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(72) Feltaláló(k):
HANNA, Mazen, Lutz FL 33549 (US)
SHAN, Ning, Tampa FL 33647 (US)
CHENEY, Miranda, Tampa FL 33647 (US)
WEYNA, David, Tampa FL 33612 (US)
HOUCK, Raymond, K., Oakmont PA 15139 (US)

(73) Jogosult(ak):
Grünenthal GmbH, 52078 Aachen (DE)

(74) Képviselő:
dr. Miskolczi Mária, Budapest

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(73) Proprietor: **Grünenthal GmbH**
52078 Aachen (DE)

(72) Inventors:
- **HANNA, Mazen**
  Lutz
  FL 33549 (US)
- **SHAN, Ning**
  Tampa
  FL 33647 (US)
- **CHENEY, Miranda**
  Tampa
  FL 33647 (US)
- **WEYNA, David**
  Tampa
  FL 33612 (US)
- **HOUCK, Raymond, K.**
  Oakmont
  PA 15139 (US)

(74) Representative: **Eder, Michael et al**
df-mp Dörries Frank-Molnia & Pohlman
Patentanwälte Rechtsanwälte PartG mbB
Theatinerstrasse 16
80333 München (DE)

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EP 2 459 176 B1

Description

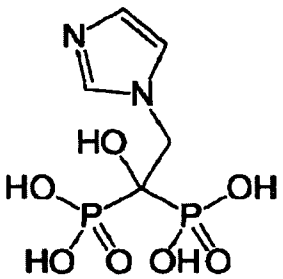
FIELD OF THE INVENTION

[0001] This disclosure pertains to improvement of the aqueous solubility and permeability of poorly permeable and sparingly water soluble drug compounds through generating novel crystalline forms of such drugs. Methods for the preparation and pharmaceutical compositions suitable for drug delivery systems that include one or more of these new forms are disclosed.

BACKGROUND OF THE INVENTION

[0002] Many Biopharmaceutic Classification System (BCS) class III or IV drugs suffer from the lack of gastrointestinal (GI) tract membrane permeability leading to poor oral bioavailability. Different strategies have been implemented to improve the permeability and subsequently the oral bioavailability of such drugs. For example, the U.S. patent application 20060068010 describes a formulation method for improving the permeability of drugs and subsequently increasing their bioavailability by granulation of the physical solid mixture of the drug with one or more amino acids, at least one intergranular hydrophilic polymer, and an additional immediate release excipient. Another application WO 200602009 A1 disclosed the increase of the oral bioavailability for poorly permeable drugs such as bisphosphonates; risedronate as one of those drugs was mixed with a chelating agent such as ethylenediaminetetraacetate (EDTA) and other excipients to make an oral dosage form. Yet another application, WO 2007093226 A1, describes a method for improving the bioavailability of ibandronate by generating a physical mixture of the drug together with a modified amino acid (acylation or sulphonation of the amino group with phenyl or cyclohexyl) and other excipients. Another application WO 2003007916 A1 reports a gastric retention system to improve the bioavailability of a poorly permeable drug, alendronate, which was orally formulated with vitamin D and released an hour after the immediate release of vitamin D. WO 2006080780 discloses yet another method to improve the permeability and bioavailability of alendronate, a poorly permeable bisphosphonate, by mixing it with a biocompatible cationic polymer (i.e. water soluble chitosan) with up to a 10:1 weight ratio of the chitosan to the drug, while the resulting mixture can be formulated into a solid or liquid oral dosage form. A further method of improving permeability of drug materials was discussed in the U.S. patent application 2007/014319 A1, where an oral dosage form was formulated by a powder mixture of a bisphosphonic acid (e.g. zoledronic acid) together with an inactive ingredient (either an ester of a medium chain fatty acid or a lipophilic polyethylene glycol ester). A similar approach was disclosed in the US application 2007/0238707 A1 where a medium length fatty acid or its derivative (6-20 carbon atom fatty acid chain) was physically mixed with a poorly permeable drug (e.g. zoledronic acid) in a capsule that was enterically coated.

[0003] Zoledronic acid, known as (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl)phosphonic acid, is depicted by the following chemical structure:



Zoledronic acid is a third generation bisphosphonate which far exceeds the previous generations in terms of efficacy and is used predominately for indications of osteoporosis, Paget's disease, hypercalcemia, and inhibition of bone metastasis. It was originally developed by Novartis and marketed as the monohydrate under the brand names Zometa® and Reclast®. Zoledronic acid was first approved in 2000 for the treatment of hypercalcemia in Canada. It was later approved for use in the US for hypercalcemia in 2001, for multiple myeloma and bone metastases from solid tumors in 2002, and for osteoporosis and Paget's disease in 2007. Clinical trials have also been conducted or are on-going exploring the use of zoledronic acid in neoadjuvant or adjuvant cancer therapy, Coleman, et al., British J Cancer 2010;102(7):1099-1105, Gnant, et al., New England J Medicine. 2009, 360 (17):679-691 and Davies, et al. J Clinical Oncology, 2010, 28(7s): Abstract 8021. Zoledronic acid is administered as an intravenous (IV) dose of 4 mg over 15 minutes for hypercalcemia of malignancy, multiple myeloma, and bone metastases from solid tumors, while an IV dose of 5 mg over 15 minutes is used for osteoporosis and Paget's disease.

[0004] Zoledronic acid is sparingly soluble in water and 0.1 N HCl solution but is freely soluble in 0.1 N NaOH. Zoledronic

acid is practically insoluble in various organic solvents.

[0005] Much effort has been taken to generate novel oral formulations of zoledronic acid through crystallization and metal salt formation to improve its aqueous solubility, permeability, and subsequent oral bioavailability. A crystalline trihydrate was disclosed in the U.S. Patent application 2006/0178439 A1 and world patent application WO2007/032808. Seven hydrated forms, an amorphous form, three monosodium salts, and eleven disodium salts with varying degrees of hydration of zoledronic acid were also disclosed in the patent application WO2005/005447 A2. Zoledronate metal salts including Na^+, Mg^{2+}, Zn^{2+} were reported in the journal of Drugs of the Future (Sorbera et al, 25(3), Drugs of the Future, (2000)). Zoledronate, zoledronic, or zoledronic salt represents the ionic form of zoledronic acid. Patent application WO2008/064849 A1 from Novartis disclosed additional metal salts including two Ca^{2+} salts, two Zn^{2+} salts, one Mg^{2+} salt, as well as a monohydrate, a trihydrate, an amorphous form, and an anhydrous form.

[0006] According to the US Food and Drug Administration (FDA) Summary Basis of Approval (SBA) for zoledronic acid, the poor oral bioavailability (approximately 1%), is partially due to its poor permeability in the GI tract. It was also noted that insoluble metal complexes were formed in the upper intestines, most commonly with calcium. Zoledronic acid has also been shown to cause severe gastric and intestinal irritations.

[0007] All of the above attempts to improve the oral bioavailability of zoledronic acid were either focused on improving the aqueous solubility by generating novel solid forms, or by mixing the drug with an inactive ingredient that has enhanced GI tract permeability. The improvement of aqueous solubility failed to improve the bioavailability of zoledronic acid, since the formation of insoluble zoledronate calcium complexes is unlikely to be prevented. On the other hand, powder mixtures of the poorly permeable drug with inactive permeability enhancers improved the bioavailability of the drug. This approach of mixing different materials with different particle sizes and size distributions could result in a poor blend/physical mixture uniformity. Constituents of the mixture could also segregate during transportation or with shaking and vibration. Additionally, the powder blends require rigorous batch-to-batch consistency to ensure the uniformity of the blend batches.

[0008] To the best of the inventors' knowledge, no attempt has been made prior to this invention towards a deliberate molecular design to create a molecular complex of the drug and additional component(s) (coformer(s)) in a single crystalline structure. The benefit of such design can lead to the elimination of all the batch to batch blend uniformity and particle segregation problems that powder blends often suffer from. In addition, this invention simplifies the manufacturing of the solid dosage form (comprised of drug and excipient) such that the final solid dosage form is, in one embodiment, a powder of the molecular complex.

[0009] Additionally, the resulting molecular complexes possess very different physicochemical properties compared to the parent drug, coformer or their physical mixture. These properties include but are not limited to melting point, thermal and electrical conductivity, aqueous solubility, rate of dissolution and permeability across the GI tract membrane. The permeability improvement could result in the enhancement of the oral bioavailability of the BCS class III and IV drugs. This is the first time that the concept of a molecular complex by design was employed to improve the permeability and subsequent bioavailability of a poorly permeable drug such as zoledronic acid. The mechanisms behind the permeability enhancement, however, are not fully understood.

[0010] The upward trend in the use of oral drugs continues especially in light of the goal to decrease the overall cost of healthcare. Orally administered drugs are becoming more preferred in various therapeutic areas including cancers. Clearly, there is an opportunity to create oral dosage forms of IV drugs where oral dosage forms do not yet exist due to their poor aqueous solubility and/or poor permeability providing a clear clinical benefit for patients. Given the fact that zoledronic acid is only approved for IV administration, there is a need to develop an oral dosage form of zoledronic acid. By using pharmaceutically acceptable and/or approved coformers to hydrogen bond with zoledronic acid, novel molecular complexes (e.g. cocrystals, salts, solvates, and mixtures thereof) with improve solubility and/or permeability can be created. These novel molecular complexes could be used in the development of an oral dosage form for zoledronic acid.

SUMMARY OF THE INVENTION

[0011] The present disclosure is directed towards generating new forms of zoledronic acid, which have the therapeutic efficacy of zoledronic acid discussed above, with improved aqueous solubility, rate of dissolution, and/or improved permeability and thus enhanced bioavailability. One aspect of the present disclosure includes novel molecular complexes of zoledronic acid that includes cocrystals, salts, and solvates (e.g. hydrates and mixed solvates as well as solvates of salts), and mixtures containing such materials. In addition, the disclosure further includes methods for the preparation of such complexes.

[0012] The disclosure further includes compositions of molecular complexes of zoledronic acid suitable for incorporation in a pharmaceutical dosage form. Specific molecular complexes pertaining to the disclosure include complexes of zoledronic acid with L-lysine, DL-lysine, and glycine.

[0013] The disclosure also includes results of an *in vivo* study of parent (pure) zoledronic acid and selected zoledronic acid complexes prepared by the methods of the invention in rat and dog models. The drug concentrations in the rat plasma and dog serum samples along with the pharmacokinetic (PK) profiles are also included.

[0014] The foregoing and other features and advantages of the disclosed technology will become more apparent from the following detailed description, which proceeds with reference to the accompanying drawings. Such description is meant to be illustrative, but not limiting, of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015]

FIG. 1 shows PXRD diffractograms of: (A = zoledronic acid, sodium zoledronic salt and water complex), (B = NaCl), (Z1 = Zoledronic acid monohydrate), (Z3 = Zoledronic acid trihydrate).
FIG. 2 is an FTIR spectrum of a complex comprising zoledronic acid, sodium zoledronic salt, and water.
FIG. 3 shows PXRD diffractograms of: (C = ammonium zoledronic salt and water complex), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 4 is an FTIR spectrum of ammonium zoledronic salt and water complex.
FIG. 5 shows PXRD diffractograms of: (D = zoledronic, L-lysine, and water complex), (E = L-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 6 is an FTIR spectrum of zoledronic, L-lysine, and water complex.
FIG. 7 shows PXRD diffractograms of: (F = zoledronic, DL-lysine, and water complex), (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 8 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.
FIG. 9 shows PXRD diffractograms of: (H = zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex), (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), (Z3 = Zoledronic acid trihydrate).
FIG. 10 is an FTIR spectrum of zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex.
FIG. 11 shows PXRD diffractograms of: (I = zoledronic, nicotinamide, and water complex), (J = nicotinamide), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 12 is an FTIR spectrum of zoledronic, nicotinamide, and water complex.
FIG. 13 shows PXRD diffractograms of: (K = zoledronic, adenine, and water complex), (L = adenine), (Z1 = Zoledronic acid monohydrate), (Z3 = Zoledronic acid trihydrate).
FIG. 14 is an FTIR spectrum of zoledronic, adenine, and water complex.
FIG. 15 shows PXRD diffractograms of: (M = zoledronic and glycine complex), (N = glycine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 16 is an FTIR spectrum of zoledronic and glycine complex.
FIG. 17 shows PXRD diffractograms of: (O = zoledronic diammonia water complex), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 18 is an FTIR spectrum of zoledronic diammonia water complex.
FIG. 19 shows PXRD diffractograms of: (P = zoledronic, DL-lysine, and water complex), (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 20 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.
FIG. 21 shows PXRD diffractograms of: (R = zoledronic, DL-lysine, and water complex), (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 22 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.
FIG. 23 shows PXRD diffractograms of: (R = zoledronic, DL-lysine, and water complex), (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 24 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.
FIG. 25 shows PXRD diffractograms of: (Q = zoledronic, L-lysine, and water complex), (E = L-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).
FIG. 26 is an FTIR spectrum of zoledronic, L-lysine, and water complex.
FIG. 27 shows the 24 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered via IV, oral, and intraduodenal (ID) routes.
FIG. 28 shows the 4 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered orally.
FIG. 29 shows the 4 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered ID.
FIG. 30 shows the 24 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered by oral gavage.
FIG. 31 shows the 4 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered orally.
FIG. 32 shows the 4 hr rat plasma PK profile of parent zoledronic acid and selected zoledronic acid complexes delivered orally.
FIG. 33 shows the dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally.

FIG. 34 shows the 4 hr dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally.

FIG. 35 shows the dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally; enteric and non-enteric coated capsules.

FIG. 36 shows the 6 hr dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally; enteric and non-enteric coated capsules.

Fig. 37 shows the dog PK data for the enteric and non-enteric coated hard gelatin capsules.

FIG. 38 shows the 24 hr dog serum PK profile of zoledronic acid complexes delivered IV and orally.

FIG. 39 shows the 4 hr dog serum PK profile of zoledronic acid complexes delivered IV and orally.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] In general, active pharmaceutical ingredients (APIs) in the pharmaceutical compositions can be prepared in a variety of different forms including prodrugs, amorphous forms, solvates, hydrates, cocrystals, salts and polymorphs. The discovery of novel API forms may provide an opportunity to improve the performance characteristics of a pharmaceutical product. Additionally, discovery of drug forms expands the array of resources available for designing pharmaceutical dosage forms with targeted release profiles or other desired characteristics.

[0017] A specific characteristic that can be targeted includes the crystal form of an API. The alteration of the crystal form of a given API would result in the modification of the physical properties of the target molecule. For example, various polymorphs of a given API exhibit different aqueous solubility, while the thermodynamically stable polymorph would exhibit a lower solubility than the meta-stable polymorph. In addition, pharmaceutical polymorphs can also differ in properties such as rate of dissolution, shelf life, bioavailability, morphology, vapor pressure, density, color, and compressibility. Accordingly, it is desirable to enhance the properties of an API by forming molecular complexes such as a cocrystal, a salt, a solvate or hydrate with respect to aqueous solubility, rate of dissolution, bioavailability, Cmax, Tmax, physicochemical stability, down-stream processibility (e.g. flowability compressibility, degree of brittleness, particle size manipulation), decrease in polymorphic form diversity, toxicity, taste, production costs, and manufacturing methods.

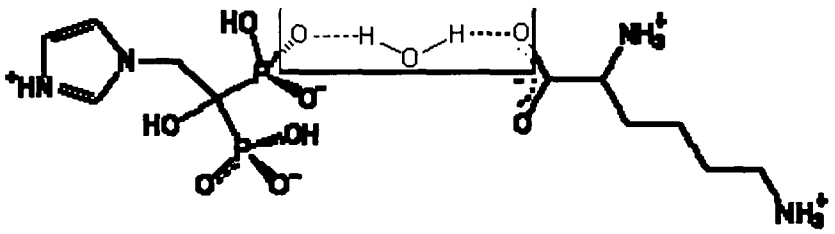
[0018] In the development of orally delivered drugs, it is often advantageous to have novel crystal forms of such drugs that possess improved properties, including increased aqueous solubility and stability. In many cases, the dissolution rate increase of drugs is desired as it would potentially increase their bioavailability. This also applies to the development of novel forms of zoledronic acid which, when administered orally to a subject could achieve a greater or similar bioavailability and PK profile when compared to an IV or other formulations on a dose-for-dose basis.

[0019] Cocrystals, salts, solvates and hydrates of zoledronic acid of the present invention could give rise to improved properties of zoledronic acid. For example, a new form of zoledronic acid is particularly advantageous if it can improve the bioavailability of orally delivered zoledronic acid. A number of novel zoledronic acid forms have been synthesized, characterized, and disclosed herein. Of particular interest are the zoledronic acid and the standard amino acids since they have indicated enhanced permeability compared with other molecular complexes of zoledronic acid. The mechanism of enhanced permeability of these complexes is not yet understood and, while not to be bound by this explanation, it is possible that they moderate the formation of the insoluble Ca^{2+} zoledronate salt resulting in more zoledronic acid to be absorbed paracellularly through the tight junctions. It must be stressed that this is a possible mechanism of enhanced permeability.

[0020] Schematic diagrams for zoledronic acid:amino acid complexes (a zoledronic acid:lysine complex and a zoledronic acid:glycine complex, two embodiments of the invention) are shown below. The diagrams show a molecular structure of the complex and possible interactions between the constituents of the complex which is different from the physical mix of the constituents.

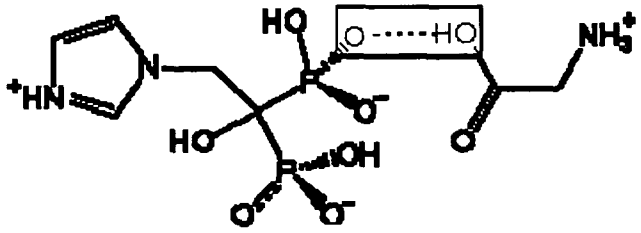
1. Zoledronic acid : lysine complex

[0021]



2. Zoledronic acid : glycine complex

[0022]



These represent one of the arrangements that molecules of the drug and the standard amino acids coformers could interact to form a stable complex that even when stressed thermally at elevated relative humidity (RH) environment have not displayed any signs of deterioration or disintegration to its original constituents. Such stability can be attributed to the hydrogen bonding (dashed line in the box) in these molecular complexes. When packing in a crystal structure these complexes have very different morphologies to that of its constituents or their physical mix as indicated by their powder X-ray diffraction (PXRD) patterns and therefore would possess different, unpredictable physicochemical properties.

[0023] In a first aspect, the present invention relates to a crystalline molecular complex comprising zoledronic acid or a salt thereof and a coformer selected from lysine or glycine. In some embodiments, the molecular complex is selected from a crystalline zoledronic acid, water, and L-lysine complex; a crystalline zoledronic acid, water, and DL-lysine complex; or a crystalline zoledronic acid, water, and glycine complex.

[0024] Described herein is a new crystal form of zoledronic acid in the form or zoledronic acid, sodium zoledronate and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 8.1, 13.3, 21.5, 24.6, and 25.6 ±0.2 degrees two-theta.

[0025] Also described herein is a new crystal form of zoledronic acid in the form of ammonium zoledronic salt and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 11.0, 14.6, 15.4, 19.9, and 29.4 ±0.2 degrees two-theta.

[0026] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, L-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.0, 14.4, 18.1, 26.0, and 29.6 ±0.2 degrees two-theta.

[0027] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, DL-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.1, 14.7, 18.0, 21.2, and 26.0 ±0.2 degrees two-theta.

[0028] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 8.8, 9.7, 17.6, 23.1, and 26.5 ±0.2 degrees two-theta.

[0029] Also described herein is a new crystal form of zoledronic acid in the form of zoledronic acid, nicotinamide, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 13.1, 15.2, 21.0, 23.9, and 26.5 ±0.2 degrees two-theta.

[0030] Also described herein is a new crystal form of zoledronic acid in the form of zoledronic, adenine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 13.6, 15.9, 19.7, 27.9, and 29.5 ±0.2 degrees two-theta.

[0031] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic and glycine complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 10.2, 17.8, 19.9, 22.9, and 28.1 ±0.2 degrees two-theta.

[0032] Also described herein is a new crystal form of zoledronic acid in the form of zoledronic diammonia water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 12.2, 13.0, 14.1, 17.1, and 19.3 ±0.2 degrees two-theta.

[0033] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, DL-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 8.3, 11.8, 12.3, 15.8, and 20.8 ±0.2 degrees two-theta.

[0034] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic acid, L-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.6, 10.7, 14.3, 21.4, 23.5 ±0.2 degrees two-theta.

[0035] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, DL-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.7, 10.8, 14.4, 18.9,

21.4 ±0.2 degrees two-theta.

[0036] The present invention discloses rat plasma or dog serum concentration levels and PK profiles of IV, orally and ID delivered zoledronic acid parent compound versus complexes of zoledronic acid created using the method of this invention.

[0037] Accordingly, in a first aspect, the present invention includes complexes of zoledronic acid with L-lysine, DL-lysine, and glycine which are capable of complexing in the solid-state, for example, through dry or solvent-drop grinding (liquid assisted grinding), heating or solvent evaporation of their solution in single or mixed solvent systems, slurry suspension, supercritical fluids or other techniques known to a person skilled in the art.

[0038] Also described herein is a zoledronic and nicotinamide complex by dissolving both compounds in water:ethylacetate (1:1 v/v) and allowing the solvent mixtures to evaporate to form crystalline material.

[0039] Another aspect of the invention provides zoledronic and glycine solid complex from dissolving both compounds in water, and allowing the solvent to evaporate to form crystalline material.

[0040] Another aspect of the invention relates to complexes of zoledronic acid and L-lysine, DL-lysine, and glycine suitable for a pharmaceutical formulation than can be delivered orally to the human body. The pharmaceutical formulation contains a therapeutically effective amount of at least one of the novel molecular complexes of zoledronic acid according to the invention and at least one pharmaceutically acceptable carrier, (also known in the art as a pharmaceutically acceptable excipient). The novel molecular complexes of zoledronic acid are therapeutically useful for the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia (TIH), cancer induced bone metastasis, Paget's disease or adjuvant or neoadjuvant therapies, discussed above.

[0041] The invention also relates to novel molecular complexes of zoledronic acid of the invention or a pharmaceutical formulation containing them for use as a medicament. A pharmaceutical formulation of the invention may be in any pharmaceutical form which contains a novel molecular complex of zoledronic acid according to the invention. The pharmaceutical formulation may be, for example, a tablet, capsule, liquid suspension, injectable, suppository, topical, or transdermal. The pharmaceutical formulations generally contain about 1% to about 99% by weight of at least one novel molecular complex of zoledronic acid of the invention and 99% to 1% by weight of a suitable pharmaceutical excipient.

[0042] Complexes of zoledronic acid and sodium, ammonium, ammonia, L-lysine, DL-lysine, nicotinamide, adenine, and glycine have been observed by their PXRD patterns and FTIR spectra.

[0043] Also provided herein are *in-vivo* data in rats concerning the oral bioavailability of zoledronic acid delivered orally and intraduodenally.

[0044] Also described herein are PK profiles of the parent compound delivered bv different routes; IV, oral and ID.

[0045] Also described herein are modified oral bioavailability values of novel zoledronic acid complexes prepared by the method of invention, compared with the orally delivered parent compound.

[0046] Another aspect of the invention provides the addition of an excess of at least one coformer to the zoledronic acid complexes, which may be the same as the coformer in the complex, a different coformer, or a mixture thereof.

[0047] Another aspect of the invention provides a method where the excess cocrystal formers consist of standard amino acids.

[0048] Also described herein are modified PK profiles of zoledronic acid complexes with excess cocrystal formers, compared with that of the orally delivered parent compound.

[0049] Also described herein are improved aqueous solubility of novel zoledronic acid complexes compared with the parent compound.

[0050] Also described herein are modified oral bioavailability values of novel zoledronic acid complexes with excess cocrystal formers, compared with the orally delivered parent compound.

[0051] Also described herein are *in vivo* data in dogs concerning the oral bioavailability of zoledronic acid delivered IV or orally.

[0052] Also described herein are modified oral bioavailability values in dogs of novel zoledronic acid complexes prepared by the method of invention delivered in gelatin capsules compared with the orally delivered parent compound.

[0053] Also described herein are modified oral bioavailability values in dogs of novel zoledronic acid complexes prepared by the method of invention delivered in enteric coated gel capsules compared with that of the parent compound.

[0054] Also described herein is a substantial improvement in oral bioavailability values in dogs of novel zoledronic acid complexes with excess cocrystal formers prepared by the method of invention delivered in hard gelatin capsules.

[0055] Also described herein is a slight improvement in oral bioavailability values for zoledronic acid in dogs via zoledronic acid and novel zoledronic acid complexes orally delivered through enteric coated capsules.

[0056] Also described herein are a reduced oral bioavailability values for zoledronic acid in dogs via novel zoledronic acid complexes with excess physical mix of coformer.

[0057] Another aspect of the invention relates to the molecular complexes, compositions and pharmaceutical compositions provided herein for use in enhancing the bioavailabilty or permeability of a bisphosphonic acid in a patient in need thereof.

[0058] The techniques and approaches set forth in the present disclosure can further be used by the person of ordinary skill in the art to prepare variants thereof, said variants are considered to be part of the inventive disclosure.

EXAMPLES

[0059] The following examples illustrate the invention without intending to limit the scope of the invention.

[0060] Zoledronic acid as a starting material used in all experiments in this disclosure was supplied by Farmkemi Limited (Wuhan Pharma Chemical Co.), China with purity of ca. 98% and was purified further via recrystallization from water. All other pure chemicals (Analytical Grade) were supplied by Sigma-Aldrich and used without further purification.

[0061] Enteric coating of gelatin capsules was contracted out to AzoPharma, Hollywood, FL, USA. A 10% w/w coating solution of Eudragit L100-55, and triethyl citrate, 9.09 and 0.91 w/w% respectively, in purified water and acetone was used in the Vector LDCS pan coater to achieve a uniform coating layer on the capsules. The coating uniformity and functionality for duodenal delivery was tested by 2 hr dissolution in simulated gastric fluid stirred at 75rpm and 37°C. All capsules remained closed for the duration of this test.

Solid phase characterization

[0062] Analytical techniques used to observe the crystalline forms include powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FTIR). The particular methodology used in such analytical techniques should be viewed as illustrative, and not limiting in the context of data collection. For example, the particular instrumentation used to collect data may vary; routine operator error or calibration standards may vary; sample preparation method may vary (for example, the use of the KBr disk or Nujol mull technique for FTIR analysis).

[0063] Fourier Transform FTIR Spectroscopy (FTIR): FTIR analysis was performed on a Perkin Elmer Spectrum 100 FTIR spectrometer equipped with a solid-state ATR accessory.

[0064] Powder X-Ray Diffraction (PXRD): All zoledronic acid molecular complex products were observed by a D-8 Bruker X-ray Powder Diffractometer using Cu Kα (λ = 1.540562 Å), 40kV, 40mA. The data were collected over an angular range of 3° to 40° 2θ in continuous scan mode at room temperature using a step size of 0.05° 20 and a scan speed of 6.17 °/min.

Example 1: Preparation of zoledronic acid, sodium zoledronic salt, and water complex.

[0065] 200 mg of zoledronic acid was slurried with 180 mg of sodium chloride in 1mL of 1:1 ethanol:water overnight. The material was filtered and rinsed. The particulate material was gathered and stored in a screw cap vial for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 1 and FIG. 2, respectively.

Example 2: Preparation of ammonium zoledronic salt and water complex.

[0066] 300 mg of zoledronic acid was slurried in 7N ammonia in methanol overnight. The material was filtered and rinsed. The particulate material was dissolved in water and left to evaporate at ambient conditions to obtain colorless plates after 1 week. The material was characterized by PXRD and FTIR corresponding to FIG. 3 and FIG. 4, respectively.

