(54) Title: CRYSTALLINE CIS-(E)-4-(3-FLUOROPHENYL)-2',3',4',9'-TETRAHYDRO-N,N-DIMETHYL-2'-(1-OXO-3-PHENYL-2-PROPENYL)-SPIRO[CYCLOHEXANE-1,1'[1H]-PYRIDO[3,4-B]INDOL]-4-AMINE

(57) Abstract: The present invention relates to crystalline forms of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'- tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1, 1 '[1 H]- pyrido[3,4-b]indol]-4-amine, pharmaceutical compositions and medicaments comprising these modifications, the use of these modifications as well as to a process for making the crystalline forms.

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Crystalline cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-
(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine

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FIELD OF THE INVENTION

The invention relates to crystalline forms of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-
N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-

15   4-amine, pharmaceutical compositions and medicaments comprising one or more of these
crystalline forms, the use of these crystalline forms as well as to processes for producing
these crystalline forms.

BACKGROUND OF THE INVENTION
20

Pharmaceutically active drugs can exist in different solid forms. For example, a drug may
exist in different crystalline forms which have different physical, physic-chemical and
chemical properties.

25   Different physical or physic-chemical properties can cause different crystalline forms of the
same drug to have largely different processing and storage performance. Such physical or
physico-chemical properties include, for example, thermodynamic stability, crystal
morphology [form, shape, structure, particle size, particle size distribution, color, degree of
crystallinity, ripple behavior, flowability, density, bulk density, powder density, apparent

30   density, vibrated density, depletability, emptyability, hardness, deformability, grindability,
compressability, compactability, brittleness, elasticity, caloric properties [particularly melting
point], solubility [particularly equilibrium solubility, pH dependence of solubility], dissolution
[particularly dissolution rate, intrinsic dissolution rate], reconstitutability, hygroscopicity,
tackiness, adhesiveness, tendency to electrostatic charging, and the like.

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In addition, different chemical properties can cause different crystalline forms of the same
drug to have largely different performance properties. For example, a crystalline form having
a low hygroscopicity (relative to other crystalline forms) can have superior chemical stability
and longer shelf-life stability (cf. R. Hilfiker, Polymorphism, 2006 Wiley VCH, pp 235-242 and

40   251-252).

5   In medicine, the treatment of pain is of great importance and although a significant number of drugs are known for and established in the treatment of pain, there remains, for instance with regard to drug-related side-effects, a demand for improved pain medication, especially for the treatment of strong/severe and/or chronic and/or neuropathic pain. Consequently, a great deal of effort is still being invested by pharmaceutical companies into the development of

10   new, improved analgesics.

One particular drug that is of great interest especially for the use in treating pain, especailly chronic and/or neuropathic pain is cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-

15   amine, which is described in WO2012013343-A1. The chemical structure of this drug is depicted below as the compound of formula (I):

(I).
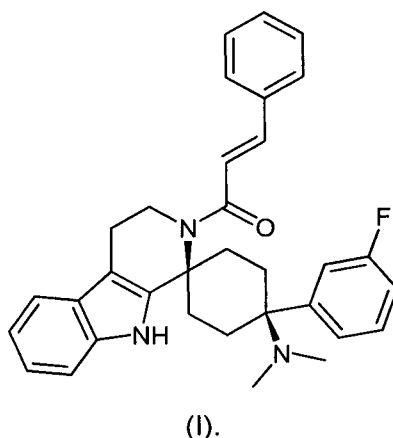
20   The solid forms of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine that are known so far are not satisfactory in every respect and consequently there is a demand for advantageous solid forms, especially crystalline forms. Especially, there is a demand for solid forms of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-

25   phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine   that   have advantageous properties for the use of this compound in pharmaceutical compositions and for use in methods of preparing such pharmaceutical compositions.

This object has been achieved by the present invention. It has surprisingly been found that

30   different crystalline forms of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine can be prepared which have advantageous properties, especially for the use in pharmaceutical compositions. These inventive crystalline forms are described herein.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 1j, 1k and 1l show the PXRD patterns of crystalline forms A, B, C, D, E, F, G, H, I, J, K, L and Q.

10

Figures 2a, 2b and 2d show the Raman spectra of crystalline forms A, B, and D.

Figures 3a, b, c, d, and e show plots of DVS experiments for crystalline forms A, B, C, D, and E.

15

DETAILED DESCRIPTION

The compound according to general formula (I) depicted above can be systematically be referred to as cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-
20   phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine, or as cis-(E)-2',3',4',9'-tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine   or   as   (E)-1-((1s,4s)-4-(dimethylamino)-4-(3-fluorophenyl)-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indol]-2'(9'H)-yl)-3-phenylprop-2-en-1-one, respectively.

25

The compound according to general formula (I) may be present as the free base. The definition of the free base of the compound according to general formula (I) as used herein includes solvates, co-crystals and crystalline forms. For the purpose of the specification, "free base" preferably means that the compound according to general formula (I) is not present in
30   form of a co-crystal or salt, particularly not in form of an acid-addition salt. The most basic functional group of the compound according to general formula (I) is its N,N-dimethylamino moiety, which thus according to the invention is preferably neither protonated nor quaternized. In other words, the free electron pair of the nitrogen atom of the N,N-dimethylamino moiety is present as a Lewis base. Methods to determine whether a chemical
35   substance is present as the free base or as a salt are known to the skilled artisan such as ^{14}N or ^{15}N solid state NMR, x-ray diffraction, x-ray powder diffraction, IR, Raman, XPS. ^{1}H-NMR recorded in solution may also be used to consider the presence of protonation.

Unless explicitly stated otherwise, all 2Θ values refer to a X-ray powder diffractogram
40   measured using CuKα radiation having a wavelength of 1.54060 Å. The terms 2Θ values and degrees 2Θ are used synonymously.

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Unless explicitly stated otherwise, all values in ppm refer to ppm by weight, i.e. ppmw.

In a first aspect, the present invention relates to a crystalline form of cis-(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-

10   1,1'(1'H)-pyrido[3,4-b]indole]-4-amine.

In a preferred embodiment of the invention, the crystalline form according to the invention has at least one X-ray powder diffraction peak (CuKα radiation) in the range of 6.5±0.2 to 8.9±0.2 (2Θ) and/or 17.2±0.2 to 18.3±0.2 (2Θ) and/or in the range of 19.7±0.2 to 20.9±0.2

15   (2Θ) .

Preferably, said X-ray powder diffraction peak exhibits a relative intensity of at least 10%, preferably of at least 20%, more preferably of at least 30%.

20   In further preferred embodiments the crystalline form according to the invention is an ansolvate or a solvate.

In some preferred embodiments the crystalline form according to the invention is an ansolvate. In other preferred embodiments the crystalline form according to the invention is a

25   solvate, preferably selected from the group of hydrates, solvates of lower alcohols, such as methanol, ethanol, 1-propanol or 2-propanol or solvates of toluene or a solvate of solvate mixtures. Preferably, the solvate is selected from the group consisting of monosolvate, hemi-solvate, disolvate, trisolvate, and mixtures thereof. In another preferred embodiment the solvate is a variable or non-stoichiometric solvate.

30

In a preferred embodiment, the crystalline form is a hydrate, preferably selected from the group consisting of monohydrate, hemi-hydrate, dihydrate, trihydrate, and mixtures thereof. In some preferred embodiments, the crystalline form is a trihydrate. In another preferred embodiment the hydrate is a variable or non-stoichiometric hydrate. In another preferred

35   embodiment the alcohol solvate is a variable or non-stoichiometric alcohol solvate.

In another preferred embodiment, the crystalline form is an alcohol solvate, preferably selected from the group consisting of methanol, ethanol or propanolate (1-propanol or 2-propanol) solvates, and the mixtures thereof, the 1-methanol solvate being particularly

40   preferred.

5   In a further preferred embodiment of the invention, the crystalline form is one which has

A: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.7 ±0.2 (2Θ), 11.9 ±0.2 (2Θ), 18.3 ±0.2 (2Θ), and 27.1 ±0.2 (2Θ) and/or one or more Raman peaks selected from the group consisting of at

10   1606 ±2 cm^{-1}, 1175 ±2 cm^{-1}, 1568 ±2 cm^{-1}, 1574 ±2 cm^{-1} and 1650 ±2 cm^{-1}; or

B: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of at 6.8 ±0.2 (2Θ), 12.1 ±0.2 (2Θ), 18.7 ±0.2 (2Θ), and 28,3 ±0.2 (2Θ); and/or one or more Raman peaks selected from the group consisting of at 1643

15   ±2 cm^{-1} and 1578 ±2 cm^{-1}; or

C: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 9.7 ±0.2 (2Θ), 11.6 ±0.2 (2Θ), 14.0 ±0.2 (2Θ), and 17.9 ±0.2 (2Θ); or

20

D: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.7 ±0.2 (2Θ), 11.6 ±0.2 (2Θ), 16.6 ±0.2 (2Θ), and 21.2 ±0.2 (2Θ); and/or one or more Raman peaks selected from the group consisting of 1612 ±2 cm^{-1} and 1199 cm^{-1}±2 cm^{-1}; or

25

E: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 6.9 ±0.2 (2Θ), 8.1 ±0.2 (2Θ), 18.3 ±0.2 (2Θ) and 20.8 ±0.2 (2Θ); or

30   F: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.7 ±0.2 (2Θ), 12.5 ±0.2 (2Θ), 20.9 ±0.2 (2Θ); or

G: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 6.6 ±0.2 (2Θ), 8.0 ±0.2 (2Θ), 18.0 ±0.2 (2Θ), and 18.9 ±0.2

35   (2Θ);

H: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 8.0 ±0.2 (2Θ), 18.2 ±0.2 (2Θ), and 28.3 ±0.2 (2Θ);; or

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I: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 11.8 ±0.2 (2Θ), 17.6 ±0.2 (2Θ) and 19.6 ±0.2 (2Θ); or

J: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 11.1 ±0.2 (2Θ), 14.5 ±0.2 (2Θ), and 19.7 ±0.2 (2Θ); or

K: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 10.0 ±0.2 (2Θ), 14.3 ±0.2 (2Θ), and 19.5 ±0.2 (2Θ); or

L: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.1 ±0.2 (2Θ), 12.0 ±0.2 (2Θ), 17.1 ±0.2 (2Θ), and 20.1 ±0.2 (2Θ); or

Q: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.2 ±0.2 (2Θ), 8.6 ±0.2 (2Θ), 17.2 ±0.2 (2Θ), and 24.4 ±0.2 (2Θ).

In a preferred embodiment of the invention, the crystalline form A exhibits in DSC analysis an endothermal event with an onset temperature in the range of 227 °C to 247°C, preferably 240 °C to 245 °C and/or a peak temperature in the range of 235 °C to 255°C, preferably 245 °C to 250 °C.

In another preferred embodiment of the invention, crystalline form A has X-ray powder diffraction peaks (CuKα radiation) of 8.7 ±0.2 (2Θ), 11.9 ±0.2 (2Θ), 18.3 ±0.2 (2Θ), and optionally 27.1 ±0.2 (2Θ).

In a further preferred embodiment of the invention the crystalline form has X-ray powder diffraction peaks (CuKα radiation) at 7.7 ±0.2 (2Θ) and/or 17.4 ±0.2 (2Θ) and/or 18.3 ±0.2 (2Θ) and at least one additional X-ray peak selected from 10.0 ±0.2 (2Θ), 15.3 ±0.2 (2Θ),15.8 ±0.2 (2Θ), 21.9 ±0.2 (2Θ), 22.2 ±0.2 (2Θ) and 27.1 ±0.2 (2Θ).

In still further preferred embodiments, the crystalline form has X-ray powder diffraction peaks (CuKα radiation) at 8.7 ±0.2 (2Θ) and 17.4 ±0.2 (2Θ) and at least one additional peak selected from the group of 10.0 ±0.2 (2Θ), 16.7 ±0.2 (2Θ), 26.2 ±0.2 (2Θ), and 27.1 ±0.2 (2Θ).

In another preferred embodiment of the invention crystalline form B exhibits in DSC analysis an endothermal event with a peak temperature in the range of 80°C to 110°C and/or an exothermal event with a peak temperature in the range of 204°C to 231°C.

5   In a further preferred embodiment of the invention crystalline form B has X-ray powder diffraction peaks (CuKα radiation) at 6.8 ±0.2 (2Θ), 12.1 ±0.2 (2Θ), 28,3 ±0.2 (2Θ), and optionally at 18,7 ±0.2 (2Θ).

It has been surprisingly found that some crystalline forms of cis-(E)-4-(3-Fluorophenyl)-
10   2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine disclosed herein have surprisingly higher stability than other forms, as is demonstrated in the examples. For instance, crystalline form A achieves significantly and surprisingly higher stability, e.g. physical and/or chemical stability than other crystalline forms.

15   The stability is important. By using the most stable modification in a medicament it may specifically be ensured that, during storage, no crystalline conversion or polymorphic conversion of the active ingredient in the pharmaceutical formulation takes place. This is advantageous, because otherwise the properties of the medicament could change as a consequence of a conversion of a less stable modification into a more stable modification. In
20   relation to the pharmacological properties of an administration form, this could lead for example to the solubility of the active ingredient changing, accompanied by a change in the release characteristics and thus also a change in the bioavailability. Lastly, this could result in inadequate storage stability of the medicament.

It has been surprisingly found that crystalline form A combines this important property for the
25   use in the formulation of dosage forms with the favorable property that it exists as an ansolvate. This is important because ansolvates represent the crystalline form of a compound which has the lowest weight per mol for that compound, thereby reducing the mass of compound required to achieve a certain dosage in a dosage form, such as a tablet, compared to crystalline forms which bind or cooperate residual solvent.

30   Suprisingly, it has also been found that of the four crystalline ansolvate forms (A, D, E and H) found, that crystalline form A is the only form of these which shows no tendency to transform into another crystalline form when heated up to its melting point, which lies in the range of about 243-250°C. The relatively high melting point is an additional advantage of crystalline form A. It has furthermore been surprisingly found that crystalline form A exhibits a higher
35   physical and/or chemical stability compared to crystalline ansolvate forms D and E during storage at selected storage conditions, i.e. elevated temperatures and/or high relative humidity. Additionally, crystalline form A was surprisingly found to be chemical more stable during storage at selected storage conditions in mixture with selected pharmaceutical excipients. Details of the properties of crystalline form A and of the other forms according the
40   invention will be discussed in greater detail in the examples below

5   A further aspect of the invention relates to a process for obtaining a crystalline form of cis-
       (E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
       spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine, comprising the steps of

       (a-1)   suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-
10   phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine in a
               solvent;

       (b-1)   separating, preferably filtering off the solid obtained in step (a-1); and

15   (c-1)   drying of the solid obtained in step (b-1).

       A further aspect of the present invention relates to a crystalline form A.

       Preferably, the crystalline form A according to the invention has one or more X-ray powder
20   diffraction peaks selected from the group consisting of about 8.7 ±0.2 (2Θ), about 11.9 ±0.2
       (2Θ), about 18.3 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ). In a further embodiment the group of
       X-ray powder diffraction peaks further comprises a peak at about 27.1 ±0.2 (2Θ).
       In some preferred embodiments, the crystalline form has an X-ray powder diffraction peak of
       about 17.8 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray
25   powder diffraction peaks of about 17.8 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ) and/or about 27.1
       ±0.2 (2Θ).

       In some preferred embodiments, crystalline form A comprises X-ray powder diffraction peaks
       of about 18.3 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ). In further preferred
30   embodiments, crystalline form A may further comprise X-ray powder diffraction peaks of
       about 17.4 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), 21.9 ±0.2 (2Θ) and about 16.7 ±0.2 (2Θ).

       In some preferred embodiments, crystalline form A comprises X-ray powder diffraction peaks
       of about 11.9 ±0.2 (2Θ), about 17,8 ±0.2 (2Θ),   about 17,4 ±0.2 (2Θ) and about 18.3 ±0.2
35   (2Θ). Optionally, X-ray powder diffraction peaks of about 15.3 ±0.2 (2Θ), about 21.9 ±0.2
       (2Θ), about 16.7 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ) are comprised.
       In another preferred embodiment the crystalline form A according to the invention has one or
       more X-ray powder diffraction peaks selected from the group consisting of about 8.7 ±0.2
       (2Θ), about 11.9 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ) and optionally
40   one or more peaks selected from about 15.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 16.7
       ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

5   In further preferred embodiments, crystalline form A comprises X-ray powder diffraction peaks of about 11.9 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ) and about 18.3 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 27.1 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about about 21.9 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), and about

10   19.7 ±0.2 (2Θ) may be comprised, either in addition to the peak of about 27.1 ±02 (2Θ) or alternatively.

In further preferred embodiments, crystalline form A comprises X-ray powder diffraction peaks of about 8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ), about 15.3 ±0.2

15   (2Θ), about 15.8 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), about 19.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ). Optionally, crystalline form A may further comprise one or more X-ray peaks selected from the group consisting of about 7.7 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ) and about 26.2 ±0.2 (2Θ). In further preferred

20   embodiments, crystalline form A additionally comprises all of the aforementioned optional X-ray peaks.

Although in the X-ray diffractogram of crystalline form A of (E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-

25   b]indole]-4-amine measured using CuKa radiation having a wavelength of 1.54060 Å the five peaks with the highest relative intensity were found to be about 11.9 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ) and about 18.3 ±0.2 (2Θ), in order to discriminate between form A and crystalline forms D, E and H it might be more advantageous to alternatively or additionally look at unique peaks in the X-ray diffractogram,

30   i.e. peaks of sufficient relative intensity at 2Θ-values where forms D, E and H do not show lines with significant intensity. Such characteristic X-ray peaks are besides those of about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ) and about 18.3 ±0.2 (2Θ) X-ray peaks of about 7.7±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

35   Consequently, in some preferred embodiments of the invention crystalline form A comprises at least one X-ray peak selected from the group consisting of about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ) and about 18.3 ±0.2 (2Θ) and at least one additional X-ray peak selected from about 7.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

5   Similarly, the X-ray peaks about 16.7 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ) might be more advantageously used to discriminate between crystalline form A and crystalline forms B, C, F and G. Consequently, in some embodiments of the invention crystalline form A comprises at least one X-ray peak at about 17.4 ±0.2 (2Θ) in combination with at least one X-ray peak selected from about 16.7

10   ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ).

Similarly, the X-ray powder diffraction peaks of about 7.7 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ) might be more advantageously used to discriminate form A from forms F, I, J, K and L.

15   Consequently, in some preferred embodiments crystalline form A comprises X-ray powder diffraction peaks of about 18.3 ±0.2 (2Θ) and about 21.7 ±0.2 (2Θ) and at least one additional peak selected from the group consisting of about 7.7 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), and about 26.2 ±0.2 (2Θ).

20   To discriminate between crystalline form A and crystalline B it might be more advantageous to use the X-ray powder diffraction peaks of about 8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ). Consequently, in some preferred embodiments of the invention crystalline form A comprises an X-ray peak at about 17.4 ±0.2 (2Θ) and at least one additional peak selected from the

25   group of about 8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ).

To discriminate between crystalline form A and crystalline form C the X-ray peaks of about 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 16.7

30   ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 19.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises the X-ray peak at about 17.4 ±0.2 (2Θ) and at least one additional peak selected from the group consisting of about 15.3 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 20.3 ±0.2

35   (2Θ) and about 27.1 ±0.2 (2Θ). Optionally, one or more X-ray peaks selected from the group consisting of about 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 19.7 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), and about 22.5 ±0.2 (2Θ).

To discriminate between crystalline form A and crystalline form D the X-ray peaks of about

40   7.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 17.8

5   ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), and about 21.9 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises at least one of the X-ray peaks selected from at about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ) and about 18.3 ±0.2 (2Θ) and at least one additional X-ray peak selected from the group consisting of about 7.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), and

10   about 21.9 ±0.2 (2Θ).

In order to discriminate between crystalline form A and crystalline form E it might be more advantageous not to rely on the the X-ray peak of about 18.3 ±0.2 (2Θ), because both polymorphic form A and E show an X-ray peak of high intensity in this area. Consequently, in

15   a preferred embodiment of the invention, form A comprises at least one X-ray peak selected about 11.9 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), and about 17.8 ±0.2 (2Θ), and at least one X-ray peak selected from the group consisting of about 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 19.7 ±0.2

20   (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

To discriminate between crystalline form A and crystalline form F, the X-ray peaks of about 7.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about   15.8

25   ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ), about 19.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises at least one X-ray peak selected from about 11.9 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), and about 17.8 ±0.2 (2Θ) and at least one additional peak selected

30   from the group consisting of about 7.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 19.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

To discriminate between crystalline form A and crystalline form G, the X-ray peaks of about

35   7.7 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises at least one or more X-ray powder diffraction peaks selected from the group consisting of about 11.9 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8

40   ±0.2 (2Θ) and about 18.3 ±0.2 and at least one additional peak selected from the group

5   consisting of about 7.7 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

To discriminate between crystalline form A and crystalline form H, the X-ray peaks of about
10   7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises at least one or more X-ray powder diffraction peaks selected from the group consisting of about 11.9 ±0.2
15   (2Θ) and about 15.3 ±0.2 (2Θ) and at least one additional peak selected from the group consisting of about 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 26.2 ±0.2 (2Θ) and about 27.1 ±0.2 (2Θ).

20   To discriminate between crystalline form A and crystalline form I, the X-ray peaks of about 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises at least one or more X-ray powder diffraction peaks selected from the group consisting of about 11.9 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ),
25   about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ) and about 18.3 ±0.2 (2Θ), and at least one additional peak selected from the group consisting of about 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 20.3 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ).

To discriminate between crystalline form A and crystalline form J, the X-ray peaks of about
30   7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, form A comprises at least one or more X-ray powder diffraction peaks selected from the group consisting of about 11.9 ±0.2 (2Θ) and 15.8 ±0.2 (2Θ), and at least one
35   additional peak selected from the group consisting of 7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), about 22.2 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ)

To discriminate between crystalline form A and crystalline form K, the X-ray peaks of about
40   7.7 ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 11.9 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 17.4

5   ±0.2 (2Θ), about 17.8 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), and about 26.2
       ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of
       the invention, form A comprises at least one or more X-ray powder diffraction peaks selected
       from the group consisting of 11.9 ±0.2 (2Θ), about 17.4 ±0.2 (2Θ), about 17.8 ±0.2 (2Θ) and
       about 18.3 ±0.2 and at least one additional peak selected from the group consisting of 7.7
10   ±0.2 (2Θ), about 8.7 ±0.2 (2Θ), about 12.3 ±0.2 (2Θ), about 21.9 ±0.2 (2Θ), and about 26.2
       ±0.2 (2Θ).

       To discriminate between crystalline form A and crystalline form L, the X-ray peaks of about
       8.7 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 15.3 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 22.5
15   ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ) might be more advantageously used. Consequently, in a
       preferred embodiment of the invention, form A comprises an X-ray peak of about 15.3 ±0.2
       and at least one additional peak selected from the group consisting of 8.7 ±0.2 (2Θ), about
       10.0 ±0.2 (2Θ), about 15.8 ±0.2 (2Θ), about 22.5 ±0.2 (2Θ), and about 27.1 ±0.2 (2Θ).

20   Crystalline form A according to the invention may further be characterized that it has a
       Raman peak at about 1606 cm⁻¹ and/or at least one Raman peak selected from the group of
       about 1175 cm⁻¹, about 1568 cm⁻¹, about 1574 cm⁻¹ and about 1650 cm⁻¹.
       Crystalline form A according to the invention may further be characterized that it has a
       Raman peak at about 1606 cm⁻¹ and/or at least one Raman peak selected from the group of
25   about 1175 cm⁻¹, about 1568 cm⁻¹, about 1574 cm⁻¹ and about 1650 cm⁻¹ and/or at least one
       Raman peak selected from the group of about 98 cm⁻¹ and about 1001 cm⁻¹. Additionally, it
       may have at least one Raman peak selected from the group consisting of about 128 cm⁻¹,
       about 170 cm⁻¹, about 676 cm⁻¹, about 1183 cm⁻¹, about 1204 cm⁻¹, about 1268 cm⁻¹, about
       1294 cm⁻¹, about 1447 cm⁻¹, about 1462 cm⁻¹, about 1584 cm⁻¹, about 2910 cm⁻¹, about 3062
30   cm⁻¹, and about 3075 cm⁻¹. Also additionally, crystalline form A may have at least one Raman
       peak selected from the group consisting of about 189 cm⁻¹, about 227 cm⁻¹, about 272 cm⁻¹,
       about 310 cm⁻¹, about 355 cm⁻¹, about 417 cm⁻¹, about 461 cm⁻¹, about 485 cm⁻¹, about 509
       cm⁻¹, about 543 cm⁻¹, about 589 cm⁻¹, about 611 cm⁻¹, about 620 cm⁻¹, about 644 cm⁻¹, about
       697 cm⁻¹, about 725 cm⁻¹, about 746 cm⁻¹, about 783 cm⁻¹, about 801 cm⁻¹, about 831 cm⁻¹,
35   about 865 cm⁻¹, about 893 cm⁻¹, about 927 cm⁻¹, about 955 cm⁻¹, about 978 cm⁻¹, about 1012
       cm⁻¹, about 1028 cm⁻¹, about 1048 cm⁻¹, about 1074 cm⁻¹, about 1111 cm⁻¹, about 1155 cm⁻¹,
       about 1244 cm⁻¹, about 1343 cm⁻¹, about 1368 cm⁻¹, about 1385 cm⁻¹, about 1407 cm⁻¹, about
       1493 cm⁻¹, about 2782 cm⁻¹, about 2834 cm⁻¹, about 2878 cm⁻¹, about 2946 cm⁻¹, about 2960
       cm⁻¹, about 2980 cm⁻¹, about 2999 cm⁻¹, about 3026 cm⁻¹ and about 3449 cm⁻¹.
40

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5   In DSC analyses, crystalline form A according to the present invention preferably exhibits an
endothermal event with a peak temperature of about 235-255 °C (i.e. the crystalline form has
a melting endotherm at about 235-255 °C), more preferably of about 237-250 °C, still more
preferably of about 240-248 °C. In some preferred embodiments crystalline form A exhibits
an endothermal event with a peak temperature of about 242-248 °C.

10

A further aspect of the present invention relates to a crystalline form B

Preferably, the crystalline form B according to the invention has one or more X-ray powder
diffraction peaks selected from the group consisting of about 6.8 ±0.2 (2Θ), about 12.1 ±0.2

15   (2Θ), about 18.7 ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ).
In a further embodiment the group of X-ray powder diffraction peaks further comprises a
peak at about 28.3 ±0.2 (2Θ). In some preferred embodiments, the crystalline form has an X-
ray powder diffraction peak of about 12.1 ±0.2 (2Θ). In some preferred embodiments the
crystalline form comprises X-ray powder diffraction peaks of about 12.1 ±0.2 (2Θ), about 18.7

20   ±0.2 (2Θ) and/or about 28.3 ±0.2 (2Θ).

In some preferred embodiments, crystalline form B comprises X-ray powder diffraction peaks
of about 12.1 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ) and about 18.7 ±0.2 (2Θ), and optionally, a
further peak at about 28.3 ±0.2 (2Θ). In further preferred embodiments, crystalline form B

25   may further comprise X-ray powder diffraction peaks of about 6.8 ±0.2 (2Θ), about 18.4 ±0.2
(2Θ), about 19.8 ±0.2 (2Θ).

Although in the X-ray diffractogram of crystalline form B of cis-(E)-4-(3-Fluorophenyl)-
2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-

30   pyrido[3,4-b]indol]-4-amine measured using CuKa radiation having a wavelength of 1.54060
Å the five peaks with the highest relative intensity were found to be about 12.1 ±0.2 (2Θ),
about 18.0 ±0.2 (2Θ) and about 18.7 ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), and about 19.8 ±0.2
(2Θ), in order to discriminate this form over crystalline forms A, D, E and H it might be more
advantageous to alternatively or additionally look at unique peaks in the X-ray diffractogram,

35   i.e. peaks of sufficient relative intensity at 2Θ-values where forms A, D, E and H do not show
lines with significant intensity. Such characteristic X-ray peaks are those of about 13.7 ±0.2
(2Θ) and about 14.2 ±0.2 (2Θ).
Consequently, in some preferred embodiments of the invention crystalline form B comprises
at least one X-ray peak selected from about 13.7 ±0.2 (2Θ) and about 14.2 ±0.2 (2Θ).

5   Similarly, the X-ray peaks of about 12.1 ±0.2 (2Θ), about 15.5 ±0.2 (2Θ), about 19.8 ±0.2 (2Θ), about 22.1 ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ) might be more advantageously used to discriminate crystalline form B over crystalline forms C, F and G. Consequently, in some embodiments of the invention crystalline form B comprises at least one X-ray peak selected from the peaks of about 12.1 ±0.2 (2Θ) and about 19.8 ±0.2 (2Θ) in combination with at least

10   one X-ray peak selected from the group of peaks consisting of about 15.5 ±0.2 (2Θ), about 22.1 ±0.2 (2Θ) and about 28.3 ±0.2 (2Θ).

To discriminate between crystalline form B and crystalline form A the X-ray peaks of about 6.8 ±0.2 (2Θ), about 13.7 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ), about 18.7 ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred

15   embodiment of the invention, form B comprises the X-ray peak at about 18.7 ±0.2 (2Θ) in combination with one or more X-ray peaks from the group consisting of about 6.8 ±0.2 (2Θ), about 13.7 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ) and about 28.3 ±0.2 (2Θ).

In some preferred embodiments, crystalline form B comprises X-ray powder diffraction peaks

20   of about 12.1 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), and about 18.7 ±0.2 (2Θ). Optionally, X-ray powder diffraction peaks of about 6.8 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ), about 19.8 ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ), are comprised.

In further preferred embodiments, the crystalline form B according to the invention comprises the X-ray powder diffraction peaks of about 6.8 ±0.2 (2Θ), about 12.1 ±0.2 (2Θ), about 18.7

25   ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ), optionally with one or more additional peaks selected from about 14.2 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), about 19.8 ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ).

In further preferred embodiments, crystalline form B comprises X-ray powder diffraction peaks of about 12.1 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), about 18.7 ±0.2

30   (2Θ), and about 19.8 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 28.3 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 6.8 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ), about 20.8 ±0.2 (2Θ), and about 15.6 ±0.2 (2Θ) may be comprised, either in addition to the peak of about 28.3 ±02 (2Θ) or alternatively. Optionally, in some preferred embodiments, crystalline form B comprises at

35   least one additional X-ray powder diffraction peak selected from of about 7,4 ±0.2 (2Θ), about 22.1 ±0.2 (2Θ) and about 13,7 ±0.2 (2Θ). In preferred embodiments, crystalline form A comprises all of the aforementioned optional additional X-ray peaks.

5   Crystalline form B according to the invention may further be characterized that it has a Raman peak at about 1643 cm^{-1} and/or one Raman peak at about 1578 cm^{-1}.

Crystalline form B according to the invention may further be characterized that it has a Raman peak at about 1643 cm^{-1} and/or one Raman peak at about 1578 cm^{-1} and/or one peak selected from the group of about 1601 cm^{-1}, about 84 cm^{-1}, about 109 cm^{-1}, about 1001

10   cm^{-1}, about 1618 cm^{-1}, about 1563 cm^{-1}, about 1643 cm^{-1}, and about 3063 cm^{-1}.

Additionally, crystalline form B may have one or more Raman peaks selected from the group consisting of about 166 cm^{-1}, about 220 cm^{-1}, about 272 cm^{-1}, about 619 cm^{-1}, about 676 cm^{-1}, about 781 cm^{-1}, about 862 cm^{-1}, about 888 cm^{-1}, about 976 cm^{-1}, about 1010 cm^{-1}, about 1029 cm^{-1}, about 1047 cm^{-1}, about 1158 cm^{-1}, about 1180 cm^{-1}, about 1203 cm^{-1}, about 1266

15   cm^{-1}, about 1300 cm^{-1}, about 1441 cm^{-1}, about 1449 cm^{-1}, about 1465 cm^{-1}, about 1578 cm^{-1}, about 2935 cm^{-1}, about 2967 cm^{-1} and about 3001 cm^{-1}.

Also additionally, crystalline form B may have one or more Raman peaks selected from the group consisting of about 333 cm^{-1}, about 365 cm^{-1}, about 387 cm^{-1}, about 405 cm^{-1}, about 435 cm^{-1}, about 463 cm^{-1}, about 505 cm^{-1}, about 541 cm^{-1}, about 590 cm^{-1}, about 643 cm^{-1},

20   about 725 cm^{-1}, about 745 cm^{-1}, about 802 cm^{-1}, about 834 cm^{-1}, about 929 cm^{-1}, about 1087 cm^{-1}, about 1112 cm^{-1}, about 1326 cm^{-1}, about 1341 cm^{-1}, about 1373 cm^{-1}, about 1405 cm^{-1}, about 1861 cm^{-1}, about 2136 cm^{-1}, about 2172 cm^{-1}, about 2328 cm^{-1}, about 2489 cm^{-1}, about 2519 cm^{-1}, about 2558 cm^{-1}, about 2772 cm^{-1}, about 2794 cm^{-1}, about 2843 cm^{-1}, about 2890 cm^{-1}, about 3153 cm^{-1}, about 3197 cm^{-1}, about 3243 cm^{-1}, about 3323 cm^{-1} and about 3459

25   cm^{-1}.

In DSC analyses, crystalline form B according to the present invention preferably exhibits an endothermal event with a peak temperature of about 80-110 °C, preferably of about 80-95°C, and/or an endothermal event with a peak temperature of about 230 to 255, preferably of

30   about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form B exhibits an endothermal event with a peak temperature of about 242-248 °C. Additionally, crystalline form B preferably exhibits an exothermal event with a peak temperature of about 140-150 °C, preferably 142 to 148 °C, more preferably 143-147 °C, and/or an exothermal event with a peak temperature of about 200-230 °C, preferably about

35   205-230 °C.

A further aspect of the present invention relates to a crystalline form C.

Preferably, the crystalline form C according to the invention has one or more X-ray powder

40   diffraction peaks selected from the group consisting of about 9.7 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), about 14.0 ±0.2 (2Θ), and about 17.9 ±0.2 (2Θ).

5   In some preferred embodiments, the crystalline form C has an X-ray powder diffraction peak
      of about 17.9 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray
      powder diffraction peaks of about 17.9 ±0.2 (2Θ), about 14.0 ±0.2 (2Θ) and/or about 13.0
      ±0.2 (2Θ).

10   In some preferred embodiments, crystalline form C comprises X-ray powder diffraction peaks
      of 17.9 ±0.2 (2Θ), about 14.0 ±0.2 (2Θ) and about 13.0 ±0.2 (2Θ). In further preferred
      embodiments, crystalline form C may further comprise X-ray powder diffraction peaks of
      about 7.1 ±0.2 (2Θ), about 9.7 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), and about 12.5 ±0.2 (2Θ).

