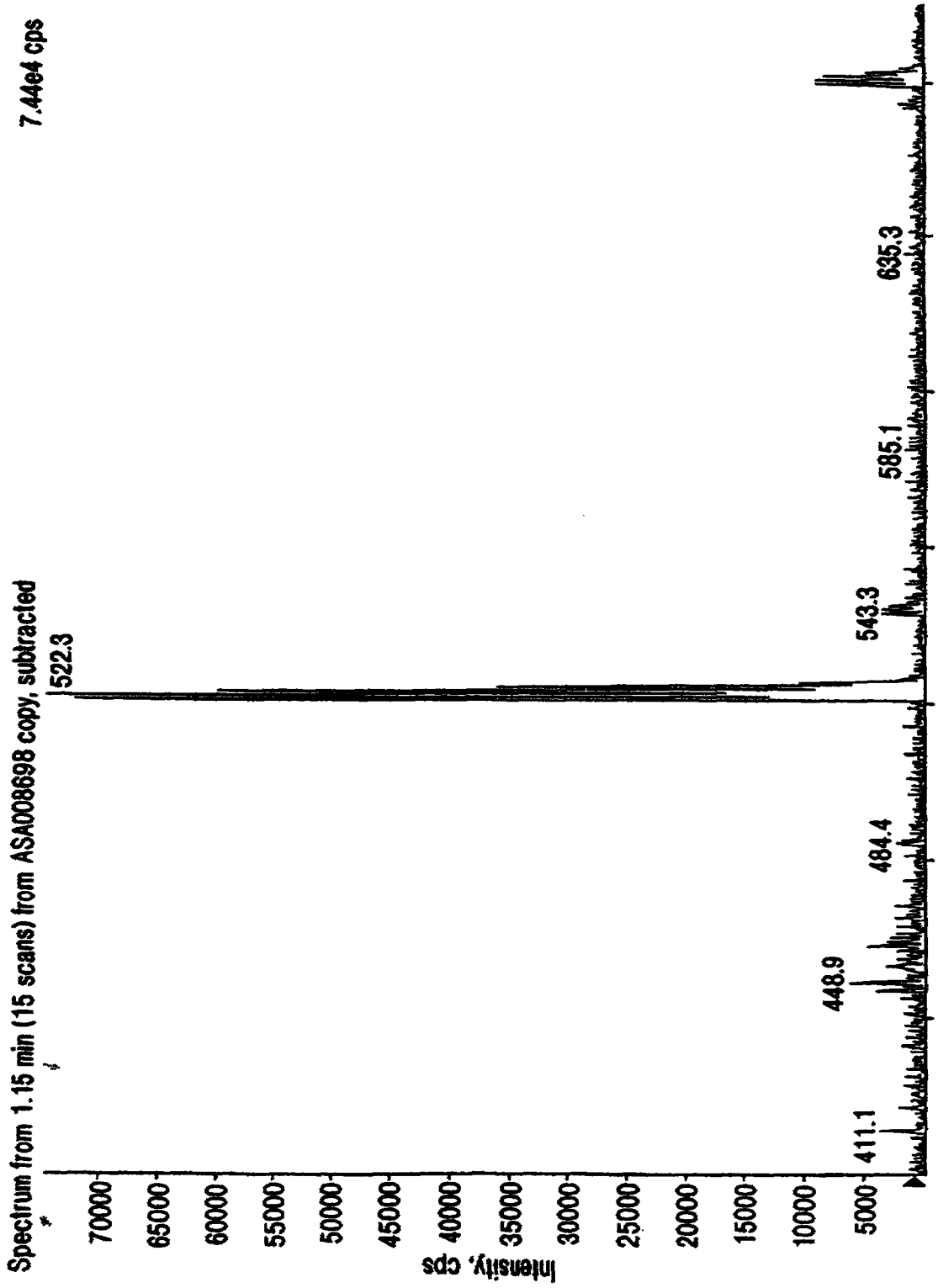

Spectrum from 1.15 min (15 scans) from ASA008698 copy, subtracted
7.44e4 cps
Intensity, cps
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
411.1
448.9
484.4
522.3
543.3
585.1
635.3
440
480
520
560
600
640
680
m/z, amu

FIG. 148

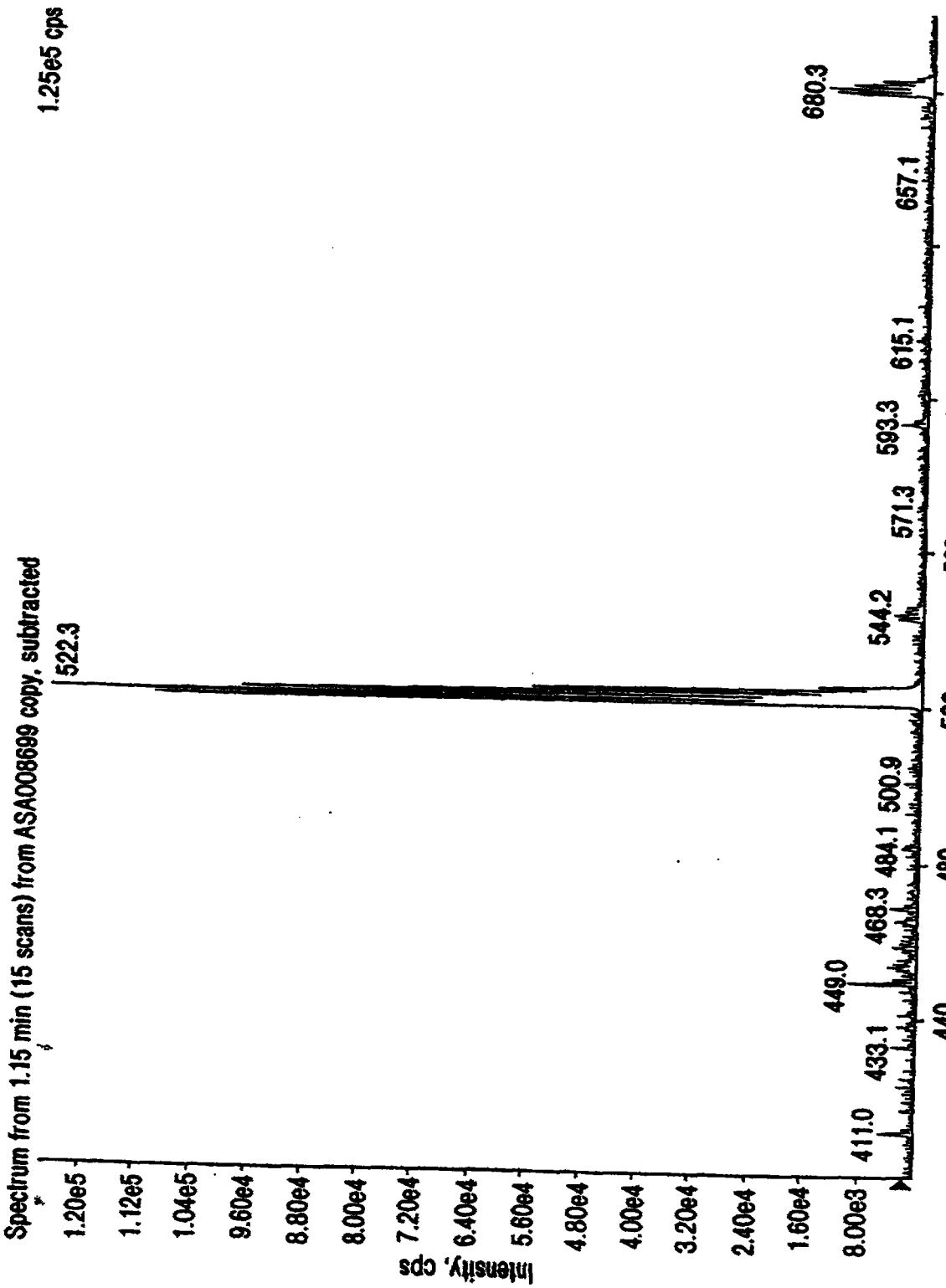

Spectrum from 1.15 min (15 scans) from ASA008699 copy, subtracted
1.25e5 cps
Intensity, cps
1.20e5
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
411.0
433.1
449.0
468.3
484.1
500.9
522.3
544.2
571.3
593.3
615.1
657.1
680.3
440
480
520
560
600
640
680

FIG. 149

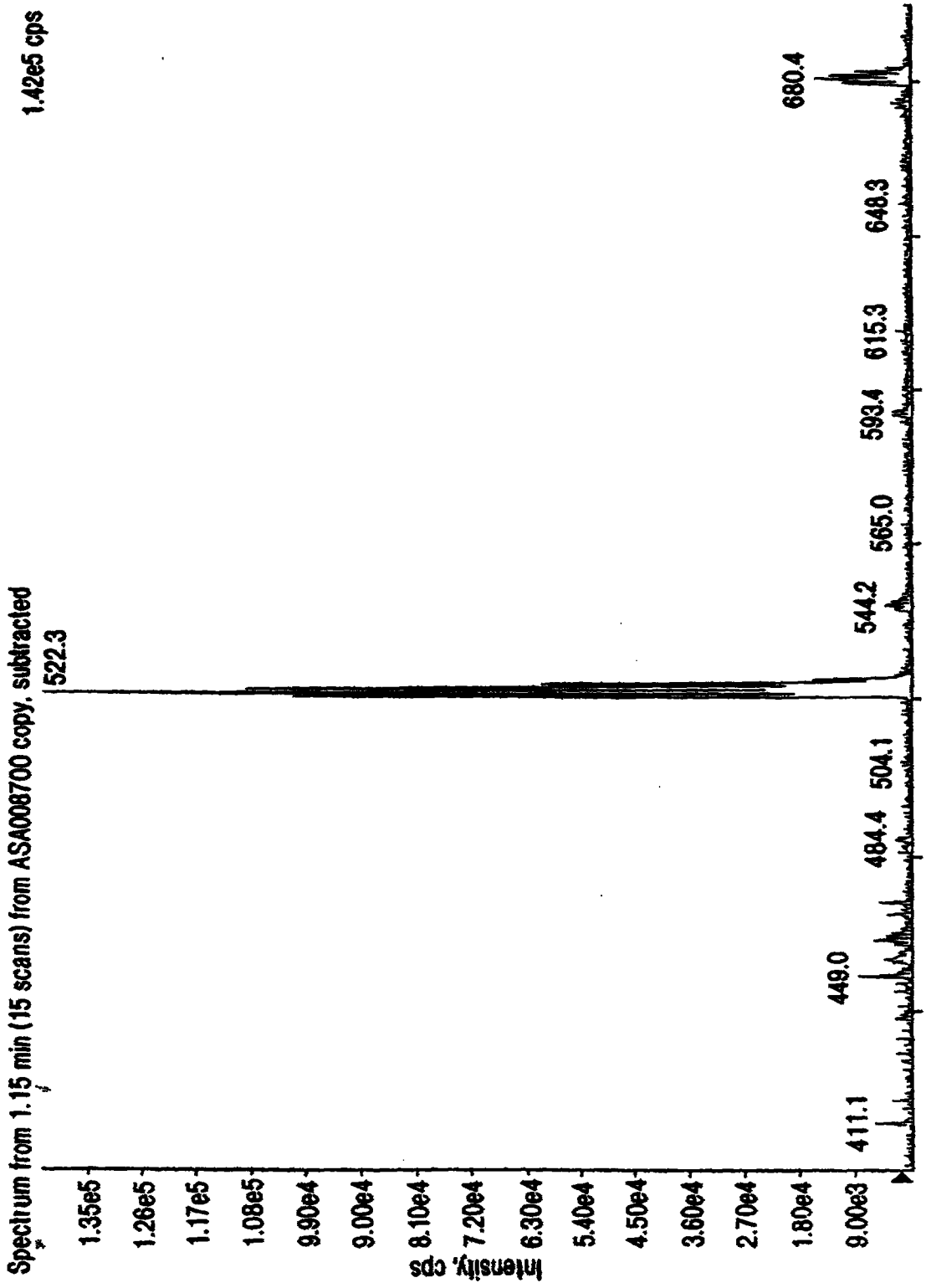

Spectrum from 1.15 min (15 scans) from ASA008700 copy, subtracted
1.42e5 cps
Intensity, cps
1.35e5
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.1
449.0
484.4
504.1
522.3
544.2
565.0
593.4
615.3
648.3
680.4
440
480
520
560
600
640
680
m/z, amu

FIG. 150

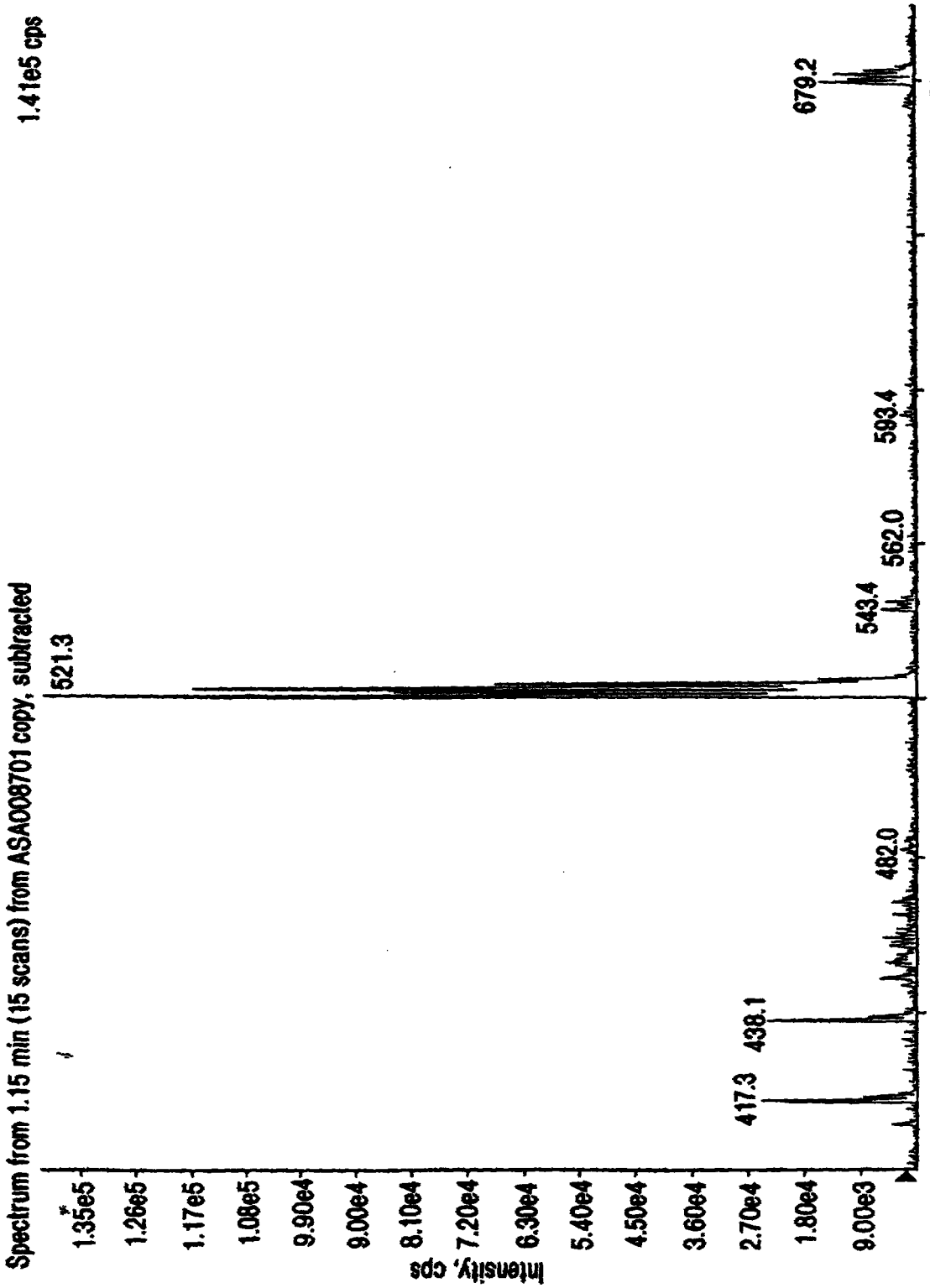

Spectrum from 1.15 min (15 scans) from ASA008701 copy, subtracted
1.41e5 cps
Intensity, cps
1.35e5
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
521.3
543.4
562.0
593.4
679.2
482.0
438.1
417.3
440
480
520
560
600
640
680
m/z, amu

FIG. 151

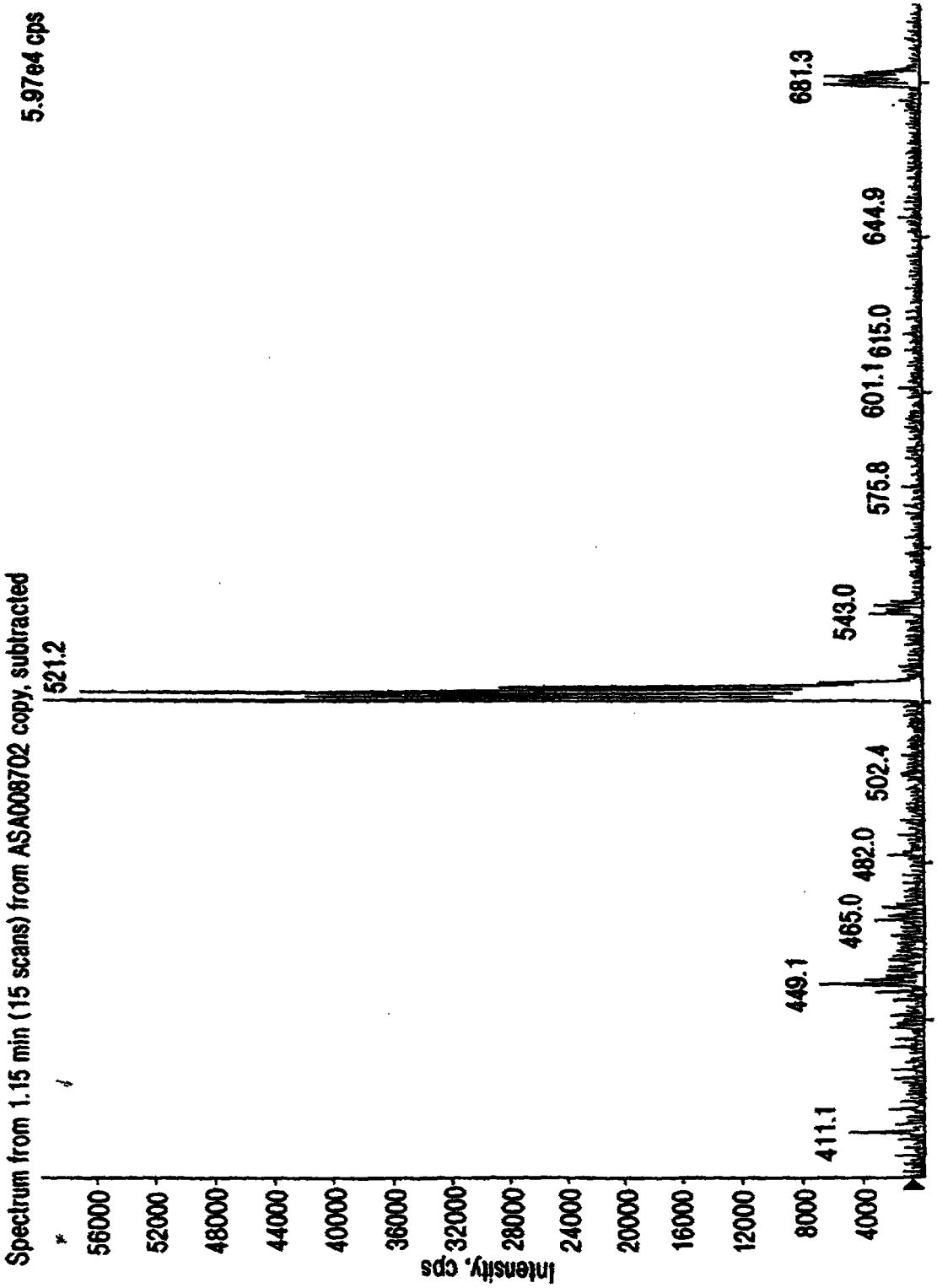

Spectrum from 1.15 min (15 scans) from ASA008702 copy, subtracted
5.97e4 cps
Intensity, cps
m/z, amu
521.2
543.0
575.8
601.1
615.0
644.9
681.3
411.1
449.1
465.0
482.0
502.4

FIG. 152

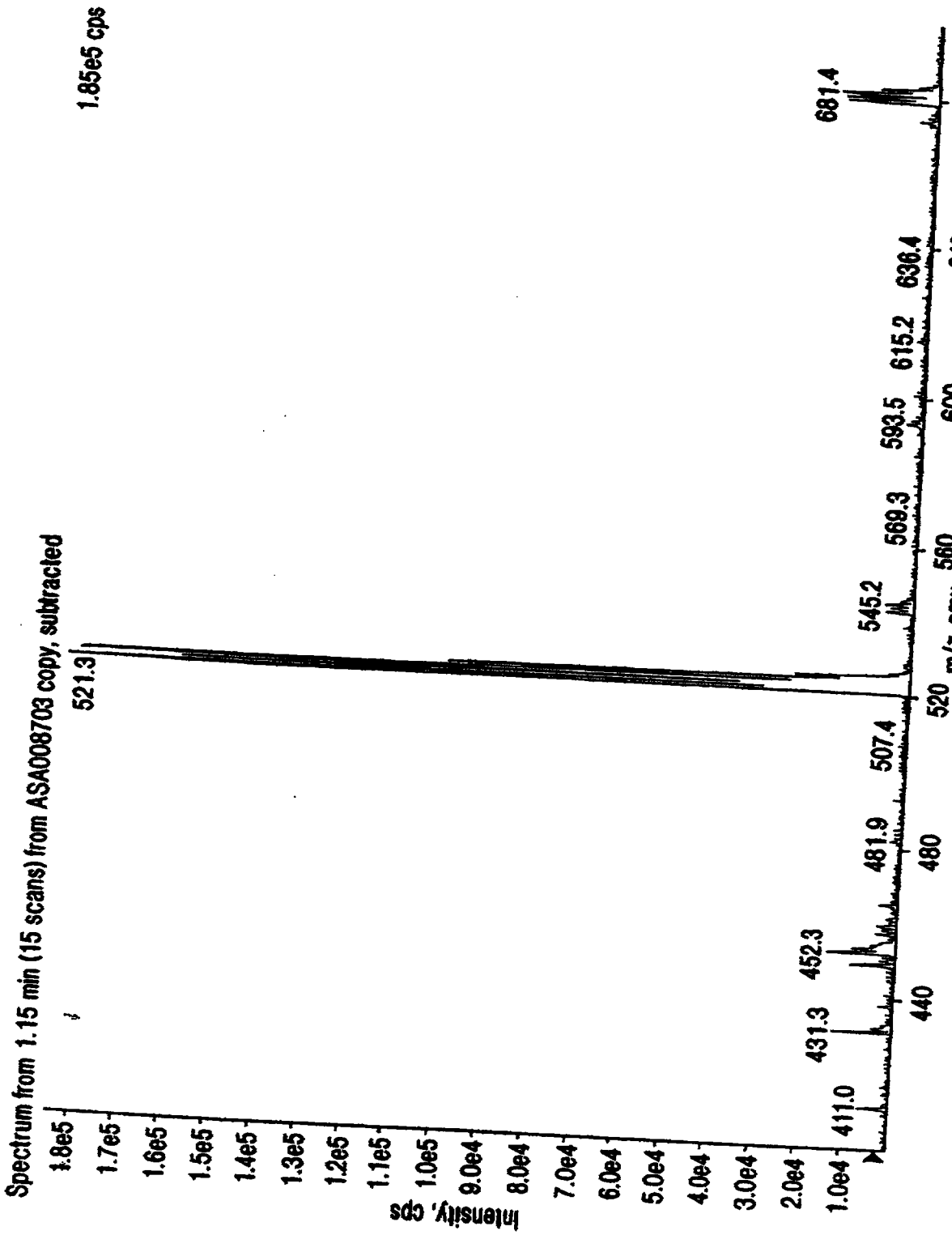

Spectrum from 1.15 min (15 scans) from ASA008703 copy, subtracted
1.85e5 cps
Intensity, cps
1.8e5
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.0
431.3
452.3
481.9
507.4
521.3
545.2
569.3
593.5
615.2
636.4
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 153

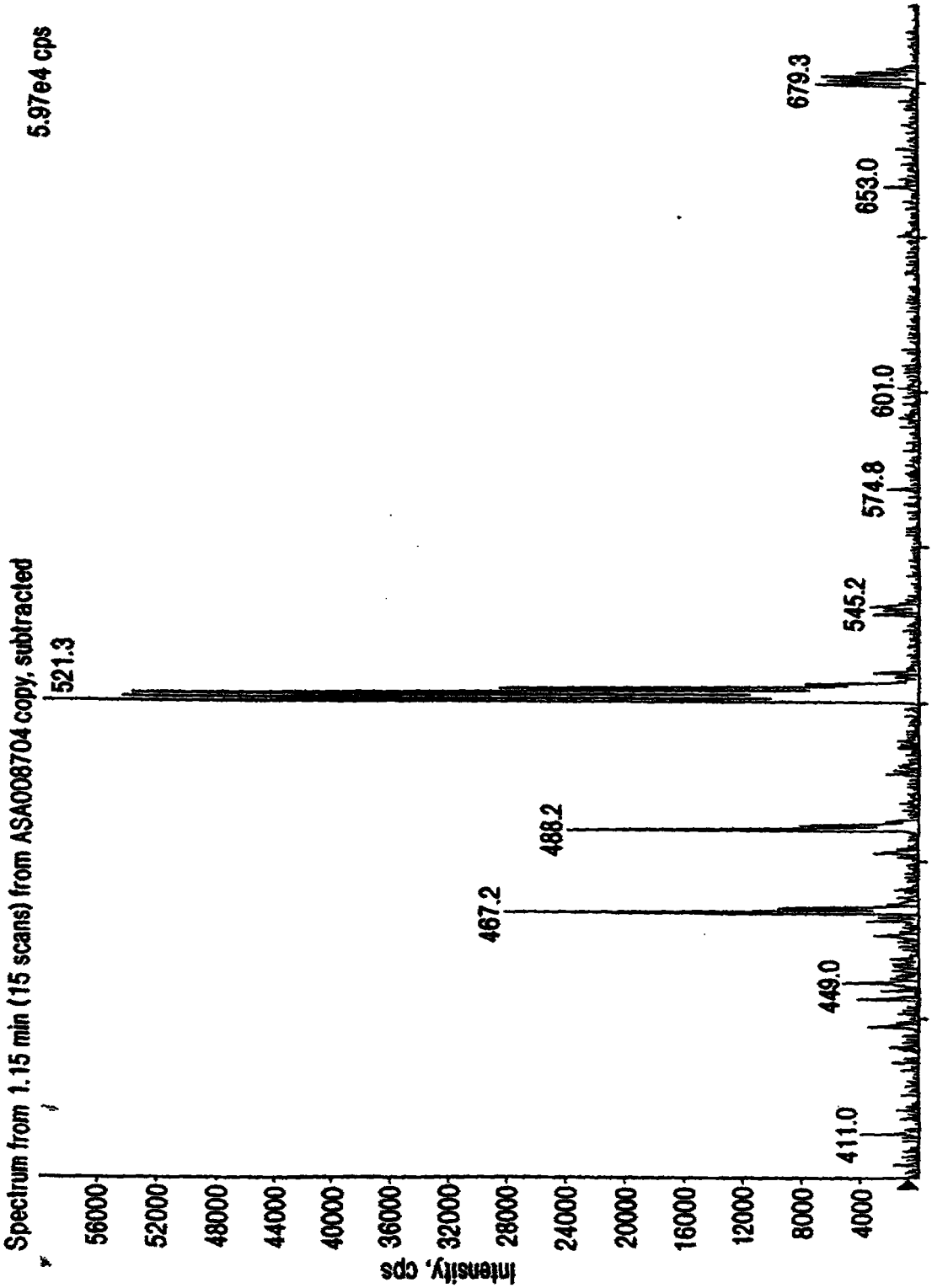

Spectrum from 1.15 min (15 scans) from ASA008704 copy, subtracted
5.97e4 cps
Intensity, cps
56000
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
411.0
449.0
467.2
488.2
521.3
545.2
574.8
601.0
653.0
679.3
440
480
520
560
600
640
680
m/z, amu

FIG. 154

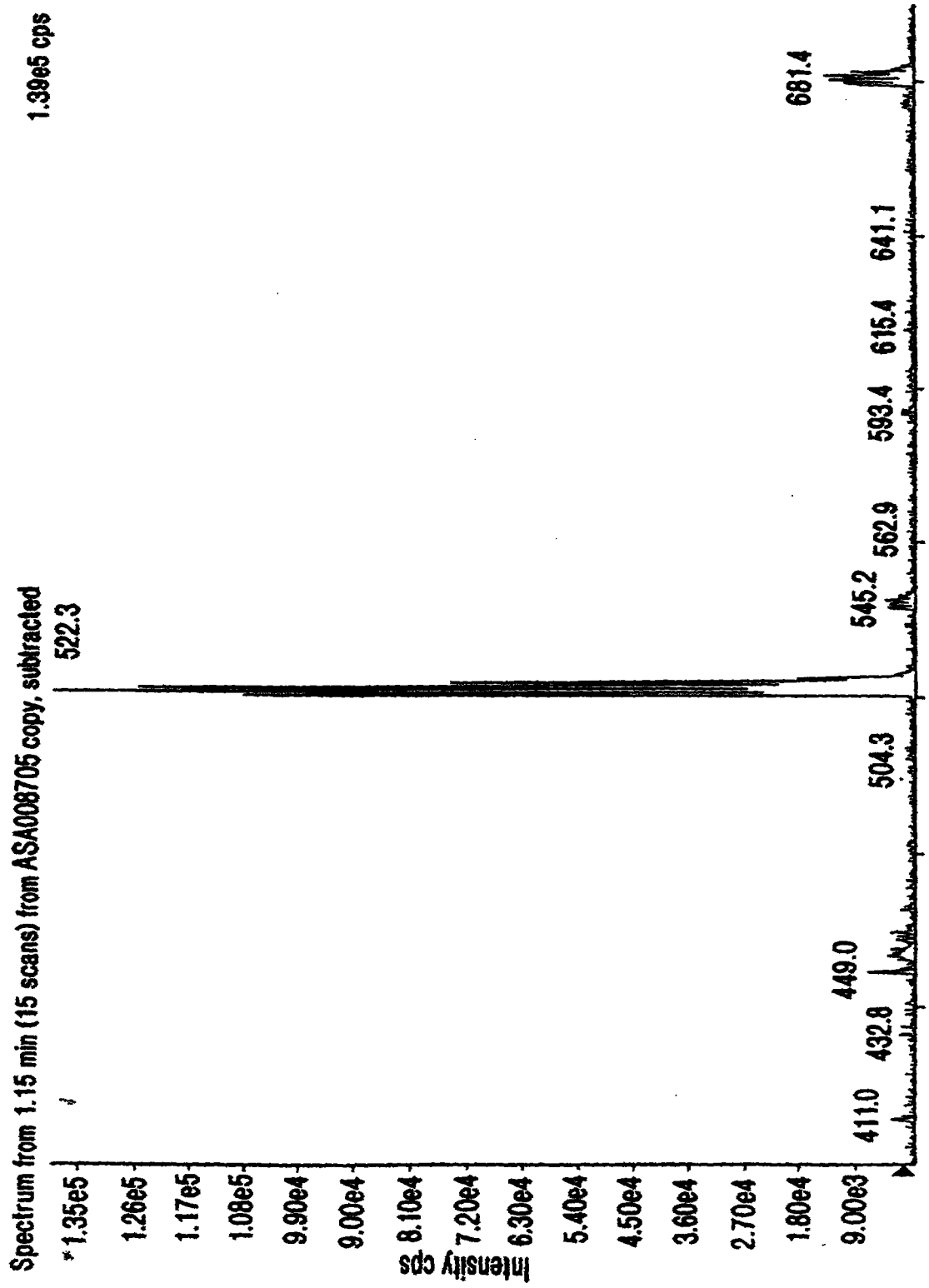

Spectrum from 1.15 min (15 scans) from ASA008705 copy, subtracted
1.39e5 cps
Intensity cps
1.35e5
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.0
432.8
449.0
504.3
522.3
545.2
562.9
583.4
615.4
641.1
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 155

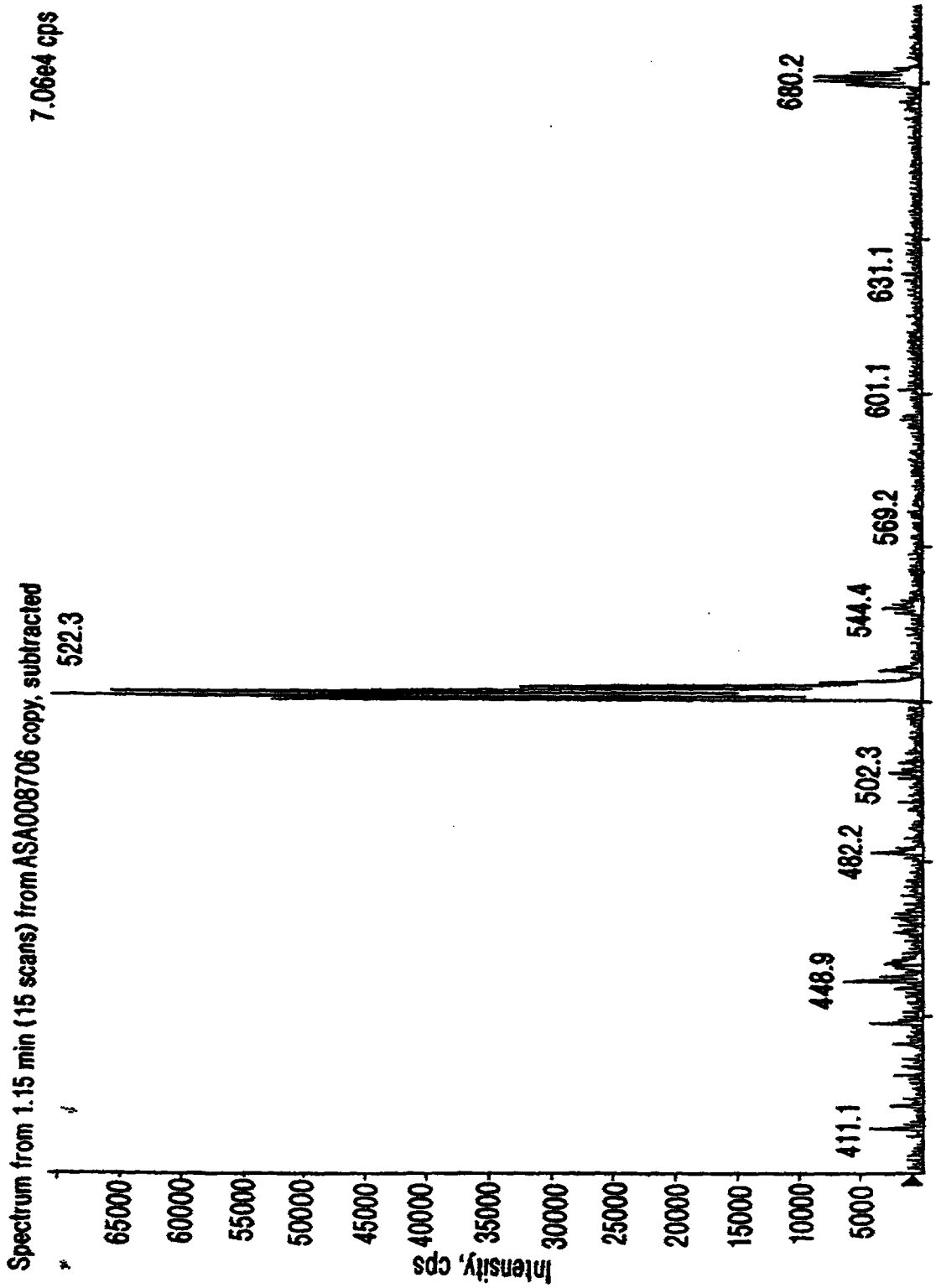

Spectrum from 1.15 min (15 scans) from ASA008706 copy, subtracted
7.06e4 cps
Intensity, cps
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
m/z, amu
440
480
520
560
600
640
680
411.1
448.9
482.2
502.3
522.3
544.4
569.2
601.1
631.1
680.2

FIG. 156

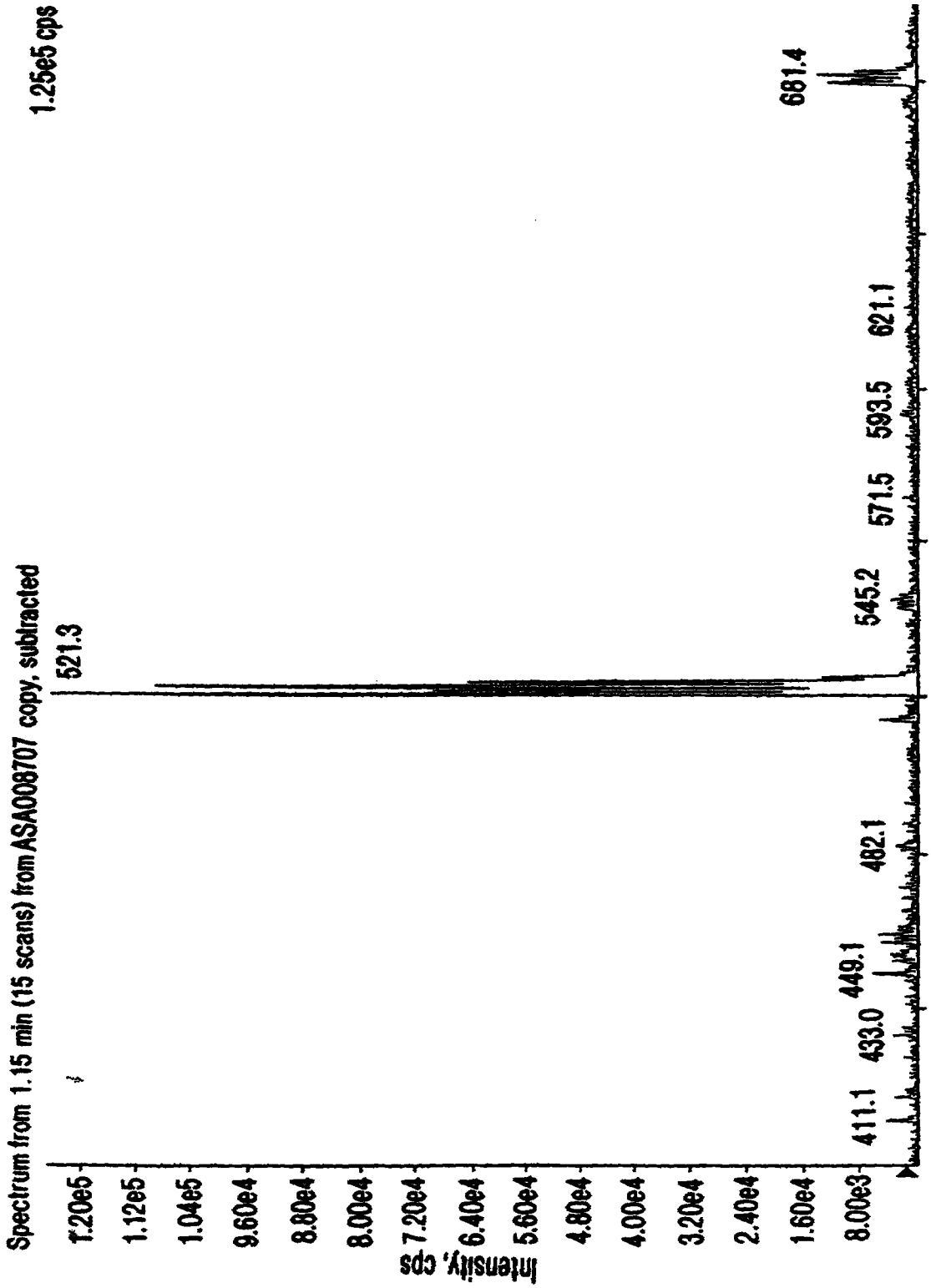

Spectrum from 1.15 min (15 scans) from ASA008707 copy, subtracted
1.25e5 cps
Intensity, cps
1.20e5
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
411.1
433.0
449.1
482.1
521.3
545.2
571.5
593.5
621.1
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 157

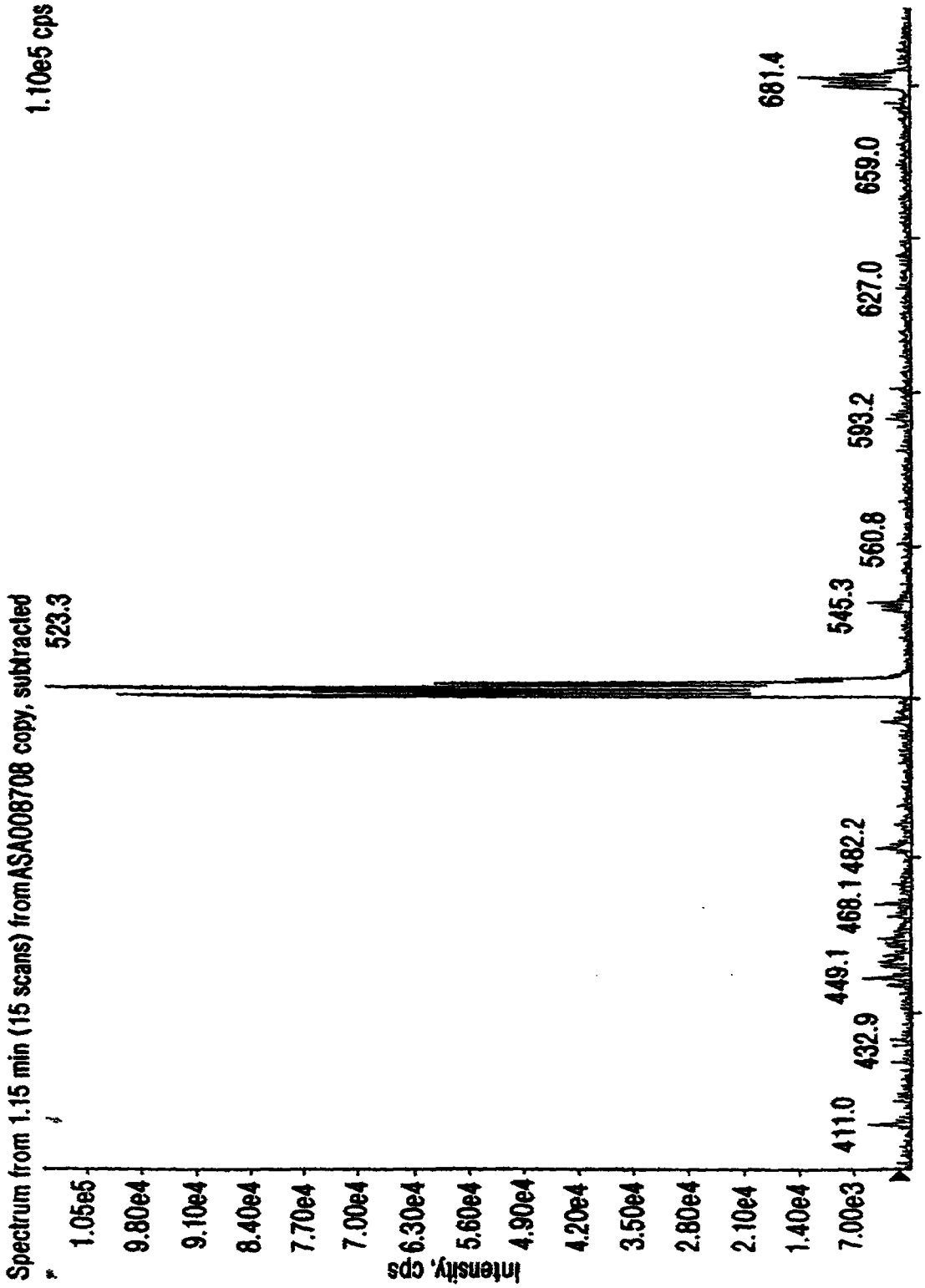

Spectrum from 1.15 min (15 scans) from ASA008708 copy, subtracted
1.10e5 cps
Intensity, cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
411.0
432.9
449.1
468.1
482.2
523.3
545.3
560.8
593.2
627.0
659.0
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 158

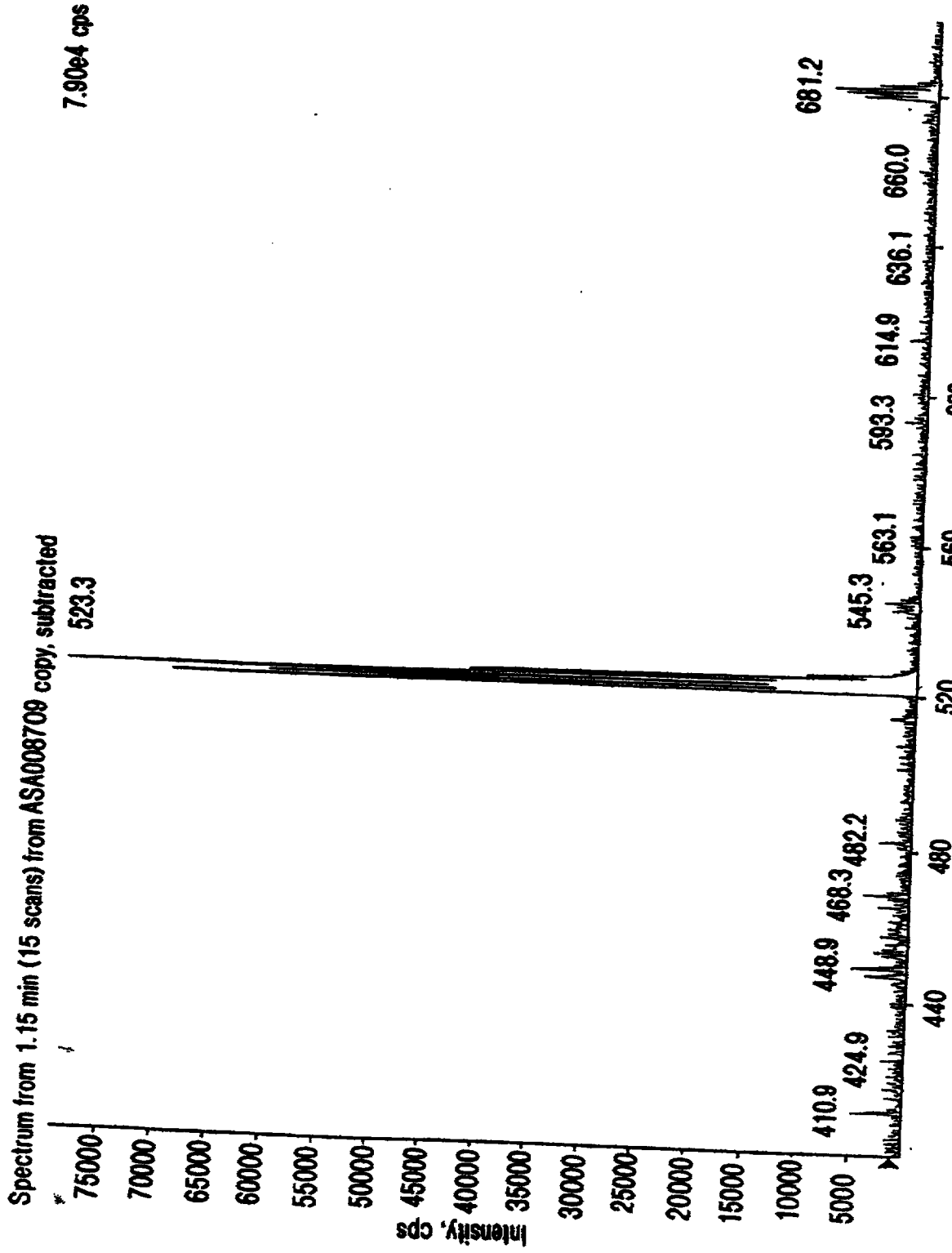

Spectrum from 1.15 min (15 scans) from ASA008709 copy, subtracted
7.90e4 cps
Intensity, cps
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
410.9
424.9
448.9
468.3
482.2
523.3
545.3
563.1
593.3
614.9
636.1
660.0
681.2
440
480
520
560
600
640
680
m/z, amu

FIG. 159

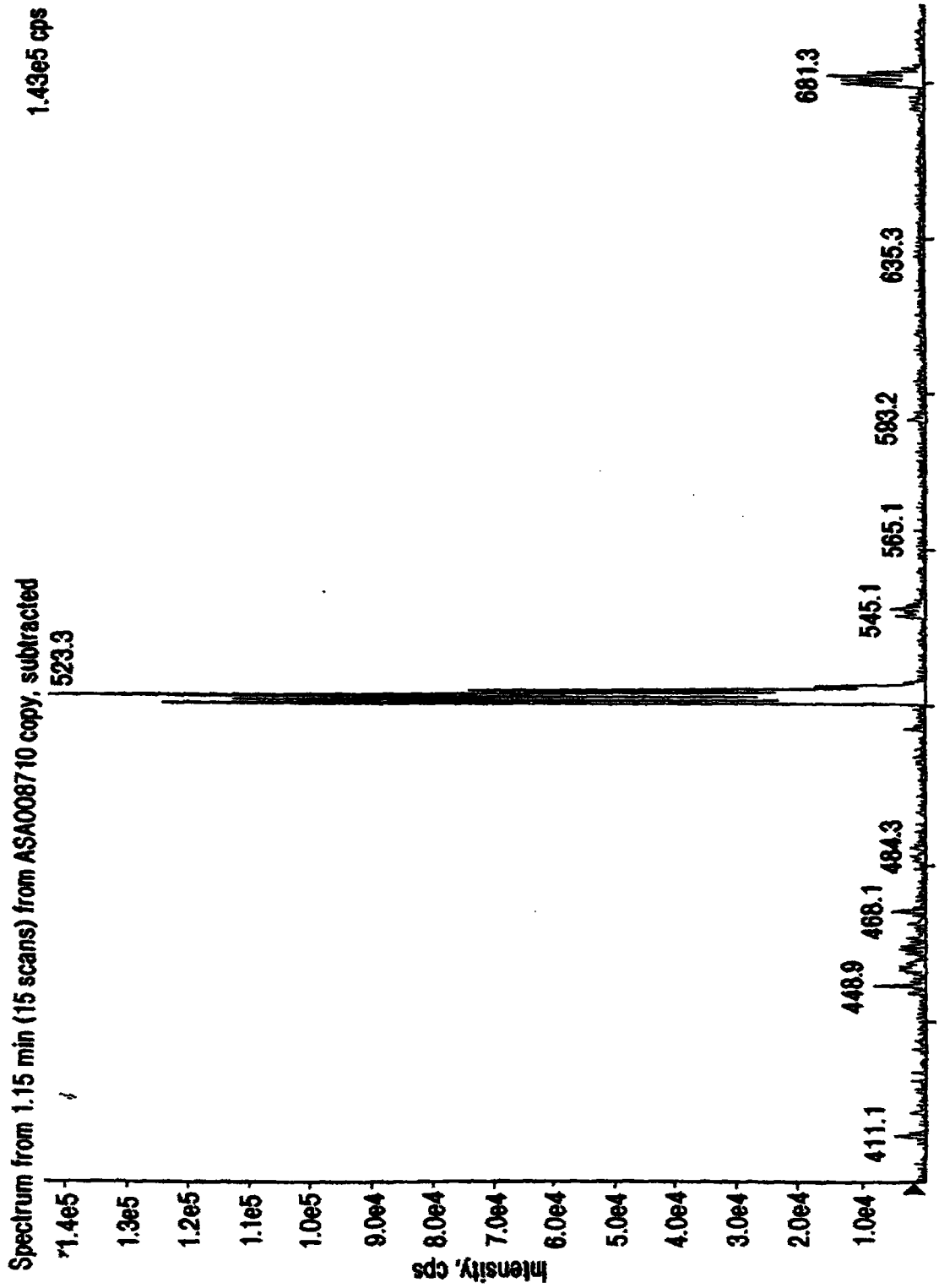

Spectrum from 1.15 min (15 scans) from ASA008710 copy, subtracted
1.43e5 cps
Intensity, cps
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
448.9
468.1
484.3
523.3
545.1
565.1
583.2
635.3
681.3
440
480
520
560
600
640
680
m/z, amu

FIG. 160

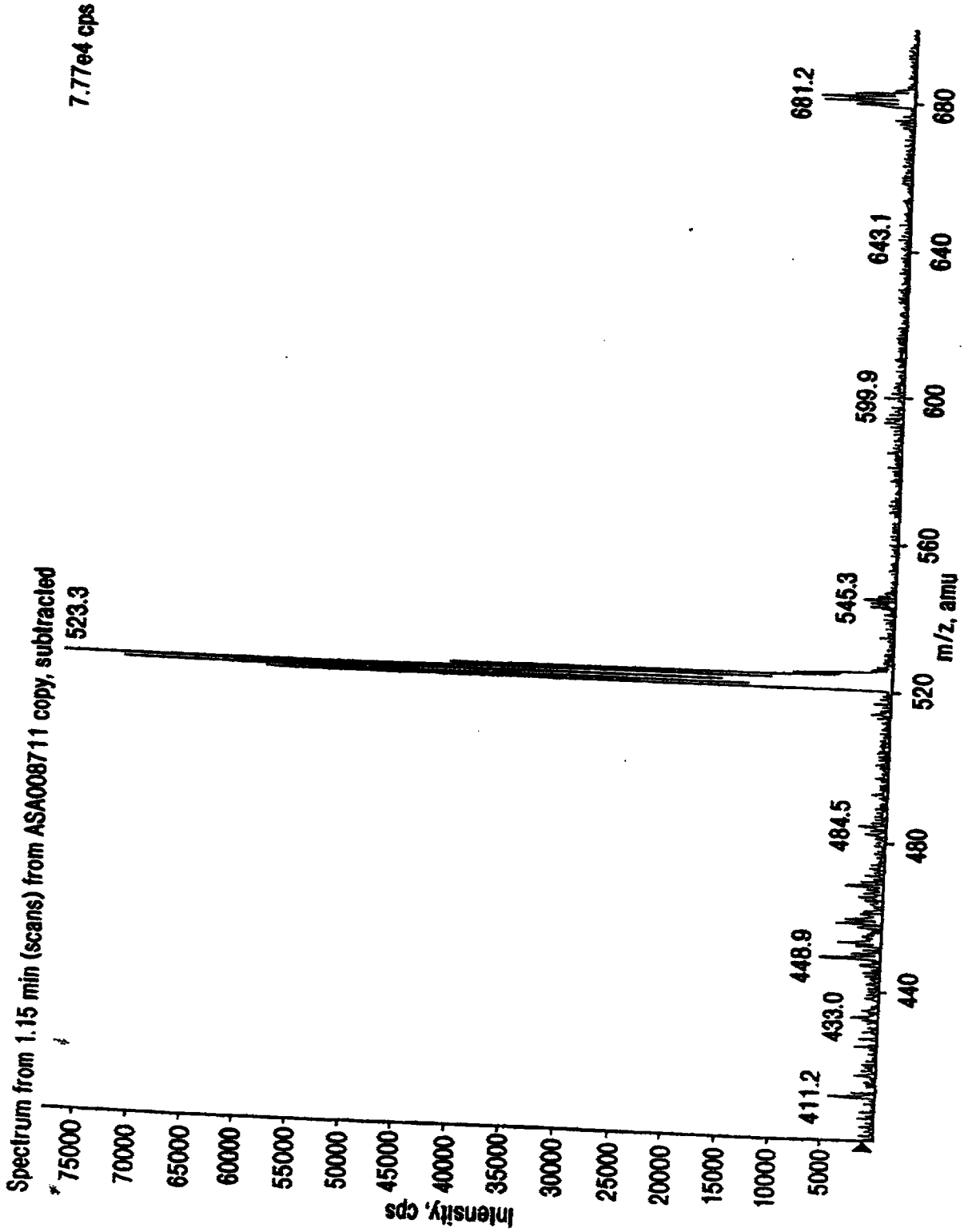

Spectrum from 1.15 min (scans) from ASA008711 copy, subtracted
7.77e4 cps
Intensity, cps
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
523.3
545.3
599.9
643.1
681.2
411.2
433.0
448.9
484.5
440
480
520
560
600
640
680
m/z, amu

FIG. 161

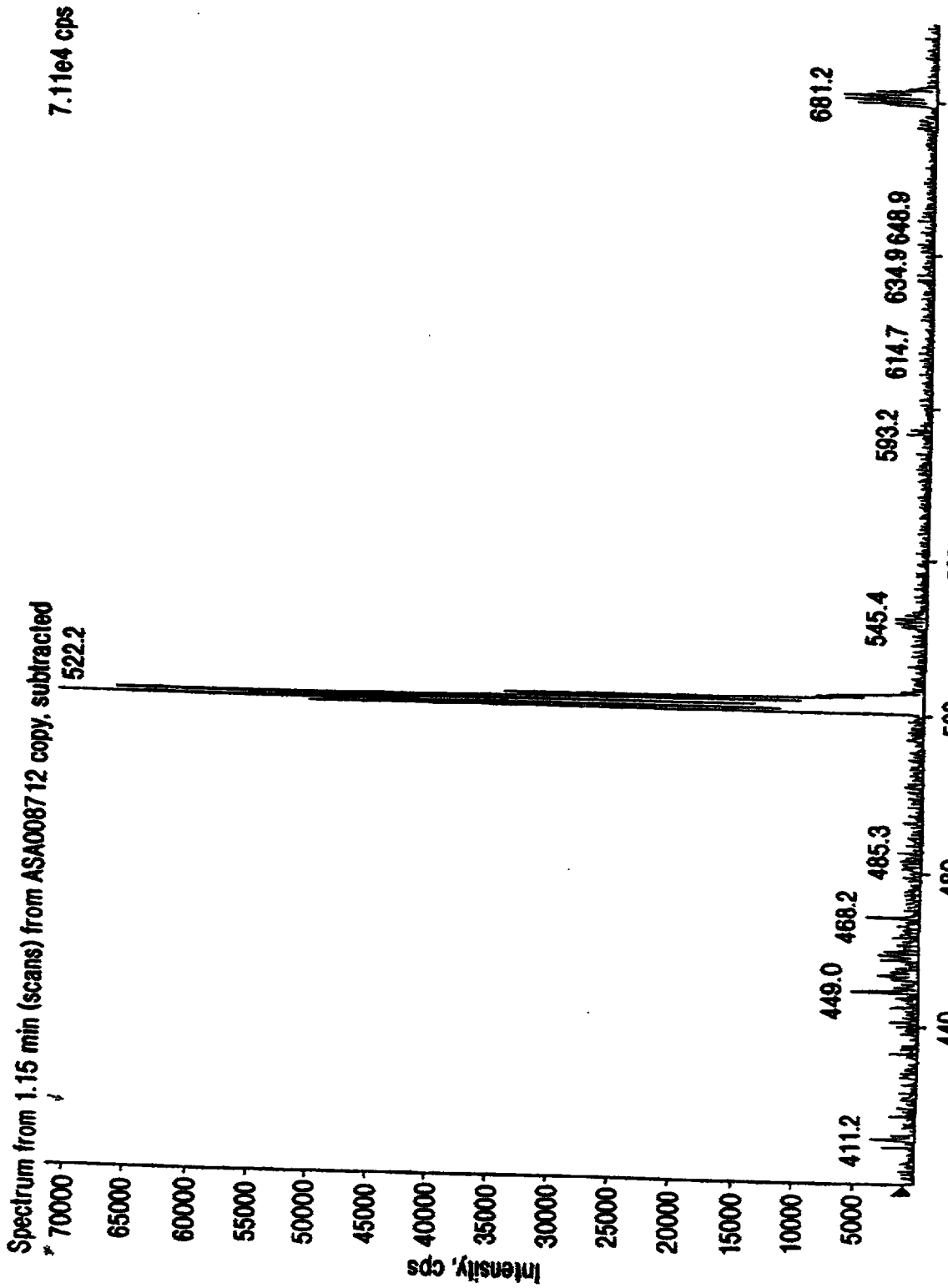

Spectrum from 1.15 min (scans) from ASA008712 copy, subtracted
7.11e4 cps
Intensity, cps
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
411.2
449.0
468.2
485.3
522.2
545.4
593.2
614.7
634.9
648.9
681.2
440
480
520
560
600
640
680
m/z, amu

FIG. 162

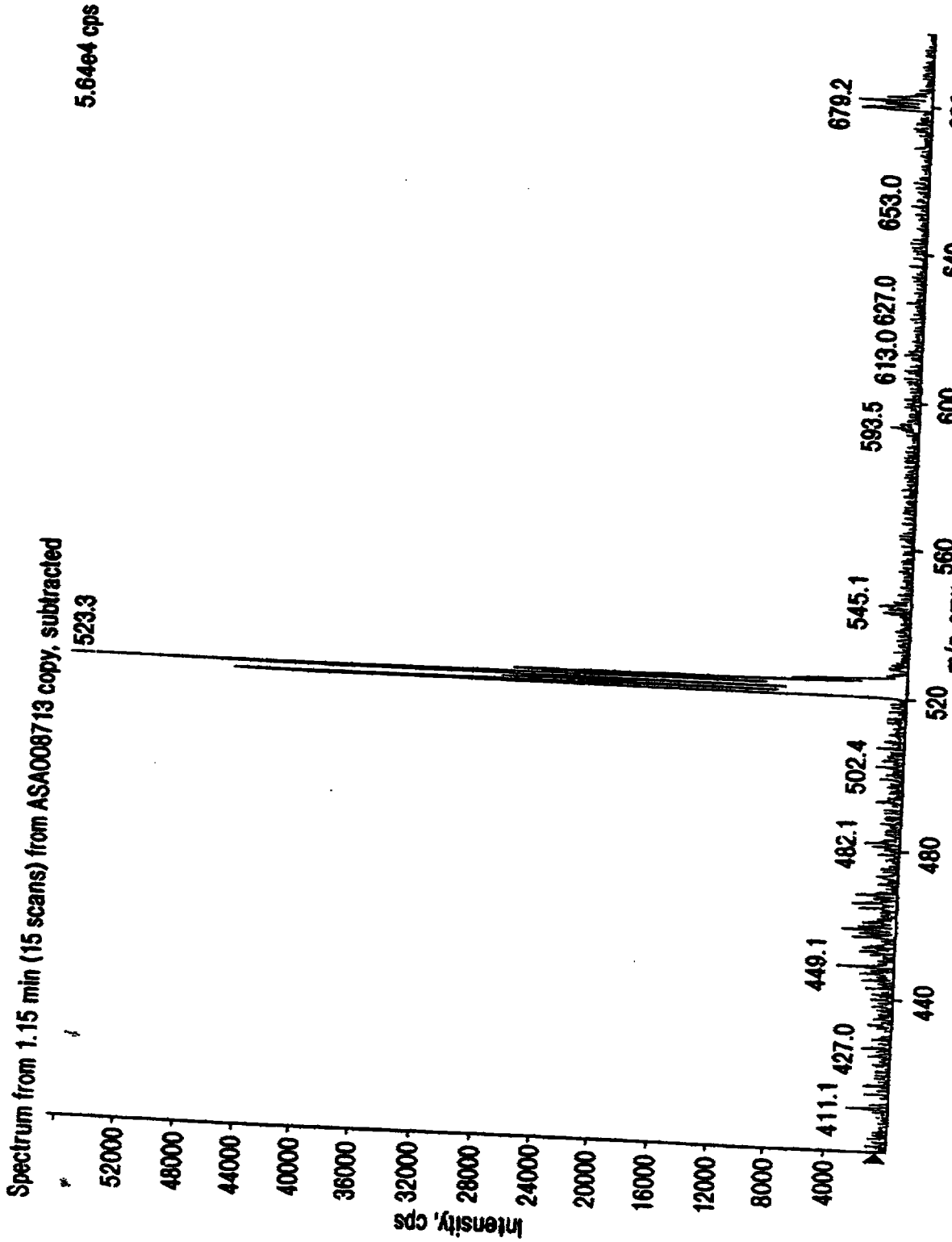

Spectrum from 1.15 min (15 scans) from ASA008713 copy, subtracted
5.64e4 cps
Intensity, cps
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
m/z, amu
411.1
427.0
449.1
482.1
502.4
523.3
545.1
583.5
613.0
627.0
653.0
679.2
440
480
520
560
600
640
680

FIG. 163

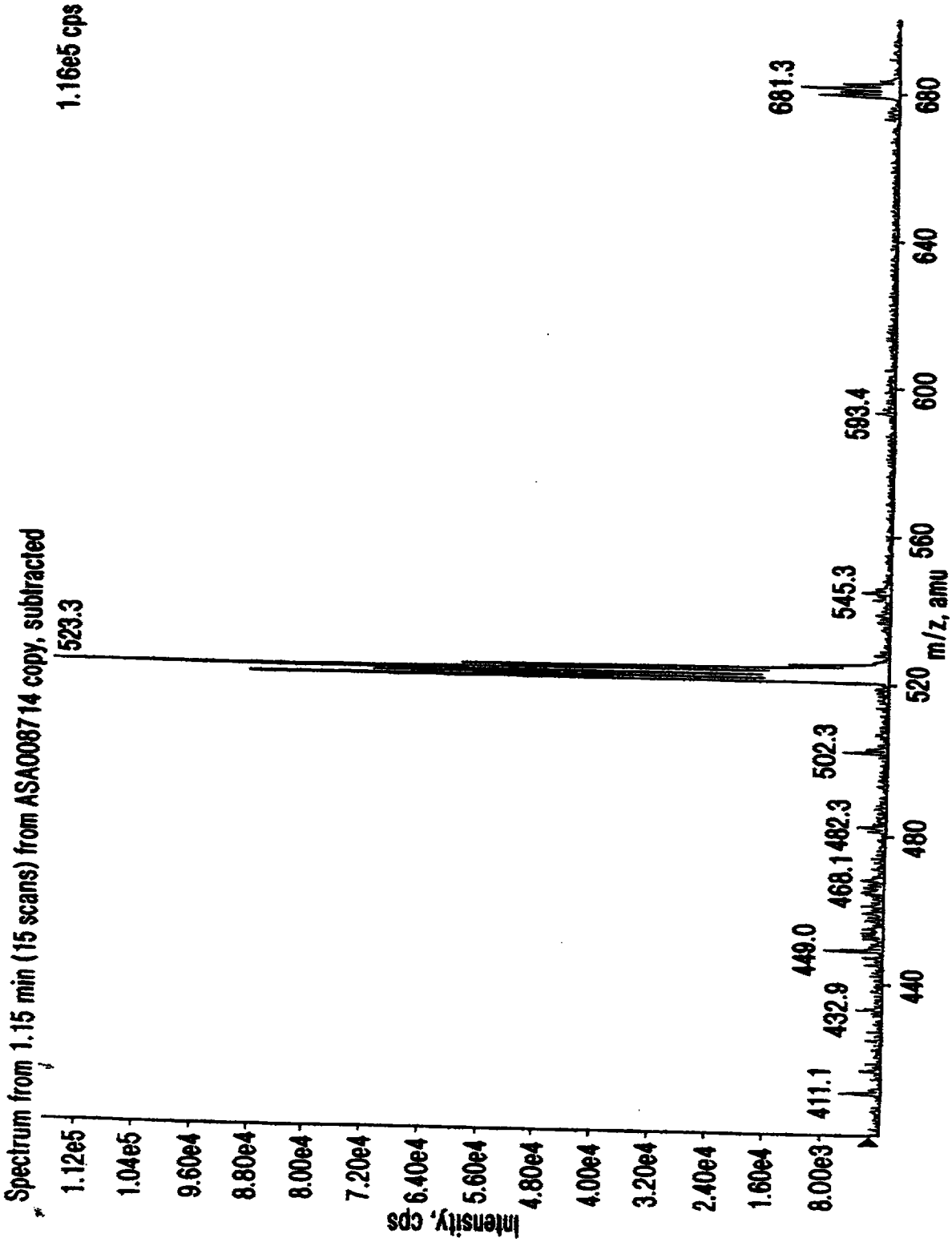

Spectrum from 1.15 min (15 scans) from ASA008714 copy, subtracted
1.16e5 cps
Intensity, cps
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
411.1
432.9
449.0
468.1
482.3
502.3
523.3
545.3
583.4
681.3
440
480
520
560
600
640
680

FIG. 164

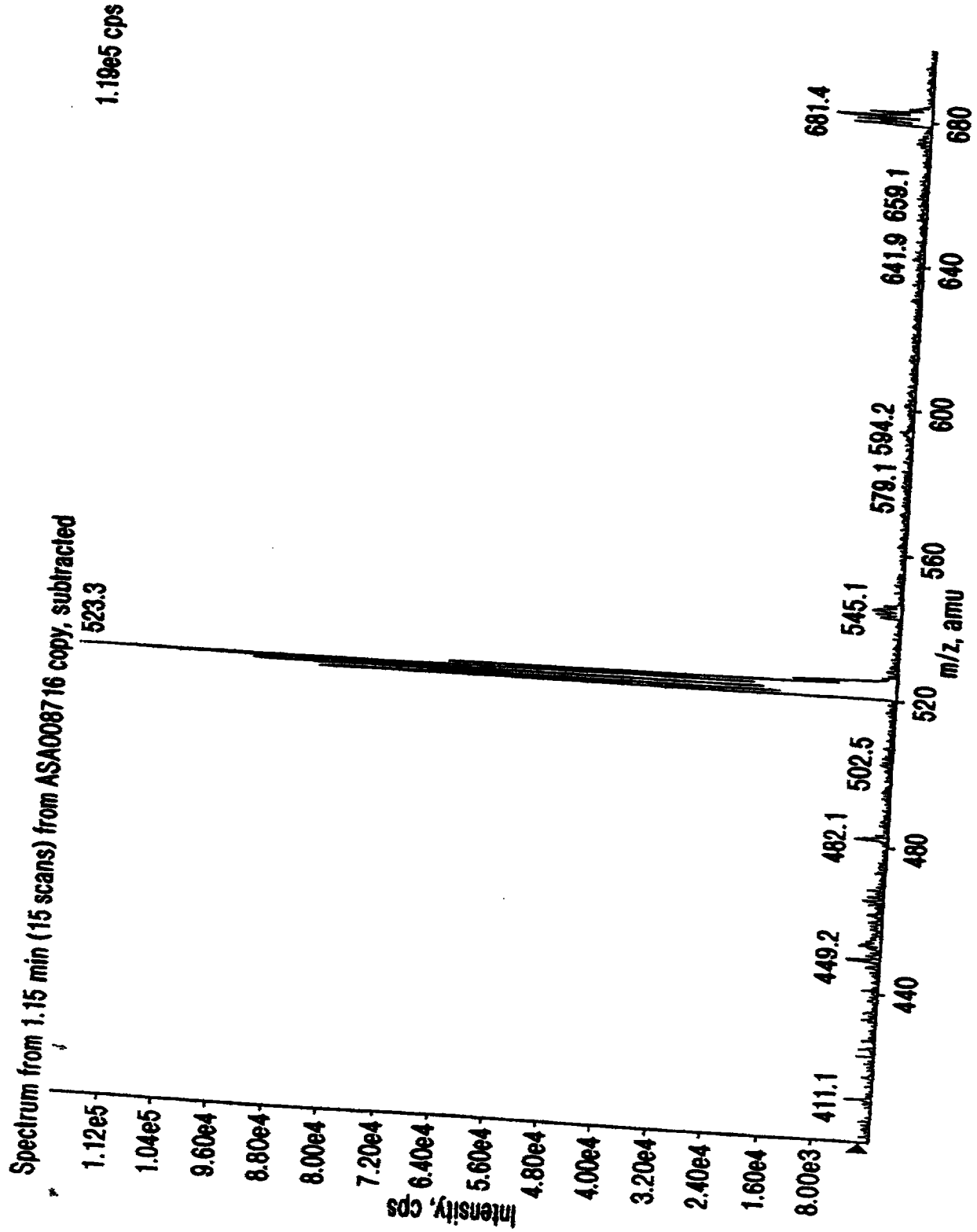

Spectrum from 1.15 min (15 scans) from ASA008716 copy, subtracted
1.19e5 cps
Intensity, cps
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
411.1
449.2
482.1
502.5
523.3
545.1
578.1
594.2
641.9
659.1
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 165