Example 3: Preparation of zoledronic, L-lysine, and water complex.

[0067] 200 mg of zoledronic acid and 54 mg of L-lysine were slurried in 2 mL of tetrahydrofuran and 200 μl of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 5 and FIG. 6, respectively.

Example 4: Preparation of zoledronic, DL-lysine, and water complex.

[0068] 204 mg of zoledronic acid and 59 mg of DL-lysine were slurried in 2 mL of tetrahydrofuran and 200 μl of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 7 and FIG. 8 respectively.

Example 5: Preparation of zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex.

[0069] 103 mg of zoledronic acid and 54 mg of DL-lysine were dissolved in 400 μl of water, capped and stirred overnight. The next day 0.25mL of ethanol was added drop wise. The vial was capped with a screw cap vial and after 1 day crystals appeared and were filtered off. The material was stored for subsequent analysis. The material was characterized by

PXRD and FTIR corresponding to FIG. 9 and FIG. 10 respectively.

Example 6: Preparation of zoledronic, nicotinamide, and water complex by solvent-drop grinding.

[0070] 99 mg of zoledronic acid was ground with 44 mg of nicotinamide and 40 μl of water was added to the solid mixture. The solids gathered after grinding were stored in screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 11 and FIG. 12, respectively.

Example 7: Preparation of zoledronic, nicotinamide, and water complex from solution crystallization.

[0071] 25 mg of zoledronic acid and 138 mg of nicotinamide were dissolved in 2mL of a water:ethylacetate mix (1:1 v/v). The solution was then allowed to stand for several hours to effect the slow evaporation of solvent. The solids gathered were characterized and produced very similar PXRD and FTIR patterns to that of Example 7 product.

Example 8: Preparation of zoledronic, adenine, and water complex by solvent-drop grinding.

[0072] 96 mg of zoledronic acid was ground with 65 mg of adenine and 60 μL of water was added to the solid mixture. The solids gathered after grinding were stored in screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 13 and FIG. 14, respectively.

Example 9: Preparation of zoledronic, adenine, and water complex from solution slurry.

[0073] 99 mg of zoledronic acid and 54 mg of adenine were slurried in 2 mL of a water:ethanol mix (1:1 v/v) overnight. The solids gathered after filtration were dried, characterized and produced very similar PXRD and FTIR patterns to that of Example 8 product.

Example 10: Preparation of zoledronic and glycine complex.

[0074] 178 mg of zoledronic acid and 45 mg of glycine were slurried in 2 mL of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 15 and FIG. 16, respectively.

Example 11: Preparation of zoledronic diammonia water complex.

[0075] 1.5 g of zoledronic acid was slurried in 7N ammonia in methanol overnight. The material was filtered and rinsed. The particulate material was dissolved in water with medium heat and left to evaporate at ambient conditions to obtain colorless blocks after 1 day. The material was characterized by PXRD and FTIR corresponding to FIG. 17 and FIG. 18, respectively.

Example 12: Preparation of zoledronic, DL-lysine, and water complex.

[0076] 200 mg of zoledronic acid and 102 mg of DL-lysine were slurried in 2 mL of tetrahydrofuran and 400 μl of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 19 and FIG. 20 respectively.

Example 13: Preparation of zoledronic, DL-lysine, and water complex.

[0077] 1 g of zoledronic acid and 283 mg of DL-lysine were slurried in 80 mL of tetrahydrofuran and 8 mL of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 21 and FIG. 22 respectively.

Example 14: Preparation of zoledronic, DL-lysine, and water complex by antisolvent method.

[0078] This complex can also be prepared by the antisolvent method by dissolving 1g of zoledronic acid and 283 mg of DL-lysine in 5 mL of hot water and adding 40 mL of ethanol as an antisolvent stirred overnight. Similar PXRD and FTIR profiles were obtained as shown in Figures 23 and 24 respectively.

Example 15: Preparation of zoledronic, L-lysine, and water complex.

[0079] 1 g of zoledronic acid and 255 mg of L-lysine were dissolved in 60 mL of hot water. 100 mL of ethanol was then added as an antisolvent. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. 25 and FIG. 26 respectively.

Example 16: The Animal PK Studies

[0080] These studies were conducted on rats and dogs as they are suitable animal models for zoledronic acid. This can be attributed to the fact that both animals have historically been used in the safety evaluation and PK screening studies and are recommended by appropriate regulatory agencies. In addition, rats and dogs have also been established as appropriate species for assessing the absorption of bisphosphonate drugs including zoledronic acid.

[0081] Pure zoledronic acid and zoledronic acid complexes prepared by the methods in this invention were delivered to the rats and dogs through IV or oral routes. Additional tests included ID administration in rats and administration of enteric coated capsules in dogs. All compounds delivered were well tolerated by the animals with no adverse events or physical abnormalities noticed.

[0082] Test Subiects: 8-week male Sprague-Dawley Rats (217-259 grams) were obtained from Hilltop Lab Animals, Scottdale, PA USA. Surgical catheters (jugular vein and intraduodenum) were implanted to the animals prior to the study. Beagle dogs from Marshall Farms, NY, USA, weighing from (9-12 kg) were used in this study. Surgical catheters (jugular vein) were implanted prior to the study.

[0083] Housing: Rats were individually housed in stainless steel cages to prevent catheter exteriorization. Acclimation (Pre-dose Phase) was for 1 day. Dogs were already in the test facility (Absorption Systems Inc., USA) and did not need acclimation.

[0084] Environment: Environmental controls for the animal room were set to maintain 18 to 26 °C, a relative humidity of 30 to 70%, a minimum of 10 air changes/hour, and a 12-hour light/12-hour dark cycle. The light/dark cycle could be interrupted for study-related activities.

[0085] Diet: For rats, water and certified Rodent Diet #8728C (Harlan Teklad) were provided. For dogs, water and the standard dog chow diet were given twice daily (every 12 hours).

[0086] Fasting: All test animals were fasted overnight before IV, oral, or ID administration of zoledronic acid or zoledronic acid complexes.

[0087] Routes of Rat Dosing: Zoledronic acid and its complex formulations were administered through IV, oral and ID. The doses administered to all study rats were measured as zoledronic acid, not as the complex form contained in the suspension:

i. IV Administration: the dose of zoledronic acid for IV administration was 0.5 mg/kg. The dose of each rat was calculated on a per rat basis (not on an average weight of all the rats in the lot).

ii. Oral gavage administration: solid suspensions were administered. The dose of each rat was calculated on a per rat basis (not on an average weight of all the rats in the lot). For solid suspensions, animals were administered 5 mg/kg of zoledronic acid or 5 mg/kg of zoledronic acid in zoledronic acid complexes contained in a suspension of PEG 400.

iii. Duodenal cannula administration: solid suspensions were administered. The dose of each rat was calculated on a per rat basis (not on an average weight of all the rats in the lot). For solid suspensions, animals were administered 5 mg/kg of zoledronic acid or 5 mg/kg of zoledronic acid in zoledronic acid complexes contained in a suspension of PEG 400.

[0088] Routes of Dog Dosing: Zoledronic acid and its complex formulations were administered IV and orally. The doses administered to all study dogs were measured as zoledronic acid in each complex, not as the complex form contained in the powder in the gelatin capsule or in solution for IV:

i. IV Administration: The dose volume of each dog was adjusted based upon the average weight of the dog.

ii. Oral administration: zoledronic acid and its equivalent of zoledronic acid complex formulations were administered through size 0 gelatin capsules based on the average weight of the dogs.

iii. Oral administration with enteric coated capsules: zoledronic acid and its equivalent of zoledronic acid complex formulations were administered through size 0 enteric coated gelatin capsules based on the average weight of the dogs.

iv. Oral administration of the molecular complexes with additional coformers: physical mixtures of zoledronic acid complexes with additional coformers were administered through size 0 gelatin capsules based on the average weight of the dogs.

[0089] Groups: Two major groups of animals were selected for the study.

Group 1, rats that contained four subgroups (I-IV) where the results of each data point on the PK profile graphs was the average drug concentration in the plasma of 3 rats.
Group 2, dog PK study contained three groups with subgroups (A, B, C, D,E and F) where the results of each data point on the PK profile graphs was the average drug concentration in the serum of 5 dogs.

Details of Group I rat dosing

[0090]

Group I (IV administration). Group members, designated IV doses are listed below

Group # I	Designation	# of rats	Dose*	Dose volume
G1	Zoledronic Acid	3	0.5 mg/kg	1 mL

IV comparator group, was conducted to calculate MAT (mean absorption time) and ka (absorption rate constant) for the oral groups.

Group II (oral gavage): Group designations and oral doses are listed below:

Group # II	Designation	# of Rats	Dose*	Dose volume mL/kg	Compound
G2	Zoledronic Acid in PEG400	3	5 mg/kg	1 mL	Zoledronic acid
G3	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic and glycine complex
G4	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, nicotinamide, and water complex
G5	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic acid, sodium zoledronic salt, and water complex
G6	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, L-lysine, and water complex
G7	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, DL-lysine, and water complex

Group III (ID administration): Group designations and oral doses are listed below:

Group # III	Designation	# of rats	Dose*	Dose volume mL/kg	Compound
G8	Zoledronic Acid in PEG400	3	5 mg/kg	1 mL	Zoledronic acid
G9	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic and glycine complex
G10	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, nicotinamide, and water complex

(continued)

Group # III	Designation	# of rats	Dose*	Dose volume mL/kg	Compound
G11	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic acid, sodium zoledronic salt, and water complex
G12	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, L-lysine, and water complex
G13	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, DL-lysine, and water complex

Group IV (oral gavage): Group designations and oral doses are listed below:

Group # IV	Compound	# of rats	Dose	Dose volume/kg	Excess coformer	Excess coformer amount mg/kg
G14	Zoledronic and glycine complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Glycine	45
G15	Zoledronic and glycine complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Glycine	25
G16	Zoledronic and glycine complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Glycine	5
G17	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	DL-lysine monohydrate	39.32
G18	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	DL-lysine monohydrate	28.08
G19	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	DL-lysine monohydrate	5.62
G20	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	n/a	n/a

[0091] Rat blood sample collection, handling and analysis: Blood (approx. 300 μL per sample) samples were withdrawn from each of 3 animals in Group I (IV administration) at eight (8) time points: 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, and 24 hrs, after initial administration of zoledronic acid or its complexes, into EDTA plasma tubes. Plasma was collected after centrifugation at 13,000 rpm for 5 min at 4°C and immediately frozen and stored at -60 to -80 °C till analysis.

[0092] Samples were thawed on the day of analysis and the amount of zoledronic acid in the samples was quantified by analyzed by LC/MS/MS method.

[0093] Details of Group 2 dog dosing: Prior to dosing, all dogs received a 20 mL dose of citric acid (24 mg/mL in water) to lower the pH of their stomach. After dosing capsules or IV, all dogs received additional 6.25 mL citric acid solution (24 mg/mL in water) as a rinse.

Group A, (IV administration). Group members, designated IV doses are listed below:

Group # A	Designation	# of fasted Dogs	Dose*	Dose volume
Leg 1	Zoledronic Acid	5	0.05 mg/kg	1 mL/kg

IV comparator group, was conducted to calculate MAT (mean absorption time) and ka (absorption rate constant) for the oral groups.

Group B (oral administration): Group designations and oral doses are listed below:

Group # B	Compound	Dosing Route	Dose of compound in the gelatin capsules	# of fasted Dogs (9-12 kg)	Dosing Solution Conc. mg/mL
Leg 2	Zoledronic acid	oral	5 mg/kg equivalent	5	n/a
Leg 3	Zoledronic and glycine complex	oral	5 mg/kg equivalent	5	n/a
Leg 4	Zoledronic, DL-lysine, and water complex	oral	5 mg/kg equivalent	5	n/a
Leg 5	Zoledronic, L-lysine, and water complex	oral	5 mg/kg equivalent	5	n/a
Leg 6	Zoledronic, DL-lysine, and water complex	oral	5 mg/kg equivalent	5	n/a

Group C (oral administration): Group designations and oral doses are listed below:

Group #C	Compound	# of fasted Dogs (9-12 kg)	Dosing Route	Dose of compound in the gelatin capsules	Excess coformer	Excess coformer amount
Leg 7	Zoledronic acid monohydrate	5	oral	56.0 mg; enteric coated capsules	n/a	n/a
Leg 8	Zoledronic and glycine complex	5	oral	67.0 mg; enteric coated capsules	n/a	n/a
Leg 9	Zoledronic, DL-lysine, and water complex	5	oral	87.7 mg	DL-lysine monohydrate	294.8 mg
Leg 10	Zoledronic, DL-lysine, and water complex	5	oral	87.7 mg; enteric coated capsules	DL-lysine monohydrate	294.8 mg
Leg 11	Zoledronic, DL-lysine, and water complex	5	oral	84.2 mg	DL-lysine monohydrate	294.8 mg
Leg 12	Zoledronic, DL-lysine, and water complex	5	oral	87.7 mg; enteric coated capsules	n/a	n/a

Group D, (15 min IV infusion): Group members, designated IV doses are listed below:

Group # D	Designation	# of fasted Dogs (9-12 kg)	Dose*	Dosing solution concentration
Leg 13	Zoledronic Acid	5	0.183 mg/kg IV	0.1 mg/mL

Group E, (oral administration): Group members, designated IV doses are listed below:

Group # E	Compound	# of fasted Dogs (9-12 kg)	Dosing Route	Dose of compound in the gelatin capsules	Excess coformer	Excess coformer amount
Leg 14	Zoledronic, DL-lysine, and water complex	2.1	oral	35.4 mg	DL-lysine monohydrate	123.8 mg
Leg 15	Zoledronic and glycine complex	5	oral	67.0 mg	DL-lysine monohydrate	294.8 mg
Leg 16	Zoledronic, L-lysine, and water complex	5	oral	87.7 mg	DL-lysine monohydrate	294.8 mg
Leg 17	Zoledronic, DL-lysine, and water complex	2.1	oral	35.4 mg	DL-lysine monohydrate	294.8 mg

Group F, (15 min IV infusion): Group members, designated IV doses are listed below:

Group # F	Designation	# of fasted Dogs (9-12 kg)	Dose*	Dosing solution concentration
Leg 18	Zoledronic Acid	5	0.12 mg/kg IV infusion	0.1 mg/mL

[0094] After initial administration of zoledronic acid or its complexes, blood (approx. 2.5 mL per sample) was withdrawn from each of 5 animals in Group A (IV administration) at 15 time points: Pre-dose (0), 2, 5, 10, 15, 30, 45min, 1, 1.5, 2, 4, 6, 8, 24 and 48 hrs and at 13 time points for Group B (oral administration): Pre-dose (0), 5, 10, 15, 30, 45min, 1, 1.5, 2, 4, 6, 8, and 24 hrs. Blood samples were placed without the use of an anticoagulant and allowed to sit at room temperature for approximately 30 minutes. Samples were then centrifuged at a temperature of 4°C, at a speed of 13,000 rpm, for 5 minutes. Serum was collected and split into two aliquots and stored frozen (- 80 °C) till analysis. Samples were thawed on the day of analysis and processed using analytical procedures for zoledronic acid containing an LC/MS/MS analysis method.

Animal PK studies results

[0095] Rat study: The results of the first rat study are summarized in Table 1; the concentrations (ng/mL) of zoledronic acid in the plasma samples are the average values of the analytical results of 3 rats. In addition, the PK profiles of the IV, oral and ID groups are shown in Figure 27. The profiles of oral and ID groups are shown in Figures 28 and 29. It suggests that some zoledronic acid complexes have improved oral bioavailability compared with that of the parent zoledronic acid. The complexes with improved bioavailability were further tested in a second rat PK study in which excess coformers were added to the zoledronic acid complexes and then administered to rats by oral gavage. The results of this second study are summarized in Table 2 and their PK profiles are shown in Figures 30, 31 and 32. These figures show improved bioavailabilities of several zoledronic acid complexes with excess coformers.

[0096] Dog study: The results of the first dog study are summarized in Table 3. The concentrations (ng/mL) of zoledronic acid are the average values of the analytical results of 5 dogs. The PK profiles of the IV and oral groups are shown in Figures 33 and 34 which represent the first four hours of the 48hr PK profile. These results and Figure 34 suggest that most if not all zoledronic acid complexes have achieved improved oral bioavailability compared to that of the parent zoledronic acid delivered orally.

[0097] The results of the second dog study are summarized in Table 4; the concentrations (ng/mL) of zoledronic acid shown are the average values of the analytical results of 5 dogs. The PK profiles of the IV and oral groups are shown in Figures 35 and 36. Figure 36 represents the first 6 hours of the 24 hour PK profile. These results and Figure 35 suggest that most if not all zoledronic acid complexes have achieved improved oral bioavailability compared with that of the parent zoledronic acid delivered orally. Specifically, there was a significant improvement in zoledronic acid bioavailability for the novel zoledronic acid complexes with excess amino acid coformer (Leg 11, Figure 37) compared to that of the

parent drug. The results have also shown that there was improvement in the bioavailability of the enterically coated capsules compared with the non-enterically coated capsules (Figure 37, Legs 7 and 2, Legs 8 and 3, Legs 12 and 4), but surprisingly the bioavailability was significantly altered when excess amino acid coformer was added to form a physical mixture to the enterically coated capsules (Figure 37, Legs 9 and 10). The reason behind it is not fully understood.

[0098] The results have shown that there is a slight increase in the oral bioavailability of zoledronic acid from the enteric coated capsules filled with neat (i.e. with no excess coformer) zoledronic acid amino acid complex. Therefore, it is expected that the excess coformer with the novel zoledronic acid complexes would also lead to increased bioavailability when delivered in enterically coated capsules. Surprisingly, when excess coformer was added to the zoledronic acid, the bioavailability of the enterically coated capsules was lower than that of the non-enterically coated capsules. This suggests that a physical powder mixture of the molecular complex and excess coformer might decrease the bioavailability when delivered to the duodenum.

[0099] The analytical results of the third dog study are shown in Table 5, which contains averaged data from five dogs. The PK profiles of the IV and oral groups are shown in Figures 38 and 39. Figure 39 represents the first 4 hours of the 24 hour PK profile.

Table 1. Rat plasma concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery.

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G1	Zoledronic acid	IV	Water	0.083333	3254.05
				0.25	1950.62
				0.5	1128.75
				1	404.28
				2	112.68
				4	30.46
				8	10.66
				24	2.98
G2	Zoledronic acid	PO	PEG 400	0.25	330.06
				0.5	267.45
				1	138.91
				2	47.72
				4	11.78
				8	2.00
				24	0.00
G3	Zoledronic and glycine complex	PO	PEG 400	0.25	648.01
				0.5	435.38
				1	200.88
				4	12.78
				8	1.46
				24	0.00

(continued)

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G4	Zoledronic, nicotinamide, and water complex	PO	PEG 400	0.25	434.61
				0.5	304.94
				1	122.35
				4	7.68
				8	1.82
				24	0.00
G5	Zoledronic acid, sodium zoledronic salt, and water complex	PO	PEG 400	0.25	278.47
				0.5	280.20
				1	171.59
				4	13.42
				8	1.78
				24	0.00
G6	Zoledronic, L-lysine, and water complex	PO	PEG 400	0.25	258.43
				0.5	249.82
				1	184.95
				4	28.70
				8	3.27
				24	0.00
G7	Zoledronic, DL-lysine, and water complex	PO	PEG 400	0.25	494.31
				0.5	379.27
				1	213.48
				4	14.57
				8	3.42
				24	0.00
G8	Zoledronic acid	ID	PEG 400	0.25	145.67
				0.5	109.92
				1	47.36
				2	12.94
				4	3.85
				8	0.97
				24	0.00
G9	Zoledronic and glycine complex	ID	PEG 400	0.25	86.51
				1	33.93
				4	1.75
				8	1.55
				24	0.00

(continued)

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G10	Zoledronic, nicotinamide, and water complex	ID	PEG 400	0.25	69.71
				1	21.03
				4	0.86
				8	0.00
				24	0.00
G11	Zoledronic acid, sodium zoledronic salt, and water complex	ID	PEG 400	0.25	39.99
				1	18.50
				4	0.71
				8	0.00
				24	0.00
G12	Zoledronic, L-lysine, and water complex	ID	PEG 400	0.25	91.21
				1	26.53
				4	0.74
				8	0.00
				24	0.00
G13	Zoledronic, DL-lysine, and water complex	ID	PEG 400	0.25	98.25
				1	34.61
				4	2.65
				8	1.02
				24	0.80

Table 2. Rat plasma concentrations for zoledronic acid complexes with excess coformers, delivered by oral gavage

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G14	Zoledronic and glycine complex and 45 mg/kg glycine	PO	PEG 400	0.0333333	14.61
				0.0833333	206.26
				0.1666667	340.19
				0.25	375.99
				0.5	321.36
				1	197.01
				4	17.35
				24	0.00

(continued)

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G15	Zoledronic and glycine complex and 25 mg/kg glycine	PO	PEG 400	0.0333333	24.48
				0.0833333	281.08
				0.1666667	502.20
				0.25	516.58
				0.5	430.10
				1	203.48
				2	73.27
				4	14.70
				24	0.00
G16	Zoledronic and glycine complex and 5 mg/kg glycine	PO	PEG 400	0.0333333	60.03
				0.0833333	365.23
				0.1666667	563.83
				0.25	625.05
				0.5	464.34
				1	209.65
				2	74.28
				4	12.17
				24	0.00
G17	Zoledronic, DL-lysine, and water complex and 39.32 mg/kg DL-lysine monohydrate	PO	PEG 400	0.0333333	168.19
				0.0833333	263.28
				0.1666667	440.26
				0.25	456.18
				0.5	385.57
				1	209.26
				2	85.65
				4	14.58
				24	0.71
G18	Zoledronic, DL-lysine, and water complex and 28.08 mg/kg DL-lysine monohydrate	PO	PEG 400	0.0333333	219.95
				0.0833333	427.02
				0.1666667	729.65
				0.25	777.54
				0.5	632.07
				1	300.86
				2	100.59
				4	21.14
				24	0.00

(continued)

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G19	Zoledronic, DL-lysine, and water complex and 5.62 mg/kg DL-lysine monohydrate	PO	PEG 400	0.0333333	53.78
				0.0833333	394.73
				0.1666667	649.52
				0.25	669.20
				0.5	530.00
				1	265.20
				2	73.31
				4	15.41
				24	0.00
G20	Zoledronic, DL-lysine, and water complex	PO	PEG 400	0.0333333	103.13
				0.0833333	352.18
				0.1666667	475.33
				0.25	505.48
				0.5	431.41
				1	224.56
				2	69.95
				4	14.96
				24	0.00

Table 3. Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (IV and oral).

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
1	0.05 mg/kg Zoledronic acid	IV	Saline solution	0	0.00
				0.0333	413.44
				0.0833	311.68
				0.1667	228.97
				0.25	178.63
				0.5	111.11
				0.75	75.91
				1	56.07
				1.5	30.35
				2	17.61
				4	4.29
				8	1.13
				24	0.00
				48	0.00
2	56.0 mg Zoledronic acid monohydrate capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	0.00
				0.25	0.31
				0.5	110.73
				0.75	97.98
				1	103.60
				1.5	80.57
				2	75.16
				4	17.86
				8	2.71
				24	0.56

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
3	67.0 mg Zoledronic and glycine complex capsule	PO	n/a	0	0.00
				0.0833	2.45
				0.1667	12.75
				0.25	37.07
				0.5	149.20
				0.75	206.14
				1	254.20
				1.5	176.11
				2	109.25
				4	20.43
				8	3.96
				24	0.97
4	87.7 mg Zoledronic, DL-lysine, and water complex capsule	PO	n/a	0	0.00
				0.0833	3.11
				0.1667	6.49
				0.25	22.55
				0.5	68.28
				0.75	162.72
				1	206.14
				1.5	149.92
				2	105.81
				4	25.51
				8	4.22
				24	0.56
5	87.7 mg Zoledronic, L-lysine, and water complex capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	3.13
				0.25	10.06
				0.5	188.52
				0.75	345.28
				1	318.97
				1.5	180.77
				2	109.23
				4	23.11
				8	9.73
				24	1.93

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
6	84.2 mg Zoledronic, DL-lysine, and water complex capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	0.20
				0.25	1.92
				0.5	106.47
				0.75	120.13
				1	108.13
				1.5	90.45
				2	54.48
				4	18.14
				8	4.35
				24	1.06

Table 4. Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery IV and oral; enteric and non-enteric coated gelatin capsules.

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
7	56.0 mg Zoledronic acid monohydrate enteric coated capsule	PO	n/a	0	0.00
				0.1667	0.00
				0.25	0.00
				0.5	0.00
				0.75	0.00
				1	9.84
				1.5	86.13
				2	109.37
				4	107.64
				6	14.15
				8	4.57
				24	0.50

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
8	67.0 mg Zoledronic and glycine complex enteric coated capsule	PO	n/a	0	0.00
				0.1667	0.00
				0.25	0.00
				0.5	0.00
				0.75	0.00
				1	4.42
				1.5	208.97
				2	274.53
				4	101.20
				6	16.71
				8	7.14
				24	2.17
9	87.7 mg Zoledronic, DL-lysine, and water complex with 294.8 mg DL-lysine monohydrate capsule	PO	n/a	0	0.00
				0.0833	13.31
				0.1667	39.76
				0.25	120.41
				0.5	364.68
				0.75	487.59
				1	499.60
				1.5	362.16
				2	254.72
				4	52.22
				6	16.61
				8	8.93
				24	2.92
10	87.7 mg Zoledronic, DL-lysine, and water complex with 294.8 mg DL-lysine	PO	n/a	0	0.00
				0.1667	0.00
				0.25	0.00
				0.5	0.00

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
	monohydrate enteric coated capsule			0.75	3.71
				1	51.32
				1.5	403.15
				2	309.08
				4	44.83
				6	13.15
				8	7.09
				24	2.66
11	84.2 mg Zoledronic, DL-lysine, and water complex with 294.8 mg DL-lysine monohydrate capsule	PO	n/a	0	0.22
				0.1667	167.03
				0.25	533.96
				0.5	878.63
				0.75	838.82
				1	633.50
				1.5	326.63
				2	185.44
				4	46.86
				6	20.26
				8	11.49
				24	5.95
12	87.7 mg Zoledronic, DL-lysine, and water complex enteric coated capsule	PO	n/a	0	0.57
				0.1667	0.60
				0.25	0.59
				0.5	0.61
				0.75	0.40
				1	132.15
				1.5	566.18
				2	402.12
				4	65.35
				6	21.02
				8	12.18
				24	4.33

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
13	0.183 mg/kg Zoledronic acid	IV	Saline solution	0	0.64
				0.0833	476.79
				0.1667	755.68
				0.25	1057.75
				0.3333	745.67
				0.4167	629.22
				0.5	522.78
				0.75	342.58
				1	245.36
				1.25	182.59
				1.5	139.77
				2	80.87
				4	23.40
				8	8.78
				24	3.84

Table 5. Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (IV and oral).

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
14	35.4 mg Zoledronic, DL-lysine, and water complex, with 123.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	0.72
				0.25	11.40
				0.5	78.95
				0.75	126.46
				1	137.38
				1.5	64.73
				2	33.38
				4	6.14
				8	0.89
				24	0.00

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
15	67.0 mg Zoledronic and glycine complex, with 294.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	2.58
				0.1667	26.13
				0.25	55.58
				0.5	225.41
				0.75	234.95
				1	221.91
				1.5	204.90
				2	117.22
				4	17.79
				8	3.34
				24	0.77
16	87.7 mg Zoledronic, L-lysine, and water complex, with 294.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	3.26
				0.1667	17.21
				0.25	213.77
				0.5	504.17
				0.75	436.00
				1	325.21
				1.5	171.42
				2	100.81
				4	23.38
				8	4.65
				24	1.48
17	35.4 mg Zoledronic, DL-lysine, and water complex, with 294.8 mg	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	13.47
				0.25	50.04
	DL-lysine monohydrate gelatin capsule			0.5	146.68
				0.75	137.24
				1	116.38
				1.5	66.70
				2	44.94
				4	8.87
				8	1.58
				24	0.21

(continued)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
18	0.12 mg/kg Zoledronic acid	IV	Saline solution	0	0.00
				0.0833	309.13
				0.1667	524.58
				0.25	717.15
				0.3333	501.70
				0.4167	392.35
				0.5	322.84
				0.75	201.78
				1	132.86
				1.25	93.22
				1.5	69.06
				2	38.38
				4	9.14
				8	3.24
				24	1.21

Table 6. Aqueous solubility of zoledronic acid (ZA) and novel zoledronic acid complexes at room temperature.