15   To discriminate between crystalline form C and crystalline form A of cis-(E)-4-(3-
      Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
      spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine it might be more advantageous to
      alternatively or additionally look at unique peaks in the X-ray diffraction diagram of C
      compared to the X-ray diffraction diagram of A. Such characteristic X-ray peaks are besides
20   those of about 9.7 ±0.2 (2Θ), about 13.0 ±0.2 (2Θ), and about 14.0 ±0.2 (2Θ) X-ray peaks of
      about 7.0 ±0.2 (2Θ), about 7.1 ±0.2 (2Θ), at about 11.3 ±0.2 (2Θ), at about 14.3 ±0.2 (2Θ), at
      about 21 ±0.2 (2Θ) and at about 21.1 ±0.2 (2Θ).
      Consequently, in some preferred embodiments of the invention crystalline form C comprises
      at least one X-ray peak selected from the group consisting of about 9.7 ±0.2 (2Θ), about 13.0
25   ±0.2 (2Θ), and about 14.0 ±0.2 (2Θ) and at least one additional X-ray peak selected from
      about 7.0 ±0.2 (2Θ), about 7.1 ±0.2 (2Θ), at about 11.3 ±0.2 (2Θ), at about 14.3 ±0.2 (2Θ), at
      about 21 ±0.2 (2Θ) and at about 21.1 ±0.2 (2Θ).

      In some preferred embodiments, crystalline form C comprises X-ray powder diffraction peaks
30   of about 17.9 ±0.2 (2Θ), about 14.0 ±0.2 (2Θ), about 13.0 ±0.2 (2Θ) and about 11.6 ±0.2
      (2Θ). Optionally, X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), of about 9.7 ±0.2
      (2Θ), about 12.5 ±0.2 (2Θ) and of about 14.3 ±0.2 (2Θ) are further comprised.
      In further preferred embodiments, the crystalline form C according to the invention comprises
      X-ray powder diffraction peaks at about 9.7 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), about 14.0 ±0.2
35   (2Θ), and about 17.9 ±0.2 (2Θ) and optionally one or more peaks selected from the group
      consisting of about 7.1 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ), of about 13.0 ±0.2 (2Θ) and of about
      14.3 ±0.2 (2Θ).
      In further preferred embodiments, crystalline form C comprises X-ray powder diffraction
      peaks of about 17.9 ±0.2 (2Θ), about 14.0 ±0.2 (2Θ), 13.0 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ)
40   and about 9.7 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 12.5

±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 11.3 ±0.2 (2Θ), and about 14.3 ±0.2 (2Θ) may be comprised, either in addition to the peak of about 12.5 ±02 (2Θ) or alternatively.

In further preferred embodiments, crystalline form C comprises X-ray powder diffraction peaks of about 7.0 ±0.2 (2Θ), about 7.1 ±0.2 (2Θ), about 9.7 ±0.2 (2Θ), about 11.3 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ), about 13.0 ±0.2 (2Θ), about 14.0 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ), about 17.9 ±0.2 (2Θ), and about 21.0 ±0.2 (2Θ). Optionally, crystalline form C may further comprise one or more X-ray peaks selected from the group consisting of about 21.1 ±0.2 (2Θ) and/or about 26.3. In some preferred embodiments, crystalline form C additionally comprises all of the aforementioned optional X-ray peaks.

In DSC analyses, crystalline form C according to the present invention preferably exhibits an endothermal event with a peak temperature of about 60-150 °C, preferably of about 100-150°C, more preferably of about 120-150 °C, and/or an endothermal event with a peak temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form B exhibits an endothermal event with a peak temperature of about 242-248 °C. Additionally, crystalline form C preferably exhibits an exothermal event with a peak temperature of about 175-220 °C, preferably 175-215 °C, more preferably 175-210 °C.

A further aspect of the present invention relates to a crystalline form D.

Preferably, the crystalline form D according to the invention has one or more X-ray powder diffraction peaks selected from the group consisting of about 8.7 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ), about and 21.2 ±0.2 (2Θ).

In some preferred embodiments, the crystalline form D has an X-ray powder diffraction peak of about 8.7 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray powder diffraction peaks of about 8.7 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ) and/or about 21.2 ±0.2 (2Θ).

In some preferred embodiments, crystalline form D comprises X-ray powder diffraction peaks of about 8.7 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ) and about 21.2 ±0.2 (2Θ). In further preferred embodiments, crystalline form D may further comprise X-ray powder diffraction peaks of about 17.2 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), about 20.0 ±0.2 (2Θ) and about 11.0 ±0.2 (2Θ).

5   To discriminate between crystalline form D and crystalline form A of cis-(E)-4-(3-
Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine it might be more advantageous to
alternatively or additionally look at unique peaks in the X-ray diffraction diagram of D
compared to the X-ray diffraction diagram of A. Such a characteristic X-ray peak is the one of

10   about 21.2 ±0.2 (2Θ).

Consequently, in some preferred embodiments of the invention crystalline form D comprises
at least one X-ray peak selected from the group consisting of about 8.7 ±0.2 (2Θ), about 11.6
±0.2 (2Θ), about 16.6 ±0.2 (2Θ), about 17.2 ±0.2 (2Θ), and the additional X-ray peak of about
and about 21.2 ±0.2 (2Θ).

15

In some preferred embodiments, crystalline form D comprises X-ray powder diffraction peaks
of about 8.7 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ), about 17.2 ±0.2 (2Θ) and about 21.2 ±0.2 (2Θ).
Optionally, X-ray powder diffraction peaks of about 11.6 ±0.2 (2Θ), about 20.0 ±0.2 (2Θ),
about 11.0 ±0.2 (2Θ), and about 17.6 ±0.2 (2Θ) may be further comprised.

20   In further preferred embodiments, crystalline form D comprises X-ray powder diffraction
peaks of about 8.7 ±0.2 (2Θ), about 11.6 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ), about and 21.2
±0.2 (2Θ) and optionally, X-ray powder diffraction peaks of about 11.0 ±0.2 (2Θ), about 17.2
±0.2 (2Θ), about 17.6 ±0.2 (2Θ), and about 20.0 ±0.2 (2Θ) may be further comprised.

25   In further preferred embodiments, crystalline form D comprises X-ray powder diffraction
peaks of about 8.7 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ), about 21.2 ±0.2 (2Θ), about 17.2 ±0.2
(2Θ)and about 11.6 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of
about 20.0 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction
peaks of about 11.0 ±0.2 (2Θ), about 17.6 ±0.2 (2Θ), and/or about 18.2 ±0.2 (2Θ) and/or

30   about 22.7 ±0.2 (2Θ) and/or about 11.3 ±0.2 (2Θ) and/or about 12.5 ±0.2 (2Θ) and/or about
26.4.2 ±0.2 (2Θ) may be comprised, either in addition to the peak of about 20.0 ±02 (2Θ) or
alternatively.

Crystalline form D according to the invention may further be characterized that it has a

35   Raman peak at about 1612 cm^{-1} and/or one Raman peak at about 1199 cm^{-1}.
Crystalline form D according to the invention may further be characterized that it has a
Raman peak at about 1612 cm^{-1} and/or one Raman peak at about 1199 cm^{-1} and/or one
peak selected from the group of about 84 cm^{-1}, about 121 cm^{-1}, about 158 cm^{-1}, about 1000
cm^{-1}, about 1563 cm^{-1}, and about 1599 cm^{-1}.

5   Additionally, crystalline form D may have one or more Raman peaks selected from the group consisting of about 237 cm^{-1}, about 268 cm^{-1}, about 294 cm^{-1}, about 335 cm^{-1}, about 372 cm^{-1}, about 402 cm^{-1}, about 434 cm^{-1}, about 466 cm^{-1}, about 489 cm^{-1}, about 503 cm^{-1}, about 542 cm^{-1}, about 618 cm^{-1}, about 675 cm^{-1}, about 782 cm^{-1}, about 886 cm^{-1}, about 1011 cm^{-1}, about 1030 cm^{-1}, about 1056 cm^{-1}, about 1154 cm^{-1}, about 1171 cm^{-1}, about 1199 cm^{-1}, about

10   1263 cm^{-1}, about 1289 cm^{-1}, about 1325 cm^{-1}, about 1447 cm^{-1}, about 1464 cm^{-1}, about 1576 cm^{-1}, about 1644 cm^{-1}, about 2946 cm^{-1}, about 2980 cm^{-1}, about 3010 cm^{-1} and about 3065 cm^{-1}.

Also additionally, crystalline form D may have one or more Raman peaks of about 579 cm^{-1}, about 646 cm^{-1}, about 696 cm^{-1}, about 711 cm^{-1}, about 727 cm^{-1}, about 799 cm^{-1}, about 834

15   cm^{-1}, about 867 cm^{-1}, about 921 cm^{-1}, about 970 cm^{-1}, about 1085 cm^{-1}, about 1115 cm^{-1}, about 1343 cm^{-1}, about 1377 cm^{-1}, about 1406 cm^{-1}, about 2792 cm^{-1}, about 2846 cm^{-1}, about 2895 cm^{-1}, about 3152 and about 3196 cm^{-1}.

In DSC analyses, crystalline form D according to the present invention preferably exhibits an

20   endothermal event with a peak temperature of about 140-180 °C, preferably of about 145-170°C, more preferably of about 145-165 °C, and/or an endothermal event with a peak temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form B exhibits an endothermal event with a peak temperature of about 242-248 °C. Additionally, crystalline form D

25   preferably exhibits an exothermal event with a peak temperature of about 200-230 °C, preferably 205-225 °C.

A further aspect of the present invention relates to a crystalline form E.

30   Preferably, the crystalline form E according to the invention has one or more X-ray powder diffraction peaks selected from the group consisting of about 6.9 ±0.2 (2Θ), about 8.1 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), and about 20.8 ±0.2 (2Θ).

In some preferred embodiments, the crystalline form E has an X-ray powder diffraction peak of about 18.3 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray

35   powder diffraction peaks of about 18.3 ±0.2 (2Θ), about 6.9.0 ±0.2 (2Θ) and/or about 8.1 ±0.2 (2Θ).

In some preferred embodiments, crystalline form E comprises X-ray powder diffraction peaks of about 18.3 ±0.2 (2Θ), about 6.9 ±0.2 (2Θ), and about 8.1 ±0.2 (2Θ). In further preferred

40   embodiments, crystalline form E may further comprise X-ray powder diffraction peaks of about 20.8 ±0.2 (2Θ), about 10.4 ±0.2 (2Θ), and about 13.8 ±0.2 (2Θ).

5

To discriminate between crystalline form E and crystalline form A cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine it might be more advantageous to alternatively or additionally look at unique peaks in the X-ray diffraction diagram of E compared to the X-ray diffraction

10   diagram of A. Such characteristic X-ray peaks are besides those of about 6.9 ±0.2 (2Θ), about 8.1 ±0.2 (2Θ) and about 20.8 ±0.2 (2Θ) X-ray peaks of about 13.7 ±0.2 (2Θ), about 28.1 ±0.2 (2Θ), about 13.9 ±0.2 (2Θ), about 21.1 ±0.2 (2Θ), and about 19.0 ±0.2 (2Θ). Consequently, in some preferred embodiments of the invention crystalline form C comprises at least one X-ray peak selected from the group consisting of about 6.9 ±0.2 (2Θ), about 8.1

15   ±0.2 (2Θ) and about 20.8 ±0.2 (2Θ) and at least one additional X-ray peak selected from about 13.7 ±0.2 (2Θ), about 28.1 ±0.2 (2Θ), about 13.9 ±0.2 (2Θ), about 21.1 ±0.2 (2Θ), and about 19.0 ±0.2 (2Θ).

In some preferred embodiments, crystalline form E comprises X-ray powder diffraction peaks

20   of about 6.9 ±0.2 (2Θ), about 8.1 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ) and about 20.8 ±0.2 (2Θ). Optionally, X-ray powder diffraction peaks of about 10.4 ±0.2 (2Θ), about 13.8 ±0.2 (2Θ), about 28.1 ±0.2 (2Θ), and/or about 13.9 ±0.2 (2Θ) and/or about 17.9 ±0.2 (2Θ) are further comprised.

25   In further preferred embodiments, crystalline form E comprises X-ray powder diffraction peaks of about 6.9 ±0.2 (2Θ), about 8.1 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), about 20.8 ±0.2 (2Θ), and about 10.4 ±0.2 (2Θ). Optionally, and X-ray powder diffraction peak of about 13.8 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 28.1 ±0.2 (2Θ), about 13.9 ±0.2 (2Θ), about 17.9 ±0.2 (2Θ) and about 16.9 ±0.2 (2Θ)

30   may be comprised, either in addition to the peak of about 13.8 ±02 (2Θ) or alternatively.

In further preferred embodiments, crystalline form E comprises X-ray powder diffraction peaks of
about 6.9 ±0.2 (2Θ), about 8.1 ±0.2 (2Θ), about 10.4 ±0.2 (2Θ), about 12.1 ±0.2 (2Θ), about

35   13.8 ±0.2 (2Θ), about 13.9 ±0.2 (2Θ), about 16.4 ±0.2 (2Θ), 16.6 ±0.2 (2Θ), about 16.9 ±0.2 (2Θ), about 17.9 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), about 18.7 ±0.2 (2Θ), about 19.0 ±0.2 (2Θ), about 20.8 ±0.2, about 21.1 ±0.2 (2Θ), about 27.5 ±0.2 (2Θ), and about 28.1 ±0.2 (2Θ).

In DSC analyses, crystalline form E according to the present invention preferably exhibits an

40   endothermal event with a peak temperature of about 135-150 °C, preferably of about 140-

5   150°C, more preferably of about 143-146 °C, and/or an endothermal event with a peak temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form E exhibits an endothermal event with a peak temperature of about 242-248 °C. Additionally, crystalline form E preferably exhibits an exothermal event with a peak temperature of about 190-210 °C,

10   preferably about 197-212 °C.

A further aspect of the present invention relates to a crystalline form F.

Preferably, the crystalline form F according to the invention has one or more X-ray powder

15   diffraction peaks selected from the group consisting of about 8.7 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ), and 20.9 ±0.2 (2Θ).

In some preferred embodiments, the crystalline form F has an X-ray powder diffraction peak of about 12.5 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray

20   powder diffraction peaks of about 8.7 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ) and/or about 20.9 ±0.2 (2Θ).

In some preferred embodiments, crystalline form F comprises X-ray powder diffraction peaks of about 8.7 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ) and about 20.9 ±0.2 (2Θ). In further preferred

25   embodiments, crystalline form F may further comprise one or more X-ray powder diffraction peaks selected from the groups consisting of about 11.3 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 25.2 ±0.2 (2Θ) and about 25.9 ±0.2 (2Θ).

In some preferred embodiments, crystalline form F comprises at least on X-ray powder

30   diffraction peak selected from the group consisting of about 8.7 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ), and about 20.9 ±0.2 (2Θ) and may optionally further comprise at least one X-ray peak selected from the group consisting of 11.3 ±0.2 (2Θ), about 16.7 ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), about 25.2 ±0.2 (2Θ), about 25.9 ±0.2 (2Θ) and about 26.3 ±0.2 (2Θ).

35   To discriminate between crystalline form F and crystalline form A of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine it might be more advantageous to alternatively or additionally look at unique peaks in the X-ray diffraction diagram of F compared to the X-ray diffraction diagram of A. Such characteristic X-ray peaks are those of

40   about 11.3 ±0.2 (2Θ), about 20.9 ±0.2 (2Θ), and about 25.2 ±0.2 (2Θ).

5   Consequently, in some preferred embodiments of the invention crystalline form F comprises
       at least one X-ray peak selected from the group consisting of about 11.3 ±0.2 (2Θ), about
       20.9 ±0.2 (2Θ), and about 25.2 ±0.2 (2Θ), and may optionally comprise one or more X-ray
       peaks selected from the group consisting of 8.7 ±0.2 (2Θ), about 12.5 ±0.2 (2Θ), about 16.7
       ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), about 25.9 ±0.2 (2Θ) and about 26.3 ±0.2 (2Θ).

10

       A further aspect of the present invention relates to a crystalline form G.

       Preferably, the crystalline form G according to the invention has one or more X-ray powder
       diffraction peaks selected from the group consisting of about 6.6 ±0.2 (2Θ), about 8.0 ±0.2

15   (2Θ) about 18.0 ±0.2 (2Θ), and about 18.9 ±0.2 (2Θ).
       In some preferred embodiments, the crystalline form G has an X-ray powder diffraction peak
       of about 6.6 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray
       powder diffraction peaks of about 6.6 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ) and/or about 18.4 ±0.2
       (2Θ).

20

       In some preferred embodiments, crystalline form G comprises X-ray powder diffraction peaks
       of about 6.6 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ) and about 18.4 ±0.2 (2Θ). In further preferred
       embodiments, crystalline form G may further comprise X-ray powder diffraction peaks of
       about 8.0 ±0.2 (2Θ), about 13.9 ±0.2 (2Θ), about 18.8 ±0.2 (2Θ) and about 19.3 ±0.2 (2Θ).

25

       In some preferred embodiments, crystalline form G comprises X-ray powder diffraction peaks
       of about 6.6 ±0.2 (2Θ), about 8.0 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ), and about 18.4 ±0.2 (2Θ).
       Optionally, X-ray powder diffraction peaks of about 13.3 ±0.2 (2Θ), 13.9 ±0.2 (2Θ), about
       18.8 ±0.2 (2Θ), and about 19.3 ±0.2 (2Θ).

30   In further preferred embodiments crystalline form G comprises the X-ray powder diffraction
       peaks (CuKα radiation) of 6.6 ±0.2 (2Θ), 8.0 ±0.2 (2Θ), 18.0 ±0.2 (2Θ), and 18.9 ±0.2 (2Θ)
       and may optionally comprise one or more additional peaks selected from the group
       consisting of about 13.3 ±0.2 (2Θ), 13.9 ±0.2 (2Θ), about 18.4 ±0.2 (2Θ), about 18.8 ±0.2
       (2Θ), and about 19.3 ±0.2 (2Θ)

35

       In further preferred embodiments, crystalline form G comprises X-ray powder diffraction
       peaks of about 6.6 ±0.2 (2Θ), about 8.0 ±0.2 (2Θ), about 18.0 ±0.2 (2Θ), about 18.4 ±0.2
       (2Θ), and about 18.9 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of
       about 19.3 ±0.2 (2Θ) may be comprised. Also optionally, one or more additional X-ray

40   powder diffraction peaks selected from the group consisting of about 7.0 ±0.2 (2Θ), about

5   10.4 ±0.2 (2Θ), about 11.8 ±0.2 (2Θ), about 12.4 ±0.2 (2Θ), about 13.3 ±0.2 (2Θ), about 13.9
       ±0.2 (2Θ), about 15.5 ±0.2 (2Θ), about 15.6 ±0.2 (2Θ), about 17.6 ±0.2 (2Θ), and about 19.7
       ±0.2 (2Θ).

       To discriminate between crystalline form G and crystalline form A of cis-(E)-4-(3-
10   Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
       spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine it might be more advantageous to
       alternatively or additionally look at unique peaks in the X-ray diffraction diagram of G
       compared to the X-ray diffraction diagram of A. Such characteristic X-ray peaks are those of
       about 6.6 ±0.2 (2Θ), about 7.0 ±0.2 (2Θ), about 8.0 ±0.2 (2Θ), about 13.3 ±0.2 (2Θ), about
15   13.9 ±0.2 (2Θ), and about 19.3 ±0.2 (2Θ). Consequently, in some preferred embodiments of
       the invention crystalline form G comprises at least one X-ray peak selected from the group
       consisting of about 6.6 ±0.2 (2Θ), about 8.0 ±0.2 (2Θ), and about 19.3 ±0.2 (2Θ), and
       optionally at least one additional X-ray peak selected from the group consisting of about 7.0
       ±0.2 (2Θ), about 13.3 ±0.2 (2Θ), and about 13.9 ±0.2 (2Θ).

20

       In DSC analyses, crystalline form G according to the present invention preferably exhibits an
       endothermal event with a peak temperature of about 65-150 °C, preferably of about 70-100
       °C, and/or an endothermal event with a peak temperature of about 230 to 255, preferably of
       about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments
25   crystalline form E exhibits an endothermal event with a peak temperature of about 242-248
       °C. Additionally, crystalline form E preferably exhibits an exothermal event with a peak
       temperature of about 200-220 °C, preferably about 204-220 °C.

       A further aspect of the present invention relates to a crystalline form H
30

       Preferably, the crystalline form H according to the invention has one or more X-ray powder
       diffraction peaks selected from the group consisting of about 7.1 ±0.2 (2Θ), about 8.0 ±0.2
       (2Θ), about 18.2 ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ).

35   In some preferred embodiments, the crystalline form H has an X-ray powder diffraction peak
       of about 18.2 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray
       powder diffraction peaks of about 8.0 ±0.2 (2Θ), about 18.2 ±0.2 (2Θ) and/or about 19.7 ±0.2
       (2Θ).

40   In some preferred embodiments, crystalline form H comprises X-ray powder diffraction peaks
       of about 8.0 ±0.2 (2Θ), about 18.2 ±0.2 (2Θ), and about 19.7 ±0.2 (2Θ), and optionally, a

5   further peak of about 18.1 ±0.2 (2Θ). In some preferred embodiments, crystalline form H may optionally further comprise X-ray powder diffraction peaks of about 17.7 ±0.2 (2Θ), about 18.8 ±0.2 (2Θ), and about 19.2 ±0.2 (2Θ).

In some preferred embodiments, crystalline form H comprises X-ray powder diffraction peaks
10   of about 8.0 ±0.2 (2Θ), about 18.1 ±0.2 (2Θ), about 18.2 ±0.2 (2Θ), and about 19.7 ±0.2 (2Θ). Optionally, further X-ray peaks of about 17.7 ±0.2 (2Θ), about 18.8 ±0.2 (2Θ), about 19.2 ±0.2 (2Θ), and about 20.7 ±0.2 (2Θ) may be comprised.

In further preferred embodiments the crystalline form H according to the invention comprises the X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 8.0 ±0.2 (2Θ), about 18.2
15   ±0.2 (2Θ), and about 28.3 ±0.2 (2Θ), and may optionally comprise one or more additional peaks selected from the group consisting of 17.7 ±0.2 (2Θ), about 18.1 ±0.2 (2Θ), about 18.3 ±0.2 (2Θ), about 18.8 ±0.2 (2Θ), about 19.2 ±0.2 (2Θ), about 19.7 ±0.2 (2Θ), and about 20.7 ±0.2 (2Θ).

In further preferred embodiments, crystalline form H comprises X-ray powder diffraction
20   peaks of about 8.0 ±0.2 (2Θ), about 18.1 ±0.2 (2Θ), about 18.2 ±0.2 (2Θ), about 19.2 ±0.2 (2Θ), and about 19.7 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 17.7 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 17.3 ±0.2 (2Θ), about 17.7 ±0.2 (2Θ), about 18.8 ±0.2 (2Θ), and about 20.7 ±0.2 (2Θ), may be comprised, either in addition to the peak of 17.7 ±02
25   (2Θ) or alternatively. Optionally, in some preferred embodiments, crystalline form H comprises at least one additional X-ray powder diffraction peak selected from about 10.4 ±02 (2Θ), about 17.5 ±02 (2Θ), about 20.9 ±02 (2Θ), about 22.3 ±02 (2Θ), and about 28.3 ±02 (2Θ). In further preferred embodiments, crystalline form H comprises all of the aforementioned optional additional X-ray peaks.
30

In order to discriminate between crystalline form H and crystalline form A it might be more advantageous to alternatively or additionally look at unique peaks in the X-ray diffractogram of crystalline form H where form A shows no lines with significant intensity. Such characteristic X-ray peaks are those of about 19.2 ±0.2 (2Θ), about 7.1 ±0.2 (2Θ), about 20.9
35   ±02 (2Θ), and about 28.3 ±02 (2Θ). Consequently, in some preferred embodiments of the invention crystalline form H comprises an X-ray peak of about 19.2 ±0.2 (2Θ), and at least one X-ray peak selected from the group consisting of about 7.1 ±0.2 (2Θ), about 20.9 ±02 (2Θ), and about 28.3 ±02 (2Θ).

5   In DSC analyses, crystalline form H according to the present invention preferably exhibits an
      endothermal event with a peak temperature of about 140-160 °C, preferably of about 145-
      160°C, more preferably of about 153-156 °C, and/or an endothermal event with a peak
      temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about
      240-248 °C. In some preferred embodiments crystalline form H exhibits an endothermal
10   event with a peak temperature of about 242-248 °C. Additionally, crystalline form H
      preferably exhibits an exothermal event with a peak temperature of about 150-190 °C,
      preferably about 163-175 °C.

      A further aspect of the present invention relates to a crystalline form I
15
      Preferably, the crystalline form I according to the invention has one or more X-ray powder
      diffraction peaks selected from the group consisting of about 7.1 ±0.2 (2Θ), about 11.8 ±0.2
      (2Θ), about 14.3 ±0.2 (2Θ), and about 17.5 ±0.2 (2Θ).

20   In some preferred embodiments, crystalline form I has an X-ray powder diffraction peak of
      about 17.5 ±0.2 (2Θ). In some preferred embodiments crystalline form I comprises X-ray
      powder diffraction peaks of about 7.1 ±0.2 (2Θ) and about 17.5 ±0.2 (2Θ).
      In some preferred embodiments, crystalline form I comprises X-ray powder diffraction peaks
      of about 7.1 ±0.2 (2Θ), about 11.8 ±0.2 (2Θ) and about 17.5 ±0.2 (2Θ), and optionally, a
25   further peak at about 12.7 ±0.2 (2Θ). In further preferred embodiments, crystalline form I may
      further comprise X-ray powder diffraction peaks of about 14.2 ±0.2 (2Θ), about 14.6 ±0.2
      (2Θ), and about 15.7 ±0.2 (2Θ).

      In some preferred embodiments, crystalline form I comprises X-ray powder diffraction peaks
30   of about 7.1 ±0.2 (2Θ), about 11.8 ±0.2 (2Θ), about 12.7 ±0.2 (2Θ), and about 17.5 ±0.2 (2Θ).
      Optionally, X-ray powder diffraction peaks of about 14.2 ±0.2 (2Θ), about 14.6 ±0.2 (2Θ),
      about 15.7 ±0.2 (2Θ), and 19.6 ±0.2 (2Θ) are additionally comprised.
      In further preferred embodiments, crystalline form I comprises X-ray powder diffraction peaks
      of about 7.1 ±0.2 (2Θ), about 11.8 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ), and about 17.5 ±0.2 (2Θ)
35   and may optionally comprise additional peaks selected from the group consisting of about
      12.7 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ), about 14.6 ±0.2 (2Θ), about 15.7 ±0.2 (2Θ), and 19.6
      ±0.2 (2Θ).

      In further preferred embodiments, crystalline form I comprises X-ray powder diffraction peaks
      of about 7.1 ±0.2 (2Θ), about 11.8 ±0.2 (2Θ), about 12.7 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ), and
40   about 17.5 ±0.2 (2Θ).

5   Optionally, an additional X-ray powder diffraction peak of about 14.6 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 9.7. ±0.2 (2Θ), about 15.1 ±0.2 (2Θ), and about 15.7 ±0.2 (2Θ), and/or about 19.6 ±0.2 (2Θ) may be comprised. Optionally, in some preferred embodiments, crystalline form I comprises at least one additional X-ray powder diffraction peak selected from of about 11.0 ±0.2 (2Θ), about

10 16.4 ±0.2 (2Θ), about 17.9 ±0.2 (2Θ), about 18.9 ±0.2 (2Θ), about 21.2 ±0.2 (2Θ), about 21.6 ±0.2 (2Θ), about 22.9 ±0.2 (2Θ), and about 26.3 ±0.2 (2Θ). In some preferred embodiments, crystalline form I comprises all of the aforementioned optional additional X-ray peaks.

To discriminate between crystalline form I and crystalline form A the X-ray peaks of about 7.1

15 ±0.2 (2Θ), about 11.0 ±0.2 (2Θ), about 14.2 ±0.2 (2Θ), about 14.6 ±0.2 (2Θ), about 18.9 ±0.2 (2Θ), and about 21.2 ±0.2 (2Θ) might be more advantageously used.

Consequently, in a preferred embodiment of the invention, form I comprises at least one X-ray peak selected from the group consisting of 7.1 ±0.2 (2Θ), and about 14.2 ±0.2 (2Θ), and at least one X-ray peak selected from the group consisting of about 11.0 ±0.2 (2Θ), about

20 14.6 ±0.2 (2Θ), about 18.9 ±0.2 (2Θ), and about 21.2 ±0.2 (2Θ)18.7 ±0.2 (2Θ).

A further aspect of the present invention relates to a crystalline form J

Preferably, the crystalline form J according to the invention has one or more X-ray powder

25 diffraction peaks selected from the group consisting of about 7.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ), about 14.5 ±0.2 (2Θ), and about 19.7 ±0.2 (2Θ).

In some preferred embodiments, the crystalline form has an X-ray powder diffraction peak of about 7.1 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ) and/or about 14.5 ±0.2

30 (2Θ).

In some preferred embodiments, crystalline form A comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ) and about 19.7 ±0.2 (2Θ), and optionally, a further peak at about 14.5 ±0.2 (2Θ). In further preferred embodiments, crystalline form A may further comprise X-ray powder diffraction peaks of about 16.8 ±0.2 (2Θ), about 17.0

35 ±0.2 (2Θ), and about 20.4 ±0.2 (2Θ).

In some preferred embodiments, crystalline form J comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ), about 14.5 ±0.2 (2Θ), and about 19.7 ±0.2 (2Θ). Optionally, X-ray powder diffraction peaks of about 16.8 ±0.2 (2Θ), about 17.0 ±0.2 (2Θ),

40 about 20.4 ±0.2 (2Θ), and 23.1 ±0.2 (2Θ) are additionally comprised.

28

5   In further preferred embodiments, crystalline form J comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ), about 14.5 ±0.2 (2Θ), about 17.0 ±0.2 (2Θ), and about 19.7 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 20.4 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 15.0 ±0.2 (2Θ), about 16.6 ±0.2 (2Θ), about 16.8 ±0.2 (2Θ), and about 23.1

10   ±0.2 (2Θ) may be comprised, either in addition to the peak of about 20.4 ±02 (2Θ) or alternatively. Optionally, in some preferred embodiments, crystalline form G comprises at least one additional X-ray powder diffraction peak selected from of about 9.1 ±0.2 (2Θ) and about 15.3 ±0.2 (2Θ). In further preferred embodiments, crystalline form J comprises all of the aforementioned optional additional X-ray peaks.

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To discriminate between crystalline form J and crystalline form A the X-ray peaks of about 7.1 ±0.2 (2Θ), about 9.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ), about 14.5 ±0.2 (2Θ), about 21.3 ±0.2 (2Θ), about 23.1 ±0.2 (2Θ), about 25.3 ±0.2 (2Θ), about 28.2 ±0.2 (2Θ), and about 28.8 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of

20   the invention, form B comprises at least one X-ray peak selected from the group consisting of 7.1 ±0.2 (2Θ), about 11.1 ±0.2 (2Θ), and about 14.5 ±0.2 (2Θ), and at least one X-ray peak selected from at about 18.7 ±0.2 (2Θ) in combination with one or more X-ray peaks from the group consisting of about 9.1 ±0.2 (2Θ), about 21.3 ±0.2 (2Θ), about 23.1 ±0.2 (2Θ), about 25.3 ±0.2 (2Θ), about 28.2 ±0.2 (2Θ), and about 28.8 ±0.2 (2Θ).

25

In DSC analyses, crystalline form J according to the present invention preferably exhibits an endothermal event with a peak temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form J exhibits an endothermal event with a peak temperature of about 242-248 °C. Additionally,

30   crystalline form J preferably exhibits an exothermal event with a peak temperature of about 180-190 °C, preferably about 183-187 °C.

A further aspect of the present invention relates to a crystalline form K

35   Preferably, the crystalline form K according to the invention has one or more X-ray powder diffraction peaks selected from the group consisting of about 7.1 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ), and about 19.5 ±0.2 (2Θ).

In some preferred embodiments, crystalline form K has an X-ray powder diffraction peak of about 7.1 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray

powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ) and/or about 19.5 ±0.2 (2Θ).

In some preferred embodiments, crystalline form K comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ) and about 19.5 ±0.2 (2Θ), and optionally, a further peak at about 10.0 ±0.2 (2Θ). In further preferred embodiments, crystalline form K may further comprise X-ray powder diffraction peaks of about 15.1 ±0.2 (2Θ), about 15.4 ±0.2 (2Θ), and about 19.9 ±0.2 (2Θ).

In some preferred embodiments, crystalline form K comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ), and about 19.5 ±0.2 (2Θ). Optionally, X-ray powder diffraction peaks of about 11.2 ±0.2 (2Θ), 15.1 ±0.2 (2Θ), about 15.4 ±0.2 (2Θ), and about 19.9 ±0.2 (2Θ), are additionally comprised.

In further preferred embodiments, crystalline form K comprises X-ray powder diffraction peaks of about 7.1 ±0.2 (2Θ), about 10.0 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ), about 15.4 ±0.2 (2Θ), and about 19.4 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 15.1 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 11.2 ±0.2 (2Θ), about 15.1 ±0.2 (2Θ), and about 19.9 ±0.2 (2Θ), either in addition to the peak of about 15.1 ±02 (2Θ) or alternatively. Optionally, in some preferred embodiments, crystalline form K comprises at least one additional X-ray powder diffraction peak selected from of about 21.4 ±0.2 (2Θ) and about 27.7 ±0.2 (2Θ). In some preferred embodiments, crystalline form K comprises all of the aforementioned optional additional X-ray peaks.

To discriminate between crystalline form K and crystalline form A the X-ray peaks of about 7.1 ±0.2 (2Θ), about 11.2 ±0.2 (2Θ), about 14.3 ±0.2 (2Θ), about 21.4 ±0.2 (2Θ), about 26.7 ±0.2 (2Θ), and about 27.7 might be more advantageously used. Consequently, in a preferred embodiment of the invention, crystalline form K comprises at least one X-ray peak selected from the group consisting of about 7.1 ±0.2 (2Θ), about 11.2 ±0.2 (2Θ), and about 14.3 ±0.2 (2Θ), and at least one X-ray peak selected from about 21.4 ±0.2 (2Θ), about 26.7 ±0.2 (2Θ), and about 27.7 4 ±0.2 (2Θ).

In DSC analyses, crystalline form K according to the present invention preferably exhibits an endothermal event with a peak temperature of about 90-145 °C, preferably of about 120-140°C, more preferably of about 130-140 °C, and/or an endothermal event with a peak temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form K exhibits an endothermal

5   event with a peak temperature of about 242-248 °C. Additionally, crystalline form K preferably exhibits an exothermal event with a peak temperature of about 180-190 °C.

A further aspect of the present invention relates to a crystalline form L.

10   Preferably, the crystalline form L according to the invention has one or more X-ray powder diffraction peaks selected from the group consisting of about 8.1 ±0.2 (2Θ), about 12.0 ±0.2 (2Θ), about 17.1 ±0.2 (2Θ), and about 20.1 ±0.2 (2Θ).

In some preferred embodiments, crystalline form L has an X-ray powder diffraction peak of
15   about 8.1 ±0.2 (2Θ). In some preferred embodiments the crystalline form comprises X-ray powder diffraction peaks of about 8.1 ±0.2 (2Θ), about 17.1 ±0.2 (2Θ) and/or about 20.1 ±0.2 (2Θ).

In some preferred embodiments, crystalline form L comprises X-ray powder diffraction peaks of about 8.1 ±0.2 (2Θ), about 17.1 ±0.2 (2Θ) and about 20.1 ±0.2 (2Θ), and optionally, a
20   further peak at about 12.0 ±0.2 (2Θ). In further preferred embodiments, crystalline form K may further comprise X-ray powder diffraction peaks of about 24.3 ±0.2 (2Θ), about 21.2 ±0.2 (2Θ), and about 21.9 ±0.2 (2Θ).