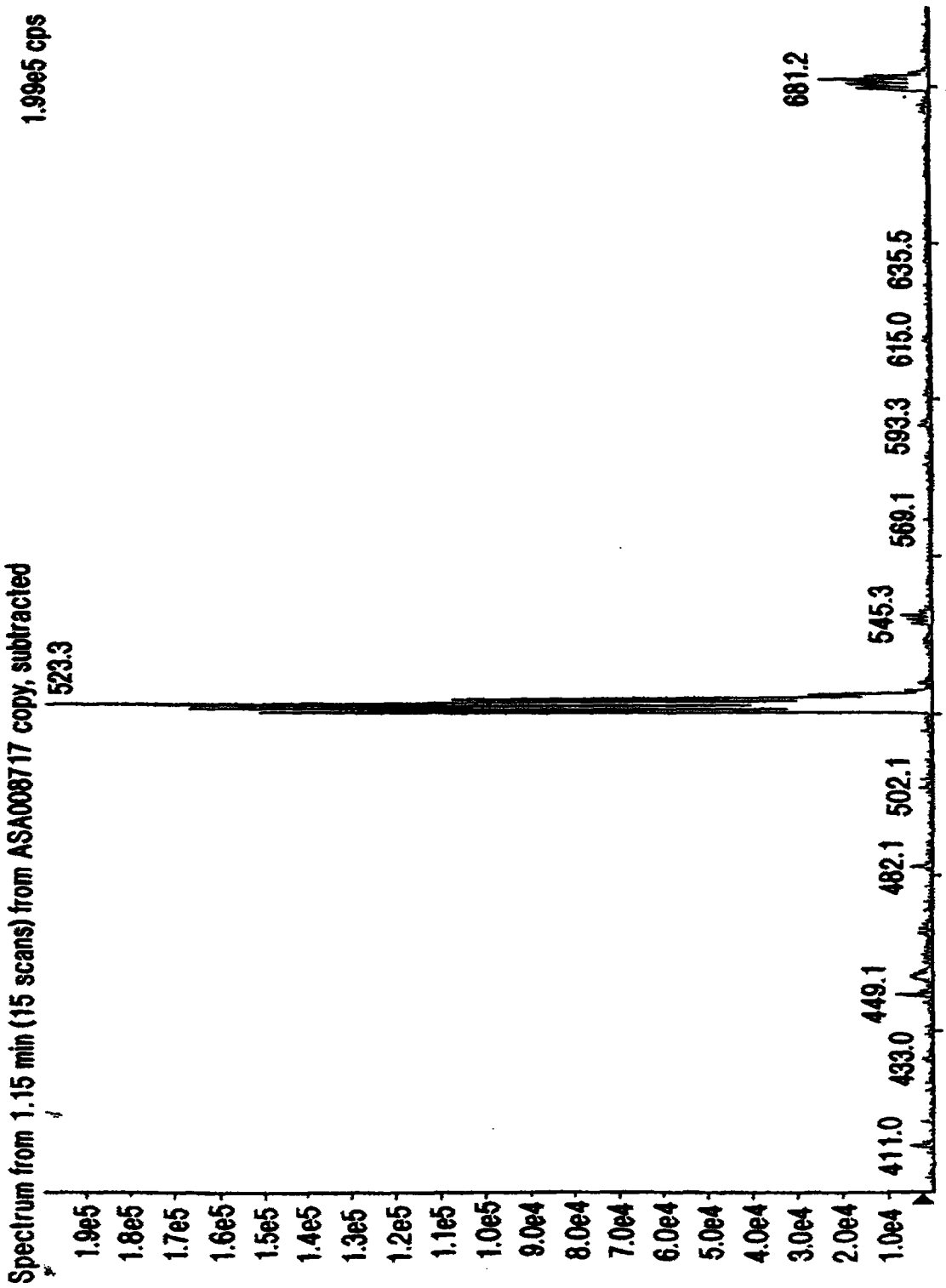

Spectrum from 1.15 min (15 scans) from ASA008717 copy, subtracted
1.99e5 cps
1.9e5
1.8e5
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.0
433.0
449.1
482.1
502.1
523.3
545.3
569.1
593.3
615.0
635.5
681.2
440
480
520
560
600
640
680
m/z, amu

FIG. 166

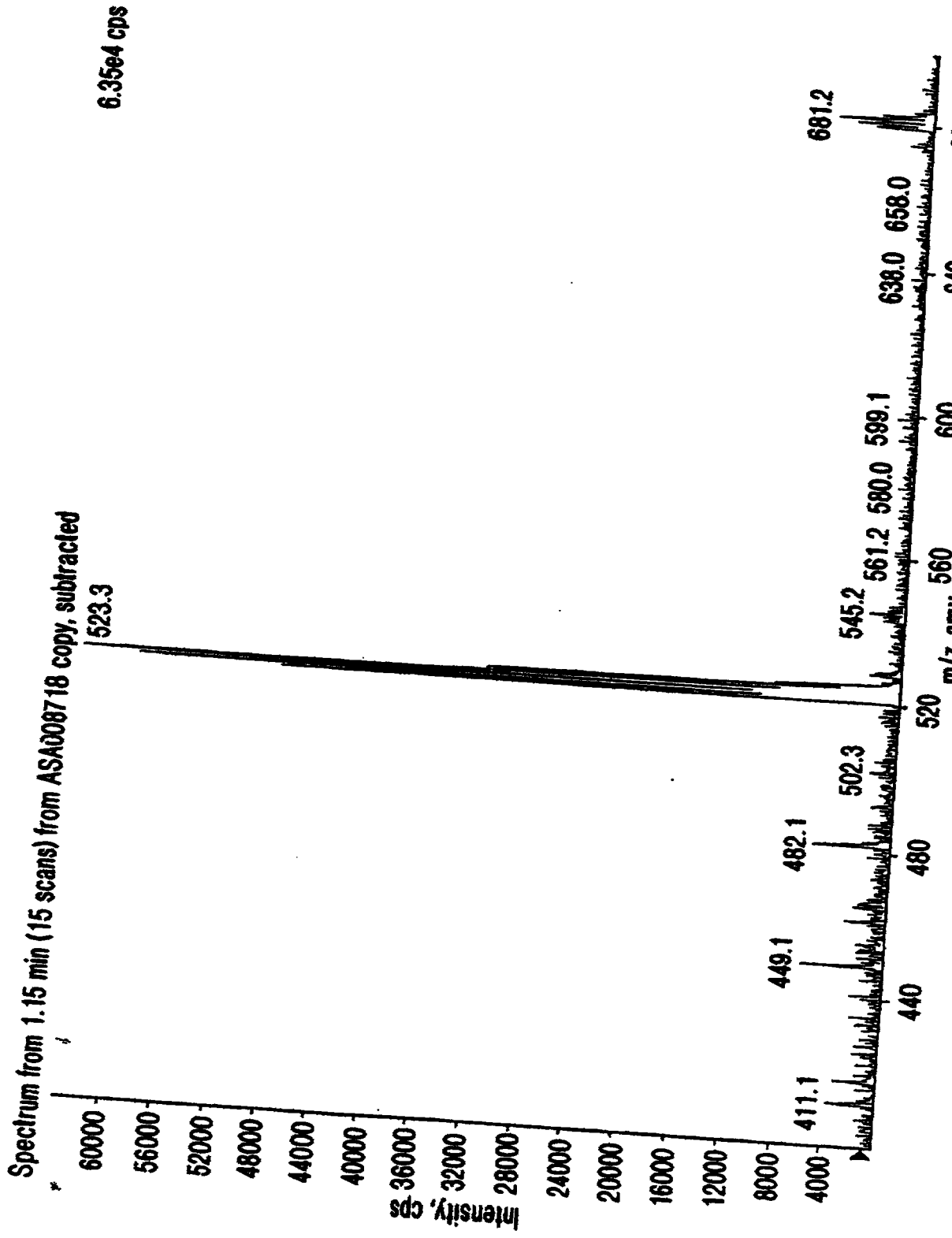

Spectrum from 1.15 min (15 scans) from ASA008718 copy, subtracted
6.35e4 cps
Intensity, cps
m/z, amu
523.3
545.2
561.2
580.0
599.1
638.0
658.0
681.2
502.3
482.1
449.1
411.1

FIG. 167

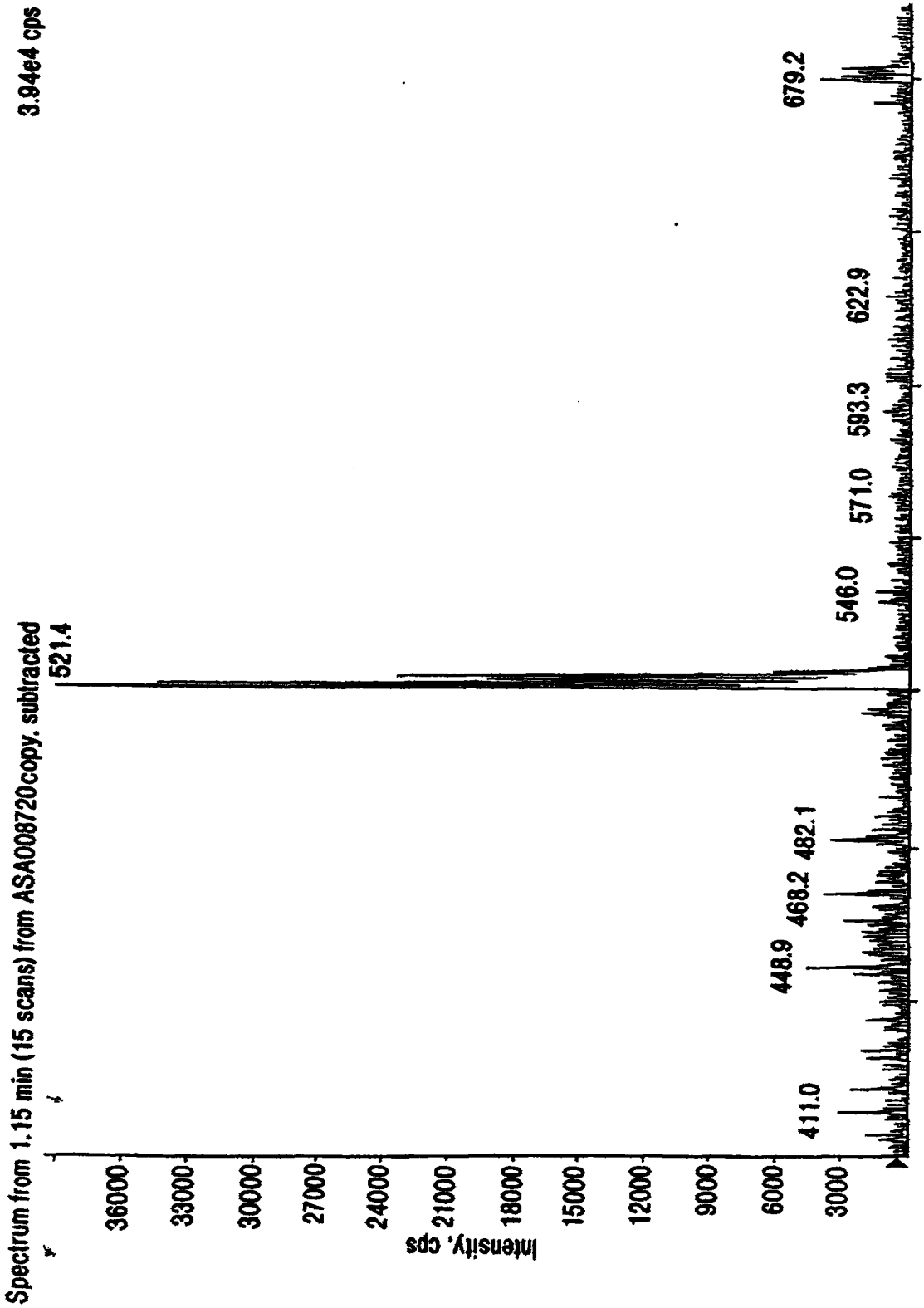

Spectrum from 1.15 min (15 scans) from ASA008720copy. subtracted
3.94e4 cps
Intensity, cps
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
521.4
411.0
448.9
468.2
482.1
546.0
571.0
593.3
622.9
679.2
440
480
520
560
600
640
680
m/z, amu

FIG. 168

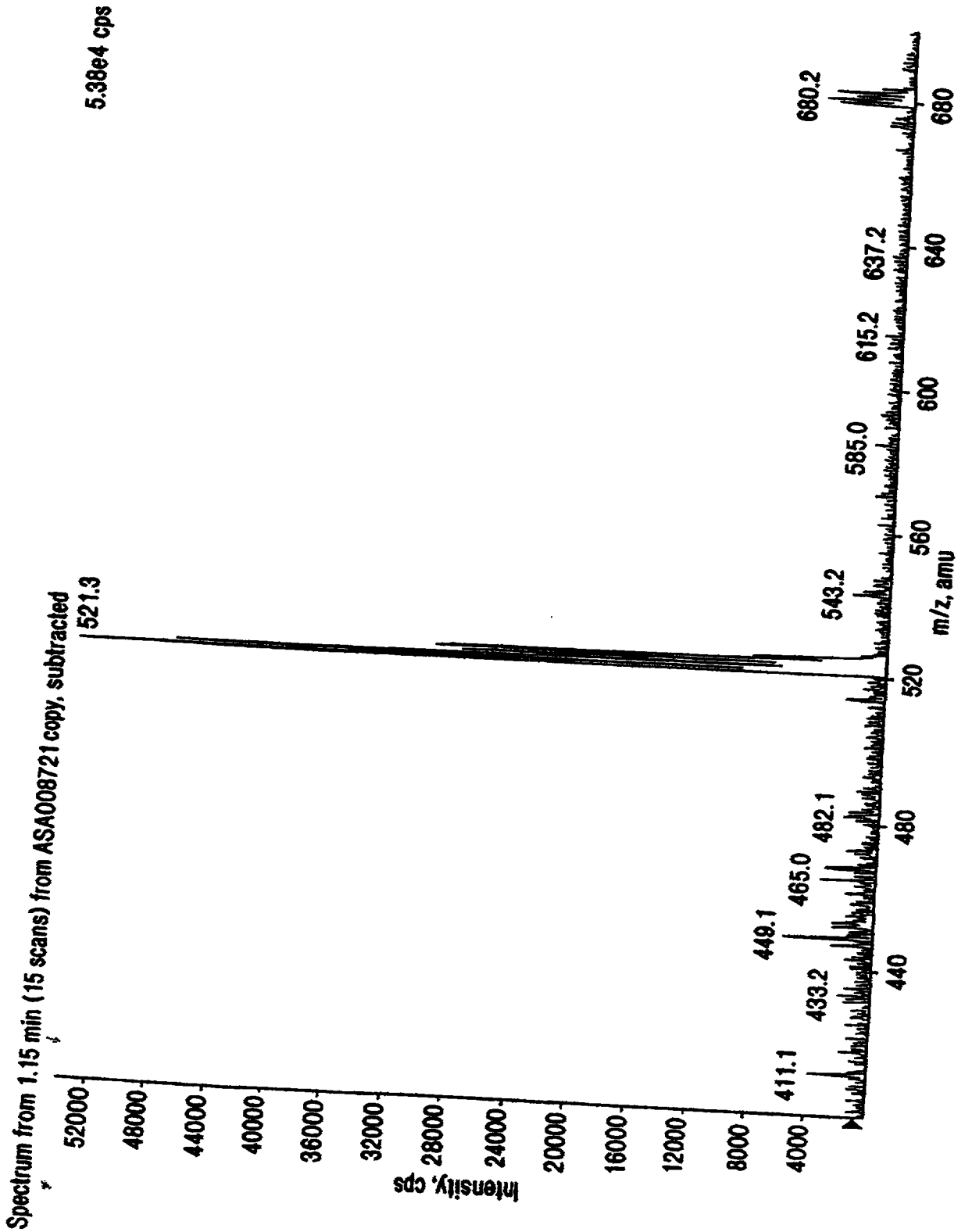

Spectrum from 1.15 min (15 scans) from ASA008721 copy, subtracted
5.38e4 cps
Intensity, cps
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
m/z, amu
411.1
433.2
449.1
465.0
482.1
521.3
543.2
585.0
615.2
637.2
680.2
440
480
520
560
600
640
680

FIG. 169

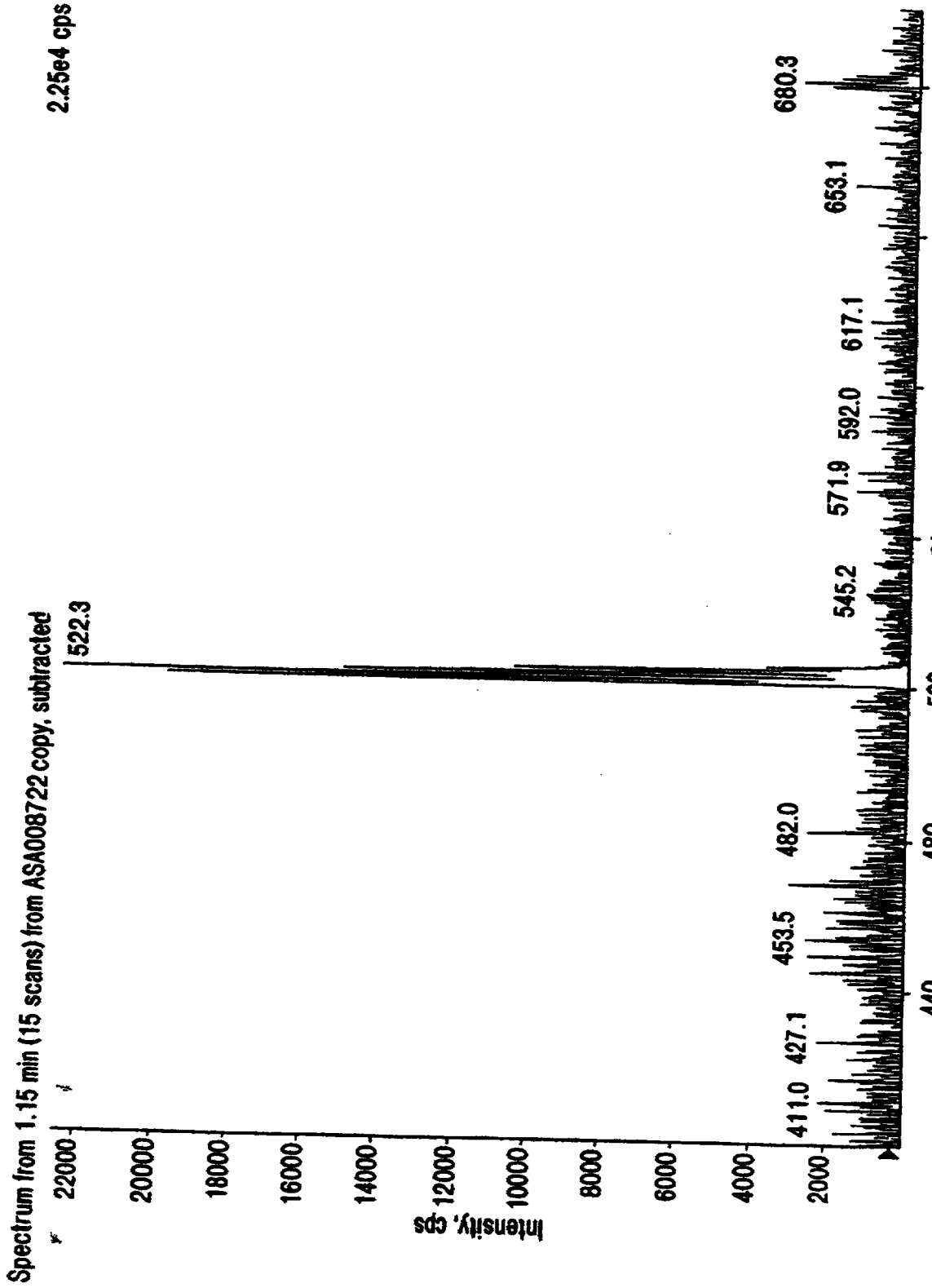

Spectrum from 1.15 min (15 scans) from ASA008722 copy, subtracted
2.25e4 cps
Intensity, cps
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
411.0
427.1
453.5
482.0
522.3
545.2
571.9
592.0
617.1
653.1
680.3
440
480
520
560
600
640
680
m/z, amu

FIG. 170

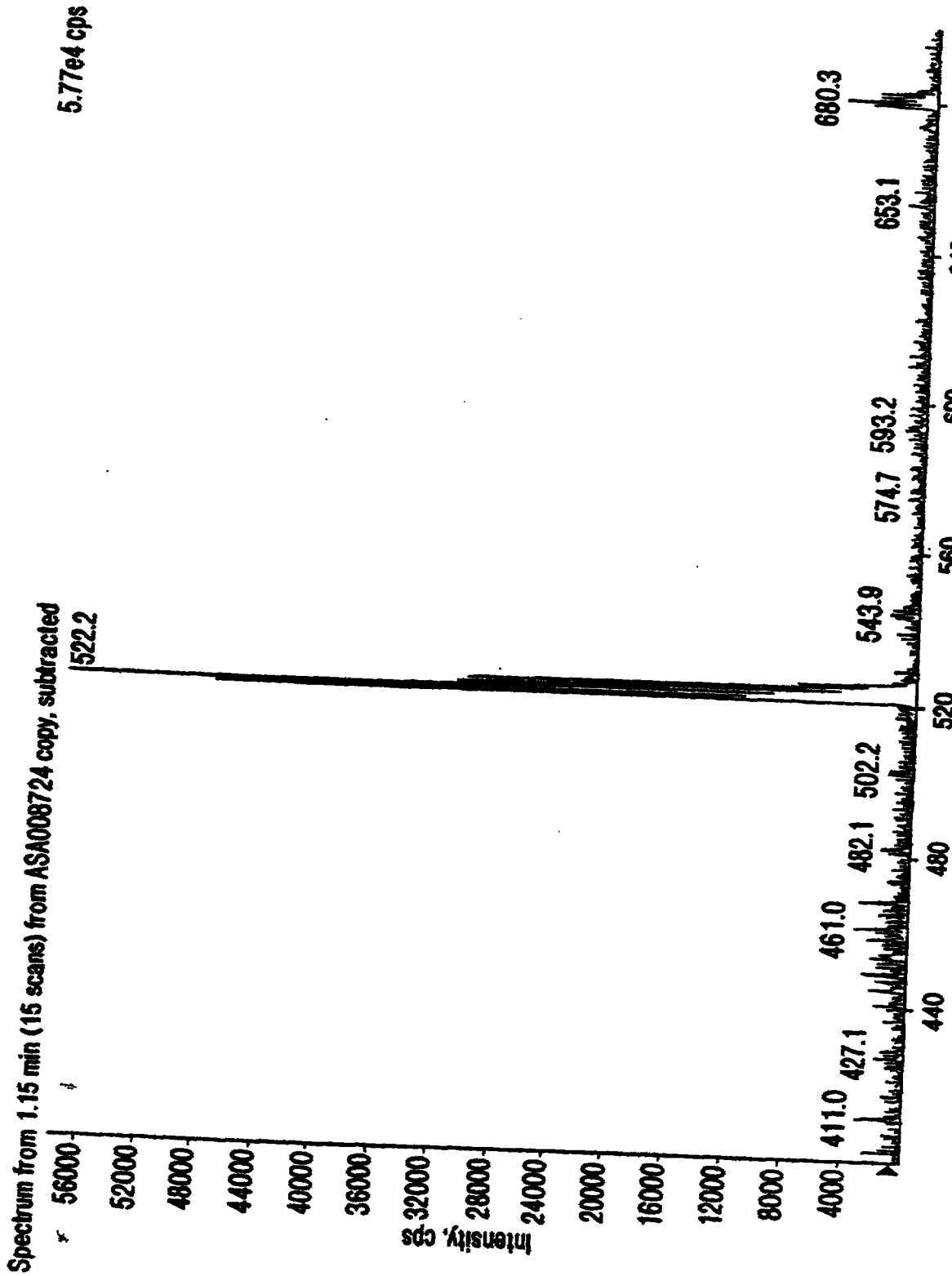

Spectrum from 1.15 min (15 scans) from ASA008724 copy, subtracted
5.77e4 cps
Intensity, cps
56000
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
411.0
427.1
461.0
482.1
502.2
522.2
543.9
574.7
593.2
653.1
680.3
440
480
520
560
600
640
680
m/z, amu

FIG. 171

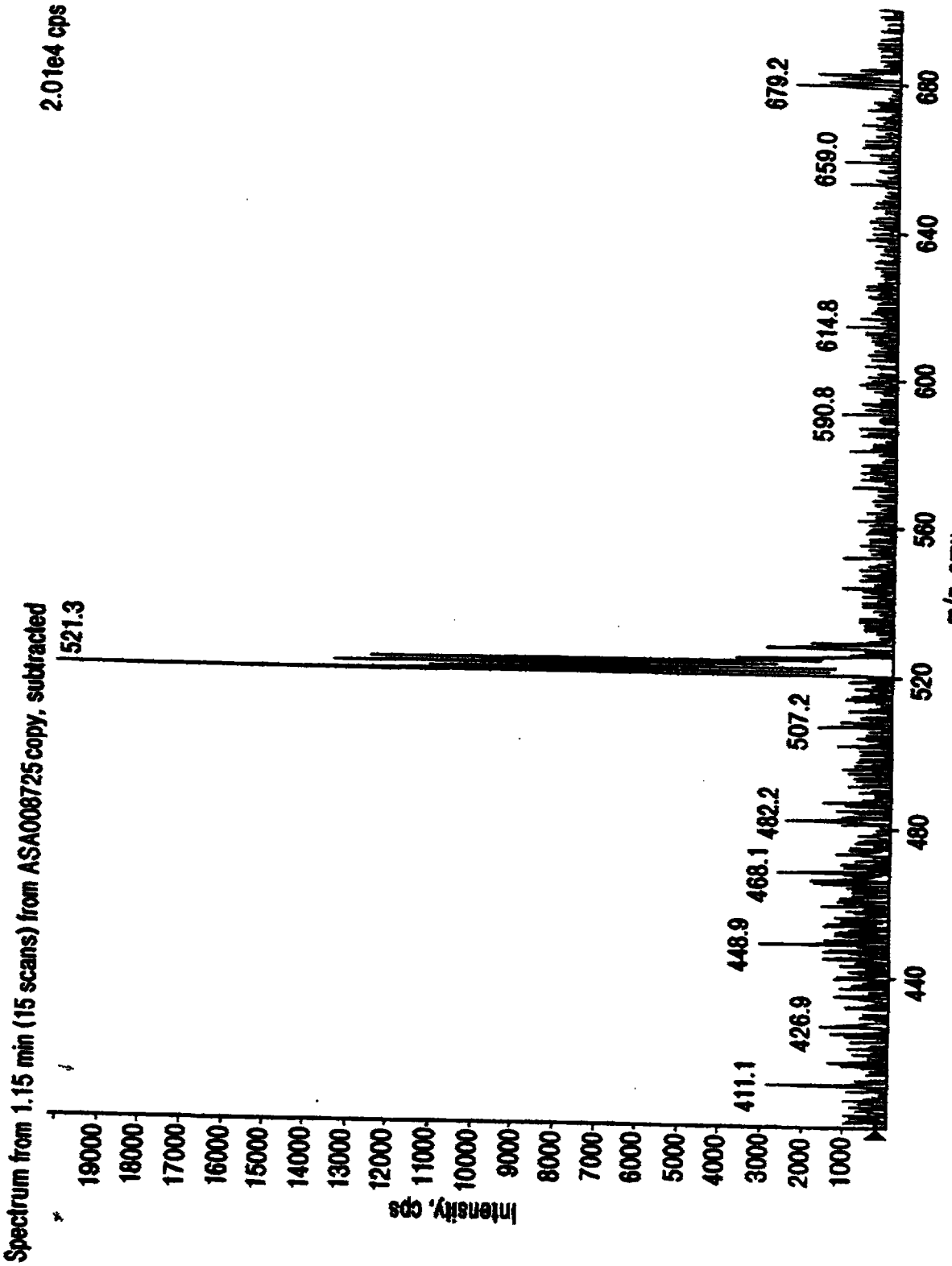

Spectrum from 1.15 min (15 scans) from ASA008725copy, subtracted
2.01e4 cps
Intensity, cps
m/z, amu
521.3
679.2
659.0
614.8
590.8
507.2
482.2
468.1
448.9
426.9
411.1

FIG. 172

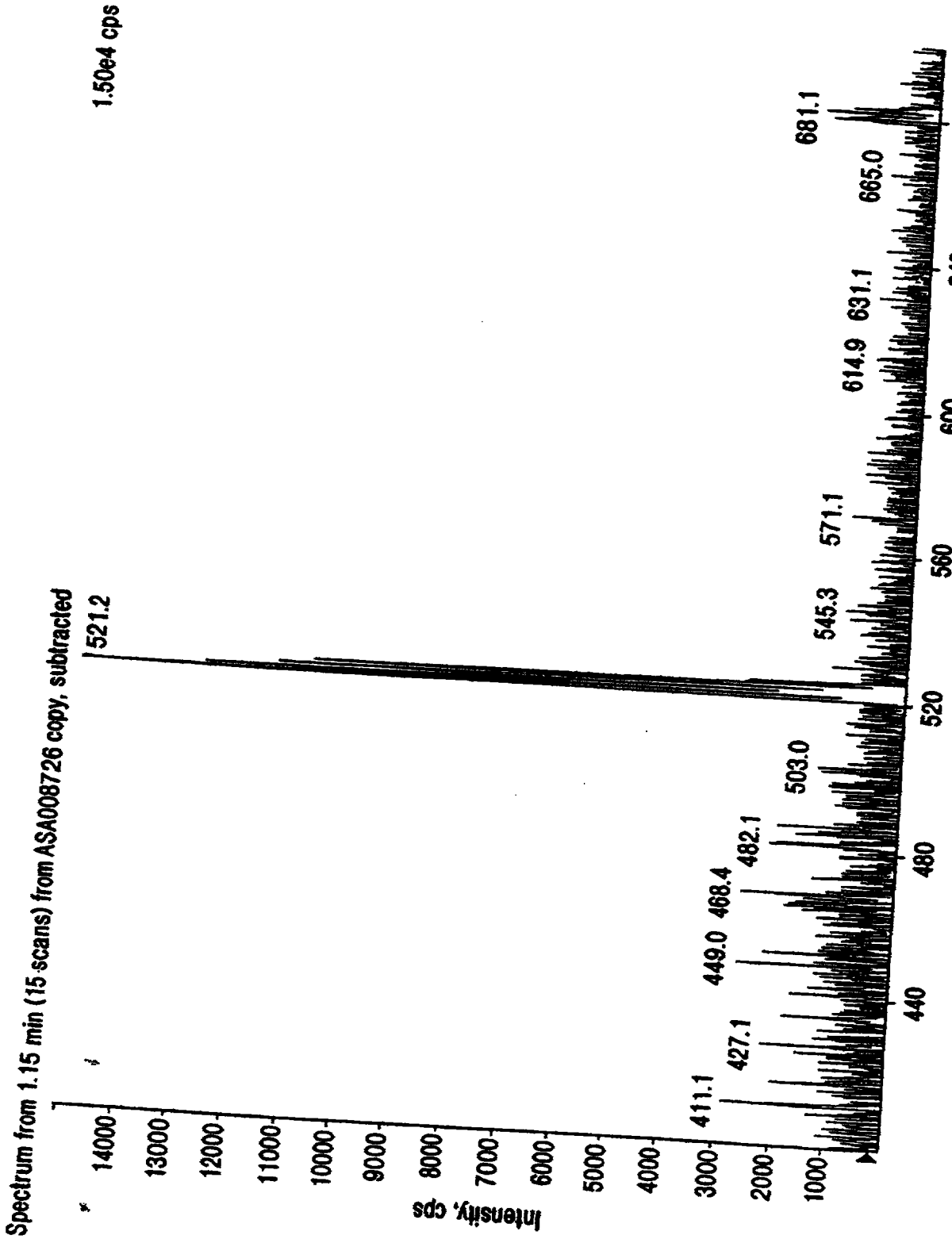

Spectrum from 1.15 min (15 scans) from ASA008726 copy, subtracted
1.50e4 cps
Intensity, cps
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
521.2
545.3
571.1
614.9
631.1
665.0
681.1
411.1
427.1
449.0
468.4
482.1
503.0
440
480
520
560
600
640
680
m/z, amu

FIG. 173

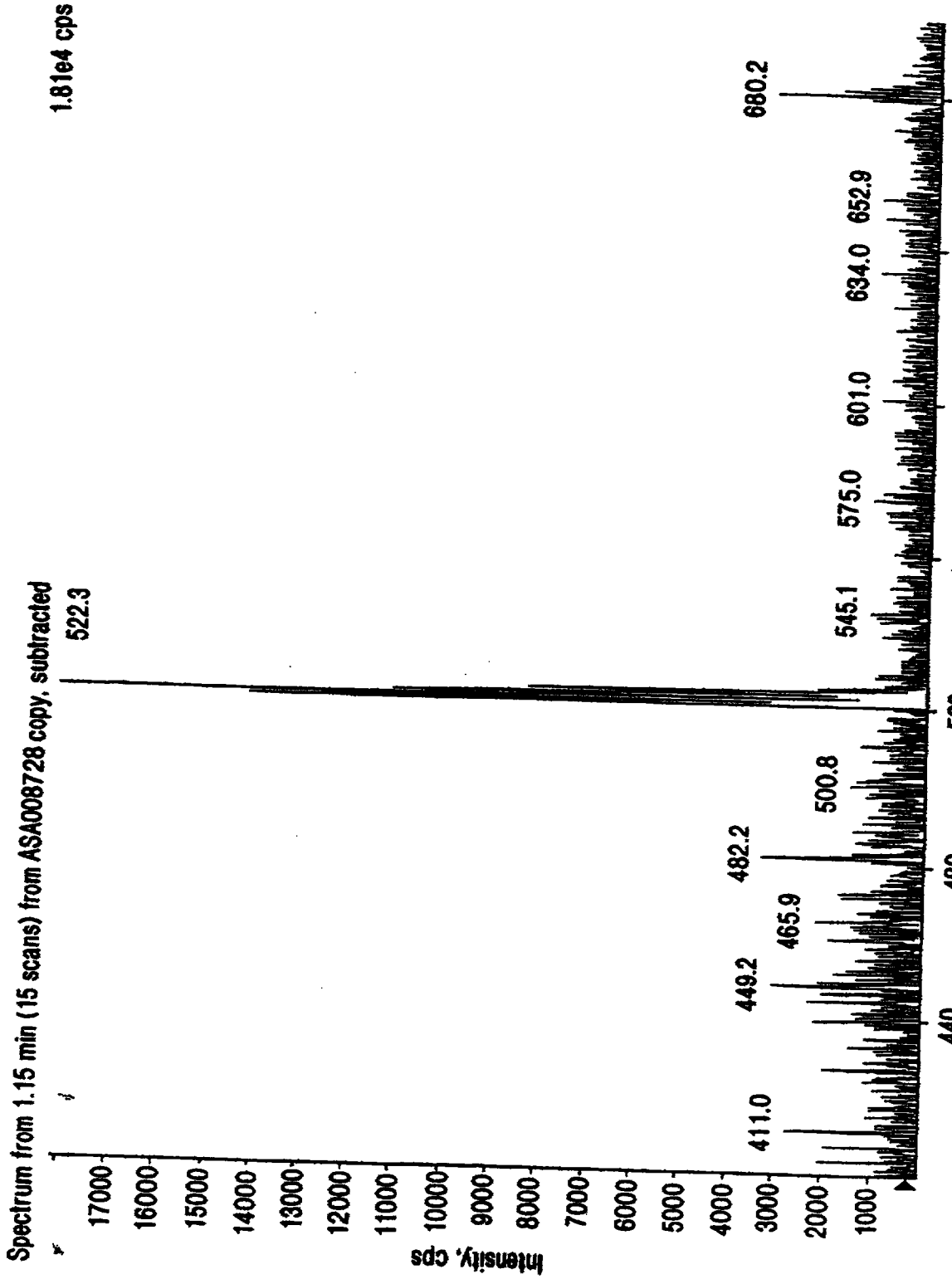

Spectrum from 1.15 min (15 scans) from ASA008728 copy, subtracted
1.81e4 cps
Intensity, cps
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
411.0
449.2
465.9
482.2
500.8
522.3
545.1
575.0
601.0
634.0
652.9
680.2
440
480
520
560
600
640
680
m/z, amu

FIG.174

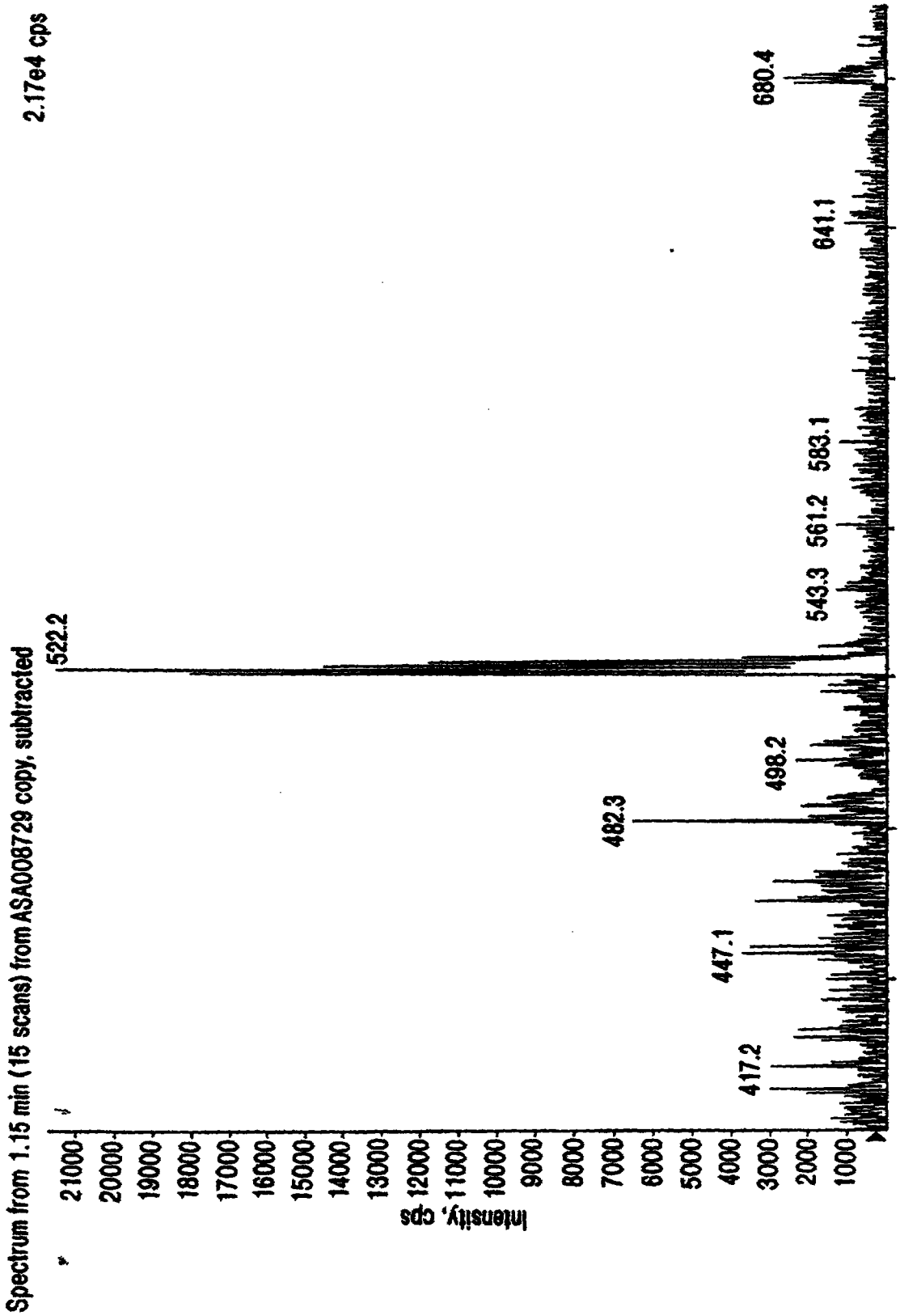

Spectrum from 1.15 min (15 scans) from ASA008729 copy, subtracted
2.17e4 cps
Intensity, cps
m/z, amu
522.2
482.3
498.2
447.1
417.2
543.3
561.2
583.1
641.1
680.4

FIG. 175

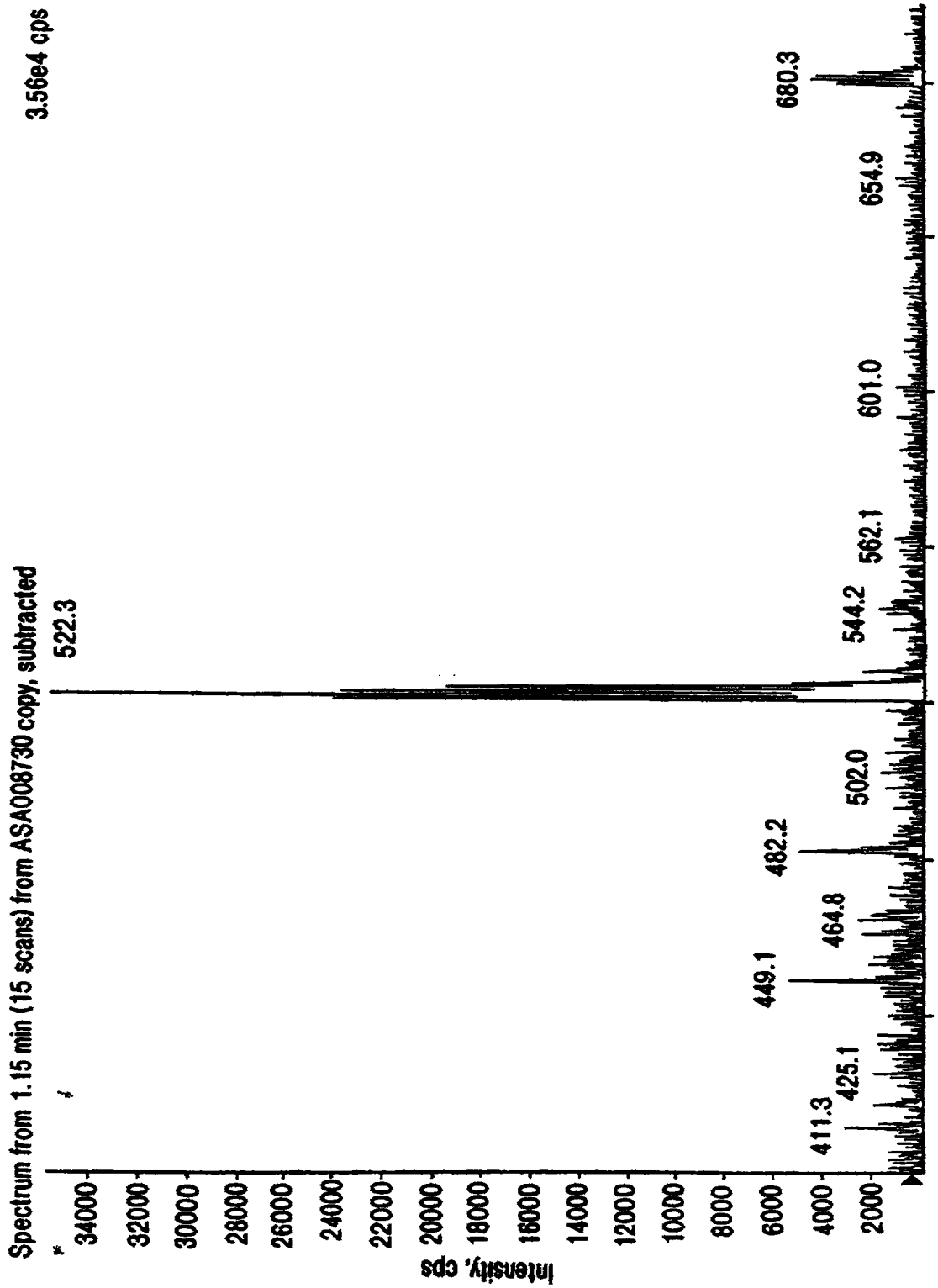

Spectrum from 1.15 min (15 scans) from ASA008730 copy, subtracted
3.56e4 cps
Intensity, cps
m/z, amu
522.3
544.2
562.1
601.0
654.9
680.3
502.0
482.2
464.8
449.1
425.1
411.3

FIG. 176

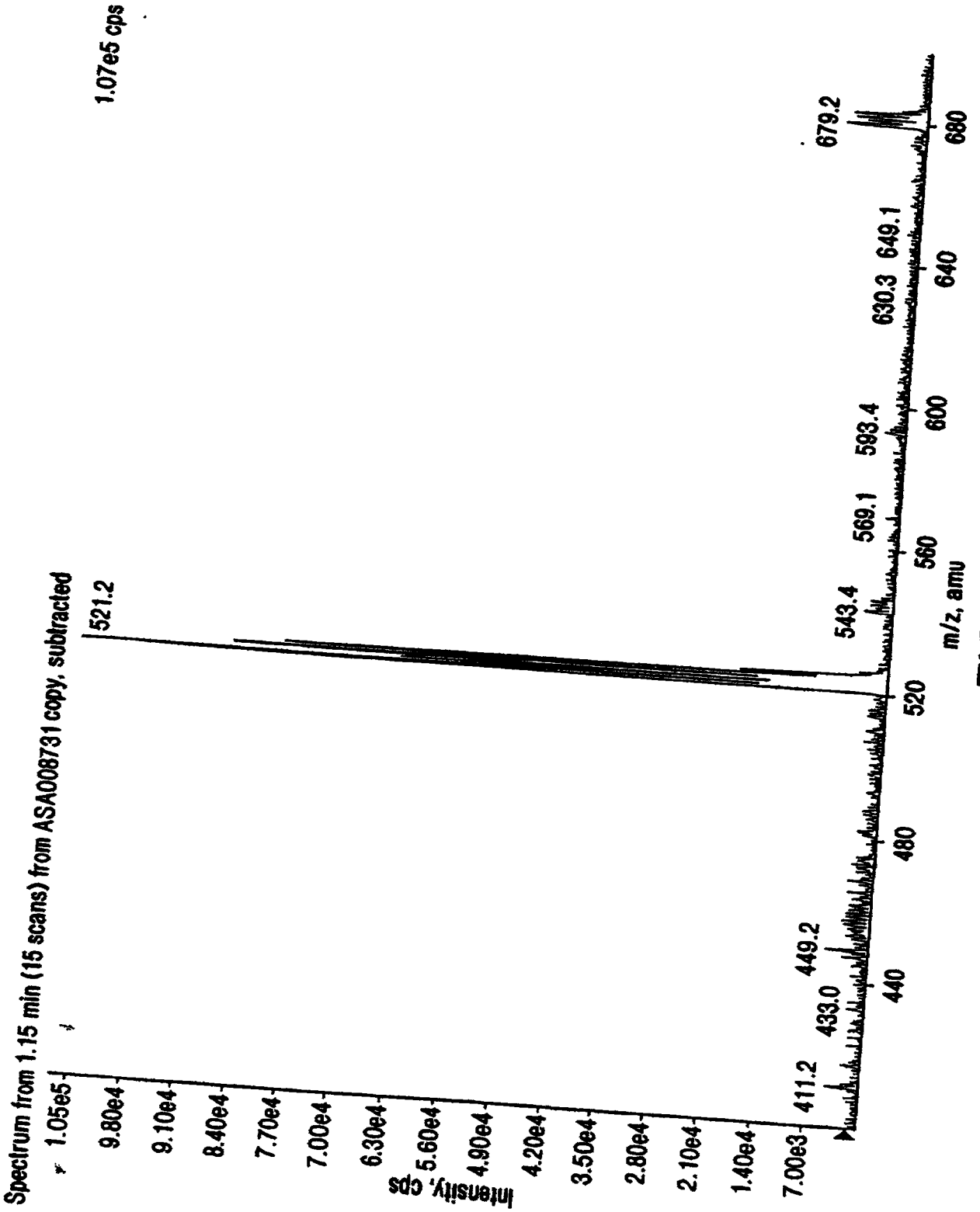

Spectrum from 1.15 min (15 scans) from ASA008731 copy, subtracted
1.07e5 cps
Intensity, cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
411.2
433.0
449.2
521.2
543.4
569.1
593.4
630.3
649.1
679.2
440
480
520
560
600
640
680
m/z, amu

FIG. 177

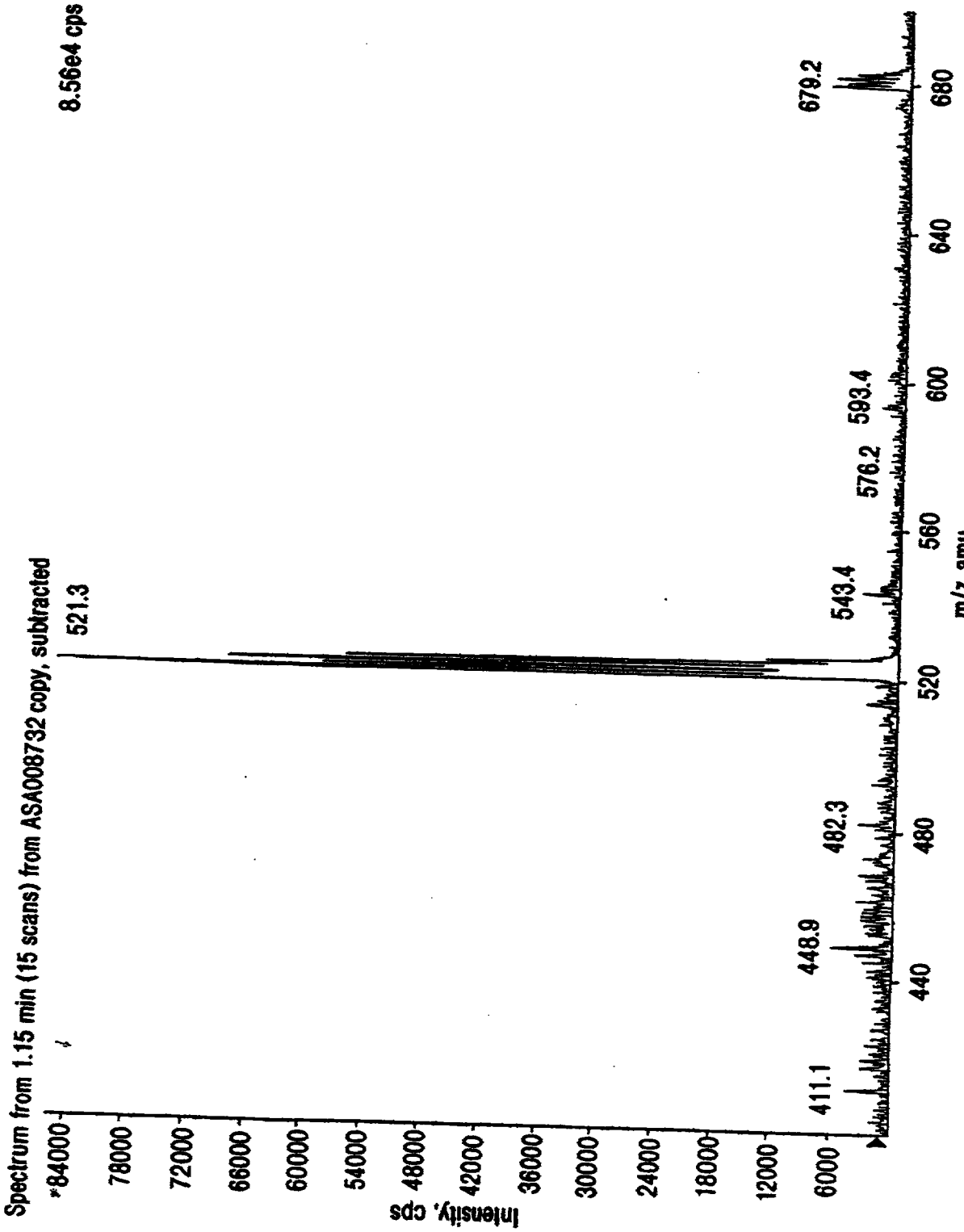

Spectrum from 1.15 min (15 scans) from ASA008732 copy, subtracted
8.56e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
m/z, amu
440
480
520
560
600
640
680
411.1
448.9
482.3
521.3
543.4
576.2
593.4
679.2

FIG. 178

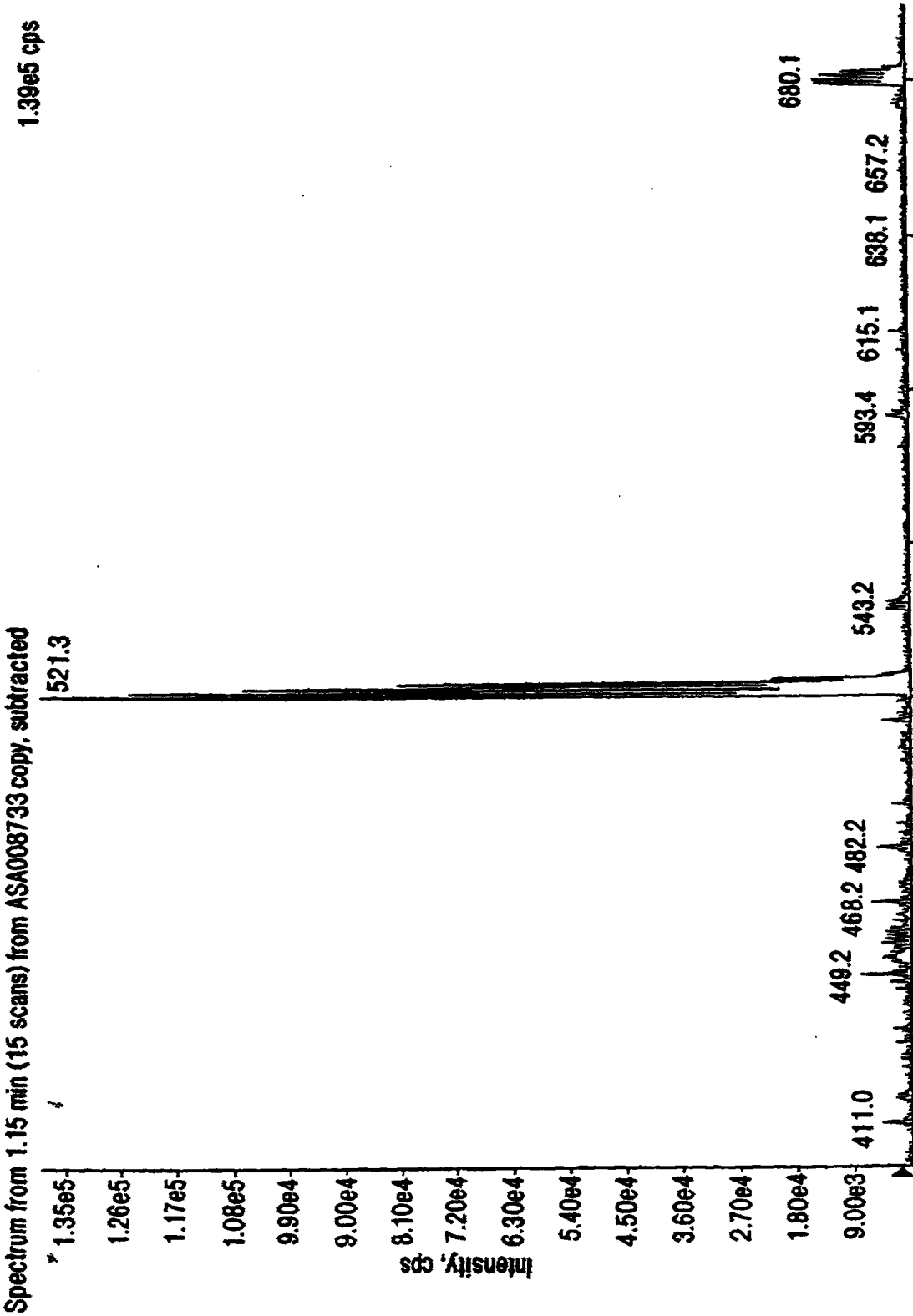

Spectrum from 1.15 min (15 scans) from ASA008733 copy, subtracted
1.39e5 cps
Intensity, cps
1.35e5
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.0
449.2
468.2
482.2
521.3
543.2
583.4
615.1
638.1
657.2
680.1
440
480
520
560
600
640
680
m/z, amu

FIG. 179

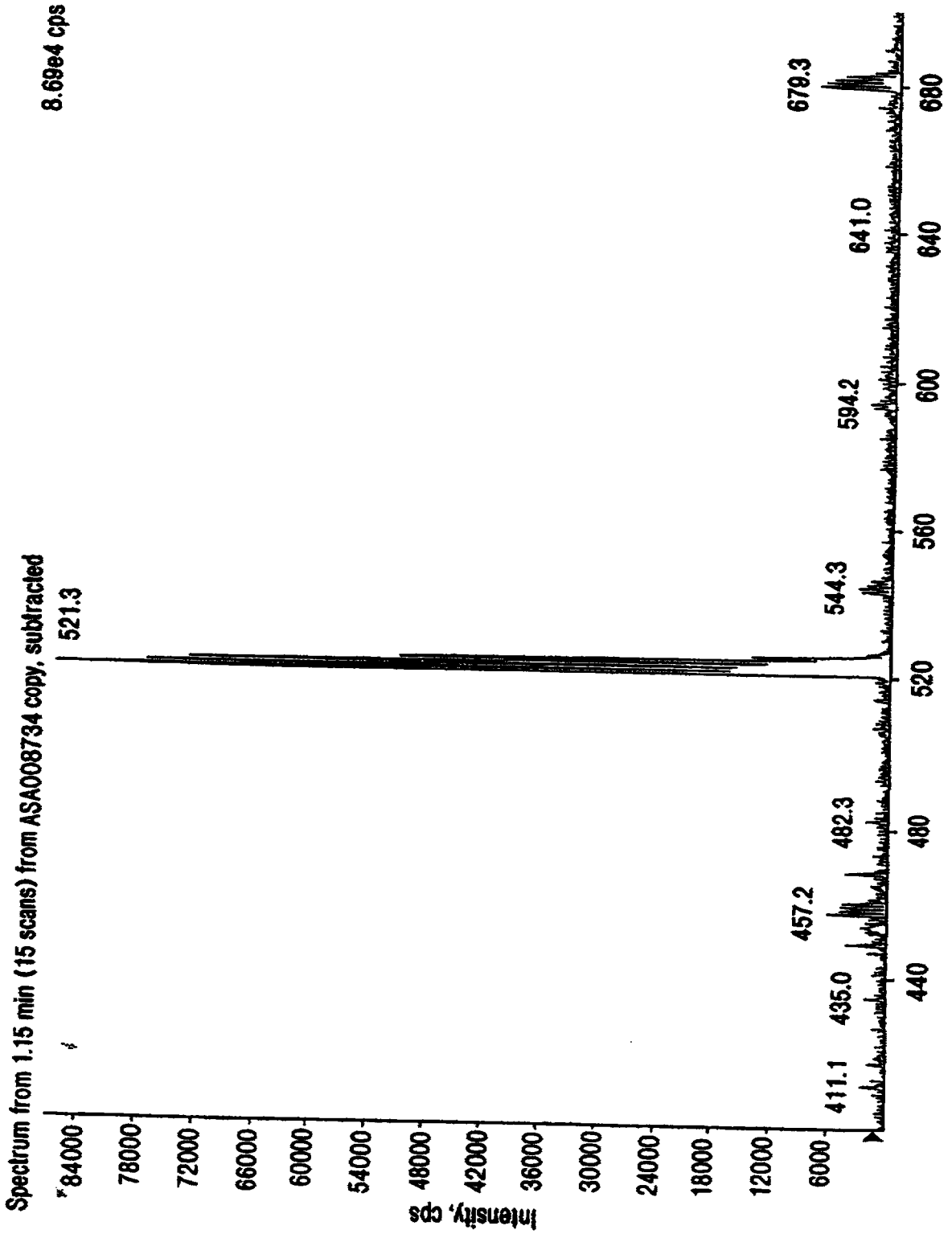

Spectrum from 1.15 min (15 scans) from ASA008734 copy, subtracted
8.69e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.1
435.0
457.2
482.3
521.3
544.3
594.2
641.0
679.3
440
480
520
560
600
640
680
m/z, amu

FIG. 180

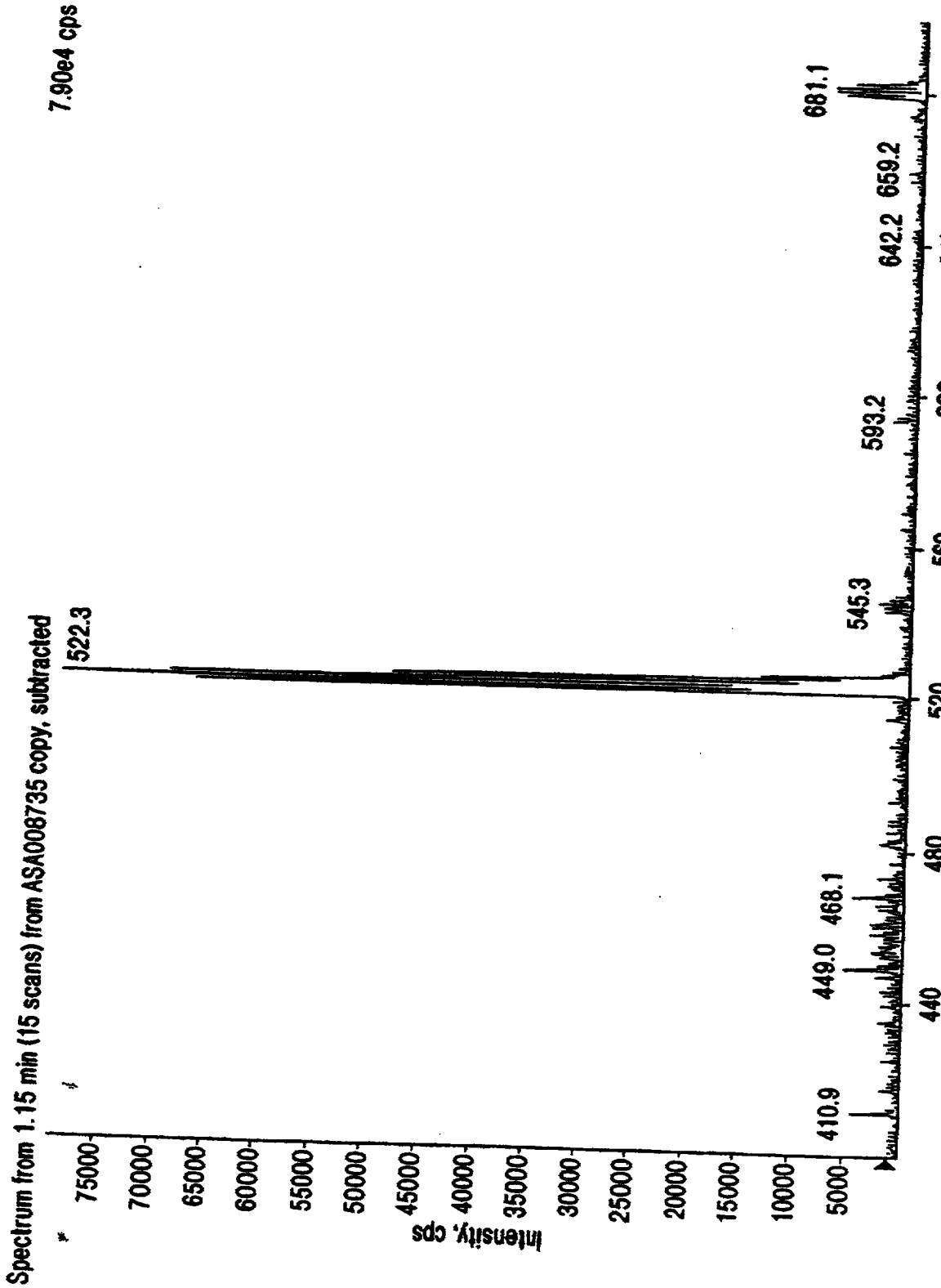

Spectrum from 1.15 min (15 scans) from ASA008735 copy, subtracted
7.90e4 cps
Intensity, cps
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
m/z, amu
440
480
520
560
600
640
680
410.9
449.0
468.1
522.3
545.3
593.2
642.2
659.2
681.1

FIG. 181

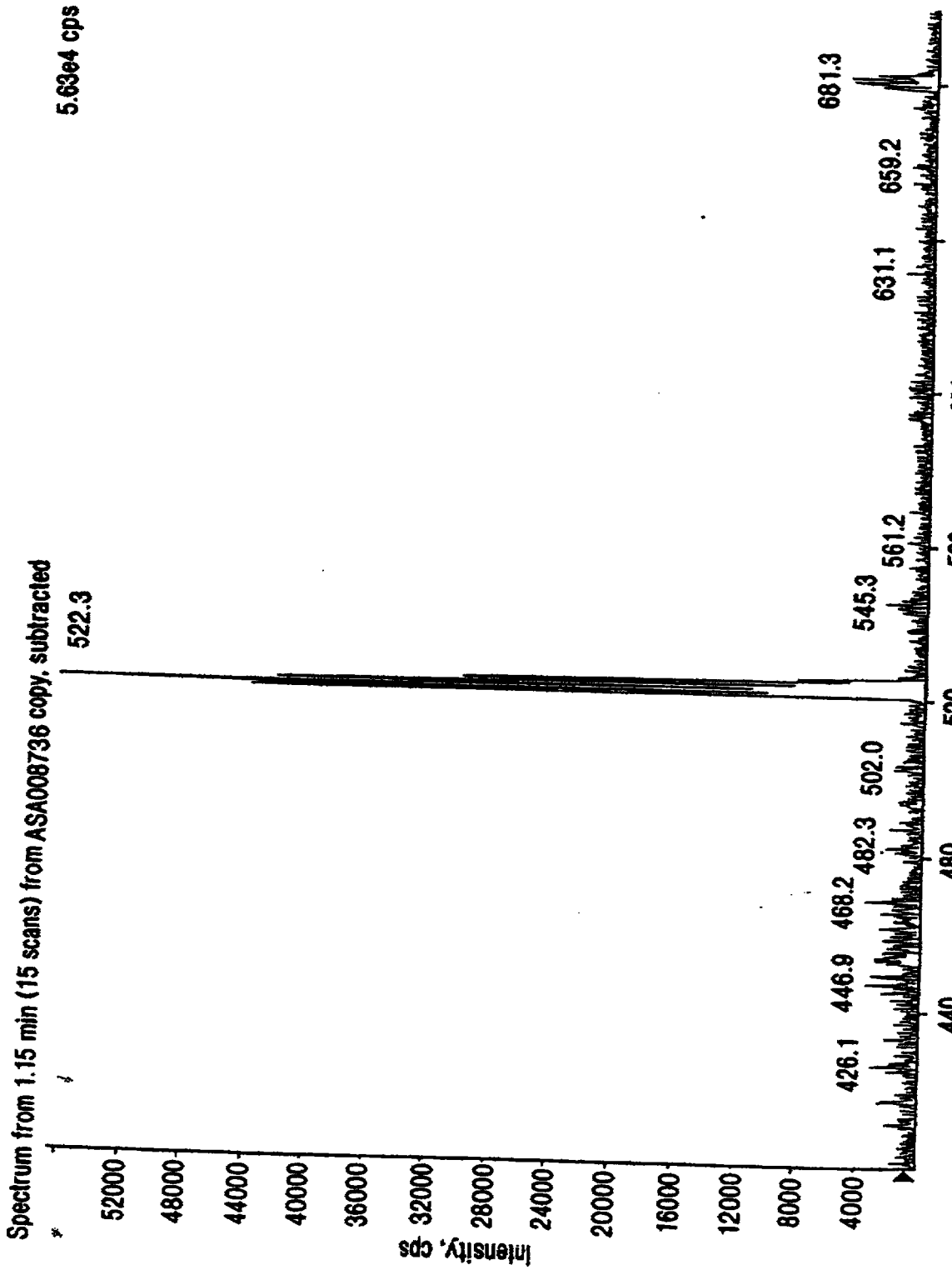

Spectrum from 1.15 min (15 scans) from ASA008736 copy, subtracted
5.63e4 cps
Intensity, cps
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
m/z, amu
440
480
520
560
600
640
680
426.1
446.9
468.2
482.3
502.0
522.3
545.3
561.2
631.1
659.2
681.3