Compound	***Conc. mg/mL***	***mMol/L (complex)***
ZA monohydrate	1.57	5.41
ZA : Glycine	11.89	34.25
ZA : L-Lysine dihydrate	8.22	18.09
ZA: DL-Lysine dihydrate	6.85	15.08
ZA : DL-Lysine monohydrate	13.9	31.86

Claims

1. A crystalline molecular complex comprising zoledronic acid or a salt thereof and a coformer selected from lysine or glycine.

2. A molecular complex selected from the group consisting of:

a crystalline zoledronic acid, water, and L-lysine complex;
a crystalline zoledronic acid, water, and DL-lysine complex;
a crystalline zoledronic acid, water, and glycine complex;
a crystalline zoledronic acid, L-lysine, and water complex **characterized by** an X-ray powder diffraction pattern having peaks at about 9.0, 14.4, 18.1, 26.0, and 29.6 ±0.2 degrees two-theta;
a crystalline zoledronic acid, L-lysine, and water complex **characterized by** an X-ray powder diffraction pattern having peaks at about 9.6, 10.7, 14.3, 21.4, 23.5 ±0.2 degrees two-theta;
a crystalline zoledronic acid DL-lysine and water complex **characterized by** an X-ray powder diffraction pattern having peaks at about 8.3, 11.8, 12.3, 15.8, and 20.8 ±0.2 degrees two-theta;
a crystalline zoledronic acid, DL-lysine, and water complex **characterized by** an X-ray powder diffraction pattern

having peaks at about 9.1, 14.7, 18.0, 21.2, and 26.0 ±0.2 degrees two-theta;
a crystalline zoledronic acid and glycine complex **characterized by** an X-ray powder diffraction pattern having peaks at about 10.2, 17.8, 19.9, 22.9, and 28.1 ±0.2 degrees two-theta;
a crystalline zoledronic acid, DL-lysine, and water complex **characterized by** an X-ray powder diffraction pattern having peaks at about 9.7, 10.8, 14.4, 18.9, 21.4 ±0.2 degrees two-theta;
a crystalline zoledronic acid, DL-lysine, ethanol, and water complex **characterized by** an X-ray powder diffraction pattern having peaks at about 8.8, 9.7, 17.6, 23.1, and 26.5 ±0.2 degrees two-theta;
when collecting the X-ray powder diffraction patterns over an angular range of 3° to 40° 2θ using Cu Kα radiation with λ = 1.540562 Å.

3. A composition comprising the crystalline molecular complex comprising zoledronic acid or a salt thereof and lysine according to claim 1 or claim 2, and an excess amount of lysine, glycine or mixtures thereof, preferably an excess amount of lysine.

4. A composition comprising the crystalline molecular complex comprising zoledronic acid or a salt thereof and glycine according to claim 1 or claim 2, and an excess amount of glycine, lysine or mixtures thereof, preferably an excess amount of glycine.

5. A pharmaceutical composition comprising the crystalline molecular complex of claim 1 or claim 2, or the composition of claim 3 or claim 4, and a pharmaceutically acceptable excipient.

6. The pharmaceutical composition according to claim 5, wherein the composition is an oral solid dosage form.

7. The pharmaceutical composition according to claim 6, wherein the composition is an oral dosage form selected from a tablet, a capsule, and a liquid suspension of the solid molecular complex.

8. The molecular complex according to claim 1 or claim 2, the composition according to claim 4 or claim 5, or the pharmaceutical composition according to any one of claims 6 to 8 for use as a medicament.

9. The molecular complex according to claim 1 or claim 2, the composition according to claim 3 or claim 4, or the pharmaceutical composition according to any one of claims 5 to 6 for use in the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia, cancer induced bone metastasis, Paget's disease or adjuvant or neoadjuvant cancer therapies.

10. The molecular complex according to claim 1 or claim 2, the composition according to claim 3 or claim 4, or the pharmaceutical composition according to any one of claims 5 to 7 for use in enhancing the bioavailability or permeability of zoledronic acid or a salt thereof in a patient in need thereof.

Patentansprüche

1. Kristalliner molekularer Komplex, umfassend Zoledronsäure oder ein Salz davon und einen Coformer, ausgewählt aus Lysin oder Glycin.

2. Molekularer Komplex, ausgewählt aus der Gruppe bestehend aus:

einem kristallinen Komplex aus Zoledronsäure, Wasser und L-Lysin;
einem kristallinen Komplex aus Zoledronsäure, Wasser und DL-Lysin;
einem kristallinen Komplex aus Zoledronsäure, Wasser und Glycin;
einem kristallinen Komplex aus Zoledronsäure, L-Lysin und Wasser, **gekennzeichnet durch** ein Pulverröntgenbeugungsmuster mit Peaks bei etwa 9,0, 14,4, 18,1, 26,0 und 29,6 ± 0,2 Grad Zwei-Theta;
einem kristallinen Komplex aus Zoledronsäure, L-Lysin und Wasser, **gekennzeichnet durch** ein Pulverröntgenbeugungsmuster mit Peaks bei etwa 9,6, 10,7, 14,3, 21,4, 23,5 ± 0,2 Grad Zwei-Theta;
einem kristallinen Komplex aus Zoledronsäure, DL-Lysin und Wasser, **gekennzeichnet durch** ein Pulverröntgenbeugungsmuster mit Peaks bei etwa 8,3, 11,8, 12,3, 15,8 und 20,8 ± 0,2 Grad Zwei-Theta;
einem kristallinen Komplex aus Zoledronsäure, DL-Lysin und Wasser, **gekennzeichnet durch** ein Pulverröntgenbeugungsmuster mit Peaks bei etwa 9,1, 14,7, 18,0, 21,2 und 26,0 ± 0,2 Grad Zwei-Theta;
einem kristallinen Komplex aus Zoledronsäure und Glycin, **gekennzeichnet durch** ein Pulverröntgenbeugungs-

muster mit Peaks bei etwa 10,2, 17,8, 19,9, 22,9 und 28,1 ± 0,2 Grad Zwei-Theta;
einem kristallinen Komplex aus Zoledronsäure, DL-Lysin und Wasser, **gekennzeichnet durch** ein Pulverröntgenbeugungsmuster mit Peaks bei etwa 9,7, 10,8, 14,4, 18,9, 21,4 ± 0,2 Grad Zwei-Theta;
einem kristallinen Komplex aus Zoledronsäure, DL-Lysin, Ethanol und Wasser, **gekennzeichnet durch** ein Pulverröntgenbeugungsmuster mit Peaks bei etwa 8,8, 9,7, 17,6, 23,1 und 26,5 ± 0,2 Grad Zwei-Theta;
bei Erfassung der Pulverröntgenbeugungsmuster über einen Winkelbereich von 3° bis 40° 2θ mittels Cu-Kα-Strahlung mit λ = 1,540562 Å.

3. Zusammensetzung, umfassend den kristallinen molekularen Komplex, umfassend Zoledronsäure oder ein Salz davon und Lysin, nach Anspruch 1 oder Anspruch 2 und eine überschüssige Menge von Lysin, Glycin oder Mischungen davon, vorzugsweise eine überschüssige Menge von Lysin.

4. Zusammensetzung, umfassend den kristallinen molekularen Komplex, umfassend Zoledronsäure oder ein Salz davon und Glycin, nach Anspruch 1 oder Anspruch 2 und eine überschüssige Menge von Glycin, Lysin oder Mischungen davon, vorzugsweise eine überschüssige Menge von Glycin.

5. Pharmazeutische Zusammensetzung, umfassend den kristallinen molekularen Komplex nach Anspruch 1 oder Anspruch 2 oder die Zusammensetzung nach Anspruch 3 oder Anspruch 4 und einen pharmazeutisch akzeptablen Trägerstoff.

6. Pharmazeutische Zusammensetzung nach Anspruch 5, wobei die Zusammensetzung eine orale feste Dosierungsform ist.

7. Pharmazeutische Zusammensetzung nach Anspruch 6, wobei die Zusammensetzung eine orale Dosierungsform ist, ausgewählt aus einer Tablette, einer Kapsel und einer flüssigen Suspension des festen molekularen Komplexes.

8. Molekularer Komplex nach Anspruch 1 oder Anspruch 2, Zusammensetzung nach Anspruch 4 oder Anspruch 5 oder pharmazeutische Zusammensetzung nach einem der Ansprüche 6 bis 8 zur Verwendung als Medikament.

9. Molekularer Komplex nach Anspruch 1 oder Anspruch 2, Zusammensetzung nach Anspruch 3 oder Anspruch 4 oder pharmazeutische Zusammensetzung nach einem der Ansprüche 5 bis 6 zur Verwendung bei der Behandlung und/oder Vorbeugung von Krankheitszuständen im Zusammenhang mit Osteoporose, Hyperkalzämie, durch Krebs hervorgerufene Knochenmetastasen, Paget-Krankheit oder adjuvanten oder neoadjuvanten Krebstherapien.

10. Molekularer Komplex nach Anspruch 1 oder Anspruch 2, Zusammensetzung nach Anspruch 3 oder Anspruch 4 oder pharmazeutische Zusammensetzung nach einem der Ansprüche 5 bis 7 zur Verwendung bei der Steigerung der Bioverfügbarkeit oder Permeabilität von Zoledronsäure oder eines Salzes davon bei einem Patienten, der dessen bedarf.

Revendications

1. Complexe moléculaire cristallin comprenant de l'acide zolédronique ou un sel de celui-ci et un co-formeur choisi parmi la lysine ou la glycine.

2. Complexe moléculaire choisi dans le groupe constitué d'un :

complexe cristallin d'acide zolédronique, d'eau et de L-lysine ;
complexe cristallin d'acide zolédronique, d'eau et de DL-lysine ;
complexe cristallin d'acide zolédronique, d'eau et de glycine ;
complexe cristallin d'acide zolédronique, de L-lysine et d'eau, **caractérisé par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 9,0, 14,4, 18,1, 26,0 et 29,6 ±0,2 degrés deux-thêta ;
complexe cristallin d'acide zolédronique, de L-lysine et d'eau, **caractérisé par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 9,6, 10,7, 14,3, 21,4 et 23,5 ±0,2 degrés deux-thêta ;
complexe cristallin d'acide zolédronique, de DL-lysine et d'eau, **caractérisé par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 8,3, 11,8, 12,3, 15,8 et 20,8 ± 0,2 degrés deux-thêta ;
complexe cristallin d'acide zolédronique, de DL-lysine et d'eau, **caractérisé par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 9,1, 14,7, 18,0, 21,2 et 26,0 ± 0,2 degrés deux-thêta ;

complexe cristallin d'acide zolédronique et de glycine **caractérisé, par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 10,2, 17,8, 19,9, 22,9 et 28,1 ± 0,2 degrés deux-thêta ;
complexe cristallin d'acide zolédronique, de DL-lysine et d'eau, **caractérisé par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 9,7, 10,8, 14,4, 18,9 et 21,4 ± 0,2 degrés deux-thêta ;
complexe cristallin d'acide zolédronique, de DL-lysine, d'éthanol et d'eau, **caractérisé par** un profil de diffraction de poudre aux rayons X présentant des pics à environ 8,8, 9,7, 17,6, 23,1 et 26,5 ± 0,2 degrés deux-thêta ;
lorsqu'on collecte les motifs de diffraction de poudre aux rayons X sur une plage angulaire de 3 ° à 40 ° 2θ en utilisant un rayonnement Cu Kα avec λ = 1,540562 Å.

3. Composition comprenant le complexe moléculaire cristallin comprenant de l'acide zolédronique ou un sel de celui-ci et de la lysine selon la revendication 1 ou la revendication 2, et une quantité en excès de lysine, de glycine ou de leurs mélanges, de préférence une quantité en excès de lysine.

4. Composition comprenant le complexe moléculaire cristallin comprenant de l'acide zolédronique ou un sel de celui-ci et de la glycine selon la revendication 1 ou la revendication 2, et une quantité en excès de glycine, de lysine ou de leurs mélanges, de préférence une quantité en excès de glycine.

5. Composition pharmaceutique comprenant le complexe moléculaire cristallin selon la revendication 1 ou la revendication 2, ou composition selon la revendication 3 ou la revendication 4, et un excipient pharmaceutiquement acceptable.

6. Composition pharmaceutique selon la revendication 5, où la composition est une forme pharmaceutique solide orale.

7. Composition pharmaceutique selon la revendication 6, où la composition est une forme pharmaceutique orale choisie parmi un comprimé, une gélule et une suspension liquide du complexe moléculaire solide.

8. Complexe moléculaire selon la revendication 1 ou la revendication 2, composition selon la revendication 4 ou la revendication 5, ou composition pharmaceutique selon l'une quelconque des revendications 6 à 8, utilisable en tant que médicament.

9. Complexe moléculaire selon la revendication 1 ou la revendication 2, composition selon la revendication 3 ou la revendication 4, ou composition pharmaceutique selon l'une quelconque des revendications 5 à 6, utilisable pour le traitement et/ou la prévention d'états maladifs associés à une ostéoporose, une hypercalcémie, des métastases osseuses induites par un cancer, la maladie de Paget ou des thérapies du cancer par adjuvant ou néoadjuvant.

10. Complexe moléculaire selon la revendication 1 ou la revendication 2, composition selon la revendication 3 ou la revendication 4, ou composition pharmaceutique selon l'une quelconque des revendications 5 à 7, utilisable pour renforcer la biodisponibilité ou la perméabilité de l'acide zolédronique ou d'un sel de celui-ci chez un patient qui en a besoin.

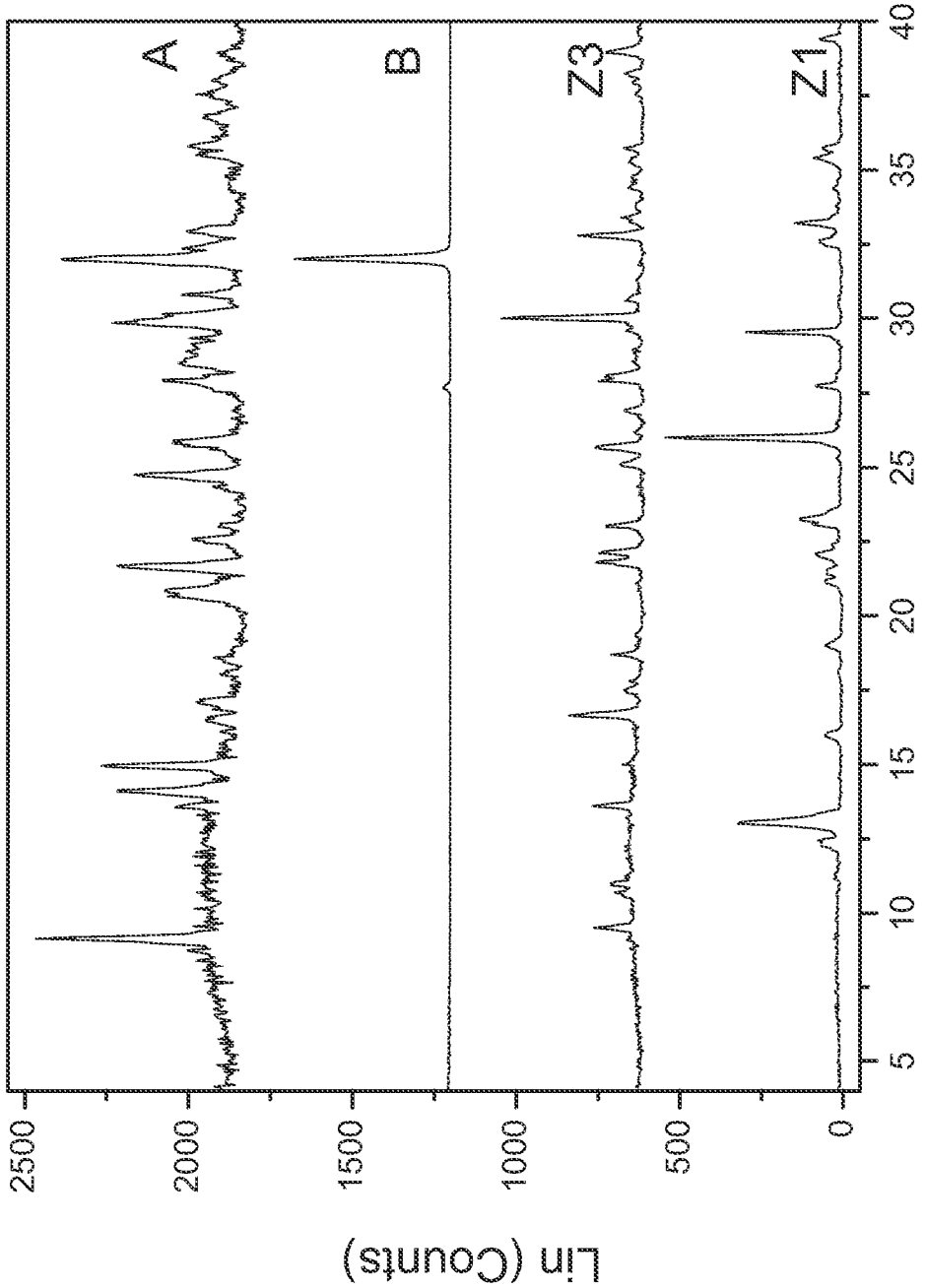

A
B
Z3
Z1
Lin (Counts)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
2-Theta - Scale

FIG. 1

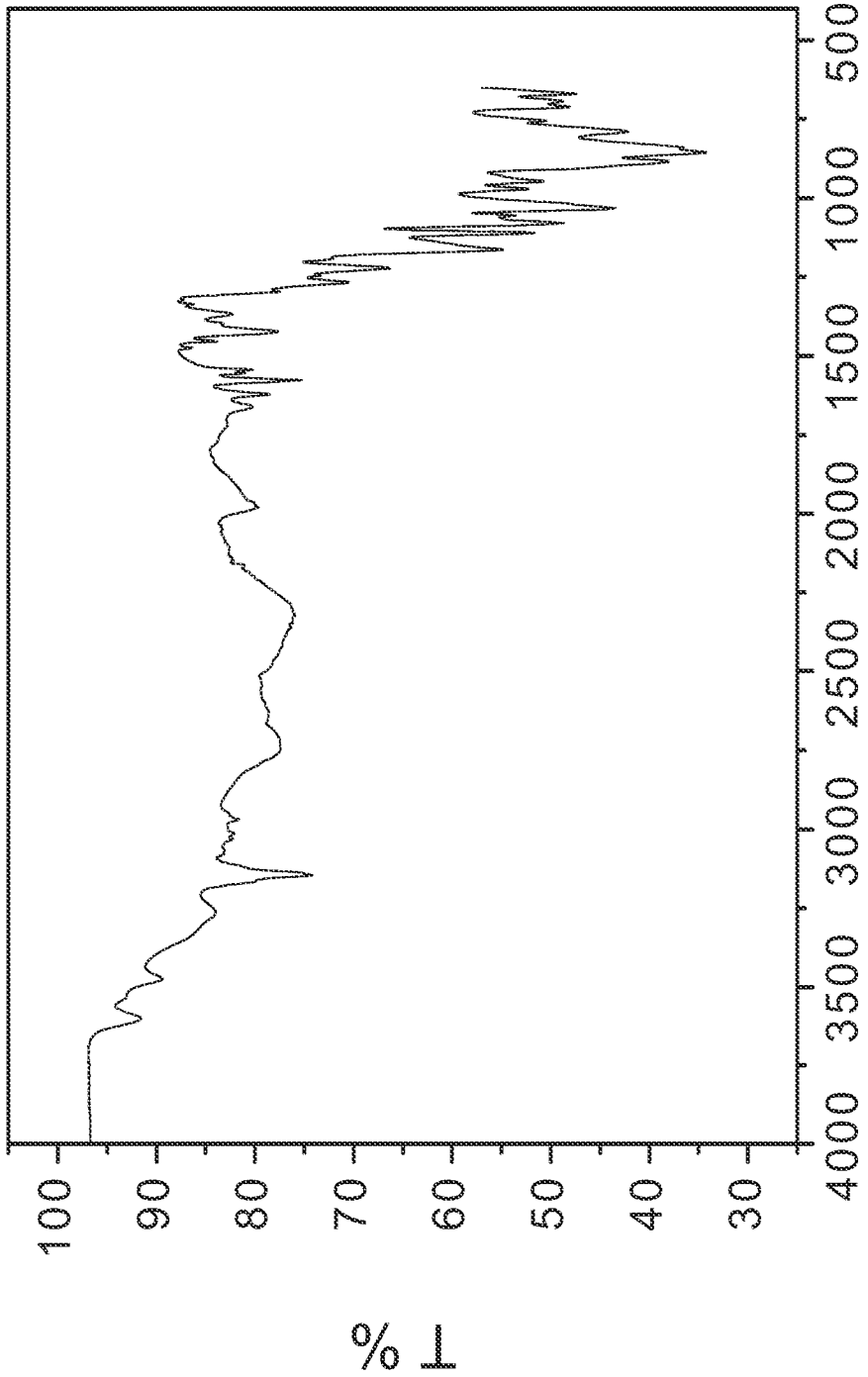

100
90
80
70
60
50
40
30
% T
4000
3500
3000
2500
2000
1500
1000
500
cm -1

FIG. 2

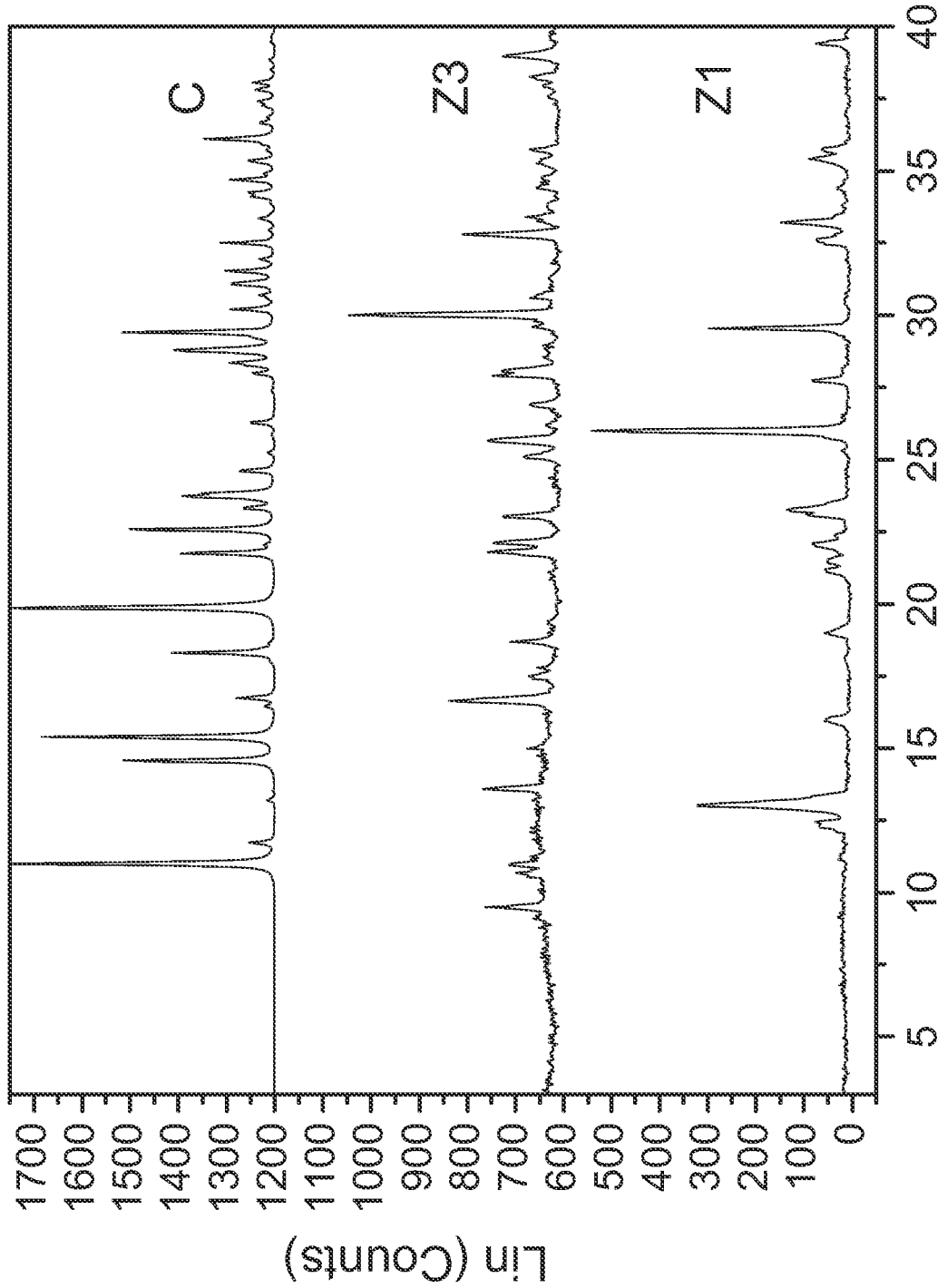

C
Z3
Z1
Lin (Counts)
2-Theta - Scale
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
5
10
15
20
25
30
35
40