In some preferred embodiments, crystalline form L comprises X-ray powder diffraction peaks
25   of about 8.1 ±0.2 (2Θ), about 12.0 ±0.2 (2Θ), about 17.1 ±0.2 (2Θ), and about 20.1 ±0.2 (2Θ). Optionally, X-ray powder diffraction peaks of about 16.4 ±0.2 (2Θ), 21.2 ±0.2 (2Θ), 21.9 ±0.2 (2Θ), about and 24.3 ±0.2 (2Θ), are additionally comprised.

In further preferred embodiments, crystalline form L comprises X-ray powder diffraction peaks of about 8.1 ±0.2 (2Θ), about 12.0 ±0.2 (2Θ), about 17.1 ±0.2 (2Θ), about 20.1 ±0.2
30   (2Θ), and about 24.3 ±0.2 (2Θ). Optionally, an additional X-ray powder diffraction peak of about 21.2 ±0.2 (2Θ) may be comprised. Also optionally, additional X-ray powder diffraction peaks of about 7.7 ±0.2 (2Θ), about 16.4 ±0.2 (2Θ), and about 21.9 ±0.2 (2Θ), either in addition to the peak of about 21.2 ±02 (2Θ) or alternatively. Optionally, in some preferred embodiments, crystalline form L comprises one additional X-ray powder diffraction peak of
35   18.0 ±0.2 (2Θ). In preferred embodiments, crystalline form L comprises all of the aforementioned optional additional X-ray peaks.

To discriminate between crystalline form L and crystalline form A the X-ray peaks of about 8.1 ±0.2 (2Θ), about 21.2 ±0.2 (2Θ), and about 24.3 ±0.2 (2Θ), might be more
40   advantageously used. Consequently, in a preferred embodiment of the invention, crystalline

5   form K comprises an X-ray peak of about 8.1 ±0.2 (2⊖), about 21.2 ±0.2 (2⊖) and/or about
       24.3 ±0.2 (2⊖).

       In DSC analyses, crystalline form L according to the present invention preferably exhibits an
       endothermal event with a peak temperature of about 135 to 150°C, preferably of about 140-
10   150 °C, and/or an endothermal event with a peak temperature of about 230 to 255,
       preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred
       embodiments crystalline form L exhibits an endothermal event with a peak temperature of
       about 242-248 °C. Additionally, crystalline form L preferably exhibits an exothermal event
       with a peak temperature of about 170-210 °C, preferably about 190-210 °C.

15
       A further aspect of the present invention relates to a crystalline form Q.

       Preferably, the crystalline form Q according to the invention has one or more X-ray powder
       diffraction peaks selected from the group consisting of about 8.2 ±0.2 (2⊖), about 8.6 ±0.2
20   (2⊖), about 17.2 ±0.2 (2⊖), and about 24.4 ±0.2 (2⊖).

       In some preferred embodiments, crystalline form Q has an X-ray powder diffraction peak of
       about 8.2 ±0.2 (2⊖). In some preferred embodiments the crystalline form comprises X-ray
       powder diffraction peaks of about 8.2 ±0.2 (2⊖), about 17.2 ±0.2 (2⊖) and/or about 24.4 ±0.2
25   (2⊖).
       In some preferred embodiments, crystalline form Q comprises X-ray powder diffraction peaks
       of about 8.2±0.2 (2⊖), about 17.2 ±0.2 (2⊖) and about 24.4 ±0.2 (2⊖), and optionally, a
       further peak at about 8.6 ±0.2 (2⊖). In further preferred embodiments, crystalline form Q may
       further comprise X-ray powder diffraction peaks of about 11.0 ±0.2 (2⊖), about 12.0 ±0.2
30   (2⊖), and about 16.5 ±0.2 (2⊖).

       In some preferred embodiments, crystalline form Q comprises X-ray powder diffraction peaks
       of about 8.2 ±0.2 (2⊖), about 17.2 ±0.2 (2⊖), about 24.4 ±0.2 (2⊖), and about 8.6 ±0.2 (2⊖).
       Optionally, X-ray powder diffraction peaks of about 11.0 ±0.2 (2⊖), about 12.0 ±0.2 (2⊖),
35   about 16.5 ±0.2 (2⊖) and about 20.1±0.2 (2⊖), are additionally comprised.

       In further preferred embodiments, crystalline form Q comprises X-ray powder diffraction
       peaks of about 8.2 ±0.2 (2⊖), about 8.6 ±0.2 (2⊖), about 17.2 ±0.2 (2⊖), about 24.4 ±0.2
       (2⊖), and about 16.5 ±0.2 (2⊖). Optionally, an additional X-ray powder diffraction peak of
       about 11.0 ±0.2 (2⊖) may be comprised. Also optionally, X-ray powder diffraction peaks of

5   about 11.5 ±0.2 (2Θ), 12.0 ±0.2 (2Θ), about 16.5 ±0.2 (2Θ) and about 20.1±0.2 (2Θ) are additionally comprised.

Optionally, in some preferred embodiments, crystalline form Q comprises one additional X-ray powder diffraction peak of 21.3 ±0.2 (2Θ). In preferred embodiments, crystalline form Q comprises all of the aforementioned optional additional X-ray peaks.

10

To discriminate between crystalline form Q and crystalline form A the X-ray peaks of about 8.2 ±0.2 (2Θ), about 11.0 ±0.2 (2Θ), about 21.3±0.2 (2Θ), and about 24.4 ±0.2 (2Θ) might be more advantageously used. Consequently, in a preferred embodiment of the invention, crystalline form Q comprises an X-ray peak of about 8.2 ±0.2 (2Θ), about 11.0 ±0.2 (2Θ)

15 and/or about 24.4 ±0.2 (2Θ) and may optionally comprise an X-ray peak of about 21.3 ±0.2 (2Θ).

In DSC analyses, crystalline form Q according to the present invention preferably exhibits at least one endothermal event with a peak temperature of about 115 to 140°C, preferably of

20 about 130-140 °C, and/or an endothermal event with a peak temperature of about 155 to 165 and/or an endothermal event with a peak temperature of about 230 to 255, preferably of about 237-250 °C, more preferably of about 240-248 °C. In some preferred embodiments crystalline form L exhibits an endothermal event with a peak temperature of about 242-248 °C. Additionally, crystalline form Q preferably exhibits an exothermal event with a peak

25 temperature of about 180-210 °C, preferably about 185-205 °C.

Another aspect of the present invention relates to a process for the production of the crystalline form according to the invention.

30 In a preferred embodiment, the process comprises the step of

(a-1)   suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine in a solvent.

35

In step (a-1) cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine can be partially or even completely dissolved in the solvent.

40 Conventional solvents known to persons skilled in the art may be used as solvents in a suspension of this type, such as water or organic solvents selected from the group consisting

5   of alcohols such as methanol, ethanol, n-propanol, iso-propanol and n-butanol; esters such
       as ethyl acetate, n-propyl acetate, iso-propyl acetate, n-butyl acetate and iso-butyl acetate;
       ketones such as acetone, 2-butanone, pentan-2-one, pentan-3-one, hexan-2-one and hexan-
       3-one; ethers such as tert-butyl methyl ether, diethylether, tetrahydrofuran, diisopropylether
       and 1,4-dioxane; nitriles such as acetonitril; aromatic hydrocarbons such as toluene;
10   saturated hydrocarbons such as n-pentane, n-hexane and n-heptane; chlorinated
       hydrocarbons such as dichloromethane and chloroform; and also N-methyl-2-pyrrolidone,
       dimethyl formamide and dimethyl sulfoxide; and mixtures thereof.

       In a preferred embodiment, the solvent comprises at least one alcohol selected from the
15   group consisting of methanol, ethanol, n-propanol and iso-propanol.

       In another preferred embodiment, the solvent comprises at least one organic solvent
       selected from the group consisting of n-pentane, n-hexane, tert-butylmethylether,
       ethylacetate, acetone, acetonitrile, diethylether, dichloromethane, tetrahydrofurane,
20   ethylmethylketone and toluene or mixtures thereof.

       In yet another preferred embodiment, the solvent additionally comprises water.

       In still another preferred embodiment, the solvent consists of isopropanol or a mixture of
25   isopropanol and water.
       Preferably, in the process according to the invention, step (a-1) is carried out at a
       temperature below or at the boiling point of the respective solvent, preferably at a
       temperature not higher than 120 °C, more preferably not higher than 100 °C, even more
       preferably not higher than 90°C, and in particular in a temperature range of 40°C to 90°C.

30

       Preferably, in the process according to the invention, the suspension/solution obtained in
       step (a-1) is stirred for a time period of at least 0.3 h, preferably in the range of 0.3 h to 5
       days, preferably 0.3 h to 4 days, more preferably 0.3 h to 2 days, still more preferably 0.3 h
       to 1 day, even more preferably between 0.3h to 12 h, especially preferably 0.3 to 2h.

35

       Preferably, the process according to the invention further comprises the step

       (b-1)   separating, preferably filtering off the solid obtained in step (a-1).

40   In preferred embodiments of the process according to the invention separation step (b-1)
       comprises the addition step of cooling the suspension or solution obtained in step (a-1) prior
       to the separation of the solid. This is especially preferred if step (a-1) is carried out at

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5   elevated temperatures and/or if cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-
     2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine   is
     completely or partially dissolved in the solvent.

     Preferably, the process according to the invention further comprises the step
10
     (c-1)   drying of the solid obtained in step (b-1).

     Preferably, in the process according to the invention, step (c-1) takes place under air.
     However, drying under vacuum, more preferably at a vacuum of 0 to 900 mbar, even more
15   preferably at a vacuum of 1 to 500 mbar, and in particular at a vacuum of 10 to 200 mbar is
     also possible.

     Preferably, in the process according to the invention, step (c-1) takes place in a temperature
     range from 0 to 75°C, preferably from 10°C to 60°C more preferably from 20 to 55°C.
20
     By a preferred embodiment of the process according to the present invention crystalline form
     A can be obtained. This preferred embodiment comprises the steps of

     (a-1')   suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-
25   phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine for at least
               0.3h in a solvent at a temperature in the range of 20°C and the boiling point of the
               solvent, wherein the solvent is selected from the group consisting of isopropanol and
               a mixture of isopropanol and water, wherein the mixture may comprise up to 75 vol-%
               water;
30   (b-1')   separating, preferably filtering off the solid obtained in step (a-1'), and
     (c-1')   drying the solid obtained in step (b-1') at a temperature in the range of 0° to 75°C,
               preferably at a temperature in the range of 20 to 55°C, more preferably at 50°C.

     Preferably, step (b-1") comprises the additional step of cooling the suspension obtained in
35   step (a-1'), preferably to ambient temperature, prior to separating the solid from the solvent.
     Furthermore, drying step (c-1") is preferably conducted under reduced pressure.

     By a more preferred embodiment of the process according to the present invention
     crystalline form A can be obtained. This embodiment comprises the steps of
40
     (a-1'") suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-
               phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine for at least

5   0.3h in a solvent at a temperature in the range of 20°C and the boiling point of the

         solvent, wherein the solvent is selected from the group consisting of isopropanol and

         a mixture of isopropanol and water, wherein the mixture may comprise up to 75 vol-%

         water;

         (b-1''') separating, preferably filtering off the solid obtained in step (a-1'), and

10   (c-1''') drying the solid obtained in step (b-1'), preferably at a temperature in the range of 0°

         to 75°C, more preferably at a temperature in the range of 20 to 55°C, even more

         preferably at 50°C.

         Preferably, step (b-1''') comprises the additional step of cooling the suspension obtained in

15   step (a-1'''), preferably to ambient temperature, prior to separating the solid from the solvent.

         Furthermore, drying step (c-1''') is preferably conducted under reduced pressure.

         A further aspect of the invention relates to crystalline form A obtainable by the process as

         described above.

20

         In another preferred embodiment of the process according to the present invention crystalline

         form B can be obtained. This preferred embodiment comprises the step of

         (a-2)   suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-

25   phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine in a solvent

                  at a temperature in the range of 20°C to 60°C, wherein the solvent is a mixture of

                  water and an alcohol selected from the group consisting of ethanol, n-propanol and

                  isopropanol, wherein the mixture may comprise up to 50 vol.-% water, preferably up

                  to 30% water;

30   (b-2)   separating, preferably filtering off the solid obtained in step (a-2), and

         (c-2)   drying the solid obtained in step (b-2).

         Preferably, on or more of crystalline forms A, D or Q of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-

         tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-

35   pyrido[3,4-b]indol]-4-amine is suspended in step (a-2)

         In a preferred embodiment of this process, the crystalline form is step (a-2) is suspended in

         the solvent for at least 2h, preferably, at least 6 h, more preferably 12h. In further preferred

         embodiments crystalline form B is suspended in the solvent for between 2h and 14d,

         preferably between 12h and 7d, more preferably between 1d and 5d.

40   In preferred embodiments of this process, the solvent is a mixture of ethanol and water,

         wherein the mixture may contain between 99.9 and 50 vol.-% of ethanol. Preferably, the

5   mixture comprises 60 to 75 vol.-% ethanol. In additional preferred embodiments the solvent is a mixture of n-propanol and water or of isopropanol and water. Preferably, in these mixtures the n-propanol or isopropanol is present in 60 to 99 vol.-%, preferably in 75 to 97 vol.-%.

        In further preferred embodiments, the solid obtained from step (b-2) is dried in step (c-2) at a

10   temperature in the range of 20°C and 60°C, preferably 30° to 55°C, more preferably at 50°C. Optionally, the solid obtained in step (b-2) is dried in step (c-2) at reduced pressure.

        A further aspect of the invention relates to crystalline form B obtainable by the process as described above.

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        In another preferred embodiment of the process according to the present invention crystalline form C can be obtained. This preferred embodiment comprises the step of

        (a-3)   suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-

20   phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine in a solvent at a temperature in the range of 20°C and the boiling point of the solvent, wherein the solvent is methanol or a mixture of water and methanol, wherein the mixture may comprise up to 50 vol.-% water, preferably up to 25 vol.-% water;

        (b-3)   separating, preferably filtering off the solid obtained in step (a-3), and

25   (c-3)   drying the solid obtained in step (b-3).

        Preferably, one or more of crystalline forms A, D, and E of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine are suspended in step (a-2).

30   In a preferred embodiment of this process, the crystalline form in step a-3 is suspended in the solvent for a time between at least 2h and up to 14d, preferably for at least 2 h to 24h. The lower the temperature applied to the suspension in step (a-3) the longer the stirring time should be.

        In further preferred embodiments, the solid obtained from step (b-3) is dried in step (c-3) at a

35   temperature in the range of 20°C and 40°C, preferably 20° to 30°C, more preferably at 20°C. Preferably, the solid obtained in step (b-3) is in step (c-3) dried at ambient pressure.

        A further aspect of the invention relates to crystalline form C obtainable by the process as described above.

40

5   In another preferred embodiment of the process according to the present invention crystalline form D can be obtained. This preferred embodiment comprises the step of

In another preferred embodiment of the process according to the present invention crystalline form D can be obtained. This preferred embodiment comprises the step of

10

(a-4)   suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-
        phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine for at least
        0.3 h in a solvent at a temperature in the range of 20°C and the boiling point of the
        solvent, wherein the solvent is selected from the group consisting of acetonitrile,

15   acetone and water, or mixtures of acetonitrile or acetone with water;

(b-4)   separating, preferably filtering off the solid obtained in step (a-4), and

(c-4)   drying the solid obtained in step (b-3).

Preferably, crystalline forms A, E, or G are suspended in step (a-4).

20   Preferably, the solvent is acetone and the temperature at which the crystalline form is
      suspended is the boiling point of acetone. Preferable, the suspension is maintained at this
      temperature of 0.3 to 1h, preferably 0.5h.

      In a preferred embodiment, step (b-4) comprises the step of cooling the suspension to
      ambient temperature prior to separation the solvent from the solid obtained in step (a-4).

25

      A further aspect of the invention relates to crystalline form D obtainable by the process as
      described above.

      Another aspect of the invention relates to a process for the production of crystalline form E of

30   cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
      spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine.

      This process comprises the step:

              (a-4) suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-
      oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine fumarate in

35   water;

              (b-4) adding an excess of an organic base to the suspension and stirring the reaction
      mixture of at least 2h; and

              (c-4)   separating, preferably filtering off the solid obtained in step (b-4), and

              (d-4)   drying the solid obtained in step (c-4).

40

5   In a preferred embodiment the organic base in step (b-4) is a dialkyl- or trialkylamine, preferably triethylamine.

In a further preferred embodiment, step (c-4) comprises as additional step (c-4.1) at least once slurrying the isolated solid in water and separating, preferably filtering off the solid obtained in step (c-4.1).

10   In a preferred embodiment the solid obtained in step (c-4/c-4.1) is dried at 40°C to 75°C, preferably at 70°C and preferably at reduced pressure.

A further aspect of the invention relates to crystalline form E obtainable by the process as described above.

15

In a preferred embodiment the crystalline form according to the invention is subsequently transformed into an amorphous form.

Suitable methods for the preparation of amorphous forms are known to a person skilled in
20   the art. For example, amorphous forms or amorphous mixtures may be obtained by means of the following methods or combinations thereof:

i)   precipitation from solution,

ii)   lyophilization,

25   iii) spray drying,

iv)   melts extrusion,

v)   flash evaporation,

vi)   quench cooling of the melt,

vii) grinding at ambient or liquid nitrogen temperatures,

30   viii) working under protection of an inert atmosphere (e.g. gaseous nitrogen or argon), and/or

ix)   using capillary crystallization technology.

Another aspect of the invention relates to an amorphous form of cis-(E)-4-(3-Fluorophenyl)-
35   2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine, preferably to an amorphous form that is obtainable by any of the above methods or combinations thereof.

Mixtures of the crystalline forms A, B, C, D, E, F, G, H, I, J, K, L and Q, preferably mixtures of
40   two of these crystalline forms, are also included within the scope of the present invention.

5   For example, such mixtures of two crystalline forms may be obtained from one or more of the
crystalline forms A, B, C, D, E, F, G, H, I, J, K, L and Q during a crystallization process (e.g.
cooling or evaporation) or respectively during a separation process (e.g. filtration), or
respectively during a process where heat is applied (e.g. drying), or respectively during a
process where mechanical energy is inserted (e.g. milling or grinding).

10

Furthermore, such mixtures of two crystalline forms may be obtained from one or more of
crystalline forms A, B, C, D, E, F, G, H, I, J, K, L or Q by a partial uptake of hydrate water or
respectively by a partial loss of hydrate water, or respectively by a solvent/water exchange.

15   Another aspect of the invention relates to a composition comprising a mixture of at least two
crystalline forms as described herein; or a mixture of at least one crystalline form as
described herein with an amorphous form; or a mixture of at least one crystalline form as
described herein with a salt of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-
2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine   with
20   fumaric acid; in any mixing ratio.

Preferably, the degree of crystallinity, i.e. the content of crystalline form(s) of cis-(E)-4-(3-
Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine relative to the total content of cis-(E)-
25   4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-
spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine   (crystalline   form(s)   +   amorphous
form(s)) is at least 40 wt.-%, more preferably at least 60 wt.-%, still more preferably at least
80 wt.-%, yet more preferably at least 90 wt.-%, even more preferably at least 95 wt.-%, most
preferably at least 99 wt.-%, and in particular at least 99.5 wt.-%.

30

Yet a further aspect the invention relates to a pharmaceutical composition comprising at least
one crystalline form according to the invention.

In another aspect the present invention relates to methods of treating pain, comprising
35   administering a pharmaceutical composition that comprises a crystalline form as described
herein to a patient in need thereof (for example, a patient who has been diagnosed with a
pain disorder).

The term pain as used herein preferably includes but is not limited to pain selected from the
40   group consisting of neuropathic pain, diabetic neuropathic pain, chronic neuropathic pain.

5   In another aspect the present invention relates to a pharmaceutical composition comprising a crystalline form as described herein and optionally one or more suitable additives and/or adjuvants such as described below.

Preferably said pharmaceutical composition may be used for the treatment of pain.
10

In still another aspect the present invention relates to a medicament comprising a crystalline form as described herein, preferably a pharmaceutical composition as described herein. In a preferred embodiment, the medicament is a solid drug form. The medicament is preferably manufactured for oral administration. However, other forms of administration are also
15   possible, e.g. for buccal, sublingual, transmucosal, rectal, intralumbal, intraperitoneal, transdermal, intravenous, intramuscular, intragluteal, intracutaneous and subcutaneous application.

Depending on the configuration, the medicament (dosage form) preferably contains suitable
20   additives and/or adjuvants. Suitable additives and/or adjuvants in the sense of the invention are all substances known to a person skilled in the art for the formation of galenic formulations. The choice of these adjuvants and also the quantities to be used are dependent on how the medication is to be administered, i.e. orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally.
25

Furthermore, the present invention relates to a method for treating pain in a patient, preferably in a mammal, which comprises administering an effective amount of a crystalline form as described herein to a patient.

30   EXAMPLES

The following examples serve to explain the invention in more detail, but should not be interpreted as restrictive.

35   The following abbreviations are used in the examples:

The following abbreviations are used in the examples:

d	day
DMSO	dimethylsulfoxid
40 EtOAc	ethyl acetate
EtOH	ethanol

5	Ex	example
	FT-Raman	Fourier transformation Raman spectroscopy
	H	hour
	IPE	diisopropyl ether
	MeCN	acetonitril
10	MEK	2-butanone
	MeOH	methanol
	min	minute
	NMP	N-methyl-2-pyrrolidone
	1PrOH	n-propanol (1-propanol)
15	2PrOH	iso-propanol (2-propanol)
	PXRD	powder x-ray diffraction
	r.h.	relative humidity
	RT	room temperature, preferably 20-25°C
	SCXRD	single crystal X-ray diffraction
20	sec	seconds
	t	time (duration)
	T	Temperature
	TBME	tert-butyl methyl ether
	TG-FTIR	thermogravimetry coupled with Fourier transform infrared spectroscopy
25	THF	tetrahydrofuran
	XRPD	X-ray powder diffraction

In the following "compound (1)" denotes cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-

30 amine.

Unless otherwise specified, solvent mixtures are always volume/volume.

The synthesis of compound (1) is described in WO2012/013343 A1, page 48-49.

35

A) Crystalline form A

General procedure for syntheses:

40 A quantity of compound (1) is charged into a vial or flask and an amount of solvent is added.
The resulting suspension/solution is stirred (e.g. orbital shaker or overhead-stirrer) for a

5   given time at a specific temperature. Subsequently, if the suspension/solution was stirred at
an elevated temperature, it is allowed to cool to room temperature or any other
predetermined temperature to precipitate or crystallize the product and the solvent is
removed by filtration. The thus obtained solid is dried, preferably at room temperature.

10   In table 1 below, specific reaction conditions for syntheses of crystalline form A are listed.

Table 1

Example	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]	Comment
A1	D	227.7	2-propanol / 5 ml	RT	5d	Day 5 without stirring
A2	D	190	2-propanol / 10 ml	RT	3d	---
A3	D	206.1	1-propanol / 5 ml	RT	5d	Day 5 without stirring
A4	E	101	1-pentane / 2.5 ml	40	0.75d	---
A5	E	102	1-propanol / 2.5 ml	40	0.75d	---
A6.1	E	110.5	TBME / 2.5 ml	40	0.75d	---
A6.2	E	102.8	n-hexane / 2.5 ml	30	0.75d	---
A6.3	E	102	n-pentane / 2.5 ml	30	0.75d	---
A6.4	E	107	1-propanol / 2.5 ml	40	0.75d	---
A10.1	D	206.1	1-propanol / 5 ml	RT	4d	---
A10.2	D	227.7	2-propanol / 5 ml	RT	4d	---
A12	B	8300	2-propanol / 120 ml Water / 280 ml (3:7)	52	5d	After cooling to RT the suspension was stirred for an additional hour.

5

44

5   Example A13:

Crystalline form H of compound (1) can be transformed into form A by heating a sample of crystalline form H, which was filled into a quartz capillary to a temperature between 150°C to 250°C. The sample remained crystalline form A upon cooling the sample to 20 °C.

10

Example A 17: Interconversion / Slurry experiments

About 25 mg of a specific crystalline form of compound (1) and 25 mg of the same or another
15   crystalline form of compound (1) were charged into a vial and 1.0 mL of 2-Propanol was added. The vials were closed and the mixtures were stirred (via shaking using an Eppendorf Thermomixer, starting with 750 rpm, increased to 1000 rpm after 1 day) at an elevated temperature (30 ±2 °C) for 7 days. Subsequently the mixtures were cooled to 20 ±2 °C and stirred for an additional 2 hours.
20   The solids were then separated via filtration using a suction filter. To dry the thus obtained solid material an air flow was applied for 2 to 3 hours.

The crystalline form of the obtained materials was determined using XRPD. The experiments are summarized below in table 2 below.

25

Table 2:

ID	Amount compound (1)/ [mg] and crystalline forms in starting material	Resulting crystalline form
A17.1	24,8 mg D 26,2 mg D	A
A17.2	21,8 mg E 24,8 mg A	A
A17.3	24,0 mg E 23,8 mg D	A
A17.4	22,9 mg E 21,4 mg 63*	A
A17.5	20,7 mg E 22,1 mg G	A
A17.6	23,1 mg E 22,6 mg C	H
A17.8	24,5 mg E 24,2 mg 58*	A
A17.9	22,6 mg E 22,2 mg L	A + H
A17.10	23,0 mg E 34,7 mg 64*	A + H

ID	Amount compound (1)/ [mg] and crystalline forms in starting material	Resulting crystalline form
A17.11	24,0 mg E 24,4 mg A+Pks*	A
A17.12	23,6 mg E 23,3 mg P	A
A17.13	25,9 mg E 24,1 mg O	A
A17.14	24,7 mg D 25,6 mg D	A
A17.15	20,9 mg E 23,2 mg A	A
A17.16	21,8 mg E 20,9 mg D	A
A17.17	20,6 mg E 20,7 mg 63*	A
A17.18	23,3 mg E 22,7 mg G	A
A17.19	23,3 mg E 24,2 mg C	H
A17.20	25,1 mg E 25,3 mg 58*	A
A17.21	22,8 mg E 23,4 mg L	A + H
A17.22	22,6 mg E 22,2 mg 64*	A + H
A17.23	24,1 mg E 25,4 mg A+Pks*	A
A17.24	26,2 mg E 26,2 mg P	A
A17.25	25,2 mg E 24,3 mg O	A

5   [* denote crystalline material in a polymorphic form not further characterized but most likely other than the ones described herein]

From the above interconversion experiments, it becomes apparent that under these reaction conditions, crystalline form A is predominantly formed, i.e. that crystalline form A is

10   thermodynamically more stable than the other crystalline forms. This advantageous property makes crystalline form A an attractive material for use in pharmaceutical compositions.

Example A15

15   100 mg of crystalline form A of compound (1) was charged into a vial and 10 mL of a mixture ethylacetate/water 70:30 (vol/vol, i.e. 7 mL ethylacetate, 3 mL water) was added. The vial was closed and the mixture (a white suspension) was stirred (by means of shaking, 400 rpm, PLS Synthesiser) at room temperature (22 ±2 °C) for 13 days.

46

5   The solid was separated using a suction filter and dried by applying an air flow for additional 5 to 30 minutes (until the solid appeared to be dry). The resulting material was identified via x-ray powder diffraction to be crystalline form A of compound (1).

Example A16

10

0,99 g of crystalline form A of compound (1) was charged into a vial and 25 mL of ethanol p.a. was added. The vial was closed and the suspension was stirred (by means of shaking, PLS shaker, 400 rpm) at an elevated temperature (40°C ±2) for 20 h.

The mixture was cooled to 20 ±2 °C. The solid was separated using a suction filter (G4) and

15   dried by applying an air flow until the sample appeared to be dry. The white solid was subsequently left for 1 h at ambient conditions. Subsequently, it was identified via x-ray powder diffractometry to be crystalline form A of compound (1).

20   Example A18

Crystalline form A of compound (1) can be obtained by suspending in the flask fitted with a reflux condenser 34.6 g of compound (1) (e.g. as crystalline form C, E, G and/H, or any other form) in a mixture of 260 ml water and 606 ml isopropanol. The suspension is

25   subsequently heated and stirred at 100°C for 30 minutes which leads to the formation of a very fine suspension of crystalline material which settles very quickly after stirring is stopped. The reaction slurry is cooled to 20°C and the solvent mixture is removed by filtration (suction filter). The solid crystalline material is dried over night at 50°C under reduced pressure

Yield: 26 g (75 %)

30

B) Crystalline form B

General procedure for syntheses: See general procedure for syntheses of crystalline form A.

35   In table 3 below, specific reaction conditions for syntheses of crystalline form B are listed.

47

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]	Comment
B1	D	224.7	Ethanol / 5 ml	RT	5	Day 5 without stirring
B2	D	165.3	Ethanol 10.5 ml / water 4.5 ml (7:3)	RT	3	---
B3	D	176.4	Ethanol 10.5 ml / water 4.5 ml (7:3)	50	3	---
B4	D	225	Ethanol / 5 ml	RT	4	---
B6	D	488	Ethanol 21 ml / water 9 ml (7:3)	50	4,83	For the final 20h, the suspension is stirred at RT.
B7	A	101	Ethanol 7 ml / water 3 ml (7:3)	RT	13	
B9.1	Q	30.7	1-Propanol:water (8:2) 1.5 ml	RT	7	
B9.2	Q	30.0	2-Propanol:water (8:2) 1.5 ml	RT	7	

Table 3

5

48

5   Example B8: Stability of crystalline form B

       Two samples (100 mg each) of crystalline form B of compound (1) were charged into a petri
       dish and dried at 50 ±2 °C at reduced pressure (about 7 mBar) for 72 hours. The samples
       were let to cool to room temperature under ambient conditions before they were analyzed.
10   The analysis revealed that the obtained material was still compound (1) in crystalline form B.

       This example and example B7 demonstrate that in the presence of water, crystalline form B
       may form as a relatively stable polymorph or hydratealthough the water content may vary
       and/or change. The formation of form A (ansolvate) or form B (hydrate) in the presence of
15   water depends on the organic co-solvent used as the reaction medium (preferably ethanol)
       and the reaction temperature (preferable room temperature).

C) Crystalline form C

General procedure for syntheses: See general procedure for syntheses of crystalline form A. In table 4 below, specific reaction conditions for syntheses of crystalline form B are listed.

Table 4

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]	Comment
C1	E	100	Methanol / 2.5 ml	40	0.75	
C2	A	1010	Methanol / 25 ml	40	0.83	
C3	E	103	Methanol / 2.5 ml	40	0.75	
C4	A	53.7	Methanol / 2 ml	30	19	
C5.1	A	100	Methanol / 5ml	50	1	
C5.2	A	100	Methanol / 3.5 ; Water / 1.5 ml	50	1	
C6	A	100	Methanol / 7ml; Water / 3 ml	RT	13	
C7	D	650	Methanol / 150 ml	56	5	
C8	D	280	Methanol / 150 ml	80	0.125 (3h)	Reflux
C9	D	778	Methanol / 250 ml	80	0.17 (4h)	Reflux
C10	E	150	Methanol / 50 ml	70	0.125 (3h)	Solid was filtered from hot suspension.
C11	H	75	Methanol / 75 ml	50	14	

5   D) Crystalline form D

General procedure for syntheses: See general procedure for syntheses of crystalline form A. In table 5 below, specific reaction conditions for syntheses of crystalline form D are listed.

10   **Table 5**

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]	Comment
D6.1	E	116.6	Acetone / 2.5 ml	40	0.75	---
D6.2	E	113	Acetonitrile / 2.5 ml	40	0.75	---
D6.3	E	106.4	Diethylether / 7.5 ml	40	0.75	---
D6.4	E	104.5	Dichloromethane / 7.5 ml	40	0.75	---
D6.5	E	105.2	Ethylmethylketone / 2.5 ml	40	0.75	---
D8.1	A	49.7	Dichloromethane / 2 ml	30	19	
D8.2	A	53.6	Diethylether / 2 ml	30	19	
D8.3	A	73.7	Acetone / 1 ml	30	19	
D8.4.	A	95.9	THF / 0.5 ml	30	19	Solvent was removed by evaporation under ambient conditions instead of filtration.
D8.5	A	51.5	Acetonitrile / 2ml	30	19	
D9.1	A	100	Acetone / 5 ml	50	1	
D9.2	A	100	Acetone / 3.5 ml; Water / 1.5 ml	50	1	
D12.1	G	55	Acetone / 1.5 ml	RT	1	
D12.2	G	51	Dichloromethane	RT	1	

5   Examples D1, D2, D3, D4, D10, D11 and D13

In the above mentioned examples, which were carried out as described in the general procedure for syntheses of polymorph D under reaction conditions listed below in table 6, crystalline form D did not transform into another polymorphic form.

10

Table 6: Stability of crystalline form D

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]
D1	D	207.6	Acetonitrile / 5 ml	RT	5d*
D2	D	170.7	Acetone / 10.5 ml; Water / 4.5 ml	RT	3d
D3	D	188.6	Acetone / 10.5 ml; Water / 4.5 ml	50	3d
D4	D	196	Water / 10 ml	RT	3d
D10	D	208	Acetonitrile / 5ml	RT	4d
D11	D	196	Water / 10 ml	RT	4d
D13	D	517	Acetonitrile / 20 ml	50	5d**

* Day 5 without stirring. ** Day 5 at RT.

Example D14

15

238 g of crystalline form E of compound (1) are charged into a suitable reaction vessel under inert conditions (N_2-atmosphere) and 17 l of acetone are added. Whilst stirring at 130 rpm the suspension is heated to reflux (55 °C) for 30 min. The suspended solid is thereby completely dissolved. The heating is switched off and the solution is slowly cooled to 18 °C. The

20   precipitated solid is filtered off under suction via a glass frit (G3) and dried for 3 h in the air flow. The solid is further dried at 50°C in a vacuum oven under reduced pressure (p< 2mbar) for 35 h.

The dried product (136.6 g) was analyzed and identified to be crystalline form D or compound (1).

25

E) Crystalline form E

Example E1

Crystalline form can be obtained by drying crystalline form G for 2h at 100°C in ambient

30   atmosphere and pressure (e.g. in an oven).

5

Example E2

Crystalline form E of compound (1) can be obtained in high purity by reaction compound (1)
with fumaric acid to give the corresponding fumarate salt and subsequently reacting the
10   isolated salt with a base to give free compound (1) again.