FIG. 182

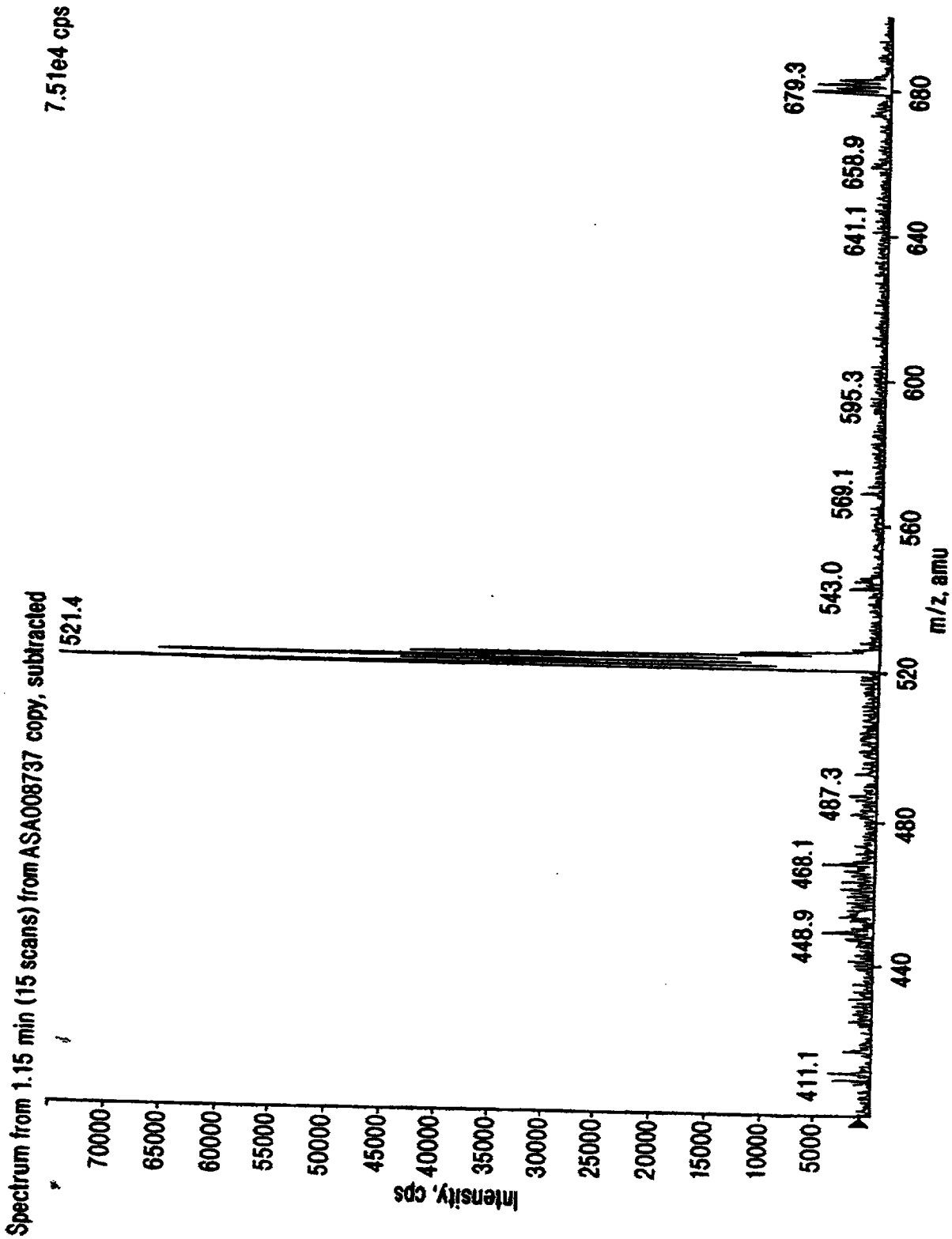

Spectrum from 1.15 min (15 scans) from ASA008737 copy, subtracted
7.51e4 cps
Intensity, cps
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
m/z, amu
411.1
448.9
468.1
487.3
521.4
543.0
569.1
595.3
641.1
658.9
679.3
440
480
520
560
600
640
680

FIG. 183

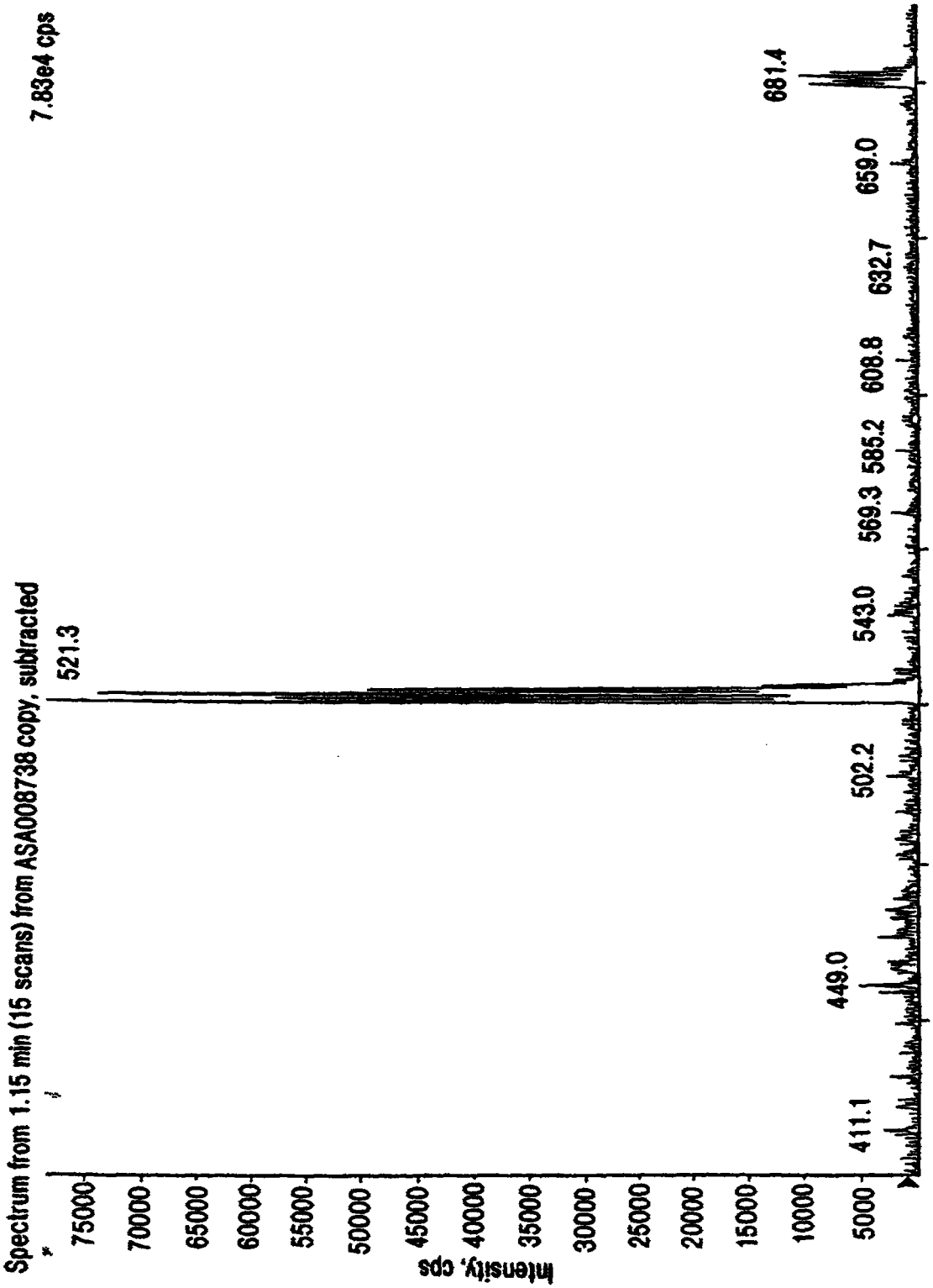

Spectrum from 1.15 min (15 scans) from ASA008738 copy, subtracted
7.83e4 cps
Intensity, cps
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
411.1
449.0
502.2
521.3
543.0
569.3
585.2
608.8
632.7
659.0
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 184

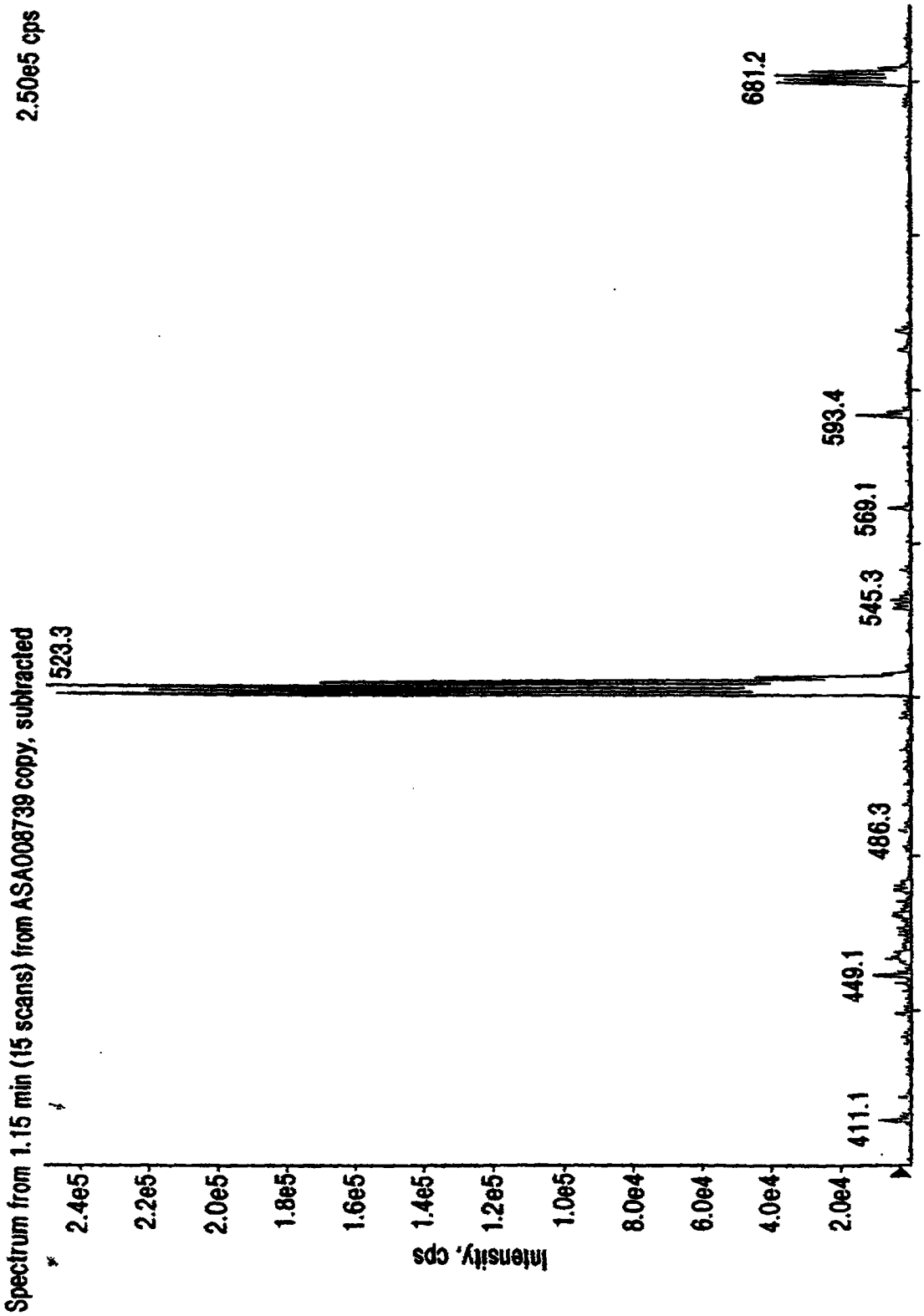

Spectrum from 1.15 min (15 scans) from ASA008739 copy, subtracted
2.50e5 cps
Intensity, cps
2.4e5
2.2e5
2.0e5
1.8e5
1.6e5
1.4e5
1.2e5
1.0e5
8.0e4
6.0e4
4.0e4
2.0e4
411.1
449.1
486.3
523.3
545.3
569.1
593.4
681.2
440
480
520
560
600
640
680
m/z, amu

FIG. 185

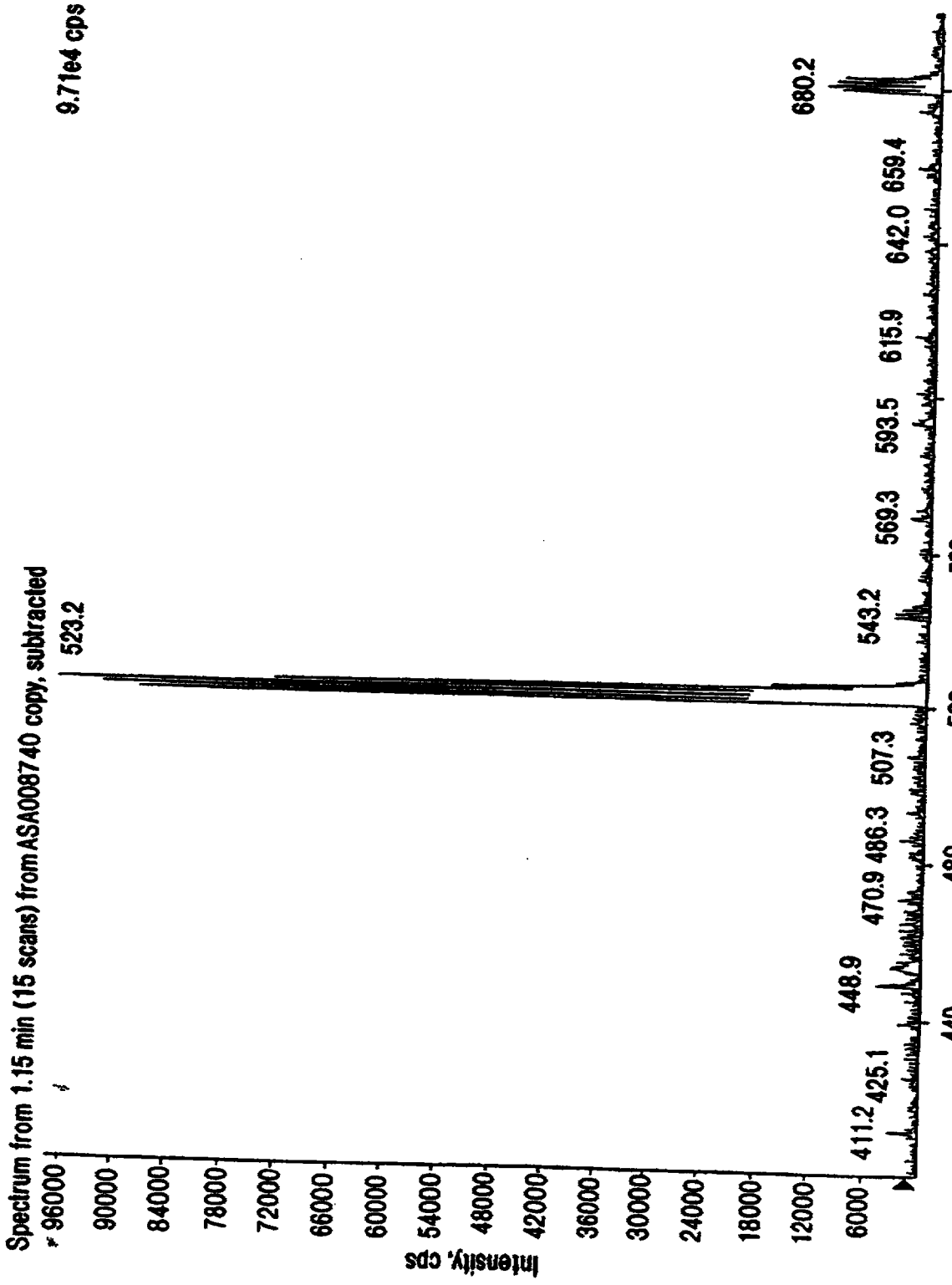

Spectrum from 1.15 min (15 scans) from ASA008740 copy, subtracted
9.71e4 cps
Intensity, cps
m/z, amu
523.2
543.2
569.3
593.5
615.9
642.0
659.4
680.2
411.2
425.1
448.9
470.9
486.3
507.3

FIG. 186

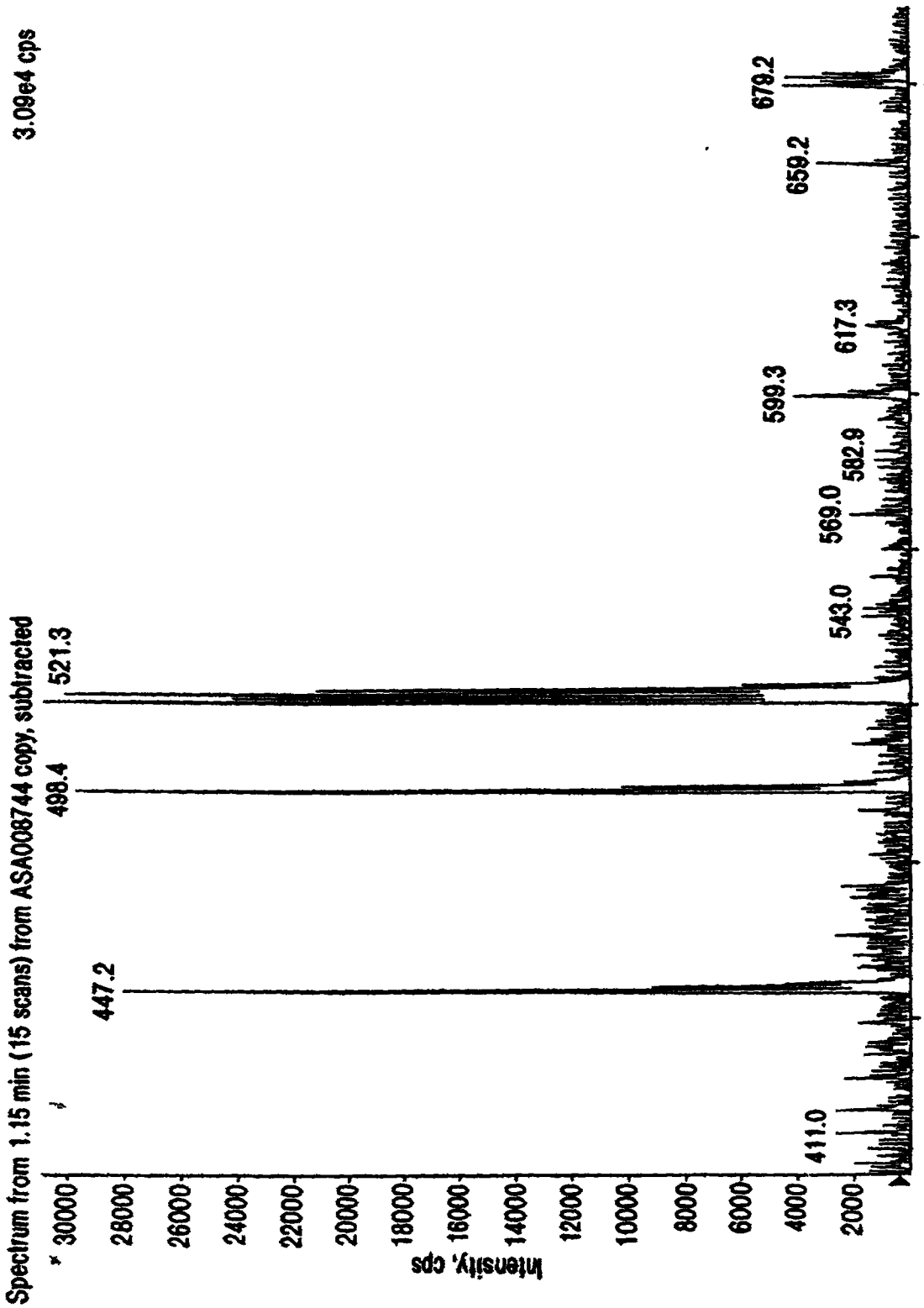

Spectrum from 1.15 min (15 scans) from ASA008744 copy, subtracted
3.09e4 cps
Intensity, cps
m/z, amu
521.3
498.4
447.2
411.0
543.0
569.0
582.9
599.3
617.3
659.2
678.2

FIG. 187

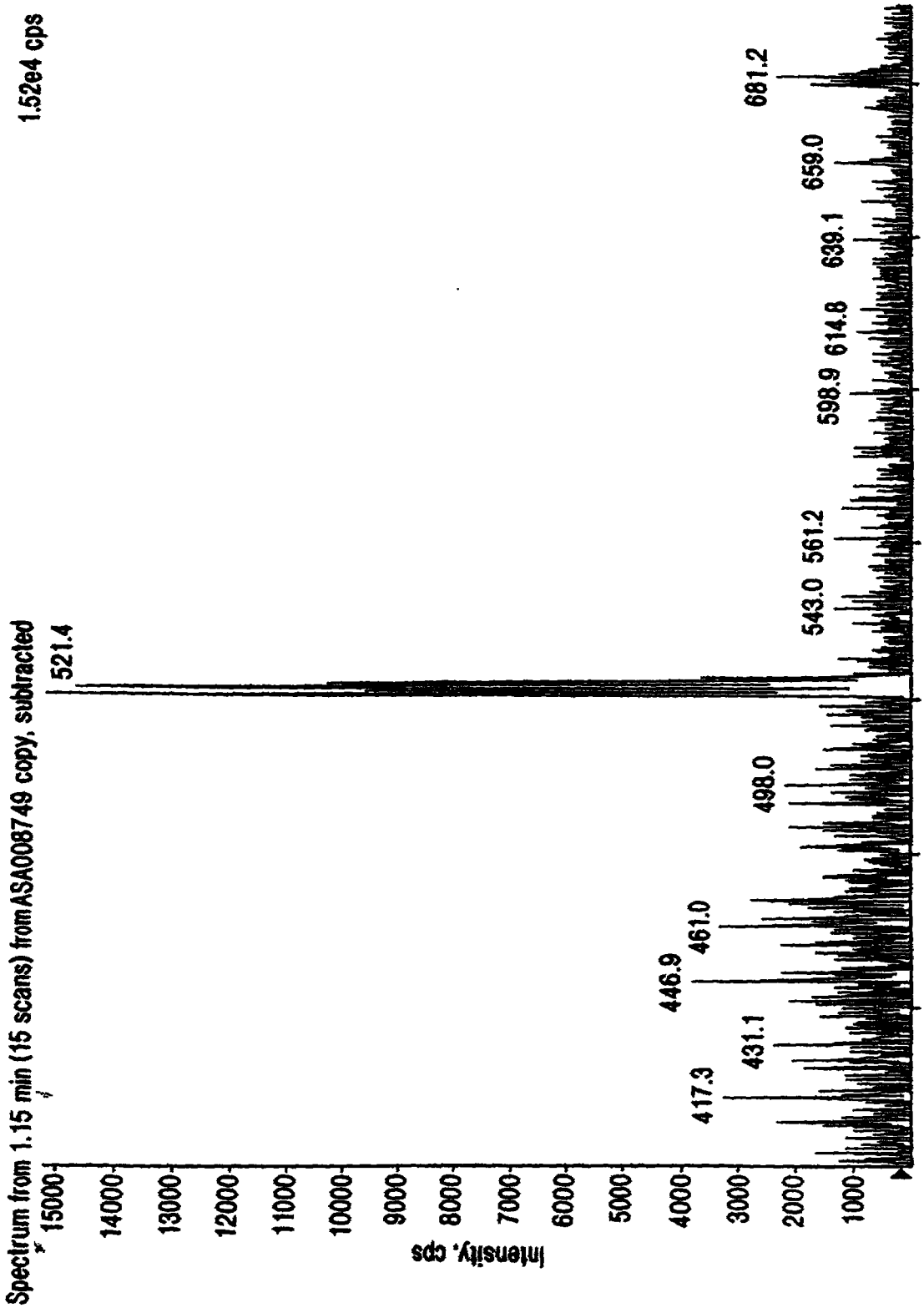

Spectrum from 1.15 min (15 scans) from ASA008749 copy, subtracted
1.52e4 cps
Intensity, cps
m/z, amu
521.4
543.0
561.2
598.9
614.8
639.1
659.0
681.2
498.0
461.0
446.9
431.1
417.3

FIG. 188

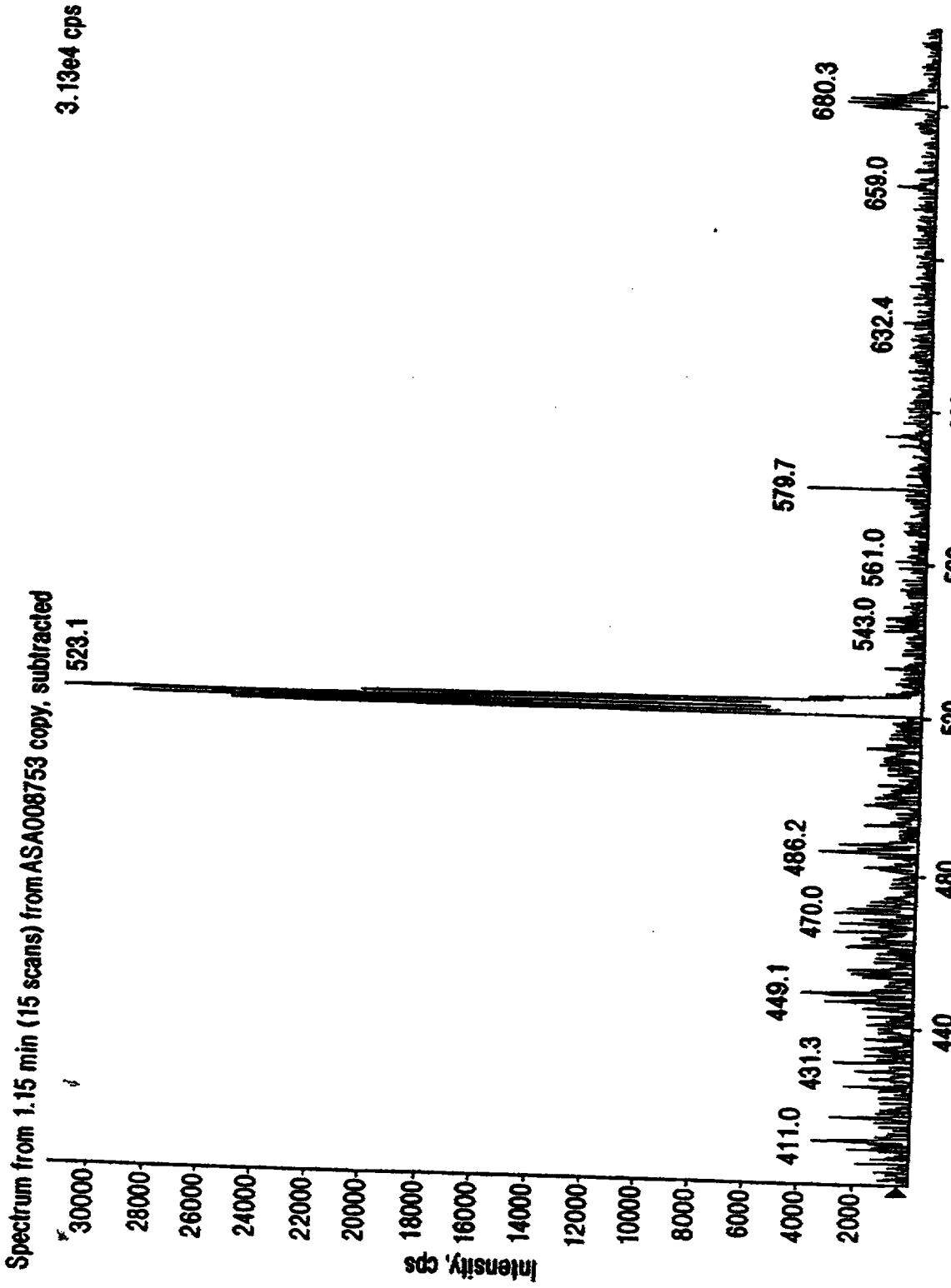

Spectrum from 1.15 min (15 scans) from ASA008753 copy, subtracted
3.13e4 cps
Intensity, cps
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
523.1
543.0
561.0
579.7
632.4
659.0
680.3
411.0
431.3
449.1
470.0
486.2
440
480
520
560
600
640
680
m/z, amu

FIG. 189

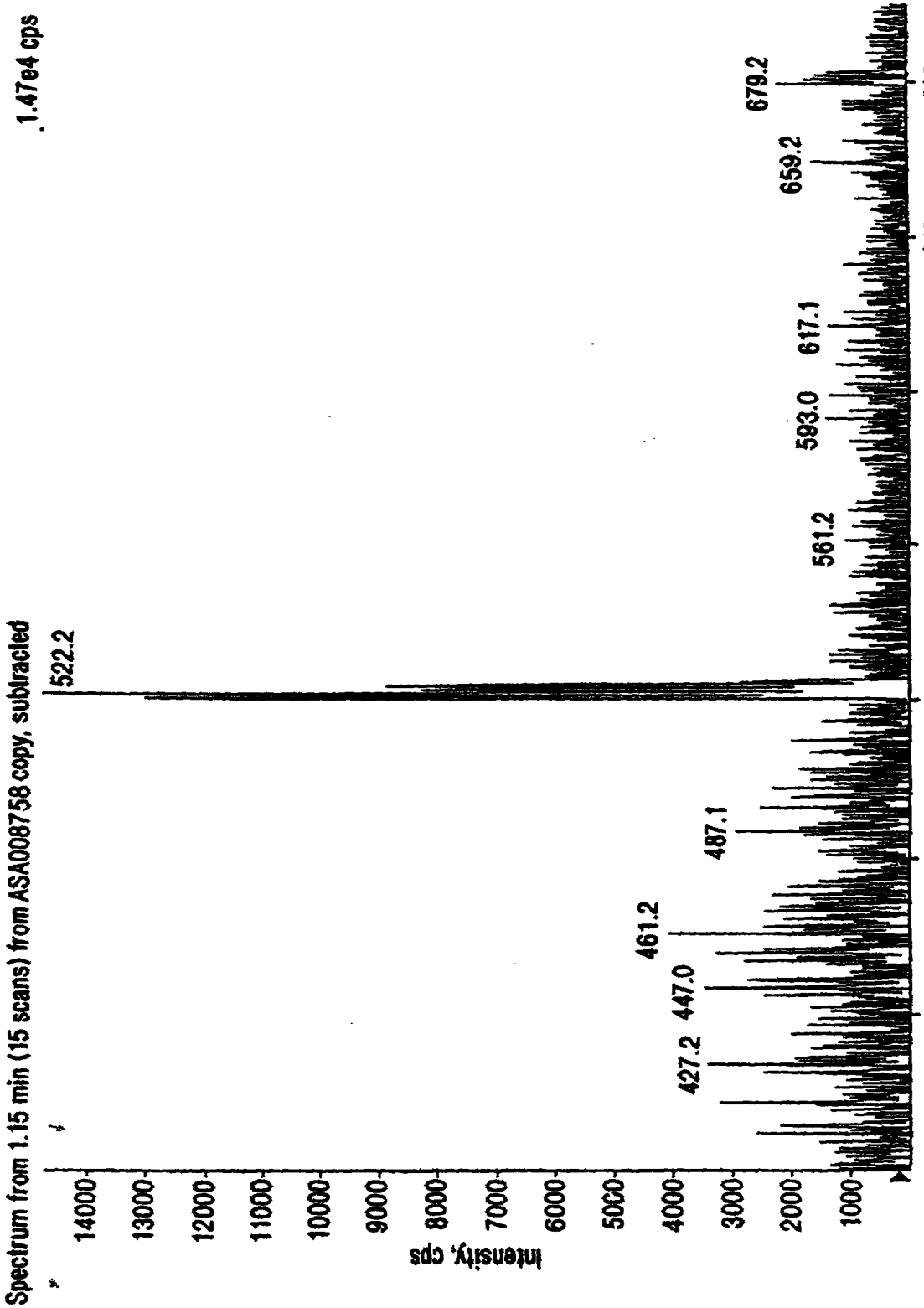

Spectrum from 1.15 min (15 scans) from ASA008758 copy, subtracted
1.47e4 cps
Intensity, cps
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
m/z, amu
440
480
520
560
600
640
680
522.2
561.2
583.0
617.1
659.2
679.2
461.2
487.1
427.2
447.0

FIG. 190

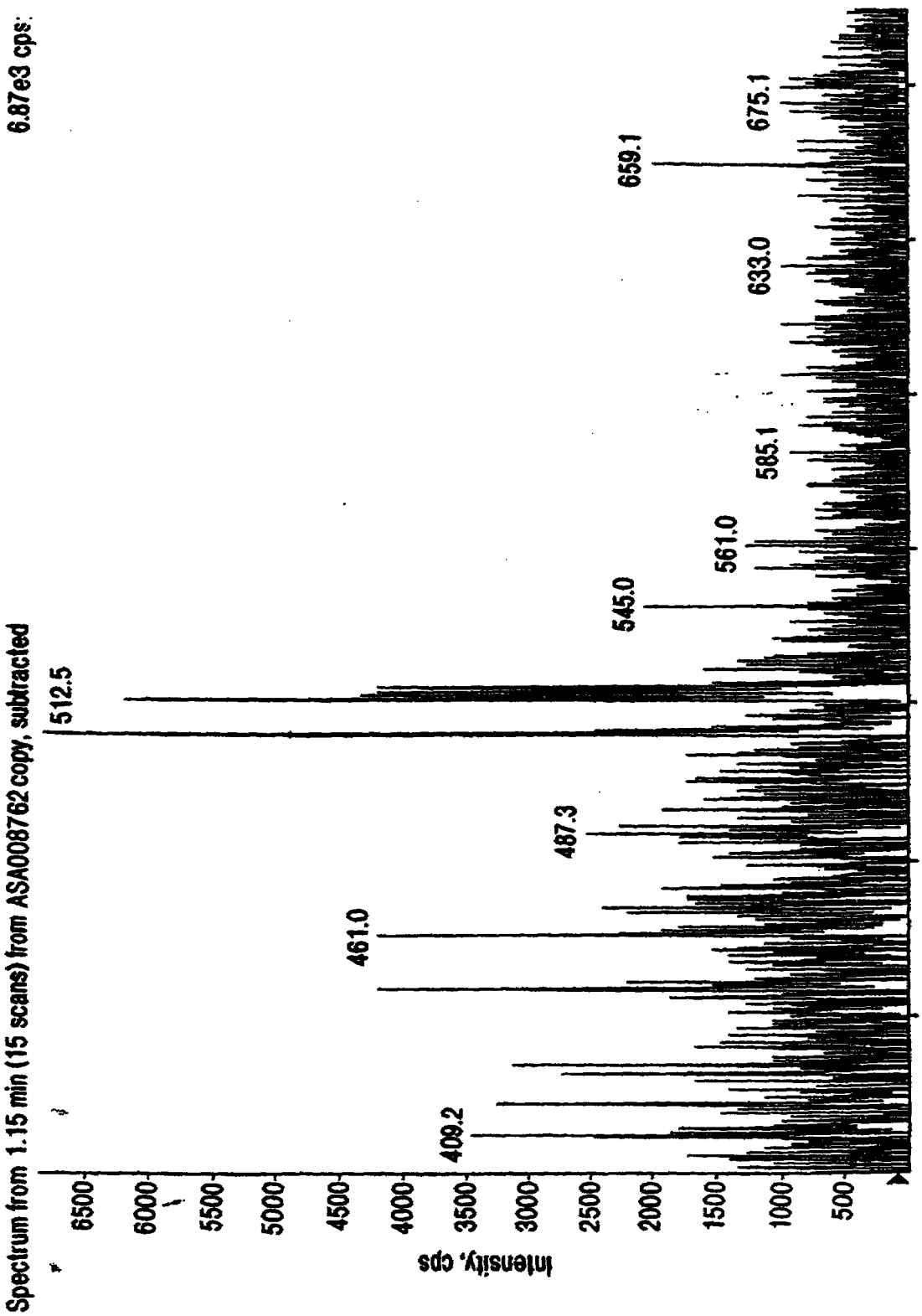

Spectrum from 1.15 min (15 scans) from ASA008762 copy, subtracted
6.87e3 cps
Intensity, cps
m/z, amu
512.5
545.0
561.0
585.1
633.0
659.1
675.1
461.0
487.3
409.2

FIG. 191

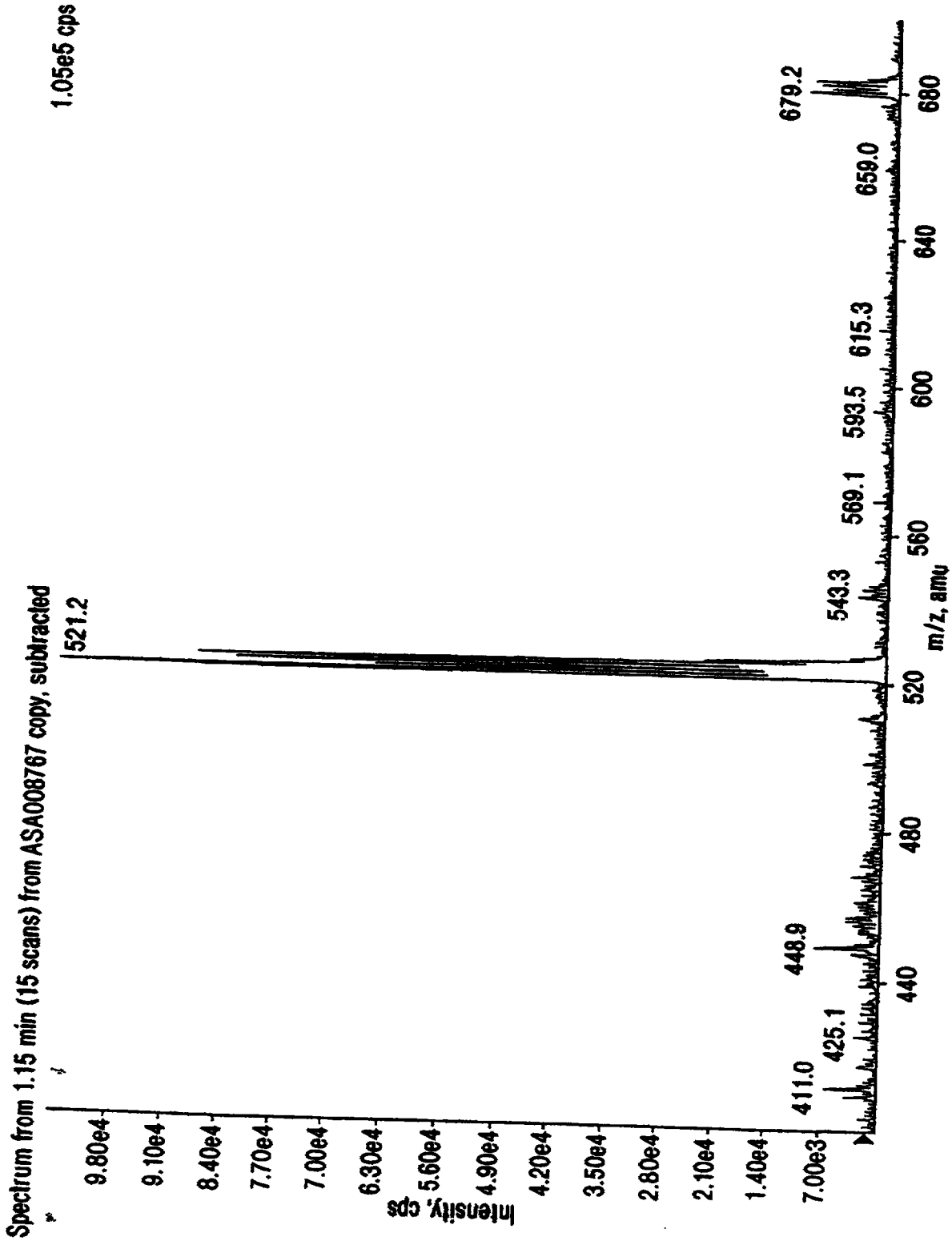

Spectrum from 1.15 min (15 scans) from ASA008767 copy, subtracted
1.05e5 cps
Intensity, cps
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
411.0
425.1
448.9
521.2
543.3
569.1
593.5
615.3
659.0
679.2
440
480
520
560
600
640
680
m/z, amu

FIG. 192

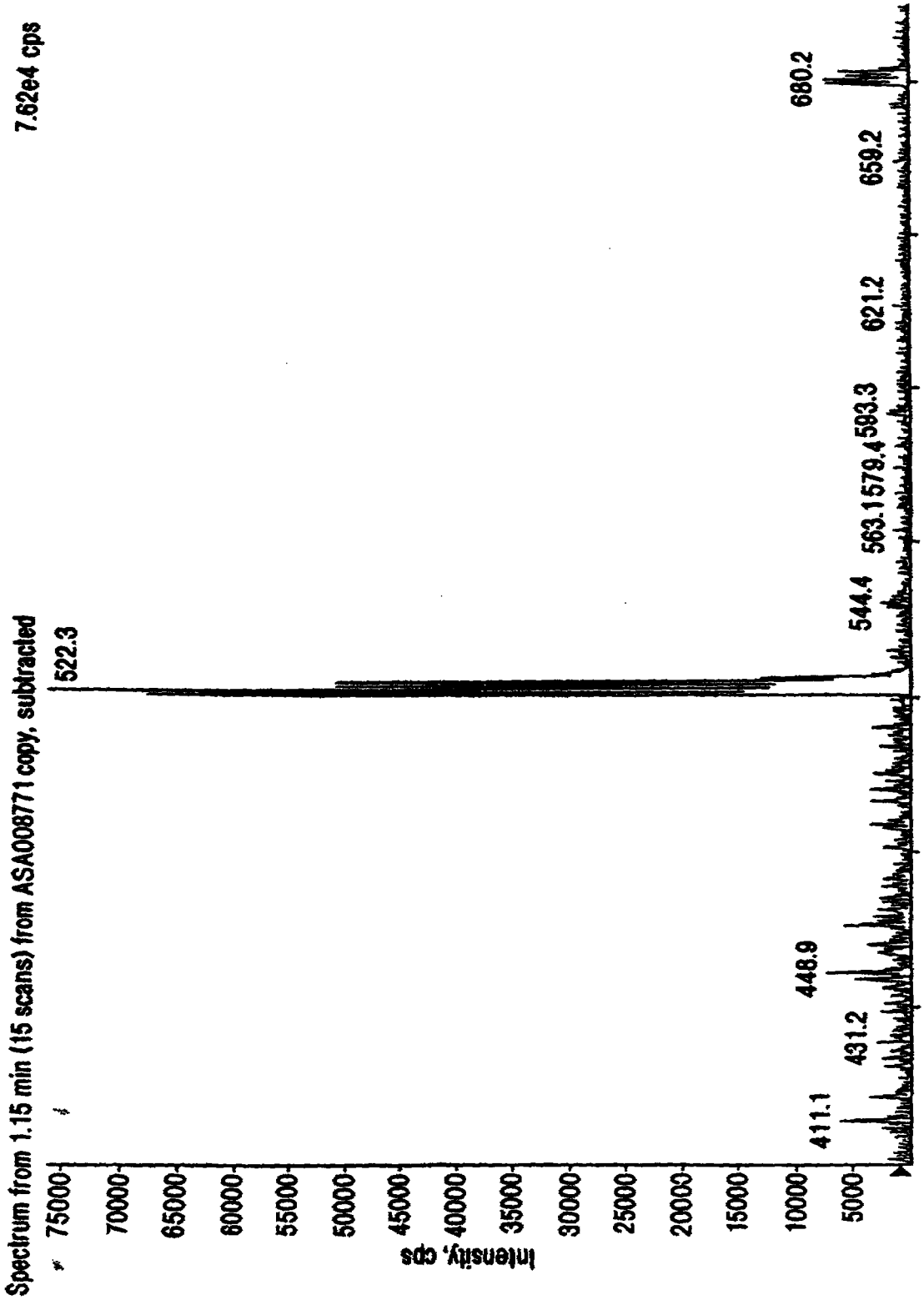

Spectrum from 1.15 min (15 scans) from ASA008771 copy, subtracted
7.62e4 cps
Intensity, cps
m/z, amu
522.3
544.4
563.1
579.4
583.3
621.2
659.2
680.2
411.1
431.2
448.9

FIG. 193

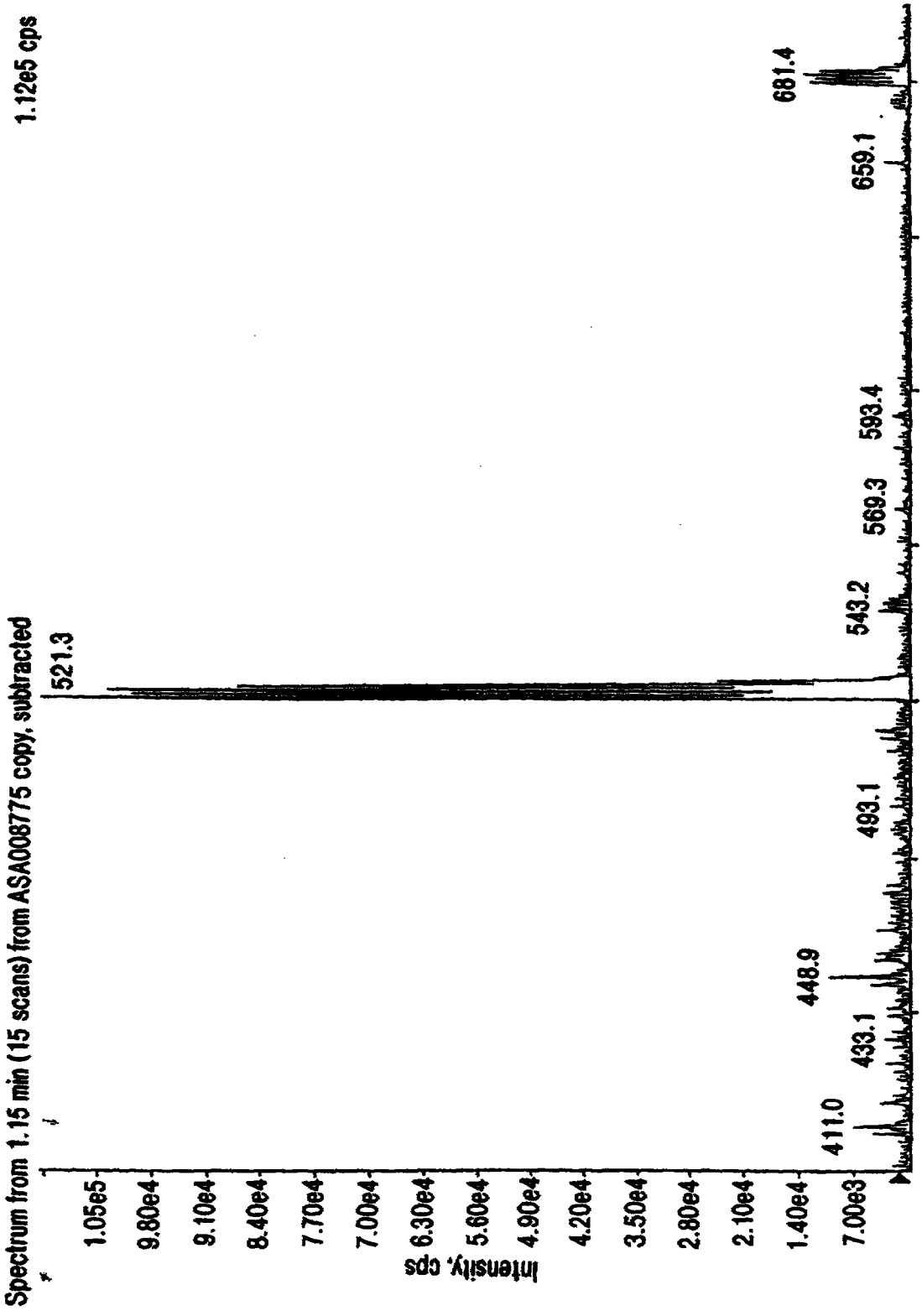

Spectrum from 1.15 min (15 scans) from ASA008775 copy, subtracted
1.12e5 cps
Intensity, cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
411.0
433.1
448.9
483.1
521.3
543.2
569.3
593.4
659.1
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 194

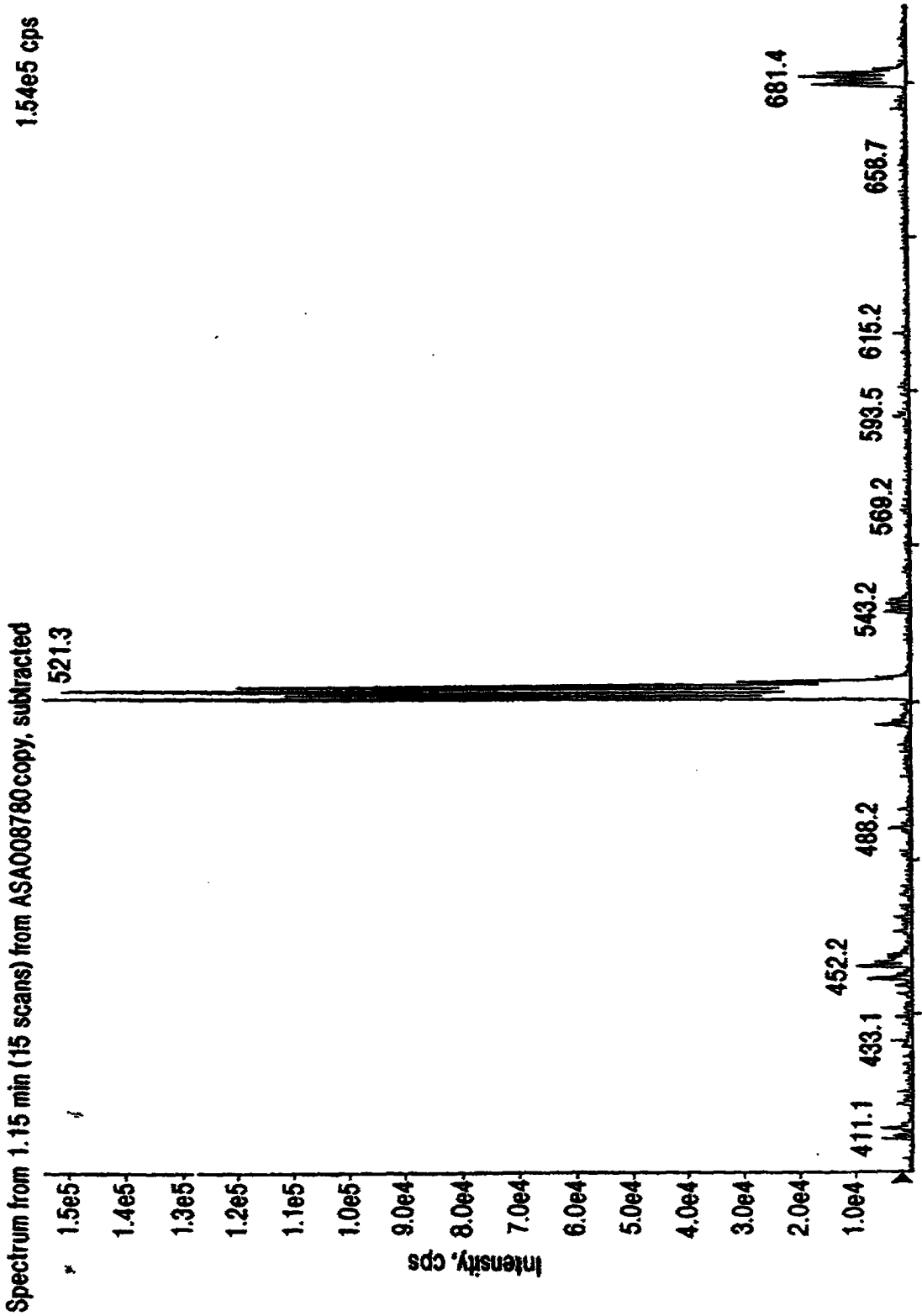

Spectrum from 1.15 min (15 scans) from ASA008780copy, subtracted
1.54e5 cps
Intensity, cps
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
433.1
452.2
488.2
521.3
543.2
569.2
593.5
615.2
658.7
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 195

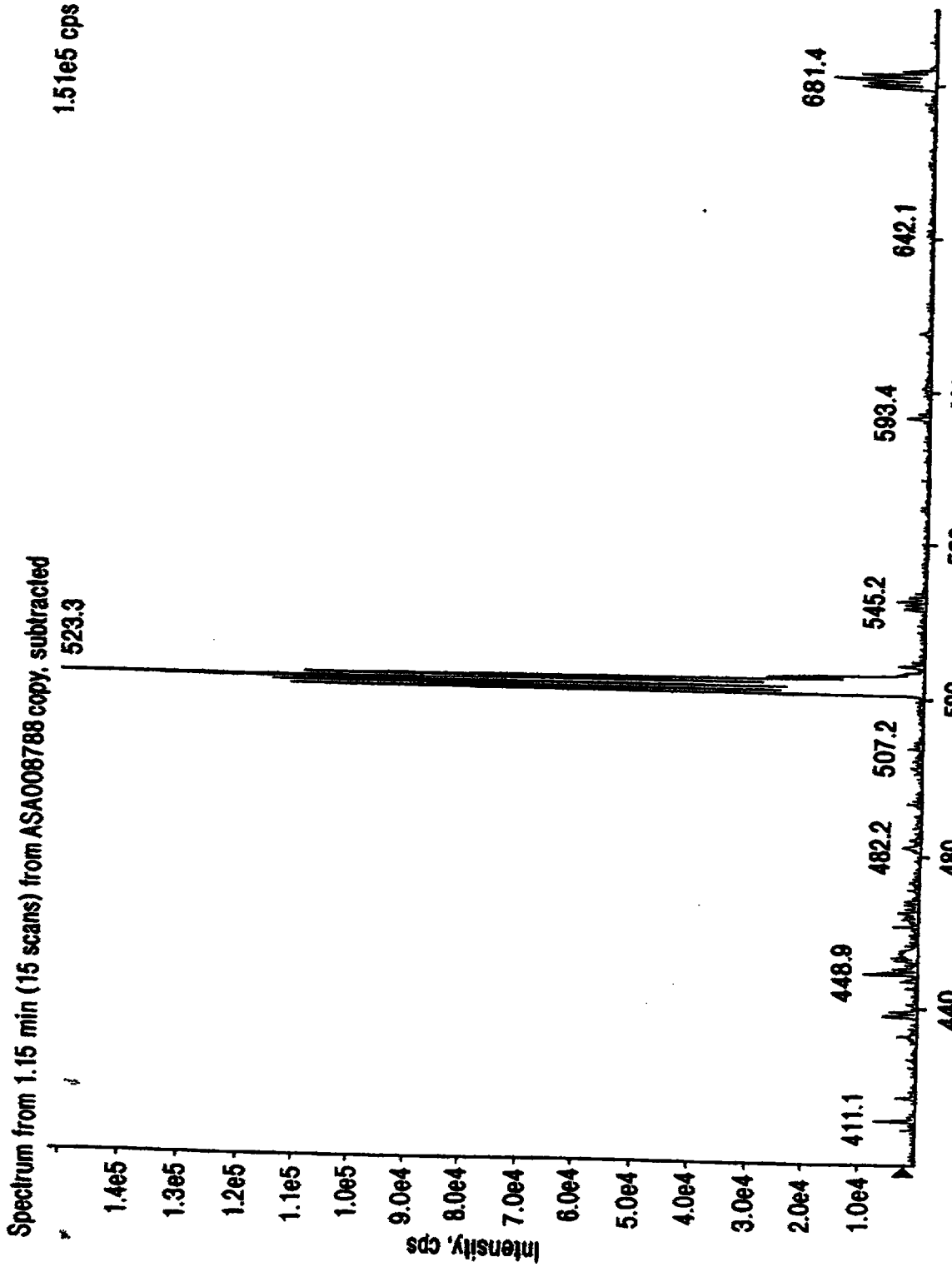

Spectrum from 1.15 min (15 scans) from ASA008788 copy, subtracted
1.51e5 cps
Intensity, cps
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
448.9
482.2
507.2
523.3
545.2
593.4
642.1
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 196

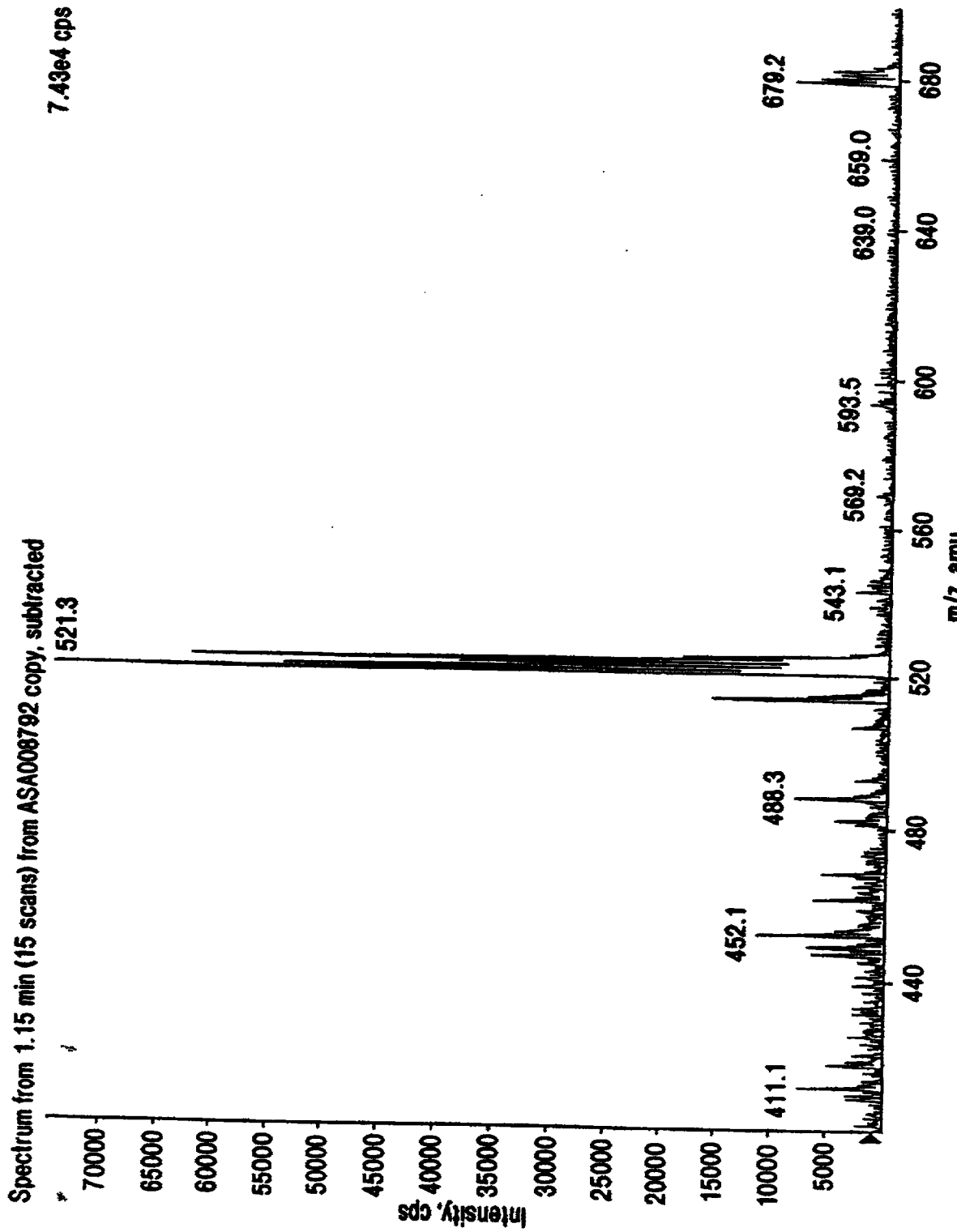

Spectrum from 1.15 min (15 scans) from ASA008792 copy, subtracted
7.43e4 cps
Intensity, cps
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
411.1
452.1
488.3
521.3
543.1
569.2
593.5
639.0
659.0
679.2
440
480
520
560
600
640
680
m/z, amu

FIG. 197

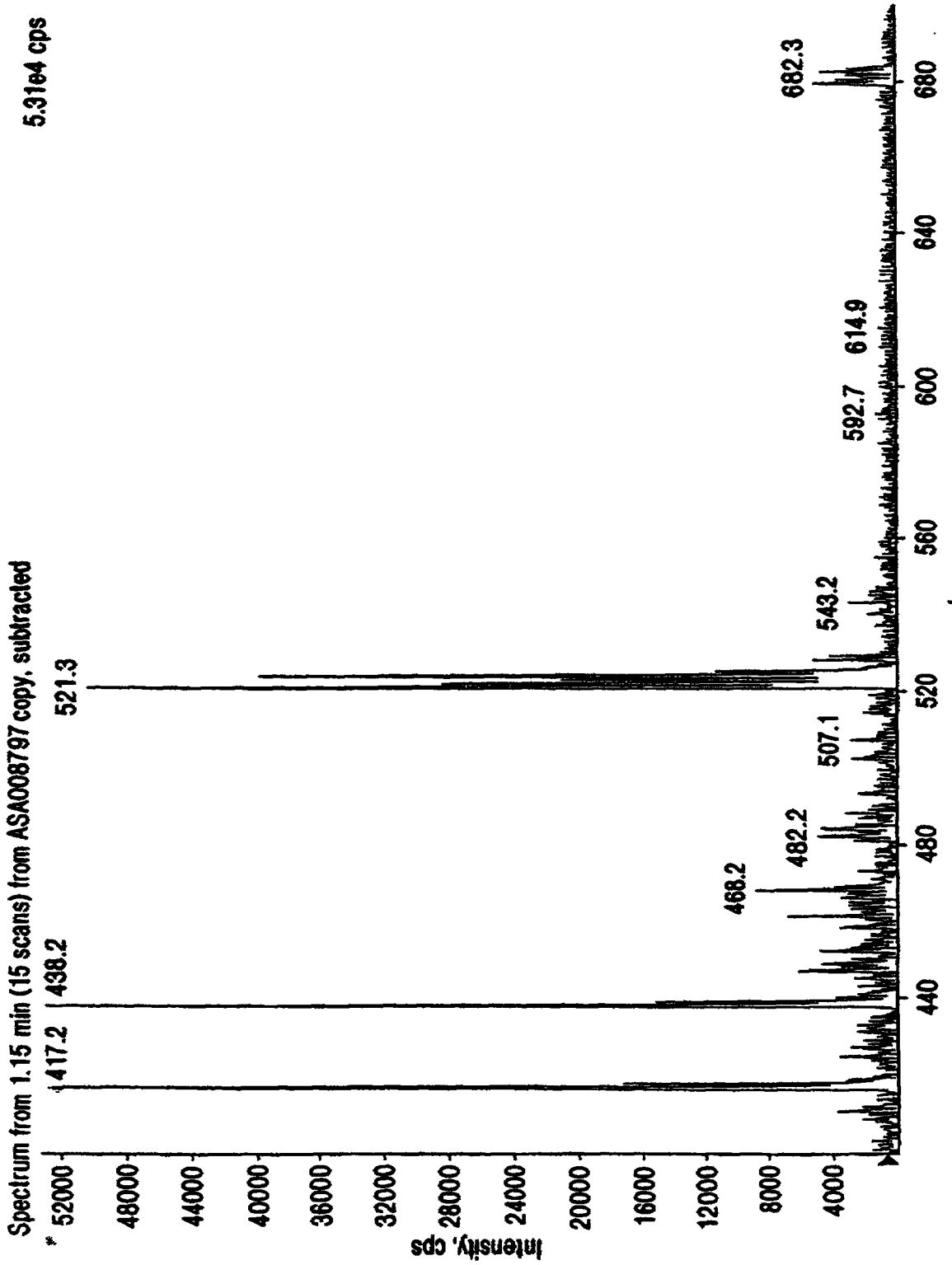

Spectrum from 1.15 min (15 scans) from ASA008797 copy, subtracted
5.31e4 cps
Intensity, cps
m/z, amu
417.2
438.2
468.2
482.2
507.1
521.3
543.2
592.7
614.9
682.3

FIG. 198

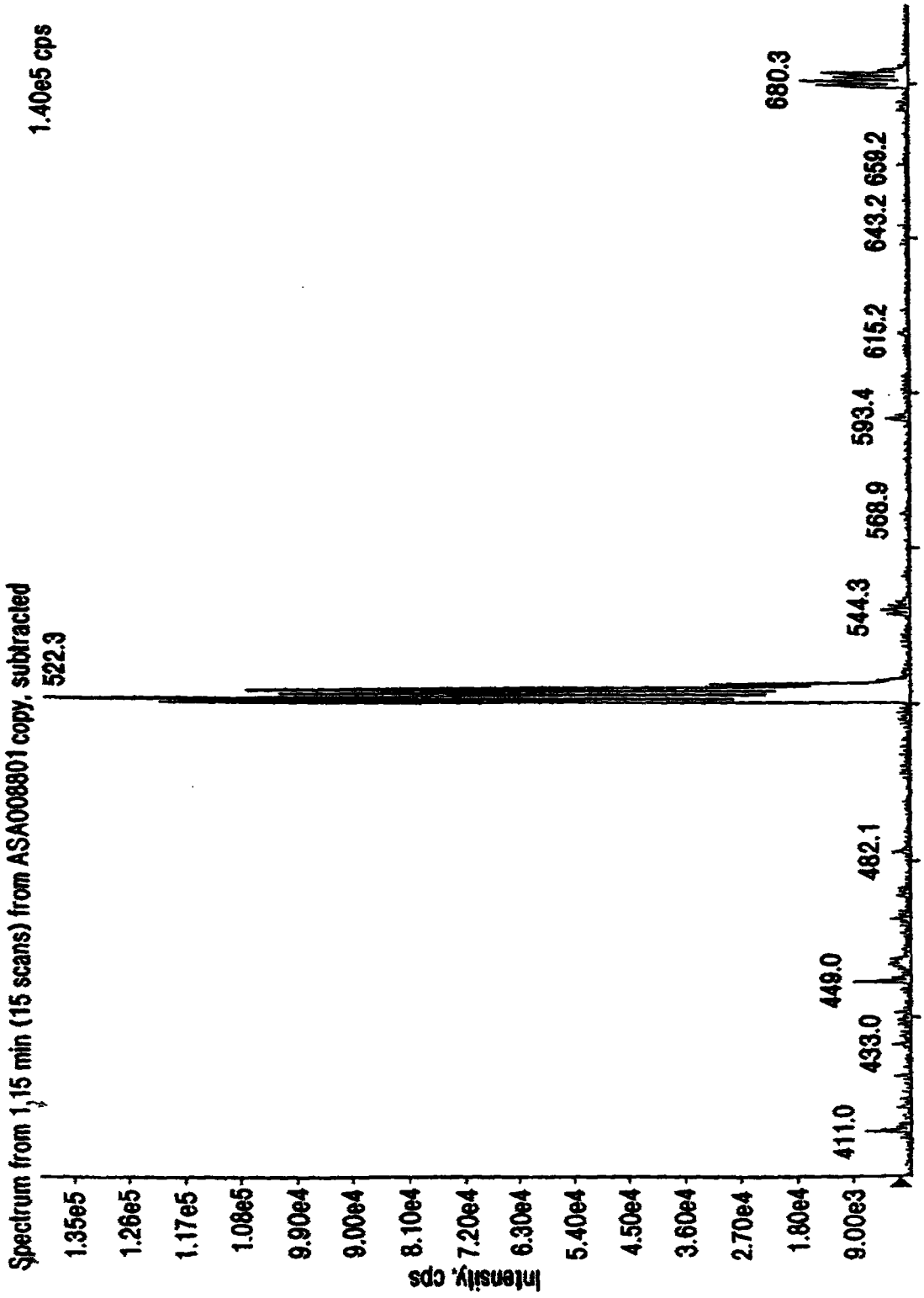

Spectrum from 1,15 min (15 scans) from ASA008801 copy, subtracted
1.40e5 cps
Intensity, cps
1.35e5
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.0
433.0
449.0
482.1
522.3
544.3
568.9
593.4
615.2
643.2
659.2
680.3
440
480
520
560
600
640
680
m/z, amu

FIG. 199

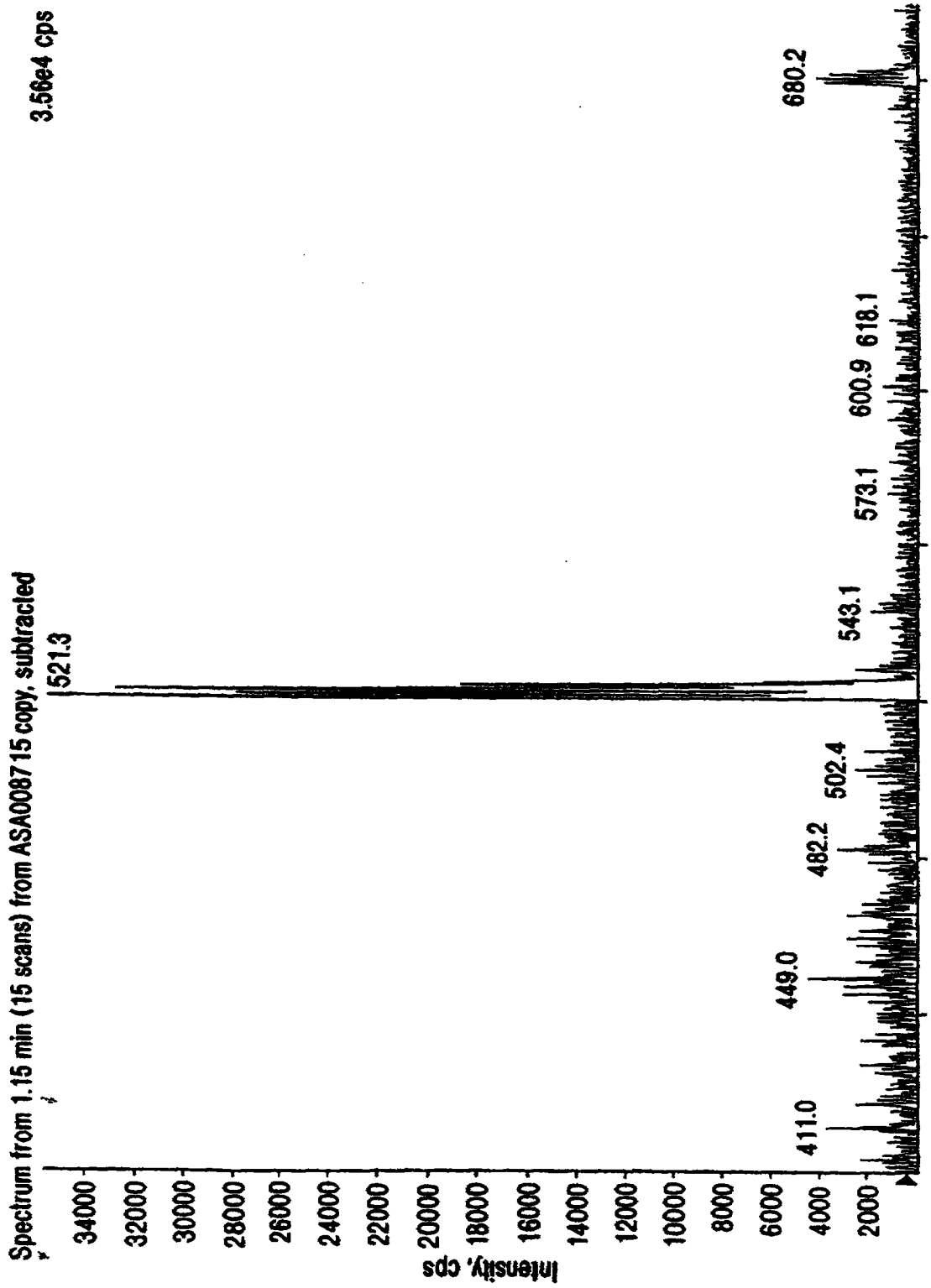

Spectrum from 1.15 min (15 scans) from ASA008715 copy, subtracted
3.56e4 cps
Intensity, cps
m/z, amu
521.3
543.1
573.1
600.9
618.1
680.2
502.4
482.2
449.0
411.0