FIG. 3

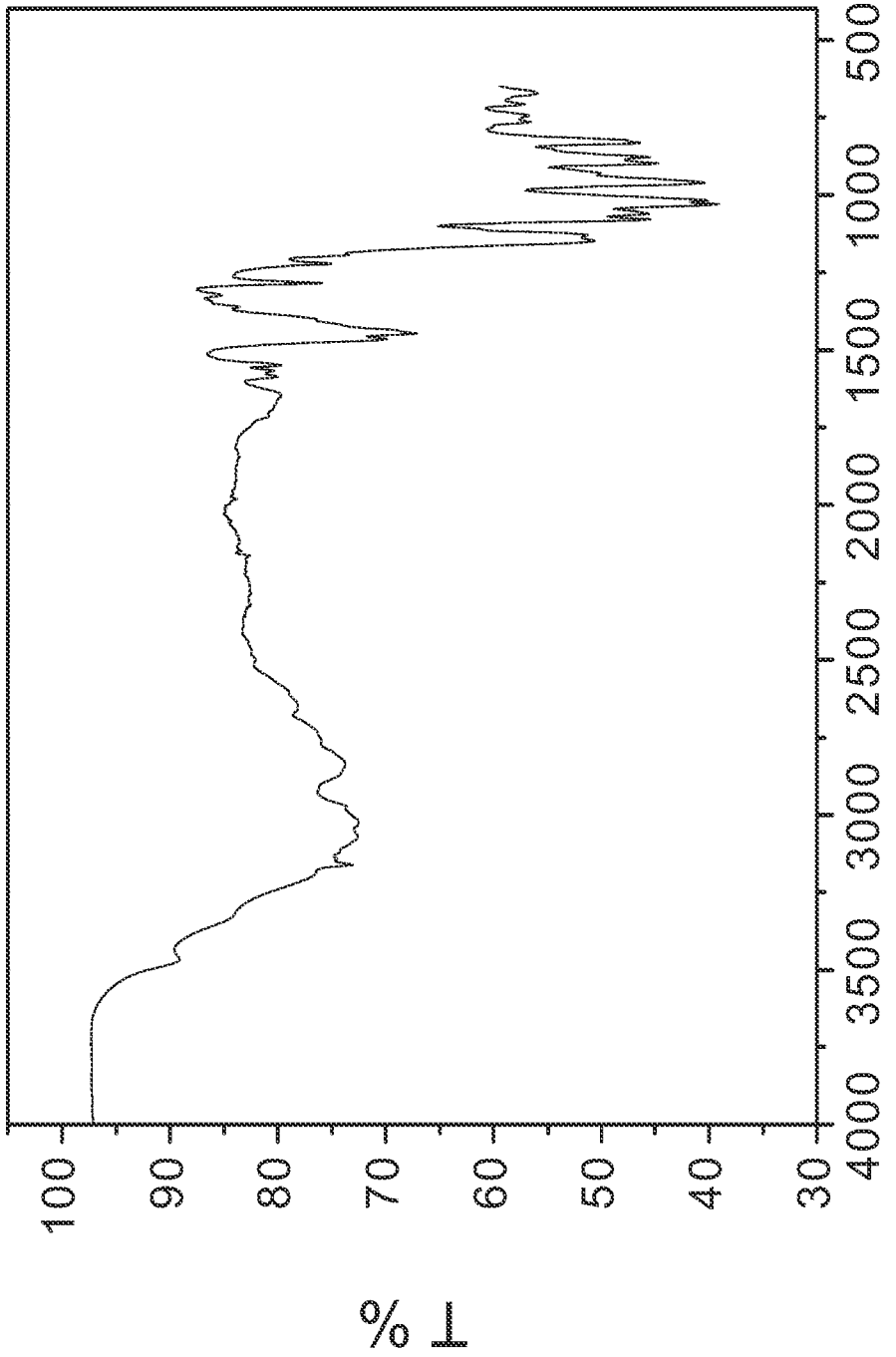

100
90
80
70
60
50
40
30
% T
4000
3500
3000
2500
2000
1500
1000
500
cm -1

FIG. 4

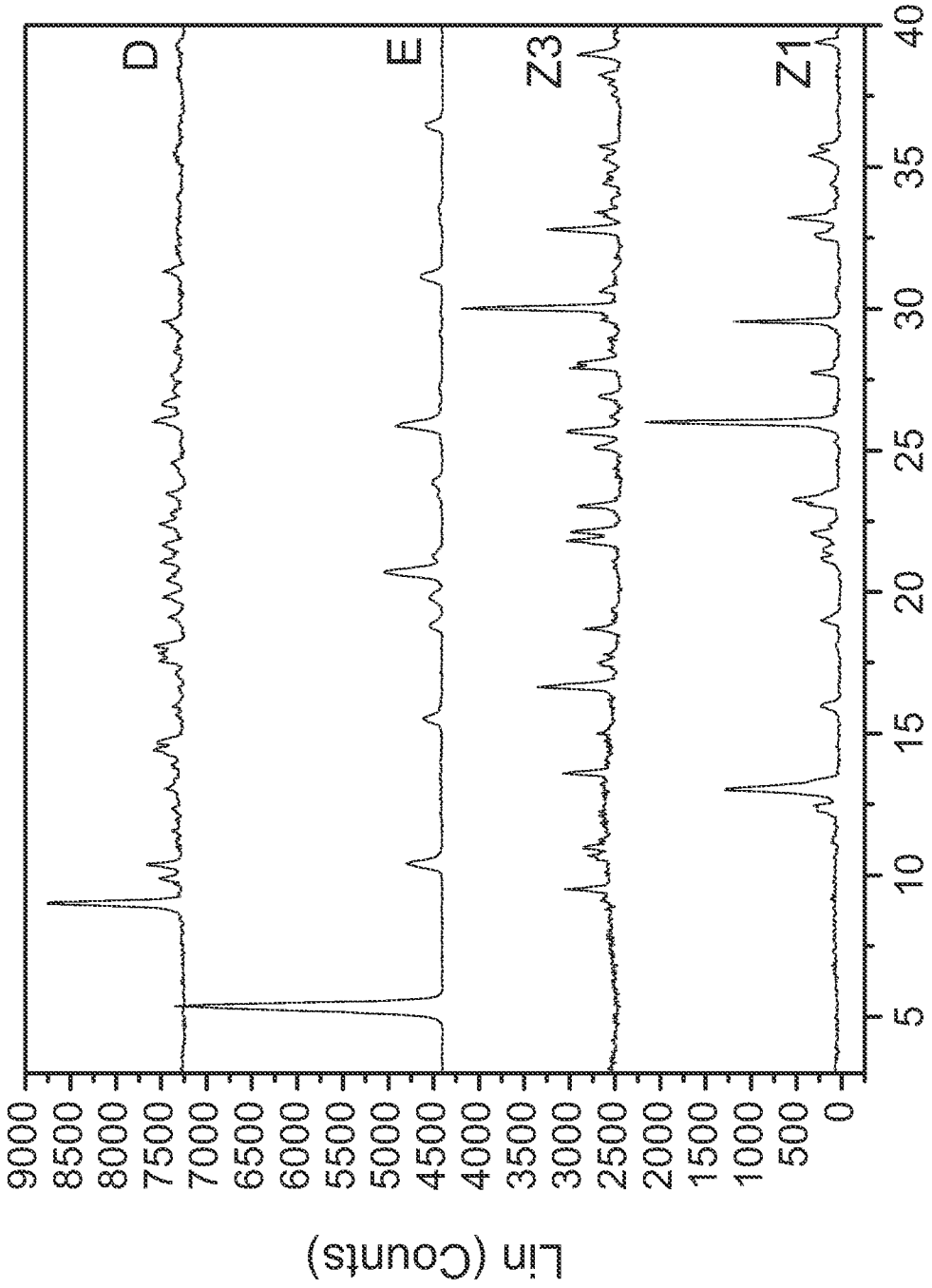

D
E
Z3
Z1
Lin (Counts)
2-Theta-Scale
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40

FIG. 5

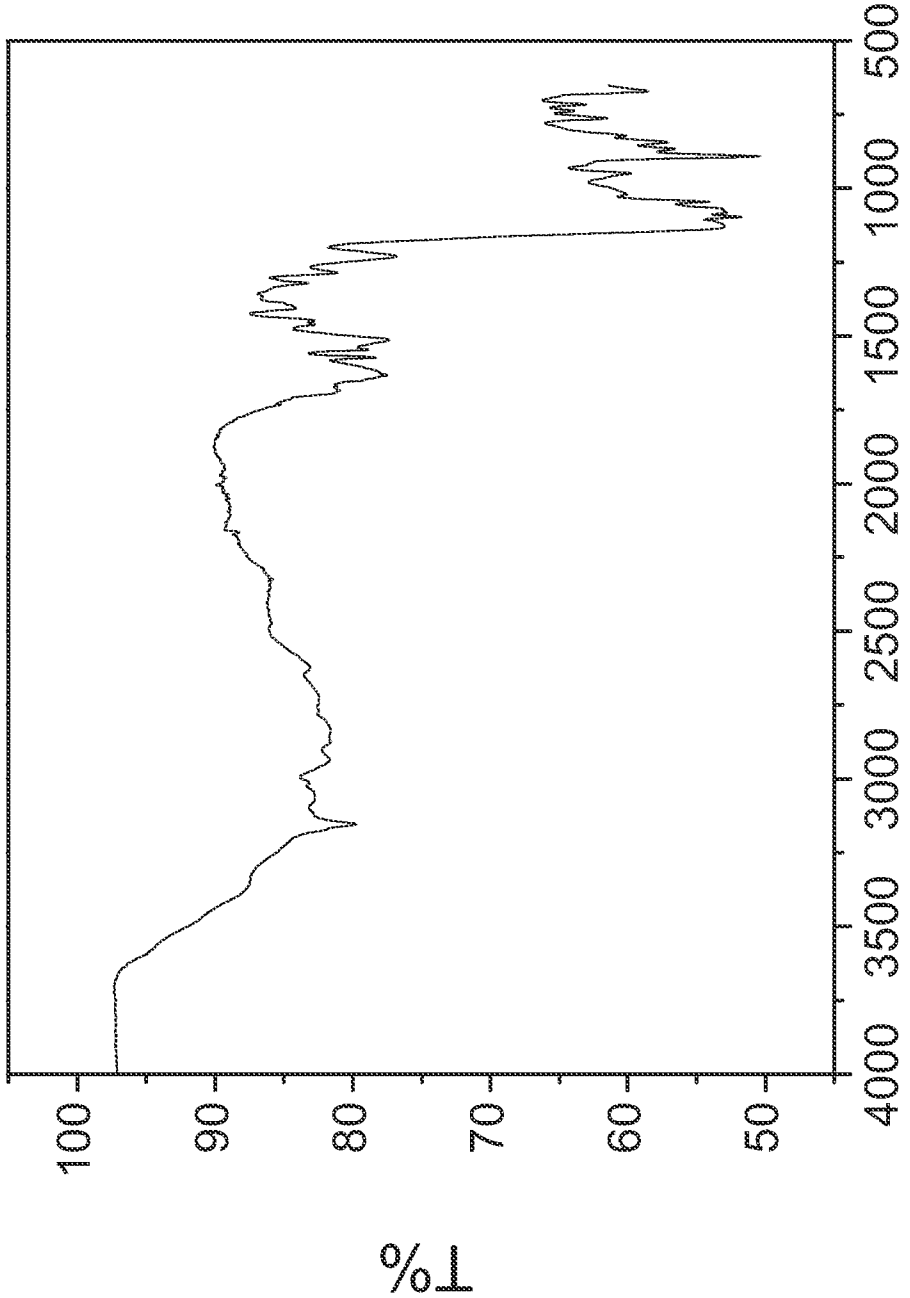


FIG. 6

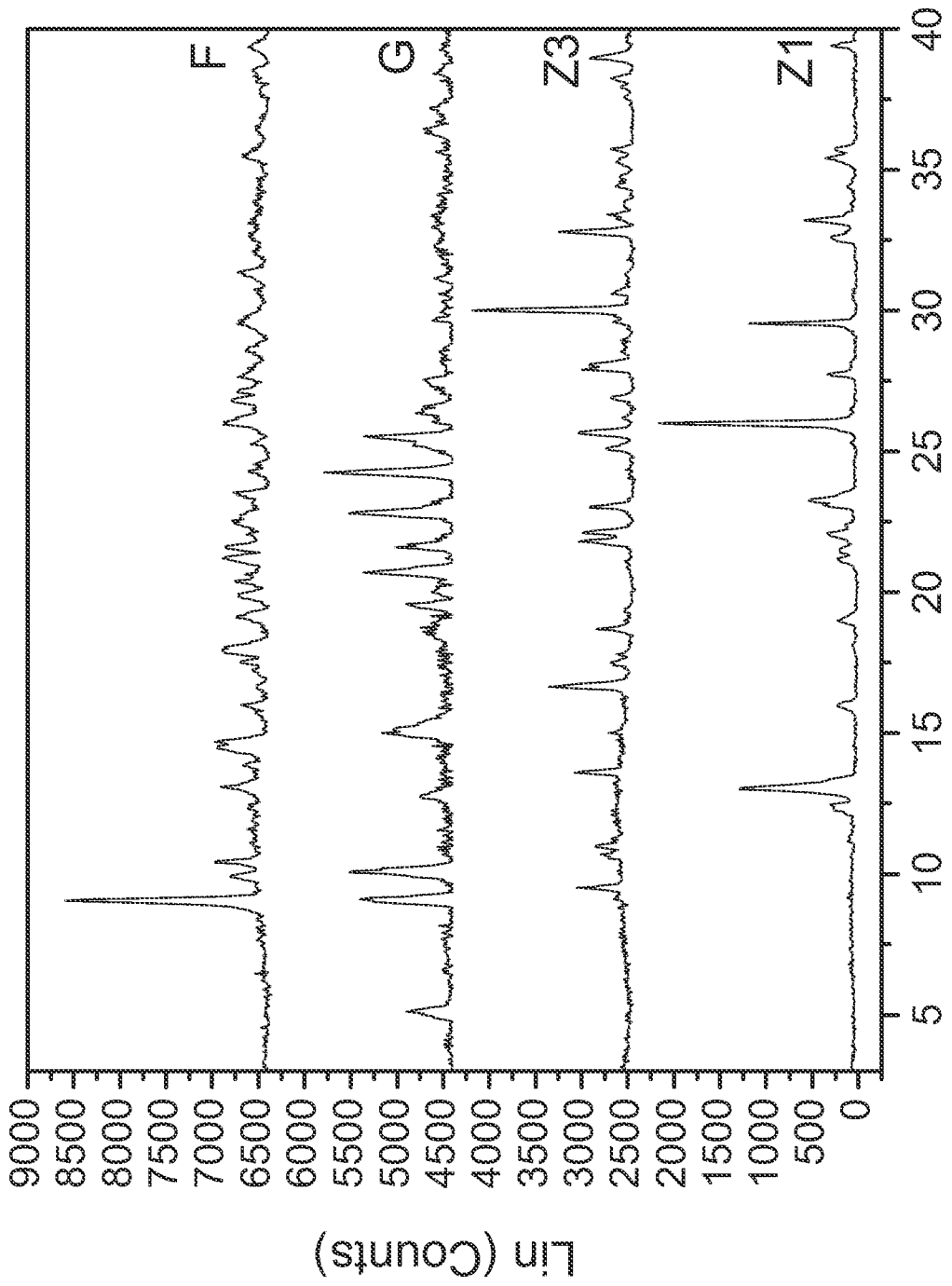

F
G
Z3
Z1
Lin (Counts)
2-Theta-Scale
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40

FIG. 7

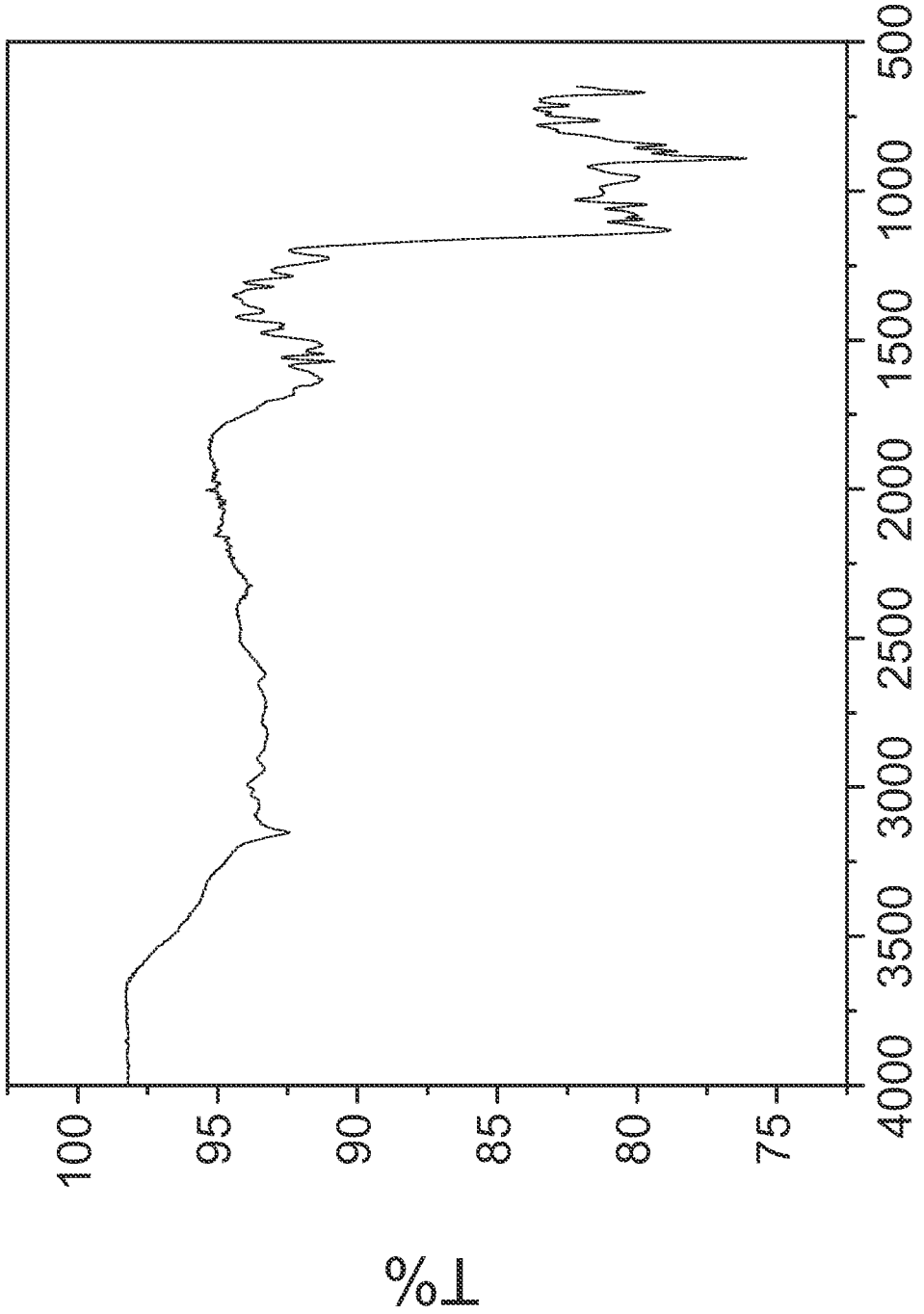


FIG. 8

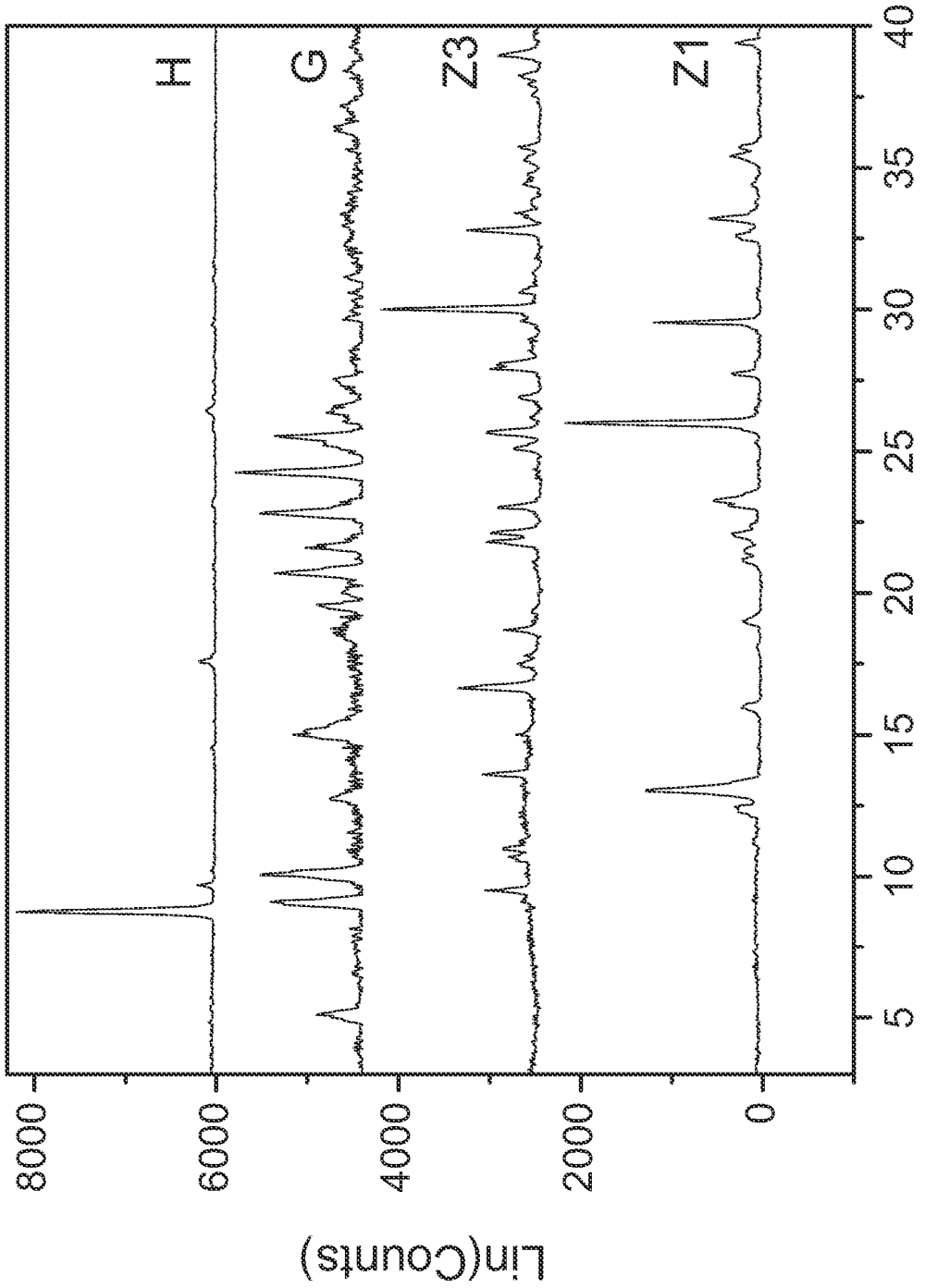

H
G
Z3
Z1
8000
6000
4000
2000
0
Lin(Counts)
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 9

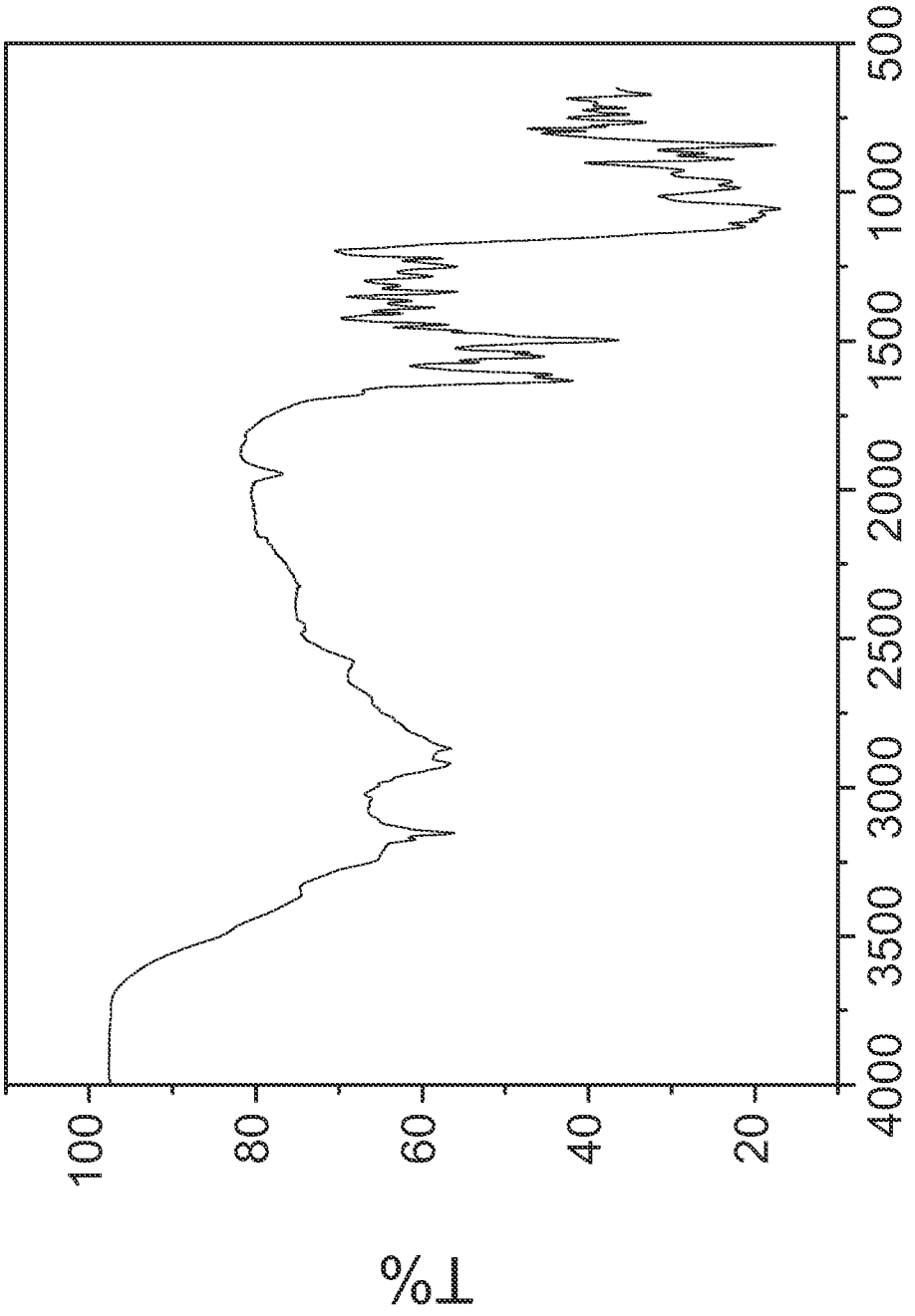


FIG. 10

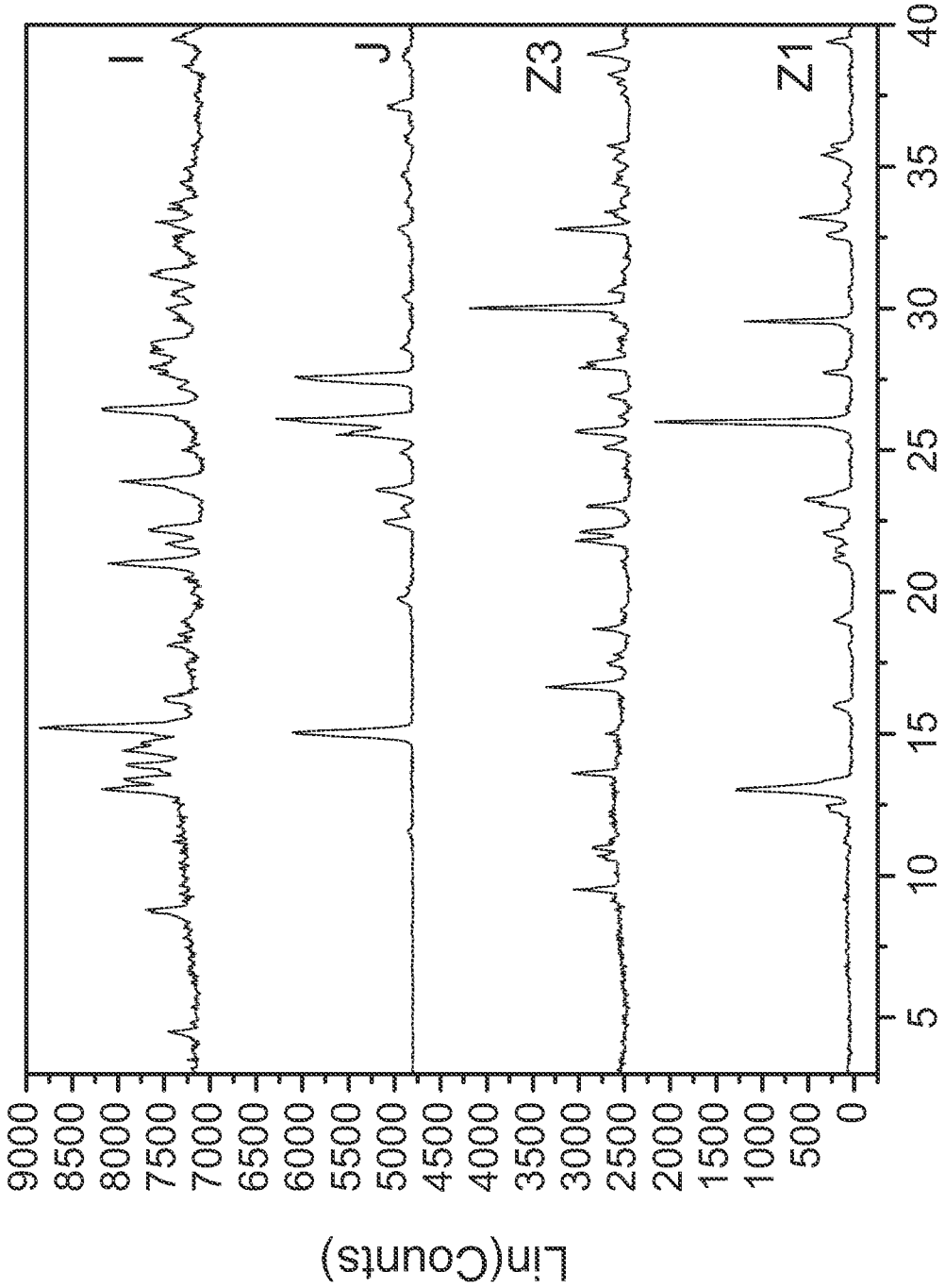

I
J
Z3
Z1
Lin(Counts)
2-Theta-Scale
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40