7l ethylacetate are charged into a reaction vessel and 1.1 equivalent of fumaric acid
(728,5mmol = 84,7g) are added to the solvent. The solvent is heated to 60°C thereby
dissolving the fumaric acid to a large degree. One equivalent of compound (1) (336 g)
15   dissolved in 10 l ethylacetate are added stepwise. A white suspension is quickly formed. The
reaction mixture is stirred for 90 minutes then the mixture is allowed to cool to ambient
temperature and stirred for another 2 days. The precipitated solid is isolated via filtration (G3
glass frit), washed three times with about 700 ml ethylacetate, dried by applying a strong air
flow with the suction pump and then further dried at 40°C in a vacuum oven at a pressure of
20   below 2mbar until no further loss of mass was observed.
The thus obtained solid (293g) was charged into a reaction vessel together with 8 l distilled
water. Whilst stirring at 150 rpm 610 ml diethylamine are added to the resulting white
suspension. Subsequently, 200 ml of ethanol are added and the reaction mixture is stirred at
24°C for 16h. Then, the solid is isolated from the suspension via filtration (G3 glass frit) and
25   slurryied 4 times in 1 l of water. The resulting solid is dried overnight on a nutsch filter with
suction. The resulting white solid was further dried for 2 days in a vacuum oven at 70°C. 250
g of (1) are isolated (74.4%).
XRPD analysis of the dried solid revealed it to be crystalline form E of compound (1).

30

F) Crystalline form F

Crystalline form F was observed during an experiment in a multi-well plate. Approximately 5
mg of either crystalline forms D or A, or a mixture of crystalline forms D and E were charged
35   into respective wells. 0.25 ml of a specific solvent were added to each well and the lid of the
plate closed. The plate was shaken at 30°C for 16h. Subsequently, the plate was allowed to
cool to RT. Upon opening, it was found, that part of the solid had been spread all over the
plate. Residual solvent was removed by evaporation from the plate and the solid samples in
the respective wells analyzed. The results are listed below in table 7.

40

5   **Table 7: Multiwell experiment**

	Starting with polymorph D and E	Starting with polymorph A	Starting with polymorph E
Acetone	F	83*	F
Acetonitrile	D	83*	D
Dichloromethane	F	D	83*
Ethylacetate	F	M	75*
Diethylether	M	F	F
Hexane	F	F	M
Methy-ethyl-ketone	M	F	M
Methanol	K	K	K
Pentane	F	F	D + peaks
1-Propanol	am**	F	77
2- Propanol	am**	A	F
Ethanol	am**	F	M
Tetrahydrofurane	am**	E + peaks	D + peaks
Toluene	M	D + peaks	am**
tBME	F	F	M
Water	M	D	E + peaks
Acetone/Water	F	F	F
Acetone/Water_1	F	F	F
Acetone/Water_2	M	M	F
Tetrahydrofurane/Hexane	am**	M	M

* numbers denote crystalline forms which were not further characterized

** am = amorphous or of poor crystallinity

"+ peaks" means that additional peaks were found in the XRPD of the solid, which were considered not to belong to the indicated crystalline form.

10

G) Crystalline form G

General procedure for syntheses: See general procedure for syntheses of crystalline form A.

In table 8 below, specific reaction conditions for syntheses of crystalline form G are listed.

15

Table 8

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]
G1	E	176.4	Ethanol / 15 ml; water / 4.5 ml	50	3

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]
G3	L	1210	Ethanol / 25 ml	40	0.83 (20h)
G4	A	1550	Ethanol / 175 ml	75 -->0*	0.65 (15.25h)*
G5.1	E	106.1	Ethanol	40	0.75
G5.2	E	115.7	1-Propanol / 2.5ml; Water / 2.5.ml	40	0.75

5   * 15min heated to 75°C, cooled to 0°C during 6h, stirred at 0°C for 9h.

H) Crystalline form H

General procedure for syntheses: See general procedure for syntheses of crystalline form A.

10   In table 9 below, specific reaction conditions for syntheses of crystalline form H are listed.

Table 9

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time [d]
H3	E	105.8	2-Propanol / 2.5 ml	40	0.75
H5	E	103	2-Propanol / 2.5 ml	40	0.75

Example H1: Interconversion experiments

15

A mixture of two different crystalline forms of compound (1) was charged into a vial and 1.0 mL of 2-Propanol was added (details see table).

The vials were closed and the mixtures were stirred (by means of shaking, Eppendorf Thermomixer, 750 rpm at first, increased to 1000 rpm after 1 d) at elevated temperature (30

20   ±2 °C) for 7 days.

Susequently, the mixtures were cooled to 20 ±2 °C and stirred for additional 2 hours.

The solids were then isolated via filtration using a suction filter. The air flow from the suction pump was applied for 2 to 3 hours to dry the isolated solid.

The results of the experiments are listed below in table 10:

25

Table 10

Ex.	Mixture of crystalline forms /[mg]	Solvent (1ml)	Temperature /°C (time)	resulting crystalline form
H1.1	23,1 mg E 22,6 mg C	2-Propanol	30 (7d) 20 (2 h)	H

Ex.	Mixture of crystalline forms /[mg]	Solvent (1ml)	Temperature /°C (time)	resulting crystalline form
H1.2	22,6 mg E 22,2 mg L	2-Propanol	30 (7d) 20 (2 h)	A + H
H1.4	23,3 mg E 24,2 mg C	2-Propanol	30 (7d) 20 (2 h)	H
H1.5	22,8 mg E 23,4 mg L	2-Propanol	30 (7d) 20 (2 h)	A + H

I) Crystalline form I

A sample of crystalline form C (characterized by X-ray diffraction) was stored for up to 4 months, during which, according to X-ray diffraction analysis, the sample converted to Polymorph I in three to four months.

It was observed that under the conditions of a variable Temperature x-ray diffraction experiment (STOE diffractometer, radiation CuKα, sample filled in quartz capillary) starting from crystalline form I upon heating in a temperature range from 30°C to 100°C the sample remained crystalline form I until it transformed into crystalline form J at higher temperature in the range from 110°C to 130°C. Upon further heating in a temperature range from 140°C to 160 °C the sample became poorly crystalline to amorphous. The sample remained poorly crystalline to amorphous upon cooling to 20 °C.

J) Crystalline form J

45 mg or 78 mg crystalline form C were stored in a vacuum oven at reduced pressure (10 mbar) at 25°C for 24h, at 41°C for 24h or at 65°C for 72 h. In all cases crystalline form C transformed into crystalline form J.

K) Crystalline form K

Example K1

39.6 mg of crystalline form C were stored in a vacuum oven at reduced pressure (5 to 10 mbar) at 50°C for 16h. It was found that crystalline form C had transformed into crystalline form K.

Example K2

5   99.5 mg of crystalline form C were stored in a vacuum oven C at reduced pressure (5 to 10
      mbar) at 60°C for 16h. It was found that crystalline form C had transformed into crystalline
      form K.

L) Crystalline form L

10

      General procedure for syntheses: See general procedure for syntheses of crystalline form A.
      In table XXX below, specific reaction conditions for syntheses of crystalline form L are listed.

Ex.	Crystalline form of starting material	Amount [mg]	Solvent / amount	T [°C]	Reaction time
L1	E	102	Toluene / 2.5 ml	40	16 h
L2	A	1110	Toluene / 30 ml	40	64 h
L3	E	101	Toluene / 2.5 ml	40	16 h
L4	A	83.9	Toluene / 1 ml	30	19 d

15

Q) Crystalline form Q

      Example Q1
      Compound (1) (6.6 g) was charged to a 250 mL flask and suspended in toluene p.a. (1.25
20   moles; 132.00mL; 115.00 g) and vigorously stirred with a magnetic stir bar for 3h at 21 °C.
      The solid was separated from the solvent by means of a suction filter, washed with 5 mL of
      toluene and subsequently washed again with another 10 mL of toluene.

      Example Q2
25

      1,08 g of crystalline form A of compound (1) was charged into a vial and 30 mL of toluene
      p.a. were added. A thick suspension was formed. The vial was closed and the suspension
      was stirred (by means of shaking, PLS shaker, 400 rpm) at elevated temperature (40°C ±2)
      for 22 h. The mixture was cooled to 22 ±2 °C and shaken for another 30 min. The solid was
30   separated using a suction filter (G4) and dried by applying the air flow from the suction pump
      for 10 min. A white fluffy solid was produced.

1) Transformation of crystalline form Q into amorphous material.

35

5   31.1 mg of crystalline form Q of compound (1) was charged into a vial and 1,5 mL of an
acetone/water mixture (8:2 vol/vol) was added. The vial was closed and the mixture (a
suspension) was stirred (by means of shaking, Eppendorf Thermomixer, 1000 rpm) at room
temperature (23 ±2 °C) for 7 days.
The solid was separated using a suction filter and dried by applying the air flow for an
10   additional 15 minutes. The resulting solid was analyzed (SM1).
The solvent from the filtrate was let to evaporate (23 ±2 °C) in a fume hood to give a second
solid material (SM2). This was also analyzed.
According to XRPD-analyses SM1 is a poorly crystalline material, SM2 amorphous.

15

Example S1: Chemical stability of crystalline forms of compound (1)

Samples of compound 1 in different crystalline forms were stored in open vials under
controlled conditions at different temperatures and rel. humidities for 28 days. Prior to
20   storage and after 14 and 28 days the content of compound (1) in the sample was determined
via HPLC and the crystalline form was measured via XRPD.

The results of this stability study are listed below in table 12:

25   **Table 12**

Ex-No.	Initial solid form	Storage [d]	T[°C]	Rel. humidity % r.H.	Resulting solid form	Content cmpd (1) [%]
S1-A1	A	0	50		A	99,58
	A	14	50		A	99,49
	A	28	50		A	99,37
S1-A2	A	0	40	75	A	99,58
	A	14	40	75	A	99,63
	A	28	40	75	A	99,39
S1-B1	B	0	50		B	84,85
	B	14	50		B	82,63
	B	28	50		B	81,26
S1-B2	B	0	40	75	B	84,85
	B	14	40	75	B	84,21
	B	28	40	75	B	83,74
S1-C1	C	0	50		C	99,67
	C	14	50		P	99,57
	C	28	50		P	99,20
S1-C2	C	0	40	75	C	99,67
	C	14	40	75	J	99,68
	C	28	40	75	J	99,44

Ex-No.	Initial solid form	Storage [d]	T[°C]	Rel. humidity % r.H.	Resulting solid form	Content cmpd (1) [%]
S1-D1	D	0	50		D	84,61
	D	14	50		D	84,65
	D	28	50		D	83,54
S1-D2	D	0	40	75	D	84,61
	D	14	40	75	D	84,27
	D	28	40	75	D	83,92
S1-E1	E	0	50		E	99,76
	E	14	50		E	97,25
	E	28	50		E	95,53
S1-E2	E	0	40	75	E	99,76
	E	14	40	75	G	99,80
	E	28	40	75	B	99,50

The data shows that the content of compound (1) of crystalline form A in the respective samples remains essentially unchanged after 28 days of open storage at the indicated temperatures and relative humidity.

Contrary to this, the other two ansolvate crystalline forms show a higher degree of chemical degradation after 28 days storage at the respective storage conditions, wherein this effect is more pronounced at 50°C with crystalline form E than with D.

Of the three ansolvate forms tested, crystalline form A is observed to be the chemically most stable one.

Furthermore, it can be seen that crystalline form E transforms into different crystalline forms at 40°C and a relative humidity of 75%. This is a disadvantage of crystalline form E compared to A and D, because it is advantageous that in the formulation of solid dosage forms the pharmaceutical active ingredient retains the same crystalline form. Be it during formulation and storage of the dosage form so that the desired pharmacokinetic properties of the dosage form are achieved after formulation and remain essentially stable over the shelf-life of the dosage form. Crystalline form C shows a comparable chemical stability to crystalline form A, but transforms into other crystalline forms during storage over 28 days at the indicated conditions.

Crystalline form B does not transform into different forms but it exhibits a higher degree of chemical degradation in the experiments, i.e. a lower chemical stability compared both to form A and C.

Example S2: Chemical stability in pharmaceutical compositions

59

5   To test the chemical stability, i.e. compatibility of different crystalline forms of compound (1), solid multi component mixtures were prepared comprising well established excipients used for solid oral dosage form and having different functions therein. The single components of each mixture were exactly weighed and intensively triturated using a mortar and a pestle. Subsequently, 10% (w/w) of compound (1) (either crystalline form A or B) were added to the

10   respective mixtures and triturated using the same method as for preparation of the excipient mixtures.

       10 g of the final mixtures were separately filled into glass vials (open or closed) and stored under the conditions outlined below in table 13. Samples were taken and analyzed initially and after 1, 2 and 3 months with respect to the content of compound (1) within the mixtures.

15

       The comparison of the data obtained for the two different crystalline forms demonstrate that chemical degradation of compound (1) occurred to a lesser degree over the duration of storage at higher temperatures (e.g. 50°C) if the compound was present in crystalline form A. Consequently, crystalline form A demonstrates superior properties compared to crystalline

20   form B with respect to chemical degradation, i.e. higher chemical stability, and therefore superior properties for the use in solid dosage forms.

Table 13

Example	crystalline form	$T_{storage}$	humidity	excipients			0 month	1 month	2 months	3 months
S2-1A	A	50°C	dry	Microcrystalline cellulose	HPMC 6 mPas	L-HPC LH21	magnesium stearate	99,64	99,59	99,59	99,62
S2-1B	B	50°C	dry	Microcrystalline cellulose	HPMC 6 mPas	L-HPC LH21	magnesium stearate	99,75	95,74	91,45	87,34
S2-2A	A	40°C	75% rel. hum.	Microcrystalline cellulose	HPMC 6 mPas	L-HPC LH21	magnesium stearate	99,64	99,61	99,60	99,66
S2-2B	B	40°C	75% rel. hum.	Microcrystalline cellulose	HPMC 6 mPas	L-HPC LH21	magnesium stearate	99,69	99,63	98,57	99,39
S2-3A	A	50°C	dry	Lactose monohydrate	PVP25	Crospovidone	Talcum	99,66	99,58	99,54	99,56
S2-3B	B	50°C	dry	Lactose monohydrate	PVP25	Crospovidone	Talcum	99,57	95,82	91,04	85,33
S2-4A	A	40°C	75% rel. hum.	Lactose monohydrate	PVP25	Crospovidone	Talcum	99,66	99,93	99,72	99,86
S2-4B	B	40°C	75% rel. hum.	Lactose monohydrate	PVP25	Crospovidone	Talcum	99,57	99,22	99,05	96,87

5

Example X1

Analysis – XRPD (X-Ray Powder Diffraction) or PXRD (Powder X-Ray Diffraction)

XRPD analyses were carried out in transmission geometry with a STOE StadiP or a Panalytical X'Pert Pro X-ray powder diffractometer in reflection geometry, monochromatised CuKα radiation being used by means of a germanium monocrystal. Measurements were carried out in an angular range between 5° and 50° in 2θ. In general, the 2θ values have an error rate of ±0.2° in 2θ.

The samples were measured without any special treatment other than the application of slight pressure to get a flat surface. An ambient air atmosphere was used. . Unless stated otherwise, measurements were performed at room temperature (i.e. 298 K (± 5 K)).

In general a baseline correction of the measured diffractograms was done using the program WinXPow (STOE).

Crystalline Form A

Table 14 shows the peak list for crystalline form A. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 14

d value [A]	2θ [°]	rel. I [%]
11,5	7,7	27
10,2	8,7	33
9,3	9,5	9
8,8	10,0	33
7,9	11,2	6
7,5	11,9	85
7,2	12,3	25
5,8	15,3	73
5,6	15,8	34
5,5	16,2	19
5,3	16,7	53

5,1	17,4	79
5,0	17,8	100
4,8	18,3	83
4,7	18,8	14
4,6	19,2	12
4,5	19,7	35
4,4	20,2	38
4,2	21,3	19
4,1	21,5	13
4,0	21,9	58
4,0	22,2	35
3,9	22,5	29

3,9	23,1	15
3,7	23,9	18
3,6	24,8	15
3,5	25,2	7
3,5	25,7	14
3,4	26,2	29
3,3	27,1	38
3,2	27,9	7
3,2	28,2	10
3,1	28,5	14
3,1	29,0	6
3,1	29,2	5

d value [Å]	2θ [°]	rel. I [%]
3,0	29,6	7
3,0	30,0	4
2,9	30,4	11
2,9	31,1	13
2,8	31,6	5
2,7	32,7	10
2,7	33,5	5
2,6	34,1	9
2,6	34,9	6
2,5	36,5	5
2,4	37,4	8
2,4	38,2	6
2,3	38,9	5
2,3	39,1	4
2,2	40,1	7
2,2	41,2	5
2,2	41,9	4
2,1	42,6	5
2,1	43,0	3
2,1	43,7	11
2,0	44,4	4
2,0	45,0	2
1,9	48,0	4

Crystalline Form B

Table 15 shows the peak list for crystalline form B. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum intensity is 100.

Table 15

d value [Å]	2θ [°]	rel. I [%]
12,9	6,8	40
12,0	7,3	29
8,8	10,0	4
8,6	10,3	10
7,6	11,6	9
7,3	12,1	100
6,8	13,0	15
6,5	13,7	21
6,3	14,1	39
5,7	15,5	30
5,6	15,8	4
5,4	16,3	7
5,3	16,8	11
5,0	17,6	12
4,9	18,0	56
4,8	18,4	52
4,7	18,7	81
4,6	19,3	18
4,5	19,5	14
4,5	19,8	46
4,4	20,2	3
4,3	20,8	38
4,0	22,1	28
4,0	22,4	19
3,9	22,7	9
3,9	23,0	5
3,8	23,3	12
3,7	24,0	2
3,6	24,4	10
3,6	25,0	4
3,5	25,4	12
3,4	26,2	8
3,3	26,9	7
3,3	27,4	3
3,2	27,8	8
3,1	28,3	46
3,1	29,2	5
3,0	29,5	3
3,0	29,7	5
3,0	30,2	2
2,9	30,8	4
2,9	31,3	3
2,8	31,9	4
2,8	32,3	3
2,7	33,4	4
2,6	34,6	2
2,5	36,4	3
2,4	36,9	4
2,4	37,3	4
2,4	37,6	7
2,3	39,9	6
2,2	40,6	4
2,2	41,3	3
2,1	42,8	5
2,0	44,3	3
2,0	45,0	2
1,9	48,7	2

Crystalline Form C

Table 16 shows the peak list for crystalline form C. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 16

d value [Å]	2θ [°]	rel. I [%]
12,7	7,0	30
12,4	7,1	42
10,7	8,3	6
9,1	9,7	51
7,8	11,3	31
7,6	11,6	55
7,1	12,5	46
6,8	13,0	58
6,3	13,9	60
6,2	14,3	32
5,9	15,1	16
5,8	15,4	19
5,1	17,5	8

5,0	17,9	100
4,5	19,8	6
4,4	20,3	8
4,2	21,0	30
4,2	21,1	29
4,0	22,2	5
3,9	22,6	19
3,9	23,0	13
3,8	23,4	9
3,8	23,6	16
3,7	24,1	19
3,5	25,1	6
3,4	26,3	23
3,3	26,7	8

3,3	27,0	9
3,2	27,7	4
3,2	28,2	3
3,1	29,2	6
3,0	29,8	5
2,9	31,3	4
2,8	31,7	8
2,7	33,3	5
2,4	37,0	7
2,3	39,7	4
2,1	42,9	5
1,9	47,4	4

Crystalline Form D

Table 17 shows the peak list for crystalline form D. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 17

d value [Å]	2θ [°]	rel. I [%]
10,2	8,7	100
8,0	11,0	15
7,8	11,3	10
7,6	11,6	22
7,1	12,5	10
6,5	13,7	9
5,6	15,8	3
5,4	16,6	27
5,1	17,2	23
5,1	17,5	15

4,9	18,2	11
4,4	20,0	20
4,2	20,9	4
4,2	21,2	24
4,1	21,7	7
4,0	22,0	6
3,9	22,7	10
3,8	23,2	3
3,7	23,9	5
3,6	24,4	4
3,6	25,0	6
3,5	25,5	5

3,4	26,0	4
3,4	26,3	10
3,3	27,1	2
3,3	27,4	2
3,2	27,7	5
3,1	28,4	5
3,1	28,8	6
3,0	29,5	5
2,7	33,3	3
2,7	33,6	3
2,1	42,4	3
2,0	46,0	2

Crystalline Form E

Table 18 shows the peak list for crystalline form E. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 18

d value [Å]	2θ [°]	rel. I [%]
12,8	6,9	35
10,9	8,1	29
10,2	8,7	4
9,2	9,6	6
9,0	9,8	6
8,5	10,4	18
8,3	10,6	9
7,3	12,1	10
7,0	12,5	8
6,4	13,8	17
6,4	13,9	16
6,2	14,3	7
5,9	15,1	4
5,6	15,9	2
5,4	16,4	12
5,3	16,6	14

d value [Å]	2θ [°]	rel. I [%]
5,2	16,9	14
5,0	17,7	6
5,0	17,9	16
4,8	18,3	100
4,8	18,7	10
4,7	18,8	4
4,7	19,0	11
4,6	19,2	6
4,6	19,4	4
4,5	19,6	8
4,4	19,9	8
4,3	20,8	22
4,2	21,1	13
4,1	21,9	3
4,0	22,2	7
3,9	22,6	5
3,9	23,0	6
3,8	23,7	7

d value [Å]	2θ [°]	rel. I [%]
3,7	24,0	5
3,6	24,6	3
3,6	24,9	2
3,5	25,3	4
3,4	26,2	4
3,3	27,2	3
3,2	27,5	10
3,2	27,8	9
3,2	28,1	16
3,1	29,0	2
3,0	29,4	2
2,8	32,3	2
2,6	34,4	4
2,5	36,2	1
2,3	38,6	2
2,2	40,5	2
2,1	42,9	2

Crystalline Form F

Table 19 shows the peak list for crystalline form F. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 19

d value [Å]	2θ [°]	rel. I [%]
10,5	8,4	8
10,2	8,7	38
9,5	9,3	1
7,8	11,3	16
7,1	12,5	100
6,5	13,6	1
6,0	14,6	1
5,6	15,7	1
5,4	16,6	6
5,3	16,7	15

d value [Å]	2θ [°]	rel. I [%]
4,9	18,2	4
4,8	18,4	11
4,4	19,9	6
4,2	20,9	47
4,2	21,1	7
4,1	21,7	4
3,9	22,6	6
3,7	23,9	4
3,7	24,3	2
3,5	25,2	14
3,5	25,5	7
3,4	25,9	13

d value [Å]	2θ [°]	rel. I [%]
3,4	26,3	10
3,3	27,1	2
3,1	28,7	2
3,0	29,4	5
2,9	30,5	4
2,9	31,1	1
2,8	32,1	1
2,7	33,2	8
2,6	34,2	2
2,6	34,6	1

Crystalline Form G

Table 20 shows the peak list for crystalline form G. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 20

d value [Å]	2θ [°]	rel. I [%]
13,3	6,6	100
12,6	7,0	12
11,0	8,0	30
9,4	9,4	6
8,5	10,4	11
7,5	11,8	10
7,1	12,4	14
6,6	13,3	16
6,4	13,9	18
5,9	15,1	4
5,7	15,5	11

5,7	15,6	10
5,0	17,6	13
4,9	18,0	59
4,8	18,4	43
4,7	18,9	39
4,6	19,3	27
4,5	19,7	13
4,4	19,9	8
4,4	20,3	5
4,3	20,6	7
4,2	21,3	4
4,1	21,6	5

3,9	22,5	6
3,8	23,3	10
3,6	24,6	5
3,5	25,3	3
3,4	26,4	2
3,3	27,0	8
3,2	27,4	9
3,2	27,7	10
3,1	28,5	4

Crystalline Form H

Table 21 shows the peak list for crystalline form H. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 21

d value [Å]	2θ [°]	rel. I [%]
17,3	5,1	4
12,4	7,1	32
11,9	7,4	10
11,0	8,0	79
8,8	10,1	5
8,5	10,4	23
7,8	11,4	4
7,5	11,8	8
7,3	12,1	4
7,1	12,4	12
6,8	13,0	12
6,4	13,8	9

6,2	14,3	12
6,1	14,5	5
6,0	14,9	7
5,7	15,5	9
5,5	16,0	5
5,5	16,0	6
5,3	16,8	15
5,2	17,1	19
5,1	17,3	40
5,1	17,5	27
5,0	17,7	60
4,9	18,1	73
4,9	18,2	100

4,7	18,8	44
4,6	19,2	66
4,6	19,4	19
4,5	19,7	74
4,4	19,9	6
4,4	20,2	15
4,3	20,7	44
4,2	20,9	26
4,2	21,1	8
4,2	21,2	8
4,1	21,5	9
4,0	22,3	6
3,9	22,8	20

3,8	23,3	6
3,7	23,7	8
3,7	24,3	6
3,6	24,6	6
3,6	24,9	4
3,5	25,4	4
3,5	25,7	9
3,4	26,1	4
3,3	26,7	8
3,3	27,0	10
3,3	27,2	14
3,2	27,6	15
3,2	28,1	18
3,2	28,3	27

3,1	28,9	7
3,1	29,1	5
3,0	29,3	7
3,0	29,9	3
2,9	30,4	8
2,9	30,9	4
2,9	31,3	5
2,8	31,7	3
2,8	32,3	5
2,7	32,9	7
2,7	33,4	7
2,6	34,6	2
2,6	35,1	3
2,5	35,9	5

2,4	37,0	8
2,4	37,5	6
2,3	38,3	3
2,3	38,8	5
2,2	40,4	3
2,2	40,7	4
2,2	41,1	2
2,2	41,5	3
2,1	42,5	5
2,0	45,9	3
1,9	47,6	3
1,8	49,3	3

Crystalline Form I

Table 22 shows the peak list for crystalline form I. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 22

d value [Å]	2θ [°]	rel. I [%]
12,5	7,1	99
9,1	9,7	47
8,0	11,0	34
7,5	11,8	78
7,0	12,7	74
6,2	14,2	59
6,1	14,6	51
5,9	15,1	44

5,6	15,7	50
5,4	16,4	31
5,1	17,5	100
4,9	17,9	35
4,7	18,9	32
4,5	19,6	49
4,2	21,2	41
4,1	21,6	41
3,9	22,9	42
3,4	26,3	31

Crystalline Form J

Table 23 shows the peak list for crystalline form J. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 23

d value [Å]	2θ [°]	rel. I [%]
12,5	7,1	100
11,8	7,5	18
9,7	9,1	43
7,9	11,1	73
7,1	12,4	20
6,1	14,5	73
5,9	15,0	50
5,8	15,3	34
5,4	16,6	51
5,3	16,8	61
5,2	17,0	72
5,0	17,9	29
4,8	18,4	22
4,5	19,7	97
4,3	20,4	70
4,2	21,3	29
3,8	23,1	55
3,5	25,3	21
3,4	26,1	27
3,4	26,4	28
3,2	28,2	24
3,1	28,8	25
3,0	30,3	11
2,6	34,1	13
2,4	37,0	11
2,3	39,3	12
2,1	42,4	11
2,1	43,9	10

Crystalline Form K

Table 24 shows the peak list for crystalline form K. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 24

d value [Å]	2θ [°]	rel. I [%]
12,4	7,1	100
8,8	10,0	56
7,9	11,2	42
7,0	12,7	17
6,2	14,3	83
5,9	15,1	50
5,8	15,4	53
5,4	16,4	27
5,3	16,8	23
4,6	19,5	76
4,5	19,9	52
4,2	21,4	28
4,0	22,4	21
3,9	23,0	13
3,6	24,4	17
3,3	26,7	27
3,2	27,7	30
2,7	33,2	12
2,4	37,0	11

Crystalline Form L

Table 25 shows the peak list for crystalline form L. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 25

d value [Å]	2θ [°]	rel. I [%]
11,4	7,7	28
10,9	8,1	100
8,3	10,7	5
7,9	11,2	4
7,4	12,0	66
6,2	14,4	9
6,0	14,9	16
5,6	15,7	9
5,4	16,4	35
5,3	16,8	13
5,2	17,1	91

D value [Å]	2θ [°]	rel. I [%]
4,9	18,0	20
4,9	18,2	4
4,7	18,7	7
4,6	19,3	7
4,4	20,1	68
4,3	20,4	8
4,3	20,6	4
4,2	21,2	39
4,1	21,5	15
4,1	21,9	39
3,9	22,5	8
3,9	23,1	8
3,8	23,3	9
3,7	24,0	9
3,7	24,3	41
3,6	25,0	2
3,4	25,8	21
3,4	26,3	5

D value [Å]	2θ [°]	rel. I [%]
3,3	26,8	11
3,3	27,0	5
3,3	27,3	6
3,2	27,5	10
3,2	27,8	4
3,2	28,0	4
3,1	28,5	17
3,1	29,0	14
3,0	30,2	3
2,9	30,6	1
2,9	31,0	4
2,9	31,3	5
2,8	31,6	2
2,8	32,0	3
2,7	33,0	3
2,7	33,8	4
2,6	34,4	3
2,6	34,9	2

D value [Å]	2θ [°]	rel. I [%]
2,5	35,8	7
2,4	36,7	2
2,4	37,5	2
2,4	38,0	3
2,3	38,7	3
2,3	39,1	3
2,3	40,0	3
2,2	40,8	3
2,2	41,1	3
2,2	41,9	3
2,1	42,5	2
2,1	43,8	2
2,0	44,7	3
2,0	45,3	3
2,0	45,8	2
1,9	48,5	3
1,9	49,0	2
1,8	49,6	3

Crystalline Form Q

Table 26 shows the peak list for crystalline form Q. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum relative intensity is 100.

Table 26

D value [Å]	2θ [°]	rel. I [%]
10,7	8,2	49
10,2	8,6	40
8,1	11,0	23
7,7	11,5	18
7,3	12,0	26
6,1	14,5	7
5,9	15,0	10
5,4	16,5	28
5,2	17,2	100
5,0	17,6	12

D value [Å]	2θ [°]	rel. I [%]
4,9	18,0	12
4,4	20,1	19
4,2	21,3	18
4,1	21,6	16
4,0	22,0	13
3,9	22,6	7
3,6	24,4	18
3,6	25,1	10
3,4	26,0	10
3,1	28,5	11
3,1	29,2	5

Calculated XRPD

X-ray powder diffractogram (XRPD) may be calculated from a single crystal diffractogram (SCXRD) measured using MoK□ radiation having a wavelength of 0.71073 Å at 100 K (± 5 K) or 130 K (± 5 K)or 230 K (± 5 K). Due to the fact that the SCXRD was determined at 100 K (± 5 K) or 130 K (± 5 K) or at 230 K (± 5 K), the peak positions determined by a XRPD measured at 298 K (± 5 K) may differ because of temperature dependent variations of the lattice parameters of the unit cell. Therefore, the uncertainty in the 2θ values is ±1.0°, preferably ±0.9°, more preferably ±0.8°, even more preferably ±0.7°, still more preferably ±0.6°, yet more preferably ±0.5°, still yet more preferably ±0.4°, particularly ±0.3°, most preferably ±0.2°, in 2θ.

SCXRD (Single Crystal X-ray Diffraction)

Polymorph A   (measure at low temperature)

SCXRD analyses of crystalline forms A was carried out with a Bruker D8-goniometer with SMART APEX CCD area detector at 100 K (± 5 K) using MoKα radiation (wavelength of 0.71073 Å, Incoatec microsource, multilayer optics).

Table 27. Crystal data and structure refinement for ansolvat_lt.