FIG. 200

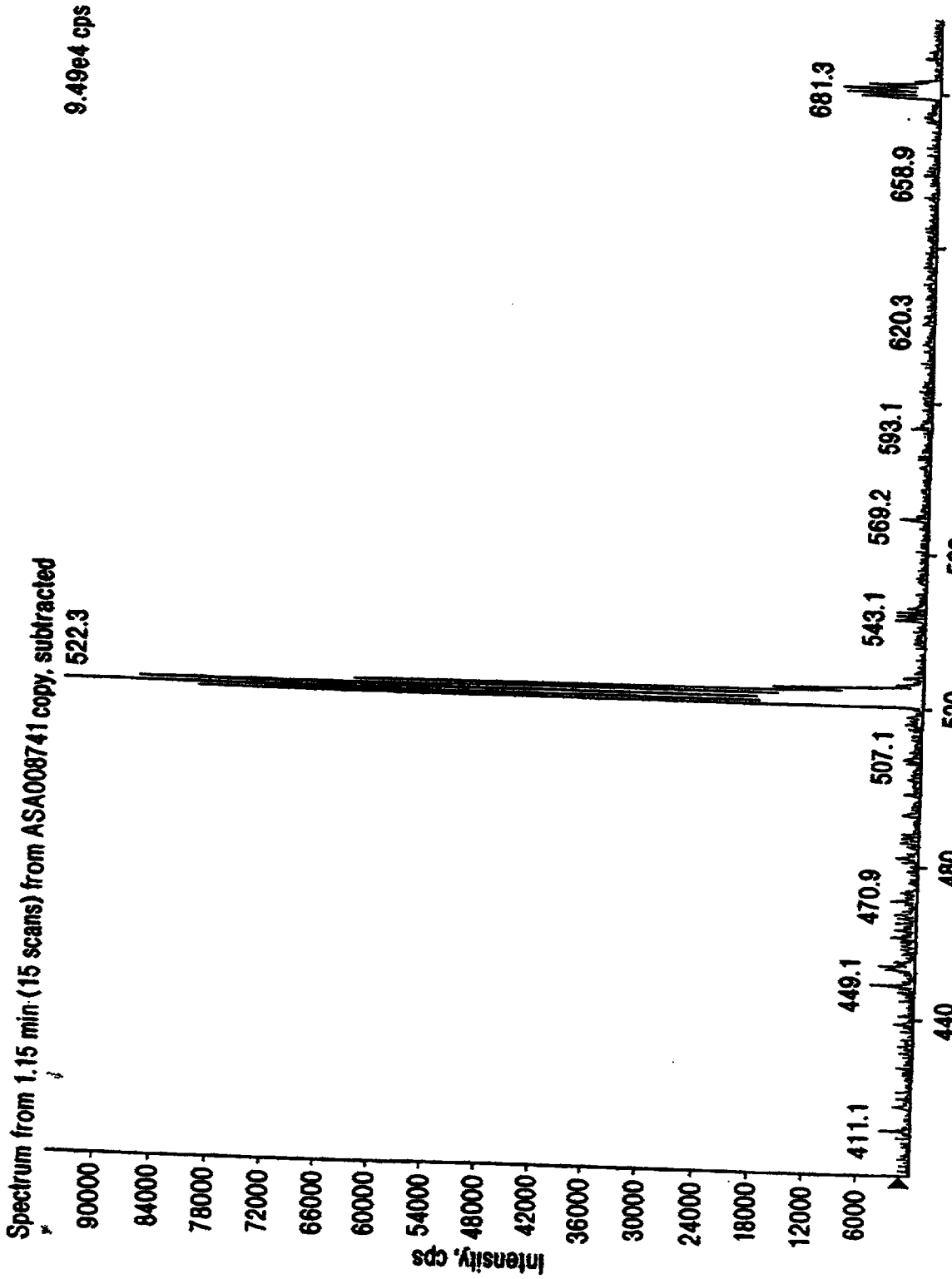

Spectrum from 1.15 min (15 scans) from ASA008741 copy, subtracted
9.49e4 cps
522.3
411.1
449.1
470.9
507.1
543.1
569.2
593.1
620.3
658.9
681.3
Intensity, cps
m/z, amu

FIG. 201

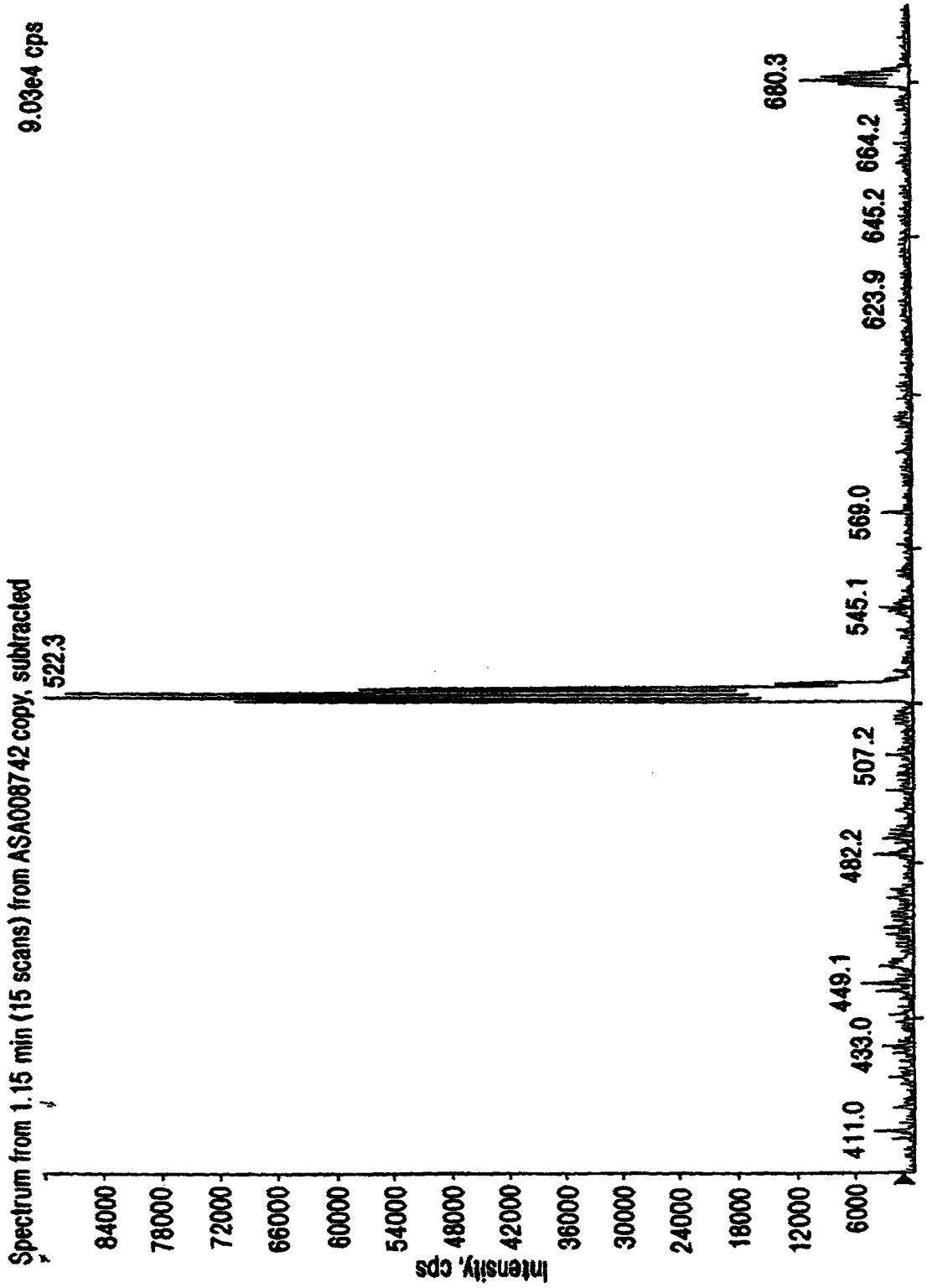

Spectrum from 1.15 min (15 scans) from ASA008742 copy, subtracted
9.03e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.0
433.0
449.1
482.2
507.2
522.3
545.1
569.0
623.9
645.2
664.2
680.3
440
480
520
560
600
640
680
m/z, amu

FIG. 202

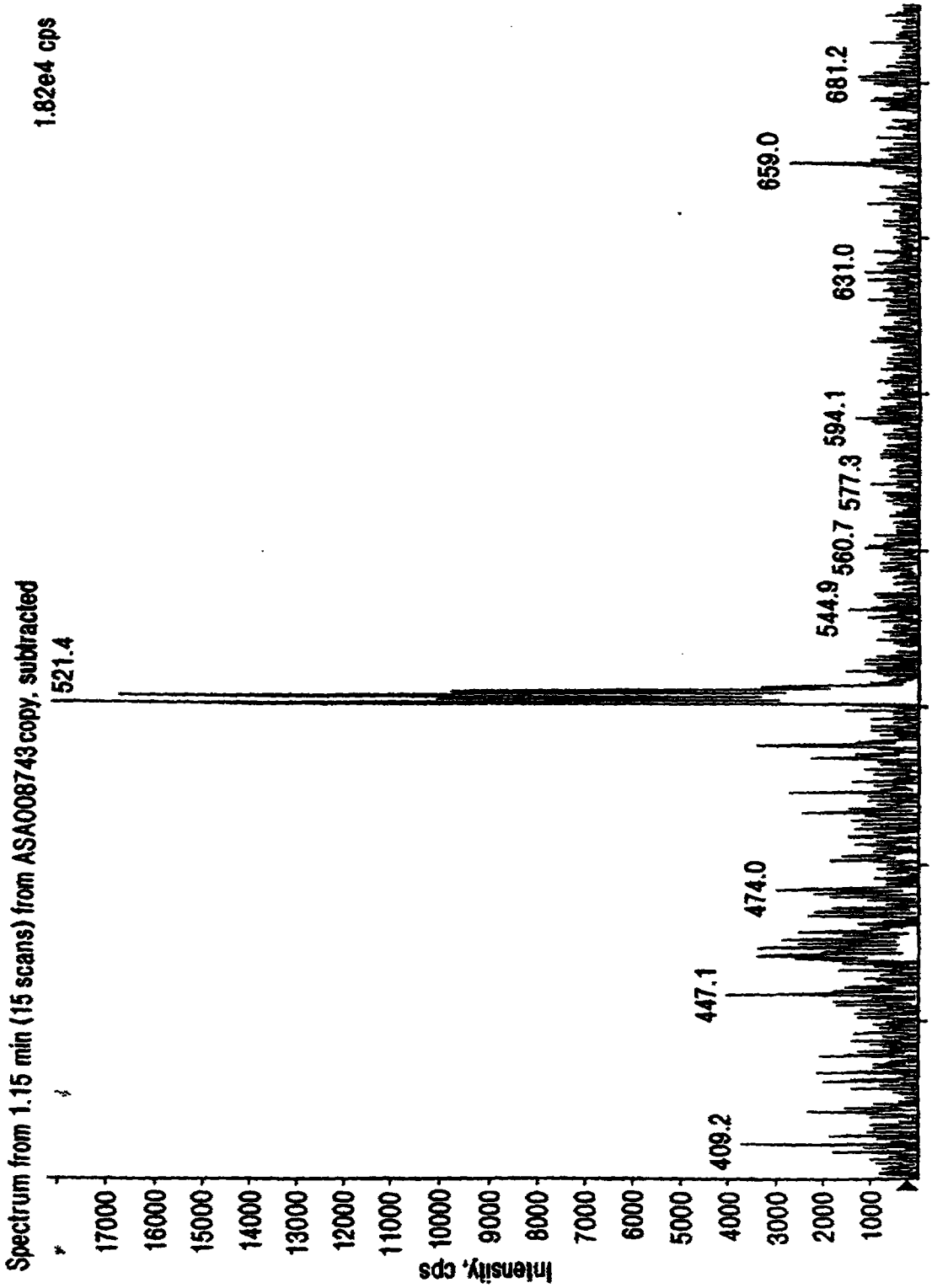

Spectrum from 1.15 min (15 scans) from ASA008743 copy, subtracted
1.82e4 cps
Intensity, cps
m/z, amu
521.4
544.9
560.7
577.3
594.1
631.0
659.0
681.2
409.2
447.1
474.0

FIG. 203

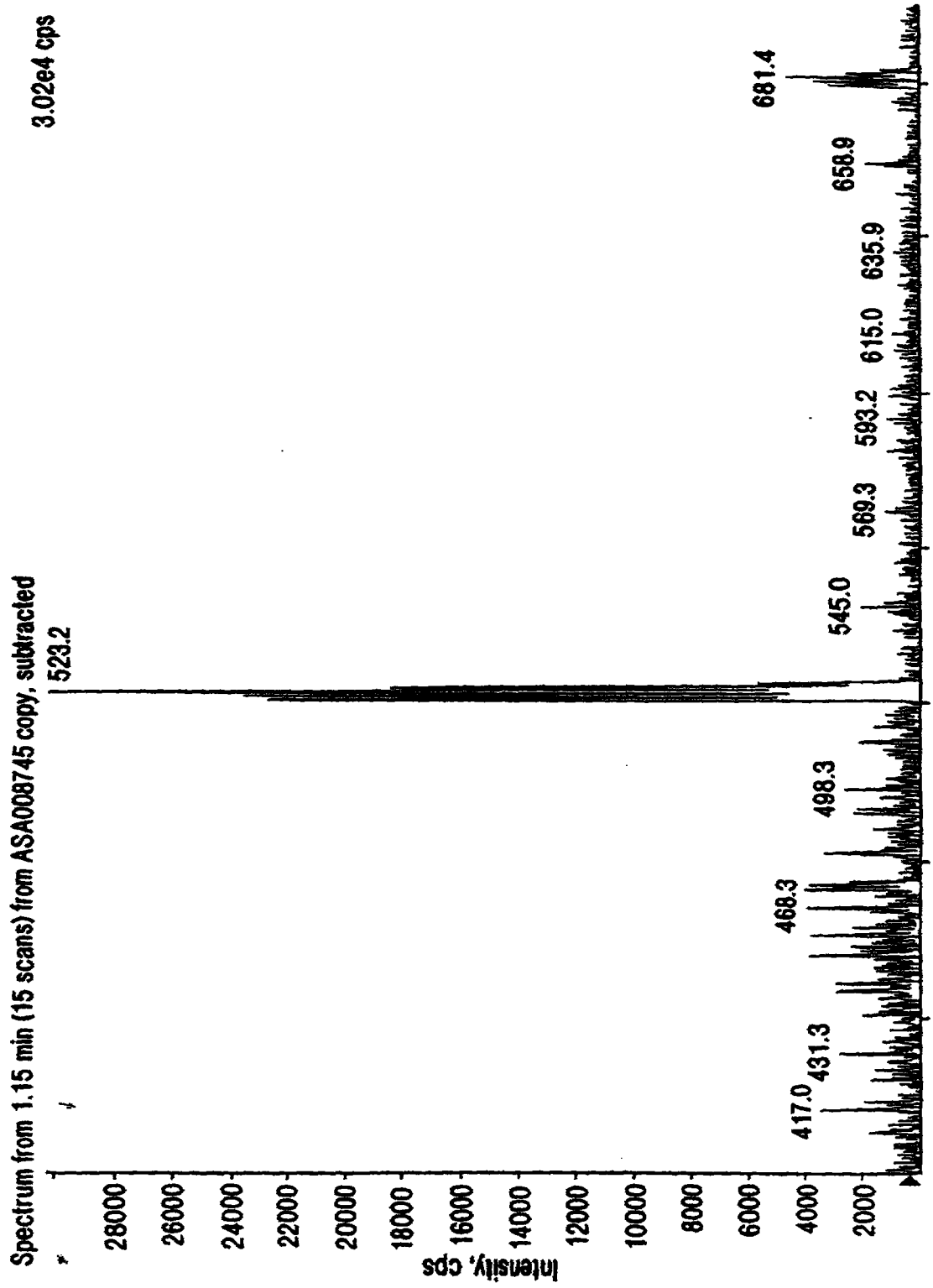

Spectrum from 1.15 min (15 scans) from ASA008745 copy, subtracted
3.02e4 cps
Intensity, cps
m/z, amu
523.2
545.0
569.3
593.2
615.0
635.9
658.9
681.4
498.3
468.3
431.3
417.0

FIG. 204

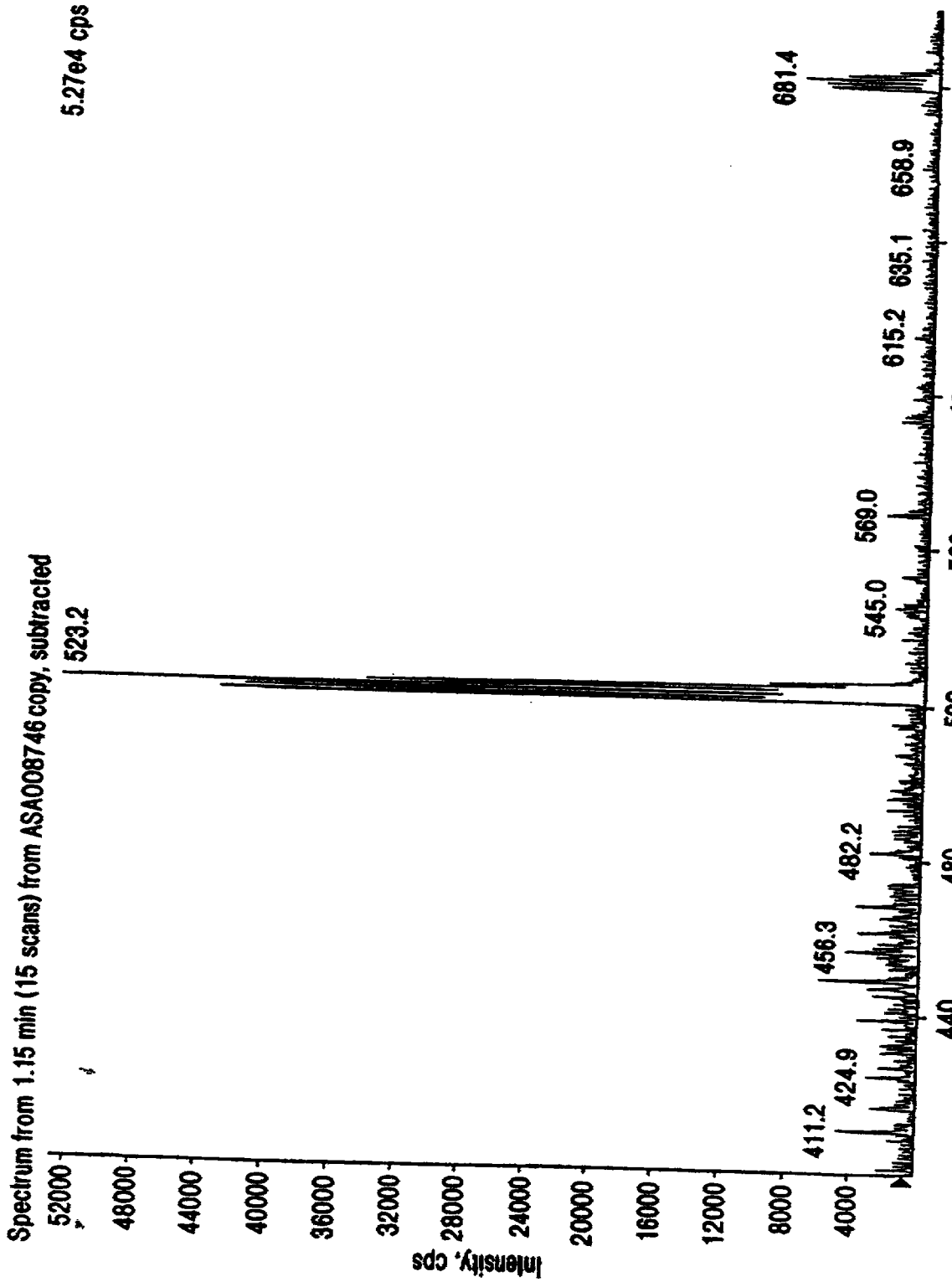

Spectrum from 1.15 min (15 scans) from ASA008746 copy, subtracted
5.27e4 cps
Intensity, cps
52000
48000
44000
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
411.2
424.9
456.3
482.2
523.2
545.0
569.0
615.2
635.1
658.9
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 205

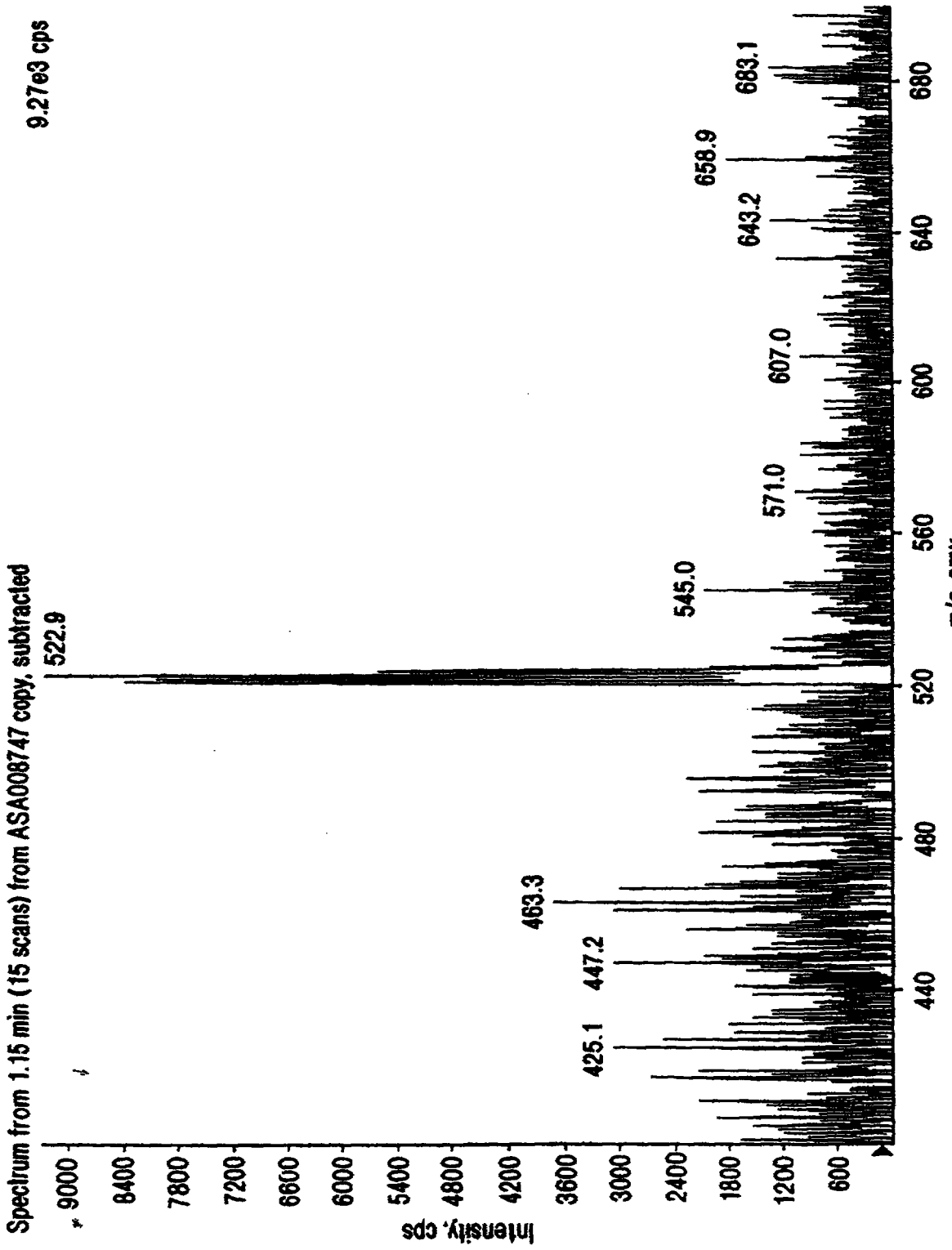

Spectrum from 1.15 min (15 scans) from ASA008747 copy, subtracted
9.27e3 cps
Intensity, cps
m/z, amu
522.9
545.0
571.0
607.0
643.2
658.9
683.1
463.3
447.2
425.1

FIG. 206

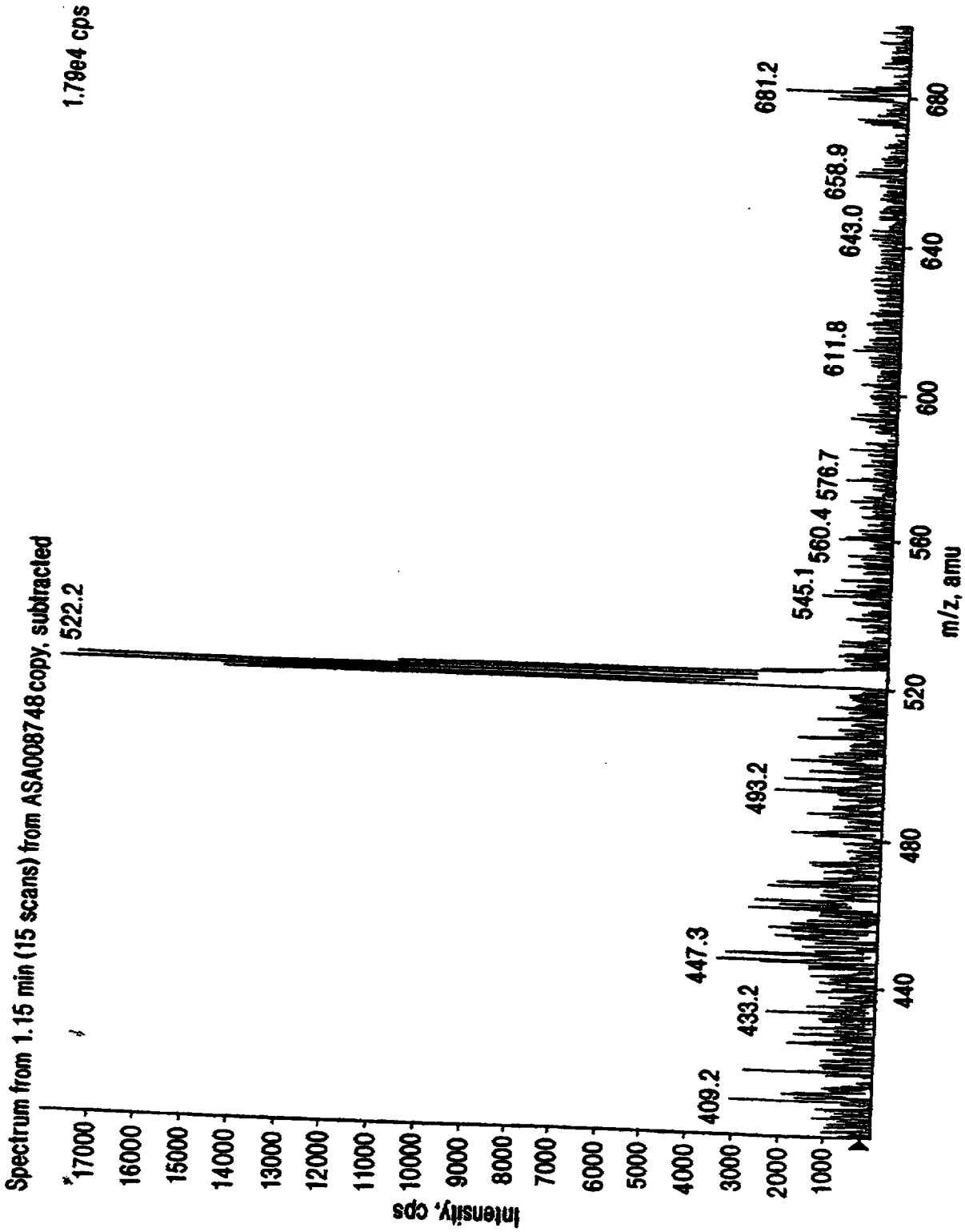

Spectrum from 1.15 min (15 scans) from ASA008748 copy, subtracted
1.79e4 cps
Intensity, cps
m/z, amu
522.2
545.1
560.4
576.7
611.8
643.0
658.9
681.2
493.2
447.3
433.2
409.2

FIG. 207

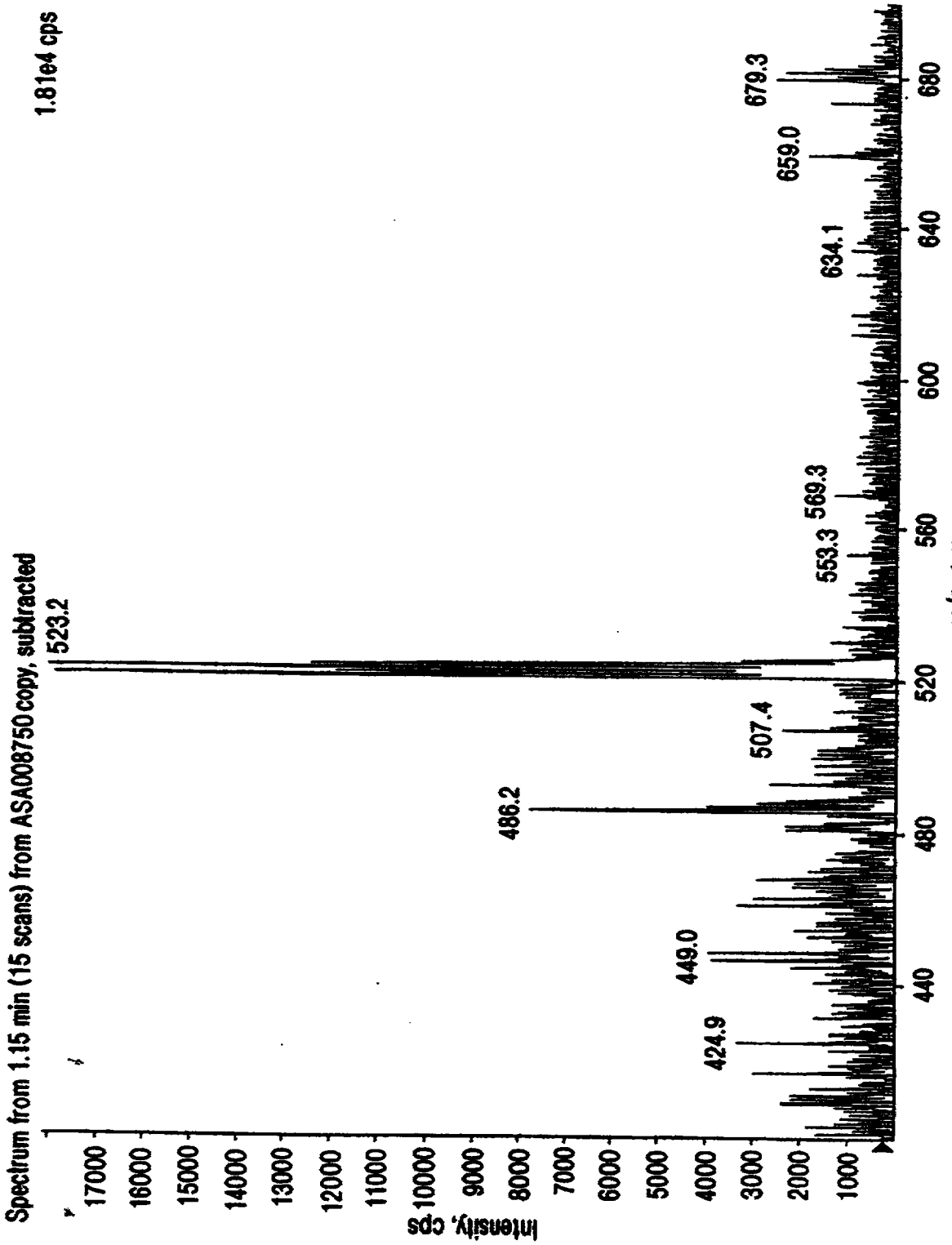

Spectrum from 1.15 min (15 scans) from ASA008750 copy, subtracted
1.81e4 cps
Intensity, cps
m/z, amu
523.2
486.2
507.4
449.0
424.9
553.3
569.3
634.1
659.0
679.3

FIG. 208

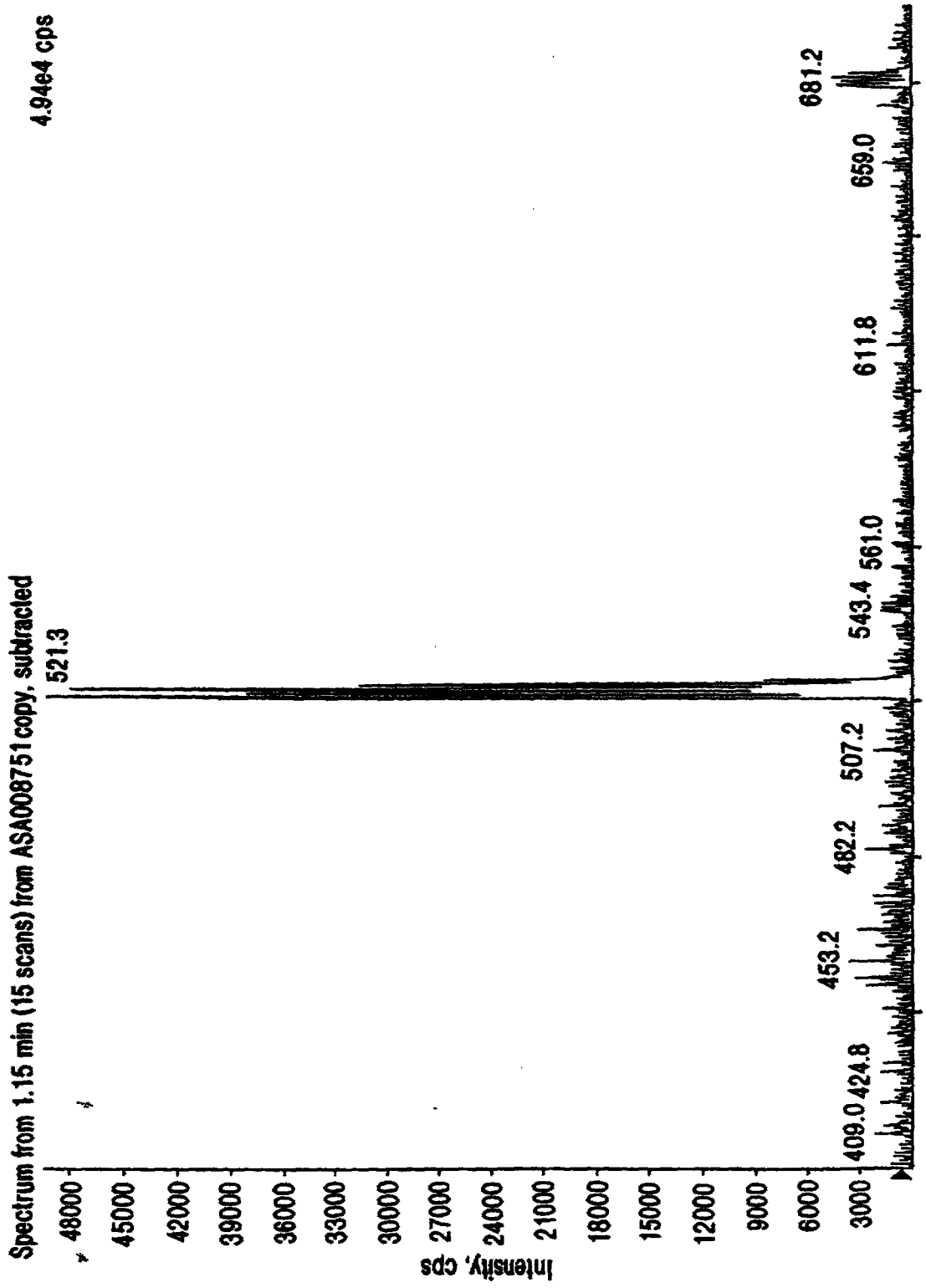

Spectrum from 1.15 min (15 scans) from ASA008751 copy, subtracted
4.94e4 cps
Intensity, cps
m/z, amu
521.3
543.4
561.0
611.8
659.0
681.2
507.2
482.2
453.2
424.8
409.0

FIG. 209

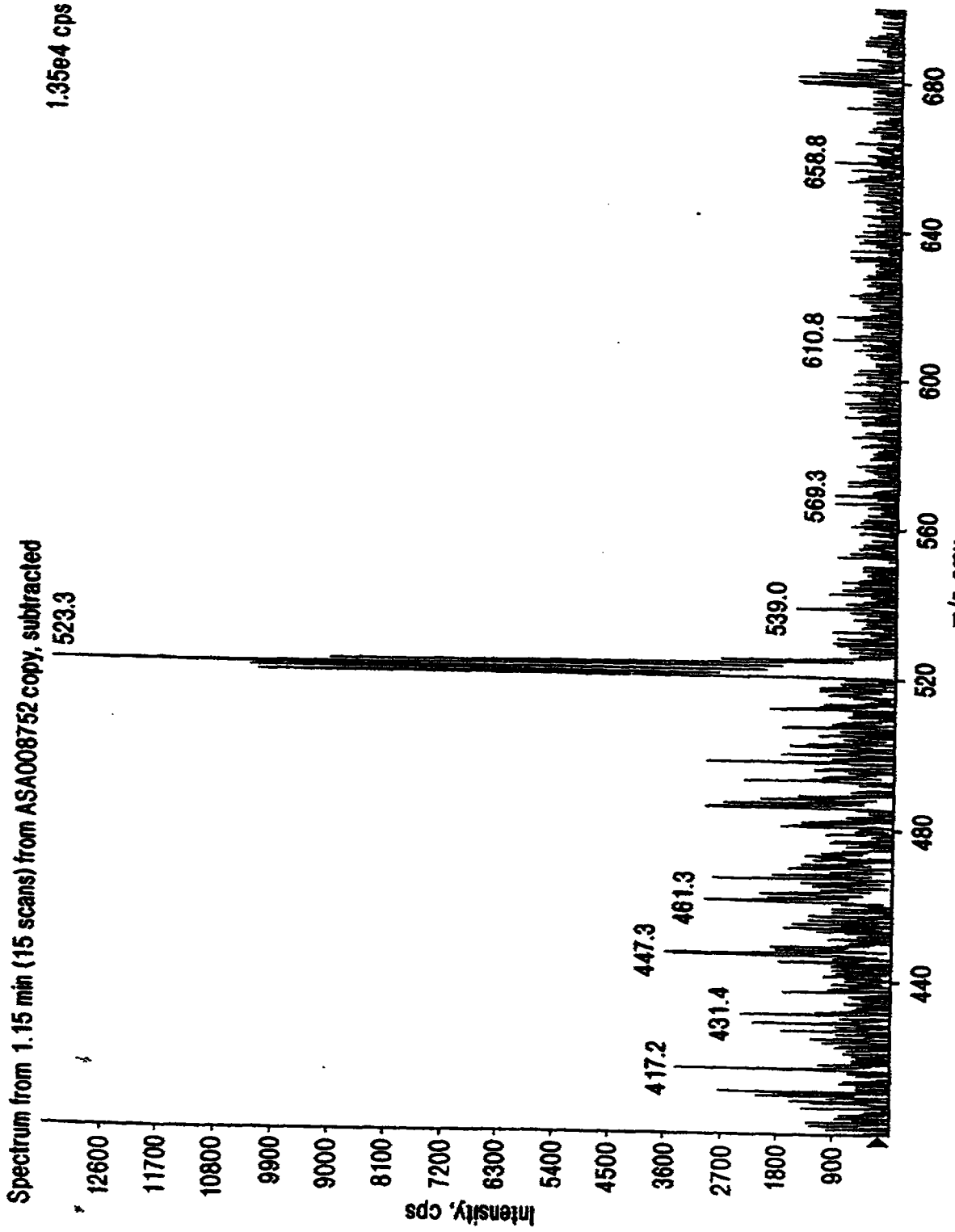

Spectrum from 1.15 min (15 scans) from ASA008752 copy, subtracted
1.35e4 cps
Intensity, cps
12600
11700
10800
9900
9000
8100
7200
6300
5400
4500
3600
2700
1800
900
m/z, amu
440
480
520
560
600
640
680
417.2
431.4
447.3
461.3
523.3
539.0
569.3
610.8
658.8

FIG. 210

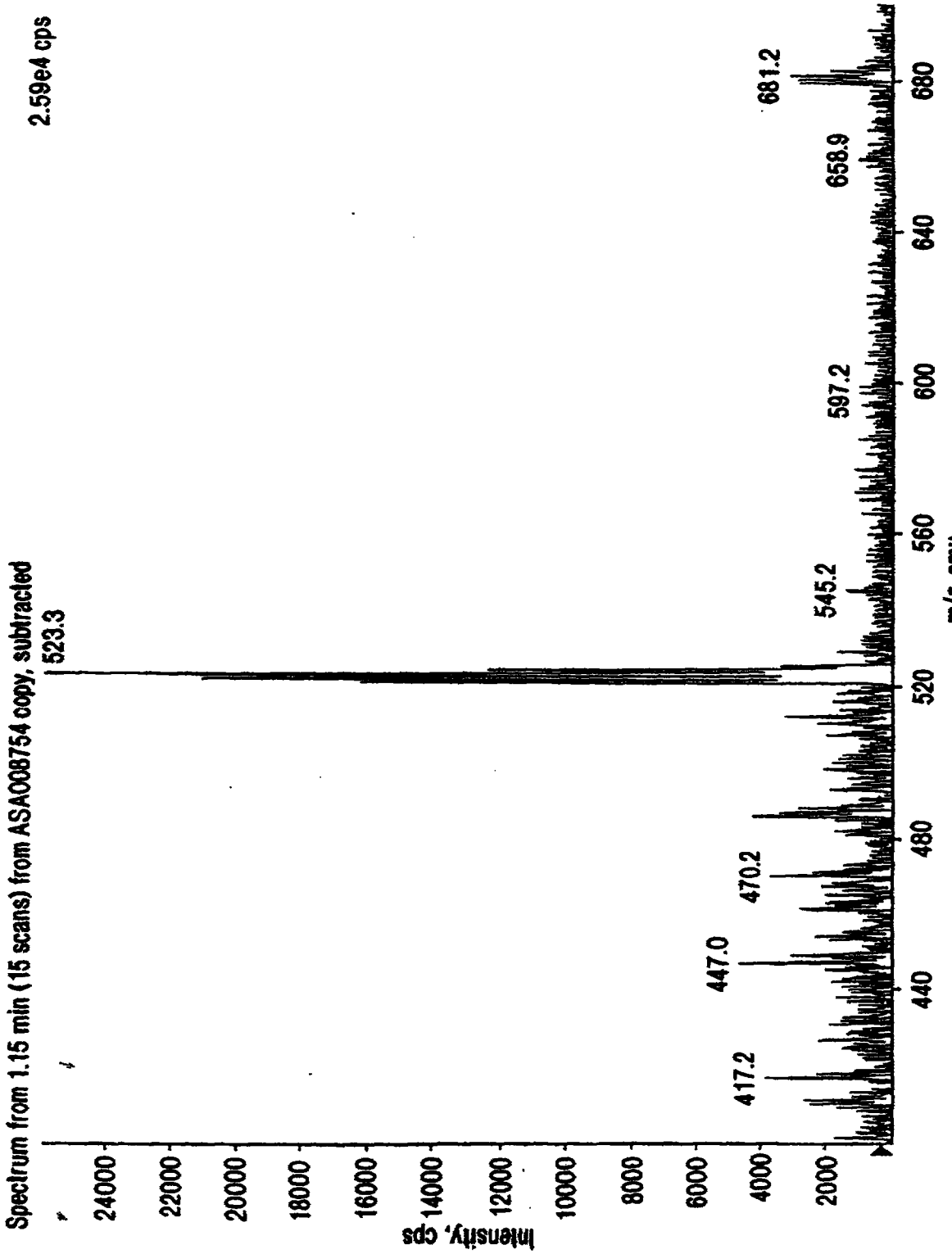

Spectrum from 1.15 min (15 scans) from ASA008754 copy, subtracted
2.59e4 cps
Intensity, cps
m/z, amu
523.3
545.2
597.2
658.9
681.2
417.2
447.0
470.2

FIG. 211

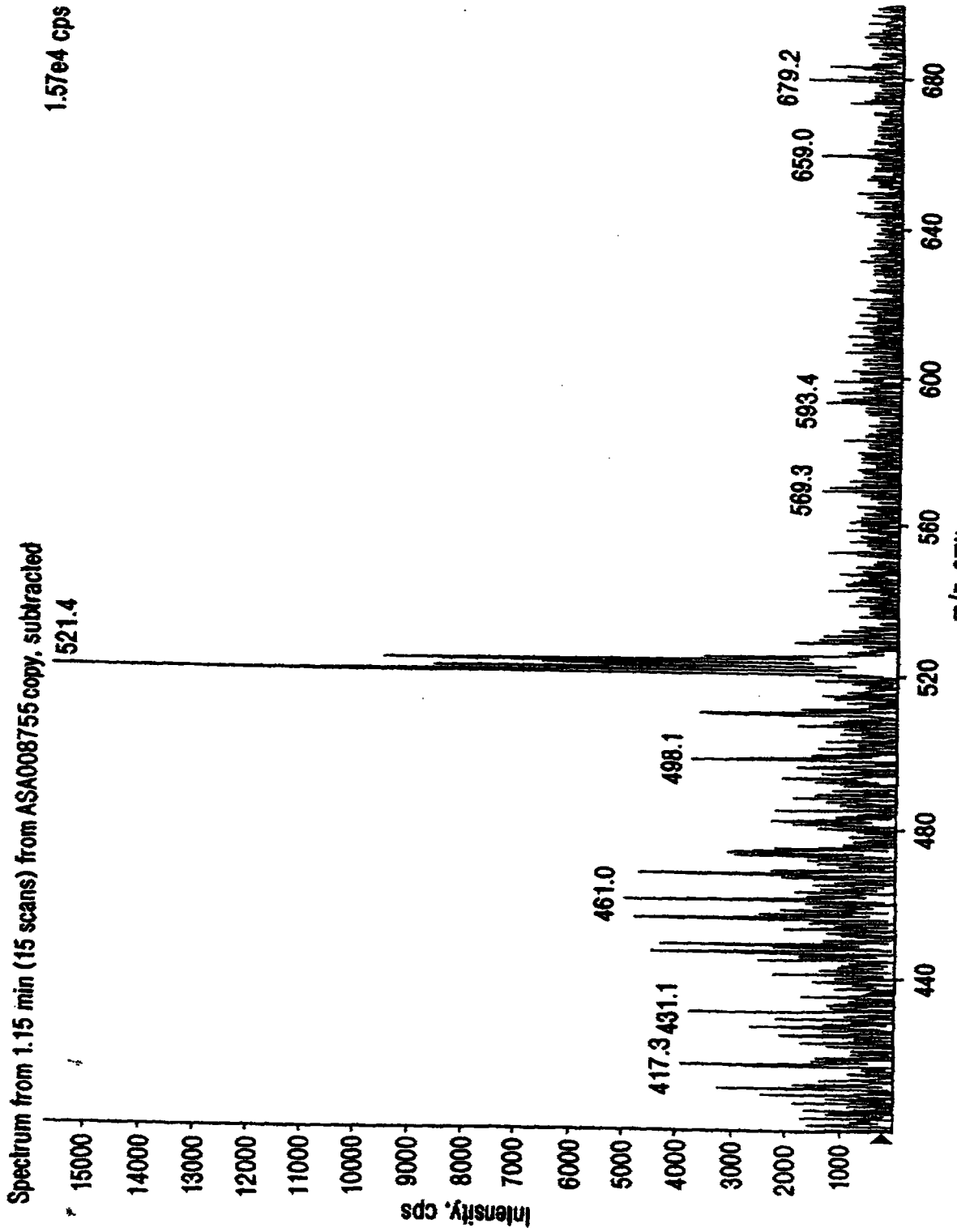

Spectrum from 1.15 min (15 scans) from ASA008755 copy, subtracted
1.57e4 cps
521.4
461.0
498.1
417.3
431.1
589.3
593.4
659.0
679.2
Intensity, cps
m/z, amu
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
440
480
520
560
600
640
680

FIG. 212

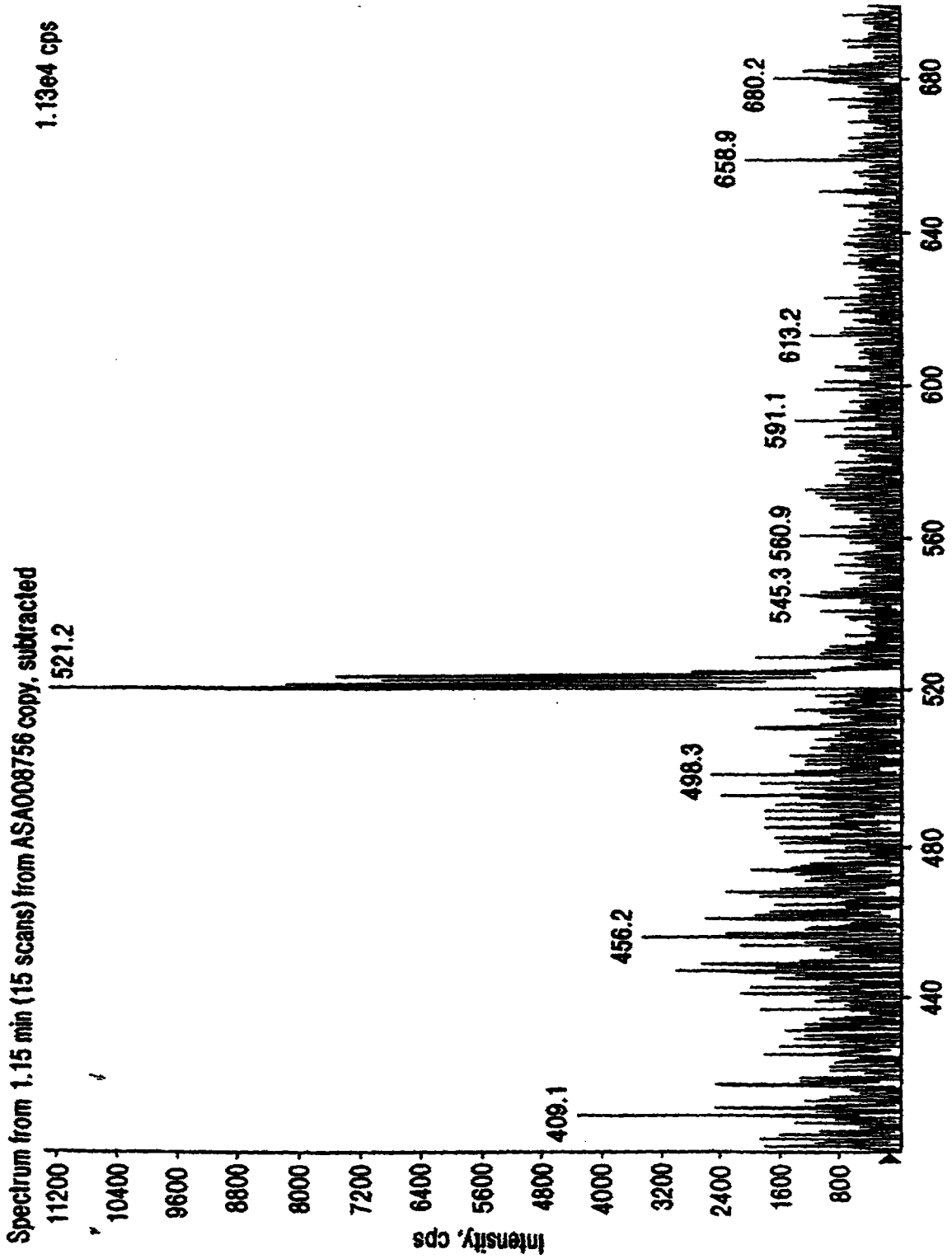

Spectrum from 1.15 min (15 scans) from ASA008756 copy, subtracted
1.13e4 cps
Intensity, cps
m/z, amu
521.2
545.3
560.9
591.1
613.2
658.9
680.2
498.3
456.2
409.1

FIG. 213

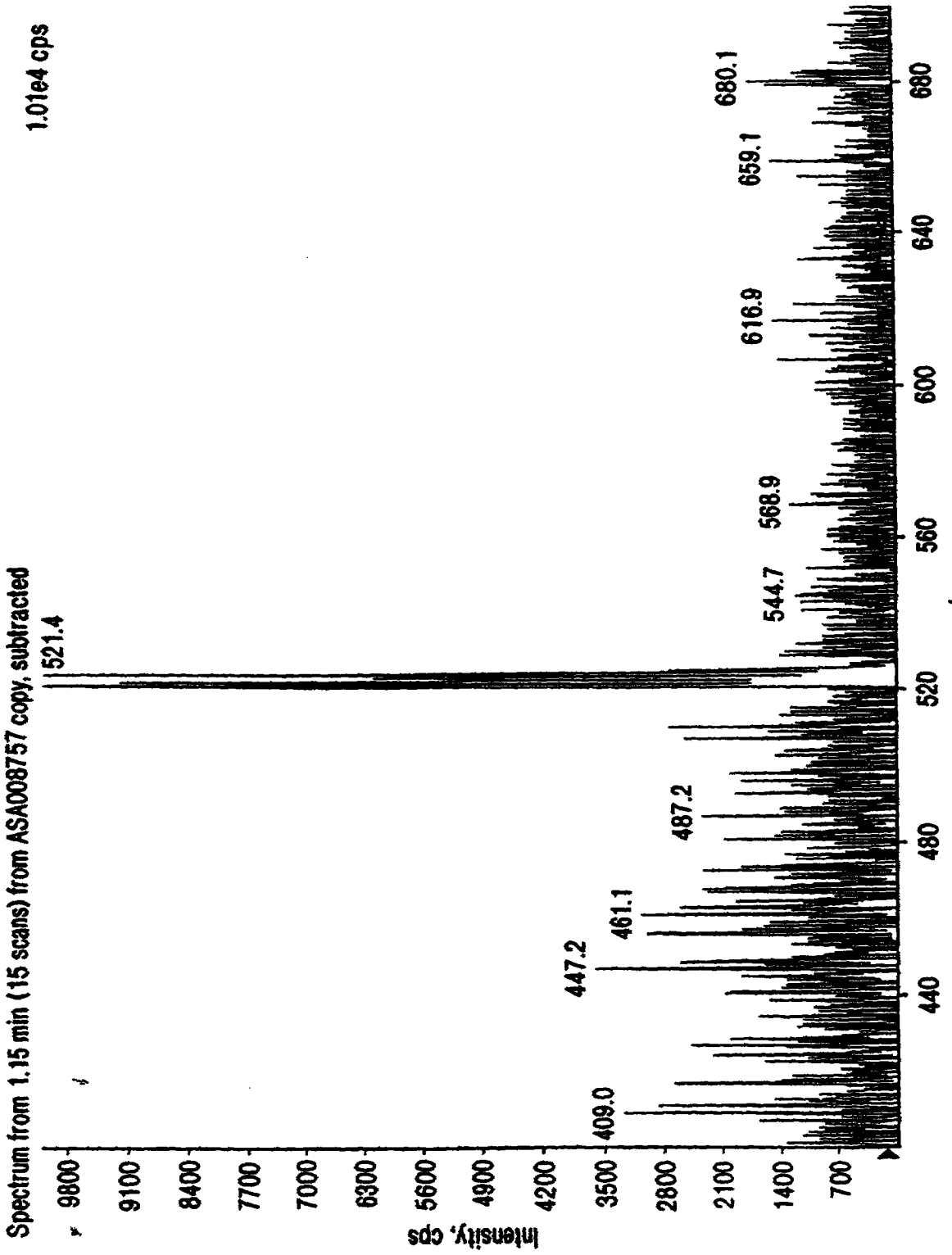

Spectrum from 1.15 min (15 scans) from ASA008757 copy, subtracted
1.01e4 cps
Intensity, cps
9800
9100
8400
7700
7000
6300
5600
4900
4200
3500
2800
2100
1400
700
m/z, amu
440
480
520
560
600
640
680
521.4
544.7
568.9
616.9
659.1
680.1
487.2
461.1
447.2
409.0

FIG. 214

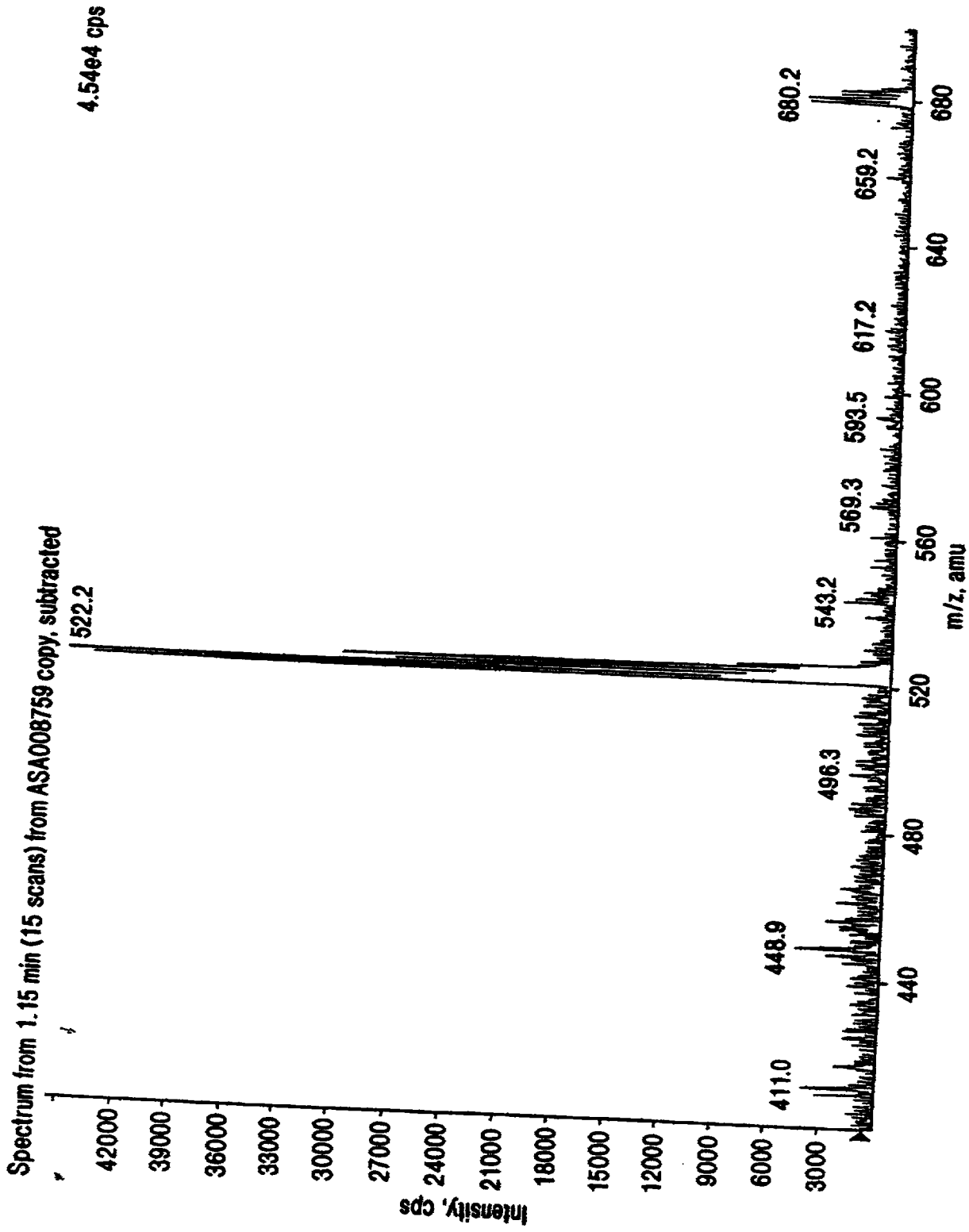

Spectrum from 1.15 min (15 scans) from ASA008759 copy, subtracted
4.54e4 cps
Intensity, cps
42000
39000
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
411.0
448.9
496.3
522.2
543.2
569.3
593.5
617.2
659.2
680.2
440
480
520
560
600
640
680
m/z, amu

FIG. 215

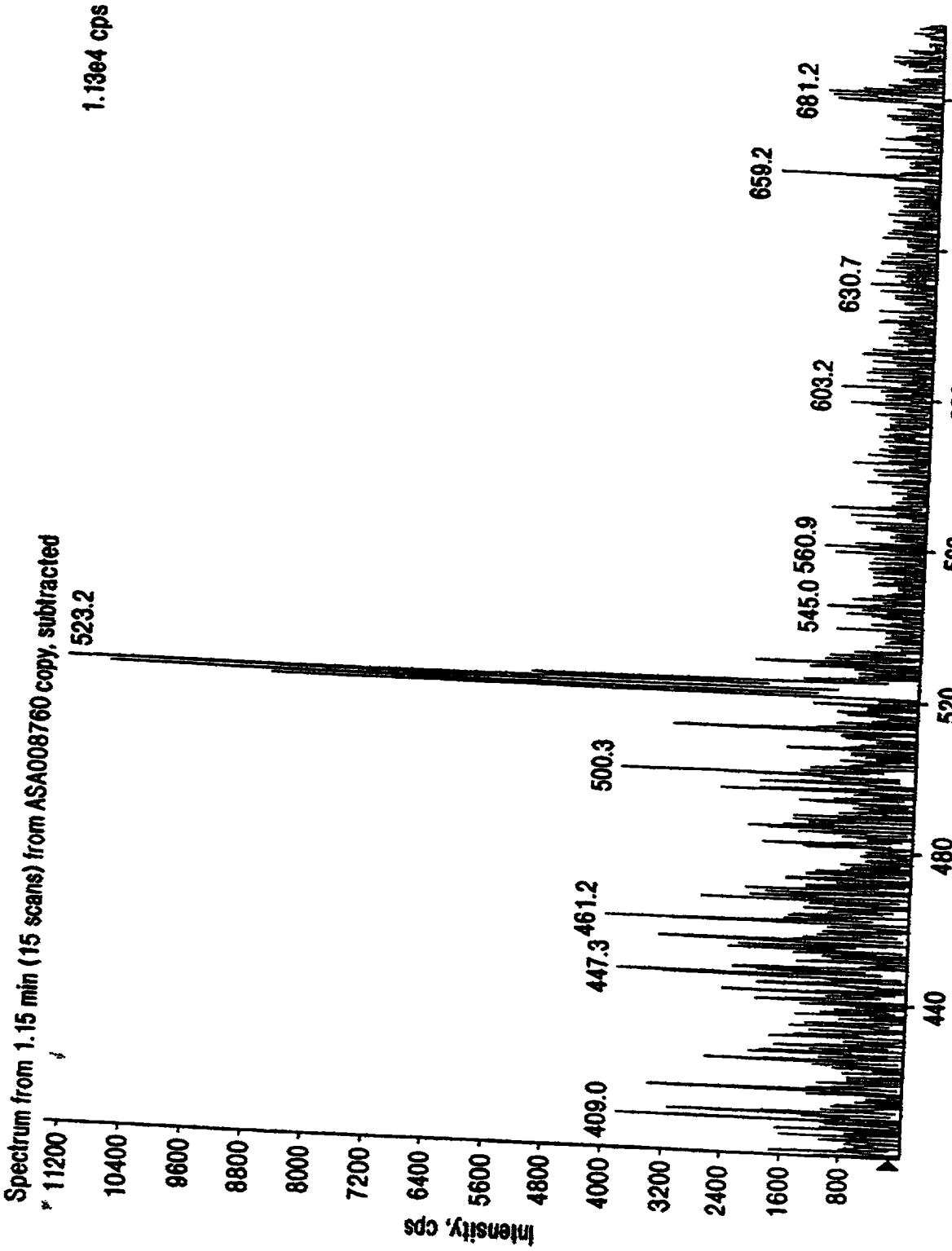

Spectrum from 1.15 min (15 scans) from ASA008760 copy, subtracted
1.13e4 cps
Intensity, cps
m/z, amu
523.2
545.0
560.9
603.2
630.7
659.2
681.2
500.3
461.2
447.3
409.0

FIG. 216

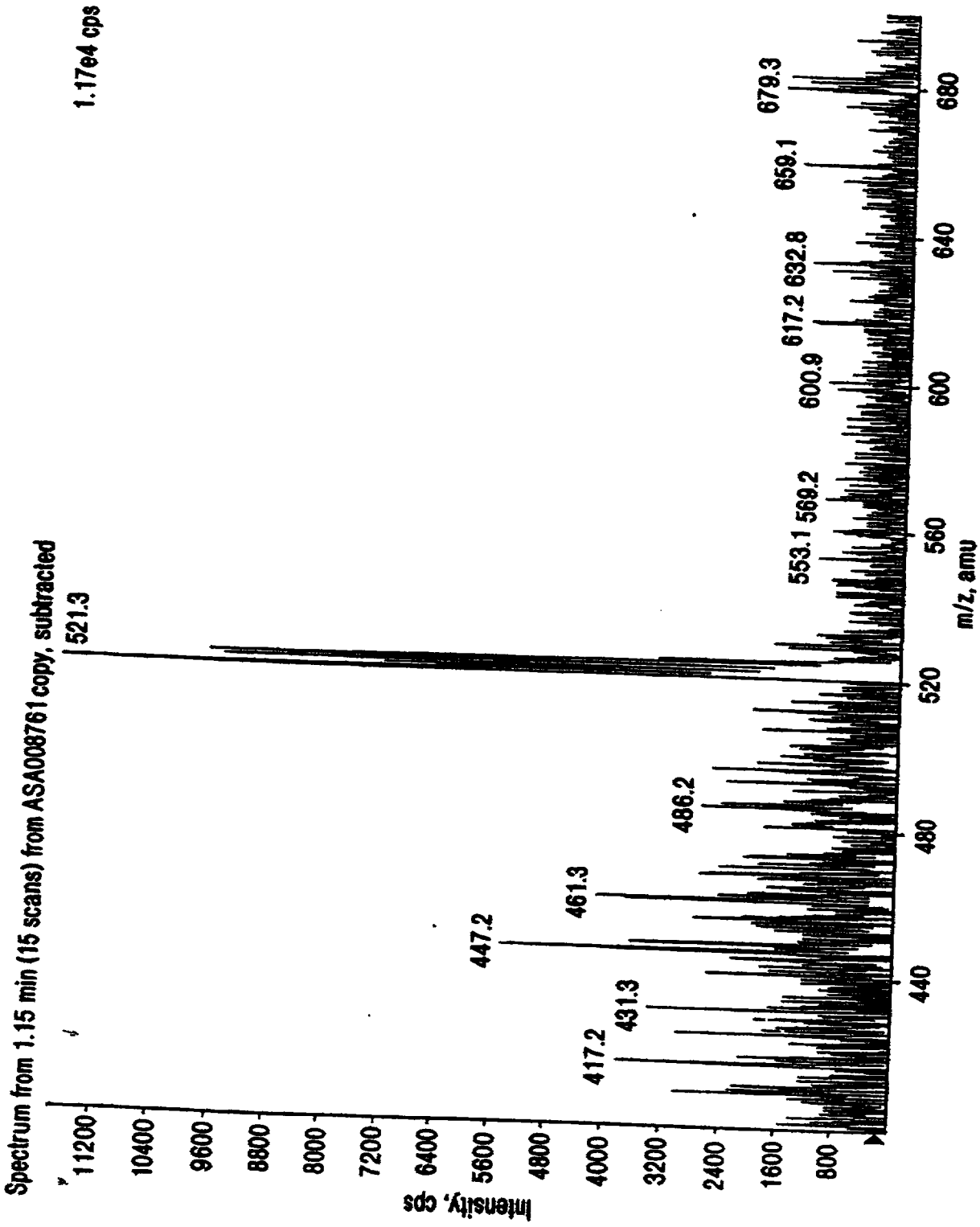

Spectrum from 1.15 min (15 scans) from ASA008761 copy, subtracted
1.17e4 cps
Intensity, cps
11200
10400
9600
8800
8000
7200
6400
5600
4800
4000
3200
2400
1600
800
521.3
553.1
569.2
600.9
617.2
632.8
659.1
679.3
447.2
461.3
486.2
417.2
431.3
440
480
520
560
600
640
680
m/z, amu

FIG. 217

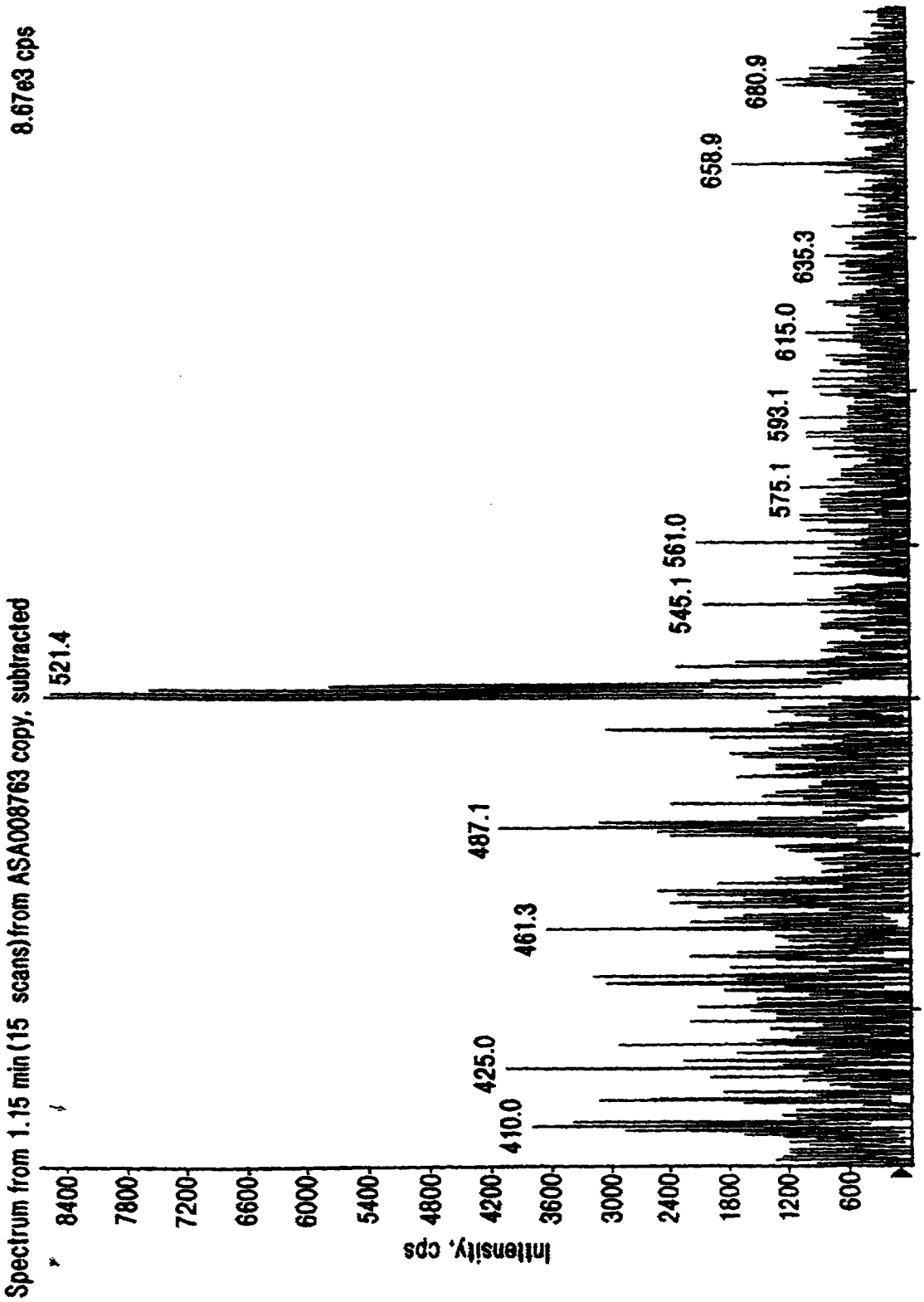

Spectrum from 1.15 min (15 scans) from ASA008763 copy, subtracted
8.67e3 cps
Intensity, cps
8400
7800
7200
6600
6000
5400
4800
4200
3600
3000
2400
1800
1200
600
m/z, amu
440
480
520
560
600
640
680
521.4
545.1
561.0
575.1
593.1
615.0
635.3
658.9
680.9
487.1
461.3
425.0
410.0