FIG. 11

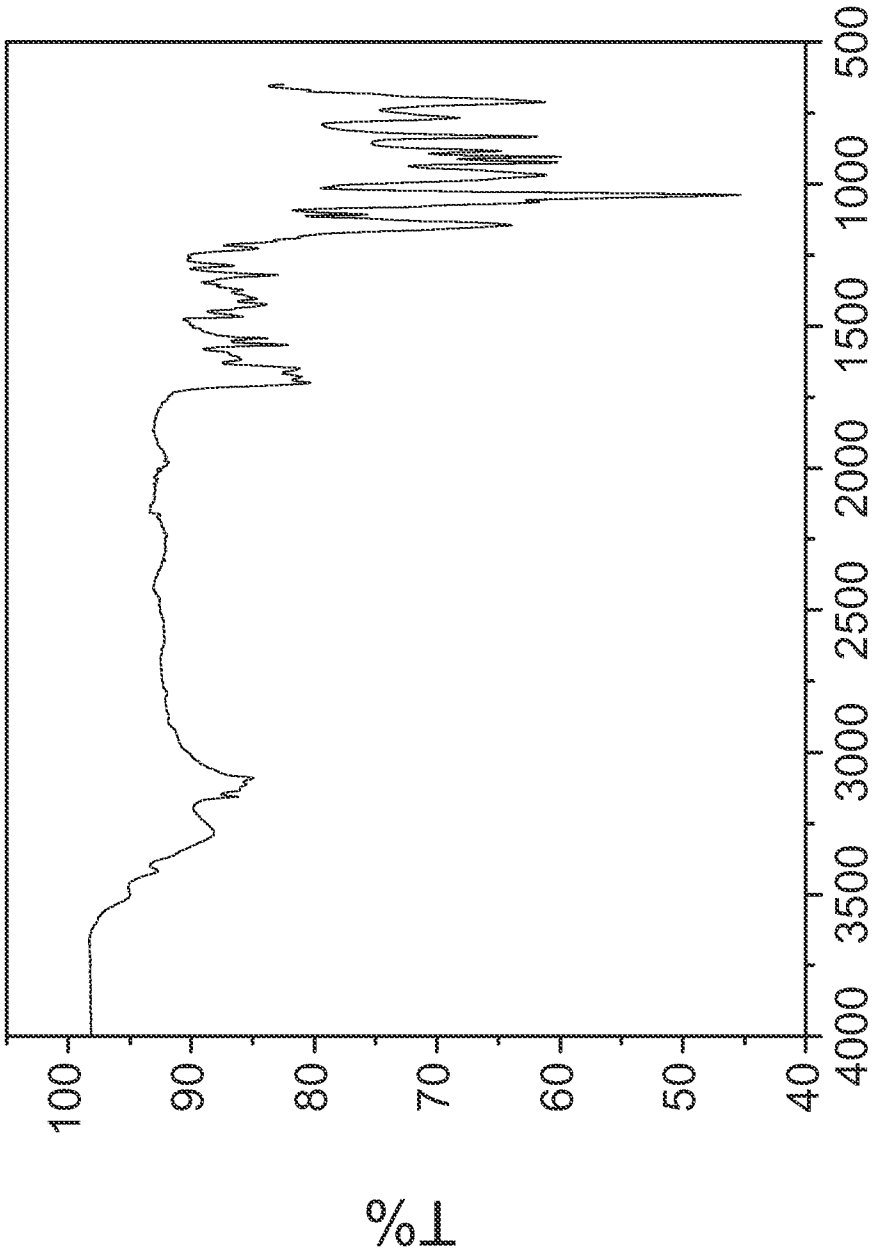

T%
100
90
80
70
60
50
40
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 12

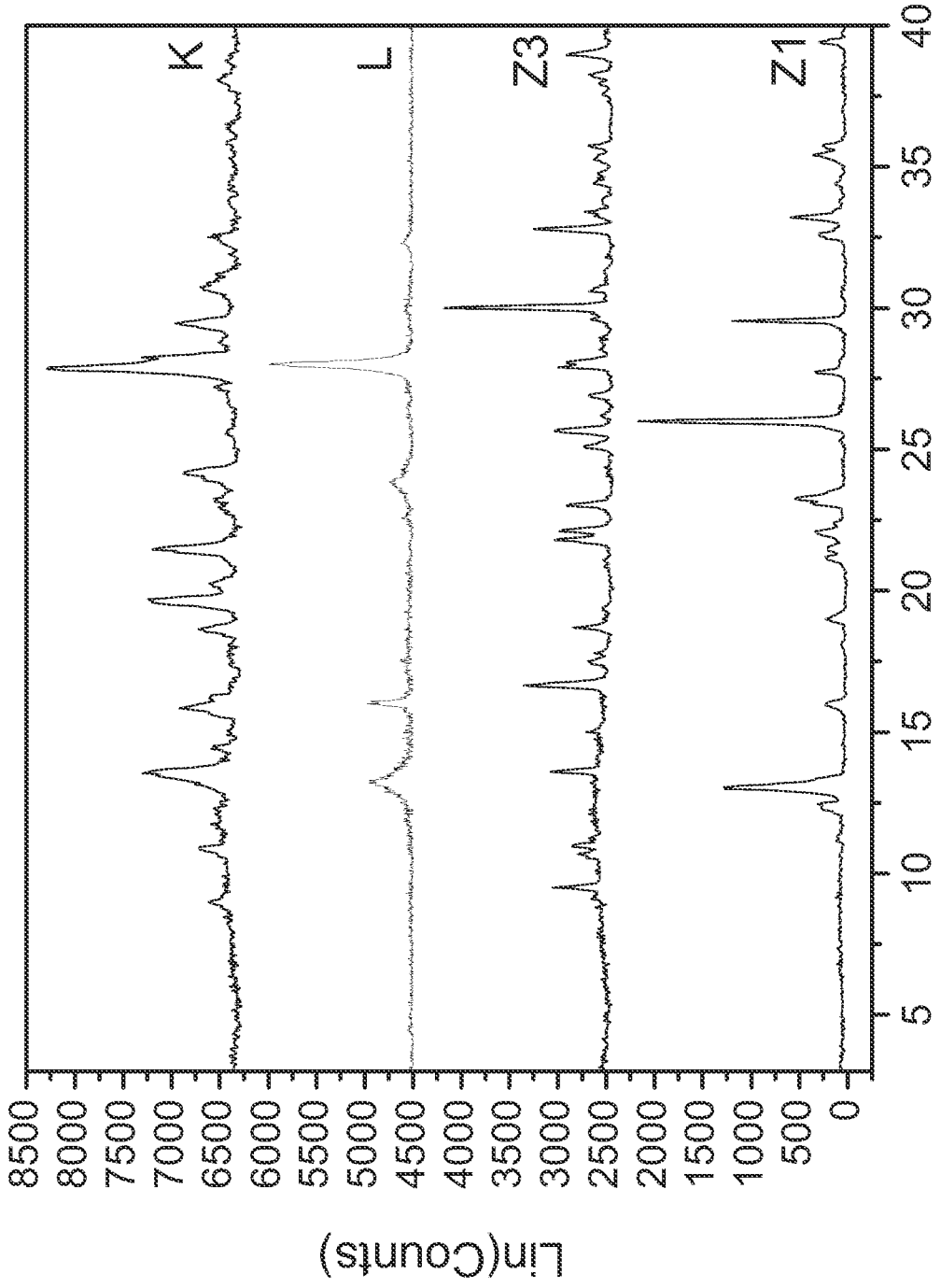

K
L
Z3
Z1
Lin(Counts)
2-Theta-Scale
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40

FIG. 13

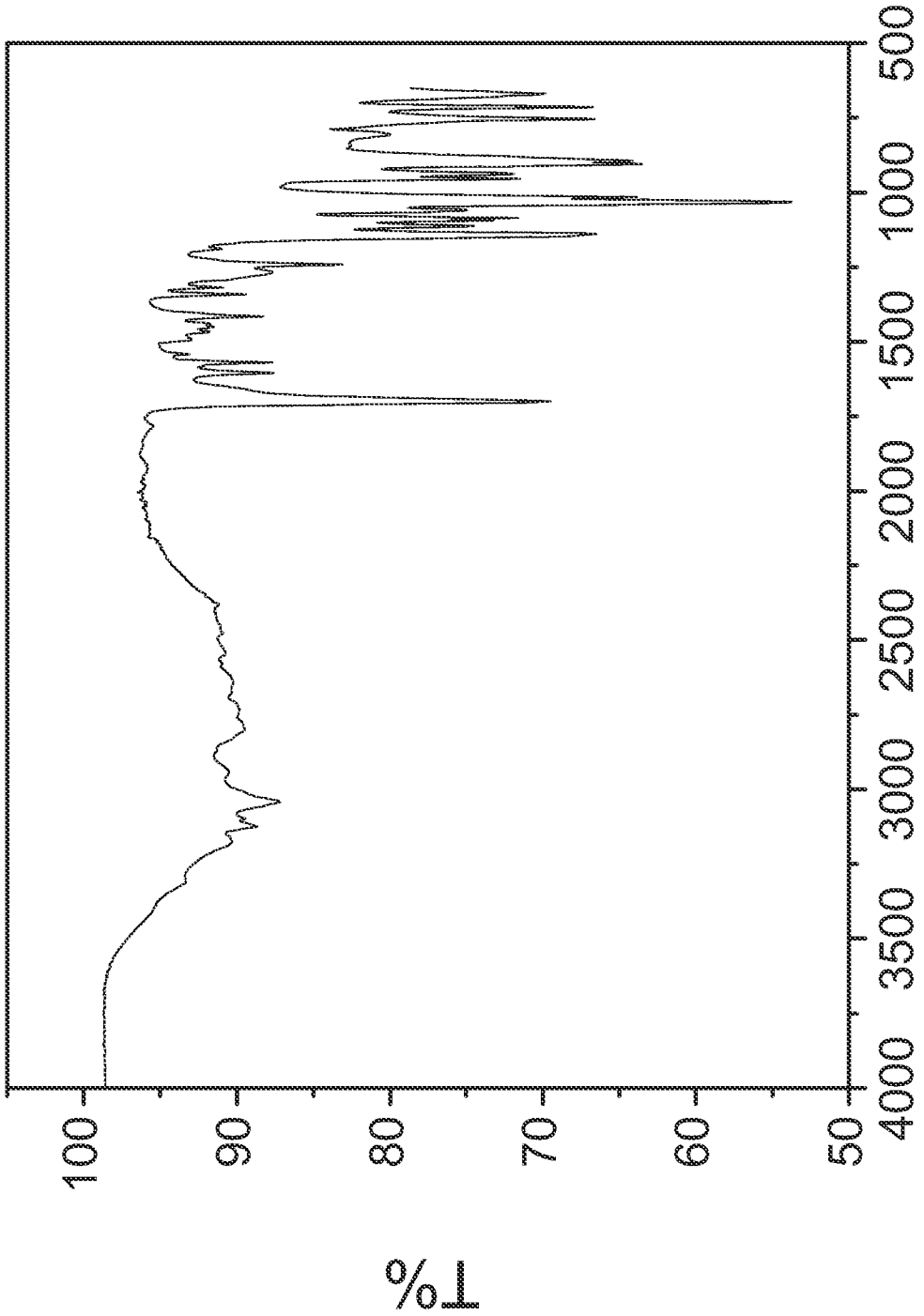


FIG. 14

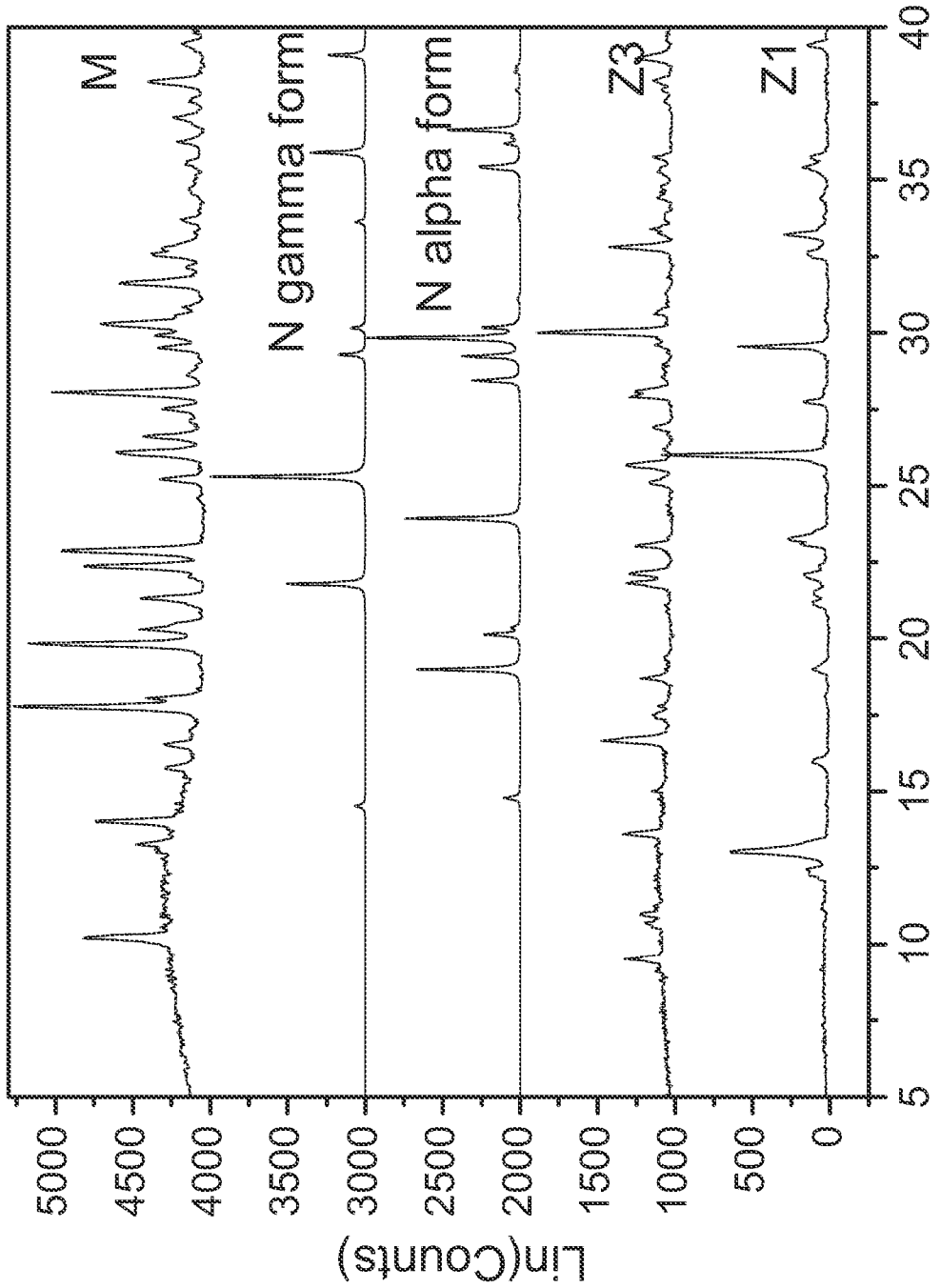

M
N gamma form
N alpha form
Z3
Z1
Lin(Counts)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
2-theta

FIG. 15

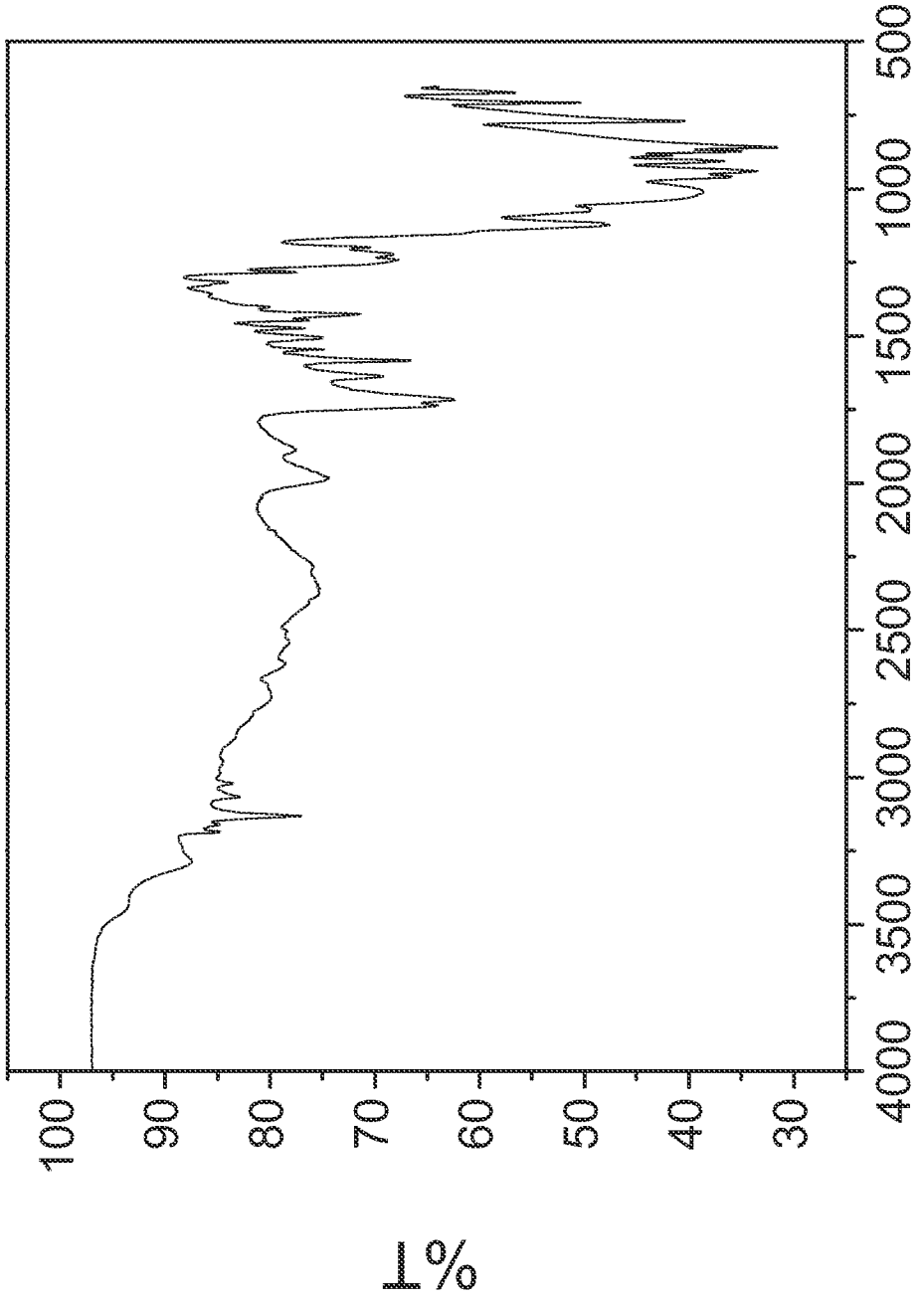

100
90
80
70
60
50
40
30
%T
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 16

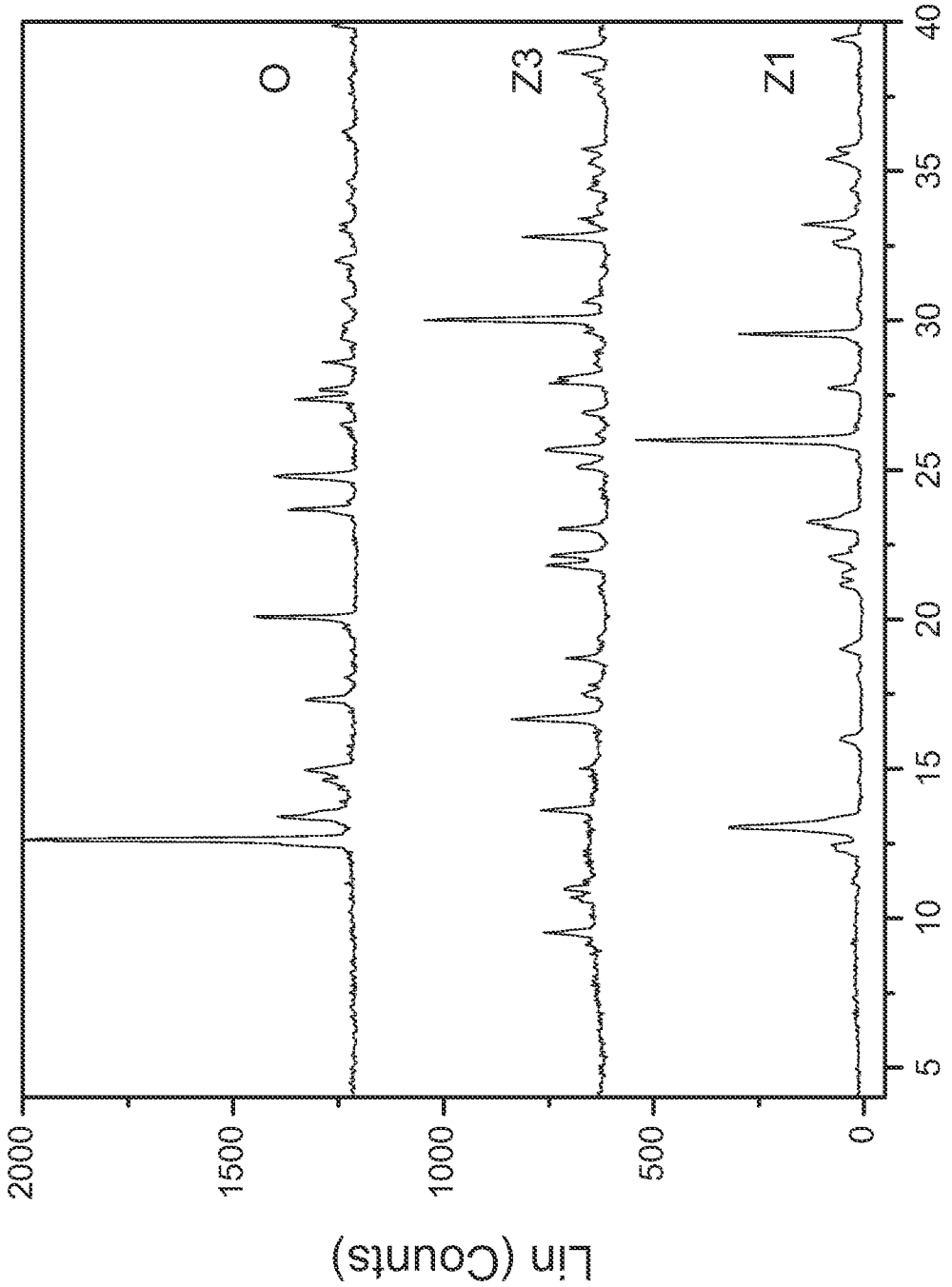

Lin (Counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
2-Theta - Scale
O
Z3
Z1

FIG. 17

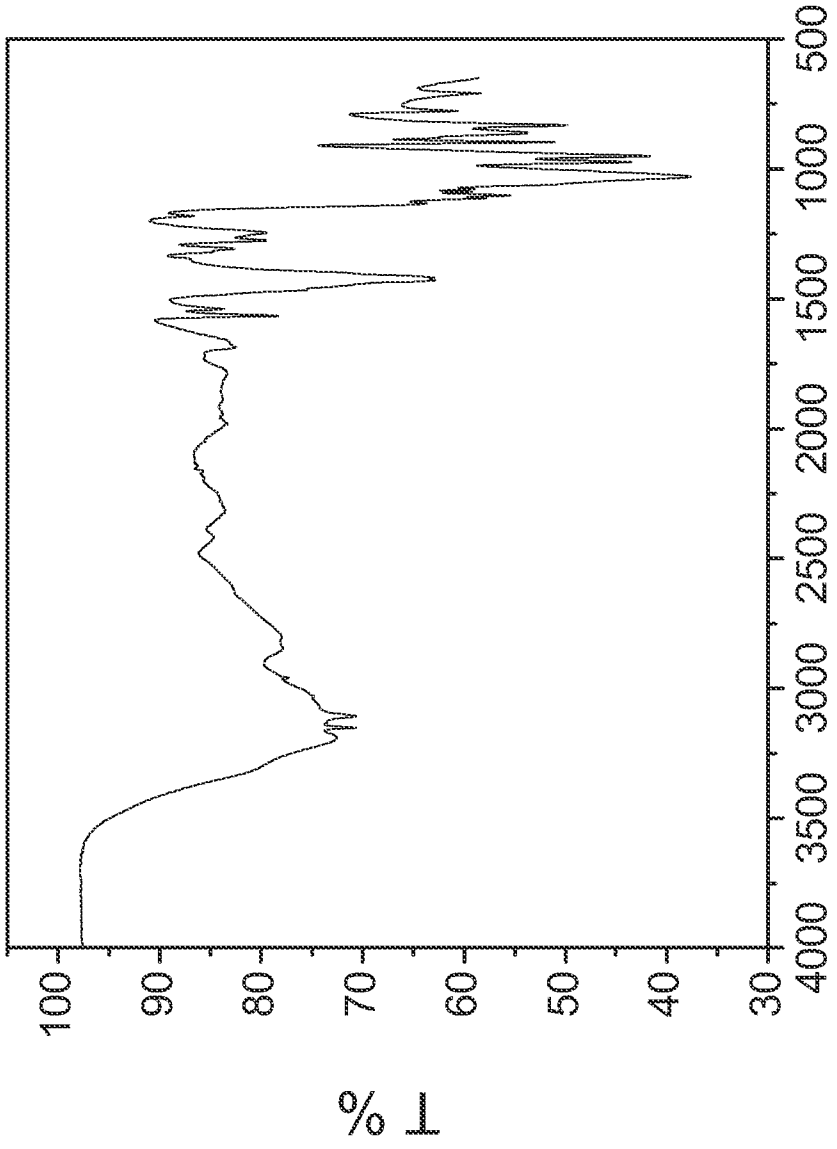

T %
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 18

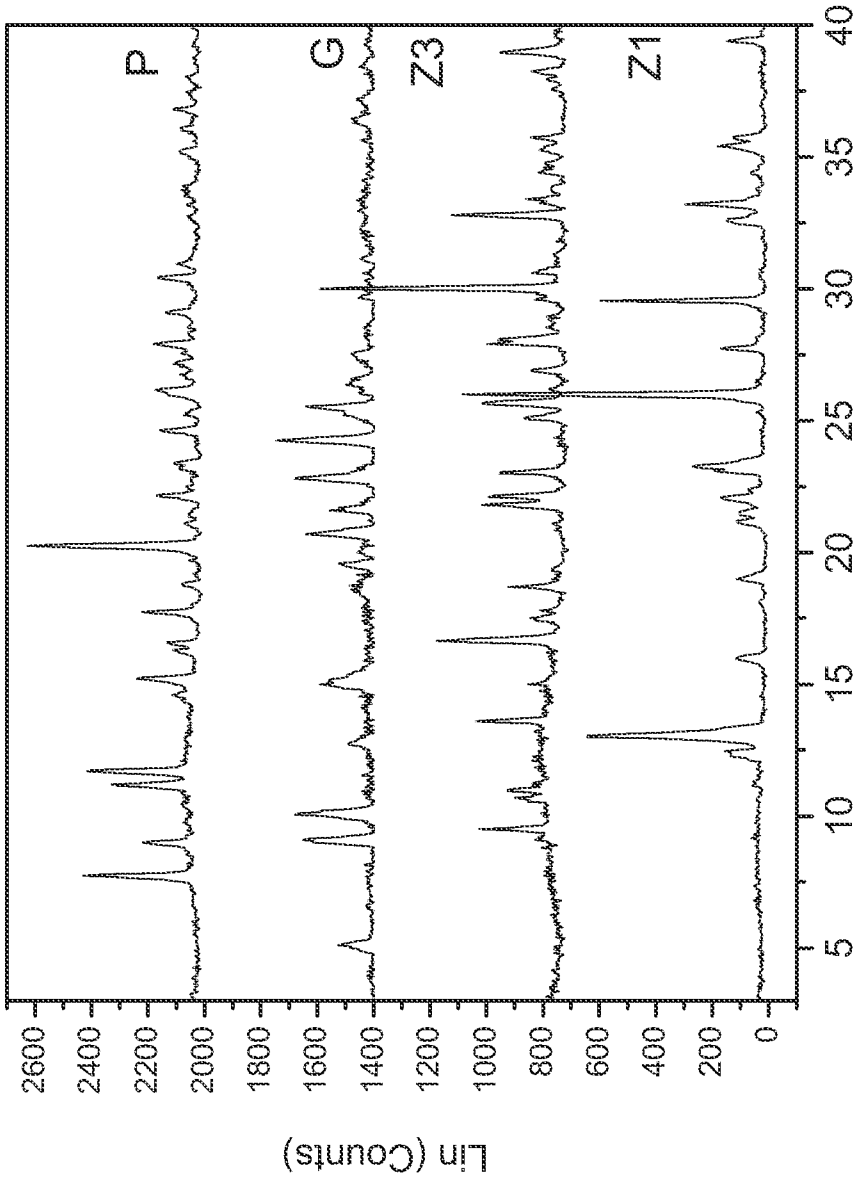

P
G
Z3
Z1
Lin (Counts)
2-Theta-Scale
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
5
10
15
20
25
30
35
40