Empirical formula	C33 H34 F N3 O
Formula weight	507.63
Temperature	100(2) K
Wavelength	.71073 A
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 12.1568(7) A alpha = 90 deg.
	b = 21.6289(12) A beta = 113.3610(10) deg.
	c = 10.9424(6) A gamma = 90 deg.
Volume	2641.3(3) A^3
Z	4
Density (calculated)	1.277 Mg/m^3
Absorption coefficient	0.082 mm^-1
F(000)	1080
Crystal size	0.45 x 0.21 x 0.08 mm
Theta range for data collection	1.82 to 28.30 deg.
Index ranges	-15<=h<=16, -27<=k<=28, -14<=l<=14
Reflections collected	30878
Independent reflections	6534 [R(int) = 0.0477]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6534 / 0 / 346
Goodness-of-fit on F^2	1.000

Final R indices [I>2sigma(I)]   R1 = 0.0497, wR2 = 0.1281
R indices (all data)   R1 = 0.0643, wR2 = 0.1405
Largest diff. peak and hole   .496 and -.260 e.A^-3

Table 28.
Atomic coordinates (x 10^4) and equivalent isotropic
displacement parameters (• ^2 x 10^3).   U(eq) is defined
as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
F(1)	-1204(1)	86(1)	877(1)	37(1)
O(1)	5159(1)	2358(1)	3238(1)	21(1)
N(1)	496(1)	2509(1)	936(1)	20(1)
N(2)	4304(1)	1813(1)	1278(1)	17(1)
N(3)	4431(1)	322(1)	3012(1)	18(1)
C(1)	-626(1)	567(1)	1675(2)	23(1)
C(2)	-32(1)	976(1)	1184(2)	20(1)
C(3)	611(1)	1466(1)	1983(1)	18(1)
C(4)	1255(1)	1945(1)	1456(1)	17(1)
C(5)	-720(1)	2372(1)	-34(2)	25(1)
C(6)	389(2)	2911(1)	1959(2)	23(1)
C(7)	1548(1)	1693(1)	300(1)	18(1)
C(8)	2454(1)	1166(1)	685(1)	18(1)
C(9)	3675(1)	1347(1)	1802(1)	17(1)
C(10)	5036(1)	2266(1)	2081(1)	16(1)
C(11)	5663(1)	2682(1)	1476(1)	18(1)
C(12)	6456(1)	3089(1)	2250(1)	19(1)
C(13)	7072(1)	3566(1)	1805(2)	20(1)
C(14)	7665(1)	4040(1)	2684(2)	26(1)
C(15)	8186(2)	4527(1)	2275(2)	33(1)
C(16)	8115(2)	4547(1)	980(2)	34(1)
C(17)	7544(1)	4073(1)	99(2)	29(1)
C(18)	7032(1)	3584(1)	506(2)	23(1)
C(19)	4616(1)	1555(1)	200(1)	21(1)
C(20)	5609(1)	1070(1)	749(2)	23(1)
C(21)	5339(1)	652(1)	1693(1)	19(1)
C(22)	4483(1)	790(1)	2172(1)	18(1)
C(23)	5276(1)	-121(1)	3095(1)	18(1)
C(24)	5862(1)	74(1)	2273(1)	19(1)
C(25)	6781(1)	-296(1)	2196(2)	22(1)
C(26)	7101(1)	-831(1)	2948(2)	26(1)
C(27)	6502(1)	-1016(1)	3749(2)	25(1)
C(28)	5576(1)	-666(1)	3830(2)	22(1)
C(29)	3343(1)	1574(1)	2947(1)	17(1)
C(30)	2476(1)	2124(1)	2558(1)	17(1)
C(31)	607(1)	1519(1)	3261(1)	20(1)
C(32)	-3(1)	1097(1)	3720(2)	23(1)
C(33)	-630(1)	608(1)	2927(2)	25(1)

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Table 29.   Bond lengths [A] and angles [deg]

F(1)-C(1)	1.3620(18)	C(20)-C(21)	1.503(2)
O(1)-C(10)	1.2307(17)	C(20)-H(20A)	.9900
N(1)-C(6)	1.4639(19)	C(20)-H(20B)	.9900
N(1)-C(5)	1.4685(19)	C(21)-C(22)	1.371(2)
N(1)-C(4)	1.4991(18)	C(21)-C(24)	1.432(2)
N(2)-C(10)	1.3785(18)	C(23)-C(28)	1.393(2)
N(2)-C(19)	1.4855(18)	C(23)-C(24)	1.415(2)
N(2)-C(9)	1.5091(17)	C(24)-C(25)	1.403(2)
N(3)-C(23)	1.3802(18)	C(25)-C(26)	1.385(2)
N(3)-C(22)	1.3856(18)	C(25)-H(25)	.9500
N(3)-H(3N)	.8663	C(26)-C(27)	1.401(2)
C(1)-C(33)	1.375(2)	C(26)-H(26)	.9500
C(1)-C(2)	1.378(2)	C(27)-C(28)	1.388(2)
C(2)-C(3)	1.398(2)	C(27)-H(27)	.9500
C(2)-H(2)	.9500	C(28)-H(28)	.9500
C(3)-C(31)	1.405(2)	C(29)-C(30)	1.533(2)
C(3)-C(4)	1.542(2)	C(29)-H(29A)	.9900
C(4)-C(7)	1.5436(19)	C(29)-H(29B)	.9900
C(4)-C(30)	1.5447(19)	C(30)-H(30A)	.9900
C(5)-H(5A)	.9800	C(30)-H(30B)	.9900
C(5)-H(5B)	.9800	C(31)-C(32)	1.389(2)
C(5)-H(5C)	.9800	C(31)-H(31)	.9500
C(6)-H(6A)	.9800	C(32)-C(33)	1.388(2)
C(6)-H(6B)	.9800	C(32)-H(32)	.9500
C(6)-H(6C)	.9800	C(33)-H(33)	.9500
C(7)-C(8)	1.523(2)		
C(7)-H(7A)	.9900	C(6)-N(1)-C(5)	107.70(12)
C(7)-H(7B)	.9900	C(6)-N(1)-C(4)	114.92(11)
C(8)-C(9)	1.5518(19)	C(5)-N(1)-C(4)	113.68(12)
C(8)-H(8A)	.9900	C(10)-N(2)-C(19)	117.99(11)
C(8)-H(8B)	.9900	C(10)-N(2)-C(9)	121.96(11)
C(9)-C(22)	1.506(2)	C(19)-N(2)-C(9)	112.14(11)
C(9)-C(29)	1.5408(19)	C(23)-N(3)-C(22)	108.75(12)
C(10)-C(11)	1.4938(19)	C(23)-N(3)-H(3N)	120.3
C(11)-C(12)	1.332(2)	C(22)-N(3)-H(3N)	130.5
C(11)-H(11)	.9500	F(1)-C(1)-C(33)	118.92(14)
C(12)-C(13)	1.466(2)	F(1)-C(1)-C(2)	117.24(14)
C(12)-H(12)	.9500	C(33)-C(1)-C(2)	123.80(14)
C(13)-C(14)	1.396(2)	C(1)-C(2)-C(3)	119.46(14)
C(13)-C(18)	1.403(2)	C(1)-C(2)-H(2)	120.3
C(14)-C(15)	1.391(2)	C(3)-C(2)-H(2)	120.3
C(14)-H(14)	.9500	C(2)-C(3)-C(31)	117.55(13)
C(15)-C(16)	1.386(3)	C(2)-C(3)-C(4)	121.08(13)
C(15)-H(15)	.9500	C(31)-C(3)-C(4)	121.32(13)
C(16)-C(17)	1.389(3)	N(1)-C(4)-C(7)	106.48(11)
C(16)-H(16)	.9500	N(1)-C(4)-C(3)	111.21(11)
C(17)-C(18)	1.388(2)	C(7)-C(4)-C(3)	112.67(12)
C(17)-H(17)	.9500	N(1)-C(4)-C(30)	110.43(11)
C(18)-H(18)	.9500	C(7)-C(4)-C(30)	105.39(11)
C(19)-C(20)	1.531(2)	C(3)-C(4)-C(30)	110.44(11)
C(19)-H(19A)	.9900	N(1)-C(5)-H(5A)	109.5
C(19)-H(19B)	.9900	N(1)-C(5)-H(5B)	109.5

H(5A)-C(5)-H(5B)	109.5
N(1)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
N(1)-C(6)-H(6A)	109.5
N(1)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
N(1)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(8)-C(7)-C(4)	114.44(12)
C(8)-C(7)-H(7A)	108.7
C(4)-C(7)-H(7A)	108.7
C(8)-C(7)-H(7B)	108.7
C(4)-C(7)-H(7B)	108.7
H(7A)-C(7)-H(7B)	107.6
C(7)-C(8)-C(9)	112.98(12)
C(7)-C(8)-H(8A)	109.0
C(9)-C(8)-H(8A)	109.0
C(7)-C(8)-H(8B)	109.0
C(9)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
C(22)-C(9)-N(2)	105.22(11)
C(22)-C(9)-C(29)	112.91(12)
N(2)-C(9)-C(29)	115.53(11)
C(22)-C(9)-C(8)	109.16(11)
N(2)-C(9)-C(8)	109.87(11)
C(29)-C(9)-C(8)	104.10(11)
O(1)-C(10)-N(2)	123.67(13)
O(1)-C(10)-C(11)	118.88(13)
N(2)-C(10)-C(11)	117.37(12)
C(12)-C(11)-C(10)	118.96(13)
C(12)-C(11)-H(11)	120.5
C(10)-C(11)-H(11)	120.5
C(11)-C(12)-C(13)	126.15(14)
C(11)-C(12)-H(12)	116.9
C(13)-C(12)-H(12)	116.9
C(14)-C(13)-C(18)	118.60(14)
C(14)-C(13)-C(12)	118.72(14)
C(18)-C(13)-C(12)	122.58(13)
C(15)-C(14)-C(13)	120.71(16)
C(15)-C(14)-H(14)	119.6
C(13)-C(14)-H(14)	119.6
C(16)-C(15)-C(14)	120.09(16)
C(16)-C(15)-H(15)	120.0
C(14)-C(15)-H(15)	120.0
C(17)-C(16)-C(15)	119.86(16)
C(17)-C(16)-H(16)	120.1
C(15)-C(16)-H(16)	120.1
C(18)-C(17)-C(16)	120.27(16)
C(18)-C(17)-H(17)	119.9
C(16)-C(17)-H(17)	119.9
C(17)-C(18)-C(13)	120.45(15)
C(17)-C(18)-H(18)	119.8
C(13)-C(18)-H(18)	119.8
N(2)-C(19)-C(20)	110.87(12)

N(2)-C(19)-H(19A)	109.5
C(20)-C(19)-H(19A)	109.5
N(2)-C(19)-H(19B)	109.5
C(20)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	108.1
C(21)-C(20)-C(19)	109.17(12)
C(21)-C(20)-H(20A)	109.8
C(19)-C(20)-H(20A)	109.8
C(21)-C(20)-H(20B)	109.8
C(19)-C(20)-H(20B)	109.8
H(20A)-C(20)-H(20B)	108.3
C(22)-C(21)-C(24)	106.88(13)
C(22)-C(21)-C(20)	122.57(14)
C(24)-C(21)-C(20)	130.55(13)
C(21)-C(22)-N(3)	109.70(13)
C(21)-C(22)-C(9)	125.74(13)
N(3)-C(22)-C(9)	124.51(12)
N(3)-C(23)-C(28)	130.03(13)
N(3)-C(23)-C(24)	107.51(13)
C(28)-C(23)-C(24)	122.45(14)
C(25)-C(24)-C(23)	118.81(14)
C(25)-C(24)-C(21)	134.01(14)
C(23)-C(24)-C(21)	107.16(13)
C(26)-C(25)-C(24)	118.90(14)
C(26)-C(25)-H(25)	120.5
C(24)-C(25)-H(25)	120.5
C(25)-C(26)-C(27)	121.20(14)
C(25)-C(26)-H(26)	119.4
C(27)-C(26)-H(26)	119.4
C(28)-C(27)-C(26)	121.30(15)
C(28)-C(27)-H(27)	119.4
C(26)-C(27)-H(27)	119.4
C(27)-C(28)-C(23)	117.31(14)
C(27)-C(28)-H(28)	121.3
C(23)-C(28)-H(28)	121.3
C(30)-C(29)-C(9)	113.19(11)
C(30)-C(29)-H(29A)	108.9
C(9)-C(29)-H(29A)	108.9
C(30)-C(29)-H(29B)	108.9
C(9)-C(29)-H(29B)	108.9
H(29A)-C(29)-H(29B)	107.8
C(29)-C(30)-C(4)	111.40(11)
C(29)-C(30)-H(30A)	109.3
C(4)-C(30)-H(30A)	109.3
C(29)-C(30)-H(30B)	109.3
C(4)-C(30)-H(30B)	109.3
H(30A)-C(30)-H(30B)	108.0
C(32)-C(31)-C(3)	121.30(14)
C(32)-C(31)-H(31)	119.4
C(3)-C(31)-H(31)	119.4
C(33)-C(32)-C(31)	120.89(14)
C(33)-C(32)-H(32)	119.6
C(31)-C(32)-H(32)	119.6
C(1)-C(33)-C(32)	117.00(14)
C(1)-C(33)-H(33)	121.5
C(32)-C(33)-H(33)	121.5

Table 30. Hydrogen coordinates (x 10^4) and isotropic
displacement parameters (• ^2 x 10^3).

	x	y	z	U(eq)
H(2)	-60	926	310	24
H(5A)	-1181	2177	421	37
H(5B)	-677	2090	-715	37
H(5C)	-1115	2756	-457	37
H(6A)	-79	3279	1538	35
H(6B)	1189	3037	2583	35
H(6C)	-15	2687	2441	35
H(7A)	797	1547	-415	22
H(7B)	1863	2036	-67	22
H(8A)	2589	1034	-111	22
H(8B)	2118	810	989	22
H(11)	5498	2658	552	21
H(12)	6640	3068	3177	23
H(14)	7712	4031	3572	31
H(15)	8592	4846	2884	40
H(16)	8456	4884	695	40
H(17)	7504	4084	-786	35
H(18)	6652	3259	-98	27
H(19A)	4886	1892	-227	25
H(19B)	3896	1363	-487	25
H(20A)	5657	824	9	28
H(20B)	6391	1277	1221	28
H(25)	7177	-180	1636	27
H(26)	7737	-1078	2921	31
H(27)	6734	-1389	4247	29
H(28)	5164	-794	4365	26
H(29A)	2973	1228	3242	20
H(29B)	4085	1695	3709	20
H(30A)	2832	2467	2239	21
H(30B)	2352	2270	3351	21
H(31)	1030	1850	3822	24
H(32)	9	1144	4588	27
H(33)	-1043	315	3236	30
H(3N)	4032	297	3514	39(6)

Table 31. Anisotropic displacement parameters (• ^2 x 10^3).
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
F(1)	42(1)	36(1)	39(1)	−16(1)	23(1)	−22(1)
O(1)	26(1)	23(1)	16(1)	−3(1)	10(1)	−6(1)
N(1)	22(1)	19(1)	18(1)	1(1)	7(1)	0(1)
N(2)	21(1)	17(1)	15(1)	−1(1)	10(1)	−4(1)
N(3)	20(1)	19(1)	20(1)	1(1)	12(1)	0(1)
C(1)	22(1)	21(1)	28(1)	−6(1)	11(1)	−5(1)
C(2)	20(1)	23(1)	19(1)	−2(1)	8(1)	−1(1)
C(3)	16(1)	18(1)	18(1)	1(1)	6(1)	1(1)
C(4)	19(1)	17(1)	15(1)	0(1)	7(1)	·0(1)
C(5)	22(1)	27(1)	23(1)	2(1)	6(1)	2(1)
C(6)	28(1)	19(1)	23(1)	0(1)	11(1)	2(1)
C(7)	20(1)	21(1)	14(1)	−1(1)	7(1)	−2(1)
C(8)	21(1)	19(1)	16(1)	−4(1)	8(1)	−4(1)
C(9)	21(1)	15(1)	16(1)	−1(1)	9(1)	−3(1)
C(10)	17(1)	15(1)	15(1)	0(1)	6(1)	0(1)
C(11)	20(1)	17(1)	16(1)	1(1)	7(1)	−1(1)
C(12)	20(1)	20(1)	18(1)	2(1)	7(1)	0(1)
C(13)	16(1)	18(1)	24(1)	2(1)	6(1)	0(1)
C(14)	23(1)	24(1)	31(1)	−3(1)	10(1)	−4(1)
C(15)	26(1)	21(1)	51(1)	−4(1)	14(1)	−5(1)
C(16)	26(1)	24(1)	51(1)	11(1)	17(1)	−3(1)
C(17)	21(1)	33(1)	32(1)	13(1)	10(1)	1(1)
C(18)	19(1)	25(1)	22(1)	3(1)	6(1)	−2(1)
C(19)	30(1)	22(1)	16(1)	−4(1)	13(1)	−7(1)
C(20)	28(1)	23(1)	24(1)	−5(1)	17(1)	−6(1)
C(21)	20(1)	19(1)	19(1)	−6(1)	10(1)	−5(1)
C(22)	20(1)	17(1)	18(1)	−2(1)	9(1)	−4(1)
C(23)	17(1)	19(1)	19(1)	−5(1)	7(1)	−3(1)
C(24)	18(1)	20(1)	20(1)	−7(1)	8(1)	−5(1)
C(25)	19(1)	25(1)	25(1)	−10(1)	10(1)	−4(1)
C(26)	20(1)	27(1)	28(1)	−10(1)	7(1)	1(1)
C(27)	26(1)	19(1)	24(1)	−3(1)	5(1)	2(1)
C(28)	22(1)	21(1)	21(1)	−3(1)	8(1)	−2(1)
C(29)	19(1)	19(1)	14(1)	−1(1)	8(1)	−3(1)
C(30)	19(1)	18(1)	15(1)	−2(1)	7(1)	−2(1)
C(31)	21(1)	22(1)	17(1)	−1(1)	7(1)	−1(1)
C(32)	23(1)	26(1)	21(1)	1(1)	11(1)	−1(1)
C(33)	24(1)	25(1)	29(1)	1(1)	14(1)	−4(1)

Example X2

Polymorph A   (measured at high temperature)

SCXRD (Single Crystal X-ray Diffraction)

SCXRD analyses of crystalline forms A was carried out with a Bruker D8-goniometer with SMART APEX CCD area detector at 230 K (± 5 K) using MoKα radiation (wavelength of 0.71073 Å, Incoatec microsource, multilayer optics).

Table 32. Crystal data and structure refinement

Empirical formula	C33 H34 F N3 O
Formula weight	507.63
Temperature	230(2) K
Wavelength	.71073 A
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 12.2651(9) A alpha = 90 deg.
	b = 21.6265(16) A beta = 112.395(2) deg.
	c = 10.9590(8) A gamma = 90 deg.
Volume	2687.6(3) A^3
Z	4
Density (calculated)	1.255 Mg/m^3
Absorption coefficient	0.081 mm^-1
F(000)	1080
Crystal size	0.45 x 0.21 x 0.08 mm
Theta range for data collection	1.80 to 28.27 deg.
Index ranges	-16<=h<=15, -27<=k<=28, -14<=l<=14
Reflections collected	31943
Independent reflections	6654 [R(int) = 0.1802]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6654 / 0 / 346
Goodness-of-fit on F^2	0.946
Final R indices [I>2sigma(I)]	R1 = 0.0625, wR2 = 0.1445
R indices (all data)	R1 = 0.1004, wR2 = 0.1600
Largest diff. peak and hole	0.323 and -0.319 e.A^-3

Table 33. Atomic coordinates (x 10^4) and equivalent isotropic
displacement parameters (• ^2 x 10^3) .   U(eq) is defined
as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
F(1)	-1154(1)	73(1)	906(1)	80(1)
O(1)	5140(1)	2339(1)	3240(1)	46(1)
N(1)	523(1)	2490(1)	956(1)	44(1)
N(2)	4294(1)	1814(1)	1283(1)	36(1)
N(3)	4436(1)	321(1)	3004(1)	39(1)
C(1)	-587(2)	552(1)	1706(2)	49(1)
C(2)	4(2)	961(1)	1214(2)	44(1)
C(3)	631(2)	1448(1)	1996(2)	37(1)
C(4)	1271(2)	1926(1)	1468(2)	38(1)
C(5)	-666(2)	2354(1)	-17(2)	57(1)
C(6)	404(2)	2894(1)	1960(2)	54(1)
C(7)	1583(2)	1676(1)	328(2)	40(1)
C(8)	2481(2)	1157(1)	705(2)	39(1)
C(9)	3674(2)	1343(1)	1810(2)	35(1)
C(10)	5019(2)	2259(1)	2092(2)	34(1)
C(11)	5639(2)	2682(1)	1497(2)	37(1)
C(12)	6430(2)	3075(1)	2249(2)	40(1)
C(13)	7046(2)	3554(1)	1808(2)	41(1)
C(14)	7639(2)	4016(1)	2688(2)	54(1)
C(15)	8160(2)	4500(1)	2280(3)	69(1)
C(16)	8091(2)	4533(1)	1016(3)	73(1)
C(17)	7520(2)	4072(1)	132(2)	64(1)
C(18)	7009(2)	3583(1)	532(2)	50(1)
C(19)	4608(2)	1562(1)	205(2)	45(1)
C(20)	5583(2)	1082(1)	734(2)	49(1)
C(21)	5331(2)	661(1)	1678(2)	40(1)
C(22)	4476(2)	790(1)	2163(2)	37(1)
C(23)	5283(2)	-116(1)	3077(2)	39(1)
C(24)	5850(2)	88(1)	2250(2)	40(1)
C(25)	6770(2)	-276(1)	2165(2)	48(1)
C(26)	7086(2)	-810(1)	2904(2)	55(1)
C(27)	6504(2)	-1002(1)	3707(2)	54(1)
C(28)	5592(2)	-658(1)	3807(2)	46(1)
C(29)	3323(2)	1567(1)	2941(2)	37(1)
C(30)	2460(2)	2108(1)	2552(2)	38(1)
C(31)	614(2)	1497(1)	3259(2)	43(1)
C(32)	6(2)	1079(1)	3721(2)	50(1)
C(33)	-606(2)	594(1)	2931(2)	54(1)

Table 34.   Bond lengths [A] and angles [deg] .

F(1)-C(1)	1.365(2)	C(19)-H(19B)	.9800
O(1)-C(10)	1.2214(18)	C(20)-C(21)	1.497(3)
N(1)-C(6)	1.455(2)	C(20)-H(20A)	.9800
N(1)-C(5)	1.472(2)	C(20)-H(20B)	.9800
N(1)-C(4)	1.502(2)	C(21)-C(22)	1.372(2)
N(2)-C(10)	1.379(2)	C(21)-C(24)	1.425(3)
N(2)-C(19)	1.479(2)	C(23)-C(28)	1.387(3)
N(2)-C(9)	1.512(2)	C(23)-C(24)	1.408(3)
N(3)-C(22)	1.383(2)	C(24)-C(25)	1.406(3)
N(3)-C(23)	1.385(2)	C(25)-C(26)	1.378(3)
N(3)-H(3N)	.8609	C(25)-H(25)	.9400
C(1)-C(33)	1.355(3)	C(26)-C(27)	1.392(3)
C(1)-C(2)	1.377(3)	C(26)-H(26)	.9400
C(2)-C(3)	1.391(3)	C(27)-C(28)	1.383(3)
C(2)-H(2)	.9400	C(27)-H(27)	.9400
C(3)-C(31)	1.396(2)	C(28)-H(28)	.9400
C(3)-C(4)	1.537(3)	C(29)-C(30)	1.527(3)
C(4)-C(7)	1.537(2)	C(29)-H(29A)	.9800
C(4)-C(30)	1.540(2)	C(29)-H(29B)	.9800
C(5)-H(5A)	.9700	C(30)-H(30A)	.9800
C(5)-H(5B)	.9700	C(30)-H(30B)	.9800
C(5)-H(5C)	.9700	C(31)-C(32)	1.384(3)
C(6)-H(6A)	.9700	C(31)-H(31)	.9400
C(6)-H(6B)	.9700	C(32)-C(33)	1.385(3)
C(6)-H(6C)	.9700	C(32)-H(32)	.9400
C(7)-C(8)	1.515(3)	C(33)-H(33)	.9400
C(7)-H(7A)	.9800		
C(7)-H(7B)	.9800	C(6)-N(1)-C(5)	108.11(16)
C(8)-C(9)	1.556(2)	C(6)-N(1)-C(4)	115.41(14)
C(8)-H(8A)	.9800	C(5)-N(1)-C(4)	113.77(16)
C(8)-H(8B)	.9800	C(10)-N(2)-C(19)	118.05(15)
C(9)-C(22)	1.502(3)	C(10)-N(2)-C(9)	121.32(13)
C(9)-C(29)	1.538(2)	C(19)-N(2)-C(9)	112.20(14)
C(10)-C(11)	1.490(2)	C(22)-N(3)-C(23)	108.89(15)
C(11)-C(12)	1.316(2)	C(22)-N(3)-H(3N)	132.3
C(11)-H(11)	.9400	C(23)-N(3)-H(3N)	118.4
C(12)-C(13)	1.469(3)	C(33)-C(1)-F(1)	119.36(19)
C(12)-H(12)	.9400	C(33)-C(1)-C(2)	123.77(19)
C(13)-C(18)	1.383(3)	F(1)-C(1)-C(2)	116.85(17)
C(13)-C(14)	1.387(3)	C(1)-C(2)-C(3)	119.68(18)
C(14)-C(15)	1.387(3)	C(1)-C(2)-H(2)	120.2
C(14)-H(14)	.9400	C(3)-C(2)-H(2)	120.2
C(15)-C(16)	1.357(3)	C(2)-C(3)-C(31)	117.03(17)
C(15)-H(15)	.9400	C(2)-C(3)-C(4)	121.23(16)
C(16)-C(17)	1.381(3)	C(31)-C(3)-C(4)	121.69(16)
C(16)-H(16)	.9400	N(1)-C(4)-C(7)	106.69(14)
C(17)-C(18)	1.383(3)	N(1)-C(4)-C(3)	111.08(15)
C(17)-H(17)	.9400	C(7)-C(4)-C(3)	113.06(15)
C(18)-H(18)	.9400	N(1)-C(4)-C(30)	110.08(15)
C(19)-C(20)	1.521(3)	C(7)-C(4)-C(30)	105.17(15)
C(19)-H(19A)	.9800	C(3)-C(4)-C(30)	110.54(14)

Angle	Value	Angle	Value
N(1)-C(5)-H(5A)	109.5	C(13)-C(18)-H(18)	119.6
N(1)-C(5)-H(5B)	109.5	N(2)-C(19)-C(20)	110.73(15)
H(5A)-C(5)-H(5B)	109.5	N(2)-C(19)-H(19A)	109.5
N(1)-C(5)-H(5C)	109.5	C(20)-C(19)-H(19A)	109.5
H(5A)-C(5)-H(5C)	109.5	N(2)-C(19)-H(19B)	109.5
H(5B)-C(5)-H(5C)	109.5	C(20)-C(19)-H(19B)	109.5
N(1)-C(6)-H(6A)	109.5	H(19A)-C(19)-H(19B)	108.1
N(1)-C(6)-H(6B)	109.5	C(21)-C(20)-C(19)	109.80(16)
H(6A)-C(6)-H(6B)	109.5	C(21)-C(20)-H(20A)	109.7
N(1)-C(6)-H(6C)	109.5	C(19)-C(20)-H(20A)	109.7
H(6A)-C(6)-H(6C)	109.5	C(21)-C(20)-H(20B)	109.7
H(6B)-C(6)-H(6C)	109.5	C(19)-C(20)-H(20B)	109.7
C(8)-C(7)-C(4)	114.70(15)	H(20A)-C(20)-H(20B)	108.2
C(8)-C(7)-H(7A)	108.6	C(22)-C(21)-C(24)	106.63(16)
C(4)-C(7)-H(7A)	108.6	C(22)-C(21)-C(20)	122.25(19)
C(8)-C(7)-H(7B)	108.6	C(24)-C(21)-C(20)	131.12(17)
C(4)-C(7)-H(7B)	108.6	C(21)-C(22)-N(3)	109.58(17)
H(7A)-C(7)-H(7B)	107.6	C(21)-C(22)-C(9)	125.71(17)
C(7)-C(8)-C(9)	113.05(15)	N(3)-C(22)-C(9)	124.67(16)
C(7)-C(8)-H(8A)	109.0	N(3)-C(23)-C(28)	130.15(17)
C(9)-C(8)-H(8A)	109.0	N(3)-C(23)-C(24)	106.96(17)
C(7)-C(8)-H(8B)	109.0	C(28)-C(23)-C(24)	122.88(18)
C(9)-C(8)-H(8B)	109.0	C(25)-C(24)-C(23)	118.18(19)
H(8A)-C(8)-H(8B)	107.8	C(25)-C(24)-C(21)	133.87(18)
C(22)-C(9)-N(2)	105.07(14)	C(23)-C(24)-C(21)	107.94(16)
C(22)-C(9)-C(29)	113.57(14)	C(26)-C(25)-C(24)	118.92(19)
N(2)-C(9)-C(29)	115.57(14)	C(26)-C(25)-H(25)	120.5
C(22)-C(9)-C(8)	108.97(15)	C(24)-C(25)-H(25)	120.5
N(2)-C(9)-C(8)	109.74(13)	C(25)-C(26)-C(27)	121.6(2)
C(29)-C(9)-C(8)	103.86(14)	C(25)-C(26)-H(26)	119.2
O(1)-C(10)-N(2)	123.79(16)	C(27)-C(26)-H(26)	119.2
O(1)-C(10)-C(11)	118.84(16)	C(28)-C(27)-C(26)	120.9(2)
N(2)-C(10)-C(11)	117.30(14)	C(28)-C(27)-H(27)	119.5
C(12)-C(11)-C(10)	120.00(16)	C(26)-C(27)-H(27)	119.5
C(12)-C(11)-H(11)	120.0	C(27)-C(28)-C(23)	117.43(19)
C(10)-C(11)-H(11)	120.0	C(27)-C(28)-H(28)	121.3
C(11)-C(12)-C(13)	126.77(17)	C(23)-C(28)-H(28)	121.3
C(11)-C(12)-H(12)	116.6	C(30)-C(29)-C(9)	113.18(14)
C(13)-C(12)-H(12)	116.6	C(30)-C(29)-H(29A)	108.9
C(18)-C(13)-C(14)	118.47(19)	C(9)-C(29)-H(29A)	108.9
C(18)-C(13)-C(12)	122.80(17)	C(30)-C(29)-H(29B)	108.9
C(14)-C(13)-C(12)	118.64(18)	C(9)-C(29)-H(29B)	108.9
C(15)-C(14)-C(13)	120.3(2)	H(29A)-C(29)-H(29B)	107.8
C(15)-C(14)-H(14)	119.9	C(29)-C(30)-C(4)	111.75(15)
C(13)-C(14)-H(14)	119.9	C(29)-C(30)-H(30A)	109.3
C(16)-C(15)-C(14)	120.7(2)	C(4)-C(30)-H(30A)	109.3
C(16)-C(15)-H(15)	119.6	C(29)-C(30)-H(30B)	109.3
C(14)-C(15)-H(15)	119.6	C(4)-C(30)-H(30B)	109.3
C(15)-C(16)-C(17)	119.8(2)	H(30A)-C(30)-H(30B)	107.9
C(15)-C(16)-H(16)	120.1	C(32)-C(31)-C(3)	121.78(18)
C(17)-C(16)-H(16)	120.1		
C(16)-C(17)-C(18)	119.9(2)	C(32)-C(31)-H(31)	119.1
C(16)-C(17)-H(17)	120.0	C(3)-C(31)-H(31)	119.1
C(18)-C(17)-H(17)	120.0	C(31)-C(32)-C(33)	120.36(19)
C(17)-C(18)-C(13)	120.8(2)		
C(17)-C(18)-H(18)	119.6	C(31)-C(32)-H(32)	119.8

| C(33)-C(32)-H(32) | 119.8 | C(1)-C(33)-H(33) | 121.3 |
| C(1)-C(33)-C(32) | 117.4(2) | C(32)-C(33)-H(33) | 121.3 |

Table 35. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (• ^2 x 10^3) for ansolvat_ht.

	x	y	z	U(eq)
H(2)	-15	910	354	52
H(5A)	-1135	2167	427	85
H(5B)	-609	2069	-675	85
H(5C)	-1038	2734	-443	85
H(6A)	-22	3265	1545	81
H(6B)	1181	3007	2588	81
H(6C)	-25	2681	2416	81
H(7A)	859	1528	-372	49
H(7B)	1889	2018	-36	49
H(8A)	2624	1029	-79	47
H(8B)	2154	802	1005	47
H(11)	5465	2669	585	45
H(12)	6620	3046	3163	49
H(14)	7687	4001	3564	65
H(15)	8565	4810	2886	82
H(16)	8432	4868	744	88
H(17)	7480	4090	-742	77
H(18)	6631	3267	-70	60
H(19A)	4872	1899	-215	54
H(19B)	3911	1372	-464	54
H(20A)	5633	841	0	59
H(20B)	6341	1290	1184	59
H(25)	7161	-157	1614	58
H(26)	7711	-1050	2864	66
H(27)	6735	-1372	4188	65
H(28)	5196	-786	4349	56
H(29A)	2964	1222	3235	44
H(29B)	4036	1692	3687	44
H(30A)	2806	2450	2234	45
H(30B)	2326	2253	3331	45
H(31)	1027	1822	3811	52
H(32)	8	1125	4574	60
H(33)	-1017	304	3234	64
H(3N)	4057	282	3518	72(7)

80

Table 36. Anisotropic displacement parameters (• ^2 x 10^3).
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
F(1)	80(1)	78(1)	96(1)	-37(1)	50(1)	-45(1)
O(1)	51(1)	53(1)	37(1)	-8(1)	20(1)	-15(1)
N(1)	42(1)	43(1)	43(1)	1(1)	12(1)	3(1)
N(2)	42(1)	37(1)	34(1)	-5(1)	17(1)	-11(1)
N(3)	38(1)	39(1)	49(1)	1(1)	25(1)	-3(1)
C(1)	42(1)	47(1)	62(1)	-13(1)	23(1)	-13(1)
C(2)	38(1)	49(1)	47(1)	-4(1)	19(1)	-5(1)
C(3)	32(1)	37(1)	40(1)	-1(1)	12(1)	1(1)
C(4)	38(1)	37(1)	38(1)	0(1)	14(1)	-2(1)
C(5)	42(1)	60(2)	60(1)	5(1)	10(1)	5(1)
C(6)	60(1)	44(1)	59(1)	3(1)	24(1)	9(1)
C(7)	39(1)	45(1)	36(1)	-1(1)	13(1)	-6(1)
C(8)	40(1)	40(1)	39(1)	-6(1)	17(1)	-9(1)
C(9)	37(1)	34(1)	36(1)	-3(1)	17(1)	-9(1)
C(10)	34(1)	35(1)	32(1)	-1(1)	11(1)	-1(1)
C(11)	37(1)	40(1)	34(1)	2(1)	12(1)	-3(1)
C(12)	38(1)	42(1)	40(1)	1(1)	13(1)	-6(1)
C(13)	31(1)	39(1)	48(1)	4(1)	10(1)	-1(1)
C(14)	45(1)	49(1)	68(1)	-6(1)	20(1)	-11(1)
C(15)	54(1)	46(2)	106(2)	-7(1)	30(1)	-15(1)
C(16)	54(2)	52(2)	113(2)	26(2)	33(2)	-8(1)
C(17)	45(1)	72(2)	75(2)	30(1)	22(1)	-3(1)
C(18)	36(1)	57(1)	52(1)	9(1)	12(1)	-8(1)
C(19)	60(1)	44(1)	37(1)	-9(1)	26(1)	-18(1)
C(20)	57(1)	47(1)	55(1)	-11(1)	35(1)	-13(1)
C(21)	41(1)	42(1)	45(1)	-12(1)	24(1)	-11(1)
C(22)	35(1)	38(1)	40(1)	-3(1)	18(1)	-8(1)
C(23)	33(1)	39(1)	45(1)	-7(1)	15(1)	-5(1)
C(24)	33(1)	43(1)	45(1)	-13(1)	17(1)	-9(1)
C(25)	37(1)	53(1)	58(1)	-20(1)	24(1)	-9(1)
C(26)	38(1)	60(2)	64(1)	-20(1)	15(1)	5(1)
C(27)	48(1)	48(1)	60(1)	-4(1)	12(1)	5(1)
C(28)	42(1)	45(1)	51(1)	-2(1)	17(1)	-2(1)
C(29)	38(1)	38(1)	36(1)	-2(1)	16(1)	-7(1)
C(30)	38(1)	37(1)	38(1)	-3(1)	15(1)	-5(1)
C(31)	39(1)	46(1)	45(1)	-4(1)	16(1)	-6(1)
C(32)	46(1)	59(2)	49(1)	0(1)	24(1)	-6(1)
C(33)	47(1)	55(1)	67(1)	-2(1)	31(1)	-12(1)

Polymorph B

<u>SCXRD (Single Crystal X-ray Diffraction)</u>

SCXRD analyses of crystalline forms A was carried out with a Bruker D8-goniometer with SMART APEX CCD area detector at 100 K (± 5 K) using MoKα radiation (wavelength of 0.71073 Å, Incoatec microsource, multilayer optics).