FIG. 218

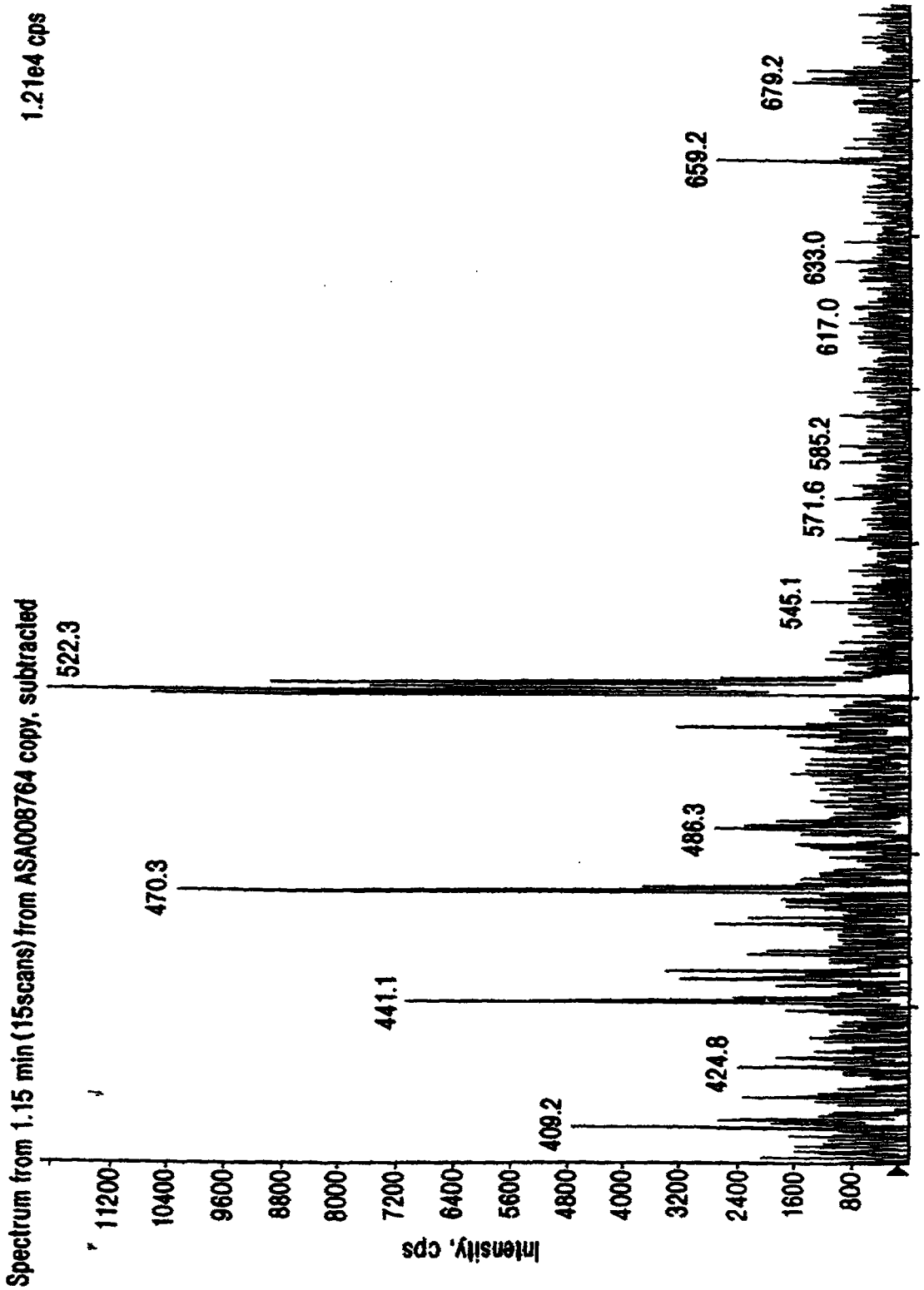

Spectrum from 1.15 min (15scans) from ASA008764 copy, subtracted
1.21e4 cps
Intensity, cps
m/z, amu
522.3
470.3
441.1
486.3
424.8
409.2
545.1
571.6
585.2
617.0
633.0
659.2
679.2

FIG. 219

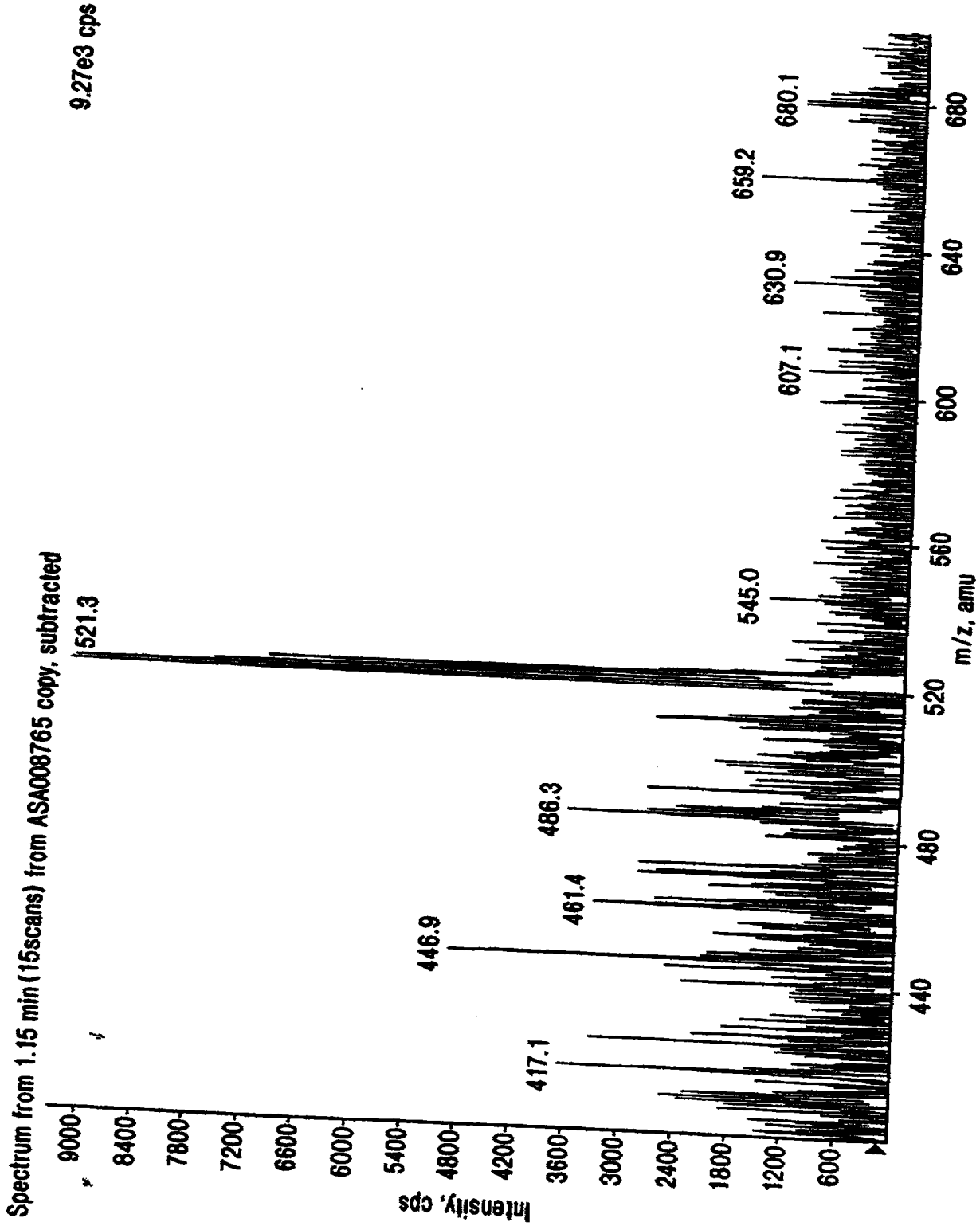

Spectrum from 1.15 min (15scans) from ASA008765 copy, subtracted
9.27e3 cps
Intensity, cps
9000
8400
7800
7200
6600
6000
5400
4800
4200
3600
3000
2400
1800
1200
600
521.3
545.0
659.2
680.1
607.1
630.9
486.3
461.4
446.9
417.1
440
480
520
560
600
640
680
m/z, amu

FIG. 220

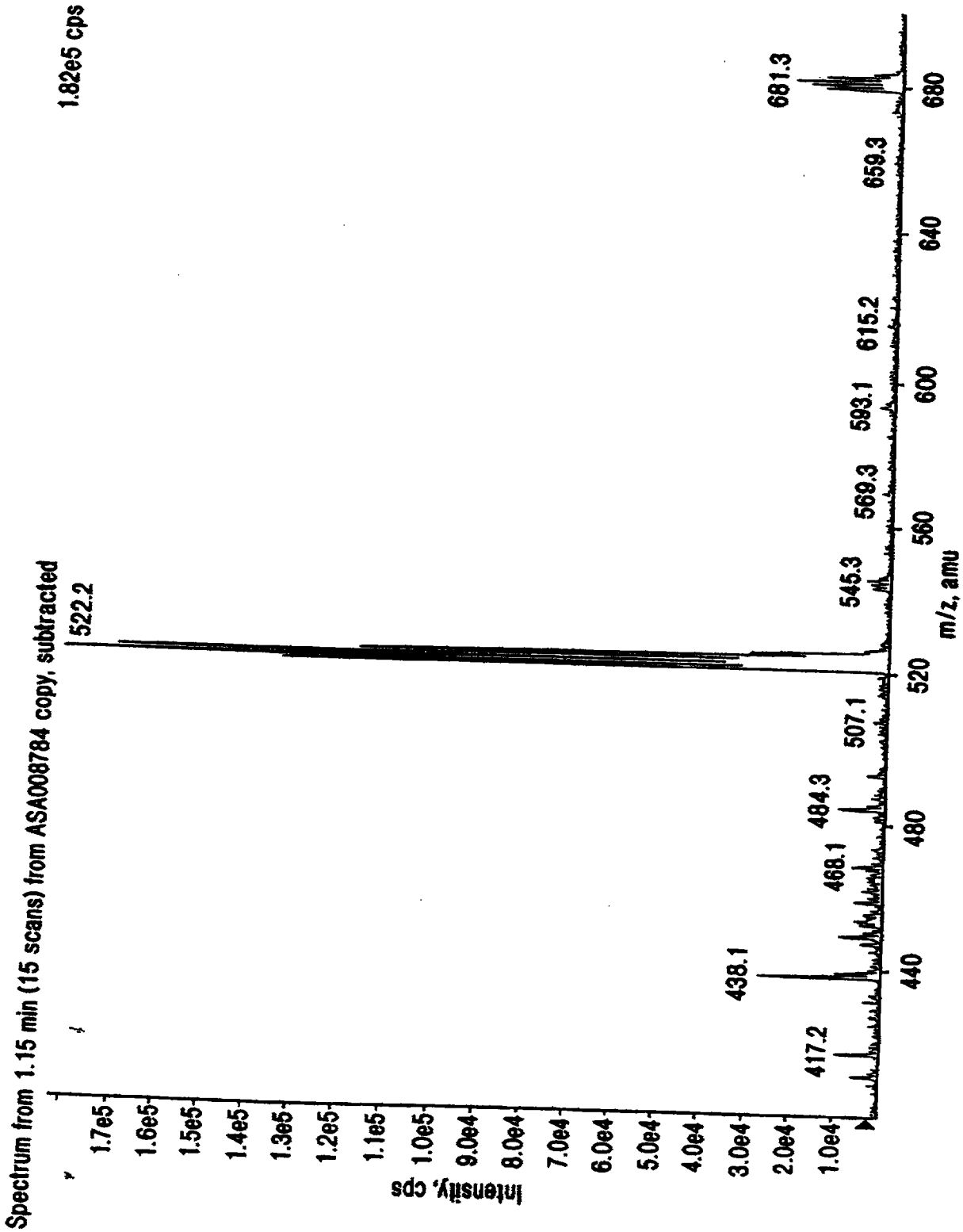

Spectrum from 1.15 min (15 scans) from ASA008784 copy, subtracted
1.82e5 cps
Intensity, cps
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
522.2
545.3
569.3
583.1
615.2
659.3
681.3
438.1
417.2
468.1
484.3
507.1
440
480
520
560
600
640
680
m/z, amu

FIG. 221

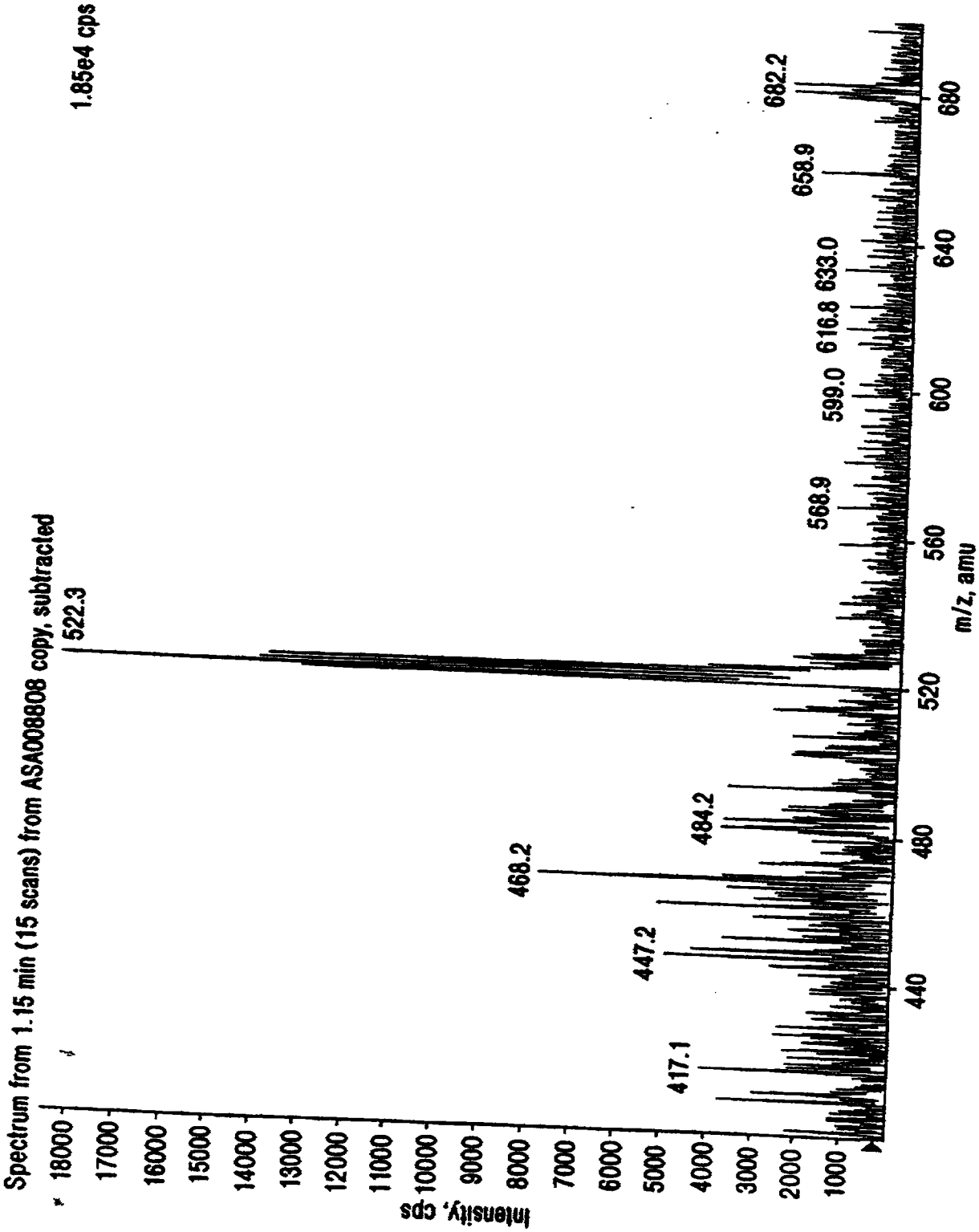

Spectrum from 1.15 min (15 scans) from ASA008808 copy, subtracted
1.85e4 cps
Intensity, cps
m/z, amu
522.3
568.9
599.0
616.8
633.0
658.9
682.2
468.2
484.2
447.2
417.1

FIG. 222

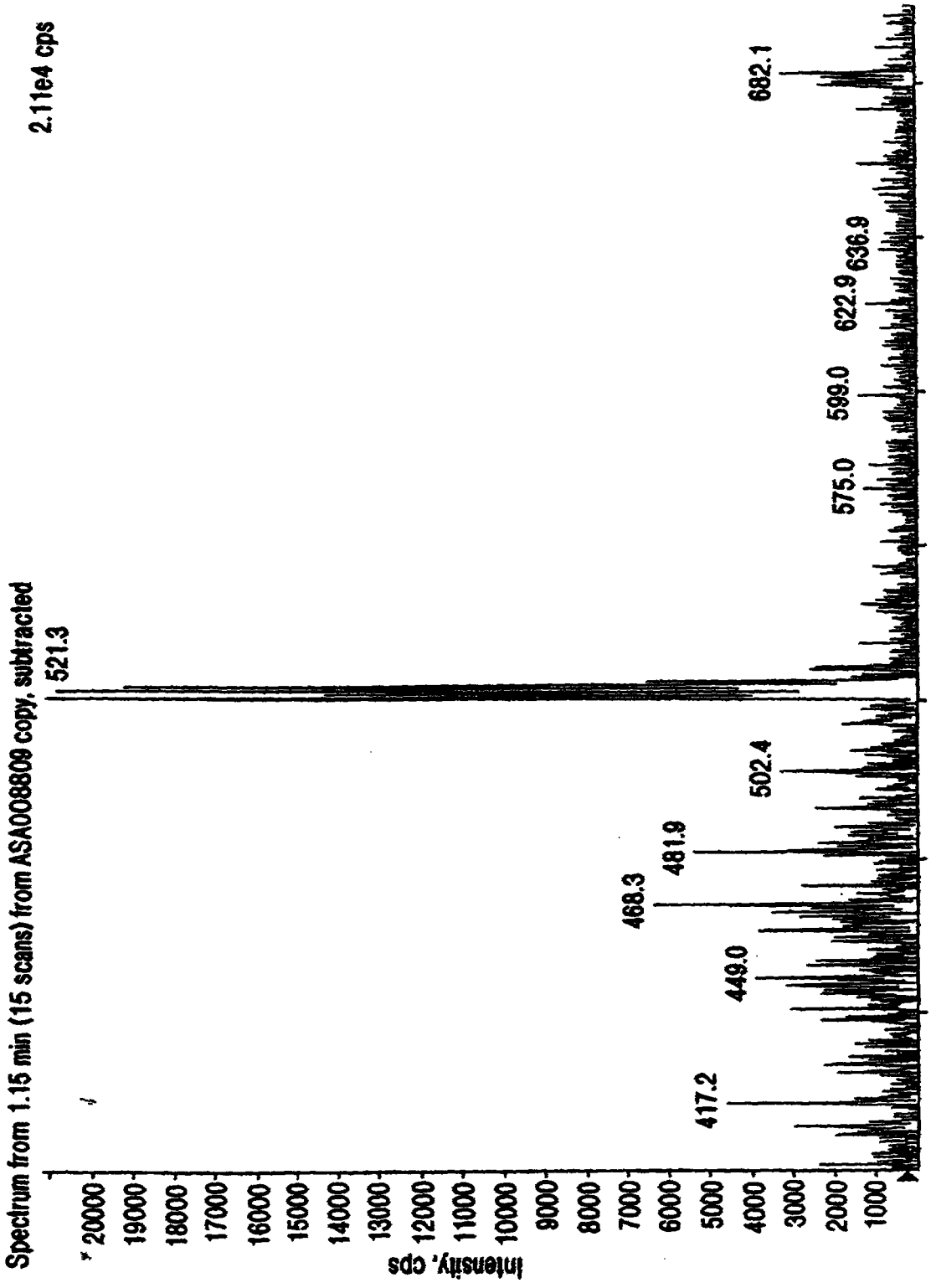

Spectrum from 1.15 min (15 scans) from ASA008809 copy, subtracted
2.11e4 cps
Intensity, cps
m/z, amu
521.3
682.1
636.9
622.9
599.0
575.0
502.4
481.9
468.3
449.0
417.2

FIG. 223

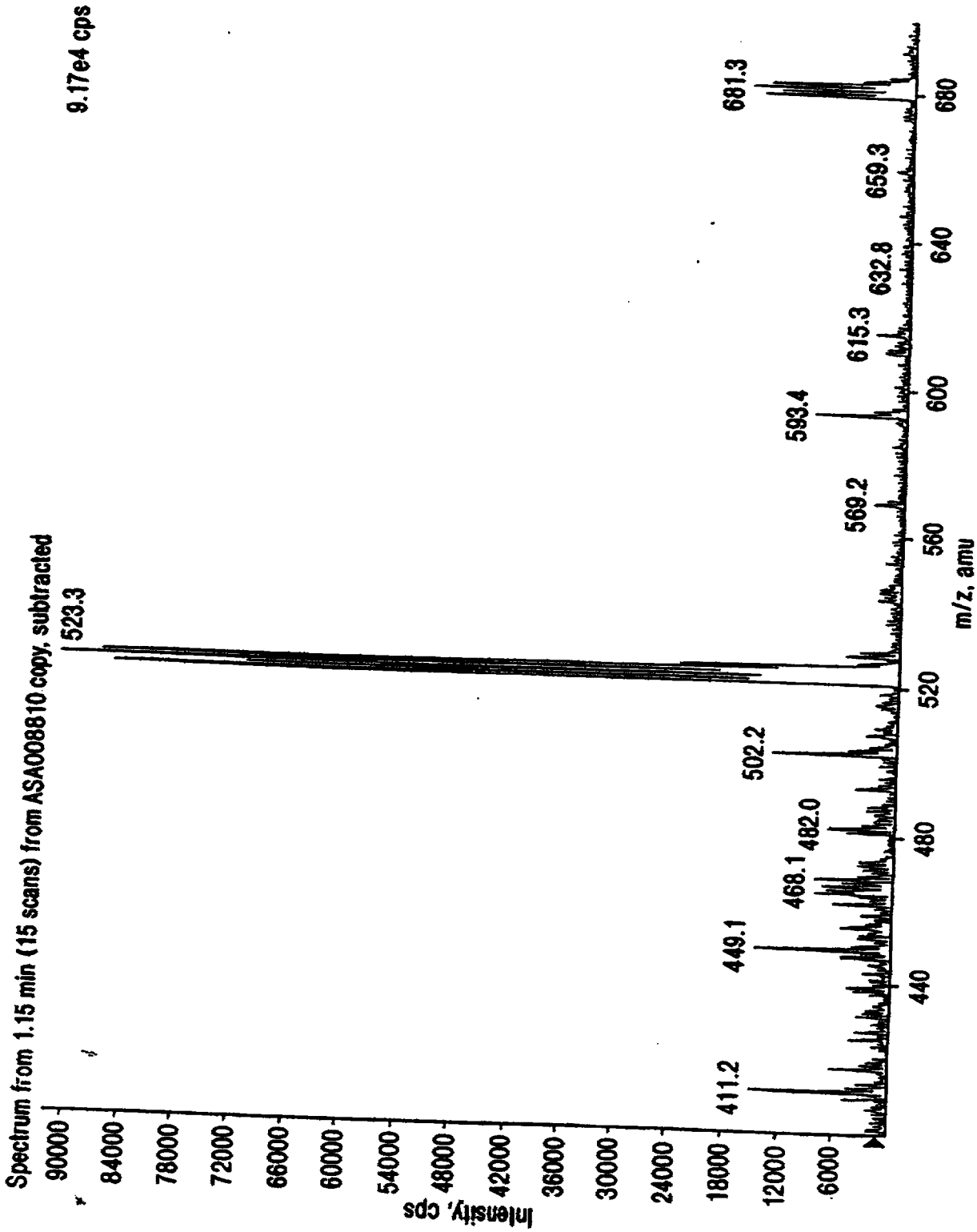

Spectrum from 1.15 min (15 scans) from ASA008810 copy, subtracted
9.17e4 cps
Intensity, cps
90000
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
523.3
411.2
449.1
468.1
482.0
502.2
569.2
593.4
615.3
632.8
659.3
681.3
440
480
520
560
600
640
680
m/z, amu

FIG. 224

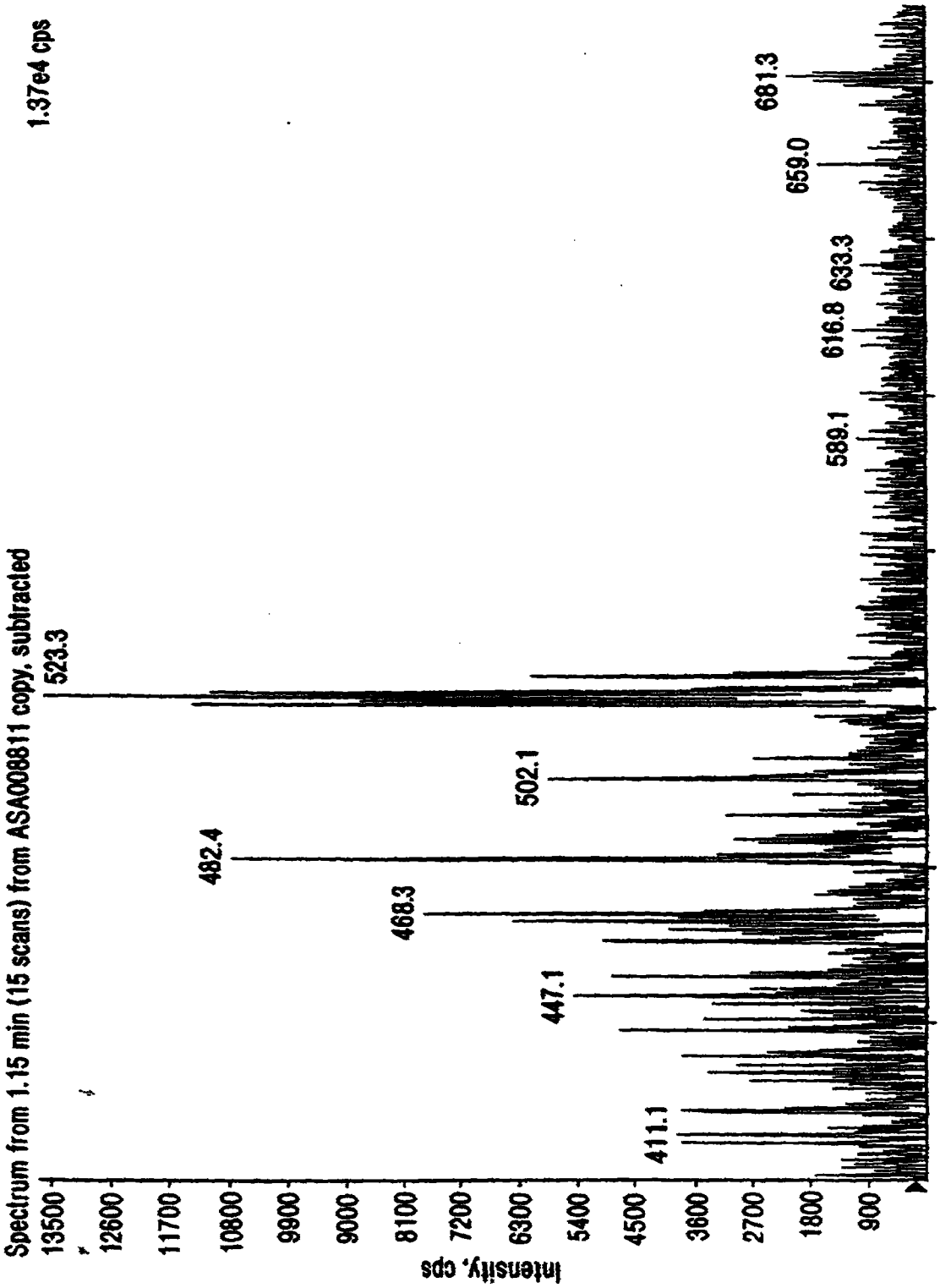

Spectrum from 1.15 min (15 scans) from ASA008811 copy, subtracted
1.37e4 cps
Intensity, cps
m/z, amu
523.3
482.4
468.3
502.1
447.1
411.1
589.1
616.8
633.3
659.0
681.3

FIG. 225

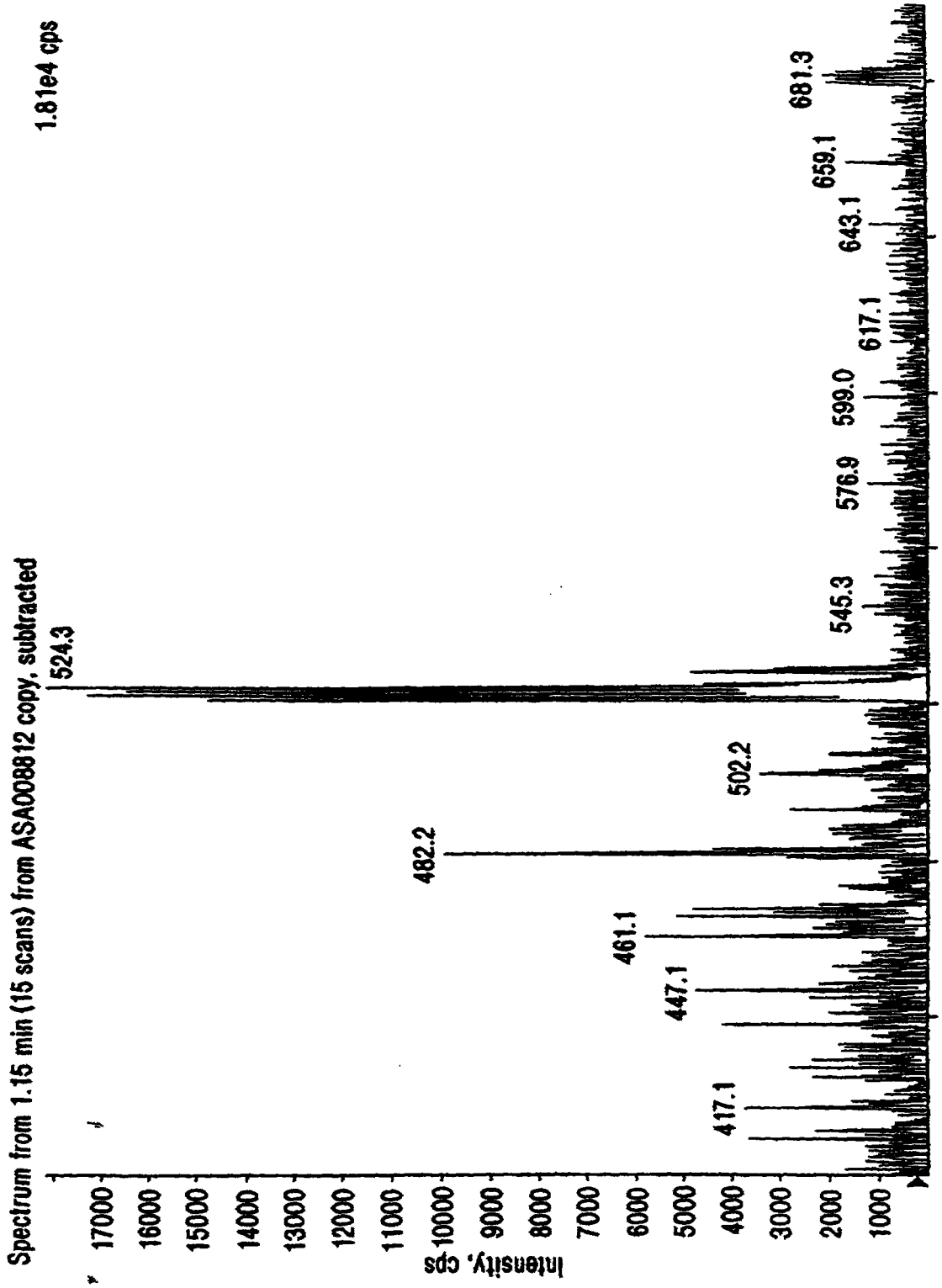

Spectrum from 1.15 min (15 scans) from ASA008812 copy, subtracted
1.81e4 cps
Intensity, cps
m/z, amu
524.3
482.2
502.2
461.1
447.1
417.1
545.3
576.9
599.0
617.1
643.1
659.1
681.3

FIG. 226

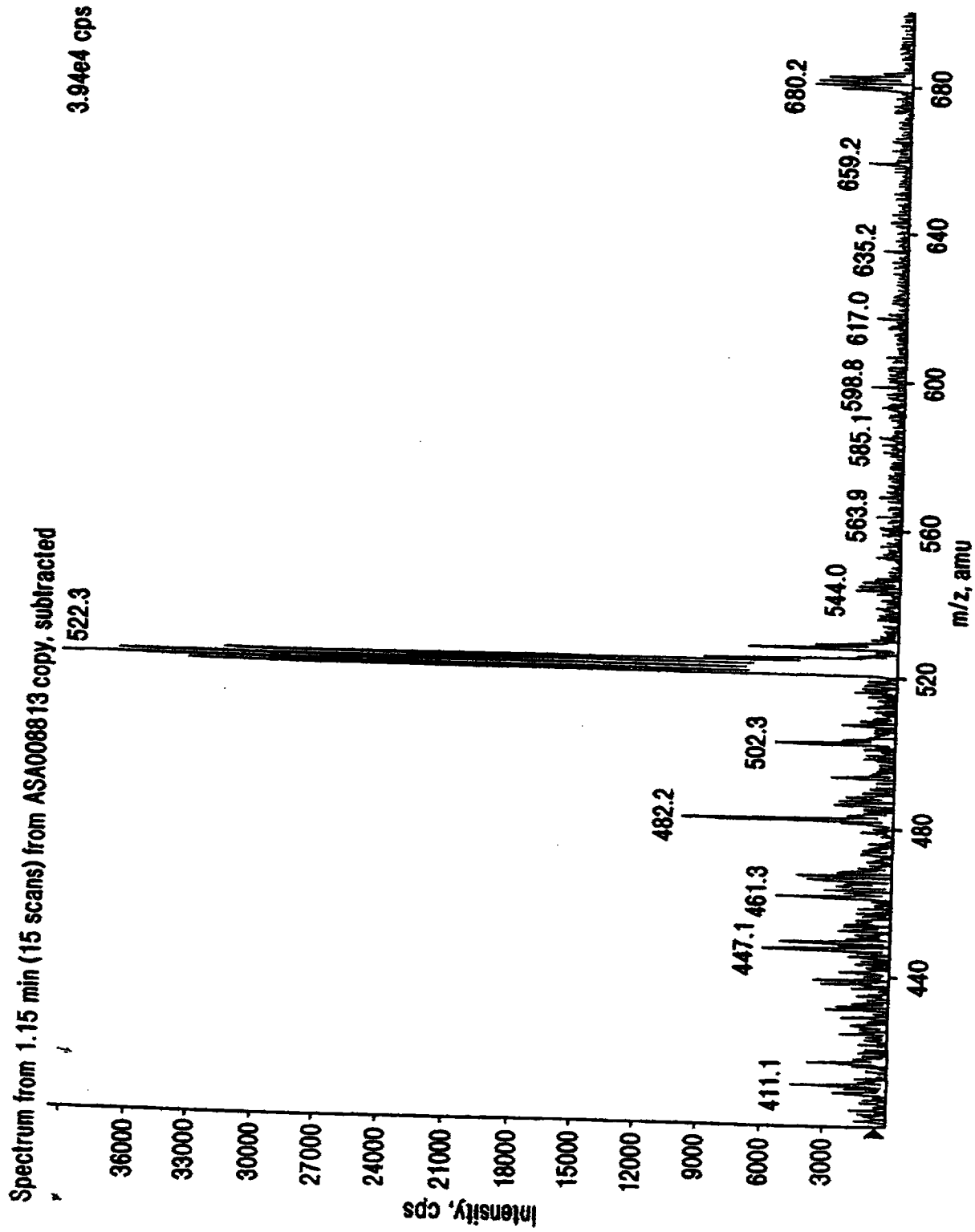

Spectrum from 1.15 min (15 scans) from ASA008813 copy, subtracted
3.94e4 cps
Intensity, cps
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
411.1
447.1
461.3
482.2
502.3
522.3
544.0
563.9
585.1
598.8
617.0
635.2
659.2
680.2
440
480
520
560
600
640
680
m/z, amu

FIG. 227

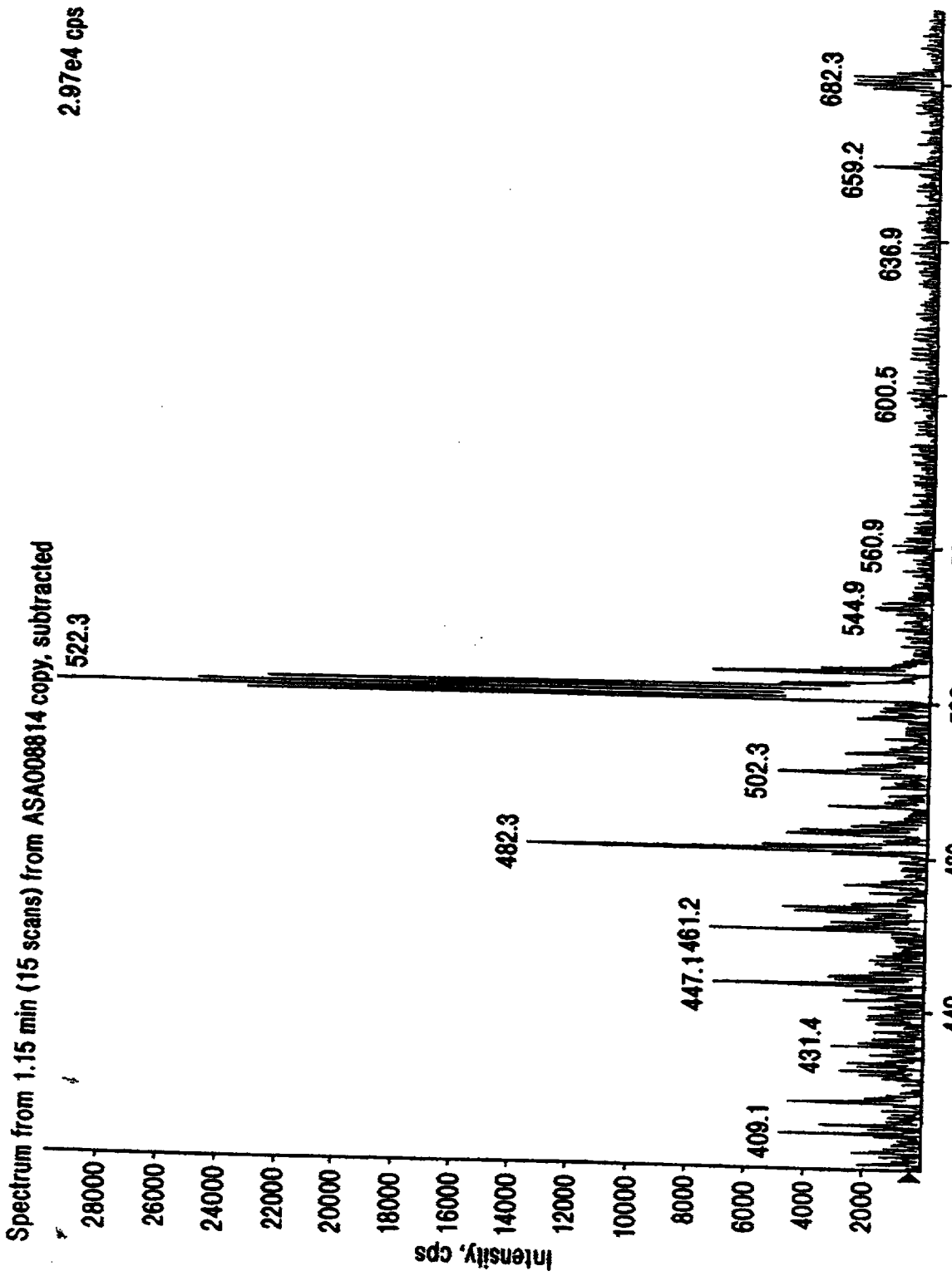

Spectrum from 1.15 min (15 scans) from ASA008814 copy, subtracted
2.97e4 cps
Intensity, cps
m/z, amu
522.3
482.3
502.3
447.1
461.2
431.4
409.1
544.9
560.9
600.5
636.9
659.2
682.3

FIG. 228

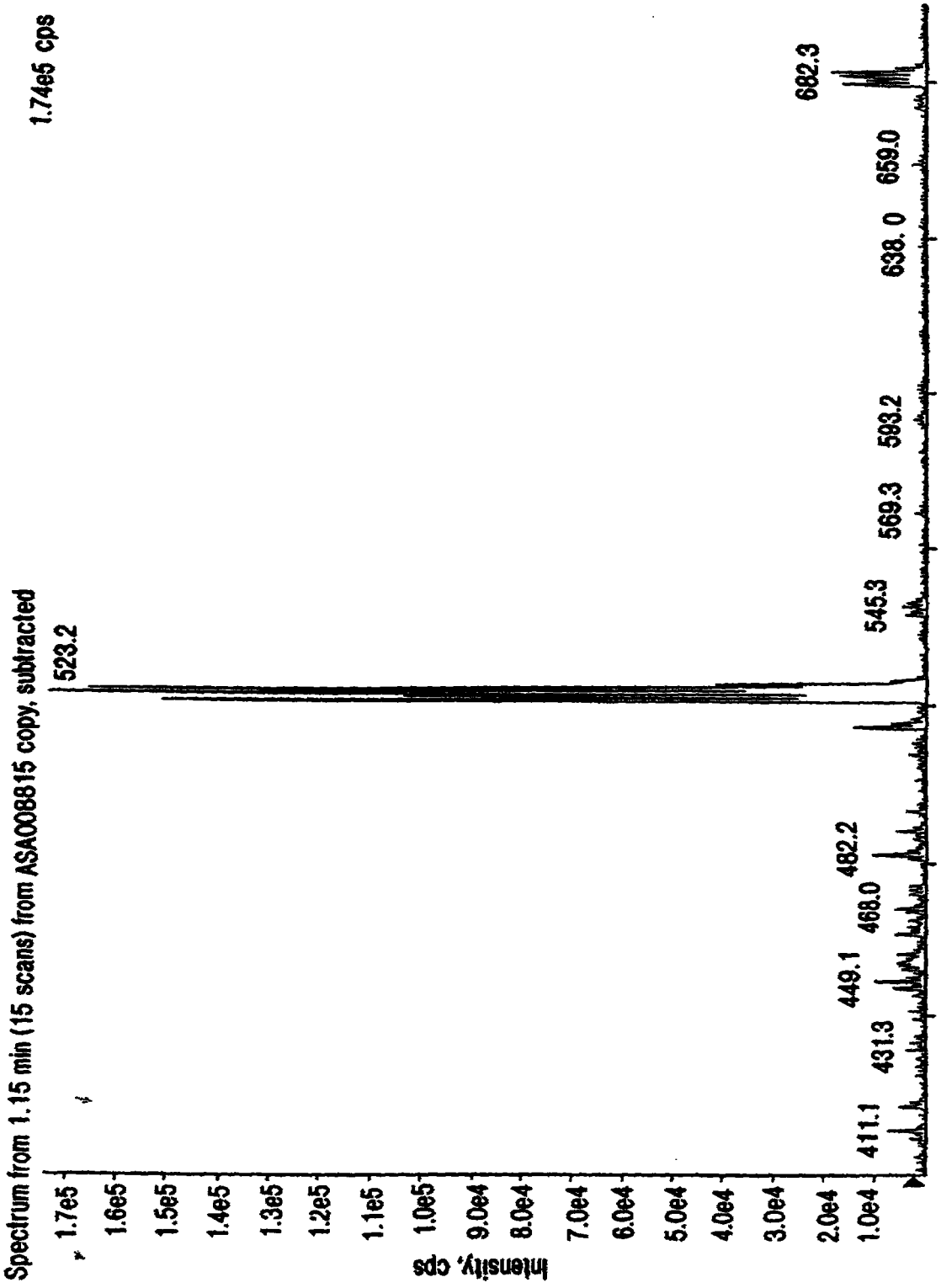

Spectrum from 1.15 min (15 scans) from ASA008815 copy, subtracted
1.74e5 cps
Intensity, cps
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
431.3
449.1
468.0
482.2
523.2
545.3
569.3
583.2
638.0
659.0
682.3
440
480
520
560
600
640
680
m/z, amu

FIG. 229

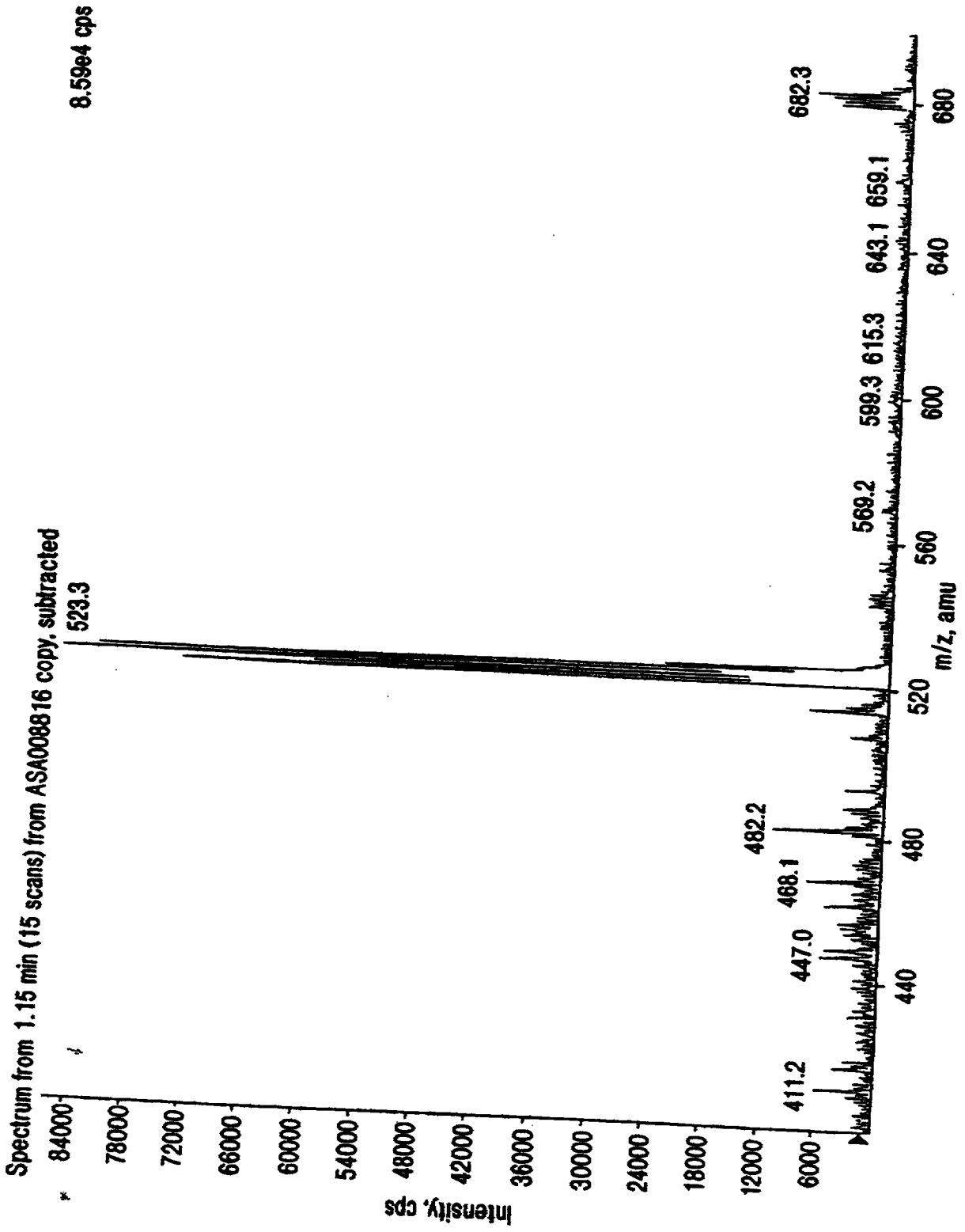

Spectrum from 1.15 min (15 scans) from ASA008816 copy, subtracted
8.59e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
523.3
411.2
447.0
468.1
482.2
569.2
589.3
615.3
643.1
659.1
682.3
440
480
520
560
600
640
680
m/z, amu

FIG. 230

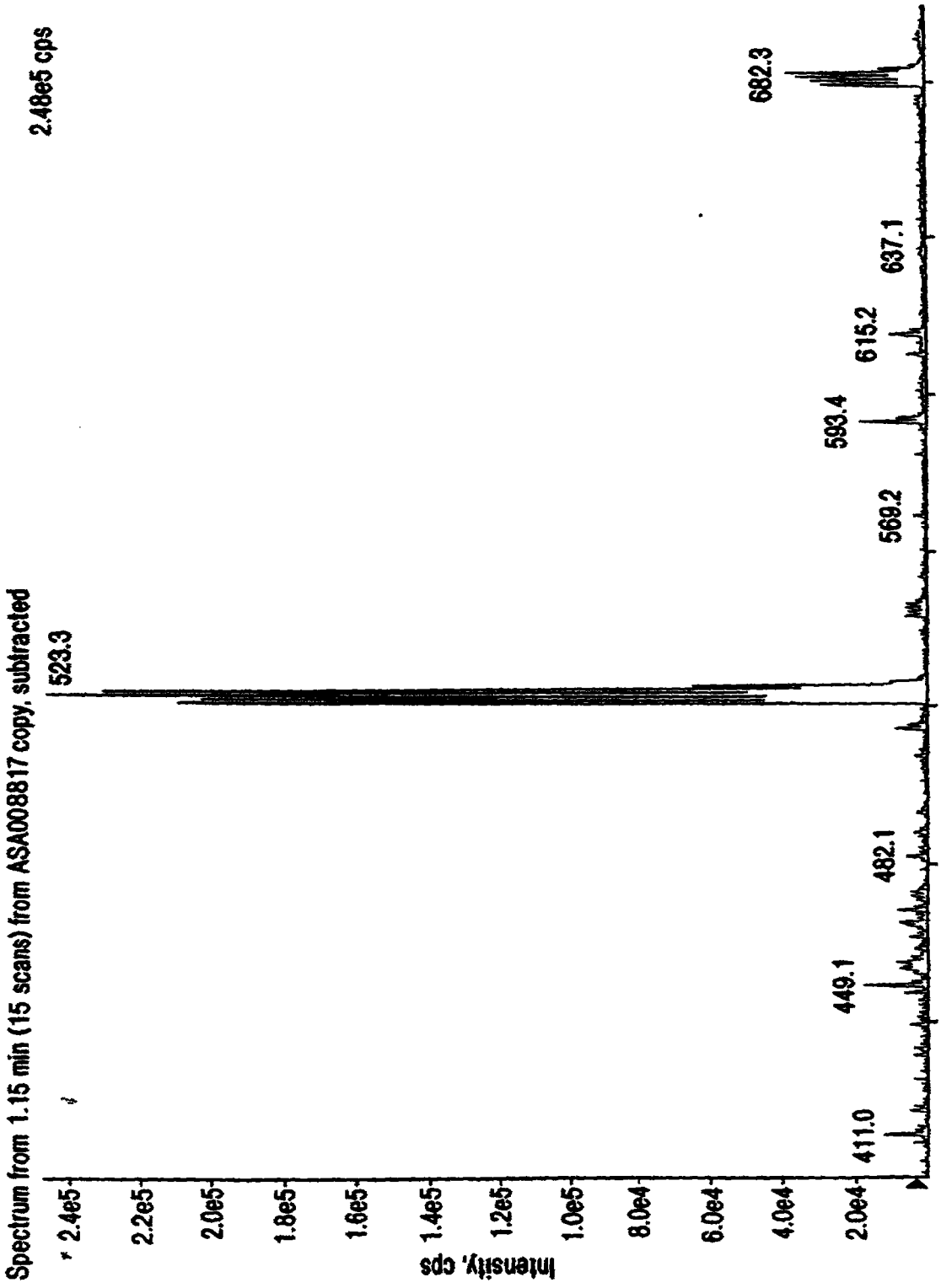

Spectrum from 1.15 min (15 scans) from ASA008B17 copy, subtracted
2.48e5 cps
Intensity, cps
2.4e5
2.2e5
2.0e5
1.8e5
1.6e5
1.4e5
1.2e5
1.0e5
8.0e4
6.0e4
4.0e4
2.0e4
411.0
449.1
482.1
523.3
569.2
583.4
615.2
637.1
682.3
440
480
520
560
600
640
680
m/z, amu

FIG. 231

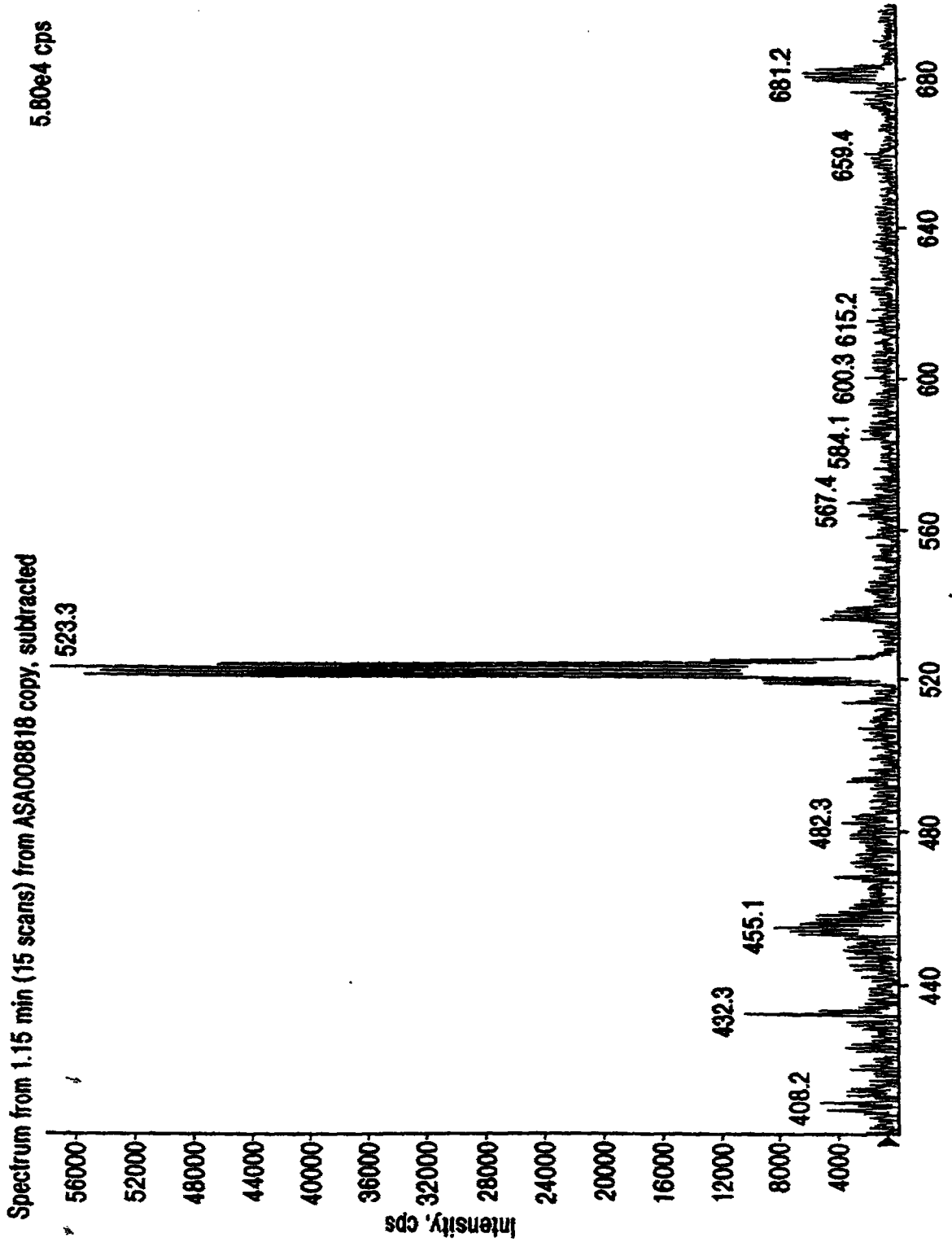

Spectrum from 1.15 min (15 scans) from ASA008818 copy, subtracted
5.80e4 cps
Intensity, cps
m/z, amu
523.3
567.4
584.1
600.3
615.2
659.4
681.2
482.3
455.1
432.3
408.2

FIG. 232

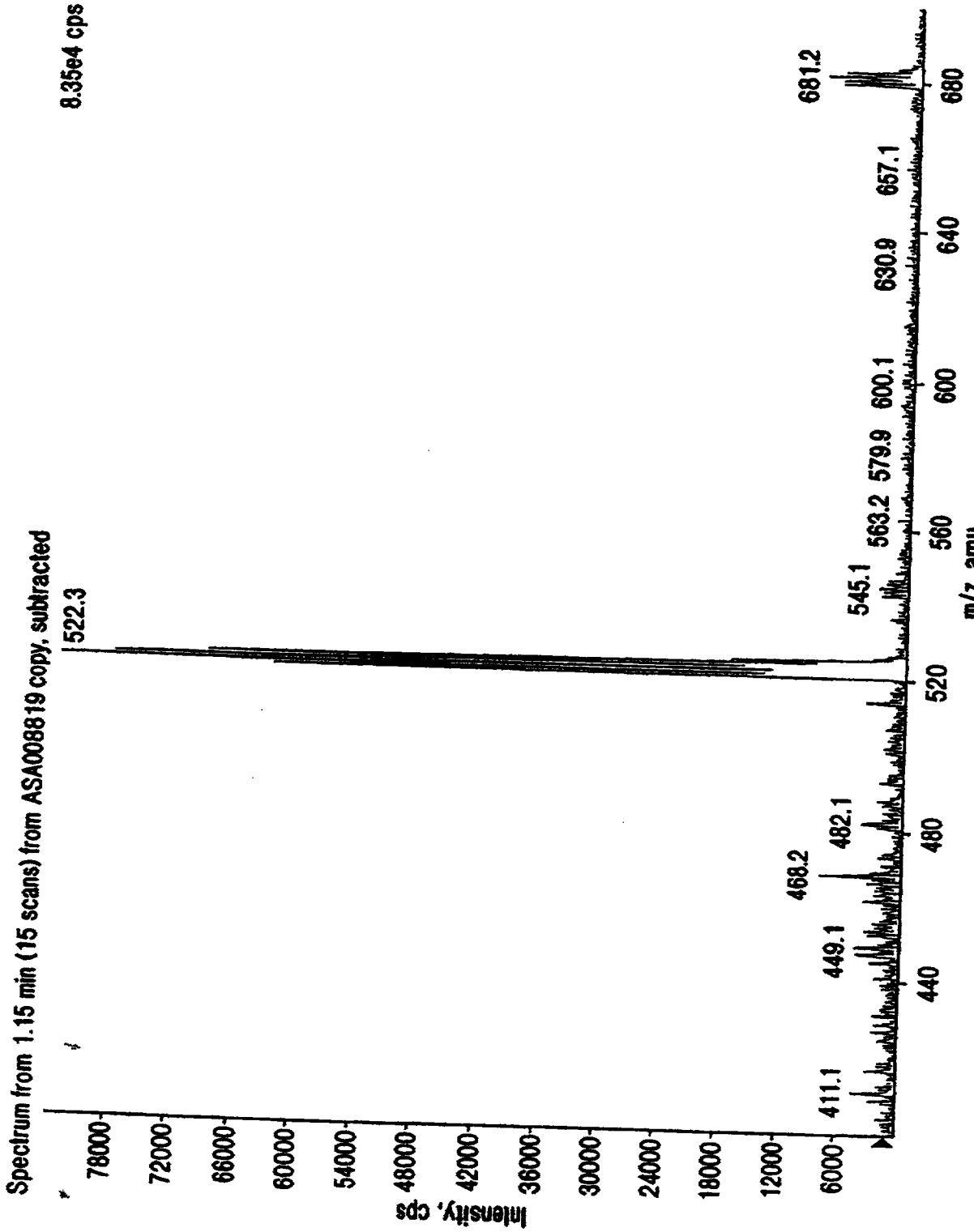

Spectrum from 1.15 min (15 scans) from ASA008819 copy, subtracted
8.35e4 cps
Intensity, cps
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.1
449.1
468.2
482.1
522.3
545.1
563.2
579.9
600.1
630.9
657.1
681.2
440
480
520
560
600
640
680
m/z, amu

FIG. 233

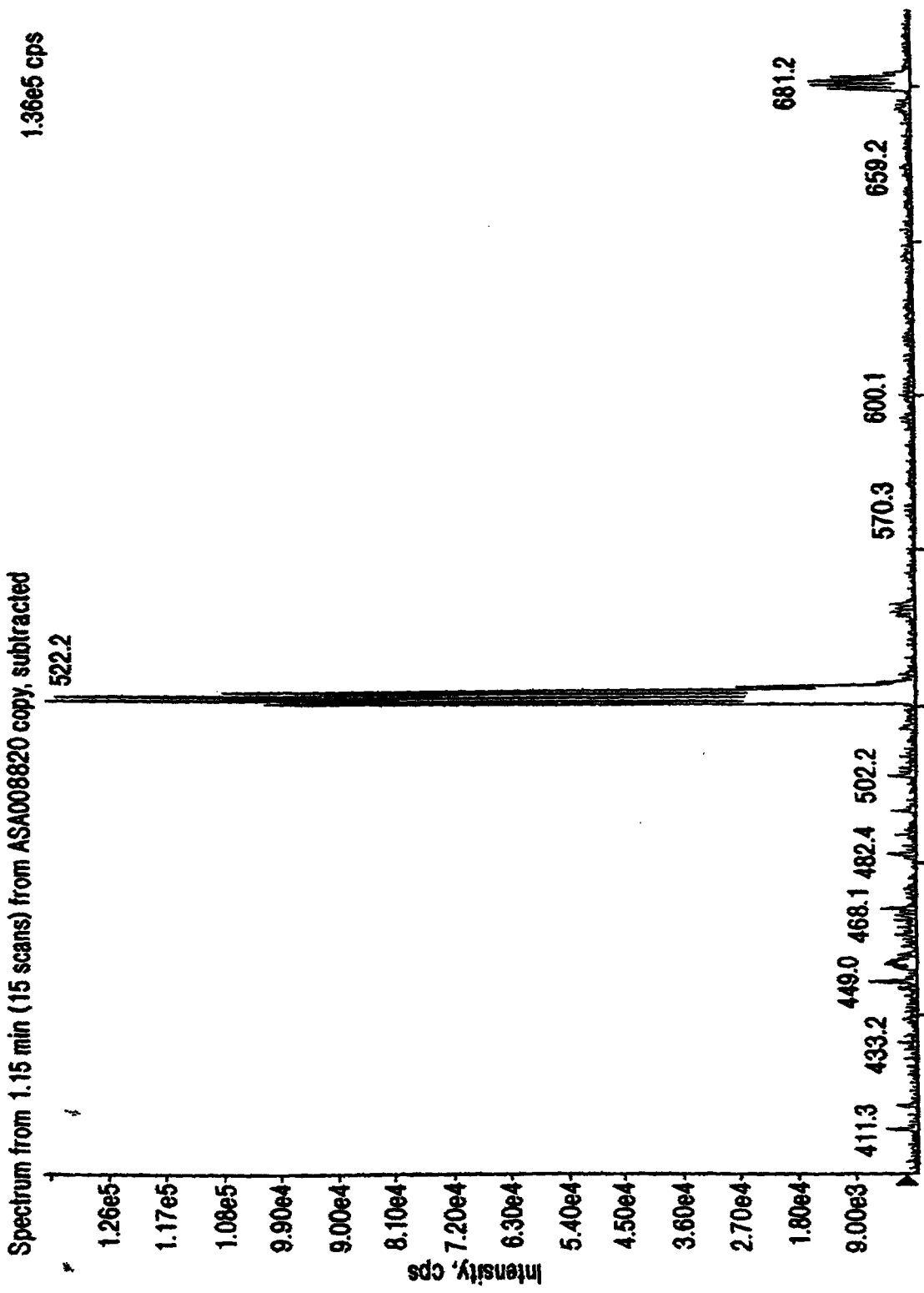

Spectrum from 1.15 min (15 scans) from ASA008820 copy, subtracted
1.36e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
m/z, amu
411.3
433.2
449.0
468.1
482.4
502.2
522.2
570.3
600.1
659.2
681.2
440
480
520
560
600
640
680

FIG. 234

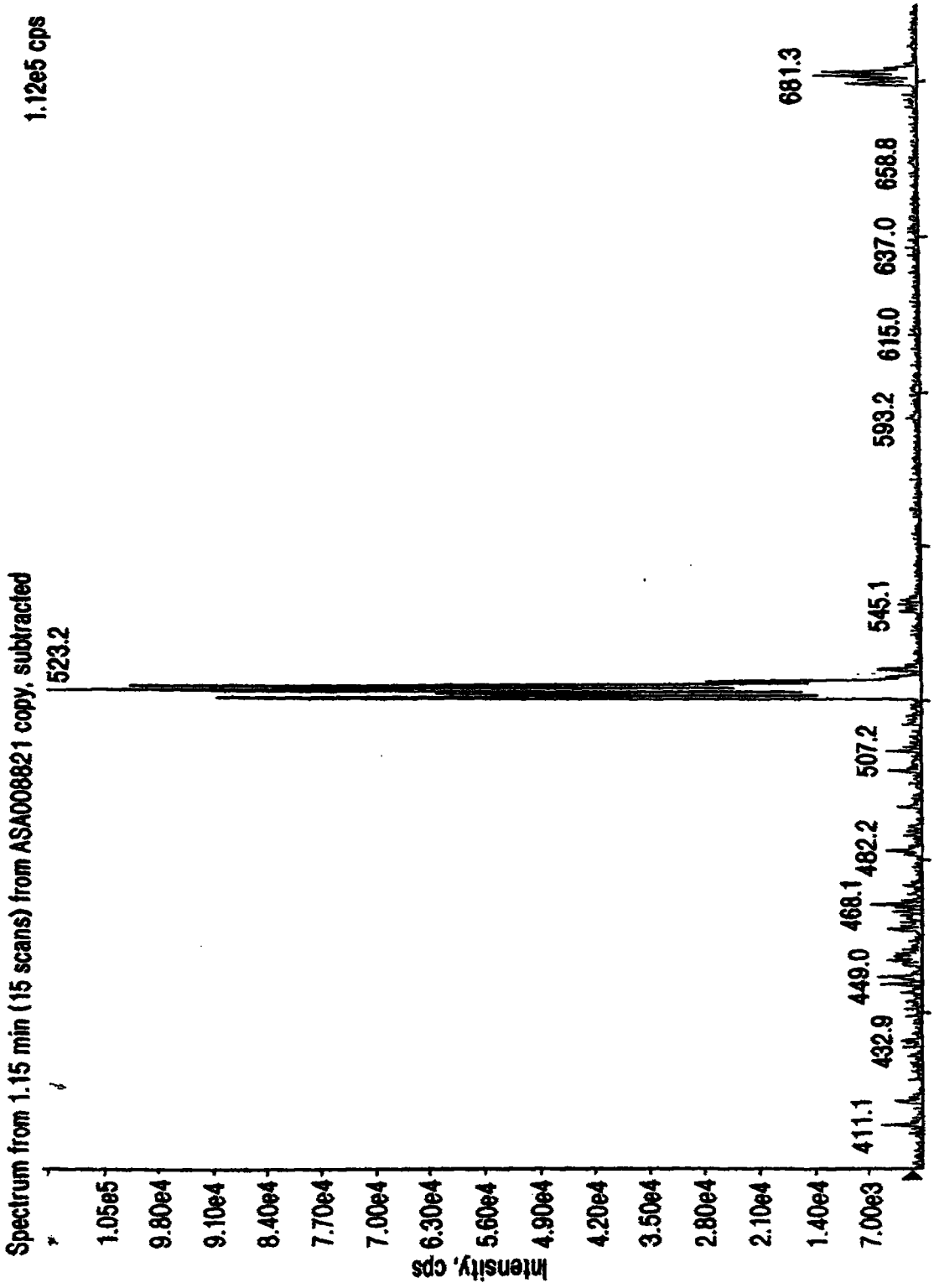

Spectrum from 1.15 min (15 scans) from ASA008821 copy, subtracted
1.12e5 cps
Intensity, cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
411.1
432.9
449.0
468.1
482.2
507.2
523.2
545.1
593.2
615.0
637.0
658.8
681.3
440
480
520
560
600
640
680
m/z, amu