FIG. 19

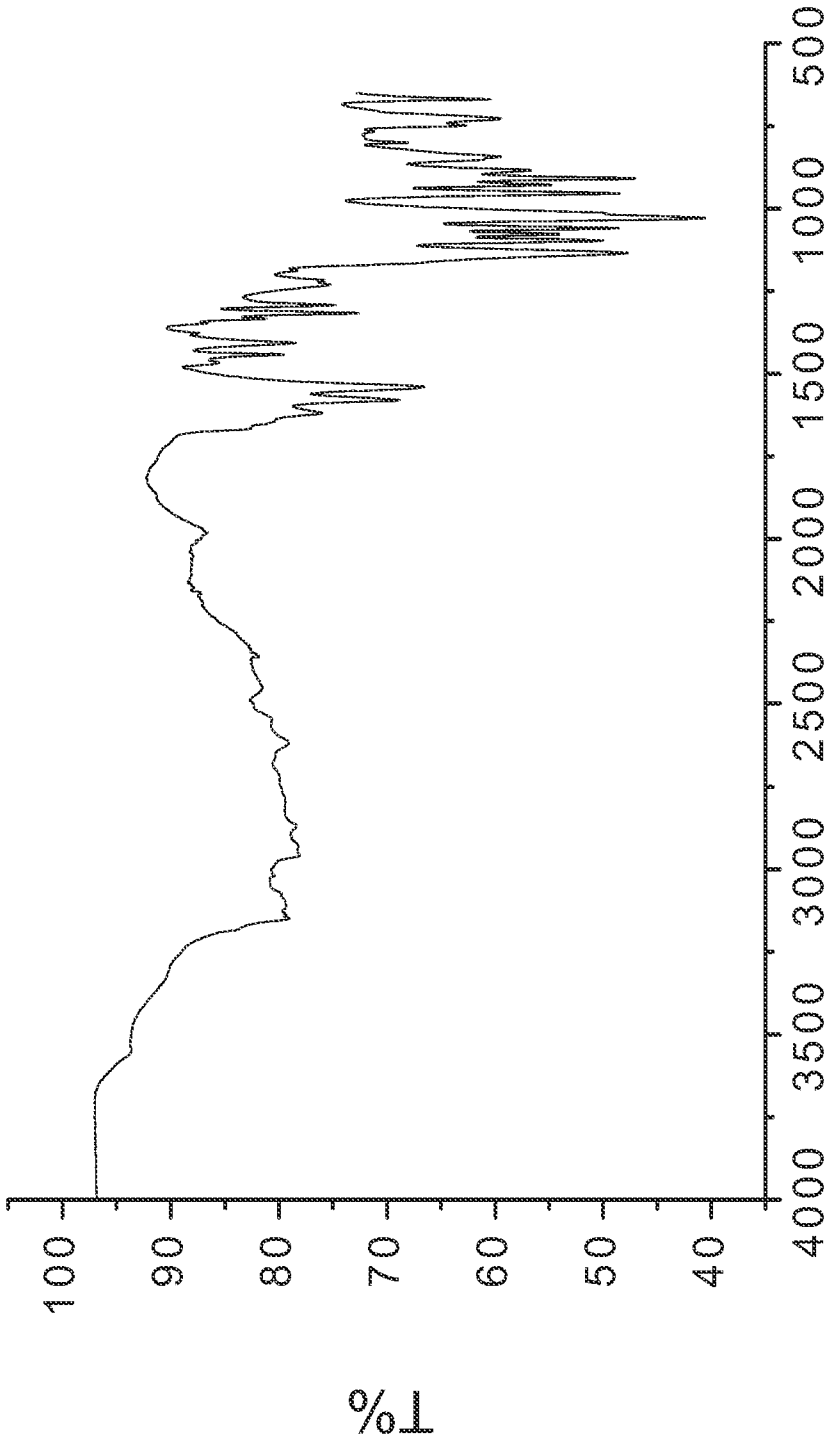

T%
100
90
80
70
60
50
40
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 20

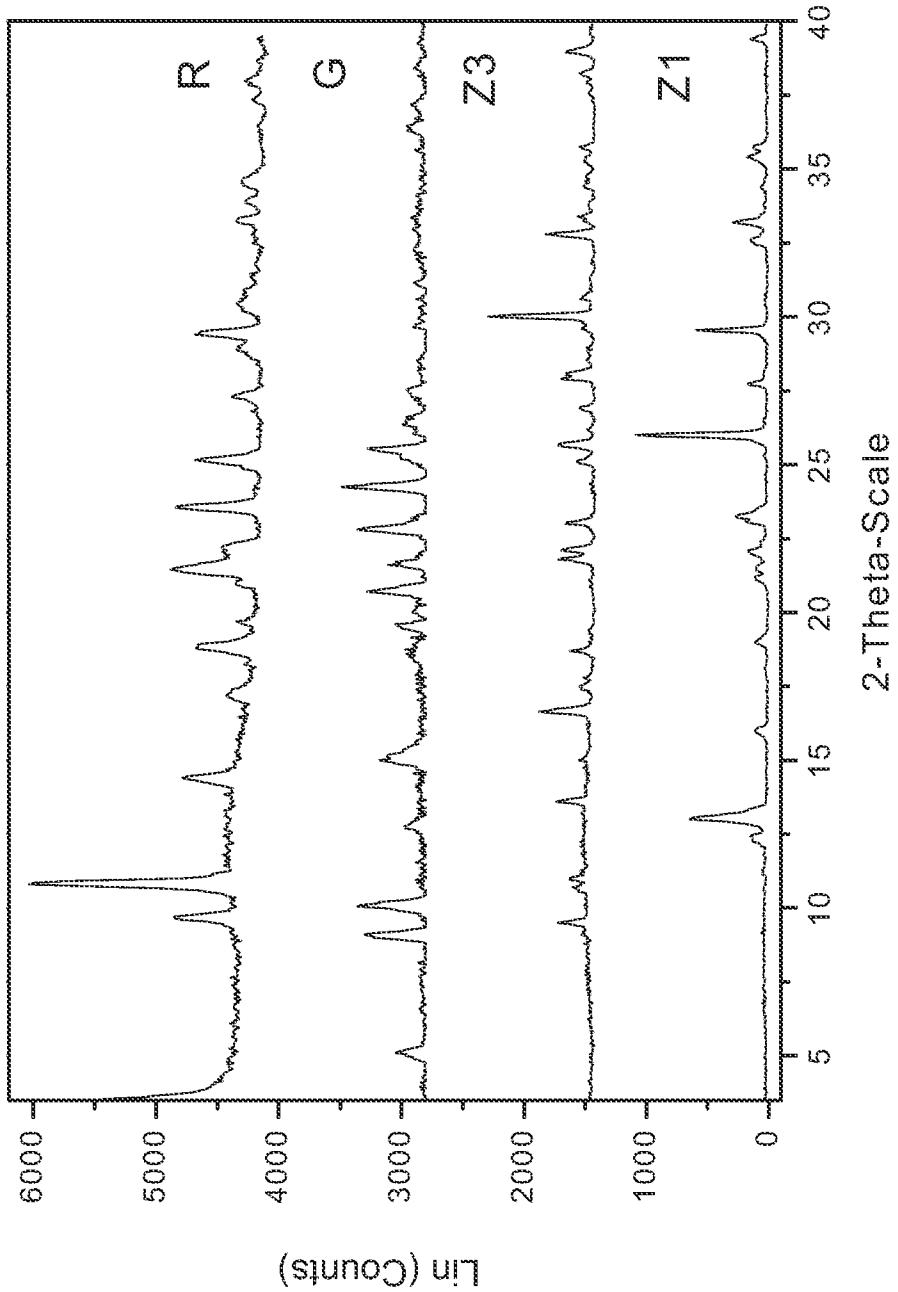

R
G
Z3
Z1
Lin (Counts)
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 21

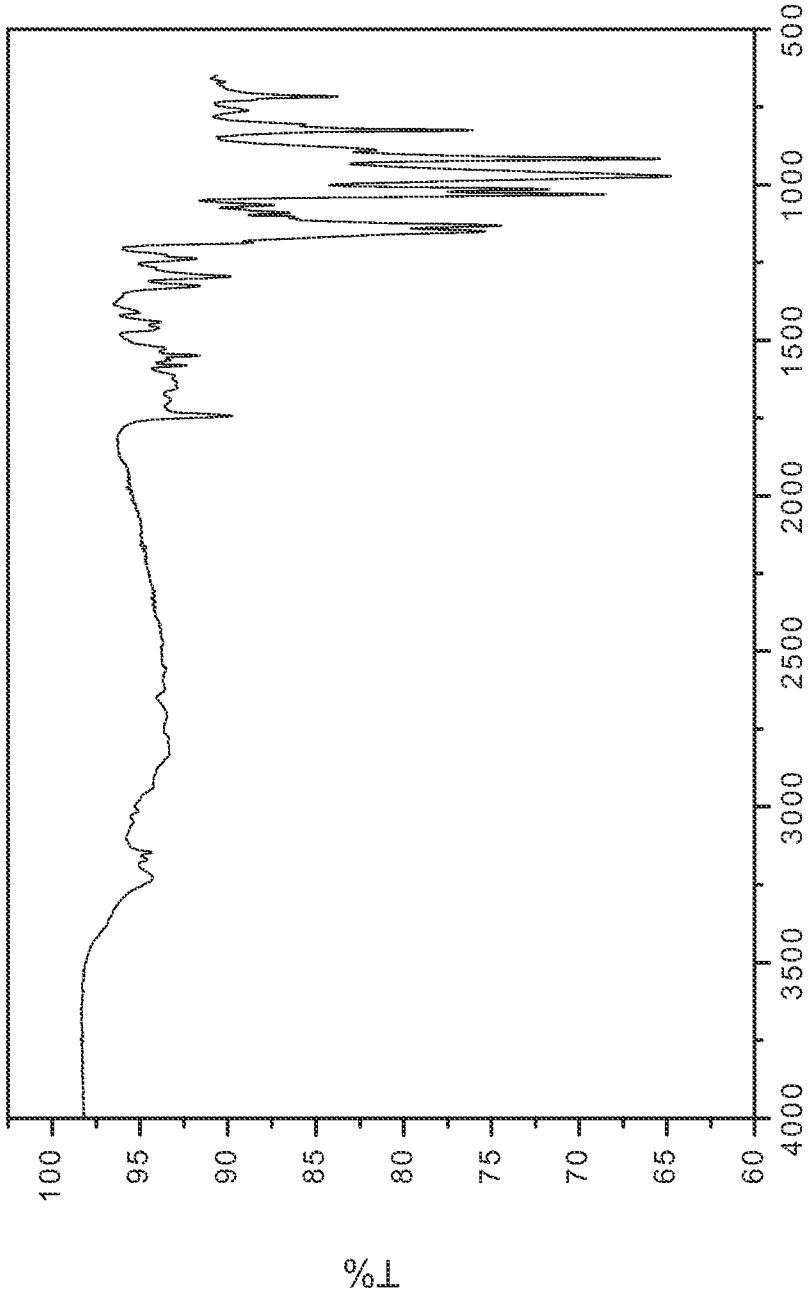

100
95
90
85
80
75
70
65
60
%T
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 22

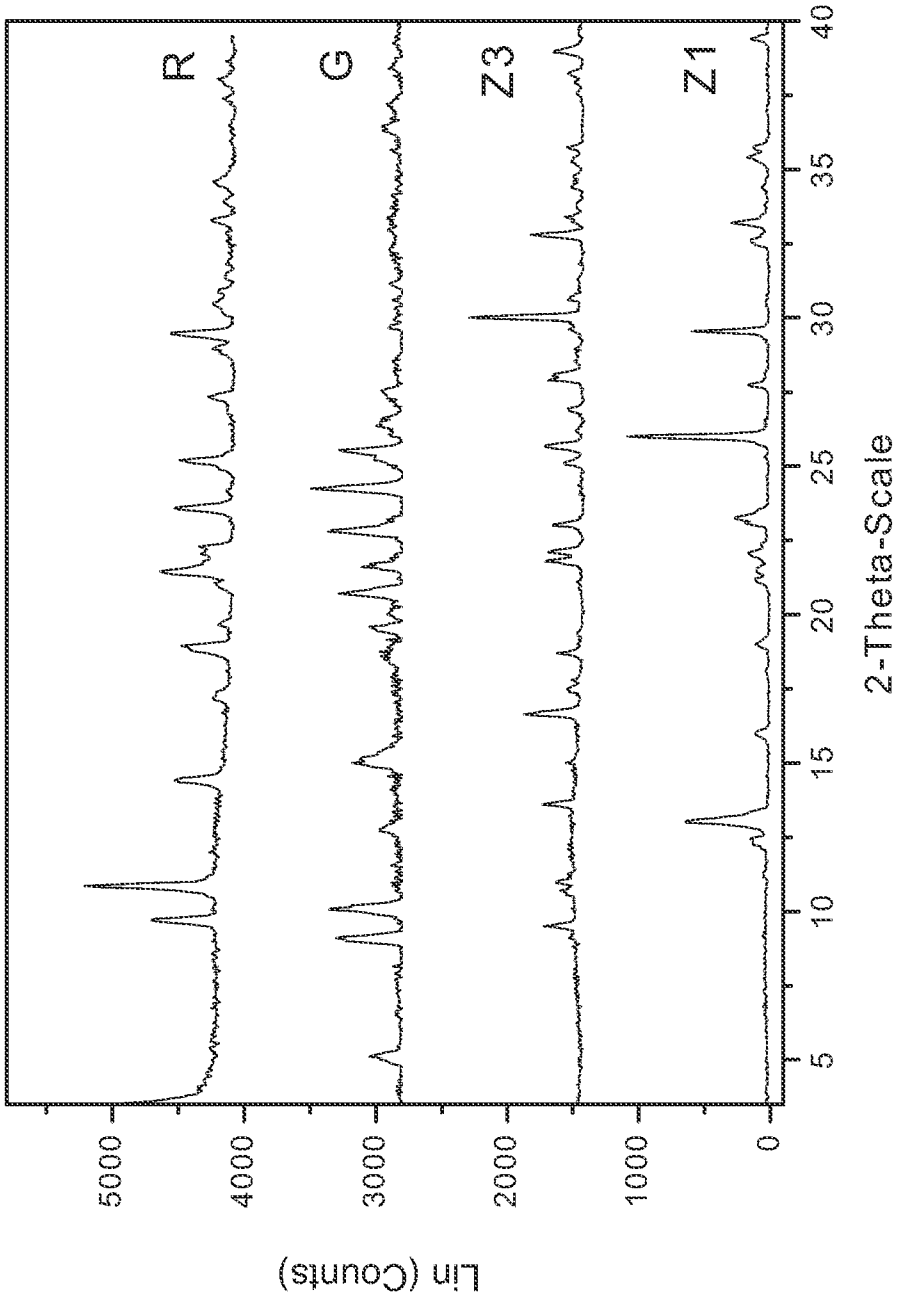

R
G
Z3
Z1
Lin (Counts)
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 23

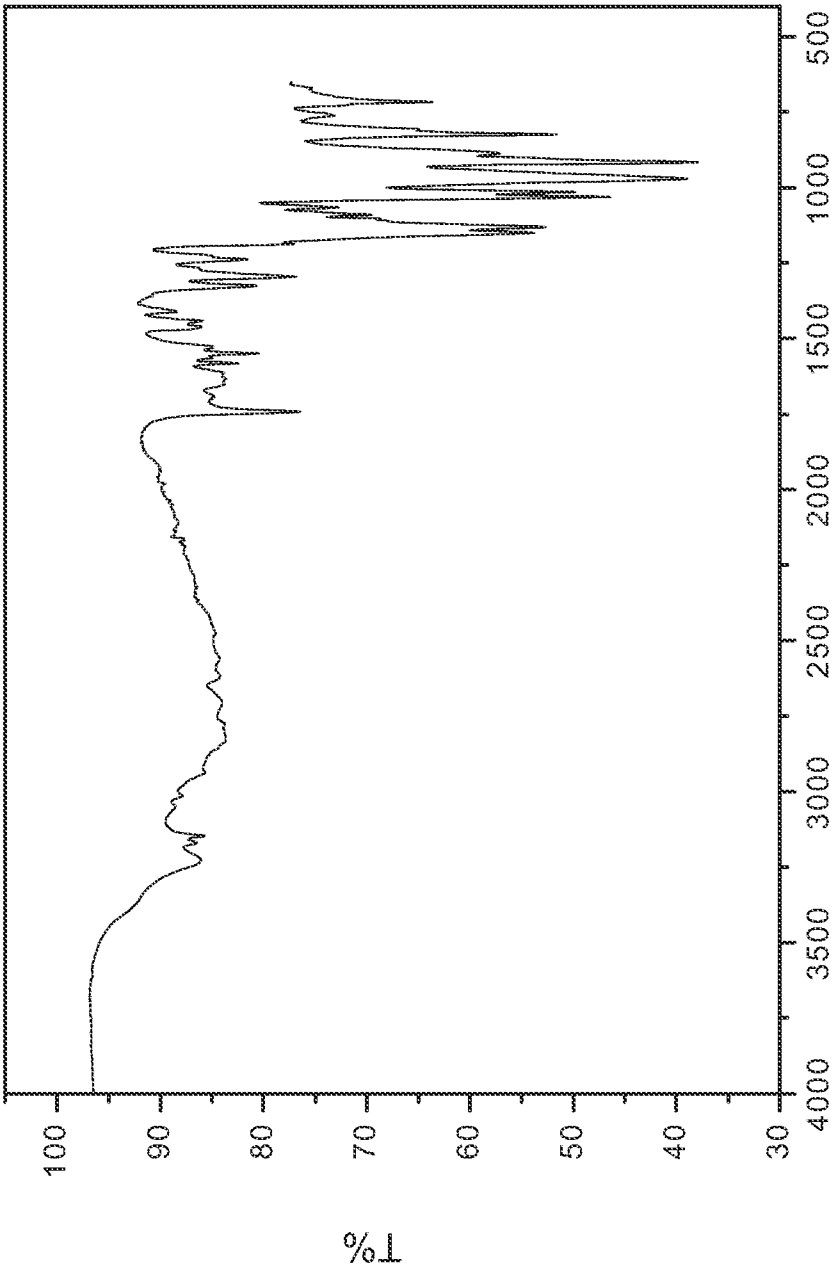

T%
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 24

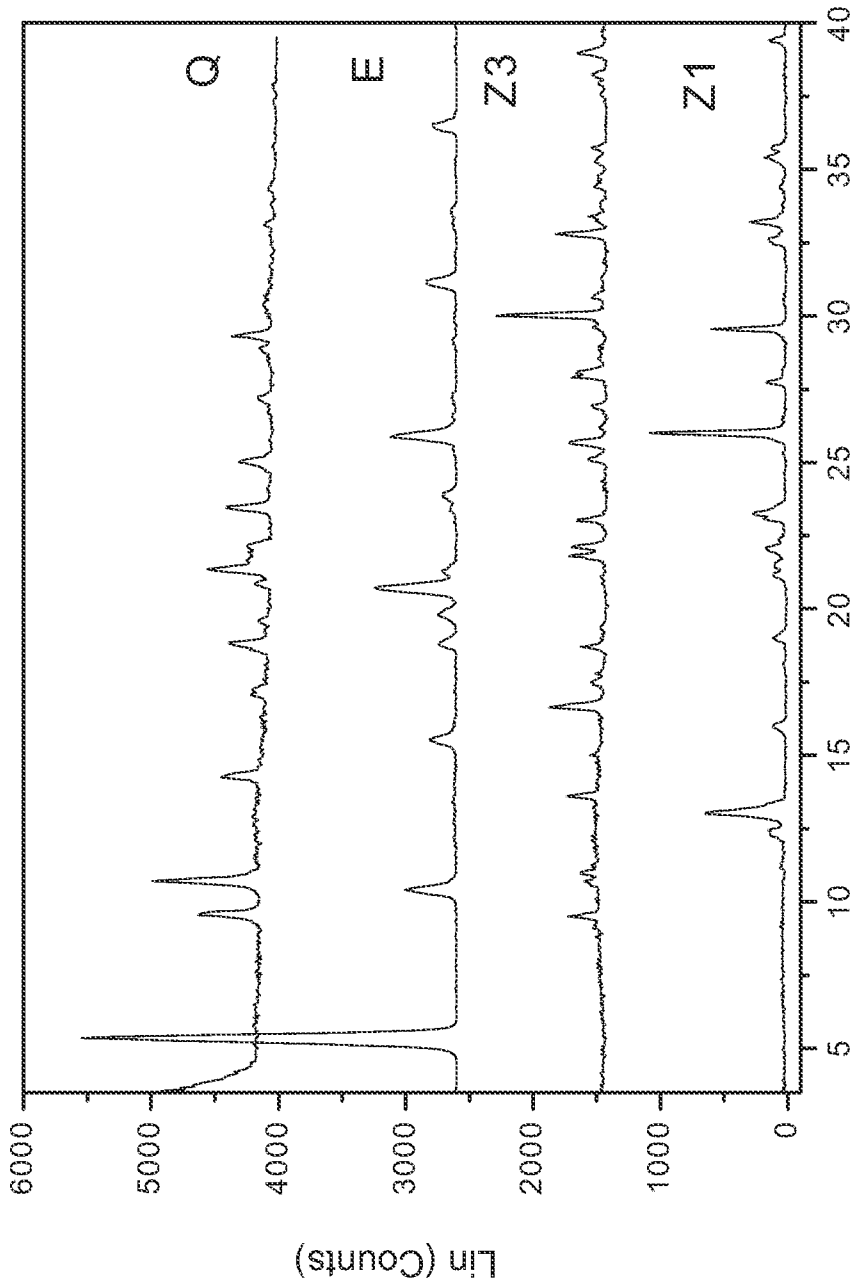

Q
E
Z3
Z1
Lin (Counts)
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 25

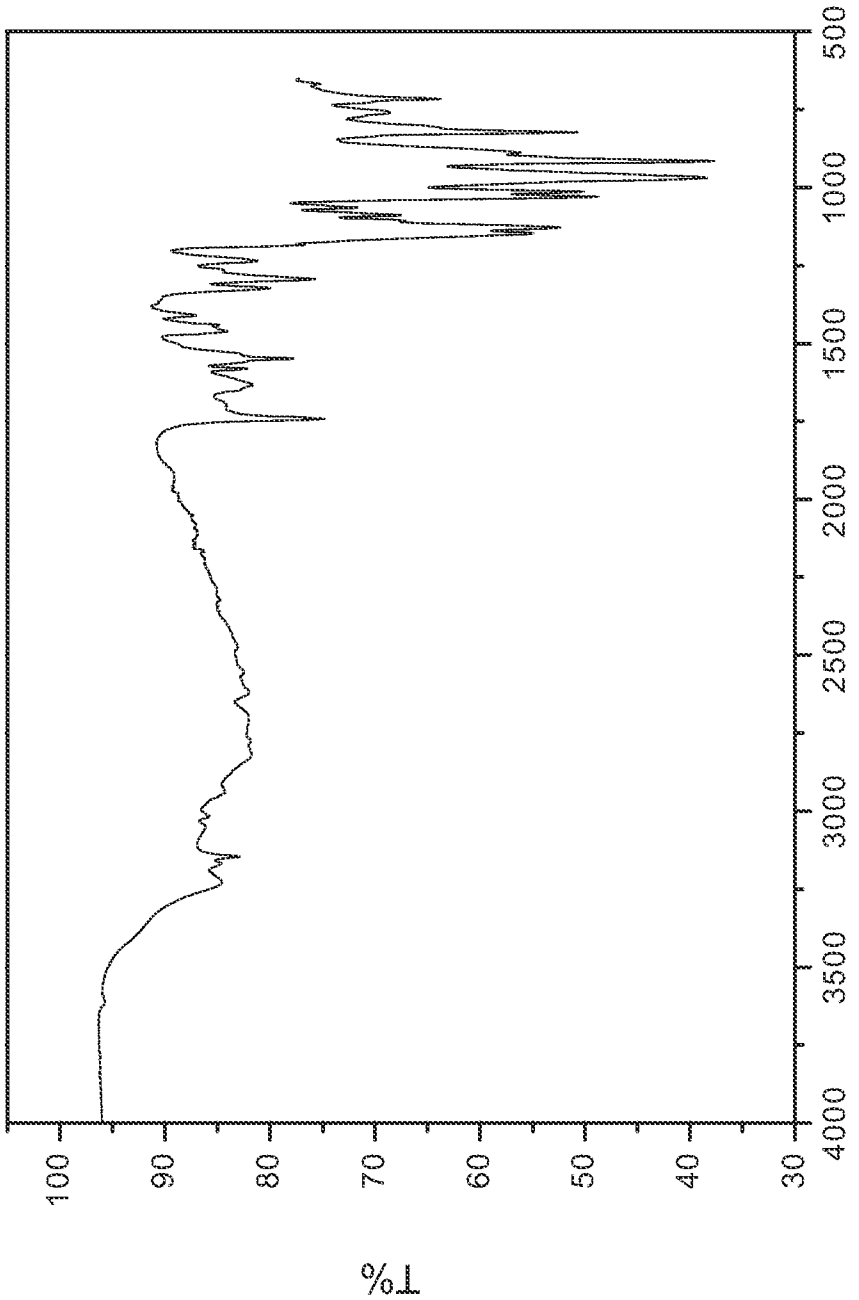

T%
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 26

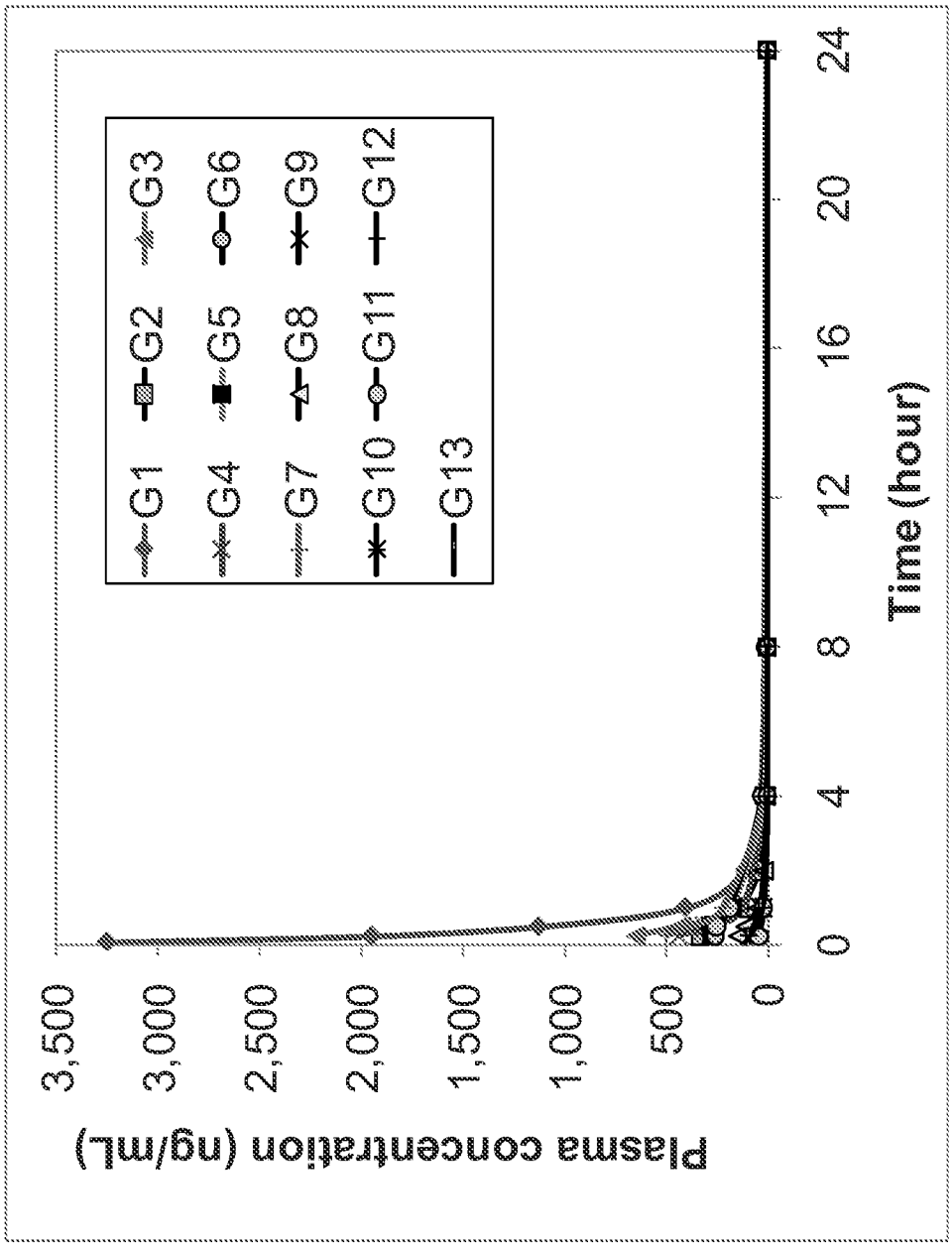

Plasma concentration (ng/mL)
3,500
3,000
2,500
2,000
1,500
1,000
500
0
0
4
8
12
16
20
24
Time (hour)
G1
G2
G3
G4
G5
G6
G7
G8
G9
G10
G11
G12
G13