Table 37. Crystal data and structure refinement

Identification code	GM391-063-P1A1
Empirical formula	C33 H40 F N3 O4
Formula weight	561.68
Temperature	100(2) K
Wavelength	.71073 A
Crystal system	Orthorhombic
Space group	P b c a
Unit cell dimensions	a = 9.6937(12) A alpha = 90 deg.
	b = 25.858(3) A beta = 90 deg.
	c = 23.491(3) A gamma = 90 deg.
Volume	5888.2(13) A^3
Z	8
Density (calculated)	1.267 Mg/m^3
Absorption coefficient	0.088 mm^-1
F(000)	2400
Crystal size	0.31 x 0.08 x 0.02 mm
Theta range for data collection	1.73 to 17.30 deg.
Index ranges	-8<=h<=8, -21<=k<=21, -19<=l<=19
Reflections collected	17449
Independent reflections	1797 [R(int) = 0.0904]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1797 / 48 / 172
Goodness-of-fit on F^2	1.200
Final R indices [I>2sigma(I)]	R1 = 0.1515, wR2 = 0.3024
R indices (all data)	R1 = 0.1580, wR2 = 0.3055
Largest diff. peak and hole	.840 and -.560 e.A^-3

Table 38. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (• ^2 x 10^3) .   U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
F(1)	3998(14)	561(5)	-65(6)	103(4)
O(1)	3137(11)	3318(4)	1280(4)	25(3)
N(1)	5513(13)	1742(5)	1773(5)	28(3)
N(2)	5488(14)	3380(5)	1096(5)	27(3)
N(3)	5620(13)	3217(5)	-476(5)	28(3)
C(1)	5090(2)	866(8)	147(9)	68(4)
C(2)	4810(2)	1264(7)	499(8)	54(4)
C(3)	5880(19)	1543(7)	733(7)	39(3)
C(4)	5623(17)	1971(6)	1163(7)	29(3)
C(5)	4444(16)	1347(6)	1830(7)	30(4)
C(6)	6828(17)	1541(6)	2007(7)	36(5)
C(7)	4322(17)	2265(6)	1046(7)	29(3)
C(8)	4417(17)	2636(6)	550(7)	28(3)
C(9)	5599(17)	3021(6)	599(7)	26(3)
C(10)	4323(18)	3484(6)	1405(7)	29(3)
C(11)	4500(18)	3800(6)	1921(7)	28(3)
C(12)	3543(17)	4105(6)	2110(7)	27(3)
C(13)	3517(18)	4420(6)	2622(7)	31(3)
C(14)	4506(18)	4318(7)	3040(7)	37(4)
C(15)	4484(19)	4648(7)	3532(7)	44(4)
C(16)	3521(19)	5025(7)	3594(8)	44(4)
C(17)	2600(2)	5106(7)	3188(7)	40(4)
C(18)	2531(19)	4802(6)	2696(7)	34(4)
C(19)	6546(17)	3776(6)	1108(7)	26(3)
C(20)	6241(17)	4176(6)	659(6)	27(3)
C(21)	5960(17)	3893(6)	121(7)	29(3)
C(22)	5736(17)	3387(6)	87(7)	27(3)
C(23)	5778(17)	3656(6)	-818(7)	31(3)
C(24)	6009(17)	4080(6)	-469(7)	30(3)
C(25)	6149(16)	4570(6)	-706(7)	31(3)
C(26)	6076(17)	4623(7)	-1292(7)	33(4)
C(27)	5877(17)	4196(6)	-1621(7)	33(4)
C(28)	5684(17)	3697(6)	-1418(7)	33(3)
C(29)	6919(16)	2703(6)	667(7)	28(3)
C(30)	6855(16)	2354(6)	1191(7)	28(3)
C(31)	7205(19)	1368(7)	588(7)	41(4)
C(32)	7420(2)	976(7)	206(8)	49(4)
C(33)	6380(2)	709(8)	-33(8)	58(4)
O(2)	526(12)	2738(4)	1134(5)	47(4)
O(3)	4823(11)	2458(4)	2660(4)	34(3)
O(4)	2311(11)	2973(4)	2428(4)	37(3)

Table 39.   Bond lengths [A] and angles [deg]

F(1)-C(1)	1.41(2)	C(19)-H(19B)	.9900
O(1)-C(10)	1.261(17)	C(20)-C(21)	1.48(2)
N(1)-C(5)	1.461(18)	C(20)-H(20A)	.9900
N(1)-C(6)	1.484(19)	C(20)-H(20B)	.9900
N(1)-C(4)	1.55(2)	C(21)-C(22)	1.328(19)
N(2)-C(10)	1.369(19)	C(21)-C(24)	1.47(2)
N(2)-C(19)	1.448(18)	C(23)-C(24)	1.39(2)
N(2)-C(9)	1.495(19)	C(23)-C(28)	1.42(2)
N(3)-C(22)	1.397(18)	C(24)-C(25)	1.39(2)
N(3)-C(23)	1.399(19)	C(25)-C(26)	1.39(2)
N(3)-H(3)	.9200	C(25)-H(25)	.9500
C(1)-C(2)	1.35(2)	C(26)-C(27)	1.36(2)
C(1)-C(33)	1.38(3)	C(26)-H(26)	.9500
C(2)-C(3)	1.38(2)	C(27)-C(28)	1.39(2)
C(2)-H(2)	.9500	C(27)-H(27)	.9500
C(3)-C(31)	1.40(2)	C(28)-H(28)	.9500
C(3)-C(4)	1.52(2)	C(29)-C(30)	1.53(2)
C(4)-C(7)	1.50(2)	C(29)-H(29A)	.9900
C(4)-C(30)	1.55(2)	C(29)-H(29B)	.9900
C(5)-H(5A)	.9800	C(30)-H(30A)	.9900
C(5)-H(5B)	.9800	C(30)-H(30B)	.9900
C(5)-H(5C)	.9800	C(31)-C(32)	1.37(2)
C(6)-H(6A)	.9800	C(31)-H(31)	.9500
C(6)-H(6B)	.9800	C(32)-C(33)	1.35(2)
C(6)-H(6C)	.9800	C(32)-H(32)	.9500
C(7)-C(8)	1.51(2)	C(33)-H(33)	.9500
C(7)-H(7A)	.9900	O(2)-H(1W)	.8500
C(7)-H(7B)	.9900	O(2)-H(2W)	.8499
C(8)-C(9)	1.52(2)	O(3)-H(3W)	.8499
C(8)-H(8A)	.9900	O(3)-H(4W)	.8500
C(8)-H(8B)	.9900	O(4)-H(5W)	.8499
C(9)-C(29)	1.53(2)	O(4)-H(6W)	.8502
C(9)-C(22)	1.54(2)		
C(10)-C(11)	1.47(2)	C(5)-N(1)-C(6)	109.3(12)
C(11)-C(12)	1.296(19)	C(5)-N(1)-C(4)	113.5(12)
C(11)-H(11)	.9500	C(6)-N(1)-C(4)	114.6(12)
C(12)-C(13)	1.45(2)	C(10)-N(2)-C(19)	115.8(13)
C(12)-H(12)	.9500	C(10)-N(2)-C(9)	126.5(13)
C(13)-C(18)	1.38(2)	C(19)-N(2)-C(9)	113.7(12)
C(13)-C(14)	1.40(2)	C(22)-N(3)-C(23)	106.3(13)
C(14)-C(15)	1.44(2)	C(22)-N(3)-H(3)	123.1
C(14)-H(14)	.9500	C(23)-N(3)-H(3)	128.3
C(15)-C(16)	1.36(2)	C(2)-C(1)-C(33)	126(2)
C(15)-H(15)	.9500	C(2)-C(1)-F(1)	120(2)
C(16)-C(17)	1.32(2)	C(33)-C(1)-F(1)	113.9(19)
C(16)-H(16)	.9500	C(1)-C(2)-C(3)	120(2)
C(17)-C(18)	1.40(2)	C(1)-C(2)-H(2)	120.1
C(17)-H(17)	.9500	C(3)-C(2)-H(2)	120.1
C(18)-H(18)	.9500	C(2)-C(3)-C(31)	114.9(16)
C(19)-C(20)	1.51(2)	C(2)-C(3)-C(4)	121.7(17)
C(19)-H(19A)	.9900	C(31)-C(3)-C(4)	123.2(16)

C(7)-C(4)-C(3)	112.8(14)	C(15)-C(16)-H(16)	120.0
C(7)-C(4)-C(30)	109.3(12)	C(16)-C(17)-C(18)	122.6(18)
C(3)-C(4)-C(30)	111.5(14)	C(16)-C(17)-H(17)	118.7
C(7)-C(4)-N(1)	107.7(13)	C(18)-C(17)-H(17)	118.7
C(3)-C(4)-N(1)	110.3(12)	C(13)-C(18)-C(17)	118.1(17)
C(30)-C(4)-N(1)	104.9(12)	C(13)-C(18)-H(18)	120.9
N(1)-C(5)-H(5A)	109.5	C(17)-C(18)-H(18)	120.9
N(1)-C(5)-H(5B)	109.5	N(2)-C(19)-C(20)	109.4(13)
H(5A)-C(5)-H(5B)	109.5	N(2)-C(19)-H(19A)	109.8
N(1)-C(5)-H(5C)	109.5	C(20)-C(19)-H(19A)	109.8
H(5A)-C(5)-H(5C)	109.5	N(2)-C(19)-H(19B)	109.8
H(5B)-C(5)-H(5C)	109.5	C(20)-C(19)-H(19B)	109.8
N(1)-C(6)-H(6A)	109.5	H(19A)-C(19)-H(19B)	108.2
N(1)-C(6)-H(6B)	109.5	C(21)-C(20)-C(19)	107.0(13)
H(6A)-C(6)-H(6B)	109.5	C(21)-C(20)-H(20A)	110.3
N(1)-C(6)-H(6C)	109.5	C(19)-C(20)-H(20A)	110.3
H(6A)-C(6)-H(6C)	109.5	C(21)-C(20)-H(20B)	110.3
H(6B)-C(6)-H(6C)	109.5	C(19)-C(20)-H(20B)	110.3
C(4)-C(7)-C(8)	114.3(14)	H(20A)-C(20)-H(20B)	108.6
C(4)-C(7)-H(7A)	108.7	C(22)-C(21)-C(24)	105.8(14)
C(8)-C(7)-H(7A)	108.7	C(22)-C(21)-C(20)	124.6(15)
C(4)-C(7)-H(7B)	108.7	C(24)-C(21)-C(20)	129.4(14)
C(8)-C(7)-H(7B)	108.7	C(21)-C(22)-N(3)	112.4(14)
H(7A)-C(7)-H(7B)	107.6	C(21)-C(22)-C(9)	124.9(15)
C(7)-C(8)-C(9)	113.7(13)	N(3)-C(22)-C(9)	122.7(13)
C(7)-C(8)-H(8A)	108.8	C(24)-C(23)-N(3)	108.6(14)
C(9)-C(8)-H(8A)	108.8	C(24)-C(23)-C(28)	122.8(16)
C(7)-C(8)-H(8B)	108.8	N(3)-C(23)-C(28)	128.7(15)
C(9)-C(8)-H(8B)	108.8	C(23)-C(24)-C(25)	119.9(15)
H(8A)-C(8)-H(8B)	107.7	C(23)-C(24)-C(21)	107.0(14)
N(2)-C(9)-C(8)	114.3(13)	C(25)-C(24)-C(21)	132.9(15)
N(2)-C(9)-C(29)	108.3(13)	C(26)-C(25)-C(24)	118.9(16)
C(8)-C(9)-C(29)	106.5(12)	C(26)-C(25)-H(25)	120.6
N(2)-C(9)-C(22)	103.6(12)	C(24)-C(25)-H(25)	120.6
C(8)-C(9)-C(22)	114.1(13)	C(27)-C(26)-C(25)	119.4(16)
C(29)-C(9)-C(22)	109.9(13)	C(27)-C(26)-H(26)	120.3
O(1)-C(10)-N(2)	124.2(14)	C(25)-C(26)-H(26)	120.3
O(1)-C(10)-C(11)	119.1(15)	C(26)-C(27)-C(28)	125.3(16)
N(2)-C(10)-C(11)	116.7(15)	C(26)-C(27)-H(27)	117.3
C(12)-C(11)-C(10)	122.5(16)	C(28)-C(27)-H(27)	117.3
C(12)-C(11)-H(11)	118.7	C(27)-C(28)-C(23)	113.7(16)
C(10)-C(11)-H(11)	118.7	C(27)-C(28)-H(28)	123.2
C(11)-C(12)-C(13)	129.6(16)	C(23)-C(28)-H(28)	123.2
C(11)-C(12)-H(12)	115.2	C(30)-C(29)-C(9)	111.6(13)
C(13)-C(12)-H(12)	115.2	C(30)-C(29)-H(29A)	109.3
C(18)-C(13)-C(14)	121.3(15)	C(9)-C(29)-H(29A)	109.3
C(18)-C(13)-C(12)	121.0(15)	C(30)-C(29)-H(29B)	109.3
C(14)-C(13)-C(12)	117.6(15)	C(9)-C(29)-H(29B)	109.3
C(13)-C(14)-C(15)	116.3(16)	H(29A)-C(29)-H(29B)	108.0
C(13)-C(14)-H(14)	121.8	C(29)-C(30)-C(4)	111.9(13)
C(15)-C(14)-H(14)	121.8	C(29)-C(30)-H(30A)	109.2
C(16)-C(15)-C(14)	121.6(18)	C(4)-C(30)-H(30A)	109.2
C(16)-C(15)-H(15)	119.2	C(29)-C(30)-H(30B)	109.2
C(14)-C(15)-H(15)	119.2	C(4)-C(30)-H(30B)	109.2
C(17)-C(16)-C(15)	119.9(19)	H(30A)-C(30)-H(30B)	107.9
C(17)-C(16)-H(16)	120.0	C(32)-C(31)-C(3)	122.7(18)

C(32)-C(31)-H(31)	118.7		C(32)-C(33)-H(33)	123.2
C(3)-C(31)-H(31)	118.7		C(1)-C(33)-H(33)	123.2
C(33)-C(32)-C(31)	122(2)		H(1W)-O(2)-H(2W)	116.5
C(33)-C(32)-H(32)	118.9		H(3W)-O(3)-H(4W)	114.8
C(31)-C(32)-H(32)	118.9		H(5W)-O(4)-H(6W)	120.8
C(32)-C(33)-C(1)	114(2)			

Symmetry transformations used to generate equivalent atoms:

Table 40.   Hydrogen coordinates (x 10^4) and isotropic
displacement parameters (• ^2 x 10^3).

	x	y	z	U(eq)
H(3)	5255	2901	-573	34
H(2)	3885	1351	586	65
H(5A)	4716	1038	1616	45
H(5B)	3571	1481	1678	45
H(5C)	4327	1259	2232	45
H(6A)	6667	1399	2388	55
H(6B)	7503	1822	2030	55
H(6C)	7184	1268	1758	55
H(7A)	4070	2463	1392	35
H(7B)	3571	2015	971	35
H(8A)	3539	2829	519	33
H(8B)	4534	2434	195	33
H(11)	5347	3780	2122	33
H(12)	2739	4125	1880	32
H(14)	5157	4046	3000	45
H(15)	5159	4601	3820	53
H(16)	3509	5231	3929	53
H(17)	1958	5381	3233	48
H(18)	1829	4856	2420	41
H(19A)	7460	3617	1035	32
H(19B)	6569	3941	1488	32
H(20A)	5428	4385	769	33
H(20B)	7040	4410	610	33
H(25)	6291	4864	-470	37
H(26)	6164	4955	-1463	40
H(27)	5870	4243	-2022	40
H(28)	5506	3409	-1659	39
H(29A)	7055	2487	323	33
H(29B)	7718	2939	701	33
H(30A)	6767	2571	1536	34
H(30B)	7727	2156	1221	34
H(31)	7981	1527	762	50
H(32)	8344	889	106	58
H(33)	6513	439	-301	69
H(1W)	316	2664	1476	56
H(2W)	1381	2739	1053	56
H(3W)	4928	2196	2447	41
H(4W)	4046	2608	2630	41
H(5W)	1576	2797	2466	45
H(6W)	2564	3081	2102	45

Table 41. Anisotropic displacement parameters (• ^2 x 10^3).
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
F(1)	79(7)	124(8)	106(7)	-52(7)	-5(7)	4(7)

Polymorph C

SCXRD (Single Crystal X-ray Diffraction)

SCXRD analyses of crystalline form C was carried out with a Bruker D8-goniometer with SMART APEX CCD area detector at 130 K (± 5 K) using MoKα radiation (wavelength of 0.71073 Å, Incoatec microsource, multilayer optics).

Table 42. Crystal data and structure refinement

Empirical formula	C35 H42 F N3 O3
Formula weight	571.72
Temperature	130(2) K
Wavelength	.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.0215(12) A alpha = 67.547(3) deg.
	b = 13.3823(17) A beta = 81.853(4) deg.
	c = 13.7021(19) A gamma = 83.608(4) deg.
Volume	1510.4(3) A^3
Z	2
Density (calculated)	1.257 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	612
Crystal size	0.14 x 0.13 x 0.07 mm
Theta range for data collection	1.83 to 28.47 deg.
Index ranges	-11<=h<=12, -17<=k<=17, -17<=l<=17
Reflections collected	23406
Independent reflections	7011 [R(int) = 0.0494]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7011 / 0 / 395
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.0852
R indices (all data)	R1 = 0.0723, wR2 = 0.0898
Largest diff. peak and hole	.277 and -.202 e.A^-3

Table 43. Atomic coordinates (x 10^4) and equivalent isotropic
displacement parameters (• ^2 x 10^3).   U(eq) is defined
as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
F(1)	-3098(1)	14196(1)	-739(1)	32(1)
O(1)	570(1)	8487(1)	4358(1)	46(1)
N(1)	886(1)	12561(1)	2348(1)	21(1)
N(2)	1344(1)	9118(1)	2565(1)	21(1)
N(3)	-2295(1)	8634(1)	1894(1)	23(1)
C(1)	-3032(2)	13654(1)	330(1)	22(1)
C(2)	-1719(2)	13081(1)	654(1)	21(1)
C(3)	-1605(2)	12513(1)	1734(1)	20(1)
C(4)	-134(2)	11872(1)	2124(1)	20(1)
C(5)	1443(2)	13476(1)	1405(1)	27(1)
C(6)	236(2)	12982(1)	3172(1)	28(1)
C(7)	761(1)	11453(1)	1298(1)	20(1)
C(8)	27(2)	10558(1)	1155(1)	22(1)
C(9)	-176(2)	9560(1)	2203(1)	21(1)
C(10)	1559(2)	8592(1)	3624(1)	27(1)
C(11)	3118(2)	8152(1)	3852(1)	27(1)
C(12)	3357(2)	7256(1)	4687(1)	28(1)
C(13)	4800(2)	6701(1)	5015(1)	26(1)
C(14)	4822(2)	5706(1)	5861(1)	32(1)
C(15)	6161(2)	5141(1)	6172(1)	37(1)
C(16)	7506(2)	5556(1)	5641(1)	39(1)
C(17)	7505(2)	6548(1)	4805(1)	43(1)
C(18)	6168(2)	7110(1)	4500(1)	35(1)
C(19)	2259(2)	8660(1)	1837(1)	24(1)
C(20)	1656(2)	7592(1)	1967(1)	27(1)
C(21)	-15(2)	7764(1)	1943(1)	22(1)
C(22)	-813(2)	8659(1)	2029(1)	21(1)
C(23)	-2463(2)	7688(1)	1749(1)	22(1)
C(24)	-1046(2)	7115(1)	1787(1)	20(1)
C(25)	-928(2)	6105(1)	1688(1)	23(1)
C(26)	-2175(2)	5710(1)	1532(1)	26(1)
C(27)	-3567(2)	6298(1)	1479(1)	29(1)
C(28)	-3723(2)	7287(1)	1589(1)	27(1)
C(29)	-1192(2)	10002(1)	2968(1)	22(1)
C(30)	-449(2)	10877(1)	3150(1)	22(1)
C(31)	-2863(2)	12573(1)	2439(1)	26(1)
C(32)	-4174(2)	13151(1)	2082(1)	28(1)
C(33)	-4280(2)	13703(1)	1011(1)	27(1)
O(2)	3399(1)	1185(1)	3038(1)	34(1)
C(34)	3411(2)	897(2)	4142(1)	51(1)
O(3)	5196(1)	178(1)	1887(1)	34(1)
C(35)	5215(2)	942(1)	836(1)	41(1)

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Table 44. Bond lengths [A] and angles [deg].

F(1)-C(1)	1.3706(15)	C(20)-C(21)	1.5020(18)
O(1)-C(10)	1.2214(16)	C(20)-H(20A)	.9900
N(1)-C(5)	1.4708(17)	C(20)-H(20B)	.9900
N(1)-C(6)	1.4711(17)	C(21)-C(22)	1.3628(18)
N(1)-C(4)	1.5082(17)	C(21)-C(24)	1.4301(19)
N(2)-C(10)	1.3809(18)	C(23)-C(28)	1.3873(19)
N(2)-C(19)	1.4747(16)	C(23)-C(24)	1.4120(18)
N(2)-C(9)	1.5044(17)	C(24)-C(25)	1.3992(18)
N(3)-C(22)	1.3813(17)	C(25)-C(26)	1.3714(19)
N(3)-C(23)	1.3815(18)	C(25)-H(25)	.9500
N(3)-H(3N)	.890(15)	C(26)-C(27)	1.4009(19)
C(1)-C(2)	1.3694(18)	C(26)-H(26)	.9500
C(1)-C(33)	1.3701(19)	C(27)-C(28)	1.379(2)
C(2)-C(3)	1.3943(18)	C(27)-H(27)	.9500
C(2)-H(2)	.9500	C(28)-H(28)	.9500
C(3)-C(31)	1.3981(18)	C(29)-C(30)	1.5255(19)
C(3)-C(4)	1.5430(18)	C(29)-H(29A)	.9900
C(4)-C(30)	1.5397(18)	C(29)-H(29B)	.9900
C(4)-C(7)	1.5407(18)	C(30)-H(30A)	.9900
C(5)-H(5A)	.9800	C(30)-H(30B)	.9900
C(5)-H(5B)	.9800	C(31)-C(32)	1.3817(19)
C(5)-H(5C)	.9800	C(31)-H(31)	.9500
C(6)-H(6A)	.9800	C(32)-C(33)	1.379(2)
C(6)-H(6B)	.9800	C(32)-H(32)	.9500
C(6)-H(6C)	.9800	C(33)-H(33)	.9500
C(7)-C(8)	1.5185(18)	O(2)-C(34)	1.4122(18)
C(7)-H(7A)	.9900	O(2)-H(2O)	.959(19)
C(7)-H(7B)	.9900	C(34)-H(34A)	.9800
C(8)-C(9)	1.5468(18)	C(34)-H(34B)	.9800
C(8)-H(8A)	.9900	C(34)-H(34C)	.9800
C(8)-H(8B)	.9900	O(3)-C(35)	1.4115(18)
C(9)-C(22)	1.5010(19)	O(3)-H(3O)	.897(17)
C(9)-C(29)	1.5405(18)	C(35)-H(35A)	.9800
C(10)-C(11)	1.491(2)	C(35)-H(35B)	.9800
C(11)-C(12)	1.3259(19)	C(35)-H(35C)	.9800
C(11)-H(11)	.9500		
C(12)-C(13)	1.4643(19)	C(5)-N(1)-C(6)	108.13(11)
C(12)-H(12)	.9500	C(5)-N(1)-C(4)	114.35(10)
C(13)-C(18)	1.389(2)	C(6)-N(1)-C(4)	114.17(10)
C(13)-C(14)	1.392(2)	C(10)-N(2)-C(19)	115.06(11)
C(14)-C(15)	1.382(2)	C(10)-N(2)-C(9)	122.53(11)
C(14)-H(14)	.9500	C(19)-N(2)-C(9)	111.79(10)
C(15)-C(16)	1.379(2)	C(22)-N(3)-C(23)	108.44(12)
C(15)-H(15)	.9500	C(22)-N(3)-H(3N)	124.0(10)
C(16)-C(17)	1.384(2)	C(23)-N(3)-H(3N)	127.4(10)
C(16)-H(16)	.9500	C(2)-C(1)-C(33)	123.72(14)
C(17)-C(18)	1.377(2)	C(2)-C(1)-F(1)	117.76(12)
C(17)-H(17)	.9500	C(33)-C(1)-F(1)	118.52(12)
C(18)-H(18)	.9500	C(1)-C(2)-C(3)	119.65(13)
C(19)-C(20)	1.5235(19)	C(1)-C(2)-H(2)	120.2
C(19)-H(19A)	.9900	C(3)-C(2)-H(2)	120.2
C(19)-H(19B)	.9900	C(2)-C(3)-C(31)	117.19(13)

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C(2)-C(3)-C(4)	120.84(12)	C(15)-C(16)-C(17)	119.52(15)
C(31)-C(3)-C(4)	121.96(12)	C(15)-C(16)-H(16)	120.2
N(1)-C(4)-C(30)	107.89(10)	C(17)-C(16)-H(16)	120.2
N(1)-C(4)-C(7)	106.77(10)	C(18)-C(17)-C(16)	120.07(16)
C(30)-C(4)-C(7)	107.06(11)	C(18)-C(17)-H(17)	120.0
N(1)-C(4)-C(3)	111.63(11)	C(16)-C(17)-H(17)	120.0
C(30)-C(4)-C(3)	111.18(11)	C(17)-C(18)-C(13)	121.35(15)
C(7)-C(4)-C(3)	112.04(11)	C(17)-C(18)-H(18)	119.3
N(1)-C(5)-H(5A)	109.5	C(13)-C(18)-H(18)	119.3
N(1)-C(5)-H(5B)	109.5	N(2)-C(19)-C(20)	109.67(11)
H(5A)-C(5)-H(5B)	109.5	N(2)-C(19)-H(19A)	109.7
N(1)-C(5)-H(5C)	109.5	C(20)-C(19)-H(19A)	109.7
H(5A)-C(5)-H(5C)	109.5	N(2)-C(19)-H(19B)	109.7
H(5B)-C(5)-H(5C)	109.5	C(20)-C(19)-H(19B)	109.7
N(1)-C(6)-H(6A)	109.5	H(19A)-C(19)-H(19B)	108.2
N(1)-C(6)-H(6B)	109.5	C(21)-C(20)-C(19)	108.06(11)
H(6A)-C(6)-H(6B)	109.5	C(21)-C(20)-H(20A)	110.1
N(1)-C(6)-H(6C)	109.5	C(19)-C(20)-H(20A)	110.1
H(6A)-C(6)-H(6C)	109.5	C(21)-C(20)-H(20B)	110.1
H(6B)-C(6)-H(6C)	109.5	C(19)-C(20)-H(20B)	110.1
C(8)-C(7)-C(4)	113.56(11)	H(20A)-C(20)-H(20B)	108.4
C(8)-C(7)-H(7A)	108.9	C(22)-C(21)-C(24)	107.31(12)
C(4)-C(7)-H(7A)	108.9	C(22)-C(21)-C(20)	122.89(12)
C(8)-C(7)-H(7B)	108.9	C(24)-C(21)-C(20)	129.73(12)
C(4)-C(7)-H(7B)	108.9	C(21)-C(22)-N(3)	109.76(12)
H(7A)-C(7)-H(7B)	107.7	C(21)-C(22)-C(9)	125.41(12)
C(7)-C(8)-C(9)	111.94(11)	N(3)-C(22)-C(9)	124.79(12)
C(7)-C(8)-H(8A)	109.2	N(3)-C(23)-C(28)	130.61(13)
C(9)-C(8)-H(8A)	109.2	N(3)-C(23)-C(24)	107.78(12)
C(7)-C(8)-H(8B)	109.2	C(28)-C(23)-C(24)	121.61(13)
C(9)-C(8)-H(8B)	109.2	C(25)-C(24)-C(23)	118.83(13)
H(8A)-C(8)-H(8B)	107.9	C(25)-C(24)-C(21)	134.51(13)
C(22)-C(9)-N(2)	105.47(10)	C(23)-C(24)-C(21)	106.66(12)
C(22)-C(9)-C(29)	114.07(11)	C(26)-C(25)-C(24)	119.45(13)
N(2)-C(9)-C(29)	113.37(11)	C(26)-C(25)-H(25)	120.3
C(22)-C(9)-C(8)	111.02(11)	C(24)-C(25)-H(25)	120.3
N(2)-C(9)-C(8)	108.77(10)	C(25)-C(26)-C(27)	120.93(14)
C(29)-C(9)-C(8)	104.15(10)	C(25)-C(26)-H(26)	119.5
O(1)-C(10)-N(2)	124.17(14)	C(27)-C(26)-H(26)	119.5
O(1)-C(10)-C(11)	119.73(13)	C(28)-C(27)-C(26)	120.94(14)
N(2)-C(10)-C(11)	116.09(12)	C(28)-C(27)-H(27)	119.5
C(12)-C(11)-C(10)	120.45(14)	C(26)-C(27)-H(27)	119.5
C(12)-C(11)-H(11)	119.8	C(27)-C(28)-C(23)	118.22(13)
C(10)-C(11)-H(11)	119.8	C(27)-C(28)-H(28)	120.9
C(11)-C(12)-C(13)	127.74(14)	C(23)-C(28)-H(28)	120.9
C(11)-C(12)-H(12)	116.1	C(30)-C(29)-C(9)	111.42(11)
C(13)-C(12)-H(12)	116.1	C(30)-C(29)-H(29A)	109.3
C(18)-C(13)-C(14)	117.84(14)	C(9)-C(29)-H(29A)	109.3
C(18)-C(13)-C(12)	122.81(13)	C(30)-C(29)-H(29B)	109.3
C(14)-C(13)-C(12)	119.32(14)	C(9)-C(29)-H(29B)	109.3
C(15)-C(14)-C(13)	121.03(15)	H(29A)-C(29)-H(29B)	108.0
C(15)-C(14)-H(14)	119.5	C(29)-C(30)-C(4)	112.79(11)
C(13)-C(14)-H(14)	119.5	C(29)-C(30)-H(30A)	109.0
C(16)-C(15)-C(14)	120.18(15)	C(4)-C(30)-H(30A)	109.0
C(16)-C(15)-H(15)	119.9	C(29)-C(30)-H(30B)	109.0
C(14)-C(15)-H(15)	119.9	C(4)-C(30)-H(30B)	109.0

H(30A)-C(30)-H(30B)	107.8	O(2)-C(34)-H(34B)	109.5
C(32)-C(31)-C(3)	121.53(14)	H(34A)-C(34)-H(34B)	109.5
C(32)-C(31)-H(31)	119.2	O(2)-C(34)-H(34C)	109.5
C(3)-C(31)-H(31)	119.2	H(34A)-C(34)-H(34C)	109.5
C(33)-C(32)-C(31)	120.88(13)	H(34B)-C(34)-H(34C)	109.5
C(33)-C(32)-H(32)	119.6	C(35)-O(3)-H(3O)	105.6(11)
C(31)-C(32)-H(32)	119.6	O(3)-C(35)-H(35A)	109.5
C(1)-C(33)-C(32)	117.02(13)	O(3)-C(35)-H(35B)	109.5
C(1)-C(33)-H(33)	121.5	H(35A)-C(35)-H(35B)	109.5
C(32)-C(33)-H(33)	121.5	O(3)-C(35)-H(35C)	109.5
C(34)-O(2)-H(2O)	110.1(11)	H(35A)-C(35)-H(35C)	109.5
O(2)-C(34)-H(34A)	109.5	H(35B)-C(35)-H(35C)	109.5

Symmetry transformations used to generate equivalent atoms:

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Table 45.   Hydrogen coordinates (x 10^4) and isotropic
displacement parameters (• ^2 x 10^3) .

	x	y	z	U(eq)
H(3N)	-3011(17)	9131(12)	1945(11)	38(5)
H(2)	-889	13070	146	25
H(5A)	591	13955	1090	41
H(5B)	2009	13201	885	41
H(5C)	2097	13880	1614	41
H(6A)	1002	13341	3337	42
H(6B)	-120	12382	3815	42
H(6C)	-607	13504	2915	42
H(7A)	882	12066	605	24
H(7B)	1774	11180	1518	24
H(8A)	653	10335	609	26
H(8B)	-966	10838	899	26
H(11)	3947	8517	3396	32
H(12)	2489	6935	5124	34
H(14)	3901	5411	6229	38
H(15)	6154	4465	6753	45
H(16)	8427	5162	5847	47
H(17)	8428	6843	4441	52
H(18)	6181	7791	3925	42
H(19A)	3316	8537	1996	28
H(19B)	2227	9176	1095	28
H(20A)	2119	7358	1383	33
H(20B)	1898	7023	2649	33
H(25)	9	5698	1730	28
H(26)	-2095	5027	1459	31
H(27)	-4415	6011	1364	35
H(28)	-4668	7683	1556	33
H(29A)	-2153	10307	2671	27
H(29B)	-1414	9401	3657	27
H(30A)	509	10567	3452	26
H(30B)	-1108	11111	3676	26
H(31)	-2814	12208	3181	31
H(32)	-5015	13168	2580	34
H(33)	-5178	14100	758	33
H(2O)	2570(2)	1694(16)	2792(15)	79(7)
H(34A)	4130	1321	4266	77
H(34B)	3705	123	4469	77
H(34C)	2407	1046	4456	77
H(3O)	4624(19)	497(14)	2292(14)	57(6)
H(35A)	4195	1084	625	62
H(35B)	5872	655	358	62
H(35C)	5591	1618	796	62

Table 46.   Anisotropic displacement parameters (• ^2 x 10^3) .
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
F(1)	32(1)	29(1)	31(1)	-8(1)	-9(1)	6(1)
O(1)	48(1)	47(1)	24(1)	0(1)	5(1)	19(1)
N(1)	23(1)	20(1)	22(1)	-8(1)	-1(1)	-2(1)
N(2)	22(1)	20(1)	21(1)	-9(1)	-1(1)	1(1)
N(3)	20(1)	20(1)	31(1)	-12(1)	-3(1)	4(1)
C(1)	26(1)	16(1)	26(1)	-7(1)	-6(1)	-2(1)
C(2)	21(1)	18(1)	25(1)	-10(1)	0(1)	-1(1)
C(3)	20(1)	15(1)	26(1)	-10(1)	-1(1)	-2(1)
C(4)	20(1)	20(1)	20(1)	-8(1)	-2(1)	0(1)
C(5)	28(1)	24(1)	29(1)	-9(1)	-1(1)	-7(1)
C(6)	33(1)	27(1)	26(1)	-13(1)	-4(1)	-2(1)
C(7)	19(1)	19(1)	19(1)	-5(1)	-2(1)	2(1)
C(8)	22(1)	22(1)	20(1)	-9(1)	-2(1)	3(1)
C(9)	19(1)	20(1)	22(1)	-9(1)	-1(1)	1(1)
C(10)	35(1)	18(1)	24(1)	-5(1)	-2(1)	3(1)
C(11)	33(1)	24(1)	22(1)	-7(1)	-4(1)	-1(1)
C(12)	33(1)	27(1)	23(1)	-9(1)	-1(1)	1(1)
C(13)	33(1)	26(1)	21(1)	-11(1)	-6(1)	2(1)
C(14)	34(1)	29(1)	28(1)	-8(1)	-3(1)	3(1)
C(15)	45(1)	30(1)	32(1)	-6(1)	-10(1)	5(1)
C(16)	36(1)	44(1)	40(1)	-17(1)	-17(1)	9(1)
C(17)	35(1)	52(1)	39(1)	-10(1)	-7(1)	-6(1)
C(18)	39(1)	34(1)	27(1)	-3(1)	-10(1)	-2(1)
C(19)	19(1)	28(1)	25(1)	-13(1)	0(1)	3(1)
C(20)	25(1)	26(1)	35(1)	-17(1)	-4(1)	5(1)
C(21)	22(1)	20(1)	23(1)	-9(1)	-1(1)	1(1)
C(22)	21(1)	20(1)	21(1)	-7(1)	0(1)	2(1)
C(23)	25(1)	20(1)	20(1)	-8(1)	-1(1)	0(1)
C(24)	21(1)	20(1)	19(1)	-7(1)	-2(1)	1(1)
C(25)	23(1)	19(1)	25(1)	-7(1)	-1(1)	1(1)
C(26)	32(1)	20(1)	26(1)	-9(1)	-2(1)	-2(1)
C(27)	26(1)	32(1)	33(1)	-14(1)	-2(1)	-6(1)
C(28)	21(1)	29(1)	32(1)	-12(1)	-3(1)	2(1)
C(29)	22(1)	20(1)	23(1)	-8(1)	1(1)	0(1)
C(30)	24(1)	20(1)	21(1)	-8(1)	0(1)	2(1)
C(31)	26(1)	23(1)	27(1)	-10(1)	1(1)	-1(1)
C(32)	21(1)	26(1)	38(1)	-15(1)	6(1)	-2(1)
C(33)	18(1)	22(1)	43(1)	-14(1)	-5(1)	2(1)
O(2)	32(1)	40(1)	31(1)	-14(1)	-8(1)	8(1)
C(34)	61(1)	56(1)	40(1)	-19(1)	-24(1)	16(1)
O(3)	32(1)	29(1)	36(1)	-11(1)	0(1)	8(1)
C(35)	40(1)	37(1)	41(1)	-12(1)	5(1)	1(1)

5   Analysis – FT Raman Spectroscopy

FT Raman spectra were recorded on a Bruker RFS100/S Raman spectrometer (Nd-YAG 100 mW laser, excitation 1064 nm, Ge detector, 64 scans, 25-3500 cm^{-1}, resolution 2 cm^{-1}).