FIG. 235

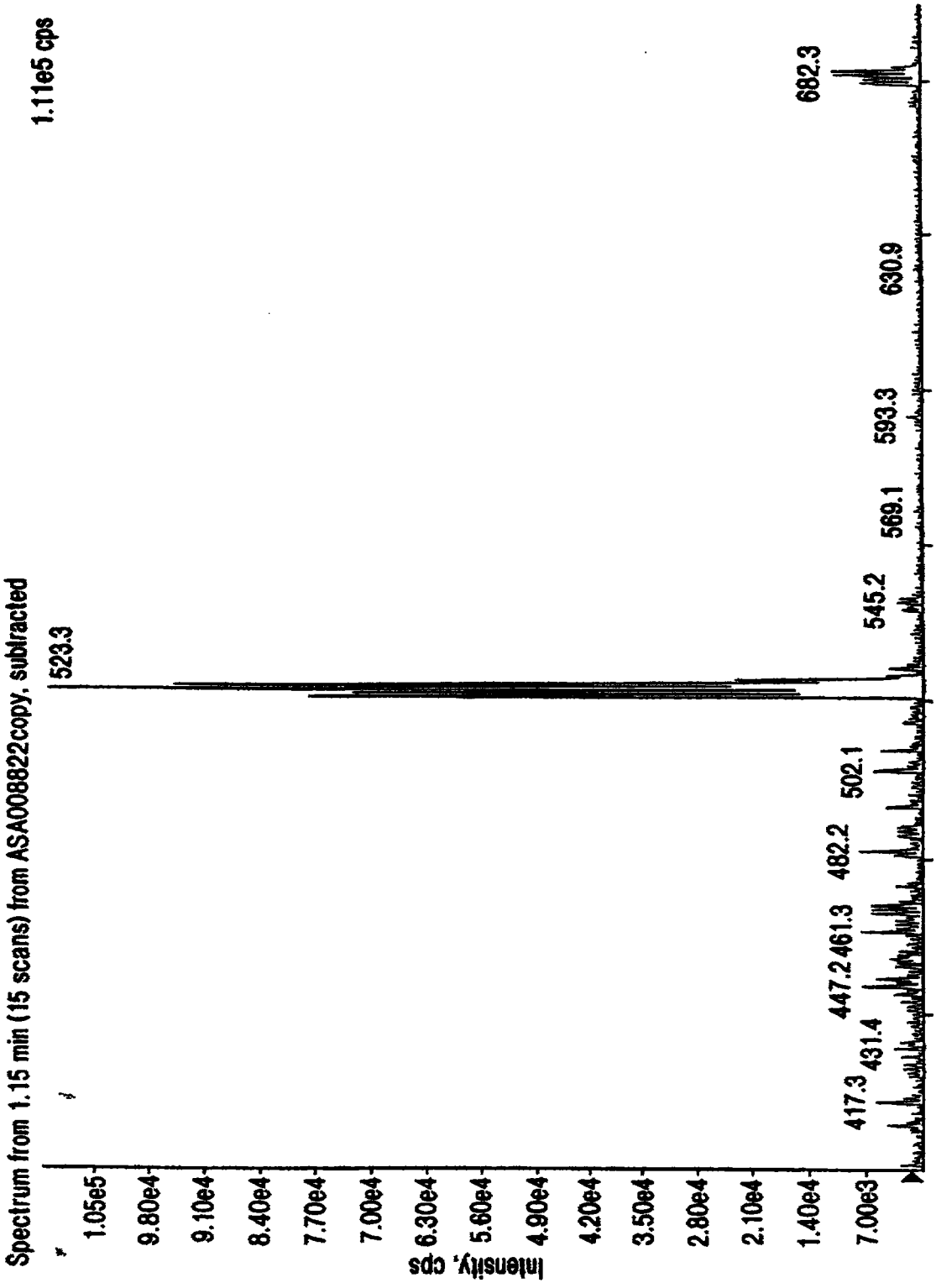

Spectrum from 1.15 min (15 scans) from ASA008822copy, subtracted
1.11e5 cps
Intensity, cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
523.3
545.2
569.1
593.3
630.9
682.3
502.1
482.2
461.3
447.2
431.4
417.3
440
480
520
560
600
640
680
m/z, amu

FIG. 236

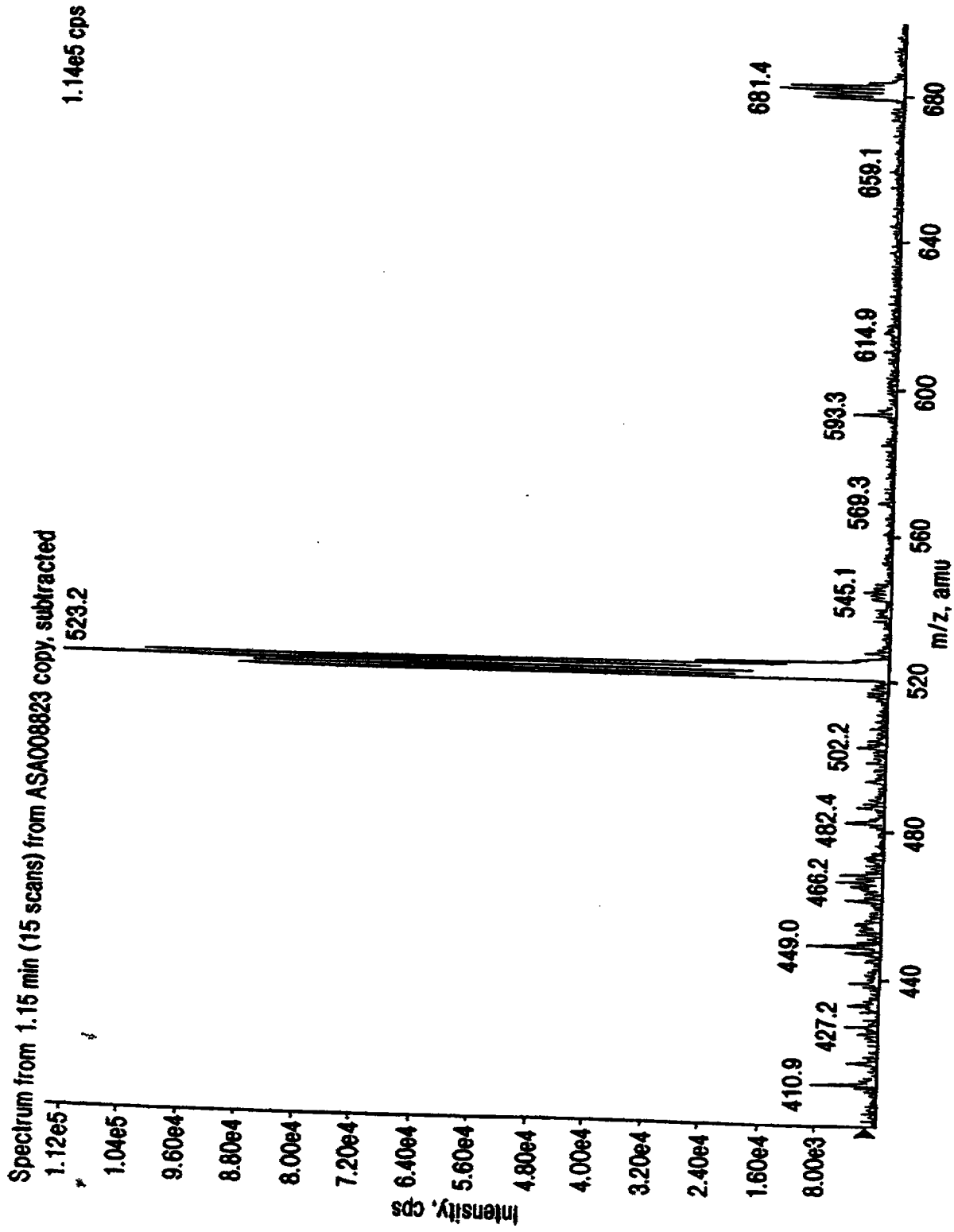

Spectrum from 1.15 min (15 scans) from ASA008823 copy, subtracted
1.14e5 cps
Intensity, cps
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
440
480
520
560
600
640
680
410.9
427.2
449.0
466.2
482.4
502.2
523.2
545.1
569.3
593.3
614.9
659.1
681.4

FIG. 237

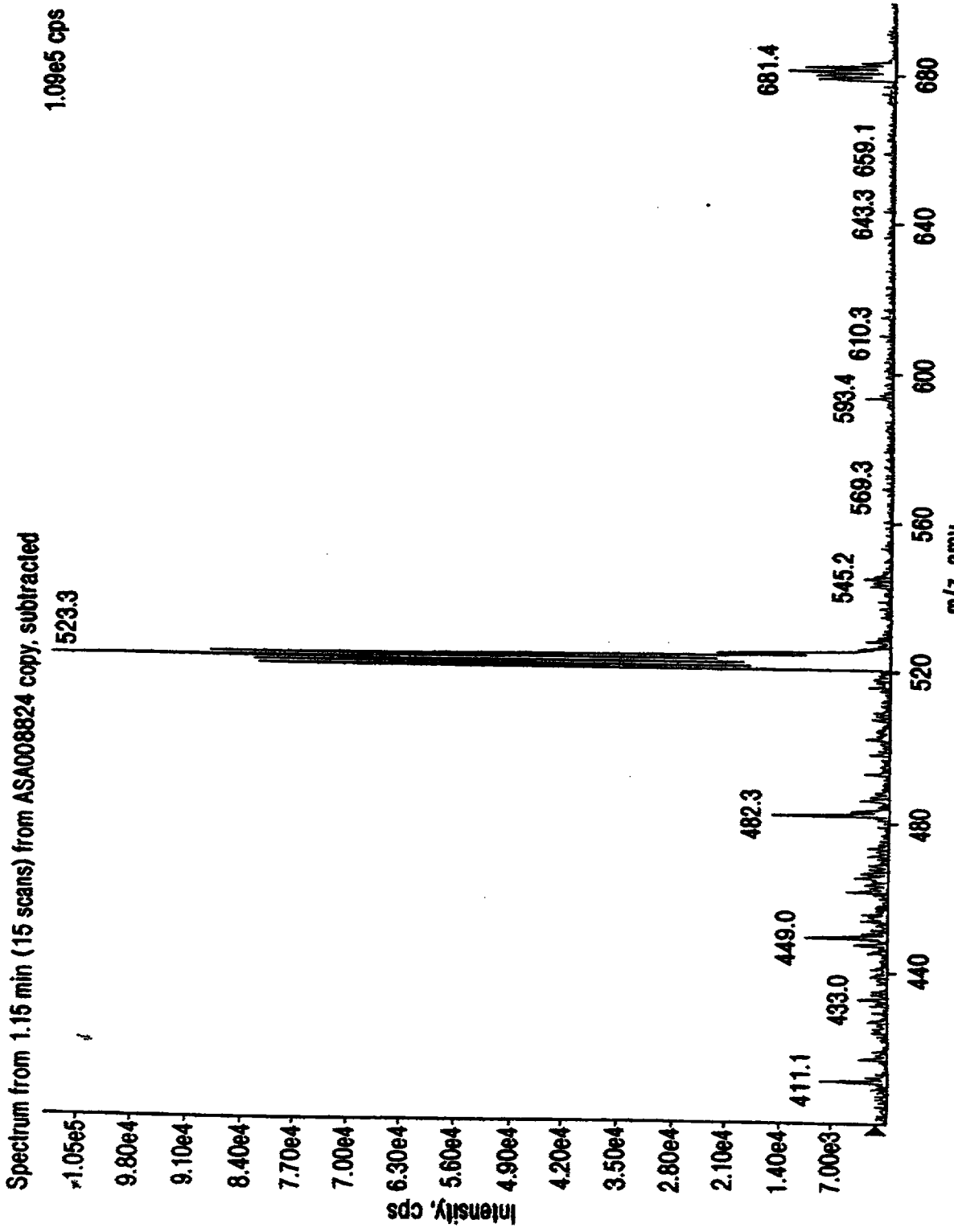

Spectrum from 1.15 min (15 scans) from ASA008824 copy, subtracted
1.09e5 cps
Intensity, cps
m/z, amu
523.3
545.2
569.3
593.4
610.3
643.3
659.1
681.4
482.3
449.0
433.0
411.1

FIG. 238

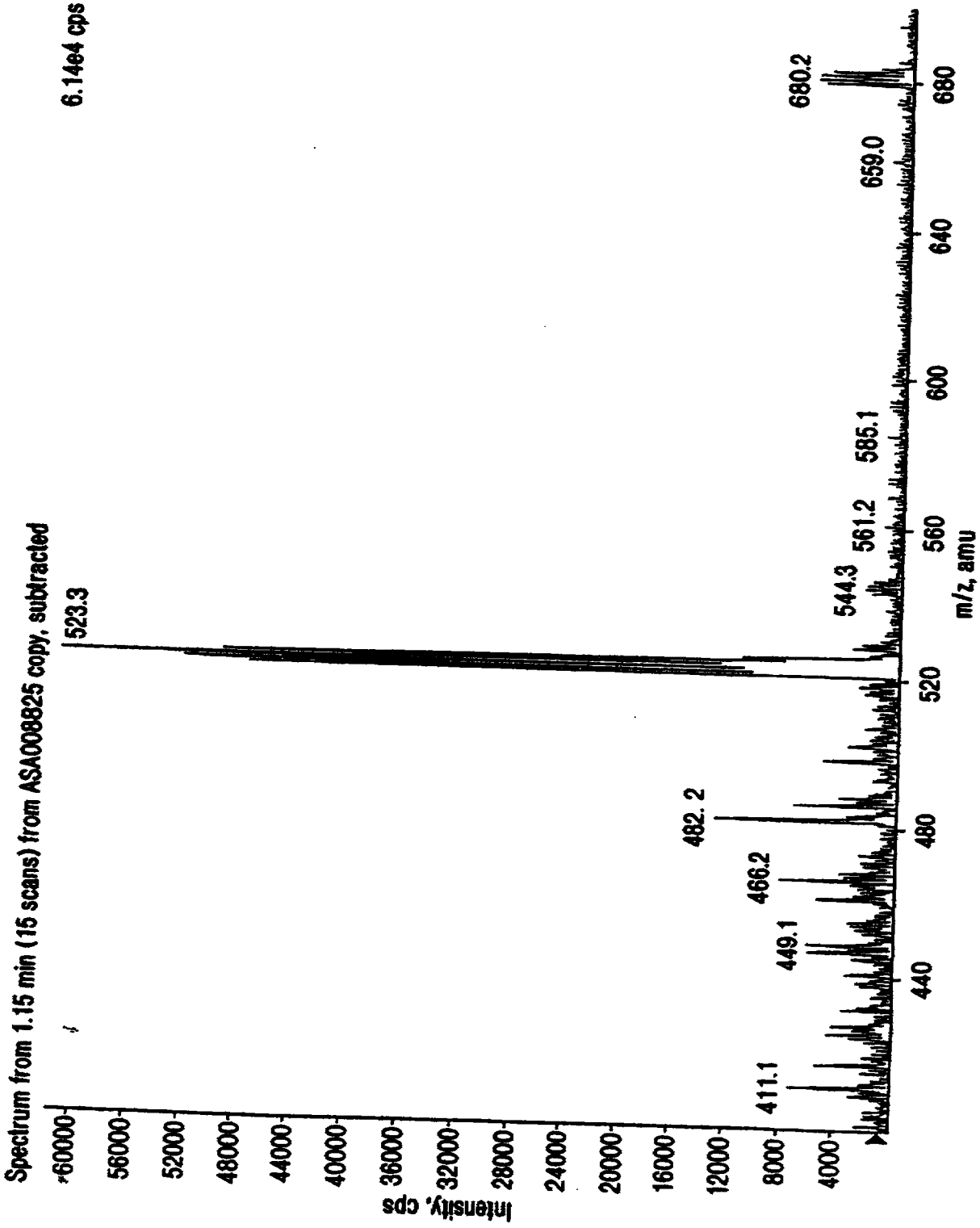

Spectrum from 1.15 min (15 scans) from ASA008825 copy, subtracted
6.14e4 cps
Intensity, cps
m/z, amu
523.3
544.3
561.2
585.1
659.0
680.2
482.2
466.2
449.1
411.1

FIG. 239

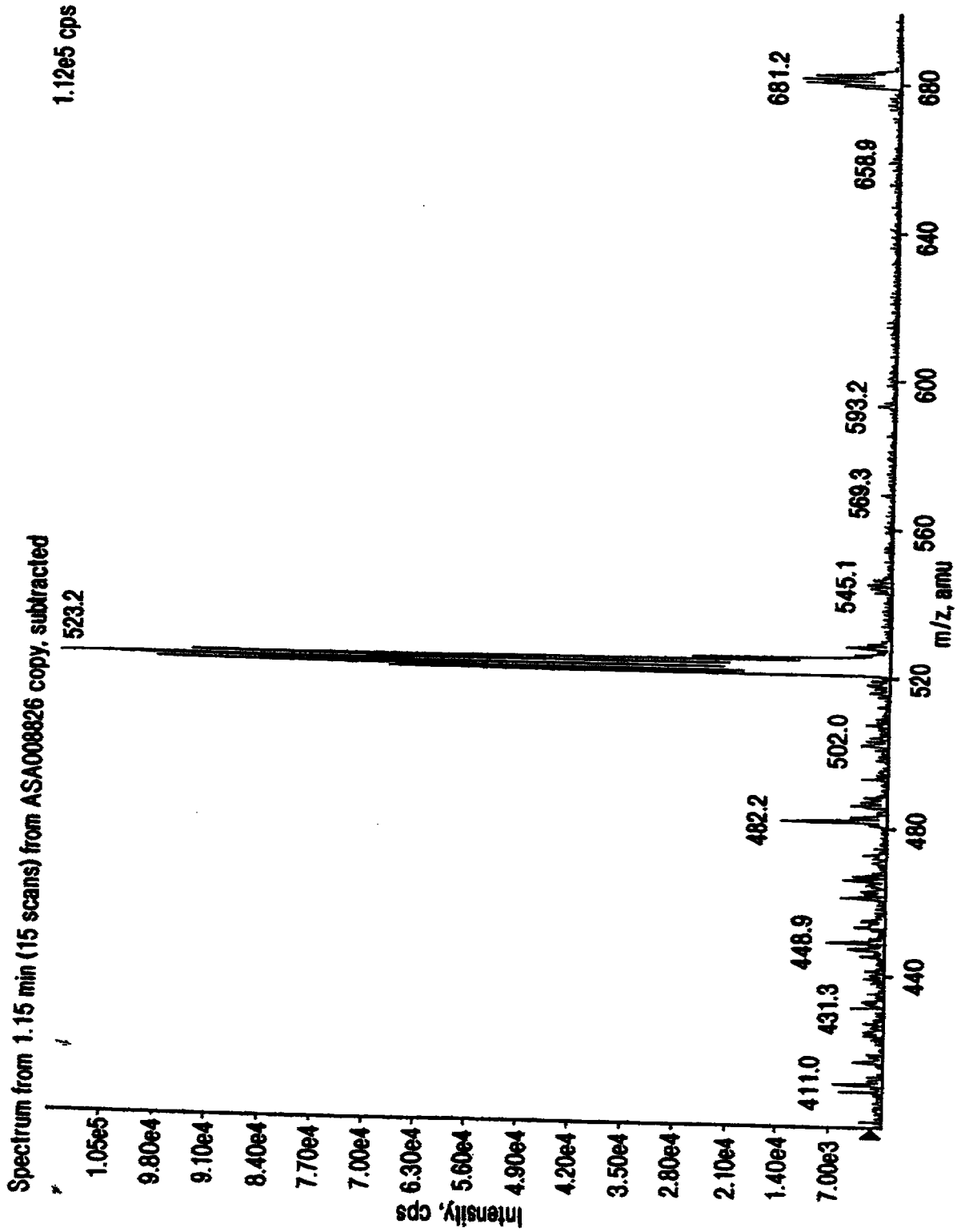

Spectrum from 1.15 min (15 scans) from ASA008826 copy, subtracted
1.12e5 cps
Intensity, cps
1.05e5
9.80e4
9.10e4
8.40e4
7.70e4
7.00e4
6.30e4
5.60e4
4.90e4
4.20e4
3.50e4
2.80e4
2.10e4
1.40e4
7.00e3
m/z, amu
440
480
520
560
600
640
680
411.0
431.3
448.9
482.2
502.0
523.2
545.1
569.3
593.2
658.9
681.2

FIG. 240

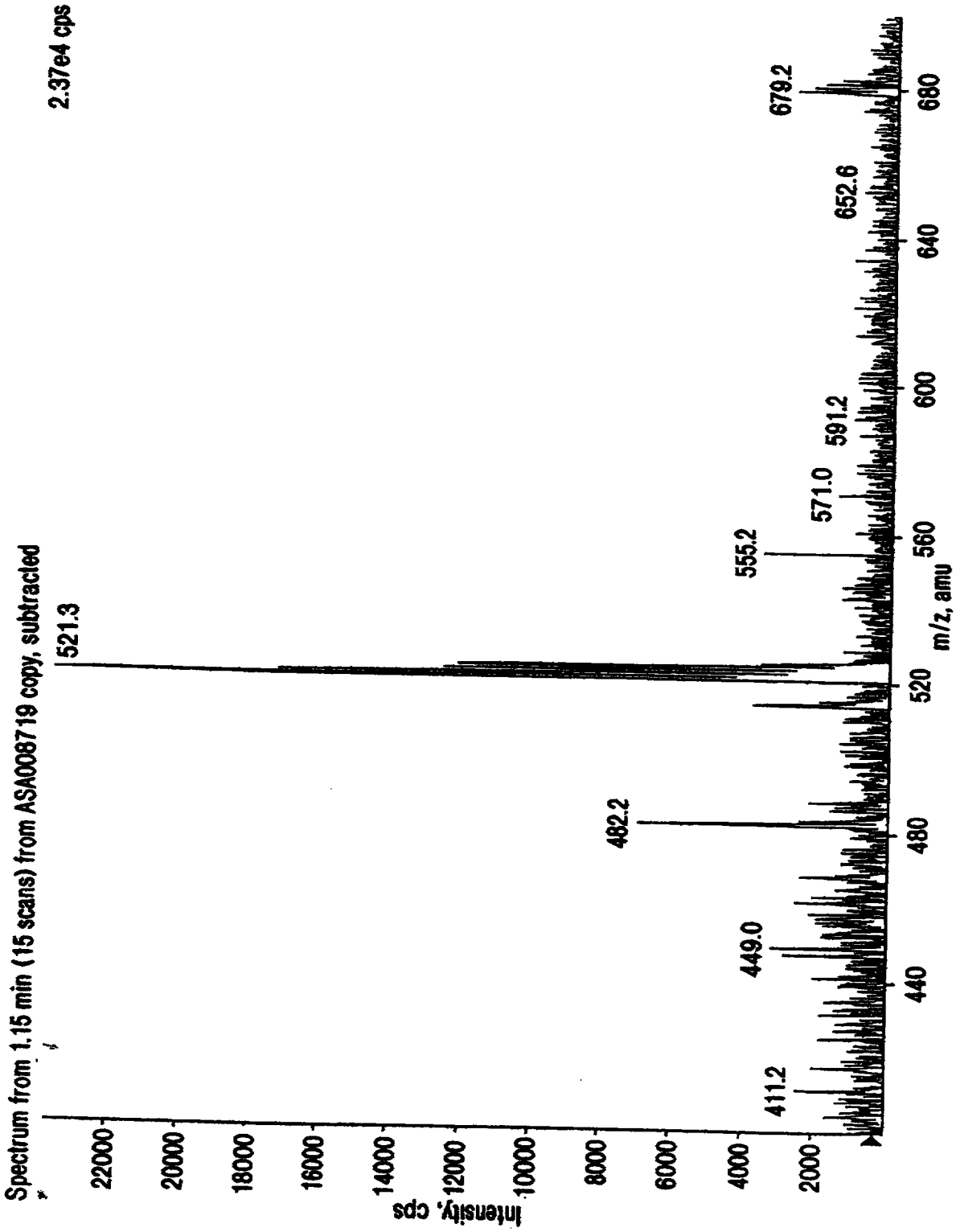

Spectrum from 1.15 min (15 scans) from ASA008719 copy, subtracted
2.37e4 cps
Intensity, cps
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
m/z, amu
520
560
600
640
680
521.3
555.2
571.0
591.2
652.6
679.2
482.2
449.0
411.2
440
480

FIG. 241

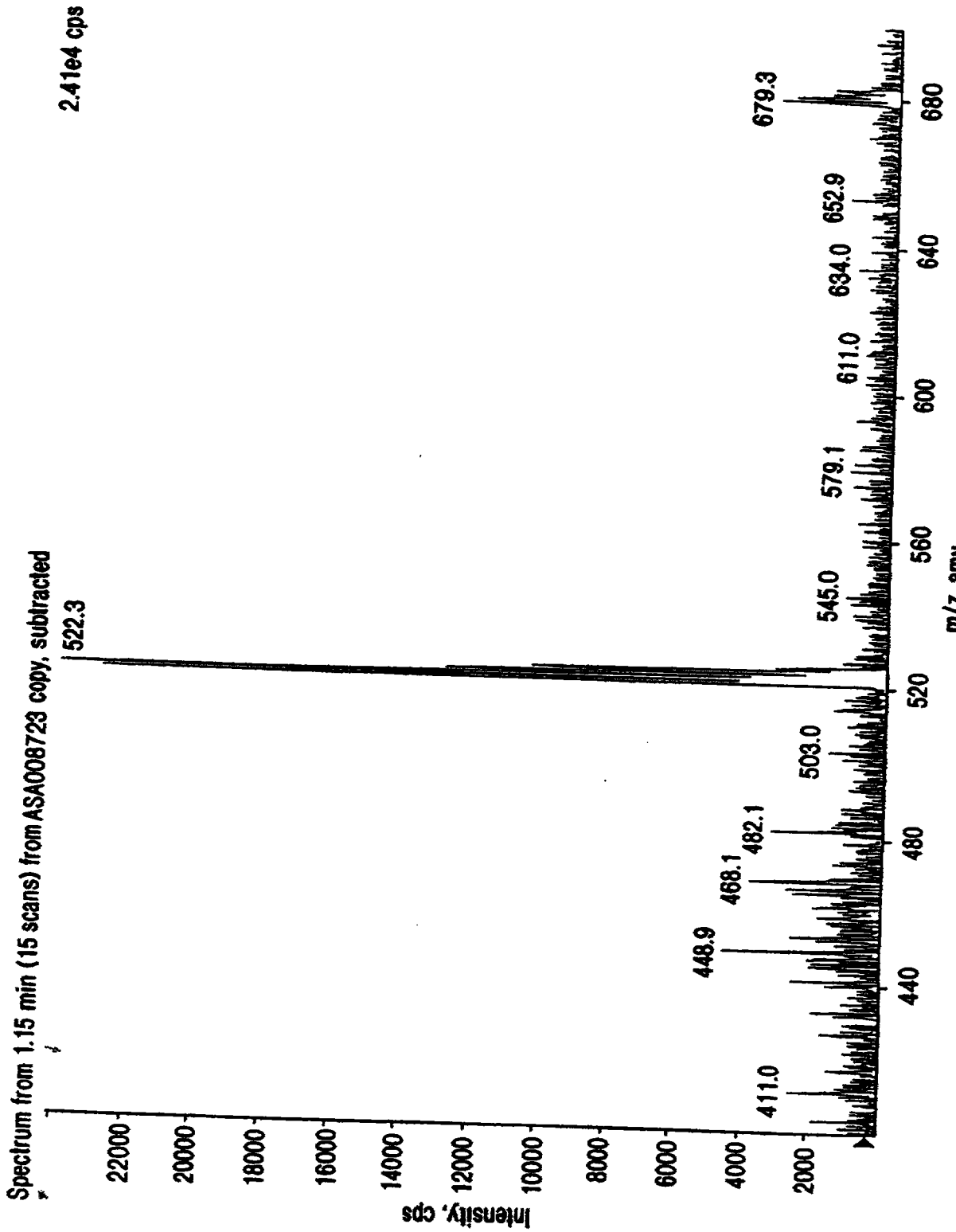

Spectrum from 1.15 min (15 scans) from ASA008723 copy, subtracted
2.41e4 cps
Intensity, cps
m/z, amu
522.3
545.0
579.1
611.0
634.0
652.9
679.3
503.0
482.1
468.1
448.9
411.0

FIG. 242

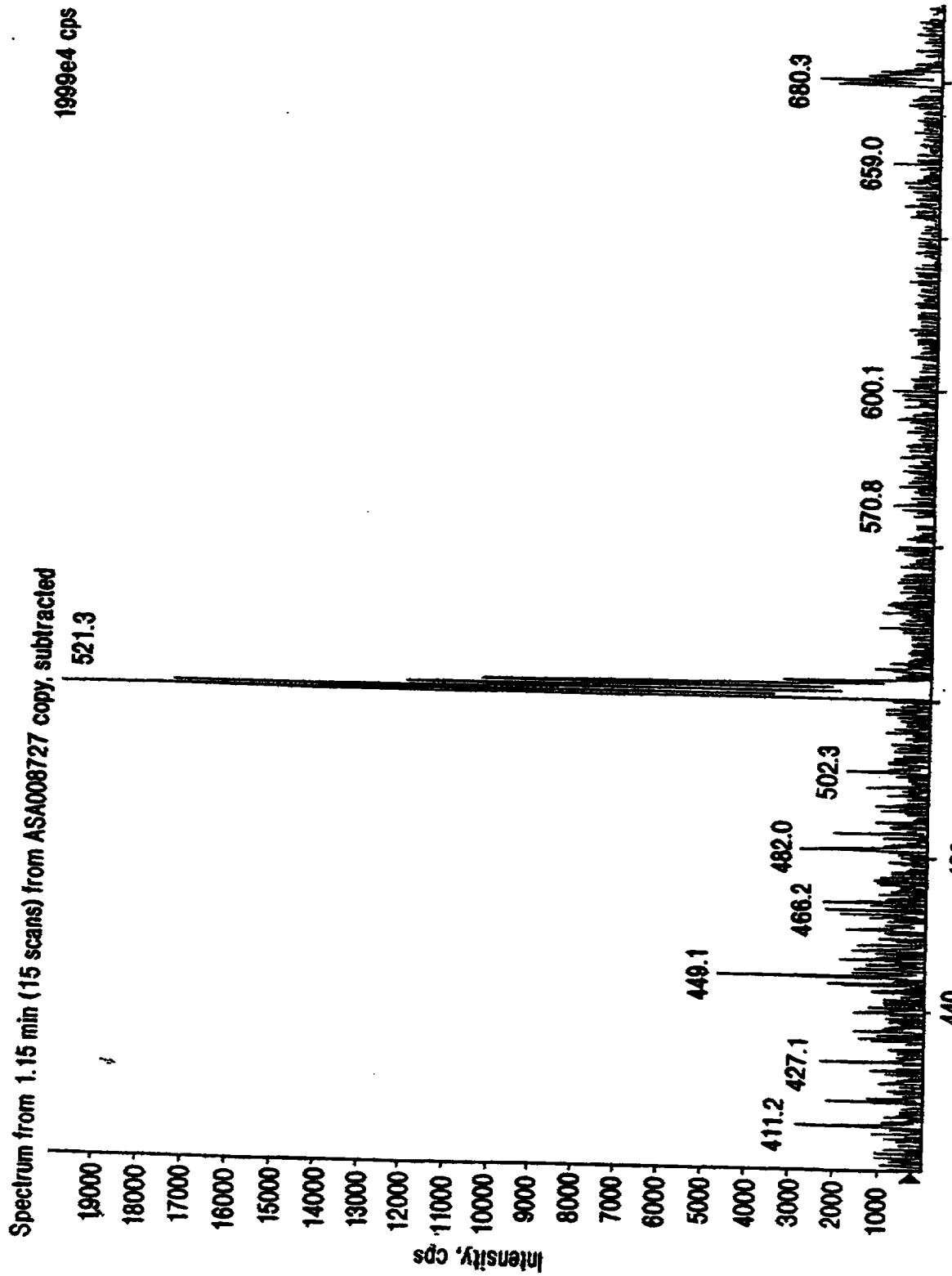

Spectrum from 1.15 min (15 scans) from ASA008727 copy, subtracted
1999e4 cps
Intensity, cps
m/z, amu
521.3
449.1
466.2
482.0
502.3
411.2
427.1
570.8
600.1
659.0
680.3

FIG. 243

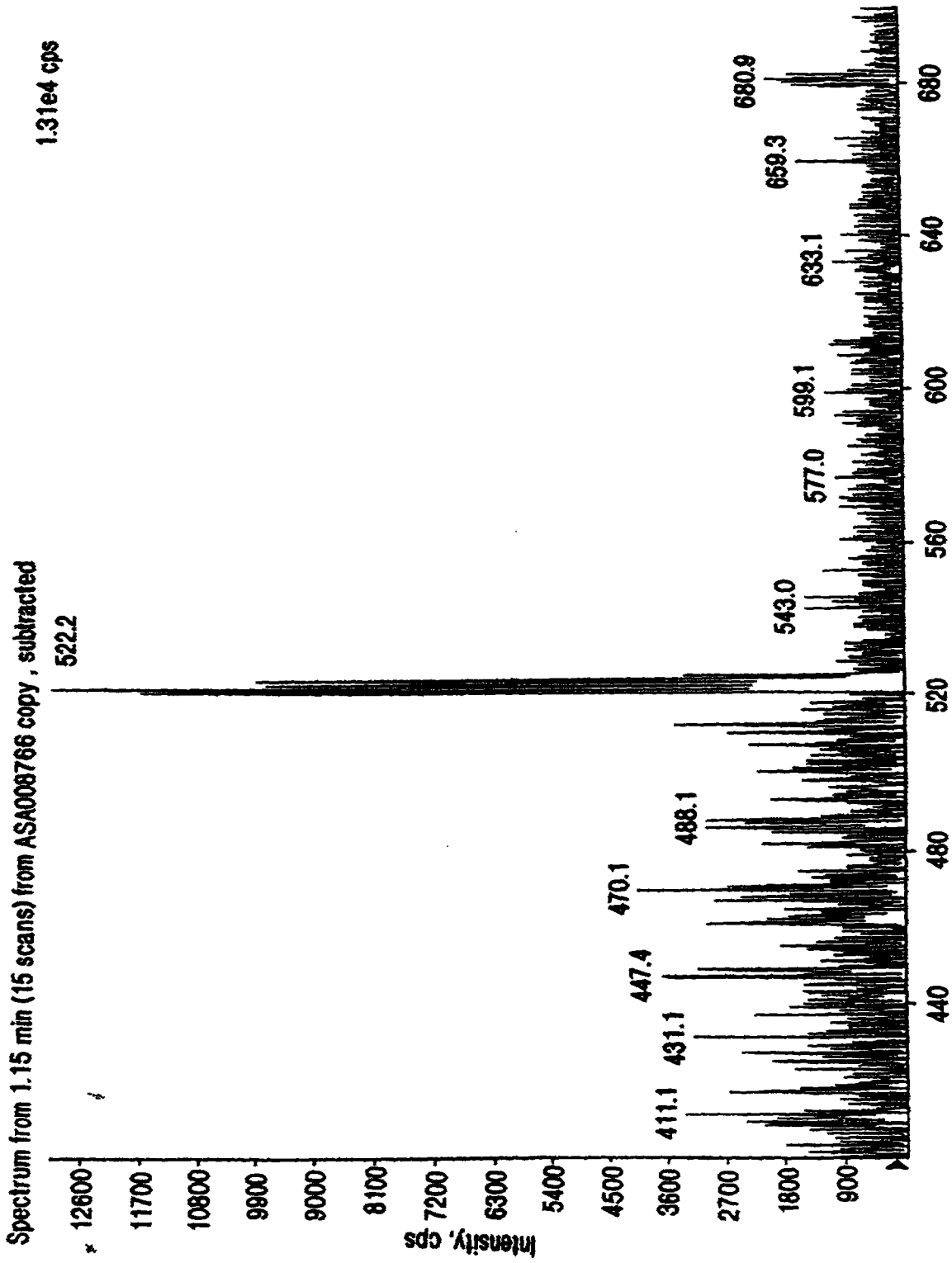

Spectrum from 1.15 min (15 scans) from ASA008766 copy , subtracted
1.31e4 cps
Intensity, cps
m/z, amu
522.2
543.0
577.0
598.1
633.1
659.3
680.9
470.1
488.1
447.4
431.1
411.1

FIG. 244

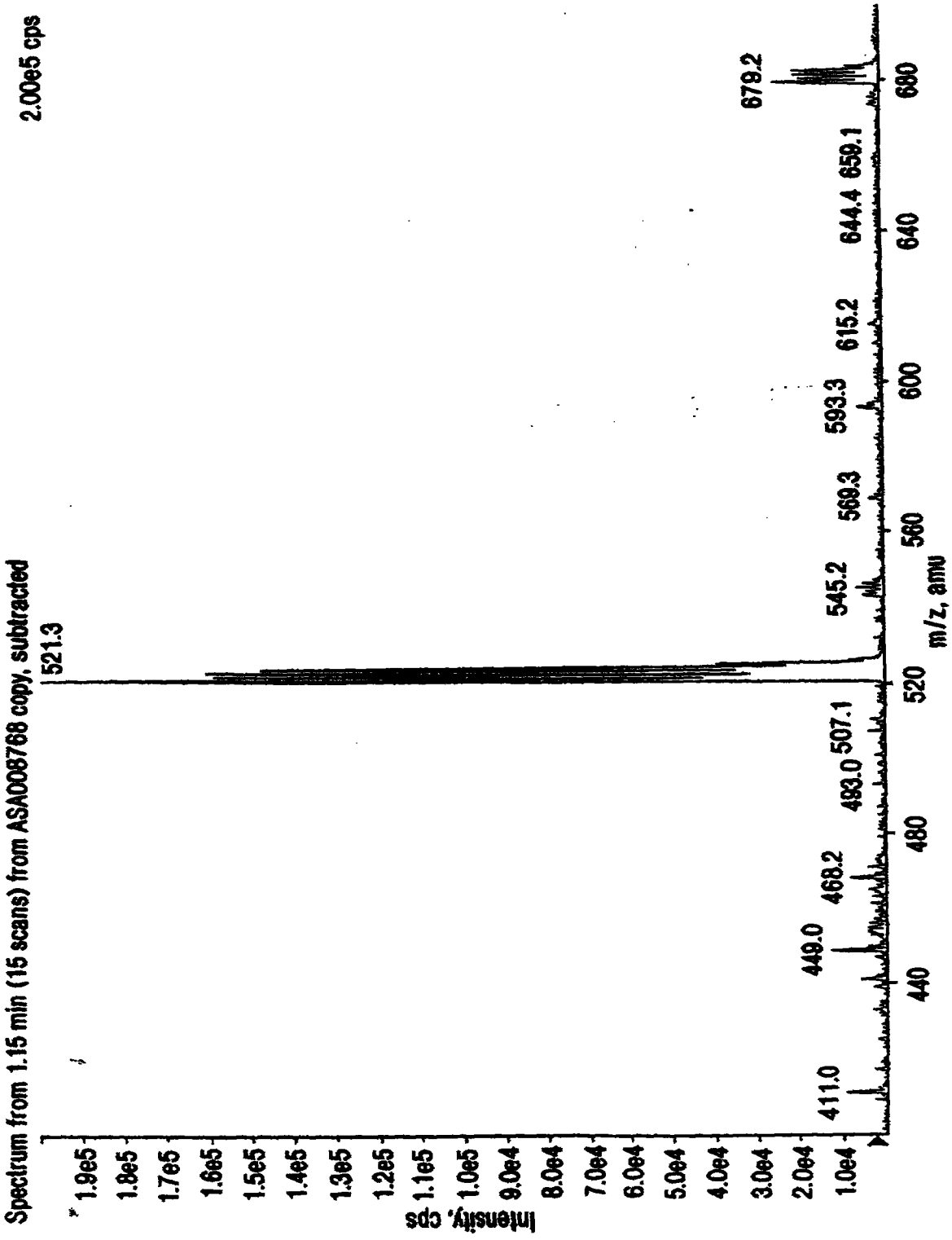

Spectrum from 1.15 min (15 scans) from ASA008768 copy, subtracted
2.00e5 cps
Intensity, cps
1.9e5
1.8e5
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.0
449.0
468.2
483.0
507.1
521.3
545.2
569.3
593.3
615.2
644.4
659.1
679.2
440
480
520
560
600
640
680
m/z, amu

FIG. 245

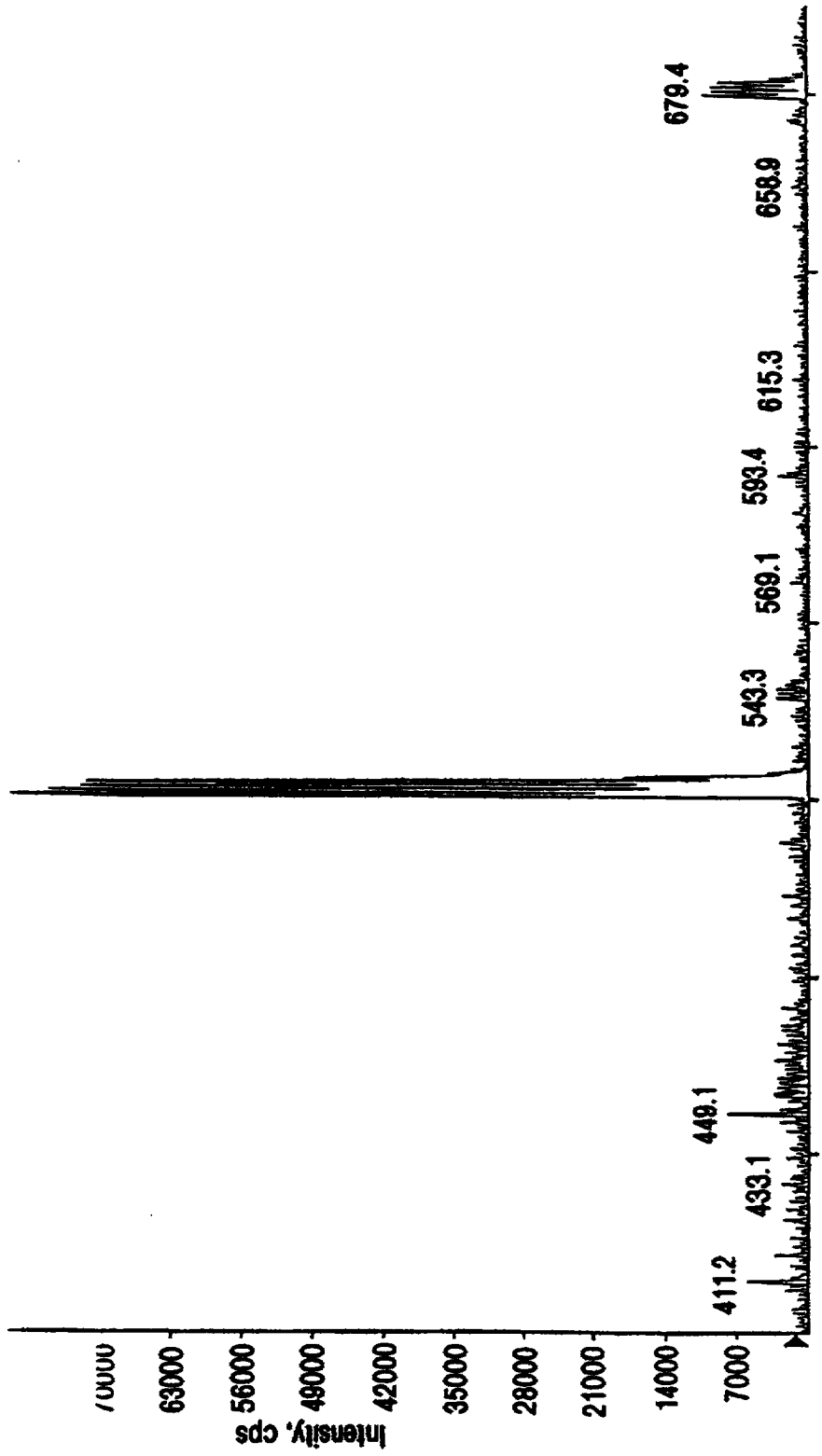

679.4
658.9
615.3
593.4
569.1
543.3
449.1
433.1
411.2
m/z, amu
Intensity, cps
63000
56000
49000
42000
35000
28000
21000
14000
7000
440
480
520
560
600
640
680

FIG. 246

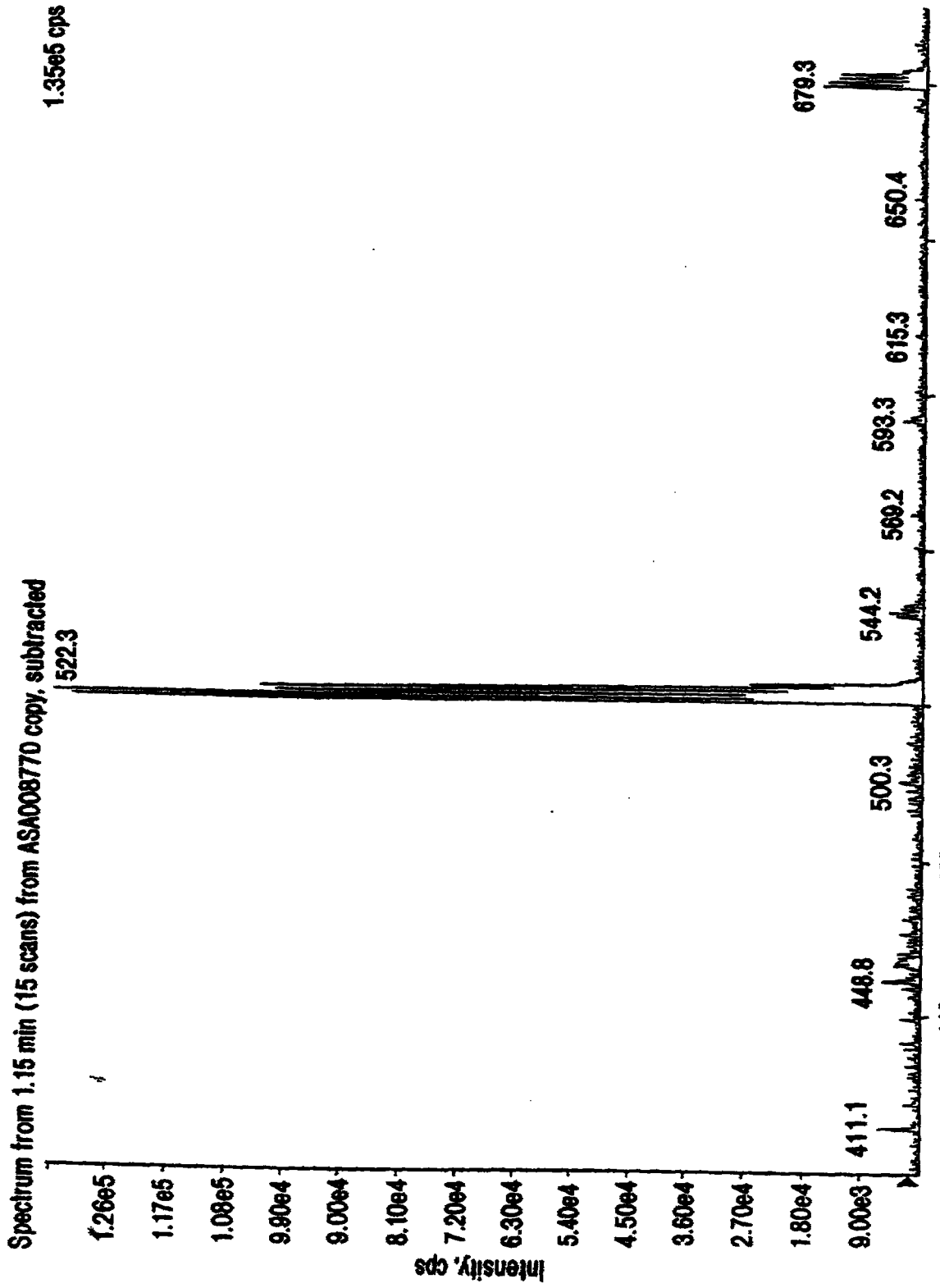

Spectrum from 1.15 min (15 scans) from ASA008770 copy, subtracted
1.35e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.1
448.8
500.3
522.3
544.2
569.2
593.3
615.3
650.4
679.3
440
480
520
560
600
640
680
m/z, amu

FIG. 247

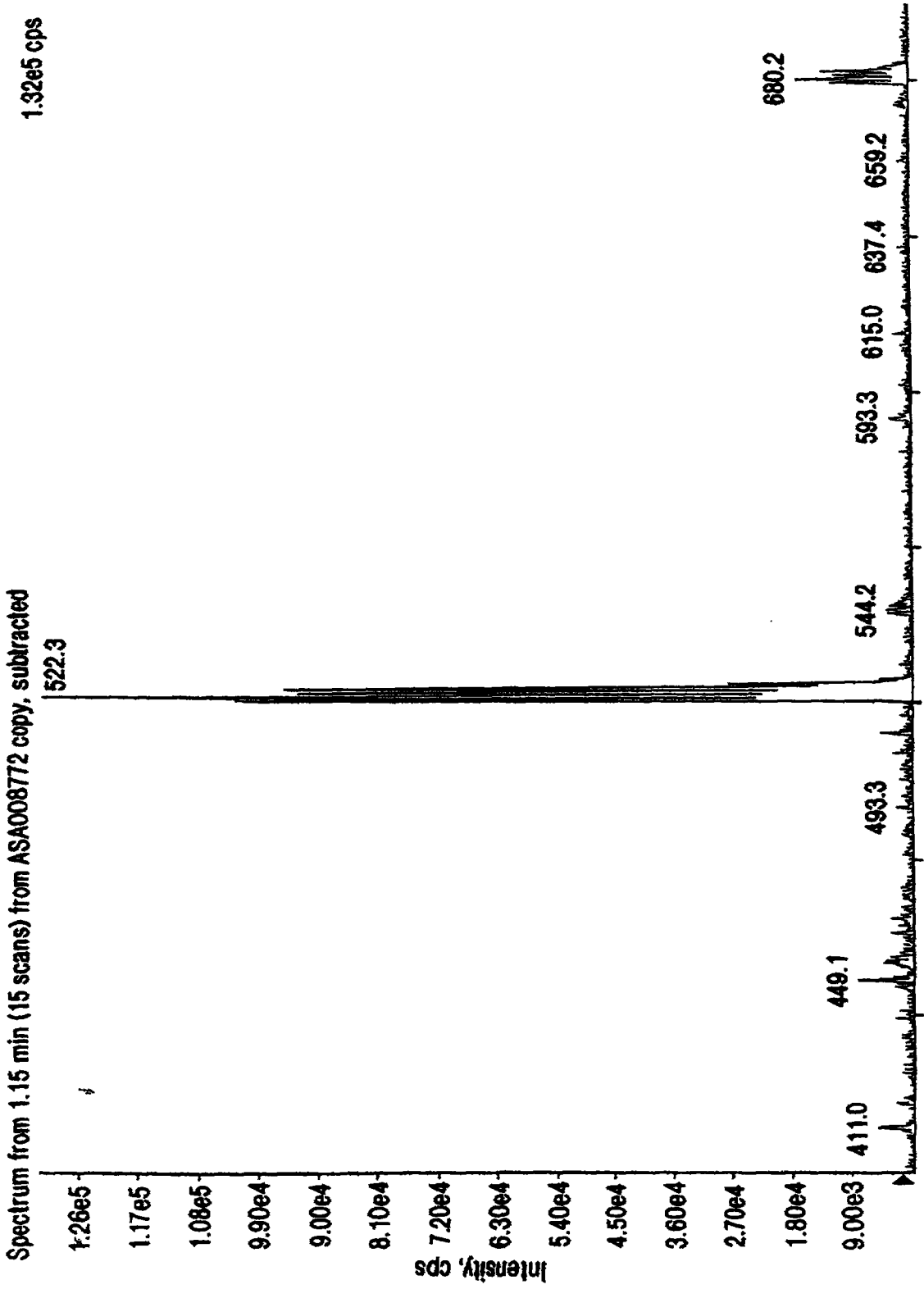

Spectrum from 1.15 min (15 scans) from ASA008772 copy, subtracted
1.32e5 cps
Intensity, cps
1.26e5
1.17e5
1.08e5
9.90e4
9.00e4
8.10e4
7.20e4
6.30e4
5.40e4
4.50e4
3.60e4
2.70e4
1.80e4
9.00e3
411.0
449.1
493.3
522.3
544.2
593.3
615.0
637.4
659.2
680.2
440
480
520
560
600
640
680
m/z, amu

FIG. 248

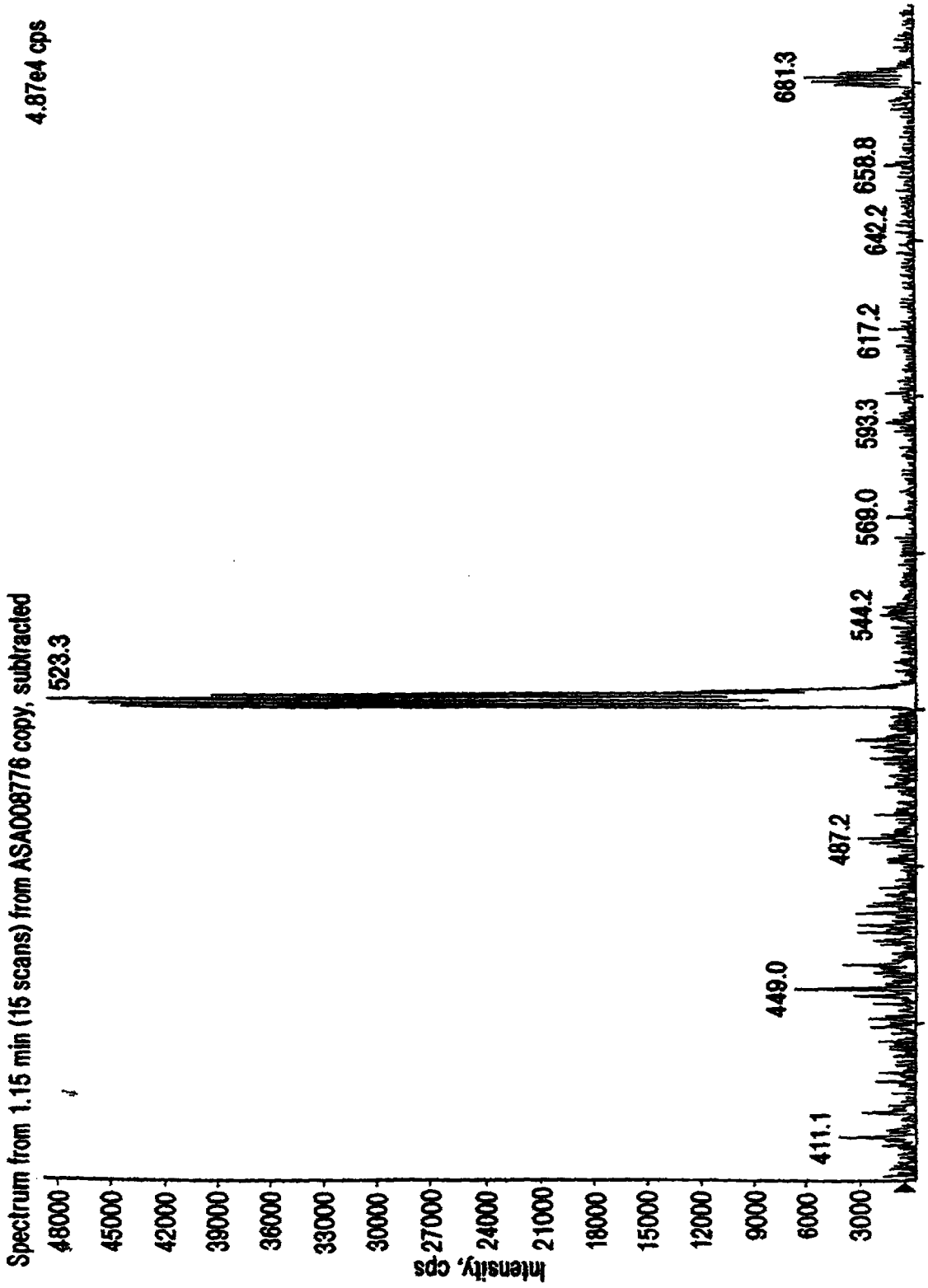

4.87e4 cps
Spectrum from 1.15 min (15 scans) from ASA008776 copy, subtracted
523.3
544.2
569.0
593.3
617.2
642.2
658.8
681.3
487.2
449.0
411.1
Intensity, cps
m/z, amu

FIG. 251

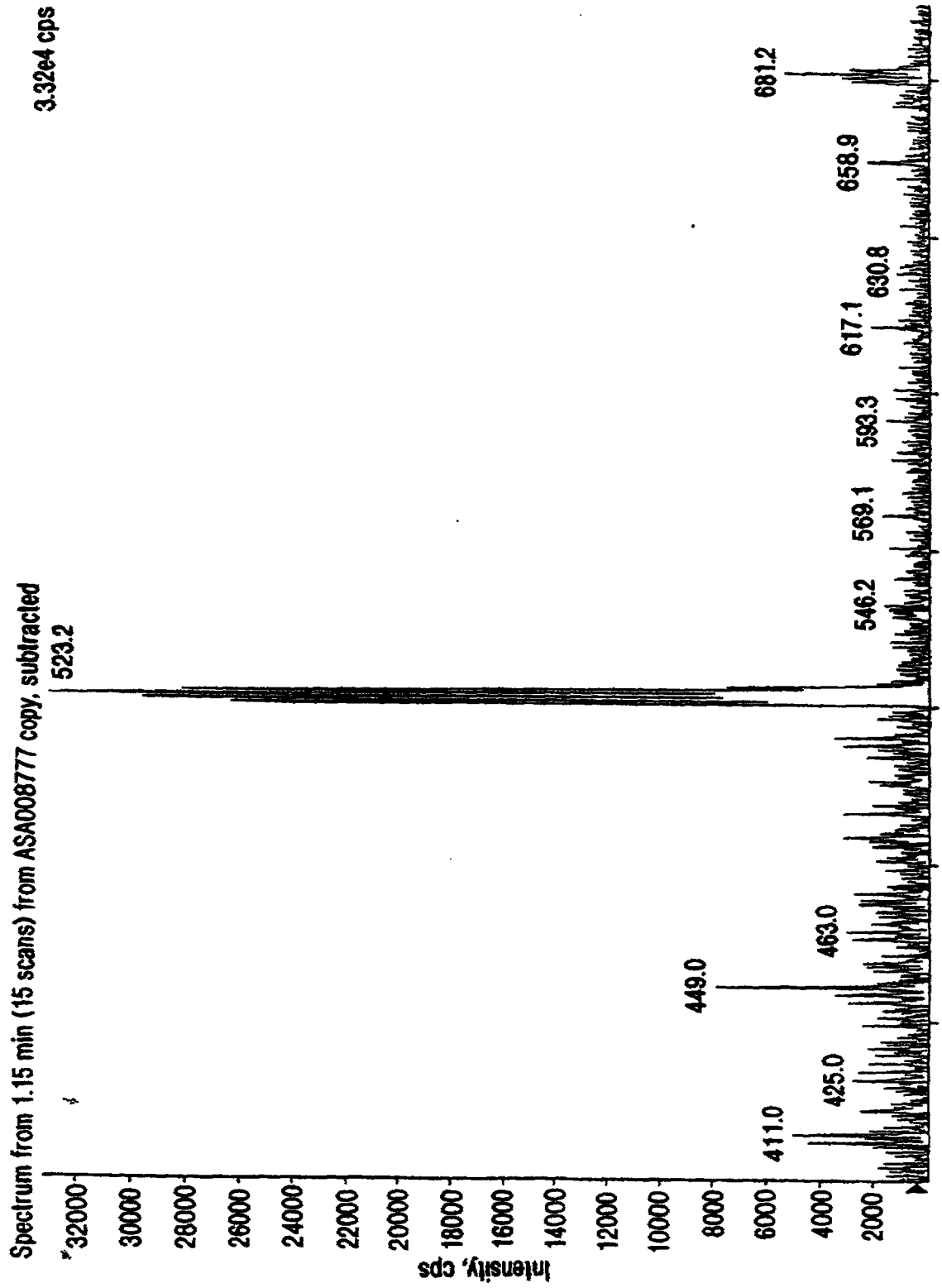

Spectrum from 1.15 min (15 scans) from ASA008777 copy, subtracted
3.32e4 cps
Intensity, cps
m/z, amu
523.2
546.2
569.1
593.3
617.1
630.8
658.9
681.2
449.0
463.0
425.0
411.0

FIG. 252

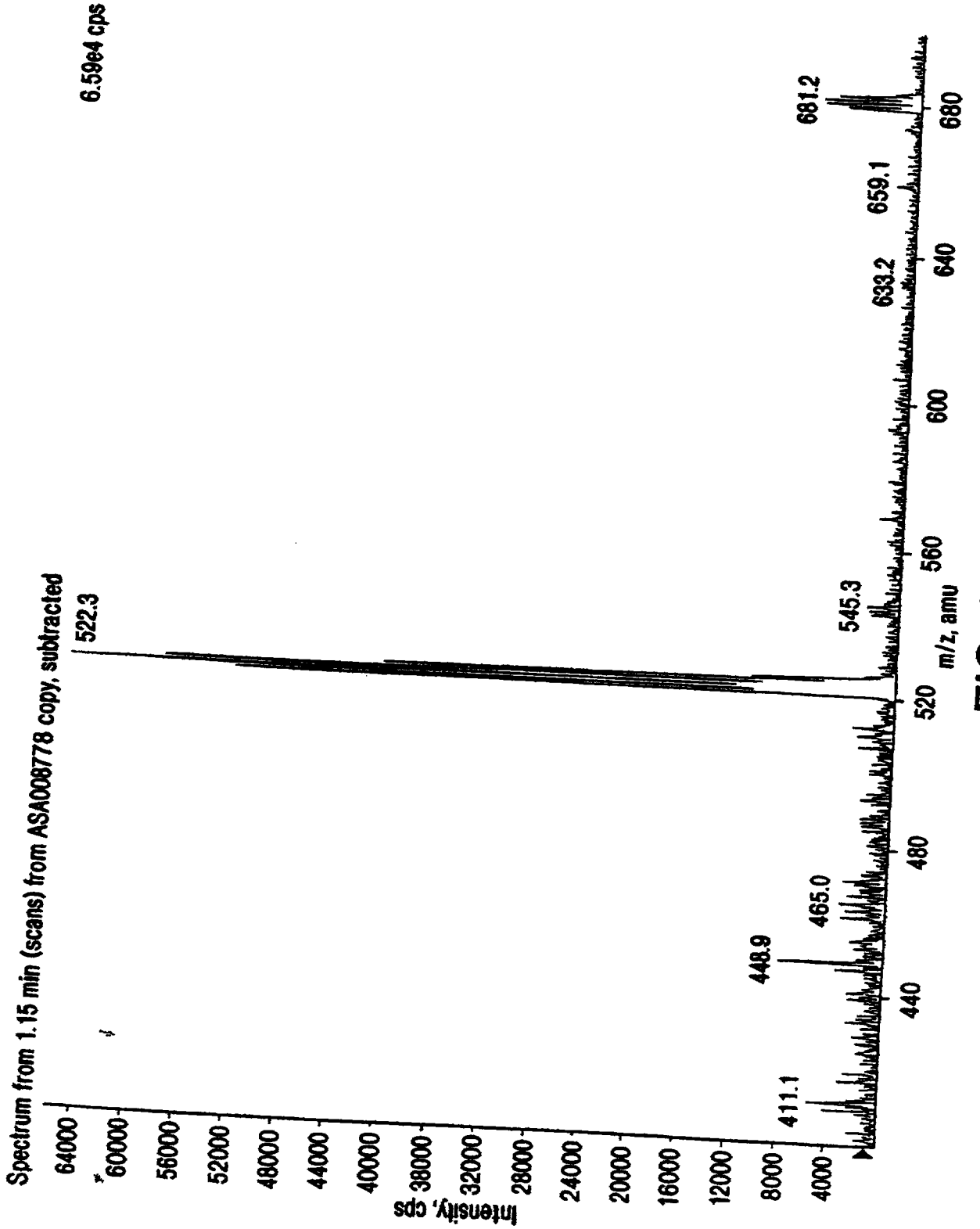

Spectrum from 1.15 min (scans) from ASA008778 copy, subtracted
6.59e4 cps
Intensity, cps
64000
60000
56000
52000
48000
44000
40000
38000
32000
28000
24000
20000
16000
12000
8000
4000
411.1
448.9
465.0
522.3
545.3
633.2
659.1
681.2
440
480
520
560
600
640
680
m/z, amu

FIG. 253

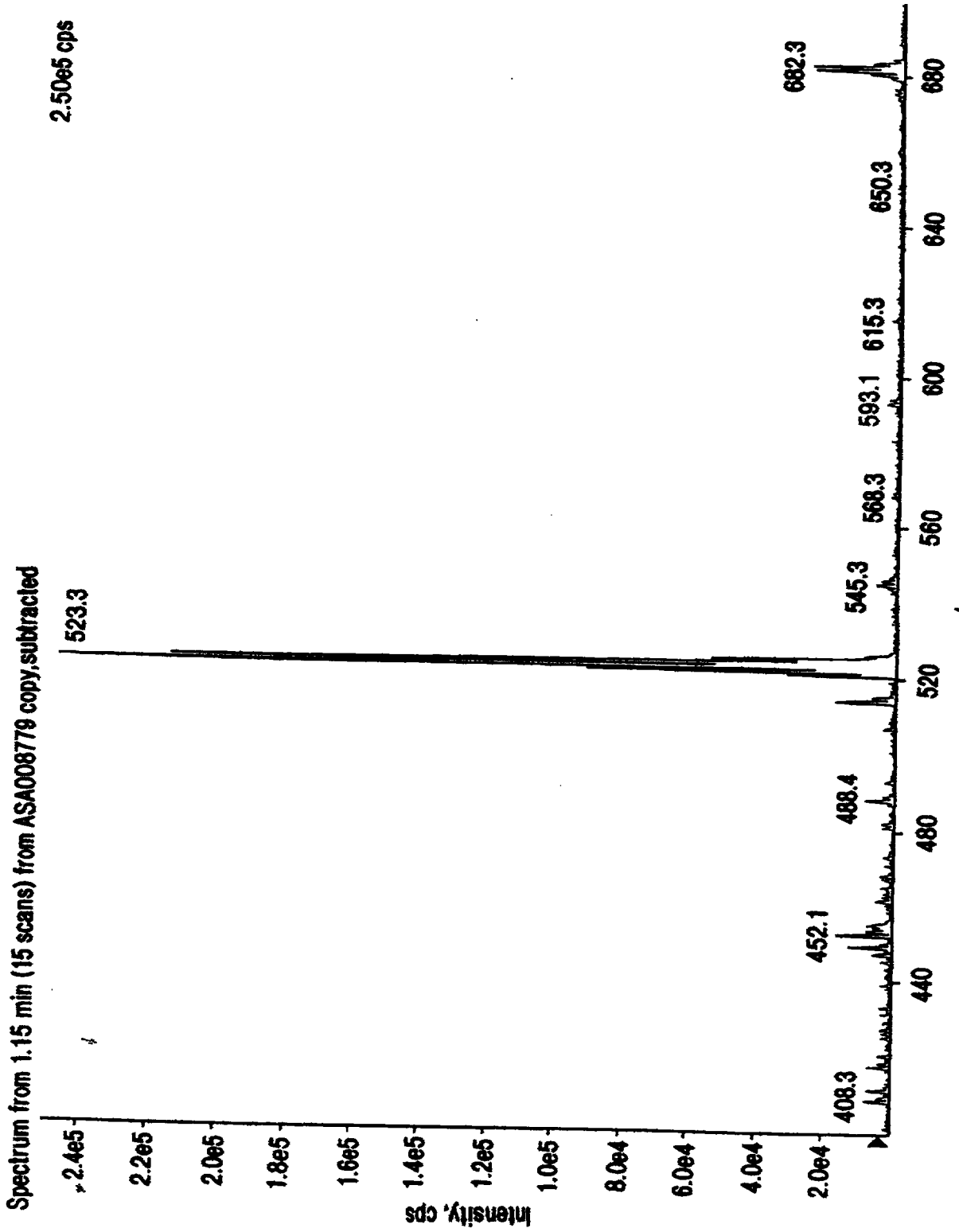

Spectrum from 1.15 min (15 scans) from ASA008779 copy,subtracted
2.50e5 cps
Intensity, cps
2.4e5
2.2e5
2.0e5
1.8e5
1.6e5
1.4e5
1.2e5
1.0e5
8.0e4
6.0e4
4.0e4
2.0e4
m/z, amun
440
480
520
560
600
640
680
408.3
452.1
488.4
523.3
545.3
568.3
593.1
615.3
650.3
682.3

FIG. 254

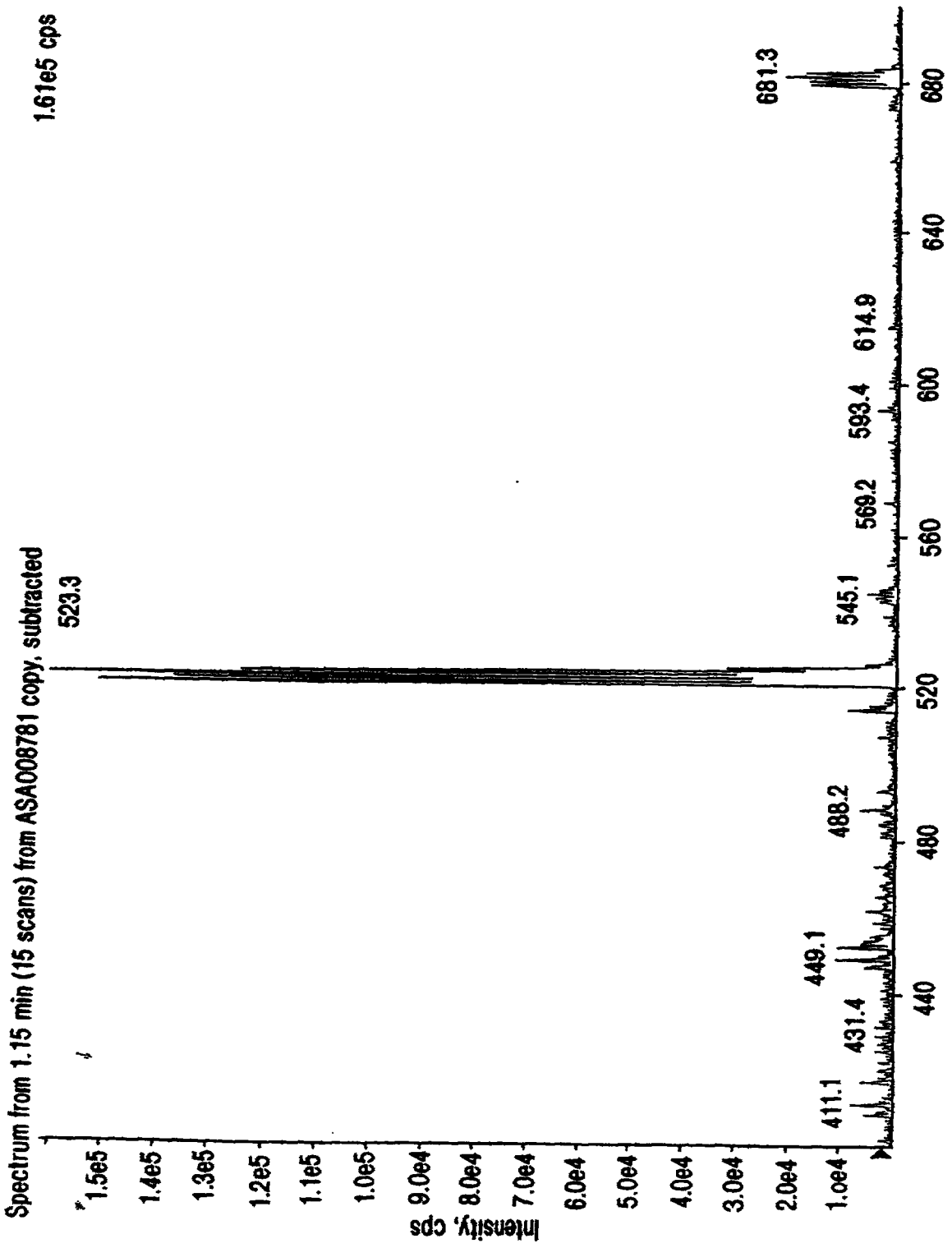

Spectrum from 1.15 min (15 scans) from ASA008781 copy, subtracted
1.61e5 cps
Intensity, cps
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.1
431.4
449.1
488.2
523.3
545.1
569.2
583.4
614.9
681.3
440
480
520
560
600
640
680
m/z,amu