FIG. 27

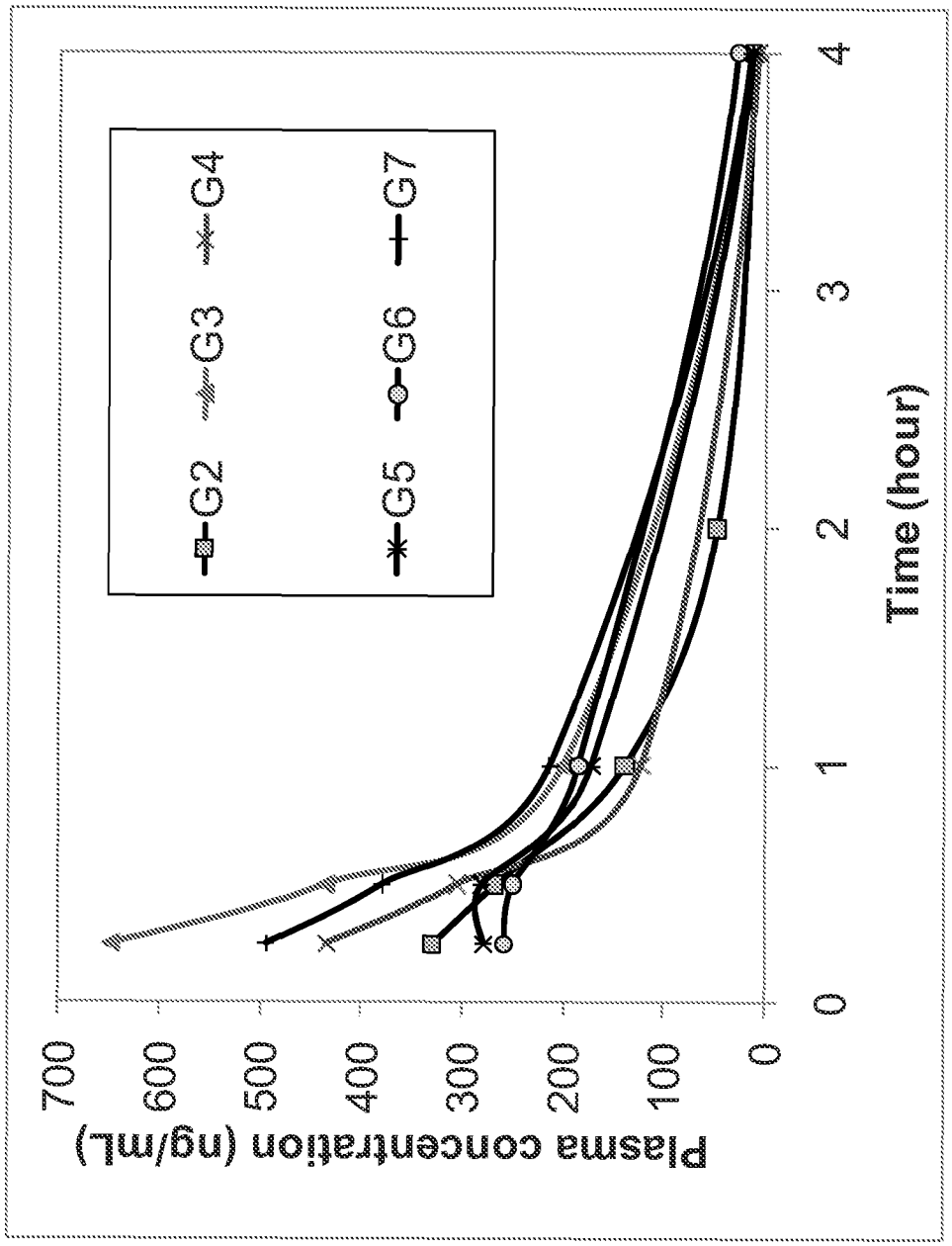

Plasma concentration (ng/mL)
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
G2
G3
G4
G5
G6
G7

FIG. 28

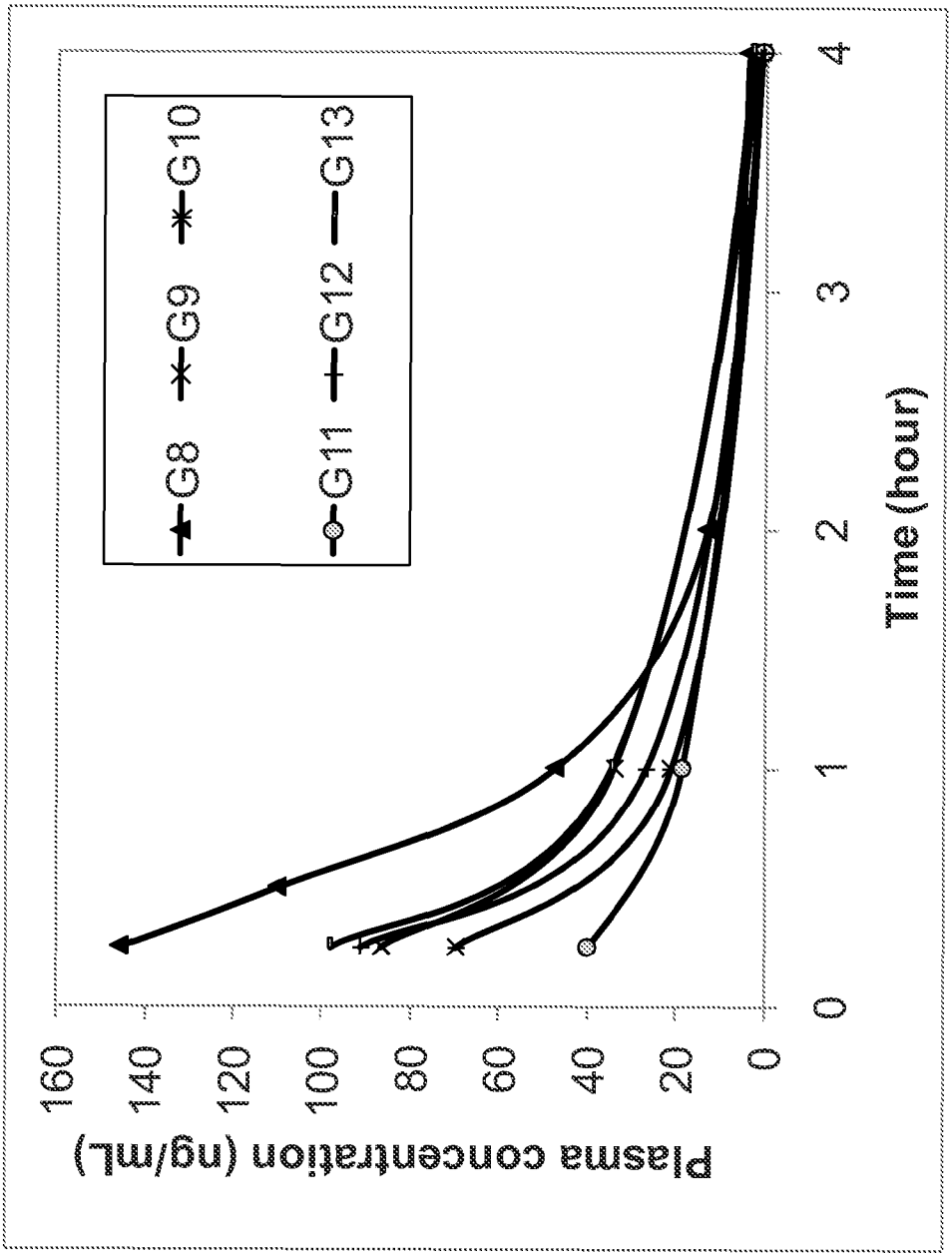

Plasma concentration (ng/mL)
160
140
120
100
80
60
40
20
0
0
1
2
3
4
Time (hour)
G8
G9
G10
G11
G12
G13

FIG. 29

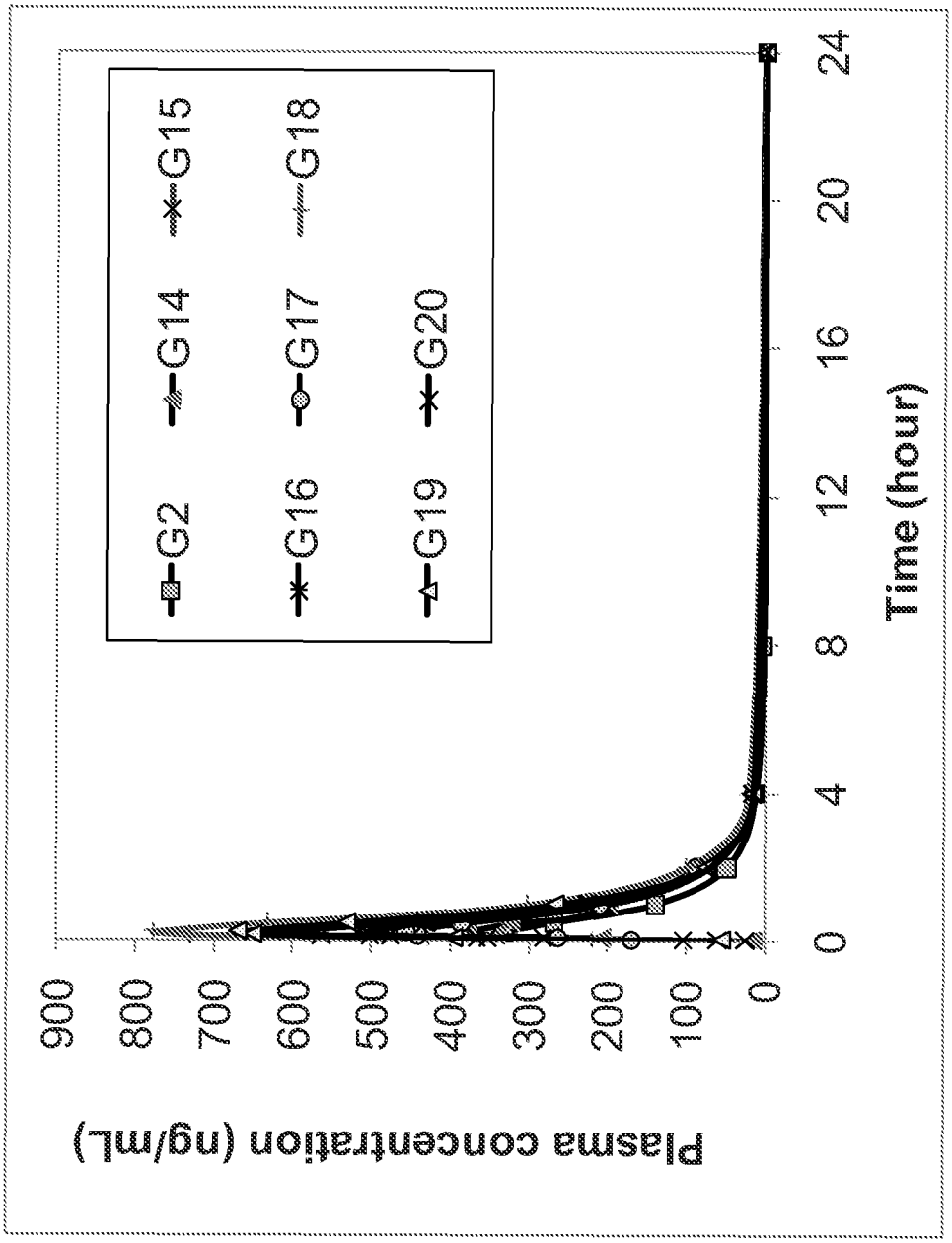

Plasma concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (hour)
G2
G14
G15
G16
G17
G18
G19
G20

FIG. 30

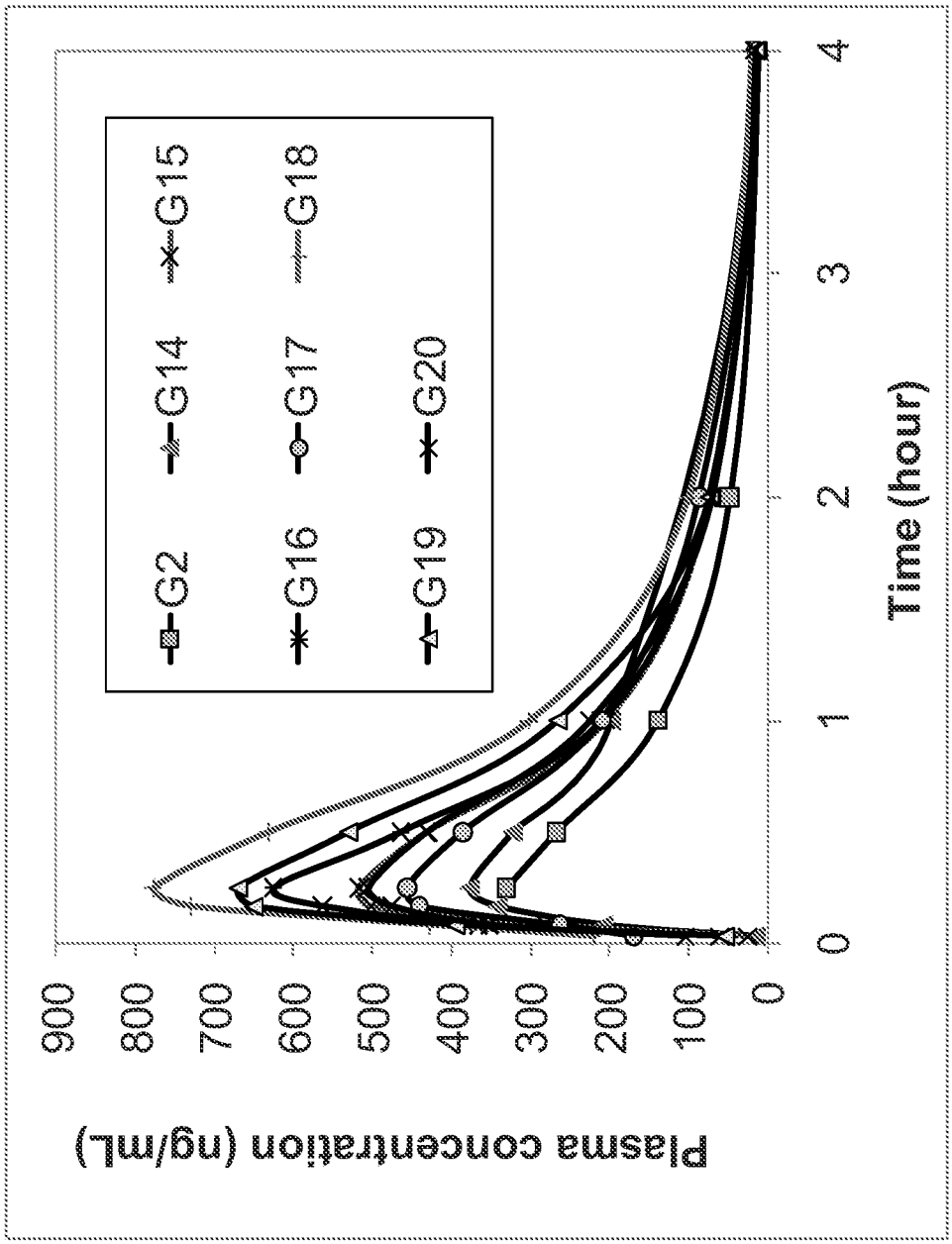

Plasma concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
G2
G14
G15
G16
G17
G18
G19
G20

FIG. 31

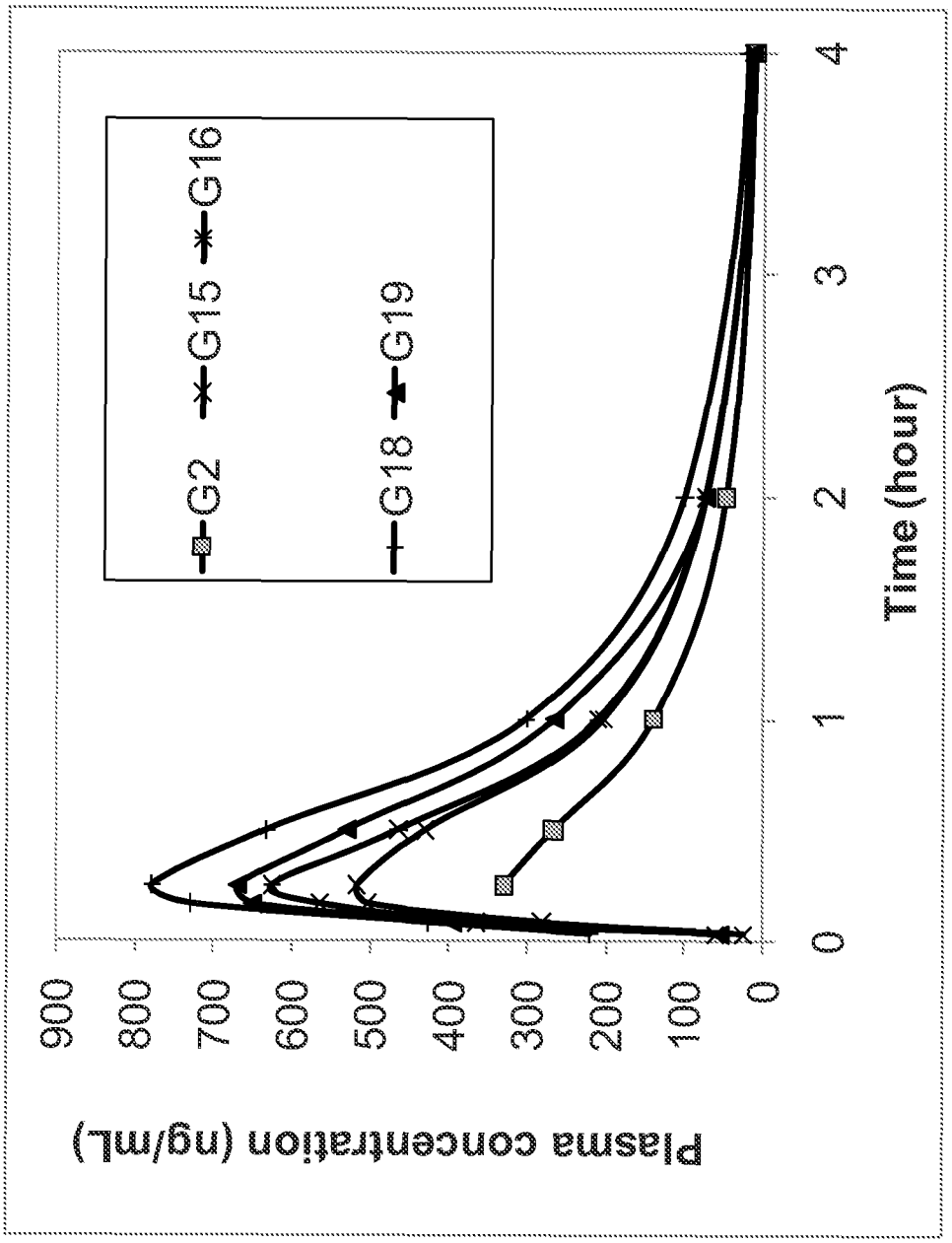

Plasma concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
G2
G15
G16
G18
G19

FIG. 32

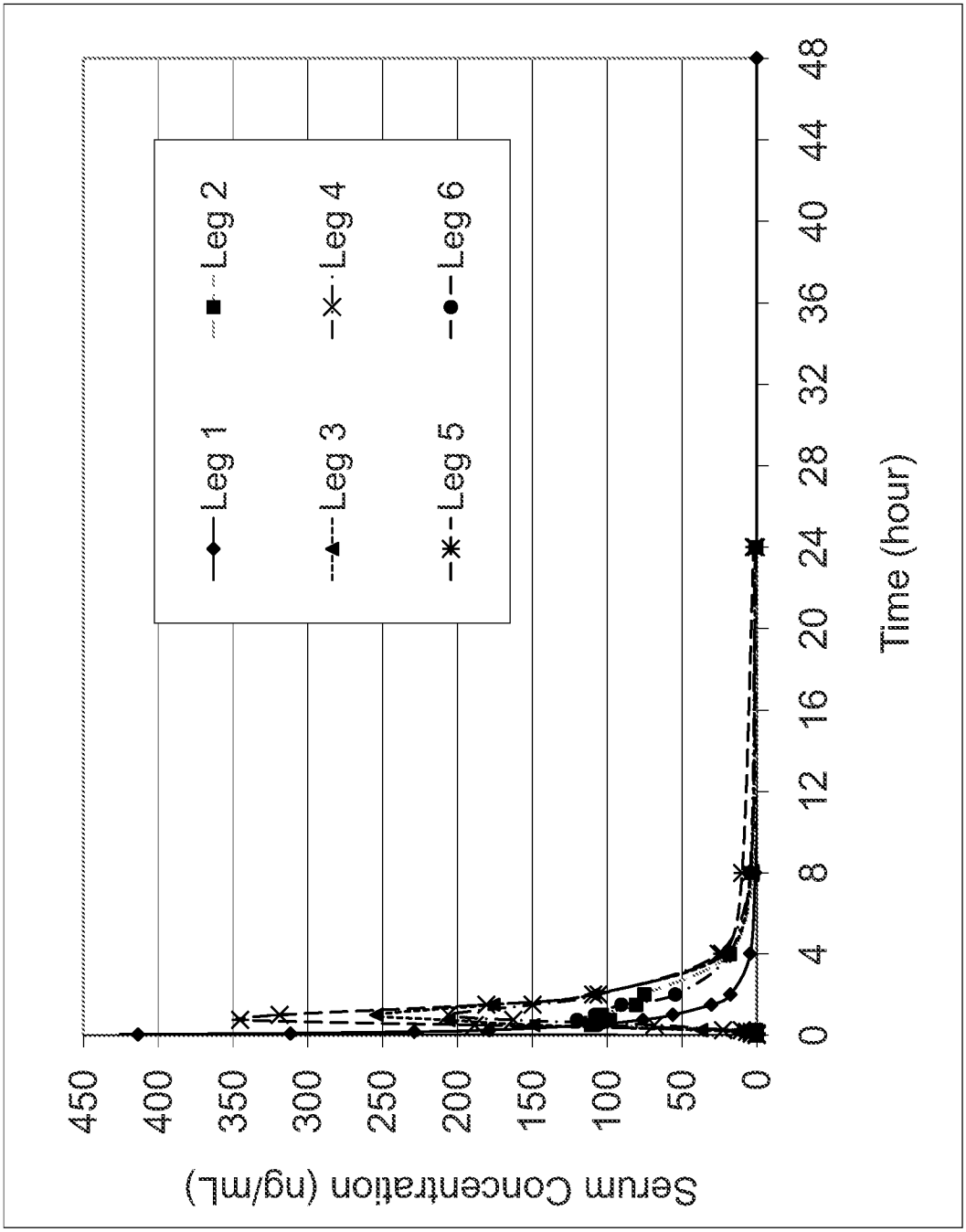

Serum Concentration (ng/mL)
450
400
350
300
250
200
150
100
50
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (hour)
Leg 1
Leg 2
Leg 3
Leg 4
Leg 5
Leg 6