10   Raman peak tables were generated using the ACD/SpecManager (Product Version12.5) software from ACD/Labs using the following parameters for the Auto Peak Picking:

Noise Factor:	0.2 (for crystalline forms A and B) 0.5 (for crystalline form D)
Minimum Peak Level:	0 % of max Intensity
Peaks:	positive
FWHH Options:	calculate automatically
Area Baseline:	zero

For the intensity classification, the absolute intensity was used and the most intense peak
15   was scaled to 100%. The classification is as follow: very strong (vs): I >90%; strong (s): 90% ≥ I >60%; medium (m): 60% ≥ I > 30%; weak (w): 30% ≥ I >10%; and very weak (vw): 10% ≥ I.

Table 47: RAMAN peak-list of crystalline form A; spectrum shown in Fig. 2a

20

No.	cm^{-1}	Intensity
1	98	M
2	128	W
3	170	W
4	189	VW
5	227	VW
6	272	VW
7	310	VW
8	355	VW
9	417	VW
10	461	VW
11	485	VW
12	509	VW
13	543	VW
14	589	VW
15	611	VW

16	620	VW
17	644	VW
18	676	W
19	697	VW
20	725	VW
21	746	VW
22	783	VW
23	801	VW
24	831	VW
25	865	VW
26	893	VW
27	927	VW
28	955	VW
29	978	VW
30	1001	M
31	1012	VW

32	1028	VW
33	1048	VW
34	1074	VW
35	1111	VW
36	1155	VW
37	1175	W
38	1183	W
39	1204	W
40	1244	VW
41	1268	W
42	1294	W
43	1343	VW
44	1368	VW
45	1385	VW
46	1407	VW
47	1447	W

48	1462	W
49	1493	VW
50	1568	W
51	1574	W
52	1584	W
53	1606	VS
54	1650	W

55	2782	VW
56	2834	VW
57	2878	VW
58	2910	W
59	2946	VW
60	2960	VW
61	2980	VW

62	2999	VW
63	3026	VW
64	3062	W
65	3075	W
66	3449	VW

5

Table 48: RAMAN peak-list of crystalline form B; spectrum shown in Fig. 2b

No	cm^{-1}	Intensity
1	84	S
2	109	S
3	166	W
4	220	W
5	272	W
6	333	VW
7	365	VW
8	387	VW
9	405	VW
10	435	VW
11	463	VW
12	505	VW
13	541	VW
14	590	VW
15	619	W
16	643	VW
17	676	W
18	725	VW
19	745	VW
20	781	W
21	802	VW
22	834	VW
23	862	W

24	888	W
25	929	VW
26	976	W
27	1001	S
28	1010	W
29	1029	W
30	1047	W
31	1087	VW
32	1112	VW
33	1158	W
34	1180	W
35	1203	W
36	1266	W
37	1300	W
38	1326	VW
39	1341	VW
40	1373	VW
41	1405	VW
42	1441	W
43	1449	W
44	1465	W
45	1563	M
46	1578	W
47	1601	VS

48	1618	S
49	1643	M
50	1861	VW
51	2136	VW
52	2172	VW
53	2328	VW
54	2489	VW
55	2519	VW
56	2558	VW
57	2772	VW
58	2794	VW
59	2843	VW
60	2890	VW
61	2935	W
62	2967	W
63	3001	W
64	3063	M
65	3153	VW
66	3197	VW
67	3243	VW
68	3323	VW
69	3459	VW

5   *Table XY3: RAMAN peak-list of crystalline form D: shown in figure 2d.*

No	cm^{-1}	Intensity
1	84	VS
2	121	M
3	158	M
4	237	W
5	268	W
6	294	W
7	335	W
8	372	W
9	402	W
10	434	W
11	466	W
12	489	W
13	503	W
14	542	W
15	579	VW
16	618	W
17	646	VW
18	675	W
19	696	VW

No	cm^{-1}	Intensity
20	711	VW
21	727	VW
22	782	W
23	799	VW
24	834	VW
25	867	VW
26	886	W
27	921	VW
28	970	VW
29	1000	M
30	1011	W
31	1030	W
32	1056	W
33	1085	VW
34	1115	VW
35	1154	W
36	1171	W
37	1199	W
38	1263	W
39	1289	W

No	cm^{-1}	Intensity
40	1325	W
41	1343	VW
42	1377	VW
43	1406	VW
44	1447	W
45	1464	W
46	1563	M
47	1576	W
48	1599	VS
49	1612	S
50	1644	W
51	2792	VW
52	2846	VW
53	2895	VW
54	2946	W
55	2980	W
56	3010	W
57	3065	W
58	3152	VW
59	3196	VW

Analysis-DSC

Differential Scanning Calorimetry (DSC): device reference Mettler Toledo DSC821 or Mettler Toledo DSC823. Unless otherwise specified, the samples were weighed in a pierced aluminium crucible. The measurement took place in a nitrogen flow in a temperature range from -50°C up to 350°C with a heating rate of 10°C/min. The temperatures specified in relation to DSC analyses are, unless otherwise specified, the temperatures of the peak onset.

In the following table, "ΔH" means "specific heat", "T_{onset}" means the "onset temperature", and "T_{peak}" means the "peak temperature" of a thermal event.

The values for ΔH, T$_{onset}$ and T$_{peak}$ for each polymorph listed below are given as ranges derived from the measurement of different samples exhibiting essentially identical x-ray powder diffractograms. If a sample exhibited more than one thermal event ΔH, T$_{onset}$ and T$_{peak}$ are listed for each event.

Table 50: DSC data

	T$_{onset}$ [°C]	T$_{peak}$ [°C]	ΔH [J/g]
Crystalline Form A	227 - 247	235 - 255	> 80
Crystalline Form B	40 - 108	80 - 110	50 - 264
	133 - 140	142 - 148	-23 - 27
	194 - 224	204 - 231	-96 - -3
	230 - 250	230 - 255	80 - 110
Crystalline Form C	50 - 145	60 - 150	5 - 200
	145 - 150	150 - 165	0 - 2
	165 - 170	170 - 175	0 - 2
	170 - 210	175 - 220	-85 - -50
	220 - 245	230 - 255	75 - 95
Crystalline Form D	30 - 55	55 - 95	10 - 85
	135 - 160	150 - 170	30 - 90
	160 - 175	160 - 180	2 - 7
	190 - 215	205 - 225	-85 - -3
	225 - 245	230 - 250	5 - 95
Crystalline Form E	34 - 41	51 - 64	3 - 7
	120 - 122	125 - 127	1 - 20
	134 - 140	143 - 146	2 - 31
	153 - 154	168 -169	2- 6
	182 - 197	196 - 210	-74 - -48
	223 - 230	230 - 250	65 - 90
Crystalline Form F	(n.d.)	(n.d.)	(n.d)
Crystalline Form G	35 - 143	67 - 149	34 – 269
	187 - 201	204 - 220	-112 - -62
	220 - 244	229 - 248	65 - 90
Crystalline Form H	135 - 145	145 - 160	40 - 80
	150 - 170	150 - 190	-60 - -20
	230 - 250	230 - 255	80 - 110
Crystalline Form I	(n.d.)	(n.d.)	(n.d)
Crystalline Form J (one sample measured)	46,7	61,2	10
	123,0	130,3	11
	186,0	196,8	-84
	222,7	232,7	86
Crystalline Form K	(n.d.)	(n.d.)	(n.d)
Crystalline Form L	100 - 120	115 - 125	4 - 50
	130 – 140	140 – 150	70 - 120

	150 - 160	155 - 175	4 - -50
	180 - 195	190 – 210	-80 - -20
	220 - 240	225 - 250	40 - 80
Crystalline Form Q	100 – 115	115 - 140	2 - 50
	130 - 140	130 -140	2 - 50
	144 - 157	155 -165	2 – 25
	175 - 190	185 - 205	-90 - -40
	210 - 225	220 - 250	20 - 105

n.d. = not determined

The above data shows for crystalline A that it has a relatively high melting point and that no transformations into other crystalline forms of compound (1) take place up to its melting point. Both of these properties are very favorable for the use of this crystalline form in the formulation of solid dosage forms.

Analysis – TG

Thermogravimetry analytical experiments were recorded with a Mettler Toledo TGA/DSC1 (open aluminium oxide crucible nitrogen atmosphere, heating rate 10°C/min, 25 up to 350°C). Results of the measurements are discussed below.

Analysis – DVS

Crystalline forms were characterized by dynamic vapor sorption (DVS) using a Porotec DVS 1000 or a SMS DVS Intrinsic water vapor sorption analyzer. For the DVS analysis, a step width of 10 % r.h. was applied allowing the samples to equilibrate and reach weight constancy (± 0.002 %) for at least 10 min on each step. All measurements were performed according to the following program: 50 % r.h. → 90 % r.h., 90 → 0 % r.h., 0 % → 90 % r.h., 90 % → 50 % r.h. A cycle with increasing humidity is also known as a sorption cycle, a cycle with decreasing humidity is also known as a desorption cycle. The details of the respective DVS measurements are shown below in table 51 and discussed further below.

The hygroscopicity of the respective crystalline forms determined via the DVS measurements was classified according to the ranges for mass increase defined in the European Pharmacopoeia: very hygroscopic (vh): increase of the mass ≥ 15 %; hygroscopic (h): increase of the mass is less than 15 % and equal or greater than 2 %; slightly hygroscopic (sh): increase of the mass is less than 2 % and equal or greater than 0.2 %; not hygroscopic

(nh): increase of the mass is less than 0.2 %; deliquescent (d): sufficient water is absorbed to form a liquid.

Table 51: DVS measurements

Measurement no.	Crystalline Form	T [°C]	Initial weight [mg]
1	A	24.9	16.7255
2	B	24.9	9.832
3	C	25.4	21.2031
4	D	24.9	7.2134
5	E	24.9	3.8075

Crystalline form A:

TGA analysis performed with samples of crystalline form A revealed that these samples do not contain any significant quantities (i.e. weight loss in TGA is less or equal than 2.0%, preferably less or equal than 1.0 %, even more preferably less or equal than 0.5%, most preferably less than 0.2%) of residual solvents. This is in line with the assumption that crystalline form A is an ansolvate form.

A sample of crystalline form A was analyzed via DVS. Crystalline form A showed no essential change, especially increase, in mass with increasing/decreasing relative humidity (-0.2 to 0.1%). Furthermore crystalline form A does not show a hysteresis bigger than 0.5 %, preferably bigger than 0.1% (see figure 3a).

DVS measurements therefor revealed that crystalline form A is not hygroscopic or just slightly hygroscopic.

Crystalline form B:

TGA analyses performed with samples of crystalline form B revealed that these samples showed a weight loss between about 5-10 % of water agreeing with a sesqui-, di- or trihydrate form. In the majority of measurements the amount of water contained therein agreed with crystalline form B representing a trihydrate form.

But the existence of crystalline form B being a hydrate with other variable or discrete states of moisture content (e.g. dihydrate) cannot be fully excluded, since dynamic vapor sorption (DVS) experiments show a significant hysteresis (i.e. > 0.5%, compare data in Figure 3b) between 10% to 40% relative humidity and a maximum weight gain, caused by moisture uptake, of about 7.4% to 10.6% in a range between 20% and 90% relative humidity.

Crystalline form C:

TGA analyses performed with samples of crystalline form C revealed that these samples exhibited a weight loss up to 9-10 % which is in accordance with the presence of two molecules of methanol per molecule of the title compound (see Figure 3c). Crystalline form C is therefore considered to be a dimethanol solvate.

Dynamic vapor sorption (DVS) experiments shows two levels of maximum weight gain, indicating that initial amounts of solvent (e.g. methanol) may be exchanged by water.

When Polymorph C is exposed to increasing moisture content (sorption cycle from 50% to 90% relative humidity) no major change in mass is observed. Upon decreasing moisture in its environment a weight loss of about 6.6 % can be observed (desorption cycle from 90 to 0% r.h.). This weight loss is not fully compensated in a subsequent sorption cycle, weight gain at 90% is only about 2.8 %. Furthermore, the next desorption cycle indicates that even more solvent is exchanged. Crystalline form C can rather easily loose or exchange solvent to form other crystalline forms (e.g. to yield crystalline form K or crystalline form J), therefore crystalline form C may also exist in crystalline states with varying solvent content.

It cannot be excluded that crystalline form C has transformed to another crystalline form (e.g. crystalline form K or crystalline form J) under conditions of the DVS experiments.

But the assumption that crystalline form C exists as a dimethanol solvate form is proven by x-ray single crystal structure analysis.

Crystalline form D:

TGA analyses performed with samples of crystalline form D obtained from solutions in different solvents, revealed residual solvent contents of between 0.1 – 4.7 %. Seen in conjunction with the results from the other analytical methods described herein, crystalline form D is considered to be an ansolvate form with varying amounts of residual solvent.

Based on the DVS experiments the existence of crystalline form D with variable solvate or non-stoichiometric content cannot be fully excluded. Sorption and desorption behavior, which shows no significant hysteresis (see Figure 3d) is indicative of a channel-type crystal structure or another structure type that easily allows moisture exchange. The DVS experiments of crystalline form D showed a maximum weight gain of about 2.0 to 8.1 % at 90% relative humidity.

It cannot be excluded that crystalline form D has transformed to another crystalline form (e.g. crystalline form G) under conditions of the DVS experiments.

Crystalline form E:

In TGA analysis performed with samples of crystalline form E, these showed a weight loss in a range from 0.1 to 5.3 %. Crystalline form E is considered to be an ansolvate form with varying amounts of residual solvent.

The existence of crystalline form E being a variable or discrete solvate (e.g. sesqui hydrate) cannot be fully excluded, since dynamic vapor sorption (DVS) experiments show a significant hysteresis between 10% and 40% relative humidity and a maximum weight gain, caused by moisture uptake, of about 4.6 to 5.8 % in a range between 20% and 90% relative humidity (see Figure 3e).

It cannot be excluded that crystalline form E has transformed to another crystalline form (e.g. crystalline form B) under conditions of the DVS experiments.

TGA analysis performed with samples of crystalline form G revealed a two-step mass loss of 2 to 7 % which is, in conjunction with the data from the other analytic methods and/or knowledge about the synthesis conditions, indicative of crystalline form G being an ethanol solvate form, preferably a hemi- or mono ethanolate, or a hygroscopic form.

The existence of crystalline form G existing in another variable or discrete solvated state cannot be excluded. Crystalline form G may contain alcohol (e.g. ethanol) or water as residual solvent.

Crystalline form H:

TGA analysis performed with a sample of crystalline form H revealed varying amount of residual solvent in the range of 2 to 8 wt-%, which in conjunction with the data from the other analytic methods suggests that polymorph H can be a non-stoichiometric or stoichiometric solvate. It cannot be excluded that crystalline form is an ansolvate.

Crystalline form J:

TGA analysis performed with a sample of crystalline form J revealed residual solvent between 2.8 % and 3.6 %, which is , in conjunction with the data from the other analytic methods and/or knowledge about the synthesis conditions, indicative of crystalline form J being a solvate or hygroscopic form.

The existence of crystalline form J existing as variable or discrete solvated state cannot be excluded. Crystalline form J may contain alcohol (e.g. methanol) or water as residual solvent.

Crystalline for K:

According TGA analysis performed with a sample of crystalline form K this sample contained residual solvent in an amount between 2.1 % and 4.0 %, which is, in conjunction with the data from other analytic methods and/or knowledge about the synthesis conditions, indicative of crystalline form K being solvate or hygroscopic form.

The existence of crystalline form K existing as variable or discrete solvated state cannot be excluded. Crystalline form K may contain alcohol (e.g. methanol) or water as residual solvent.

Crystalline form L:

TGA analysis performed with samples of crystalline form L revealed between 2 to 13% residual solvent (16.7% according to TGA), which is, in conjunction with data from other analytic methods and/or knowledge about the synthesis conditions, indicative of crystalline form J being solvate, preferably a variable or discrete toluene solvate.

Patent claims:

1. A crystalline form of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine.

2. The crystalline form according to claim 1, which has at least one X-ray powder diffraction peak (CuKα radiation) in the range of 6.5±0.2 to 8.9±0.2 (2Θ) and/or 17.2±0.2 to 18.3±0.2 (2Θ) and/or in the range of 19.7±0.2 to 20.9±0.2 (2Θ) .

3. The crystalline form according to any of the preceding claims, which is an ansolvate or a solvate.

4. The crystalline form according to claim 3, which is a hydrate or an alcohol solvate.

   .

5. The crystalline form according to any of the preceding claims, which has

   A: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.7 ±0.2 (2Θ), 11.9 ±0.2 (2Θ), 18.3 ±0.2 (2Θ), and 27.1 ±0.2 (2Θ) and/or one or more Raman peaks selected from the group consisting of at 1606 ±2 cm^{-1}, 1175 ±2 cm^{-1}, 1568 ±2 cm^{-1}, 1574 ±2 cm^{-1} and 1650 ±2 cm^{-1}; or

   B: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of at 6.8 ±0.2 (2Θ), 12.1 ±0.2 (2Θ), 18.7 ±0.2 (2Θ), and 28,3 ±0.2 (2Θ); and/or one or more Raman peaks selected from the group consisting of at 1643 ±2 cm^{-1} and 1578 ±2 cm^{-1}; or

   C: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 9.7 ±0.2 (2Θ), 11.6 ±0.2 (2Θ), 14.0 ±0.2 (2Θ), and 17.9 ±0.2 (2Θ); or

   D: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.7 ±0.2 (2Θ), 11.6 ±0.2 (2Θ), 16.6 ±0.2 (2Θ), and 21.2 ±0.2 (2Θ); and/or one or more Raman peaks selected from the group consisting of 1612 ±2 cm^{-1} and 1199 cm^{-1}±2 cm^{-1}; or

E: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 6.9 ±0.2 (2Θ), 8.1 ±0.2 (2Θ), 18.3 ±0.2 (2Θ) and 20.8 ±0.2 (2Θ); or

F: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.7 ±0.2 (2Θ), 12.5 ±0.2 (2Θ), 20.9 ±0.2 (2Θ); or

G: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 6.6 ±0.2 (2Θ), 8.0 ±0.2 (2Θ), 18.0 ±0.2 (2Θ), and 18.9 ±0.2 (2Θ);

H: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 8.0 ±0.2 (2Θ), 18.2 ±0.2 (2Θ), and 28.3 ±0.2 (2Θ);; or

I: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 11.8 ±0.2 (2Θ), 17.6 ±0.2 (2Θ) and 19.6 ±0.2 (2Θ); or

J: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 11.1 ±0.2 (2Θ), 14.5 ±0.2 (2Θ), and 19.7 ±0.2 (2Θ); or

K: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 7.1 ±0.2 (2Θ), 10.0 ±0.2 (2Θ), 14.3 ±0.2 (2Θ), and 19.5 ±0.2 (2Θ); or

L: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.1 ±0.2 (2Θ), 12.0 ±0.2 (2Θ), 17.1 ±0.2 (2Θ), and 20.1 ±0.2 (2Θ); or

Q: one or more X-ray powder diffraction peaks (CuKα radiation) selected from the group consisting of 8.2 ±0.2 (2Θ), 8.6 ±0.2 (2Θ), 17.2 ±0.2 (2Θ), and 24.4 ±0.2 (2Θ).

6. The crystalline form A according to claim 5, which in DSC analysis exhibits an endothermal event with an onset temperature in the range of 227 °C to 247°C,

preferably 240 °C to 245 °C and/or a peak temperature in the range of 235 °C to 255°C, preferably 245 °C to 250 °C.

7. The crystalline form A according to claims 5 or 6, which has X-ray powder diffraction peaks (CuKα radiation) of 8.7 ±0.2 (2Θ), 11.9 ±0.2 (2Θ), 18.3 ±0.2 (2Θ), and optionally 27.1 ±0.2 (2Θ).

8. The crystalline form according to claim 1, which has X-ray powder diffraction peaks (CuKα radiation) at 7.7 ±0.2 (2Θ) and/or 17.4 ±0.2 (2Θ) and/or 18.3 ±0.2 (2Θ) and at least one additional X-ray peak selected from 10.0 ±0.2 (2Θ), 15.3 ±0.2 (2Θ),15.8 ±0.2 (2Θ), 21.9 ±0.2 (2Θ), 22.2 ±0.2 (2Θ) and 27.1 ±0.2 (2Θ).

9. The crystalline form according to claim 1, which has X-ray powder diffraction peaks (CuKα radiation) at 8.7 ±0.2 (2Θ) and 17.4 ±0.2 (2Θ) and at least one additional peak selected from the group of 10.0 ±0.2 (2Θ), 16.7 ±0.2 (2Θ), 26.2 ±0.2 (2Θ), and 27.1 ±0.2 (2Θ).

10. The crystalline form B according to claim 5, which in DSC analysis exhibits an endothermal event with a peak temperature in the range of 80°C to 110°C and/or an exothermal event with a peak temperature in the range of 204°C to 231°C.

11. The crystalline form B according to claims 5 and 10, which has X-ray powder diffraction peaks (CuKα radiation) at 6.8 ±0.2 (2Θ), 12.1 ±0.2 (2Θ), 28,3 ±0.2 (2Θ), and optionally at 18,7 ±0.2 (2Θ).

12. A pharmaceutical composition comprising at least one crystalline form according to any of claims 1 to 11.

13. A process for preparing a crystalline form of cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine according to any of claims 1 to 12, comprising the steps of

(a-1) suspending cis-(E)-4-(3-Fluorophenyl)-2',3',4',9'-tetrahydro-N,N-dimethyl-2'-(1-oxo-3-phenyl-2-propenyl)-spiro[cyclohexane-1,1'[1H]-pyrido[3,4-b]indol]-4-amine in a solvent;

(b-1) separating, preferably filtering off the solid obtained in step (a-1); and

(c-1)   drying of the solid obtained in step (b-1).

5

Figure 1a

STOE Powder Diffraction System

Relative Intensity (%)

2Theta

Figure 1b

Figure 1c

STOE Powder Diffraction System

Relative Intensity (%)

2Theta

Figure 1d

STOE Powder Diffraction System
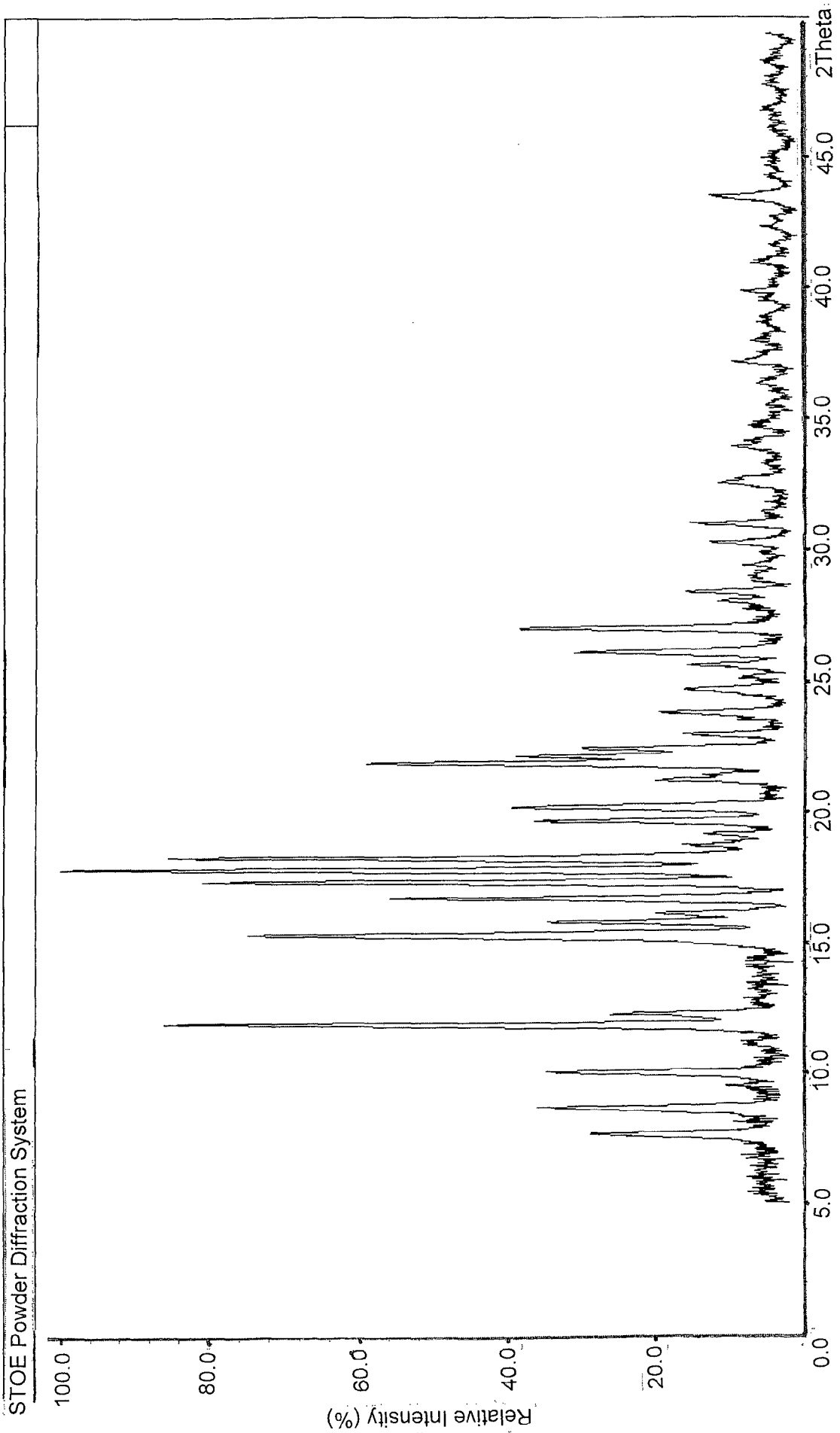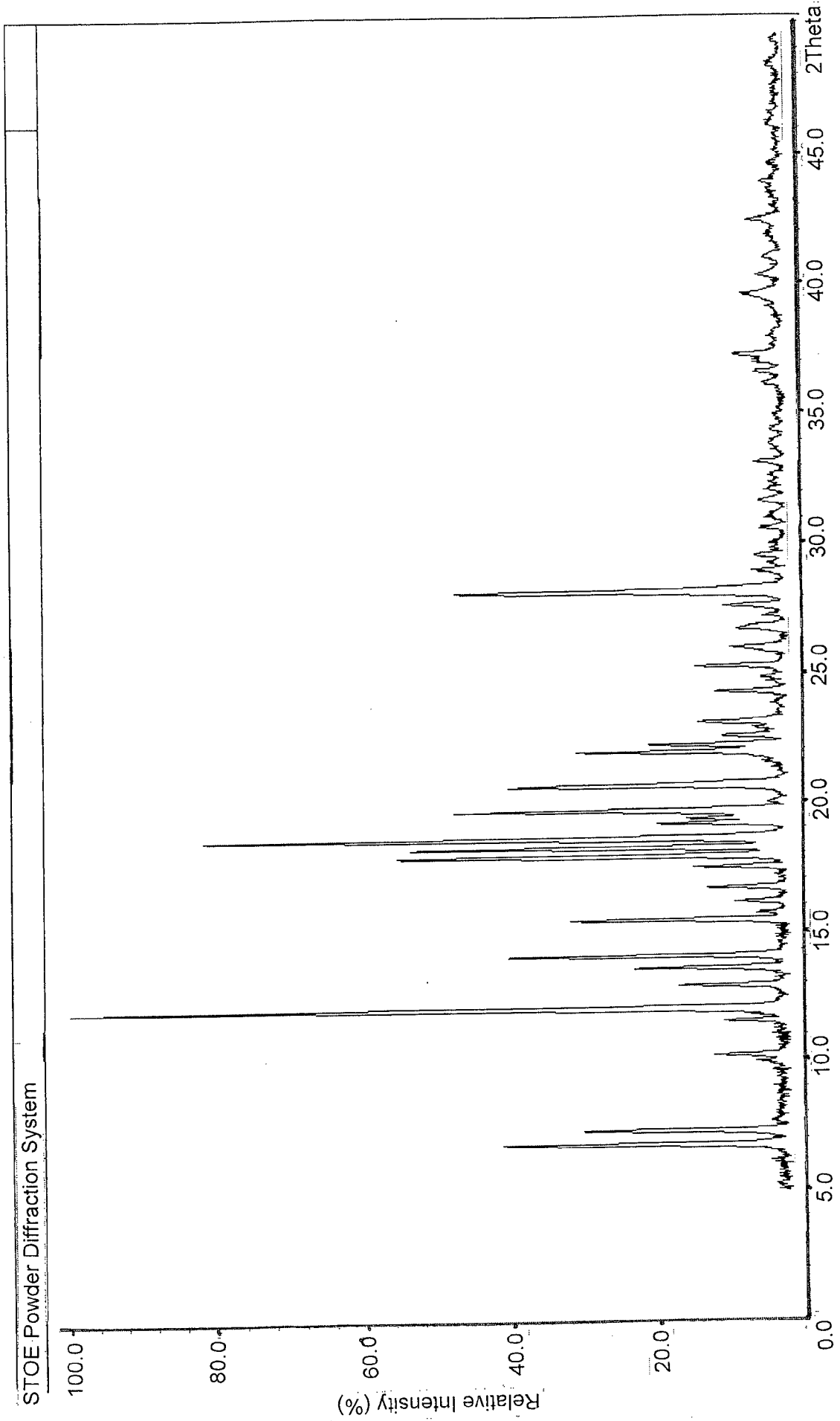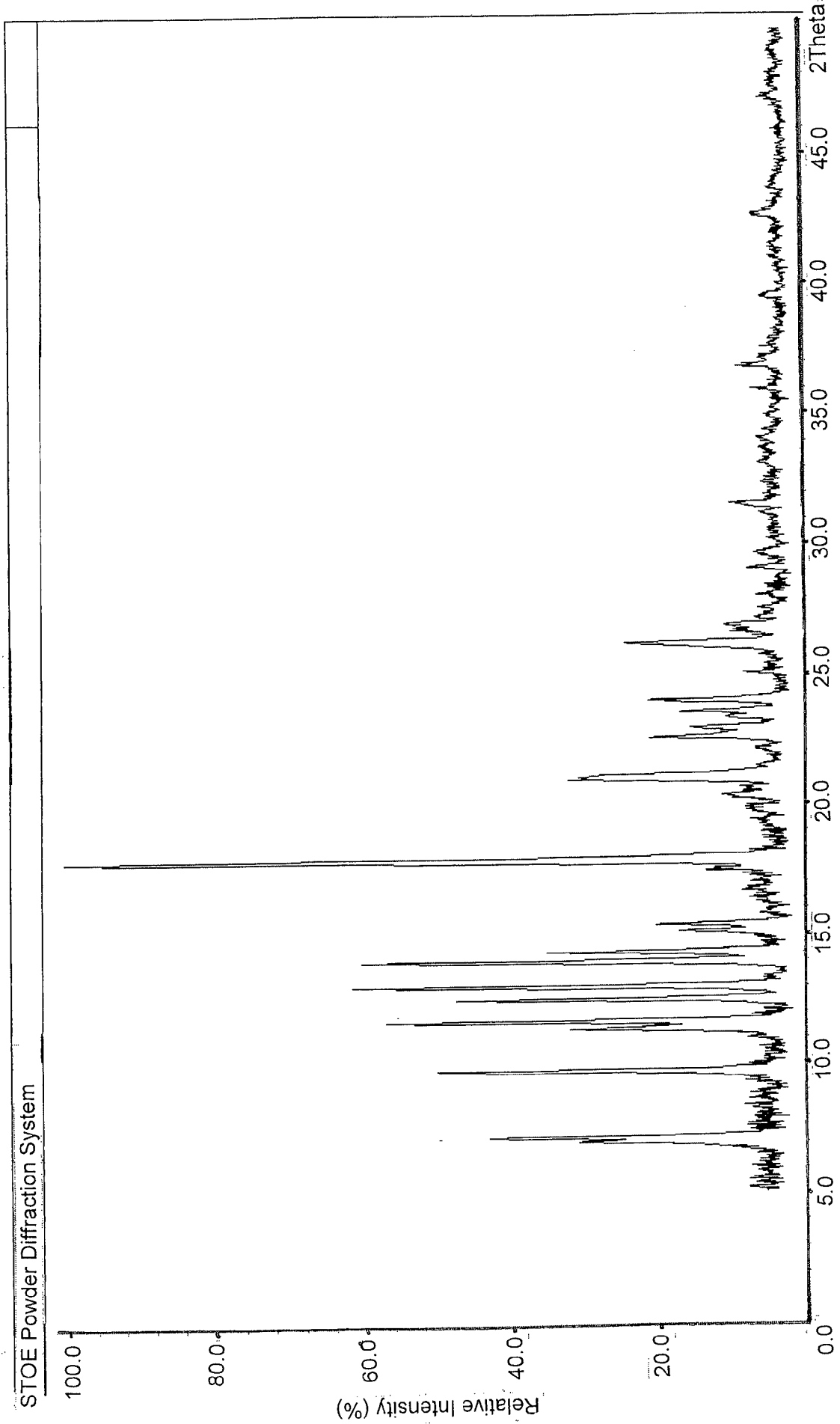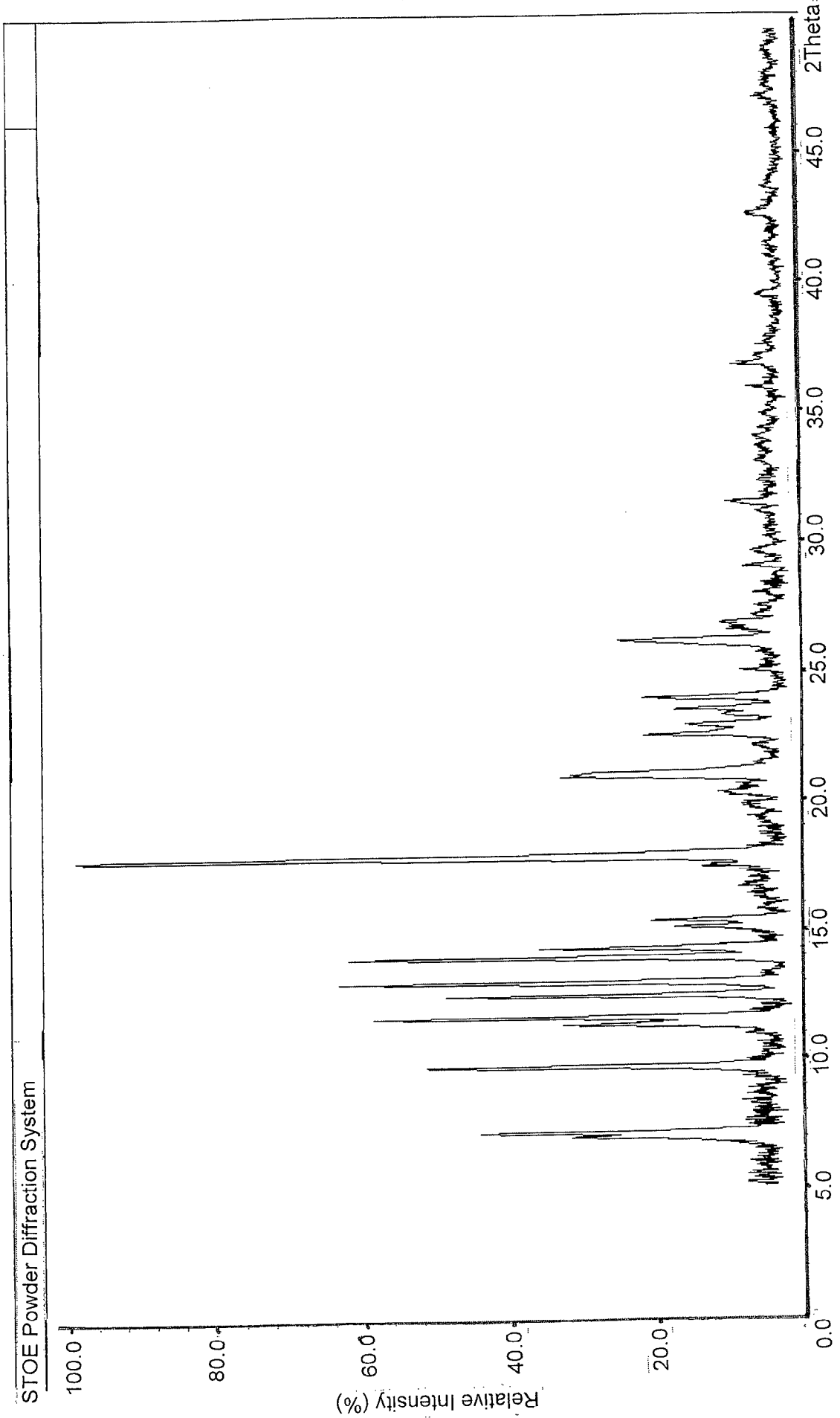
Figure 1e