FIG. 255

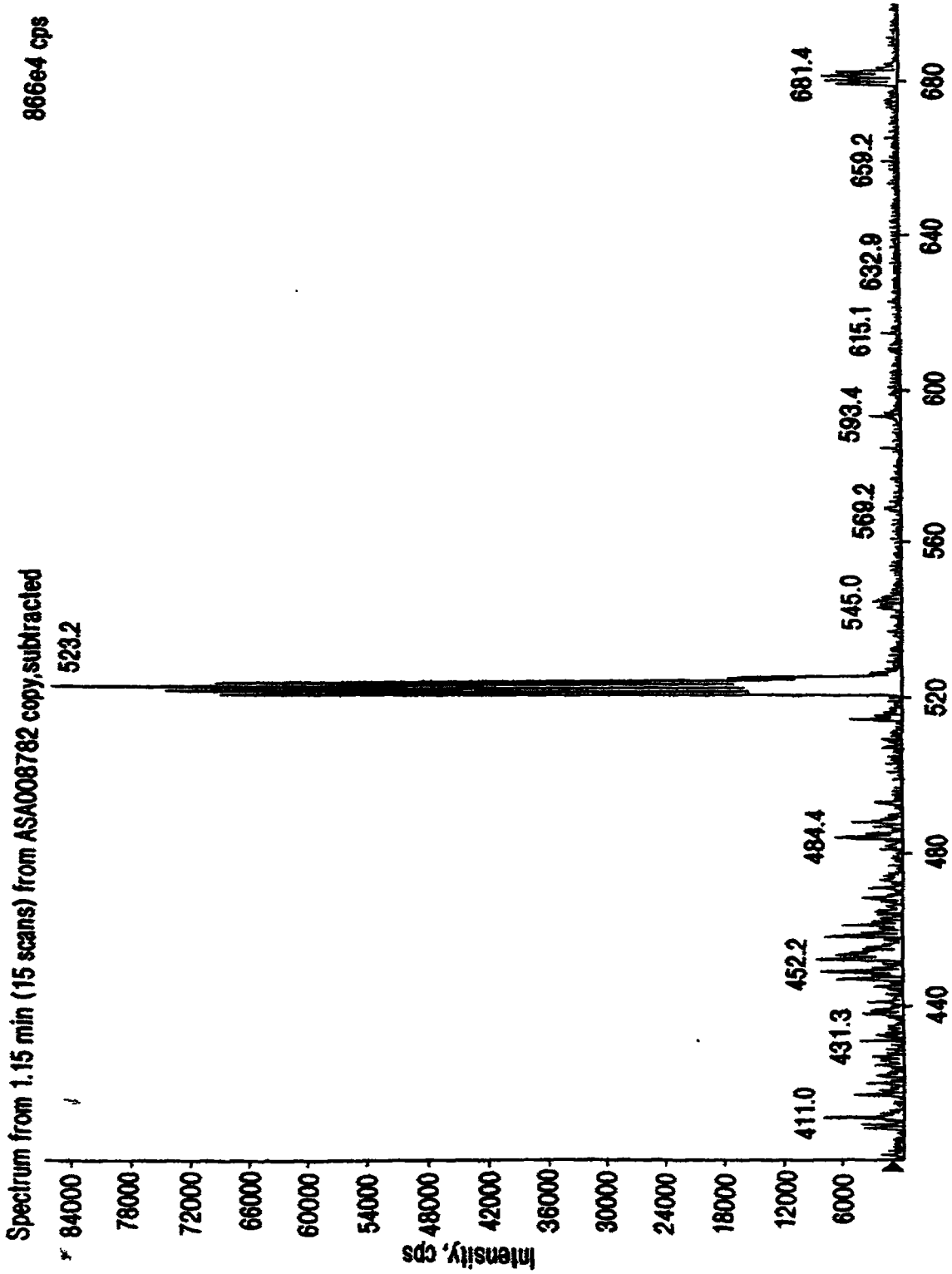

866e4 cps
Spectrum from 1.15 min (15 scans) from ASA008782 copy,subtracted
523.2
545.0
569.2
593.4
615.1
632.9
659.2
681.4
411.0
431.3
452.2
484.4
Intensity, cps
m/z, amu

FIG. 256

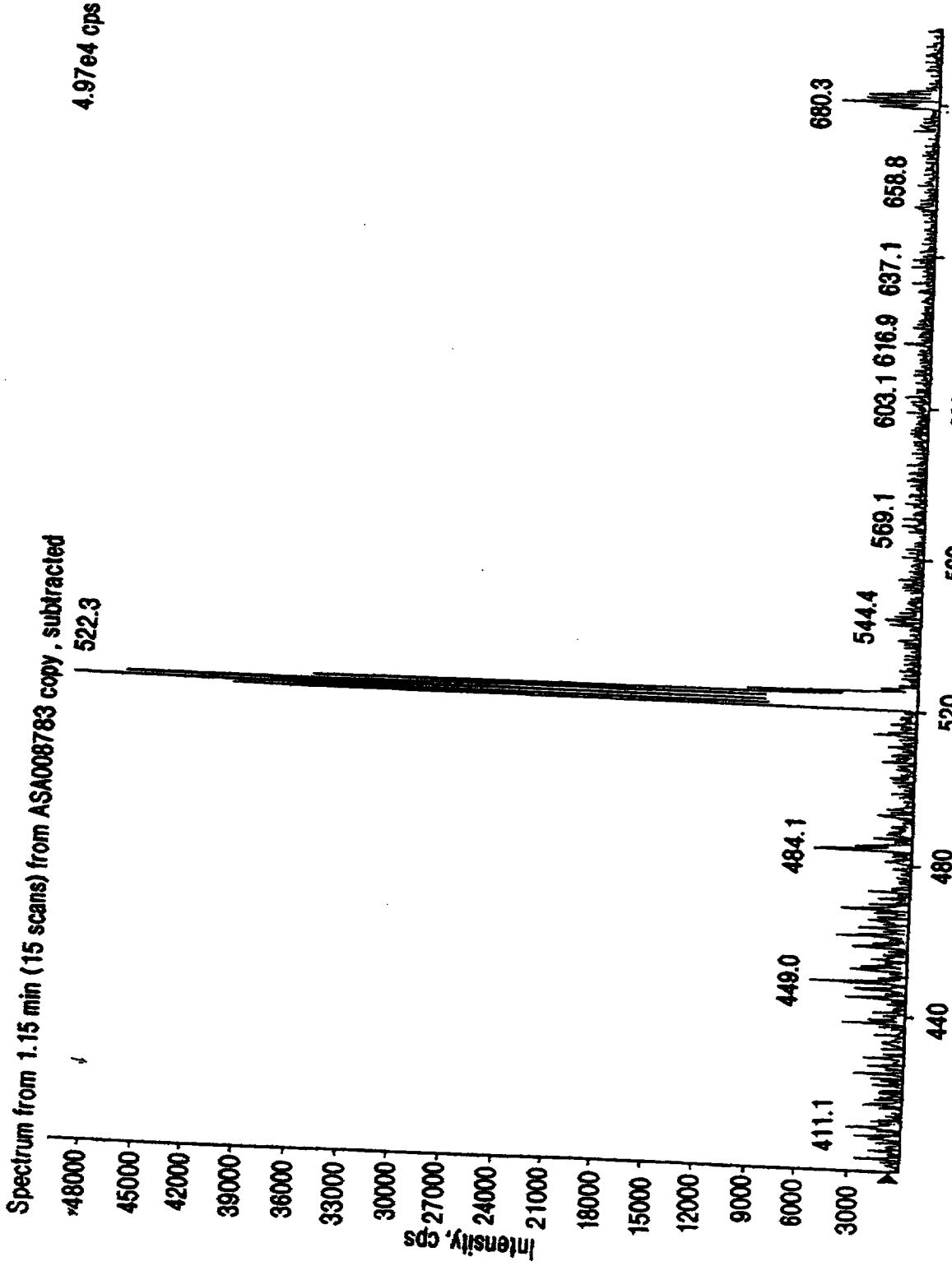

Spectrum from 1.15 min (15 scans) from ASA008783 copy , subtracted
4.97e4 cps
522.3
544.4
569.1
603.1
616.9
637.1
658.8
680.3
484.1
449.0
411.1
Intensity, cps
m/z, amu
48000
45000
42000
39000
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
440
480
520
560
600
640
680

FIG. 257

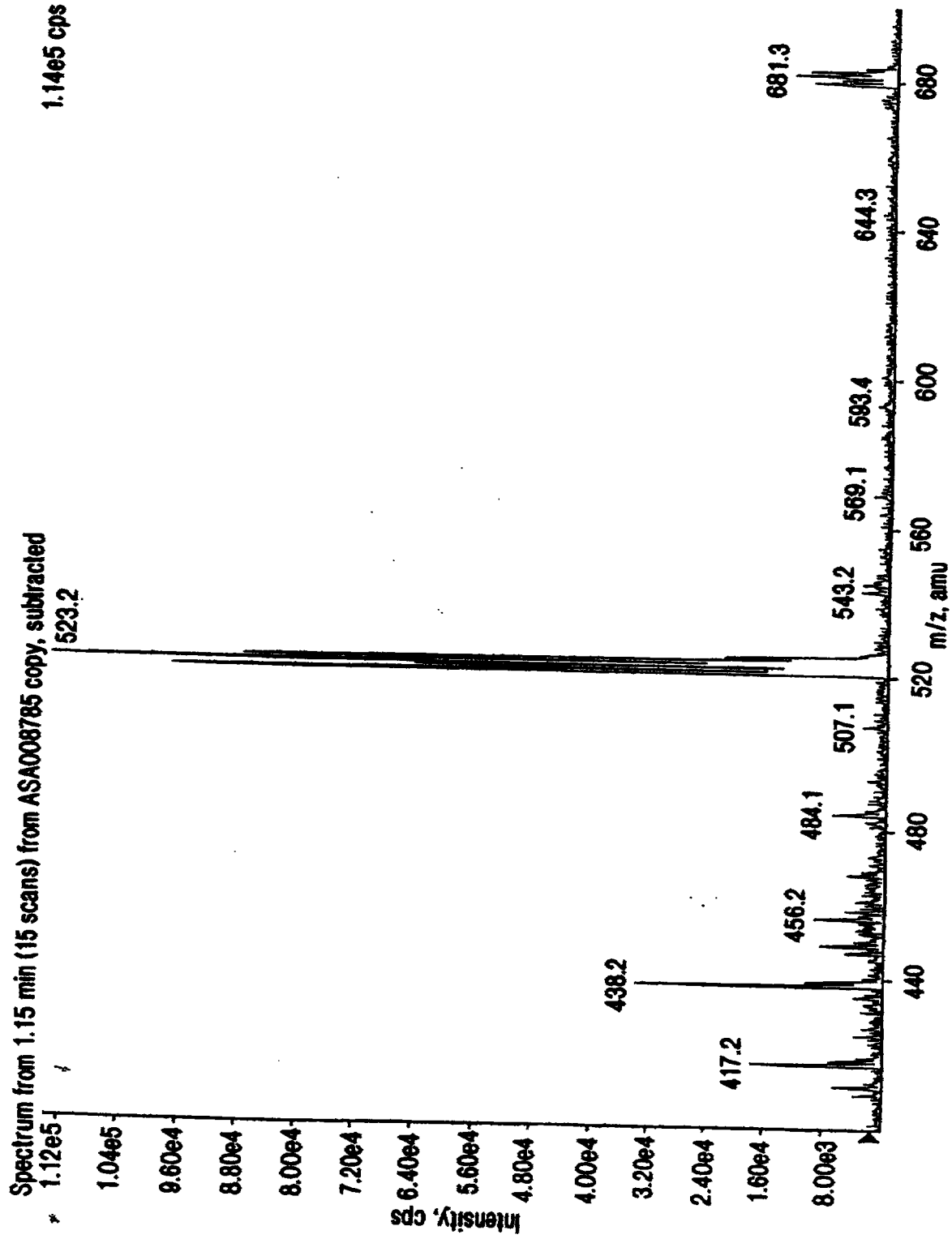

Spectrum from 1.15 min (15 scans) from ASA008785 copy, subtracted
1.14e5 cps
Intensity, cps
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
440
480
520
560
600
640
680
523.2
438.2
417.2
456.2
484.1
507.1
543.2
569.1
593.4
644.3
681.3

FIG. 258

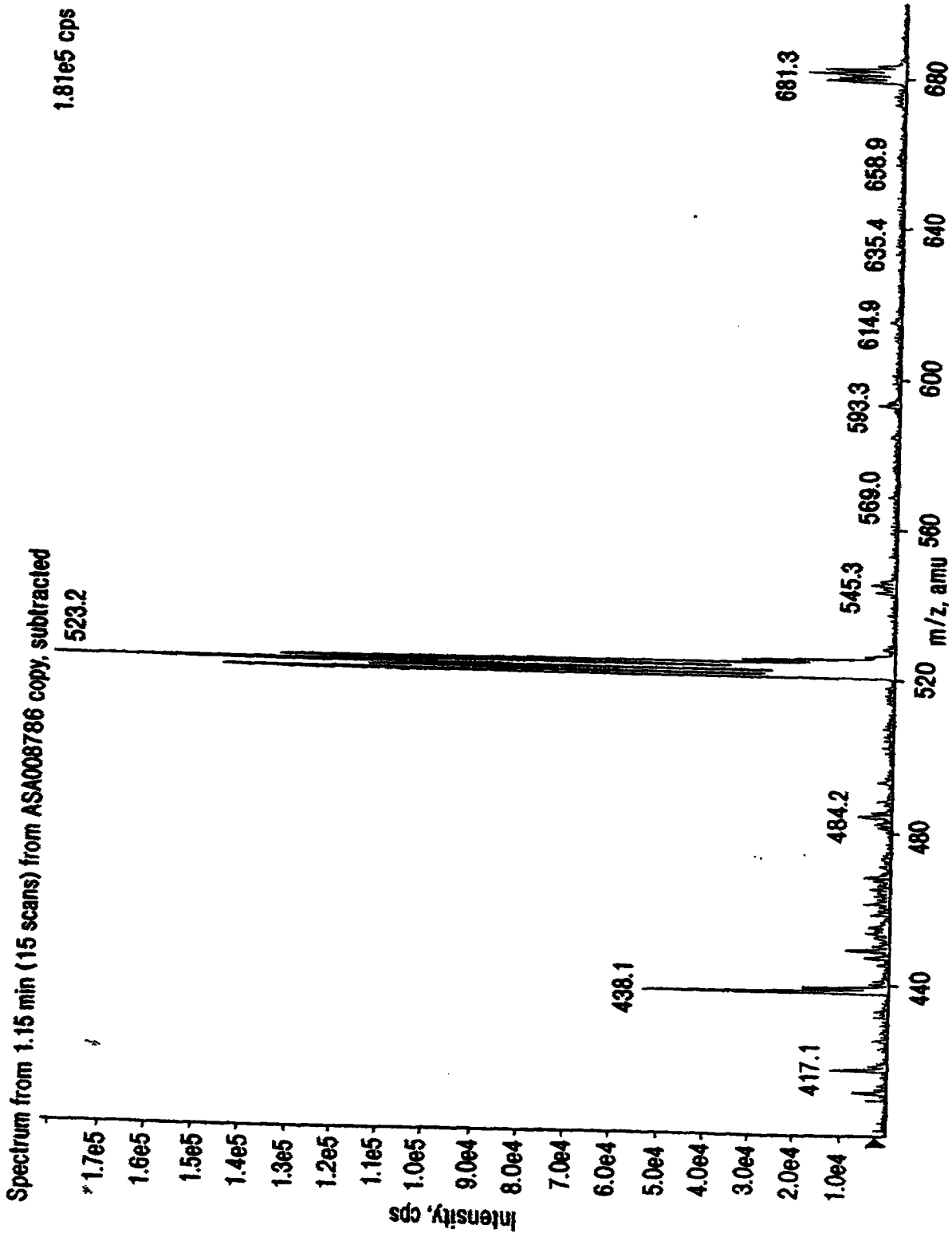

Spectrum from 1.15 min (15 scans) from ASA008786 copy, subtracted
1.81e5 cps
Intensity, cps
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
523.2
545.3
569.0
593.3
614.9
635.4
658.9
681.3
484.2
438.1
417.1
440
480
520
560
600
640
680
m/z, amu

FIG. 259

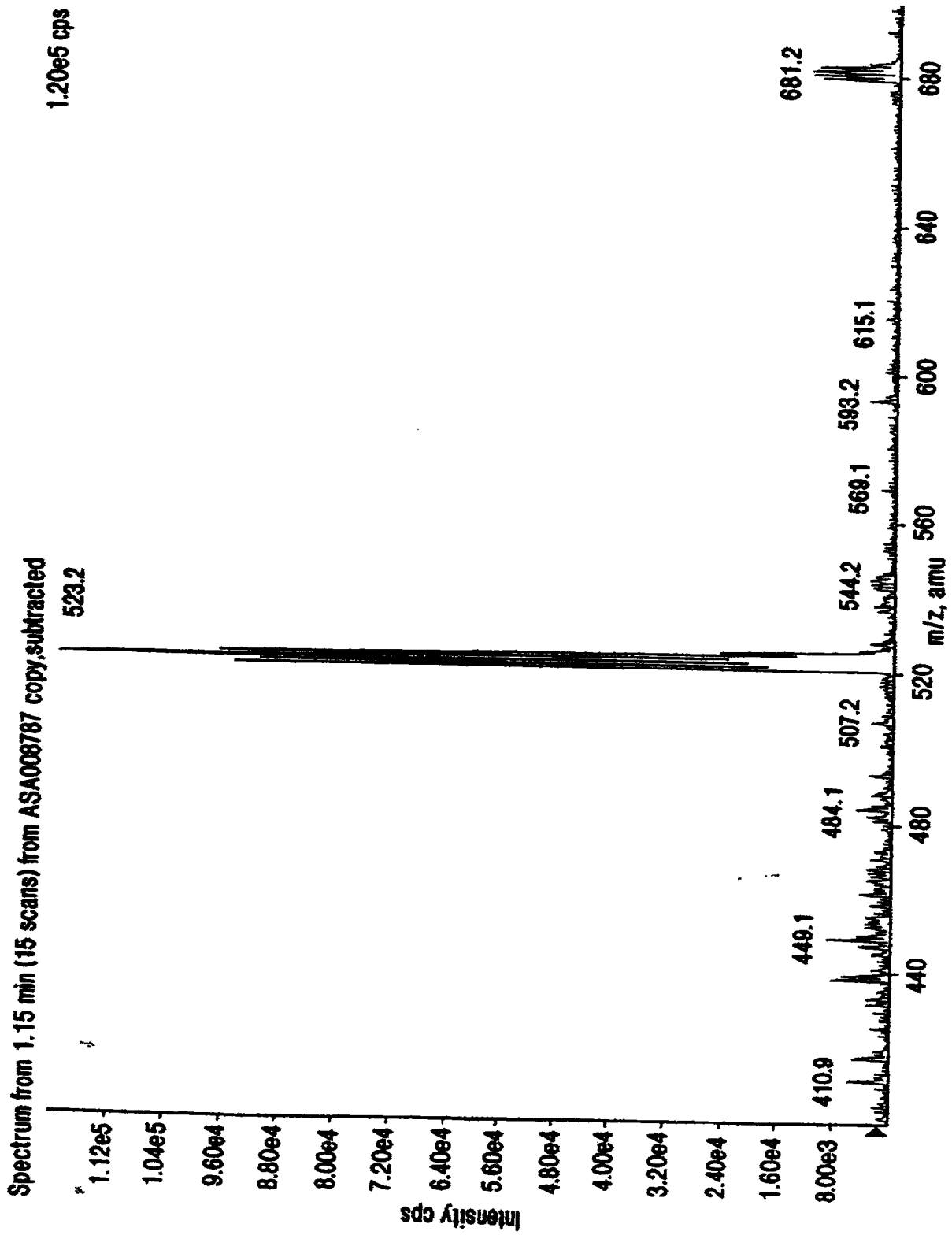

Spectrum from 1.15 min (15 scans) from ASA008787 copy,subtracted
1.20e5 cps
Intensity cps
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
m/z, amu
410.9
449.1
484.1
507.2
523.2
544.2
569.1
583.2
615.1
681.2
440
480
520
560
600
640
680

FIG. 260

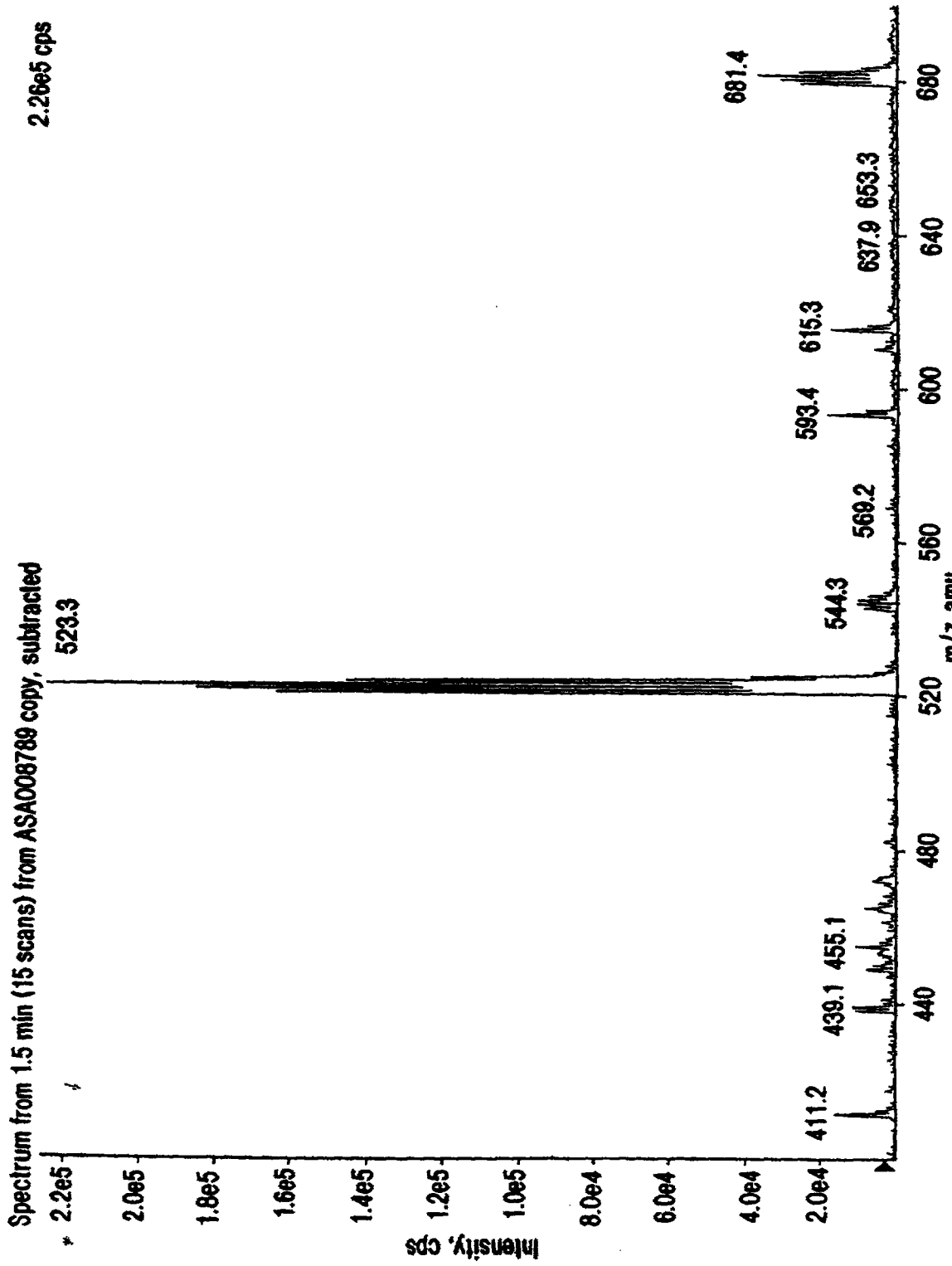

Spectrum from 1.5 min (15 scans) from ASA008789 copy, subtracted
2.26e5 cps
Intensity, cps
2.2e5
2.0e5
1.8e5
1.6e5
1.4e5
1.2e5
1.0e5
8.0e4
6.0e4
4.0e4
2.0e4
411.2
439.1
455.1
523.3
544.3
569.2
593.4
615.3
637.9
653.3
681.4
440
480
520
560
600
640
680
m/z, amu

FIG. 261

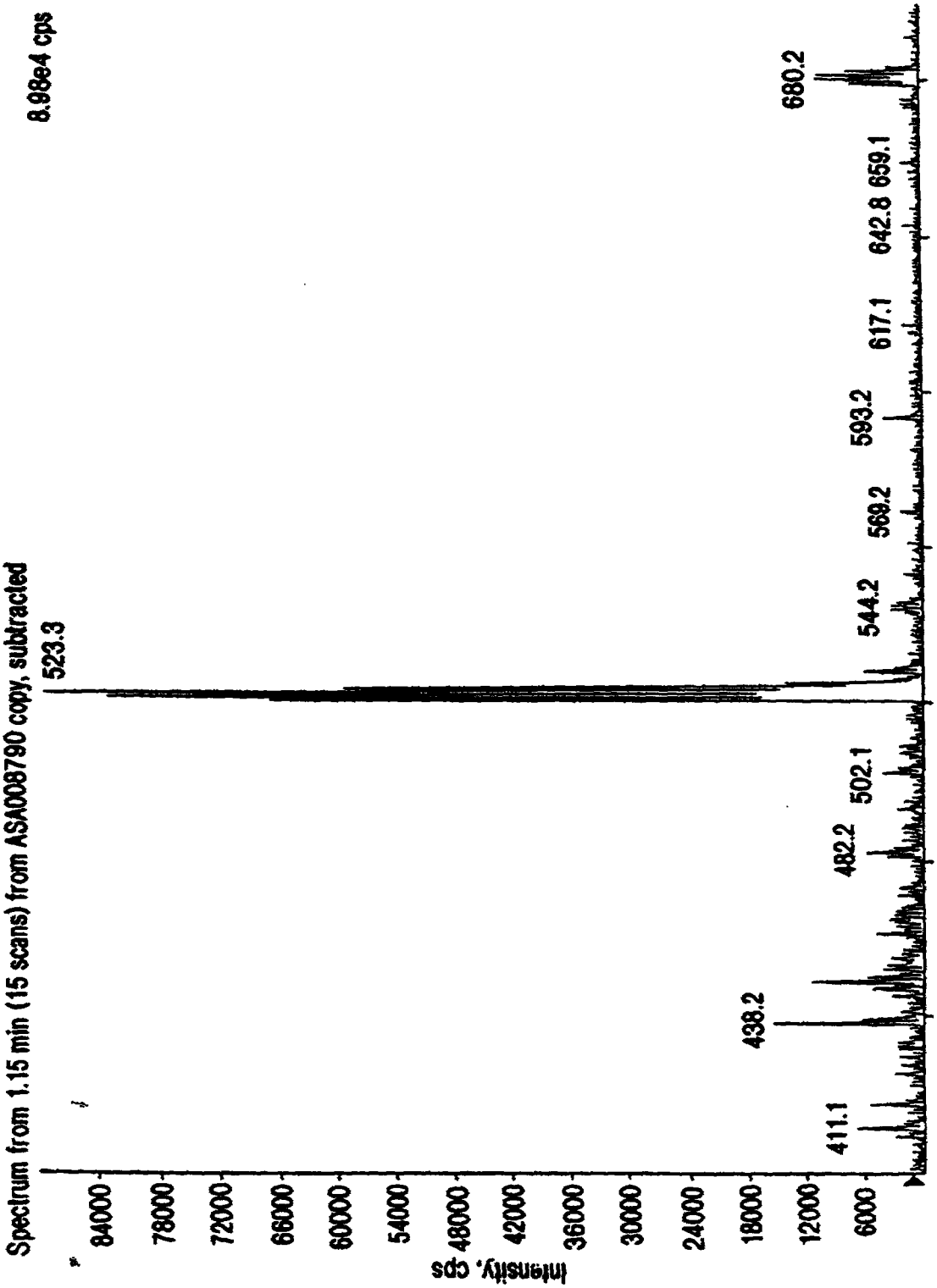

Spectrum from 1.15 min (15 scans) from ASA008790 copy, subtracted
8.98e4 cps
Intensity, cps
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
411.1
438.2
482.2
502.1
523.3
544.2
569.2
593.2
617.1
642.8
659.1
680.2
440
480
520
560
600
640
680
m/z, amu

FIG. 262

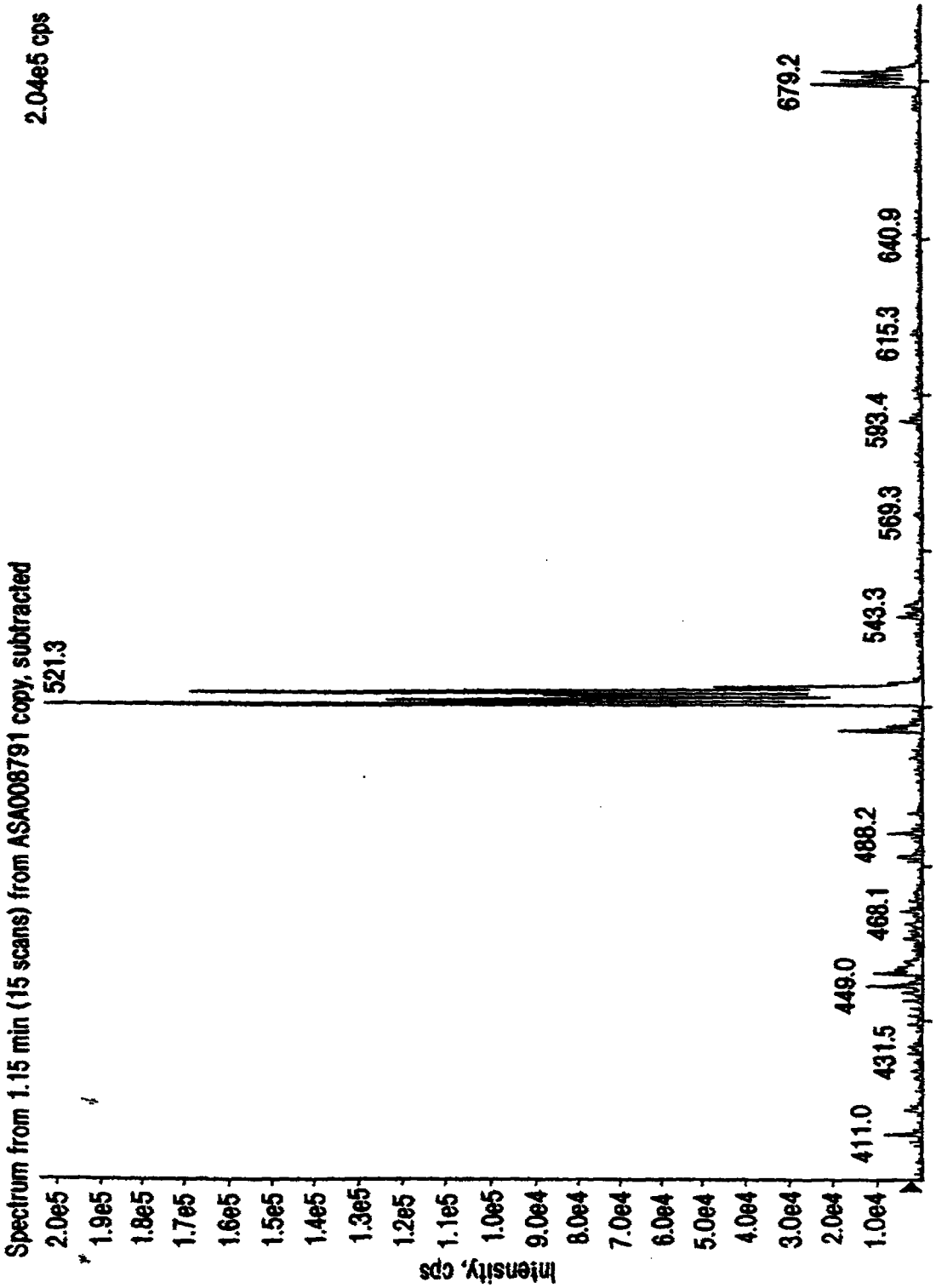

Spectrum from 1.15 min (15 scans) from ASA008791 copy, subtracted
2.04e5 cps
Intensity, cps
2.0e5
1.9e5
1.8e5
1.7e5
1.6e5
1.5e5
1.4e5
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
411.0
431.5
449.0
468.1
488.2
521.3
543.3
569.3
583.4
615.3
640.9
679.2
440
480
520
560
600
640
680
m/z, amu

FIG. 263

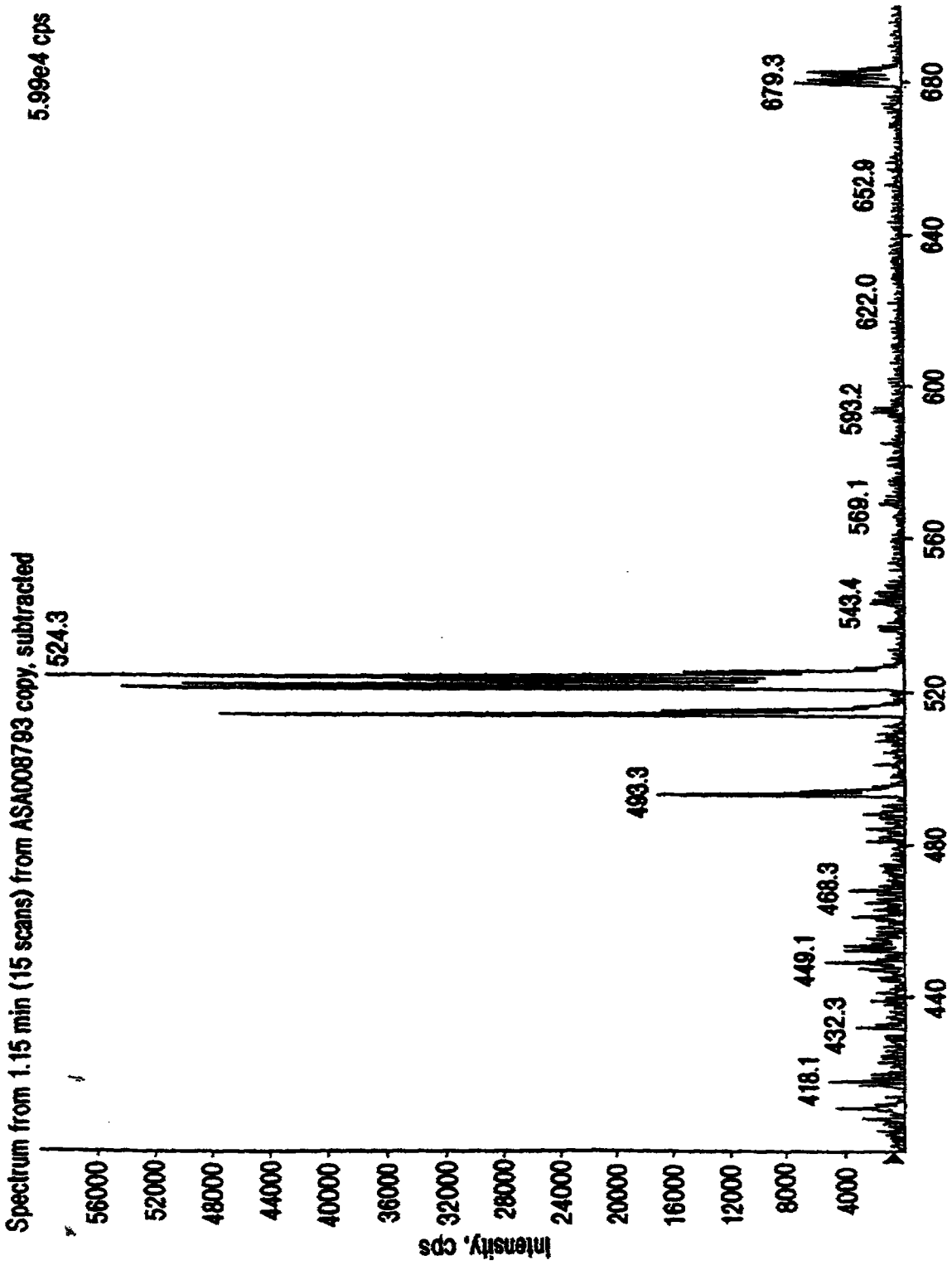

Spectrum from 1.15 min (15 scans) from ASA0008793 copy, subtracted
5.99e4 cps
Intensity, cps
m/z, amu
524.3
493.3
679.3
543.4
569.1
593.2
622.0
652.9
468.3
449.1
432.3
418.1

FIG. 264

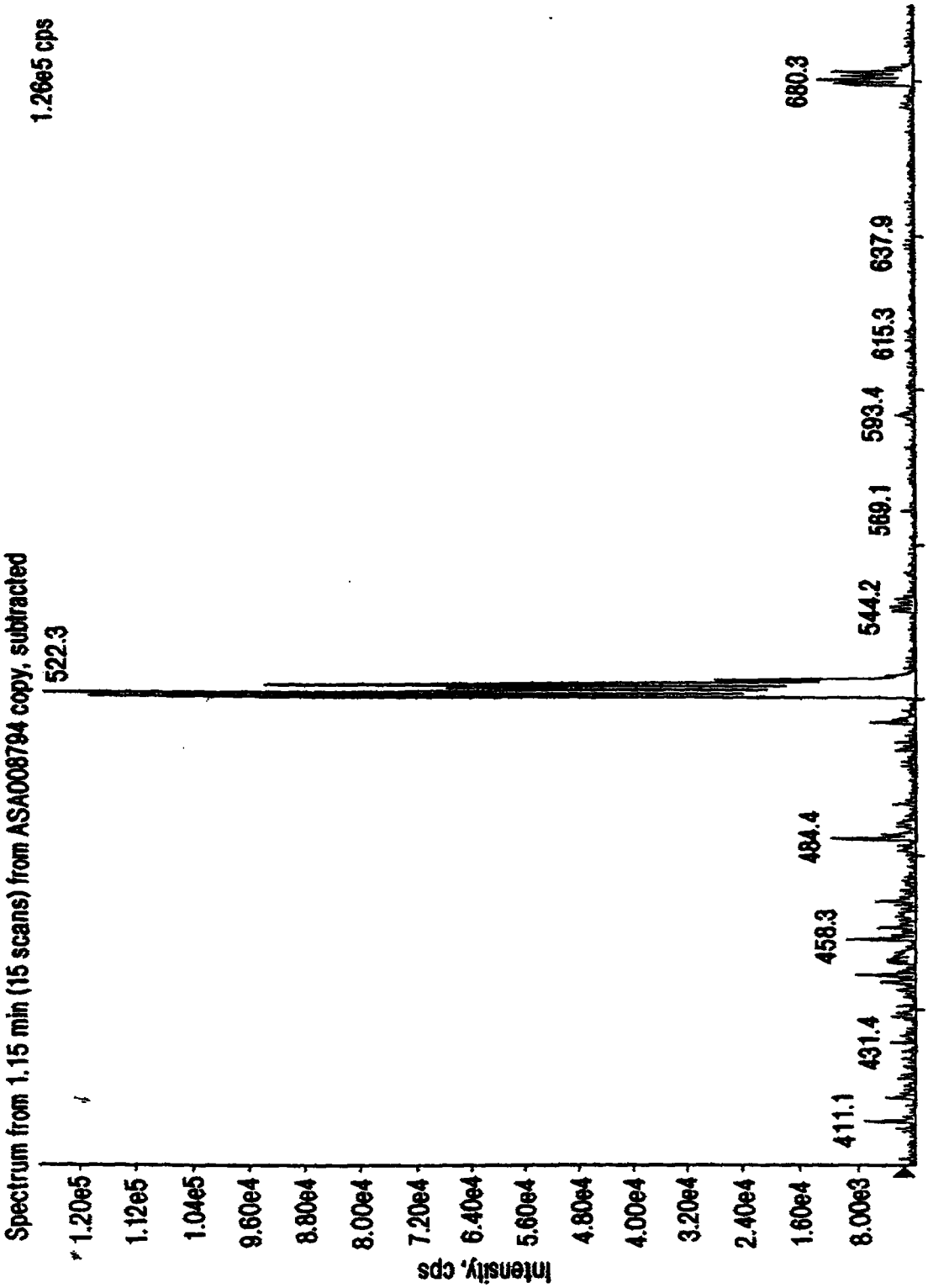

Spectrum from 1.15 min (15 scans) from ASA008794 copy, subtracted
1.26e5 cps
522.3
544.2
569.1
593.4
615.3
637.9
680.3
484.4
458.3
431.4
411.1
Intensity, cps
m/z, amu
1.20e5
1.12e5
1.04e5
9.60e4
8.80e4
8.00e4
7.20e4
6.40e4
5.60e4
4.80e4
4.00e4
3.20e4
2.40e4
1.60e4
8.00e3
440
480
520
560
600
640
680

FIG. 265

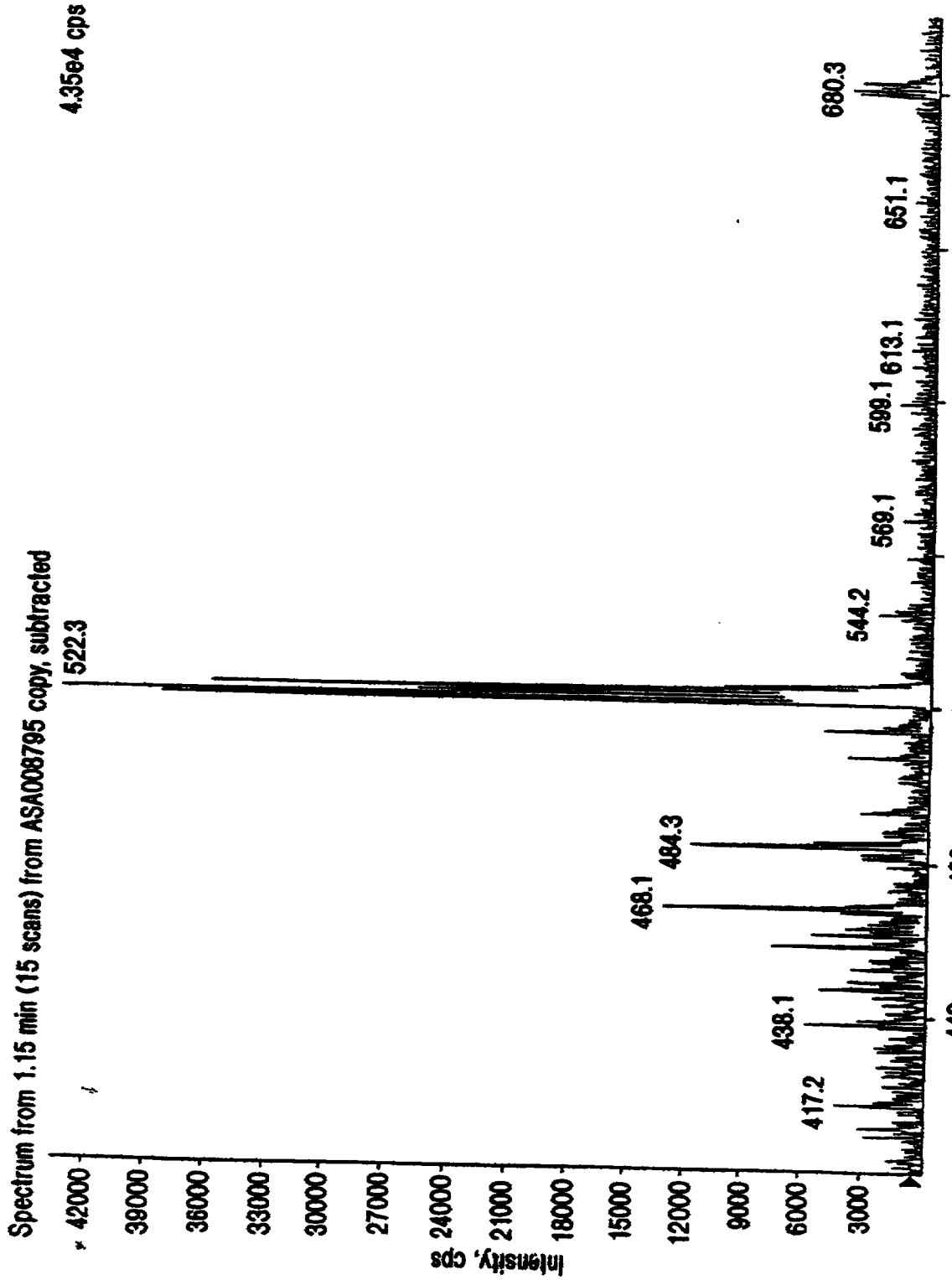

Spectrum from 1.15 min (15 scans) from ASA008795 copy, subtracted
4.35e4 cps
Intensity, cps
42000
39000
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
m/z, amu
440
480
520
560
600
640
680
522.3
544.2
569.1
598.1
613.1
651.1
680.3
468.1
484.3
438.1
417.2

FIG. 266

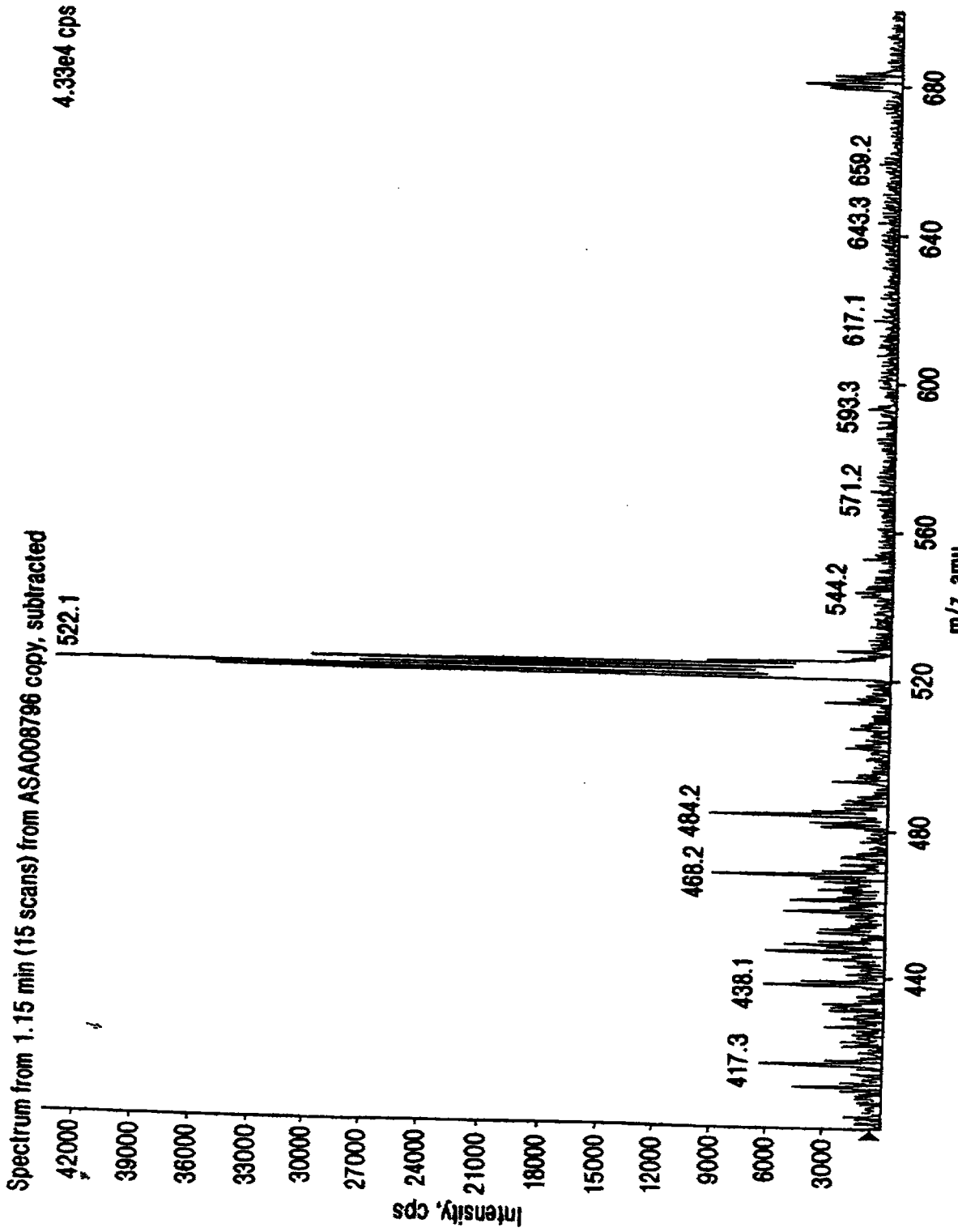

Spectrum from 1.15 min (15 scans) from ASA008796 copy, subtracted
4.33e4 cps
522.1
544.2
571.2
593.3
617.1
643.3
659.2
468.2
484.2
417.3
438.1
Intensity, cps
m/z, amu
42000
39000
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
440
480
520
560
600
640
680

FIG. 267

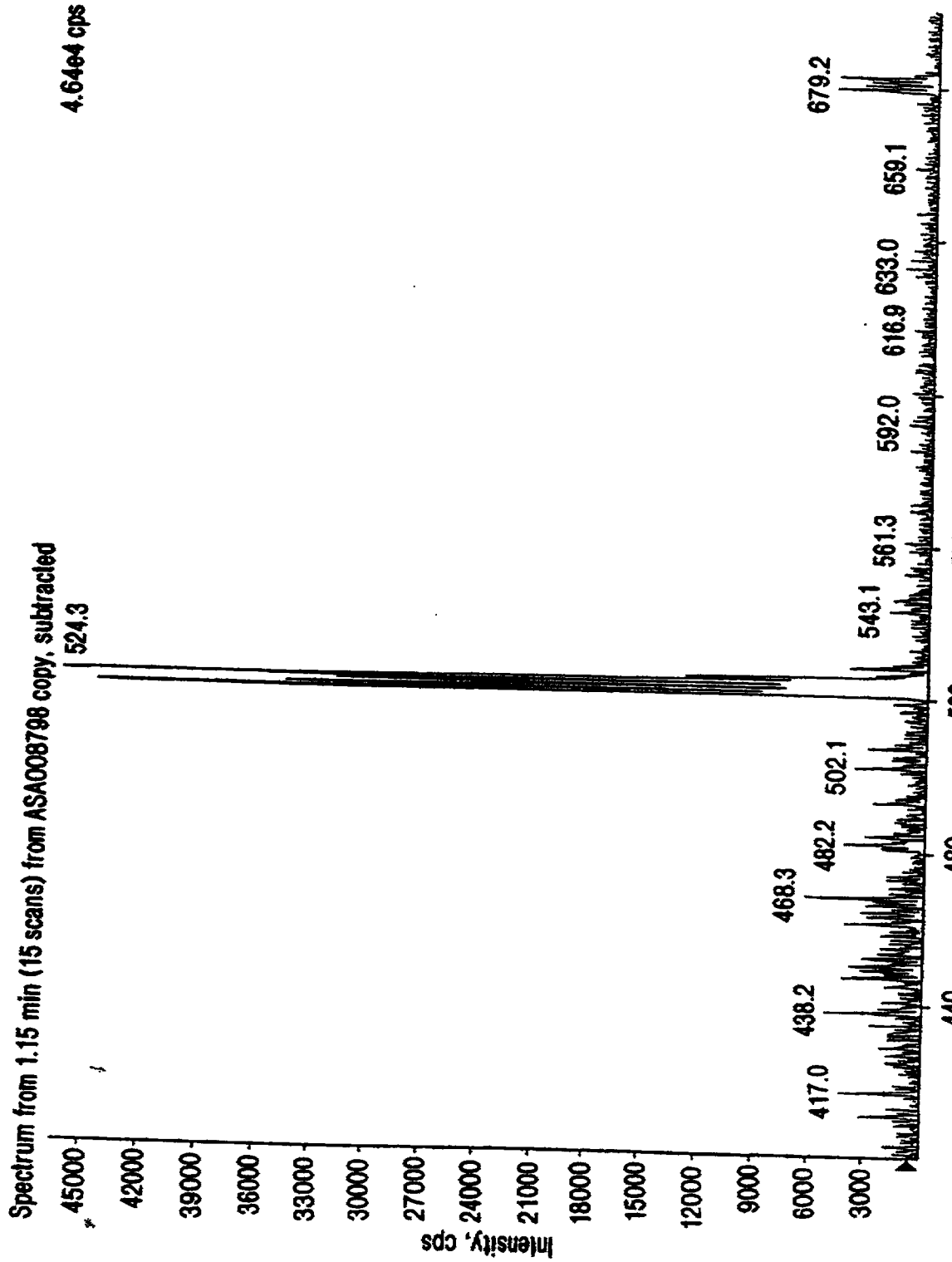

4.6464 cps
Spectrum from 1.15 min (15 scans) from ASA008798 copy, subtracted
524.3
543.1
561.3
592.0
616.9
633.0
659.1
679.2
502.1
482.2
468.3
438.2
417.0
Intensity, cps
45000
42000
39000
36000
33000
30000
27000
24000
21000
18000
15000
12000
9000
6000
3000
440
480
520
560
600
640
680
m/z, amu

FIG. 268

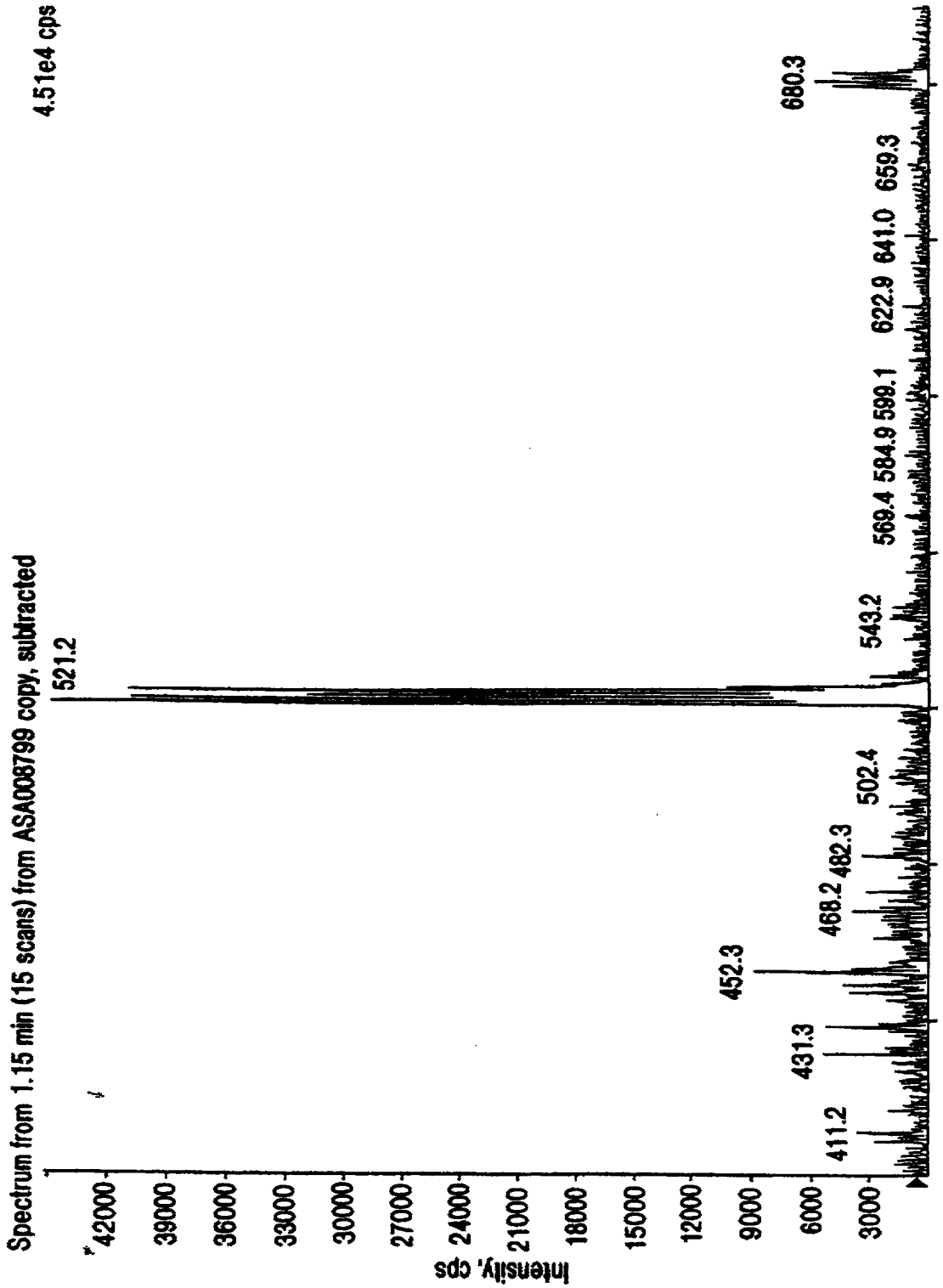

Spectrum from 1.15 min (15 scans) from ASA008799 copy, subtracted
4.51e4 cps
Intensity, cps
m/z, amu
521.2
543.2
569.4
584.9
598.1
622.9
641.0
659.3
680.3
502.4
482.3
468.2
452.3
431.3
411.2

FIG. 269

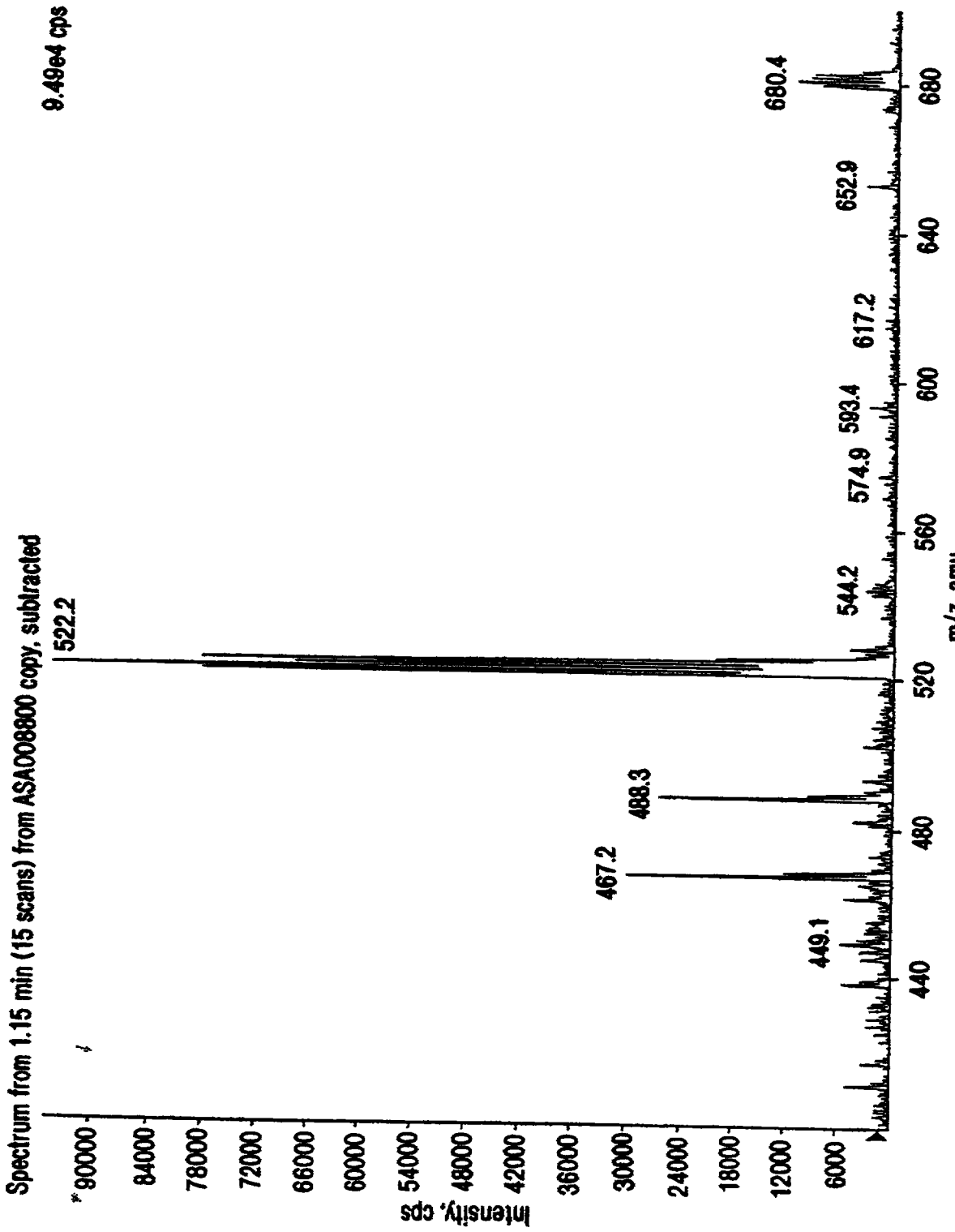

Spectrum from 1.15 min (15 scans) from ASA008800 copy, subtracted
9.49e4 cps
Intensity, cps
90000
84000
78000
72000
66000
60000
54000
48000
42000
36000
30000
24000
18000
12000
6000
m/z, amu
440
480
520
560
600
640
680
522.2
544.2
574.9
583.4
617.2
652.9
680.4
467.2
488.3
449.1

FIG. 270

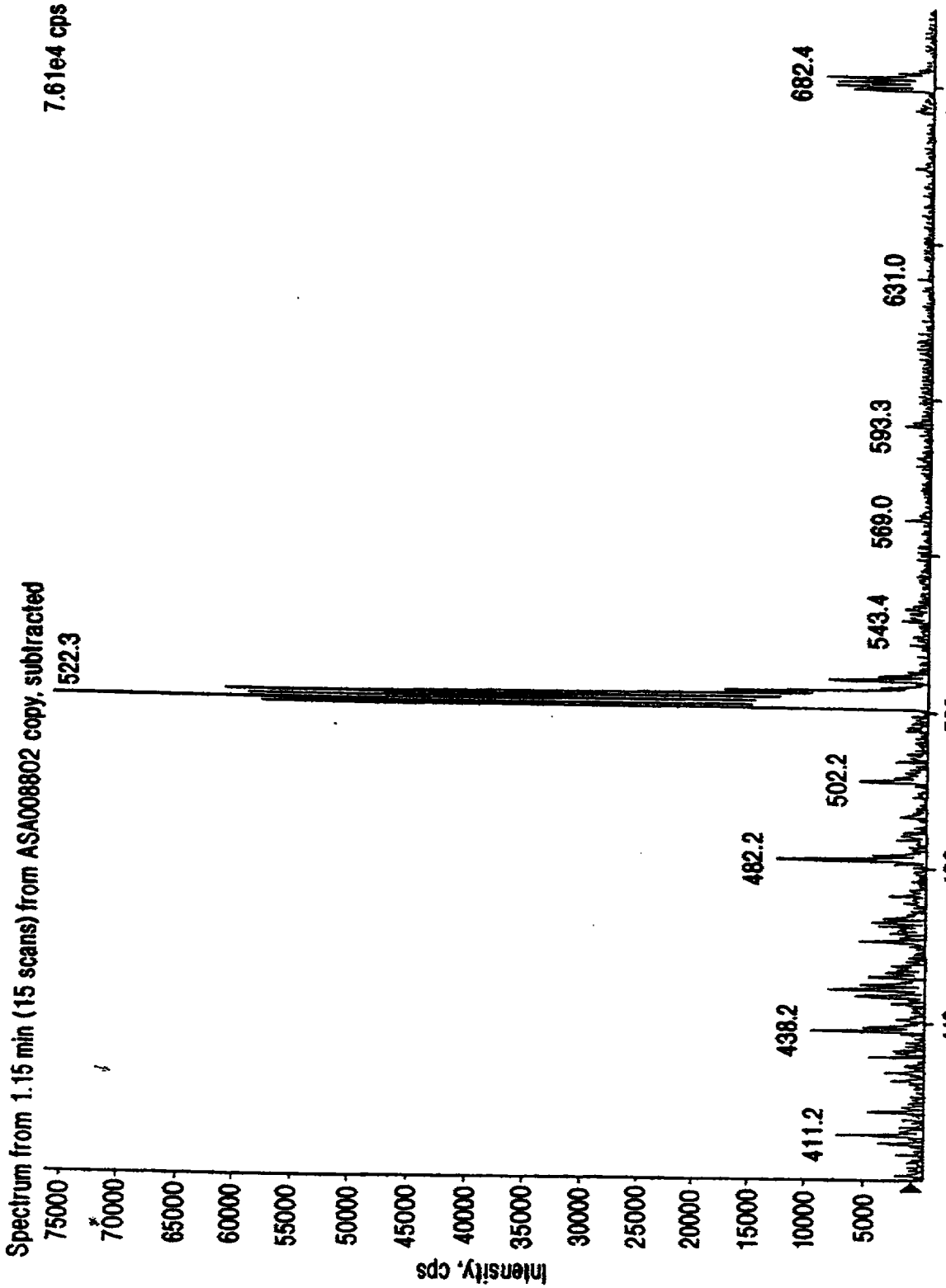

Spectrum from 1.15 min (15 scans) from ASA008802 copy, subtracted
7.61e4 cps
Intensity, cps
m/z, amu
522.3
543.4
569.0
593.3
631.0
682.4
502.2
482.2
438.2
411.2

FIG. 271

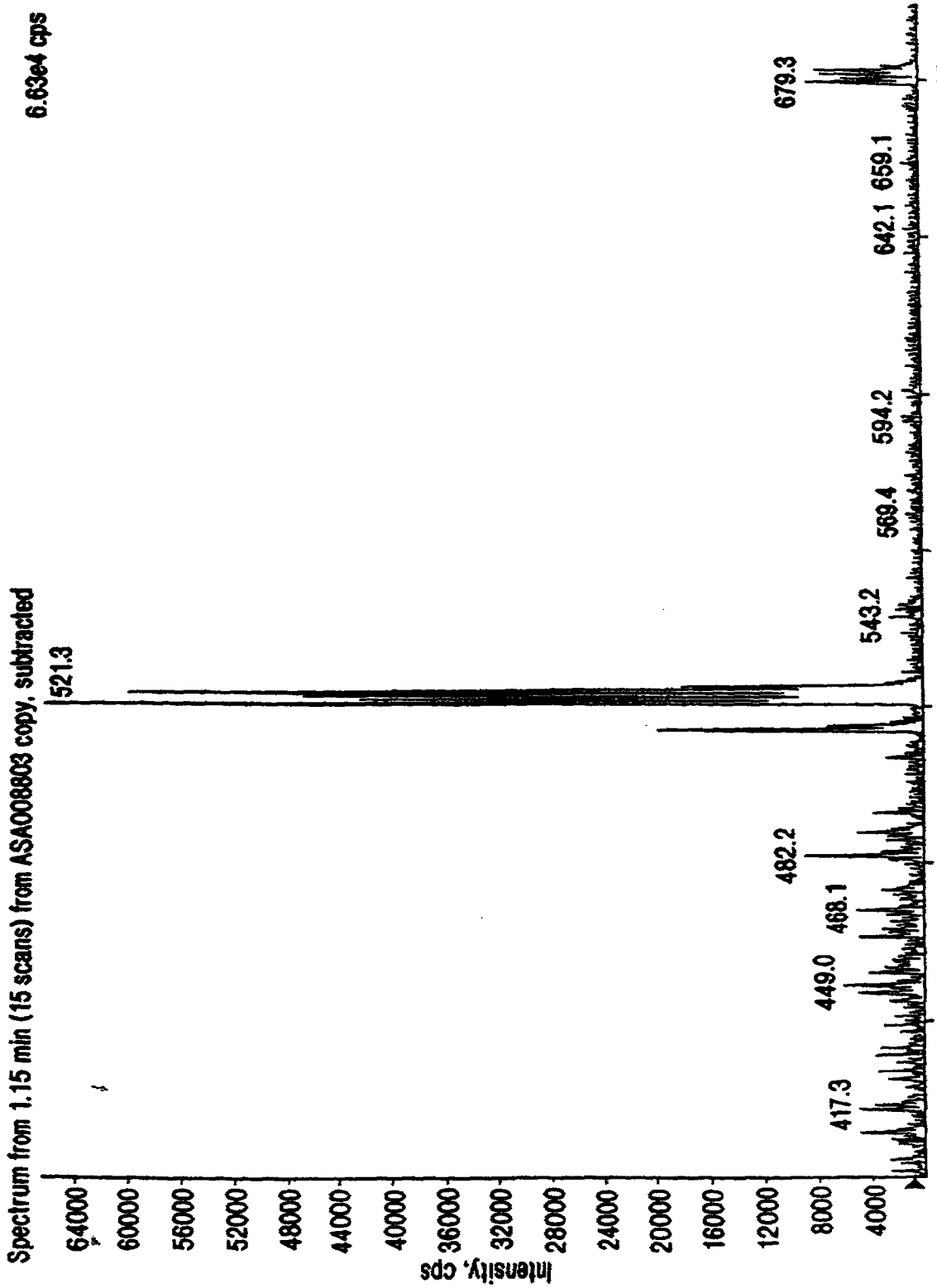

Spectrum from 1.15 min (15 scans) from ASA008803 copy, subtracted
6.63e4 cps
Intensity, cps
m/z, amu
521.3
543.2
569.4
594.2
642.1
659.1
679.3
482.2
468.1
449.0
417.3