FIG. 33

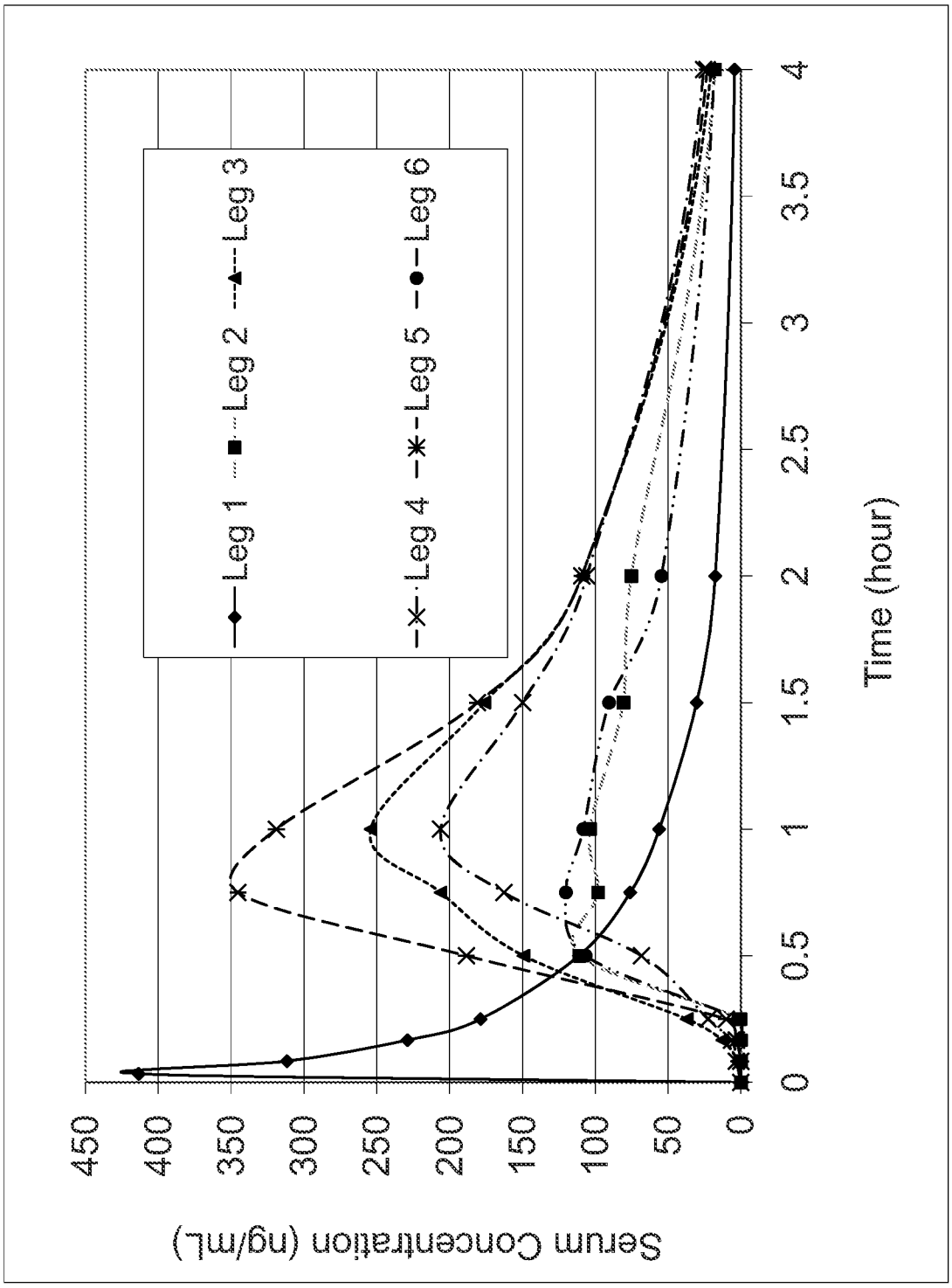

Serum Concentration (ng/mL)
450
400
350
300
250
200
150
100
50
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hour)
Leg 1
Leg 2
Leg 3
Leg 4
Leg 5
Leg 6

FIG. 34

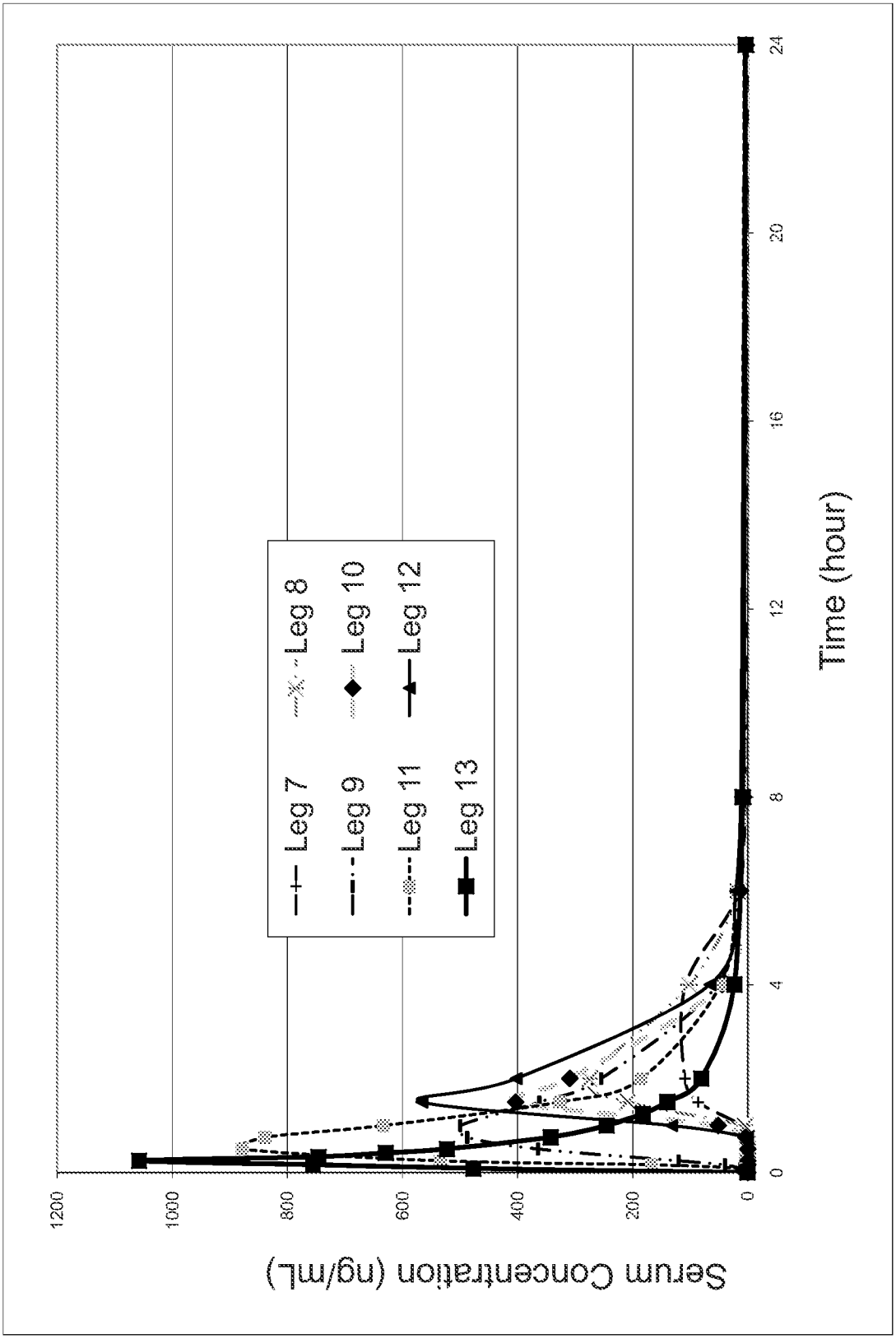

Serum Concentration (ng/mL)
1200
1000
800
600
400
200
0
Time (hour)
0
4
8
12
16
20
24
Leg 7
Leg 8
Leg 9
Leg 10
Leg 11
Leg 12
Leg 13

FIG. 35

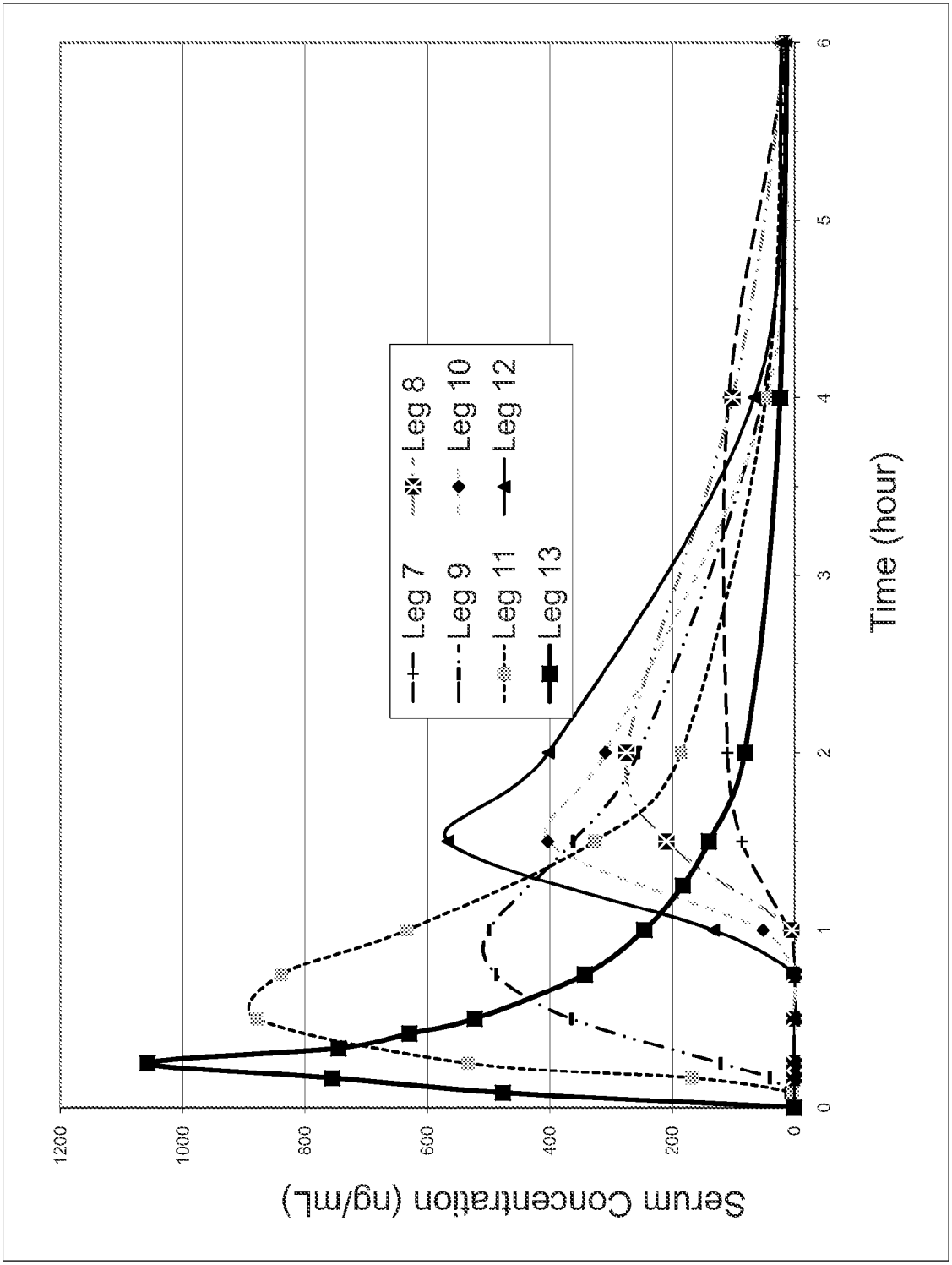

Serum Concentration (ng/mL)
1200
1000
800
600
400
200
0
0
1
2
3
4
5
6
Time (hour)
Leg 7
Leg 8
Leg 9
Leg 10
Leg 11
Leg 12
Leg 13

FIG. 36

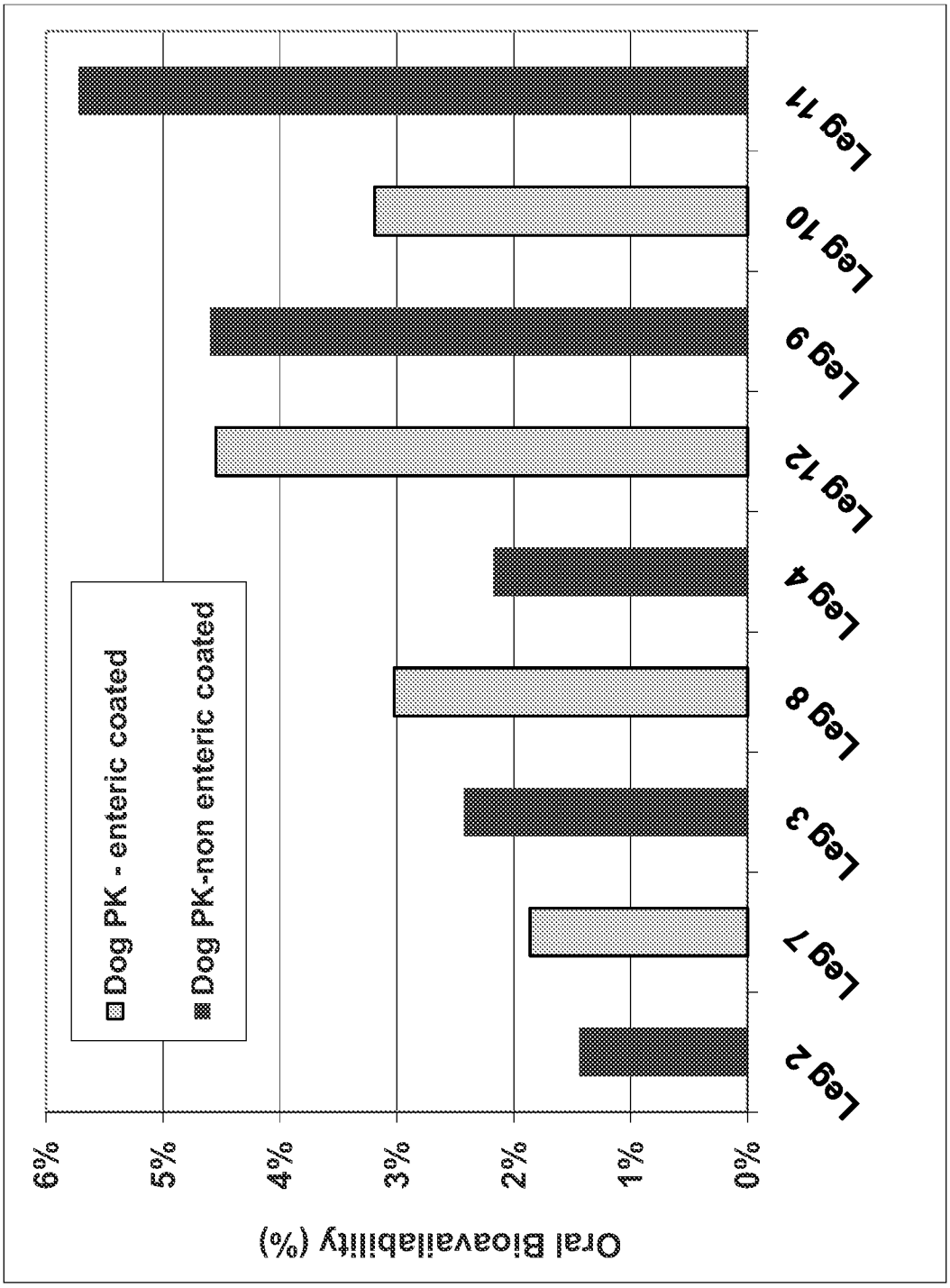

Oral Bioavailability (%)
0%
1%
2%
3%
4%
5%
6%
Dog PK - enteric coated
Dog PK-non enteric coated
Leg 2
Leg 7
Leg 3
Leg 8
Leg 4
Leg 12
Leg 9
Leg 10
Leg 11

FIG. 37

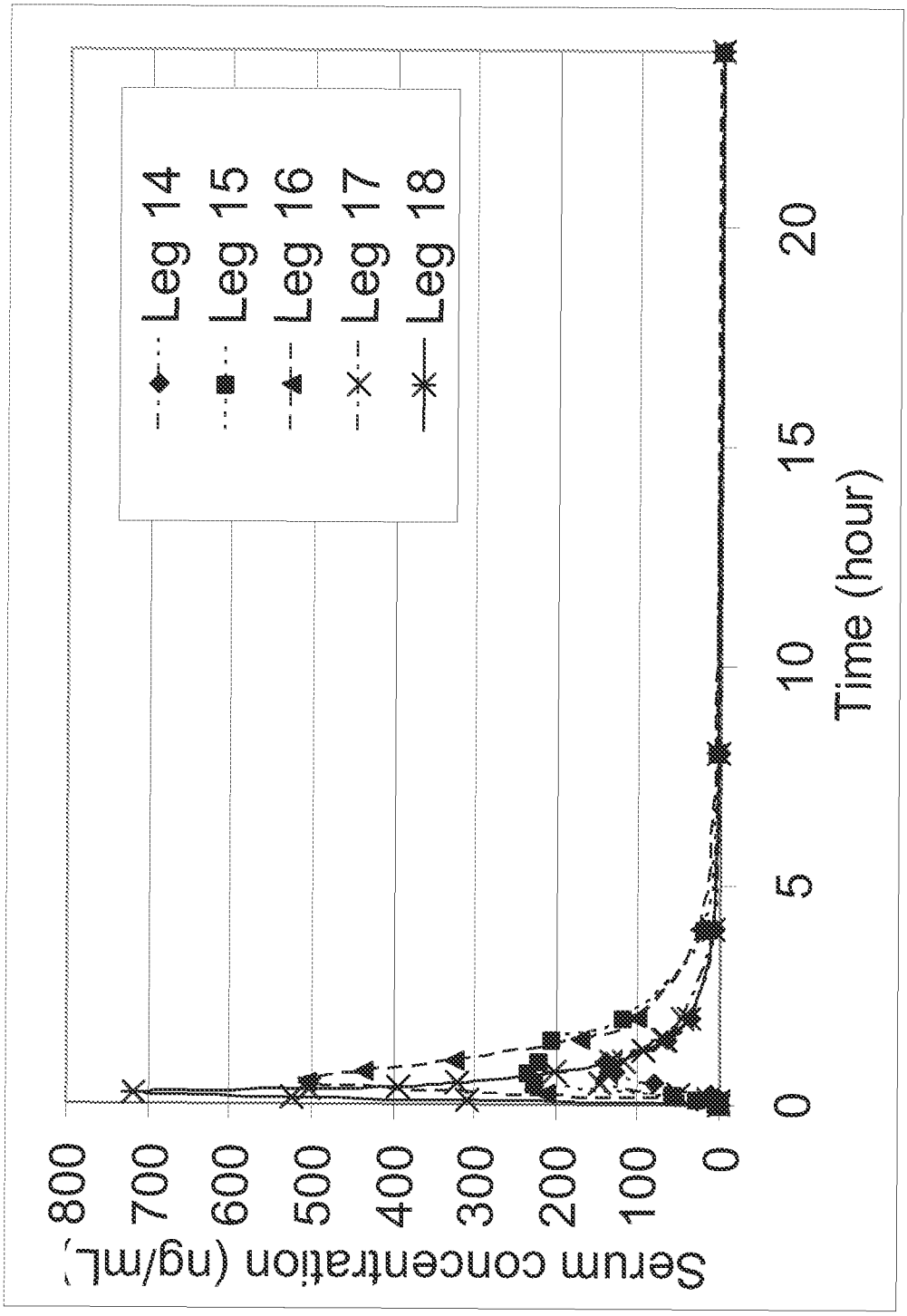

Serum concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0
5
10
15
20
Time (hour)
Leg 14
Leg 15
Leg 16
Leg 17
Leg 18

FIG. 38

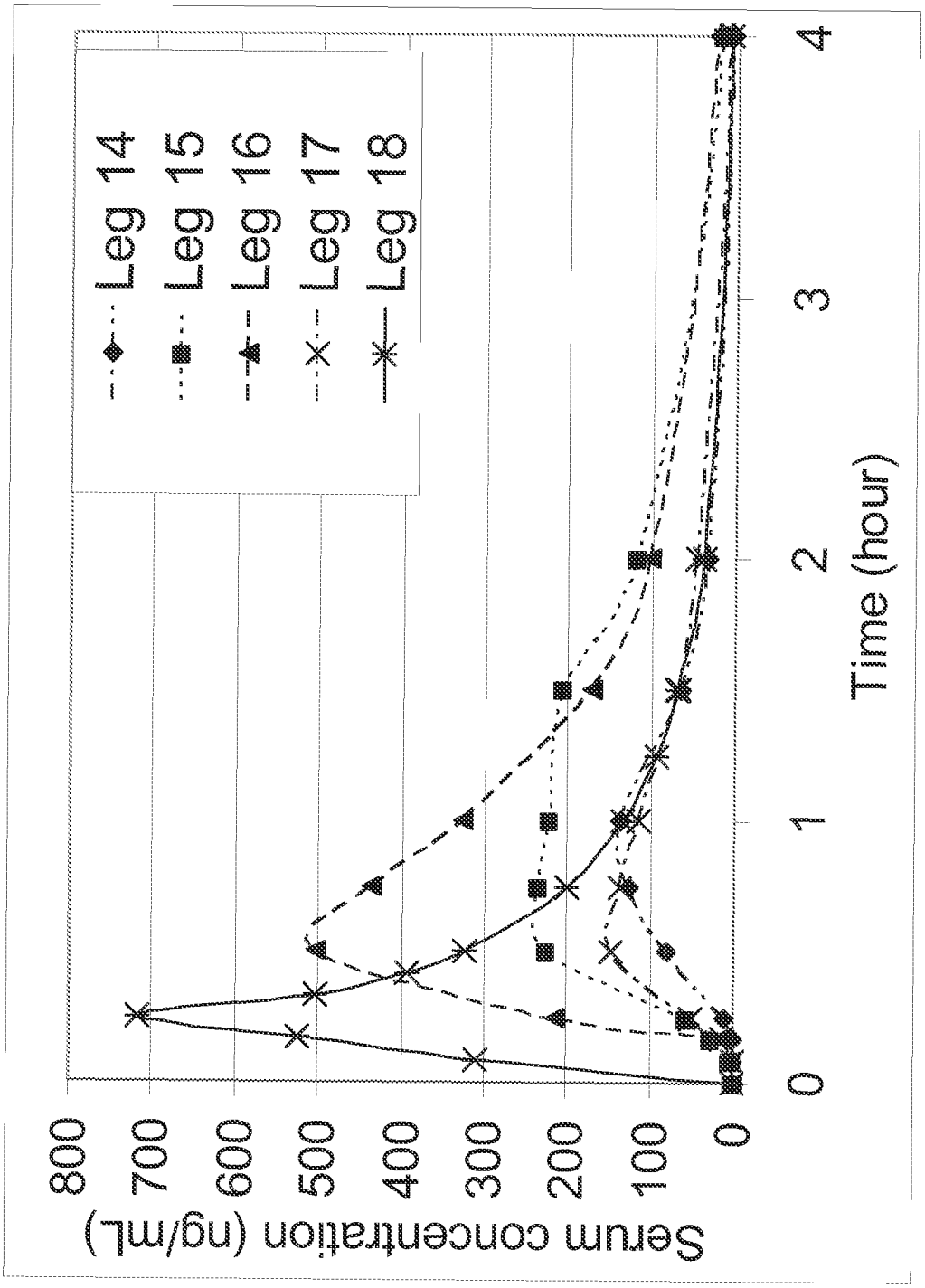

Serum concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
Leg 14
Leg 15
Leg 16
Leg 17
Leg 18

FIG. 39

REFERENCES CITED IN THE DESCRIPTION

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Az EP 2 459 176 lajstromszámú európai szabadalom igénypontjainak magyar fordítása:

1. Kristályos molekula-komplex, ami zoledronsavat vagy annak sóját és egy, a lizin vagy glicin köréből kiválasztott konformert tartalmaz.

2. Molekula-komplex, ami a következők köréből van kiválasztva:

- kristályos zoledronsav, víz és L-lizin komplex;
- kristályos zoledronsav, víz és DL-lizin komplex,
- kristályos zoledronsav, víz és glicin komplex;
- kristályos zoledronsav, L-lizin és víz komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 9,0, 11,4, 18,1, 26,0 és 29,6 ± 0,2 2 teta foknál észlelhető csúcs;
- kristályos zoledronsav, L-lizin és víz komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 9,6, 10,7, 14,3, 21,4 és 23,5 ± 0,2 2 teta foknál észlelhető csúcs;
- kristályos zoledronsav, DL-lizin és víz komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 8,3, 11,8, 12,3, 15,8 és 20,8 ± 0,2 2 teta foknál észlelhető csúcs;
- kristályos zoledronsav, DL-lizin és víz komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 9,1, 14,7, 18,0, 21,2 és 26,0 ± 0,2 2 teta foknál észlelhető csúcs;
- kristályos zoledronsav és glicin komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 10,2, 17,8, 19,9, 22,9 és 28,1 ± 0,2 2 teta foknál észlelhető csúcs;
- kristályos zoledronsav, DL-lizin és víz komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 9,7, 10,8, 14,4, 18,9 és 21,4 ± 0,2 2 teta foknál észlelhető csúcs;
- kristályos zoledronsav, DL-lizin, etanol és víz komplex, amelyre *jellemző*, hogy röntgen-pordiffraktogramjában körülbelül 8,8, 9,7, 17,6, 23,1 és 26,5 ± 0,2 2 teta foknál észlelhető csúcs;

ahol a röntgen-pordiffraktogramok 3°-tól 40°-ig terjedő 2θ szögtartományban vannak felvéve λ = 1,540562 Angström hullámhosszú Cu Kα sugárzást alkalmazva.

3. Kompozíció, ami az 1. vagy 2. igénypont szerinti, zoledronsavat vagy sóját és lizint tartalmazó molekula-komplexet tartalmaz, továbbá fölösleges mennyiségű

lizint, glicint vagy ezek keverékét, elönyösen fölösleges mennyiségû lizint is tartalmaz.

4. Kompozíció, ami az 1. vagy 2. igénypont szerinti, zoledronsavat vagy sóját és glicint tartalmazó molekula-komplexet tartalmaz, továbbá fölösleges mennyiségû glicint, lizint vagy ezek keverékét, elönyösen fölösleges mennyiségû glicint is tartalmaz.

5. Gyógyászati készítmény, ami az 1. vagy 2. igénypont szerinti kristályos molekula-komplexet vagy a 3. vagy 4. igénypont szerinti kompozíciót tartalmazza, gyógyászatilag elfogadható excipienssel együtt.

6. Az 5. igénypont szerinti gyógyászati készítmény, ahol a készítmény egy orális szilárd dózisforma.

7. A 6. igénypont szerinti gyógyászati készítmény, ahol a készítmény egy orális dózisforma, ami tabletta, kapszula, és a szilárd molekula-komplex folyadékkal képezett szuszpenziója köréből van kiválasztva.

8. Az 1. vagy 2. igénypont szerinti molekula-komplex, a 4. vagy 5. igénypont szerinti kompozíció, vagy a 6-8. igénypontok bármelyike szerinti gyógyászati készítmény gyógyszerként való felhasználásra.

9. Az 1. vagy 2. igénypont szerinti molekula-komplex, a 3. vagy 4. igénypont szerinti kompozíció, vagy az 5-6. igénypontok bármelyike szerinti gyógyászati készítmény oszteoporózissal, hiperkalcémiával, rák okozta csont-metasztázissal, Paget kórral vagy adjuváns vagy neoadjuváns rákterápiákkal összefüggő betegségállapotok kezelésére és/vagy megelőzésére.

10. Az 1. vagy 2. igénypont szerinti molekula-komplex, a 3. vagy 4. igénypont szerinti kompozíció vagy az 5-7. igénypontok bármelyike szerinti gyógyászati készítmény a zoledronsav vagy sója biológiai hozzáférhetőségének vagy permeabilitásának fokozására ezt igénylő betegeken.

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Meghatalmazott:

Dr. M[illegible]
Ügyvéd
1011 Budapest, Egy József u. 40
Tel: 212-[illegible] Fax: 212-4508