FIG. 272

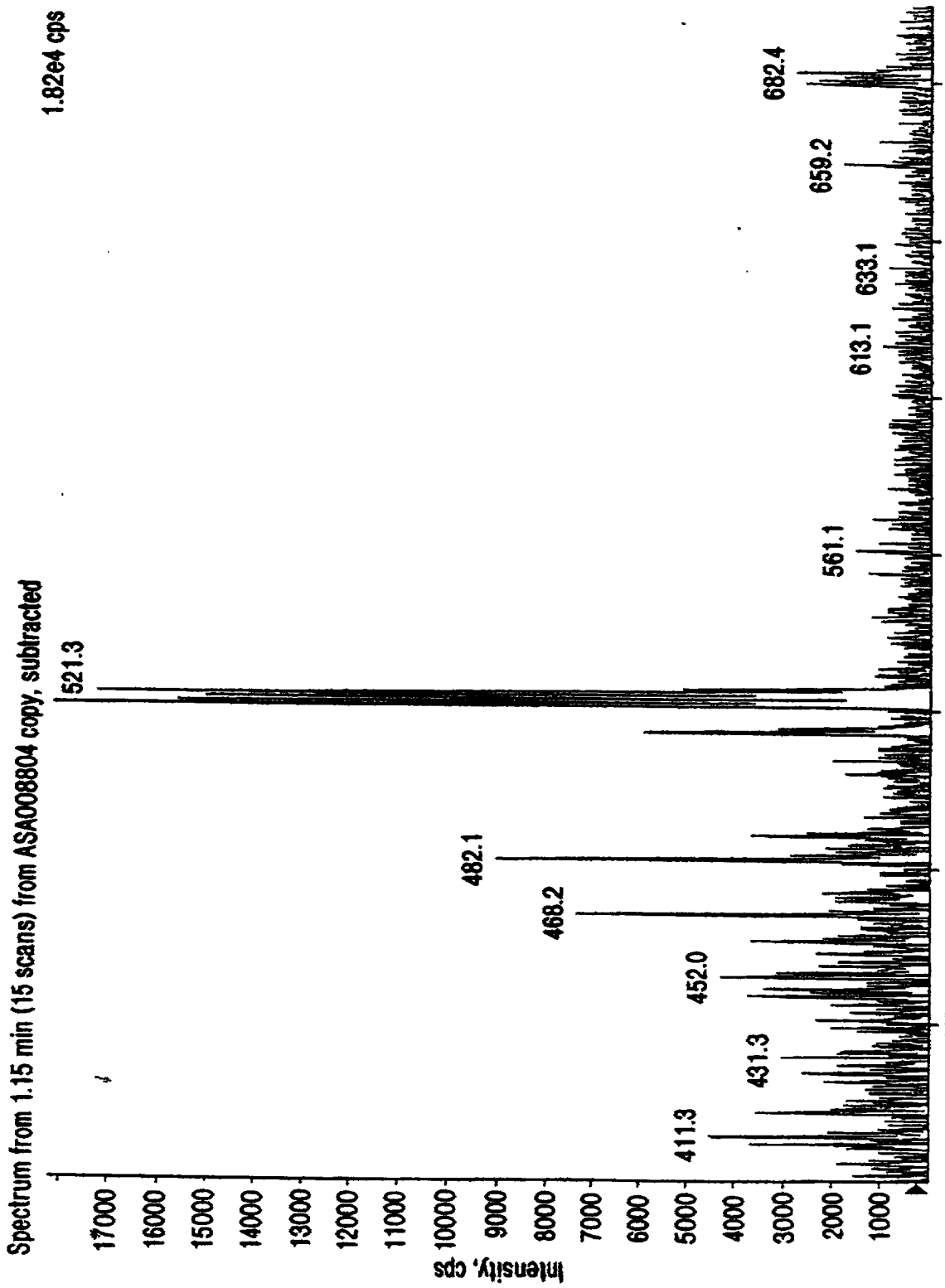

Spectrum from 1.15 min (15 scans) from ASA008804 copy, subtracted
1.82e4 cps
Intensity, cps
m/z, amu
521.3
561.1
613.1
633.1
659.2
682.4
482.1
468.2
452.0
431.3
411.3

FIG. 273

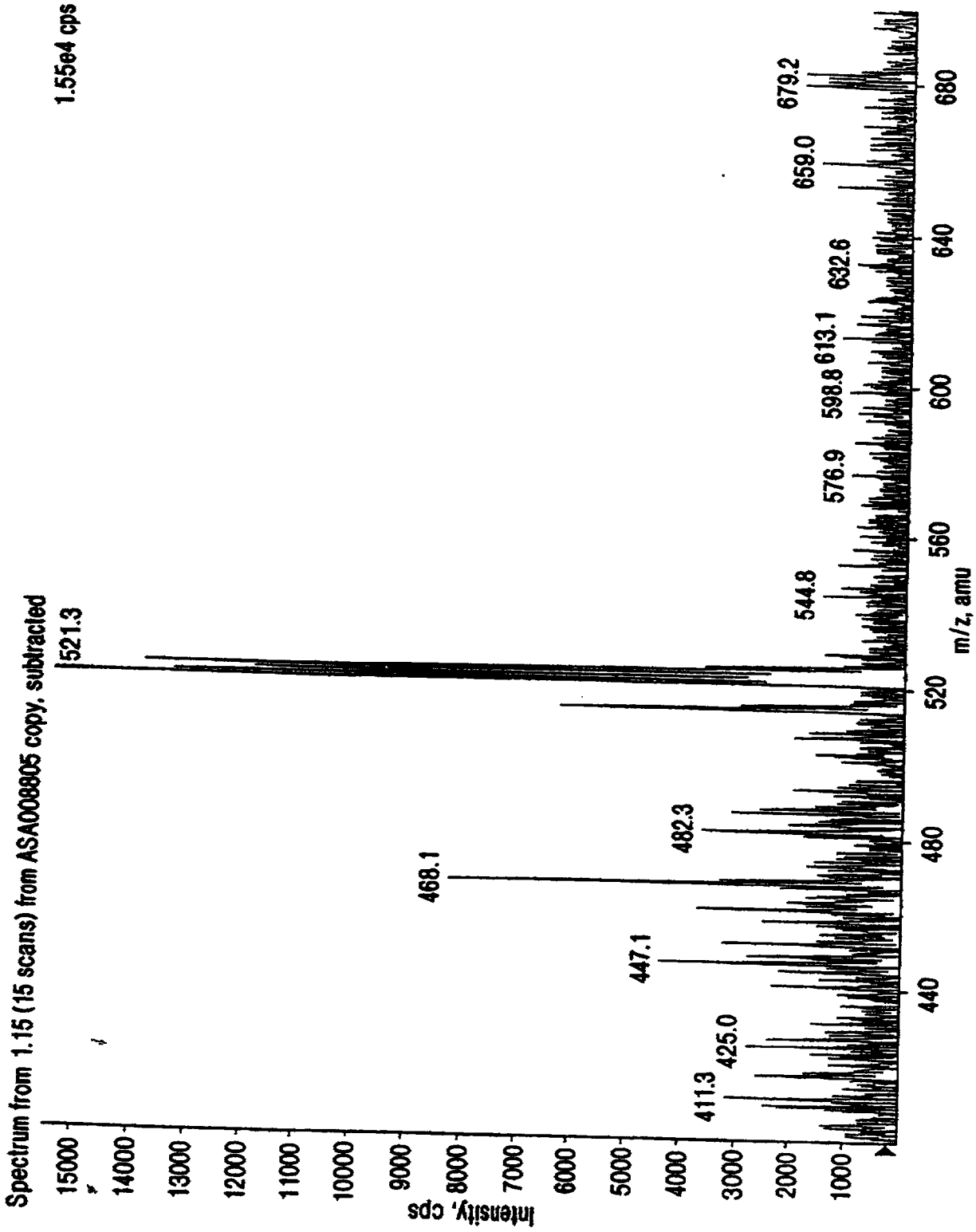

Spectrum from 1.15 (15 scans) from ASA008805 copy, subtracted
1.55e4 cps
Intensity, cps
m/z, amu
521.3
468.1
482.3
447.1
425.0
411.3
544.8
576.9
598.8
613.1
632.6
659.0
679.2

FIG. 274

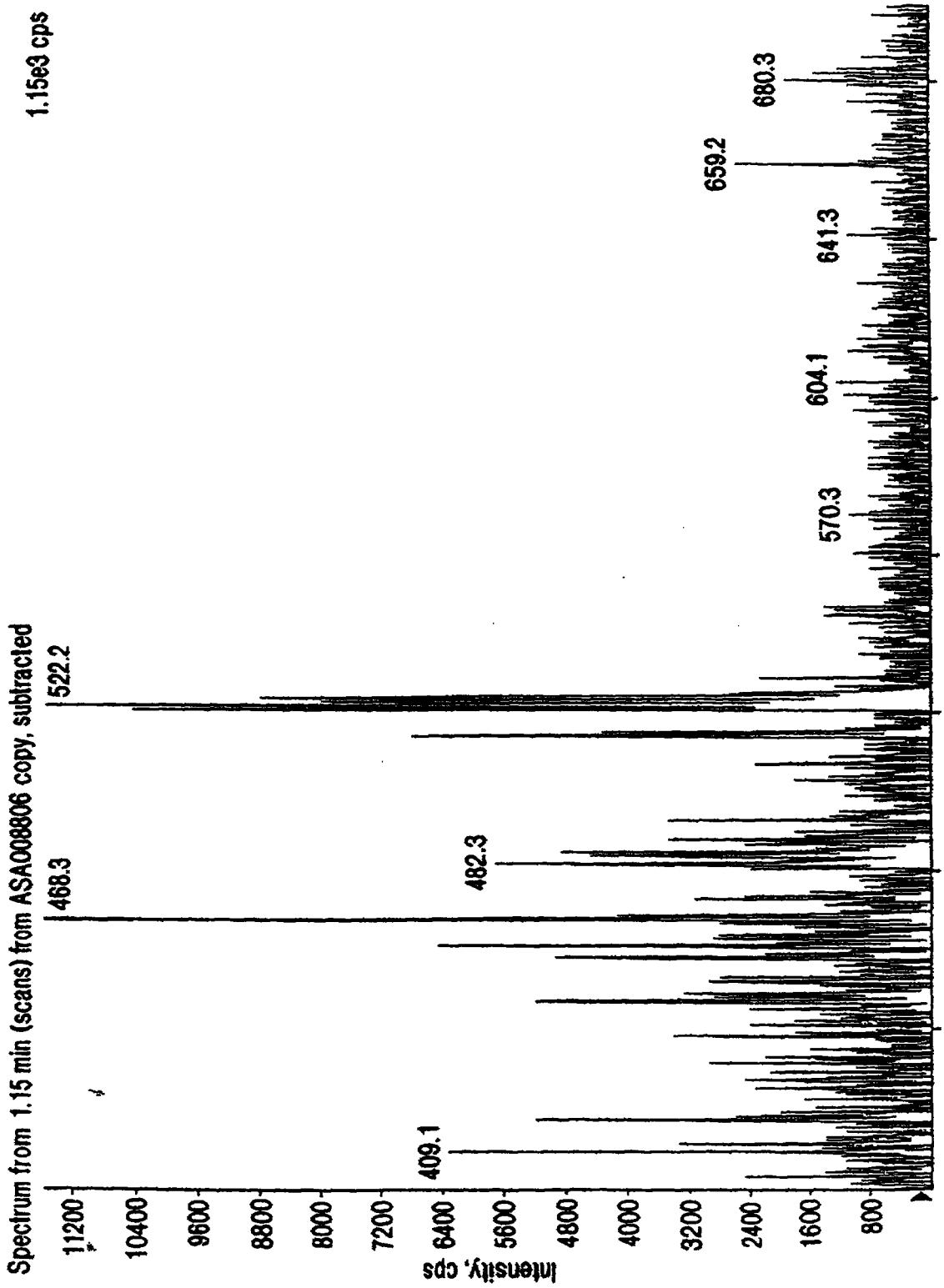

Spectrum from 1.15 min (scans) from ASA008806 copy, subtracted
1.15e3 cps
Intensity, cps
11200
10400
9600
8800
8000
7200
6400
5600
4800
4000
3200
2400
1600
800
m/z, amu
440
480
520
560
600
640
680
409.1
468.3
482.3
522.2
570.3
604.1
641.3
659.2
680.3

FIG. 275

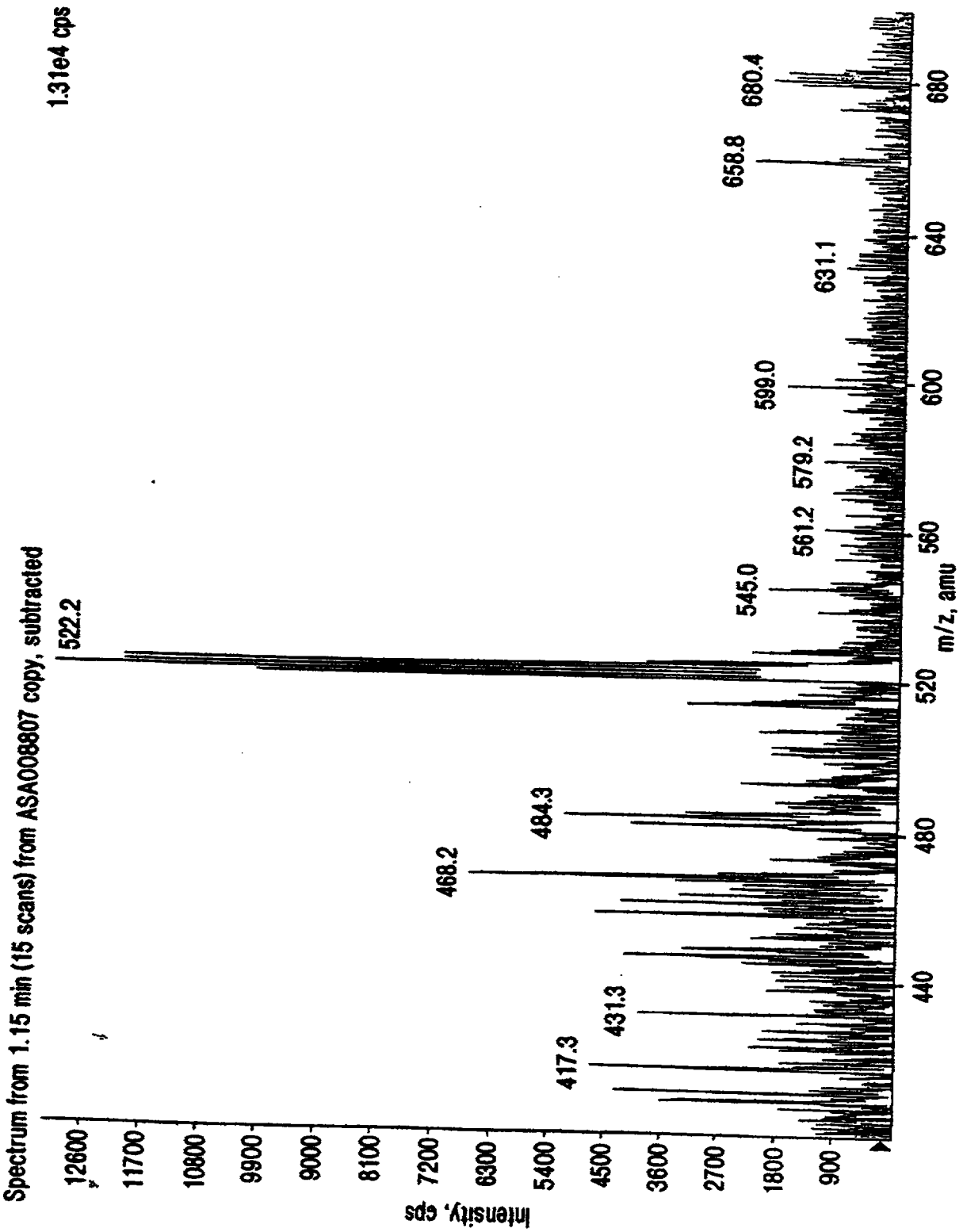
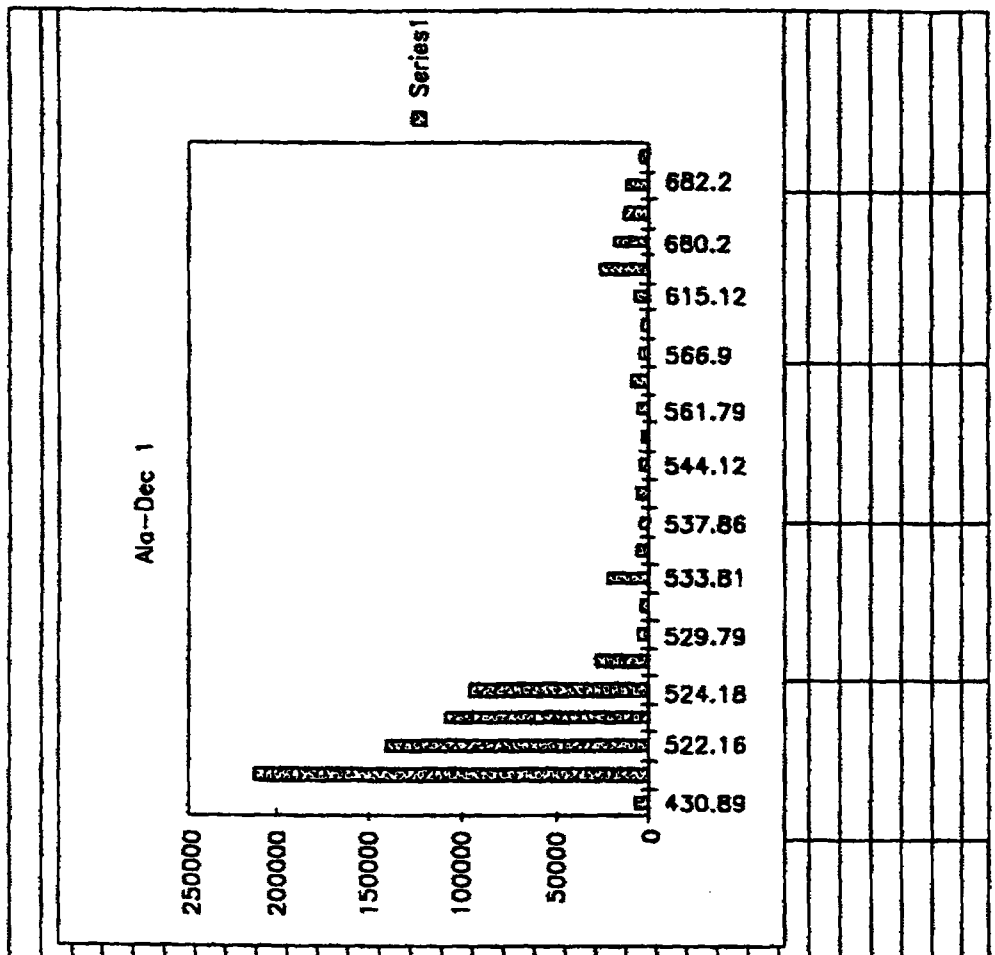
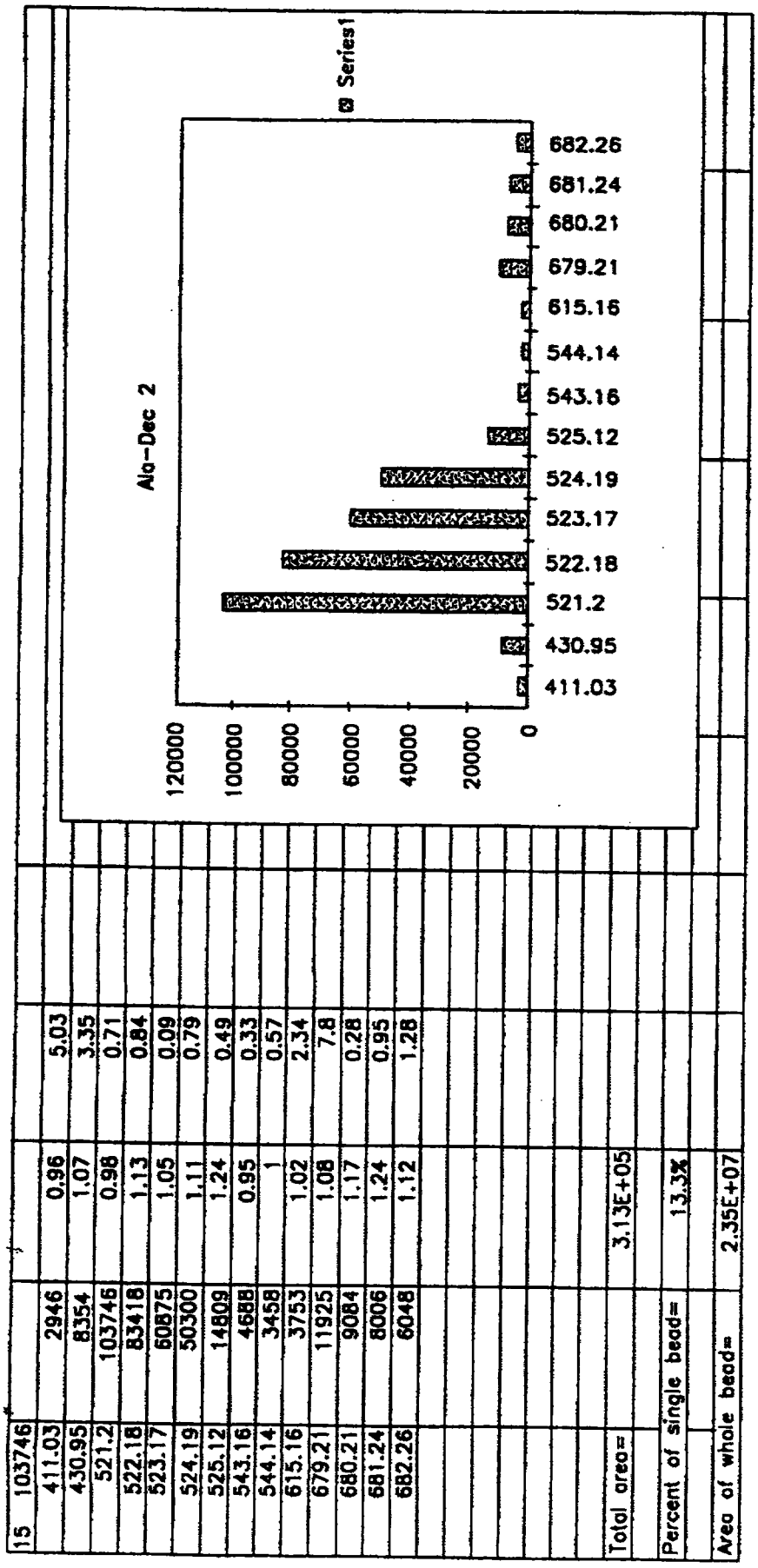

Spectrum from 1.15 min (15 scans) from ASA008807 copy, subtracted
1.31e4 cps
Intensity, cps
12600
11700
10800
9900
9000
8100
7200
6300
5400
4500
3600
2700
1800
900
m/z, amu
440
480
520
560
600
640
680
522.2
545.0
561.2
579.2
599.0
631.1
658.8
680.4
468.2
484.3
417.3
431.3

FIG. 276



25	211323			
430.89	6227	0.95	0.6	
521.21	211323	1.04	1.32	
522.16	139907	1.03	0.16	
523.17	107945	1.05	0.22	
524.18	95851	1.11	0.93	
525.11	27481	1.24	0.09	
529.79	4726	1	1.2	
531.78	3725	1	0.58	
533.81	21742	1.03	1.41	
534.81	5288	1.07	0.06	
537.86	4059	1.46	0.26	
543.14	6620	1.08	1.08	
544.12	4708	1.17	0.38	
551.83	3006	0.94	0.28	
561.79	4890	1.16	1.38	
565.92	9469	1.04	1.34	
566.9	4183	0.97	0.1	
594.04	2523	1.16	0.38	
615.12	6734	1.09	0.37	
679.25	25065	1.06	0.81	
680.2	18376	1.14	0.58	
681.27	13425	0.97	0.43	
682.2	11236	1.09	0.44	
683.31	2660	0.99	1.69	
Total area=		5.83E+05		
Percent of single bead=		13.3%		
Area of whole bead=		4.38E+07		

FIG. 277



15	103746				
411.03	2946	0.96	5.03		
430.95	8354	1.07	3.35		
521.2	103746	0.98	0.71		
522.18	83418	1.13	0.84		
523.17	60875	1.05	0.09		
524.19	50300	1.11	0.79		
525.12	14809	1.24	0.49		
543.16	4688	0.95	0.33		
544.14	3458	1	0.57		
615.16	3753	1.02	2.34		
679.21	11925	1.08	7.8		
680.21	9084	1.17	0.28		
681.24	8006	1.24	0.95		
682.26	6048	1.12	1.28		
Total area=		3.13E+05			
Percent of single bead=		13.3%			
Area of whole bead=		2.35E+07			

FIG. 278

14 103167			
411.02	2942	1.15	7.84
430.92	5634	1.02	0.89
521.21	103167	1.05	1.42
522.14	86825	1.11	0.77
523.17	51004	1.05	0.18
524.18	38497	1.12	1.02
537.87	4138	1.06	2.23
543.27	3078	0.82	0.09
544.18	2793	0.93	0.56
679.25	11593	1.06	0.62
680.2	10952	1.11	0.68
681.25	6430	1.03	0.61
682.29	3746	0.76	0.09
Total area=		2.79E+05	
Percent of single bead=		13.3%	
Area of whole bead=		2.10E+07	

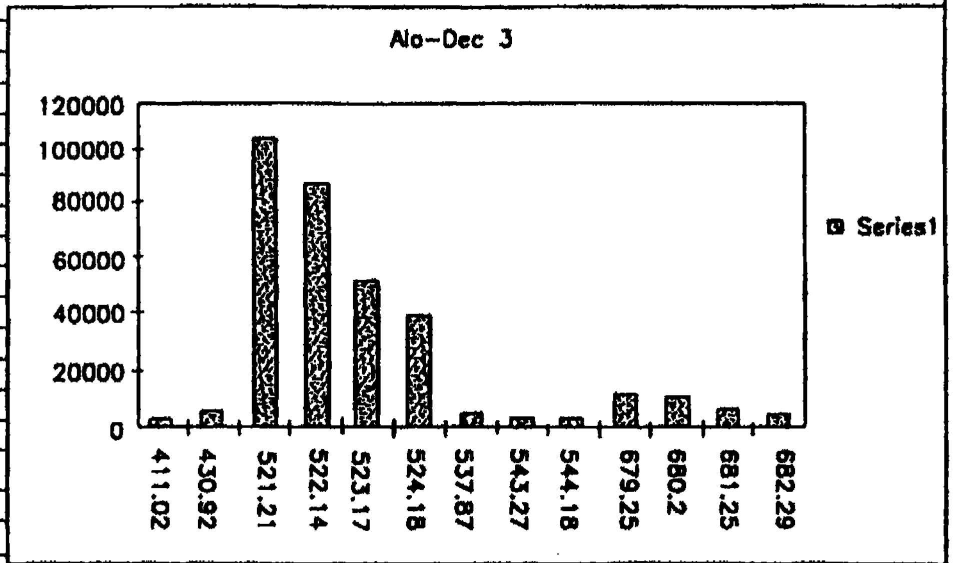


FIG. 279

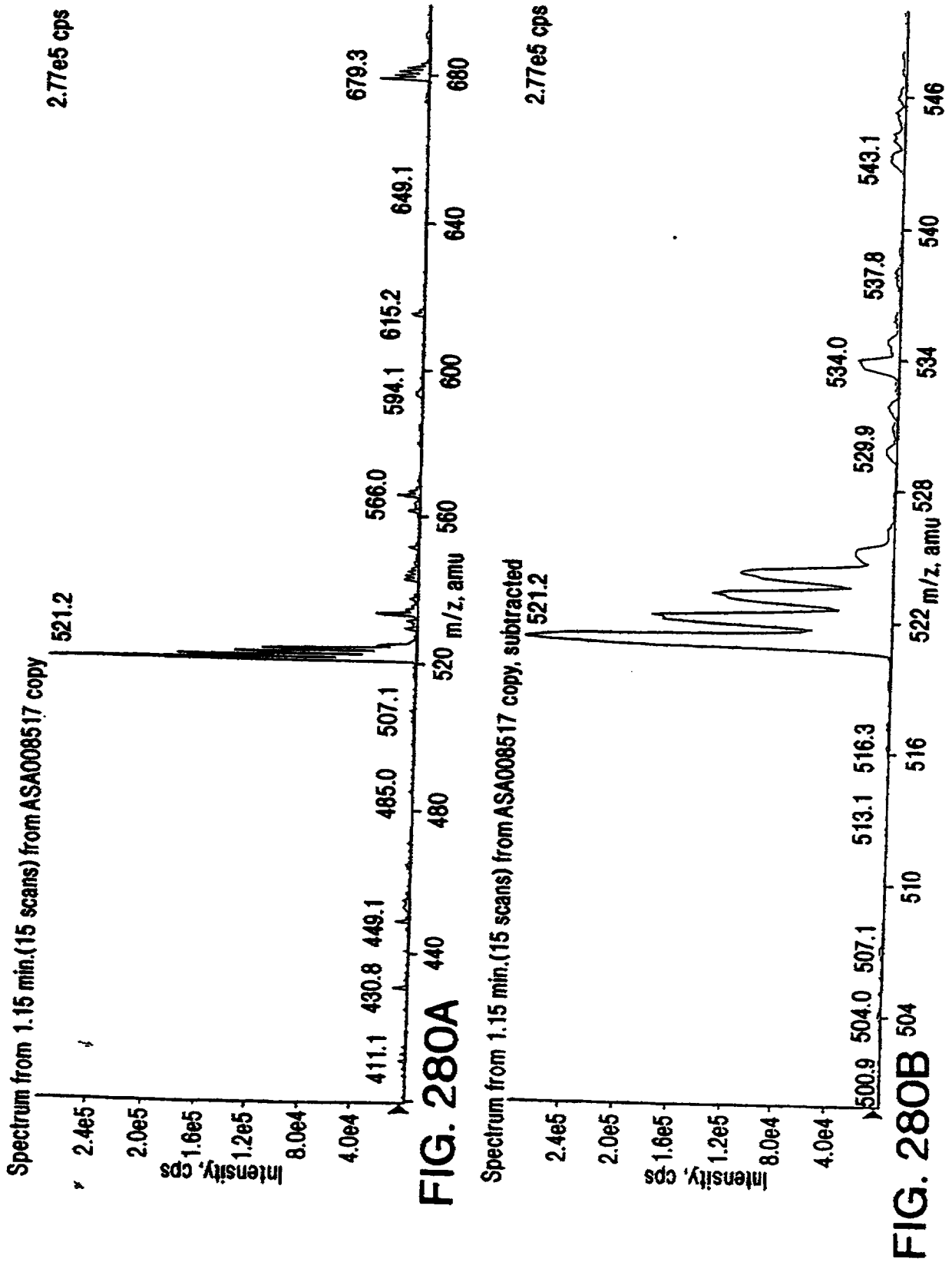


FIG. 280A

FIG. 280B

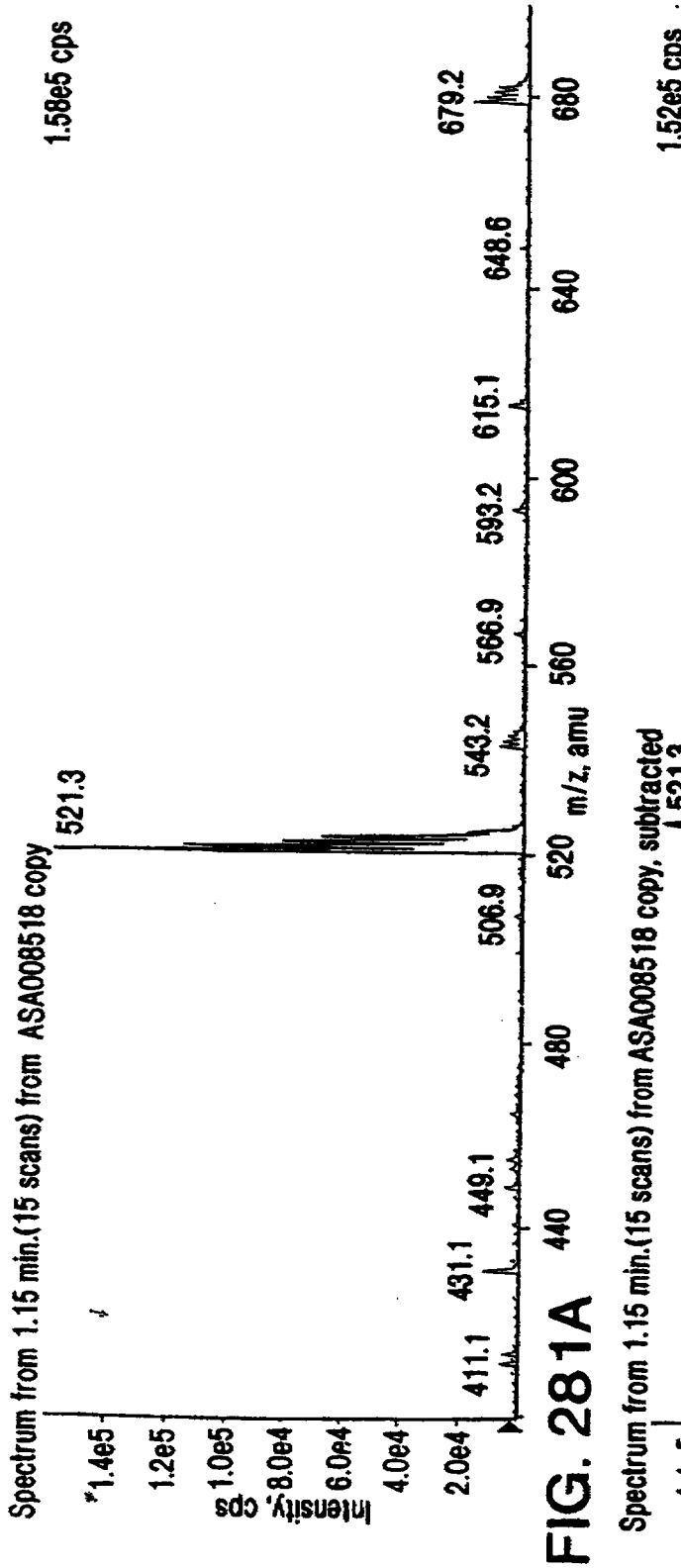


FIG. 281A

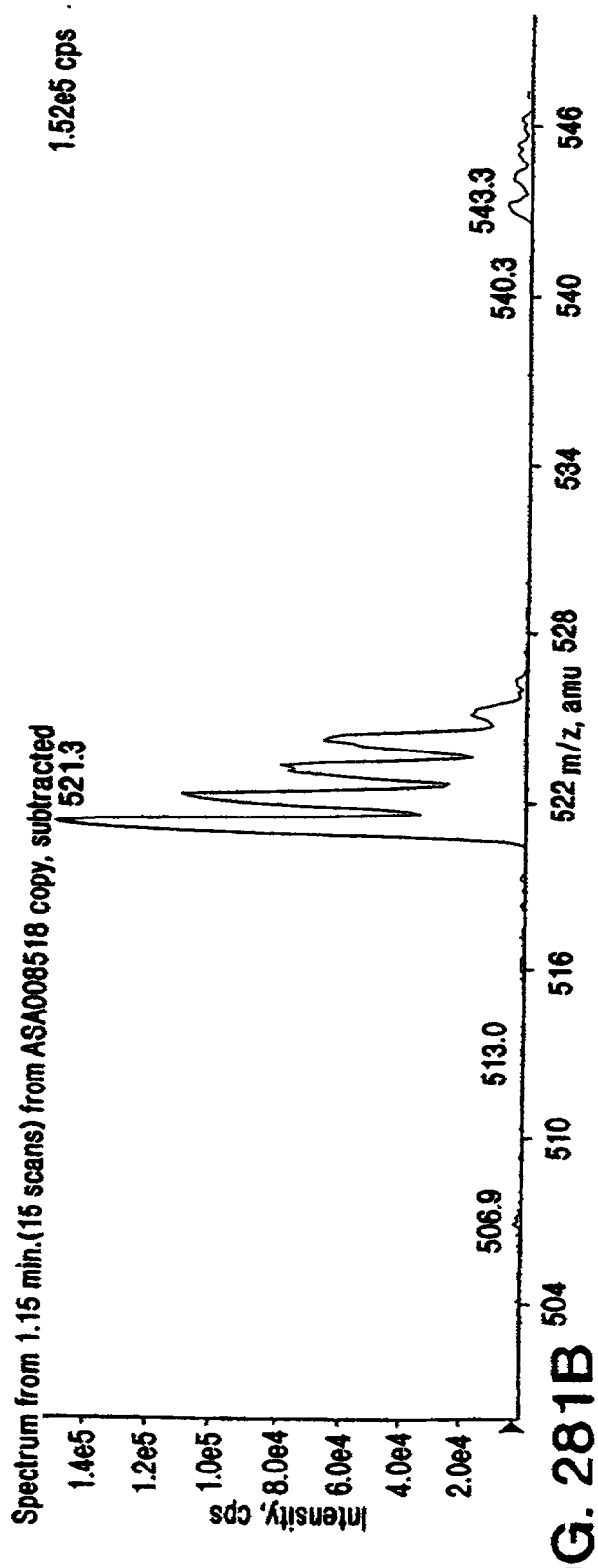


FIG. 281B

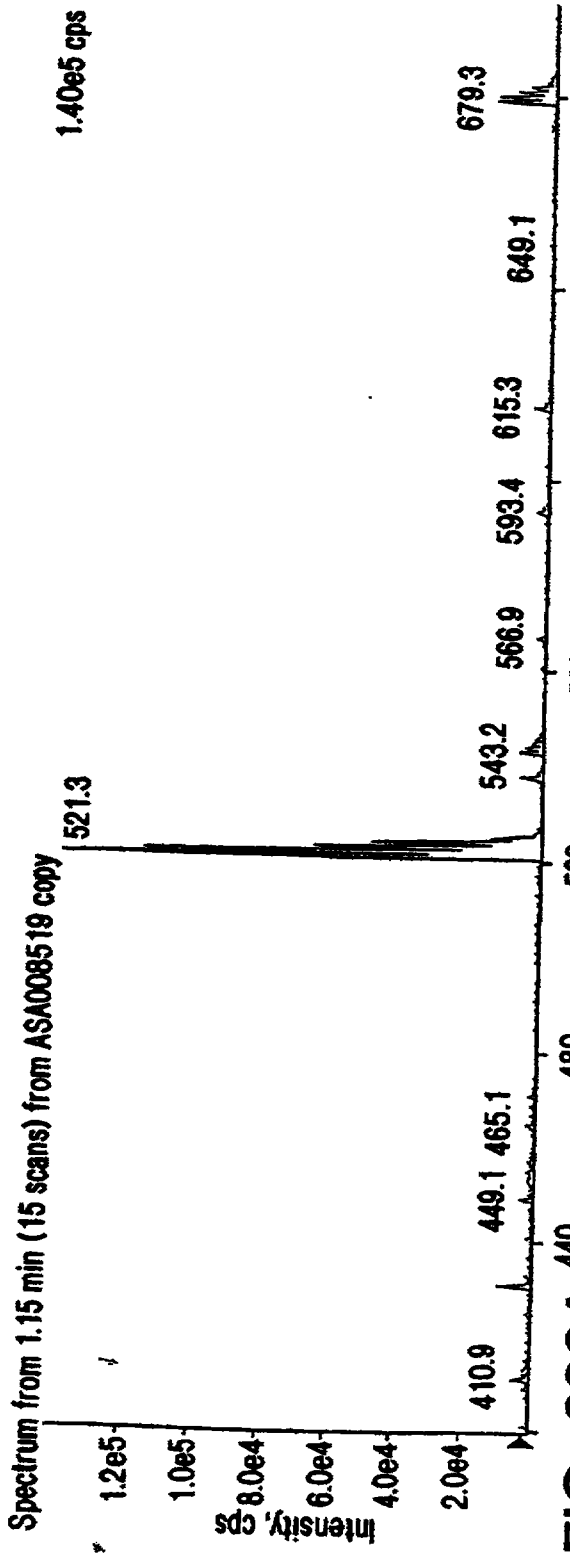


FIG. 282A

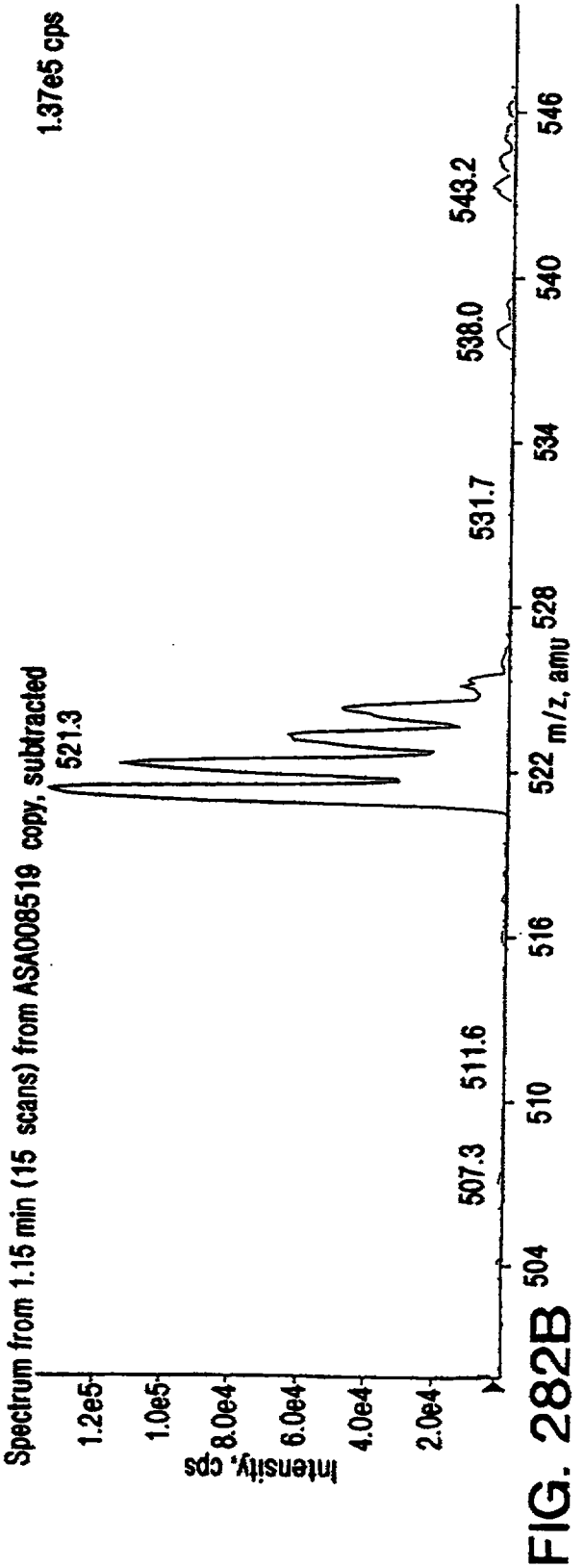


FIG. 282B

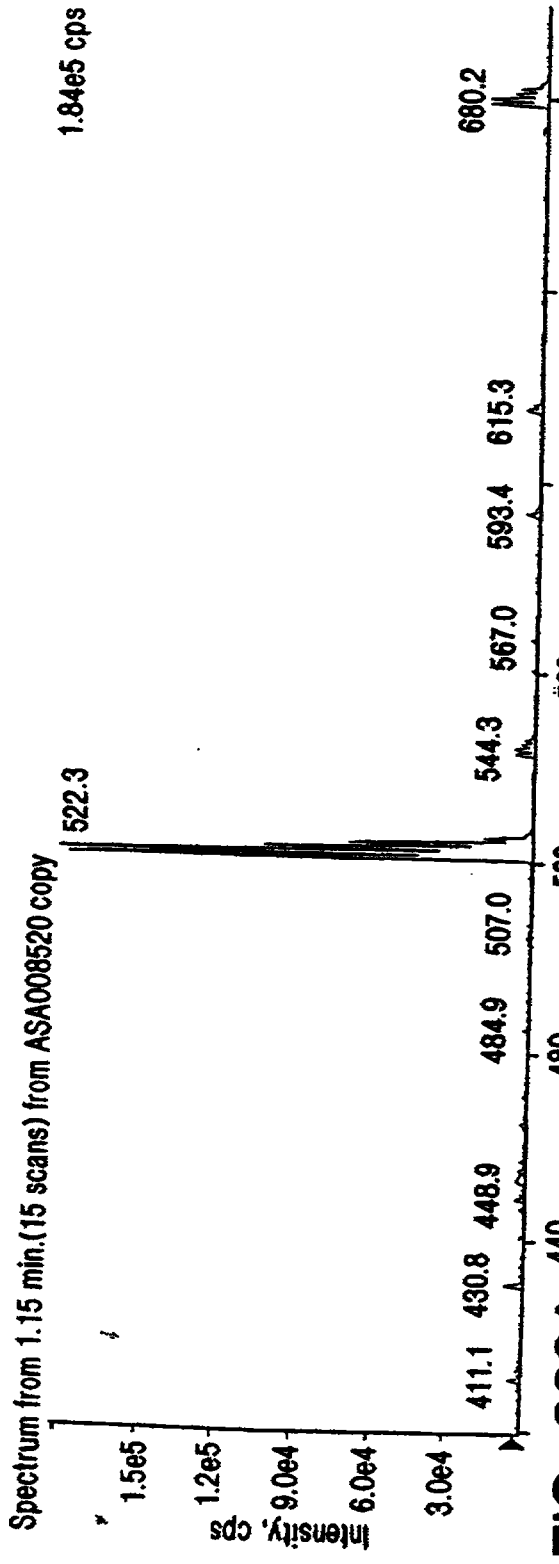


FIG. 283A

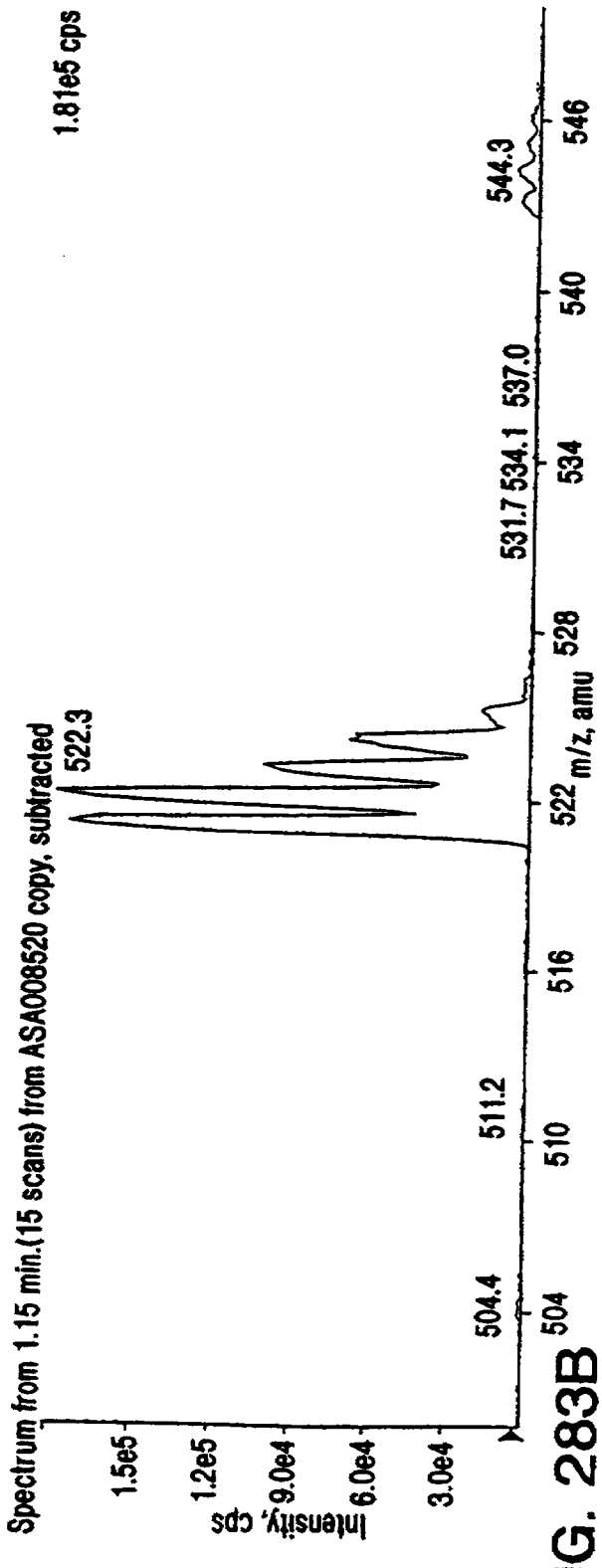


FIG. 283B

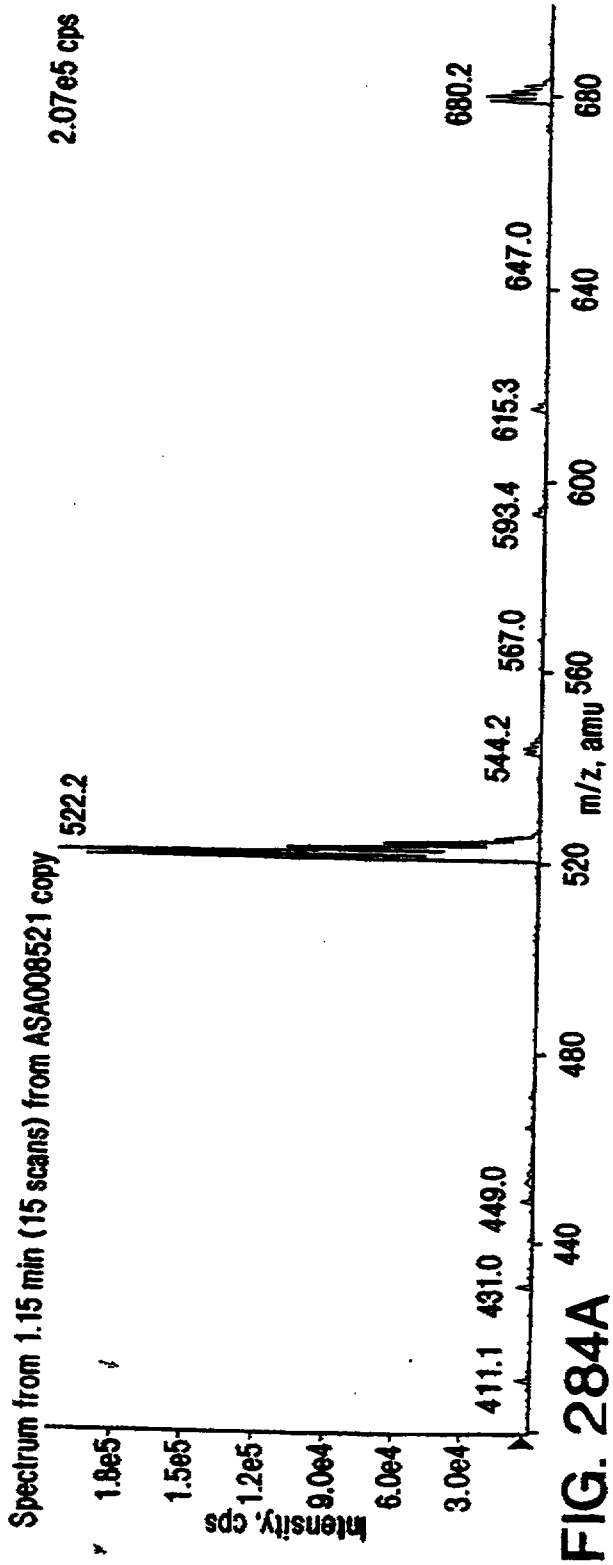


FIG. 284A

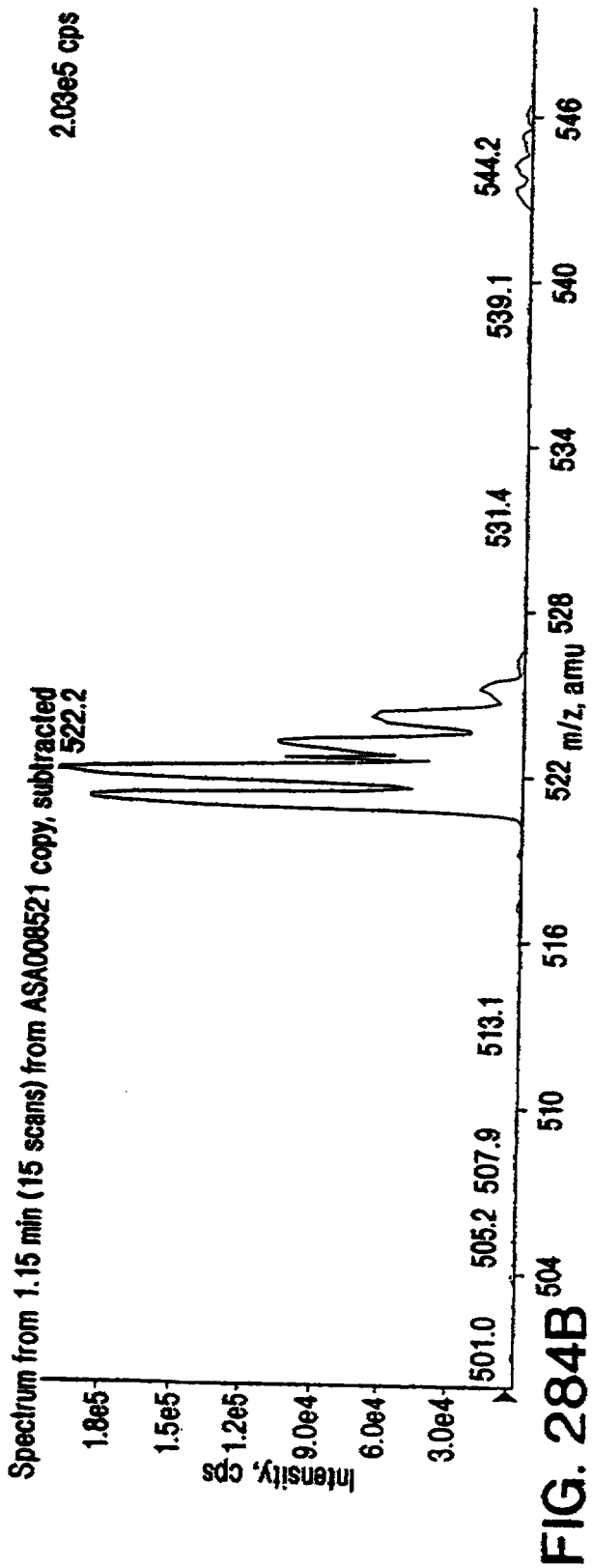


FIG. 284B

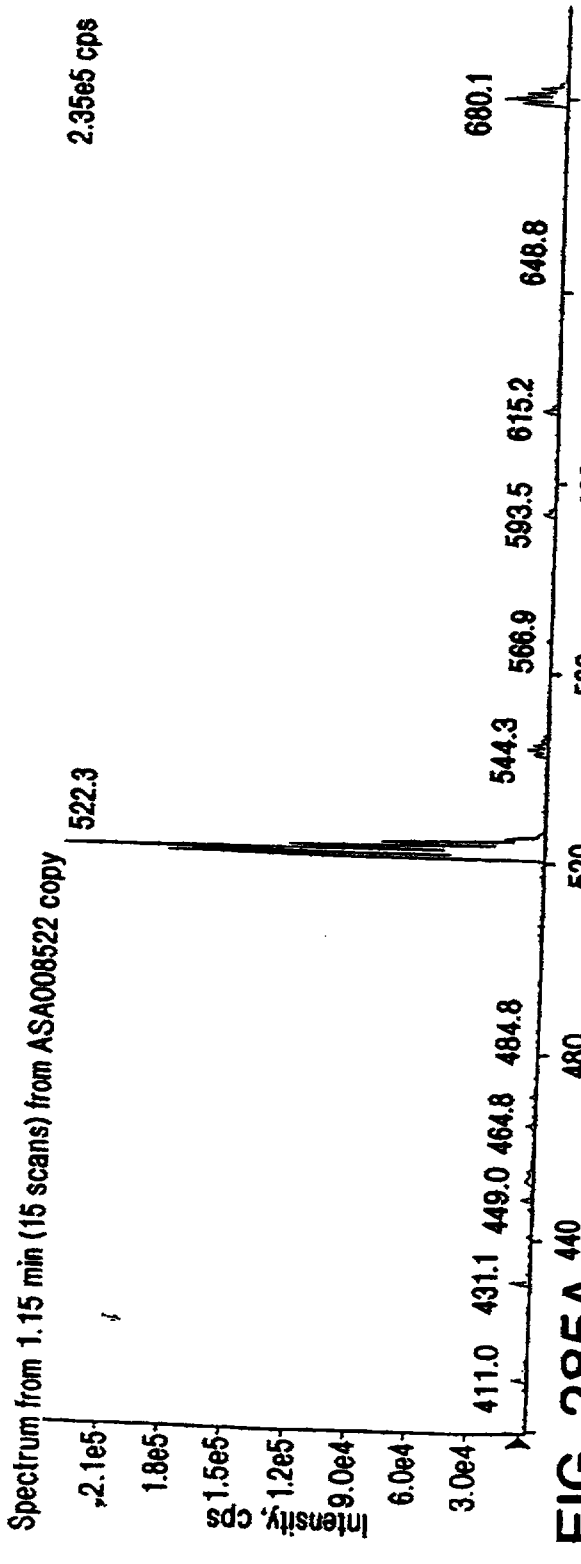


FIG. 285A

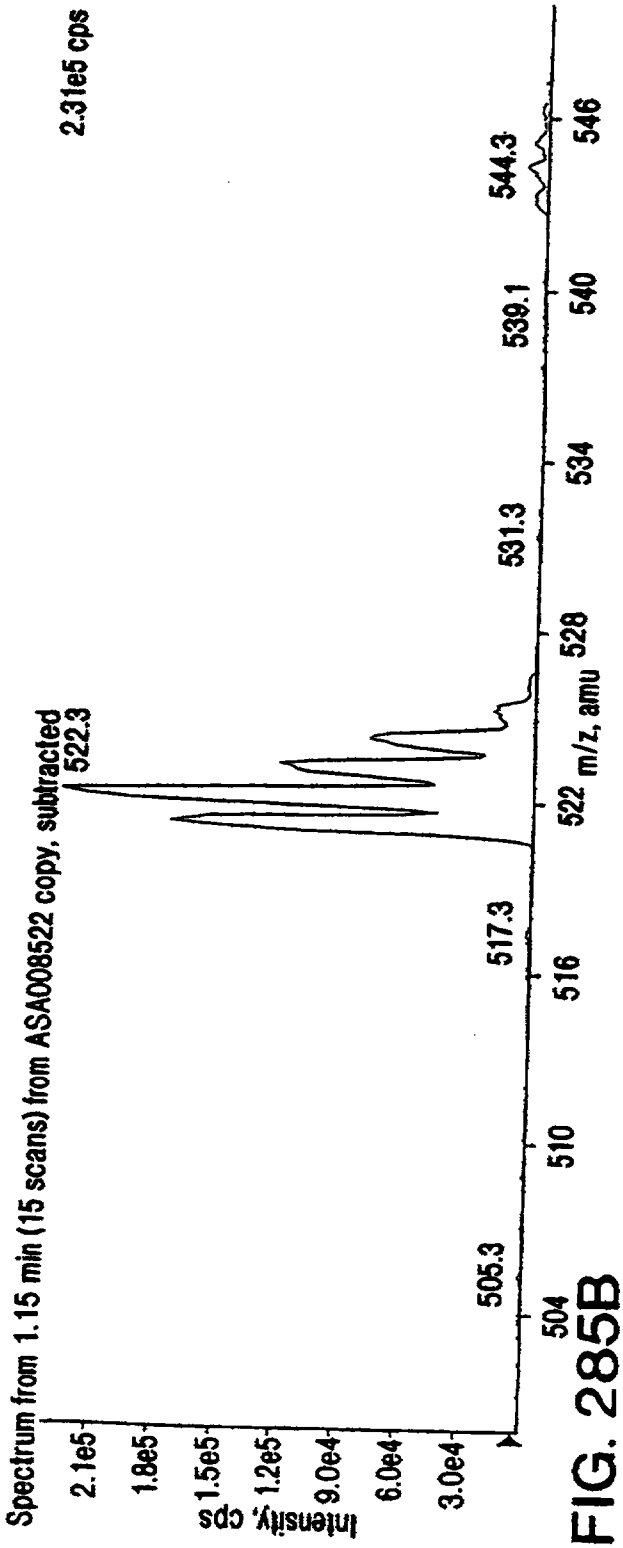


FIG. 285B

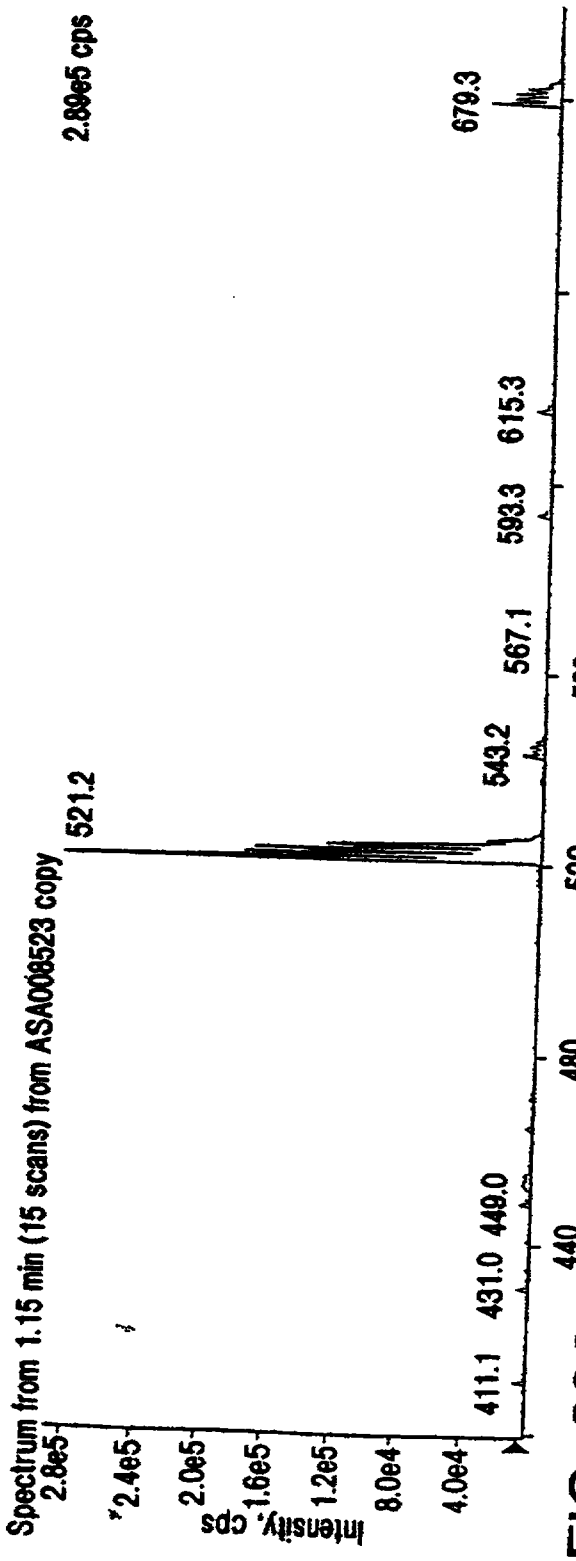


FIG. 286A

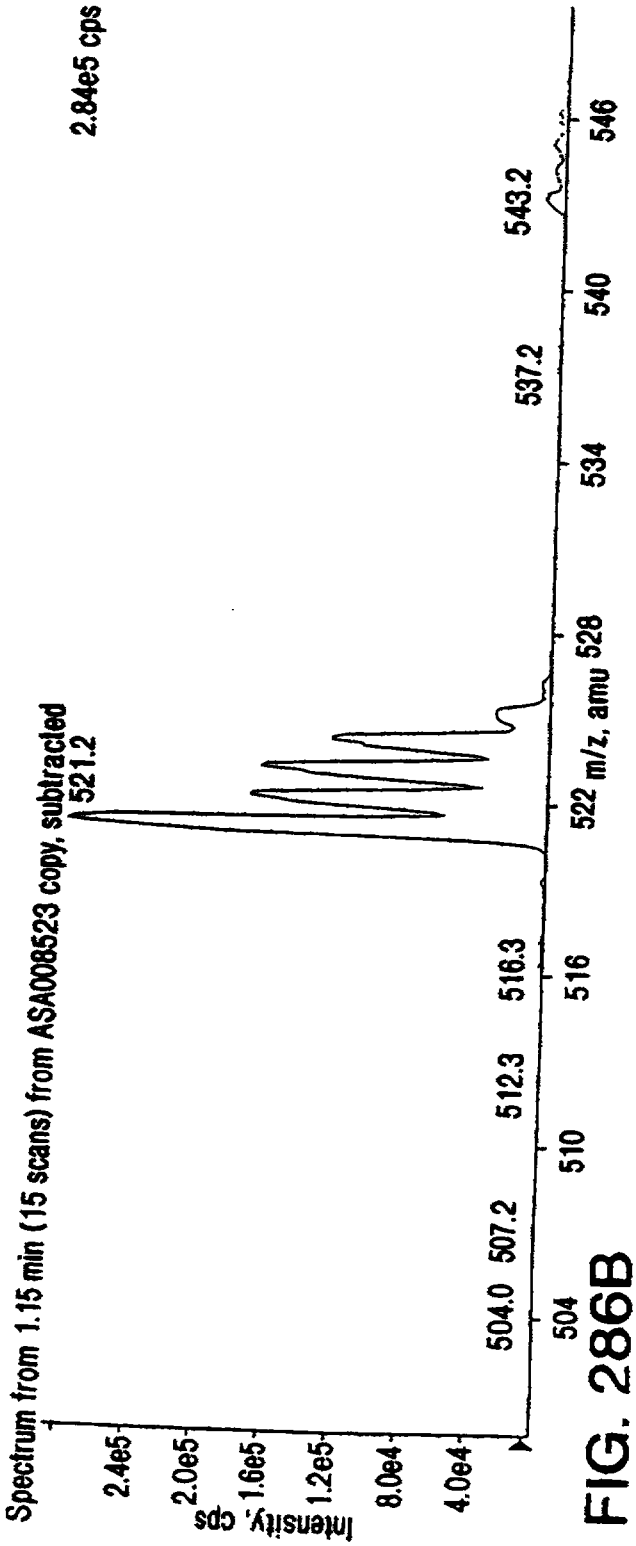


FIG. 286B

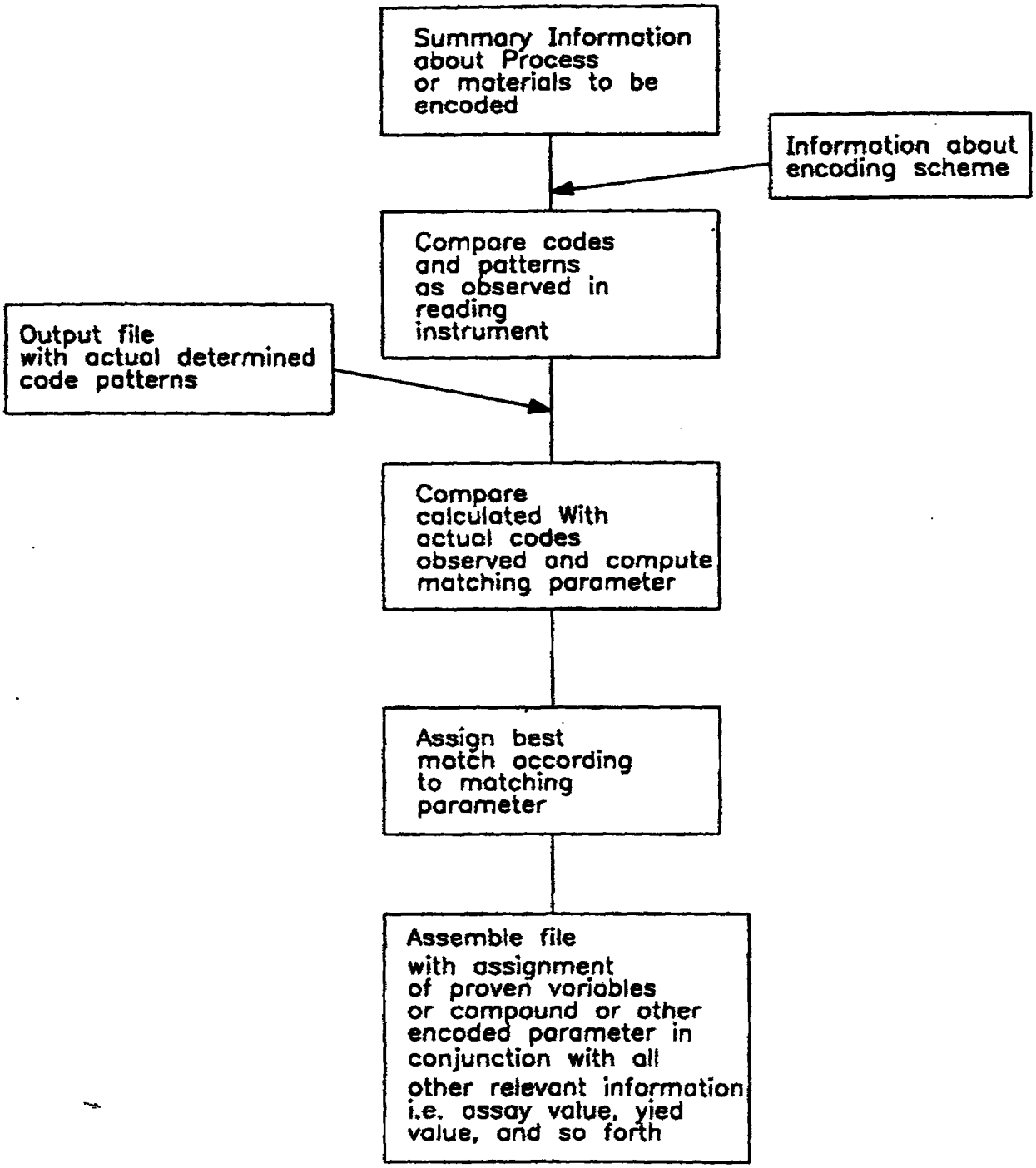

Summary Information about Process or materials to be encoded
Information about encoding scheme
Compare codes and patterns as observed in reading instrument
Output file with actual determined code patterns
Compare calculated With actual codes observed and compute matching parameter
Assign best match according to matching parameter
Assemble file with assignment of proven variables or compound or other encoded parameter in conjunction with all other relevant information i.e. assay value, yied value, and so forth

FIG. 287

CORRECTED VERSION*

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(57) Abstract

The insertion of isotopically labeled portions into solid state combinatorial synthesis constructs followed by mass spectrometer, mass-based nuclear magnetic resonance spectrometry or mass-based infrared spectrometry analysis allows for the physical, non-chemical encoding of large numbers of combinatorial synthesis products.

*(Referred to in PCT Gazette No. 30/1998, Section II)