Figure 1f

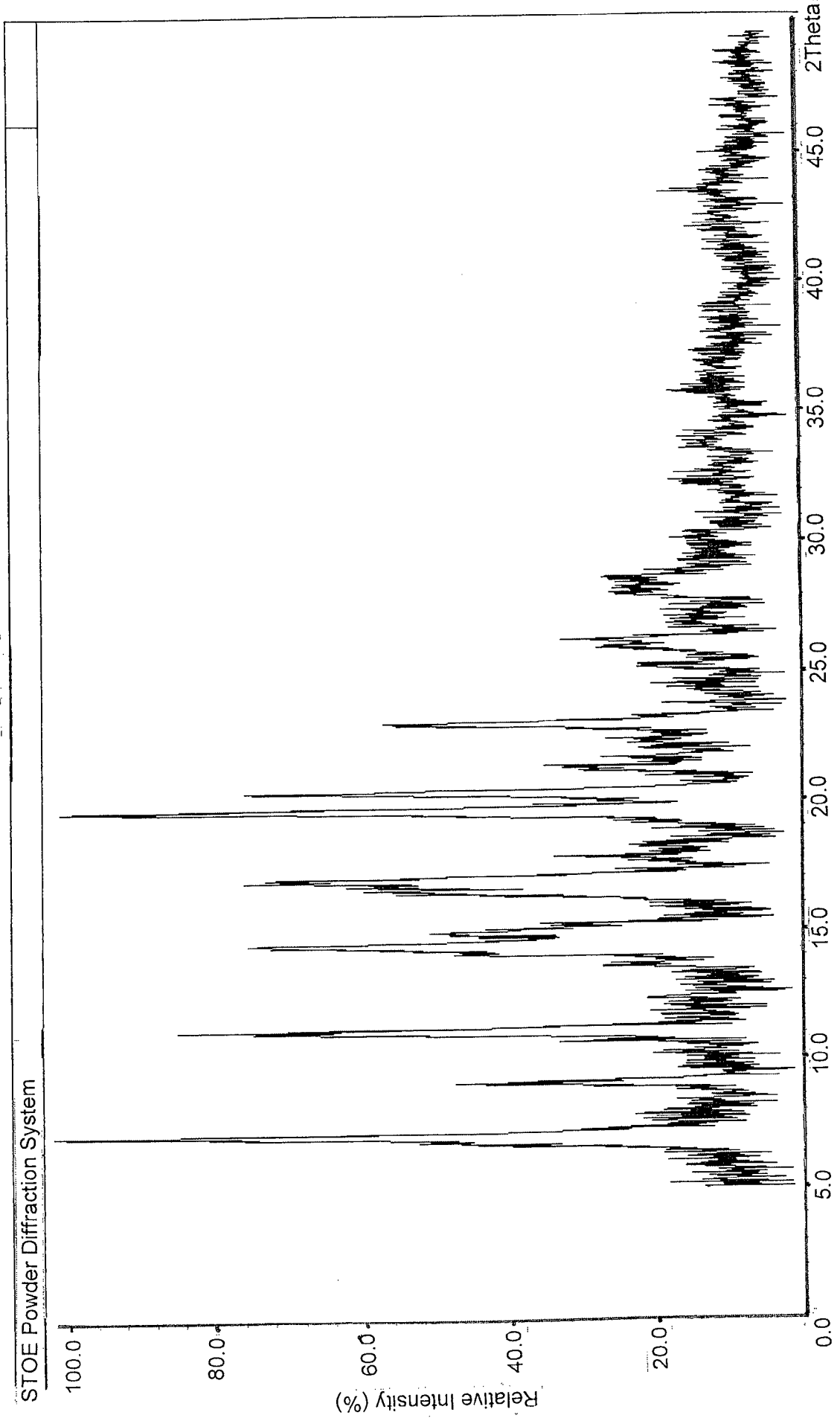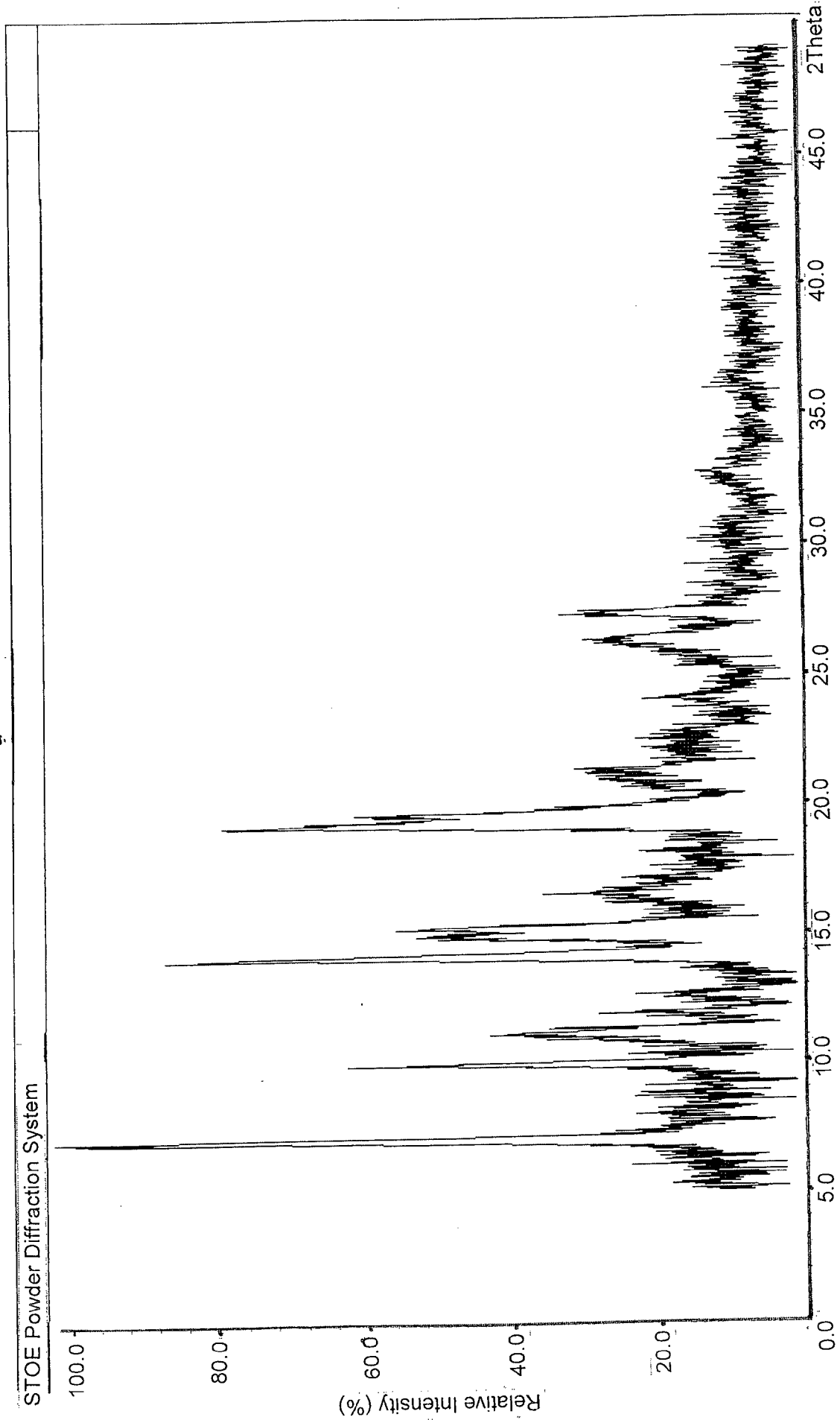Figure 1g
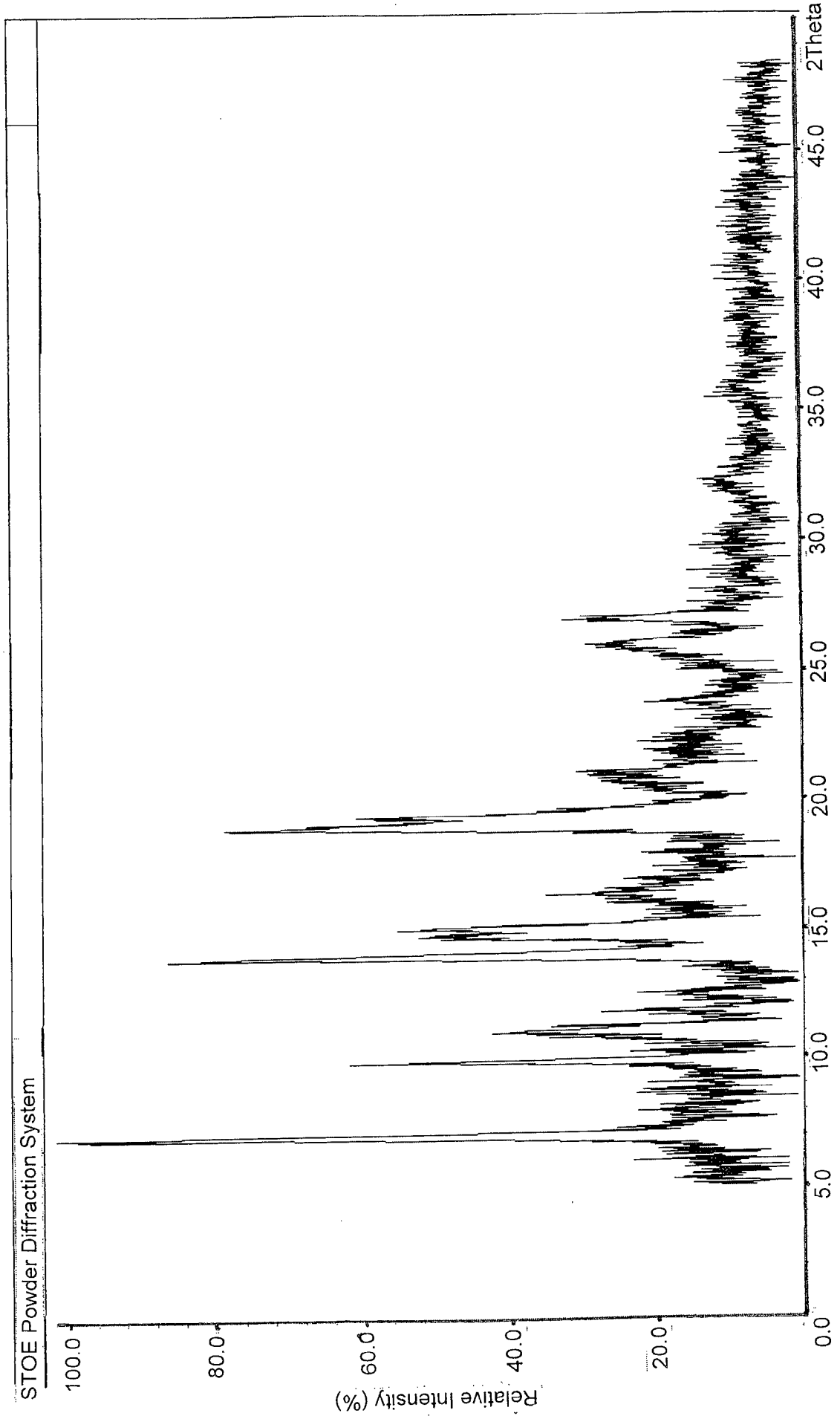

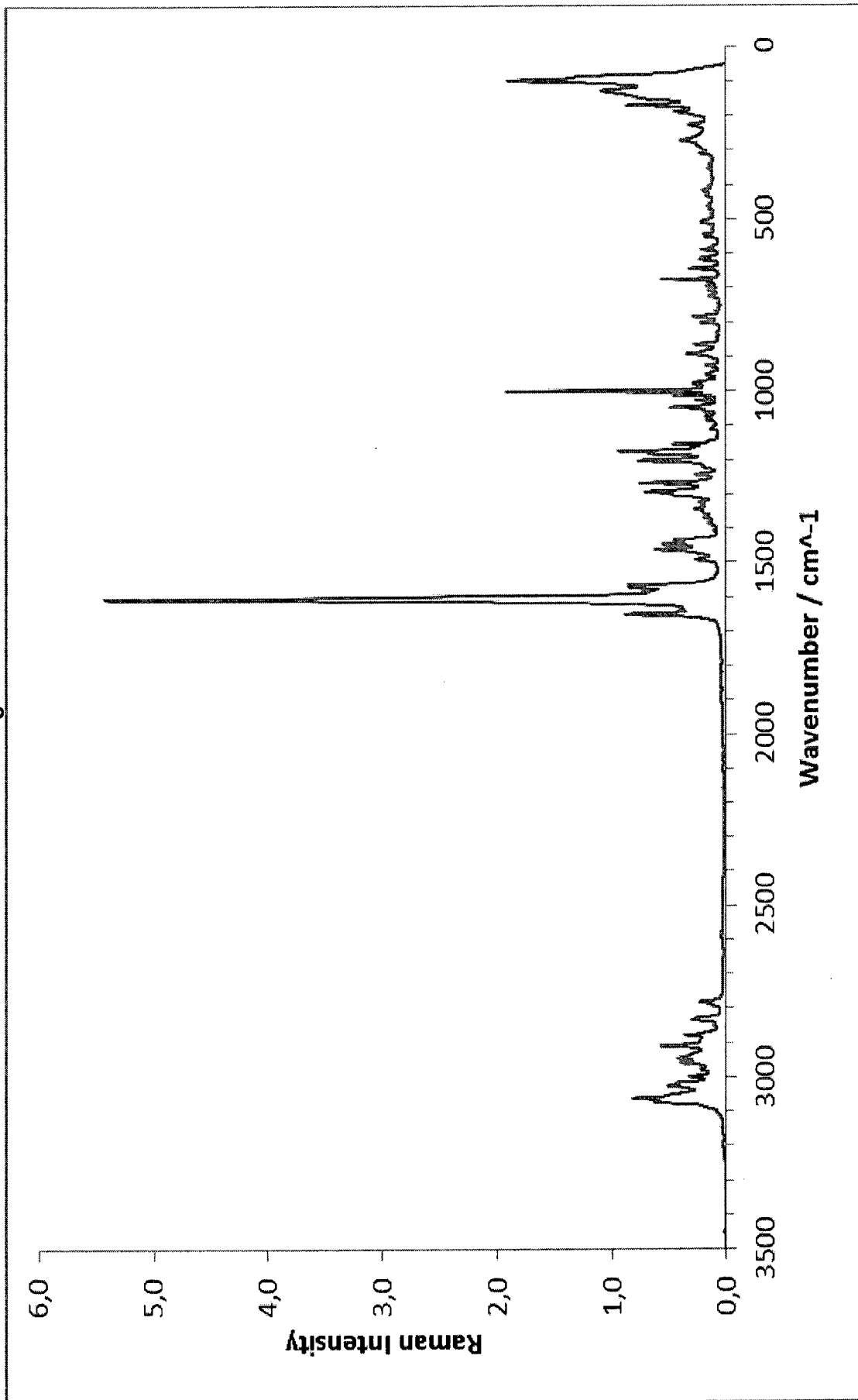STOE Powder Diffraction System
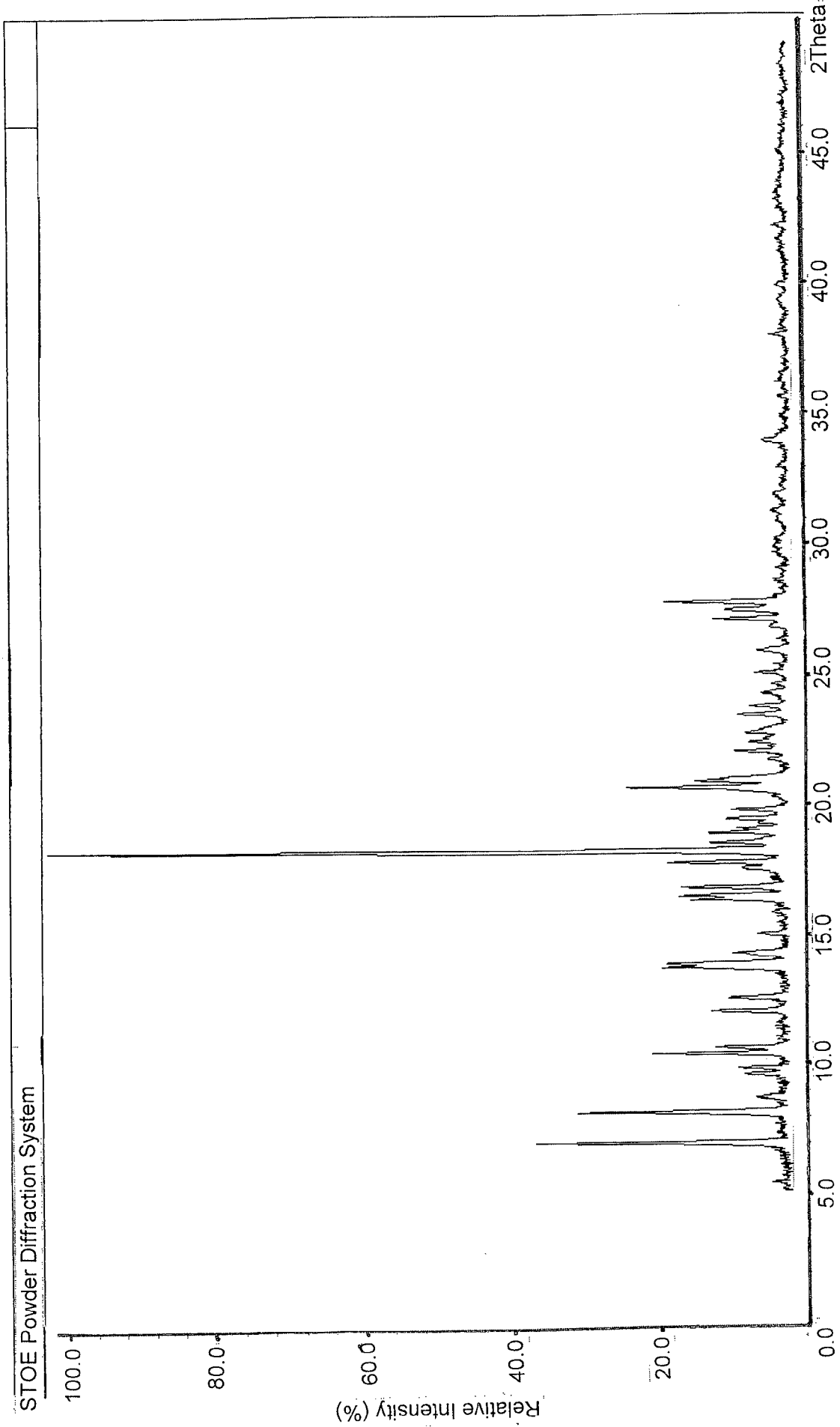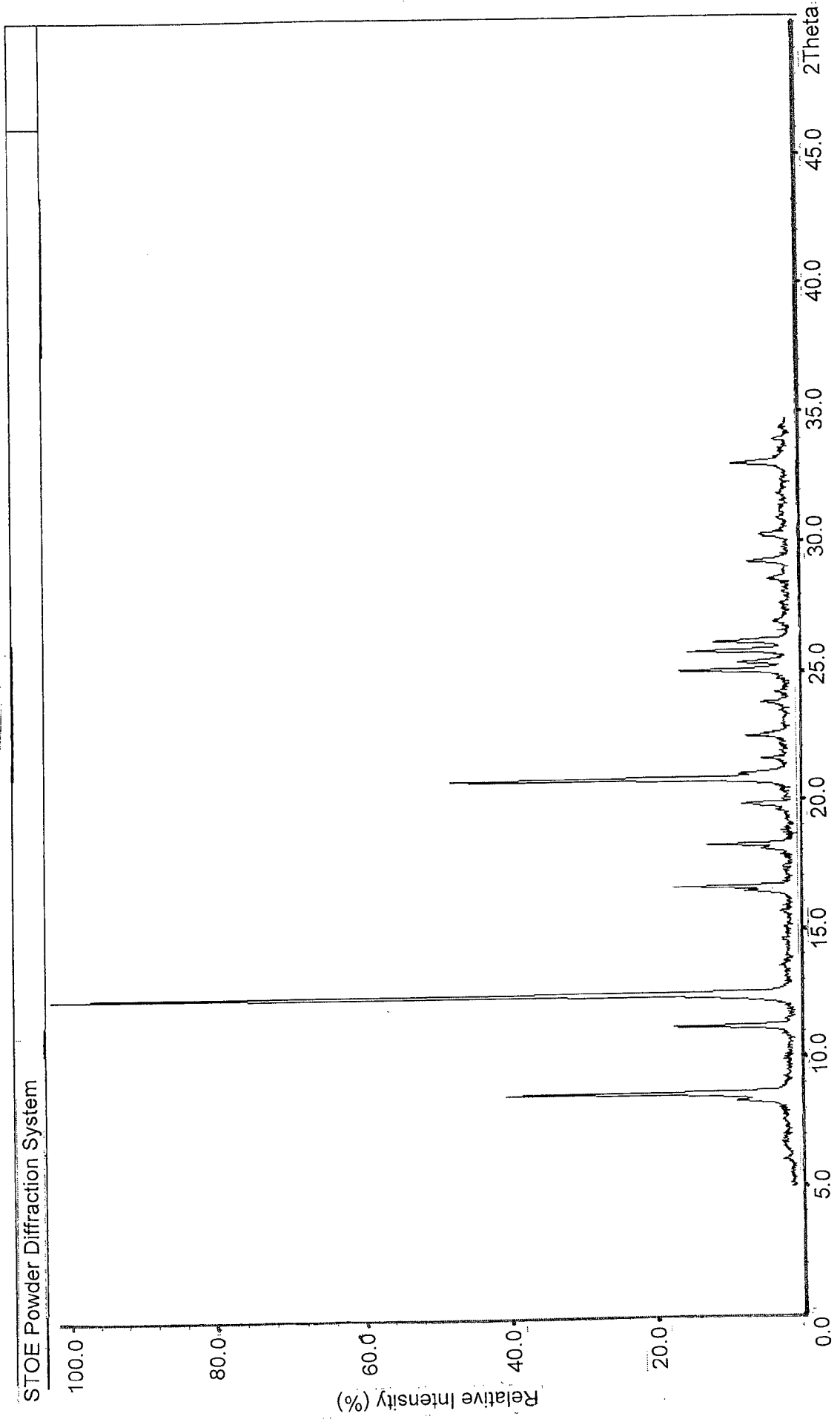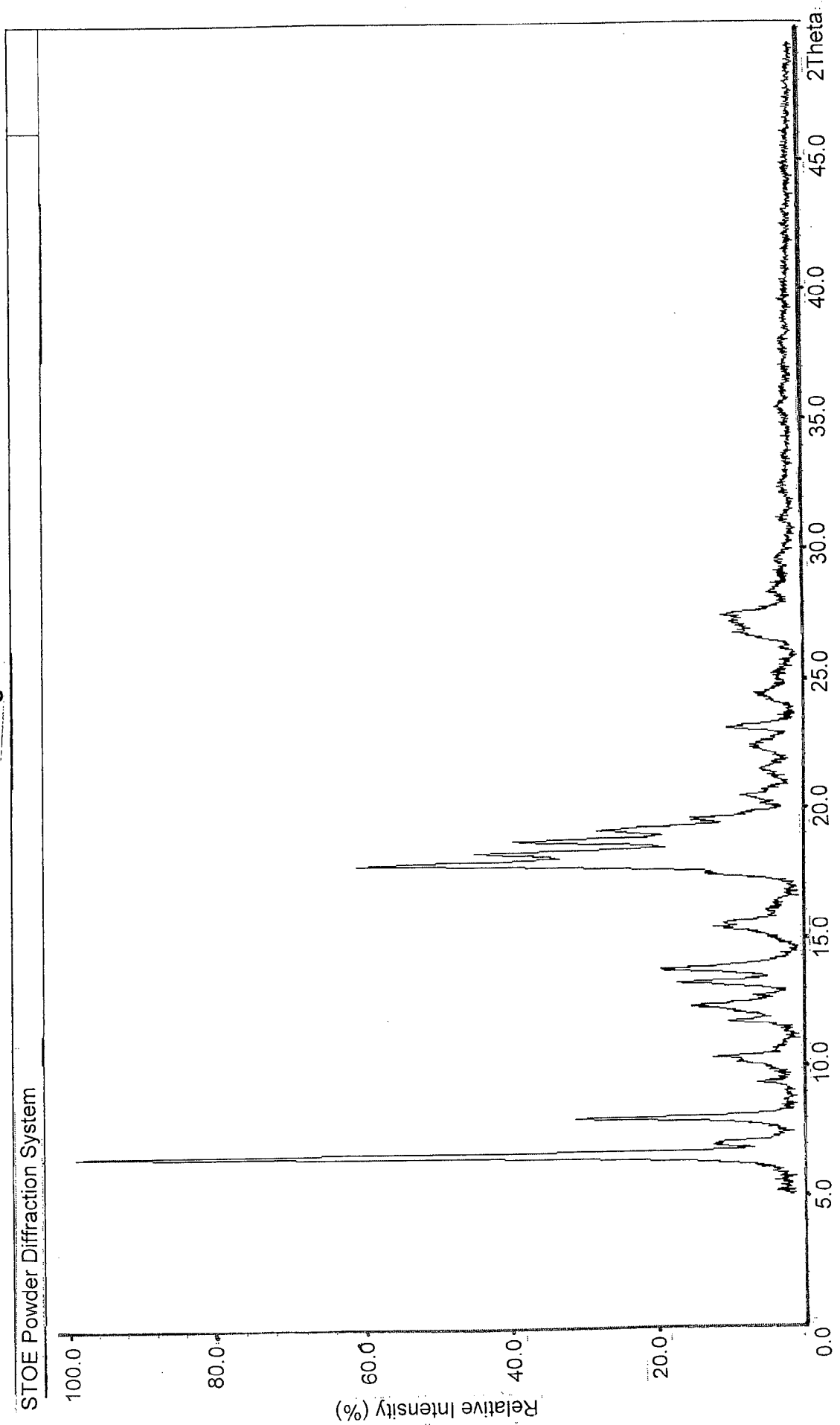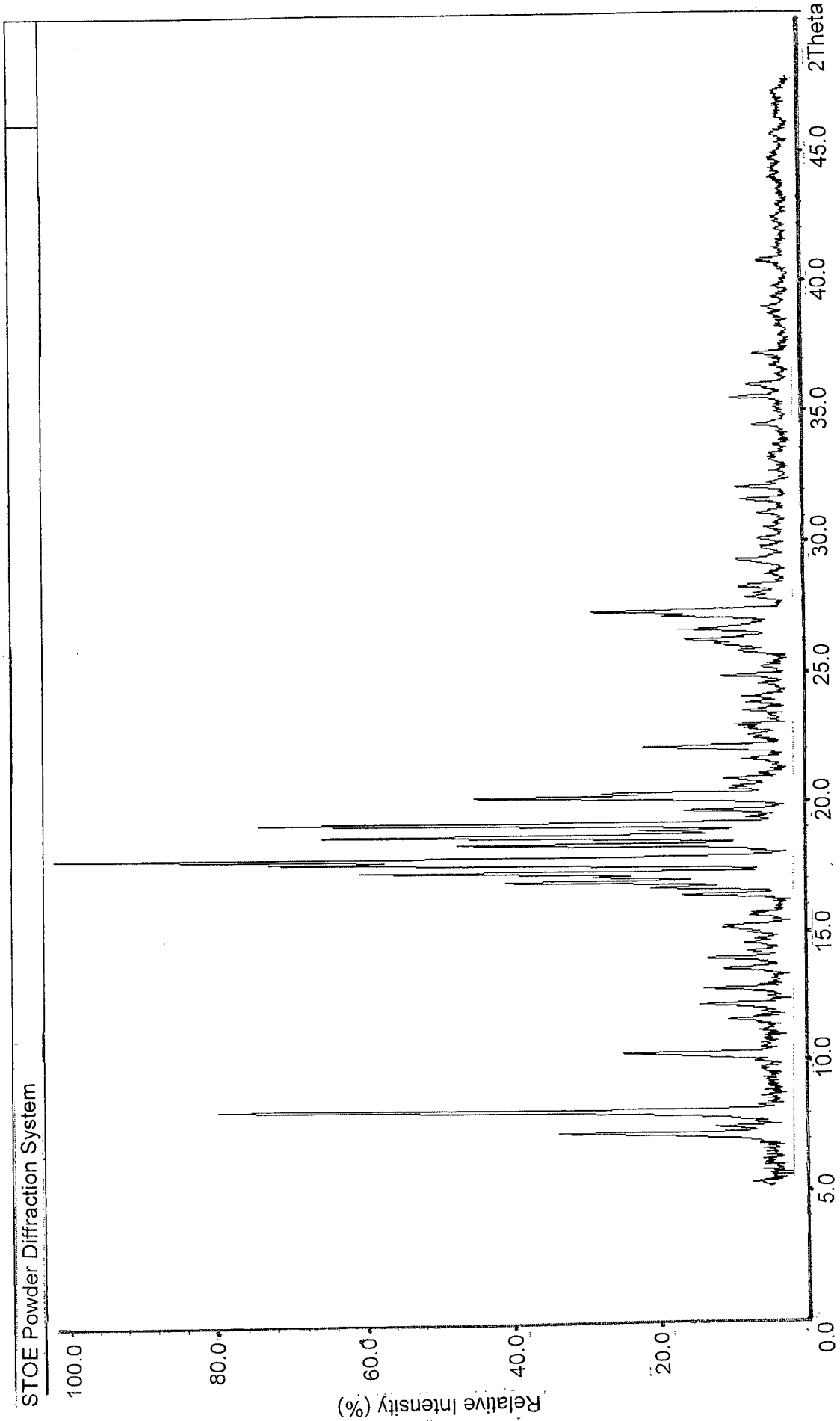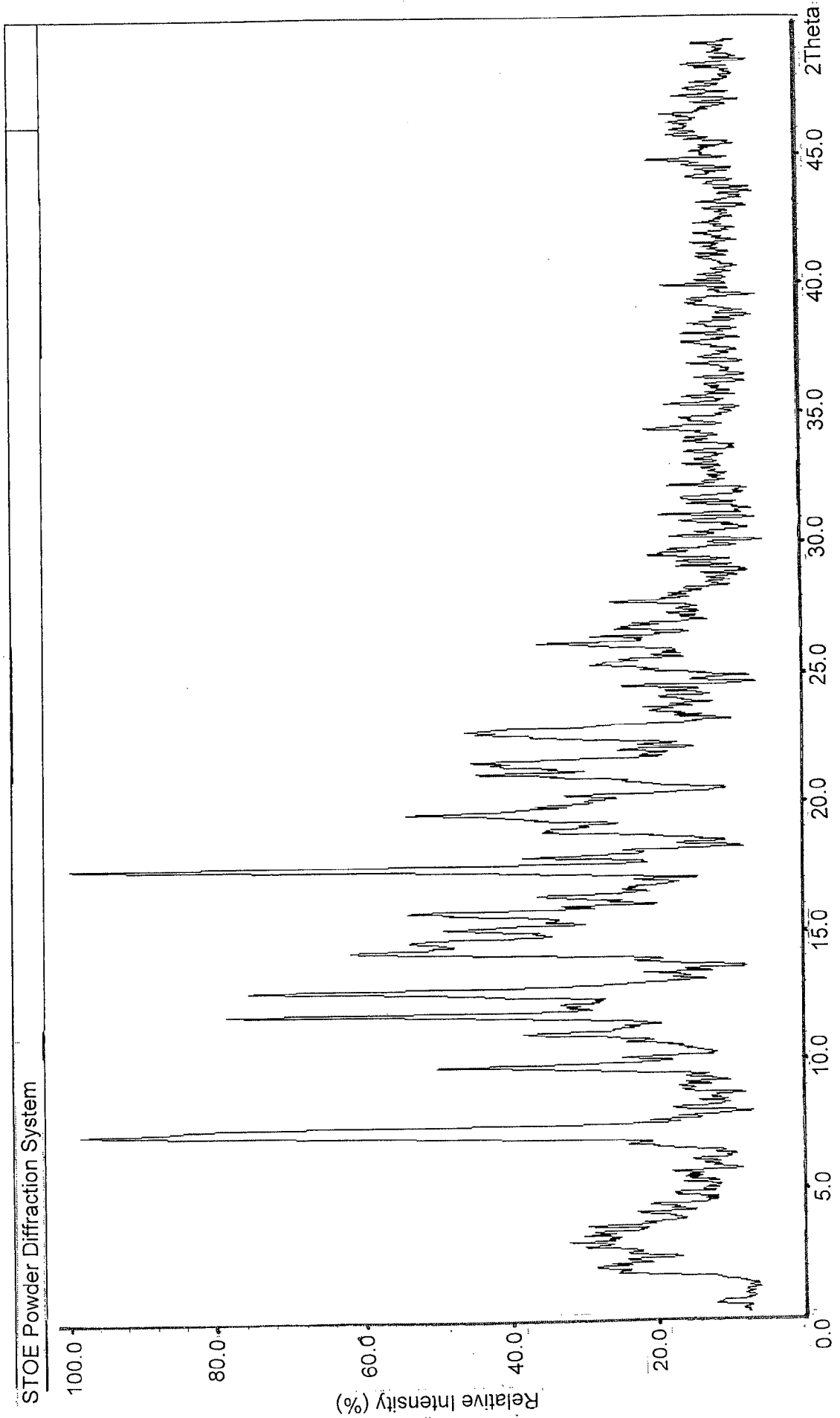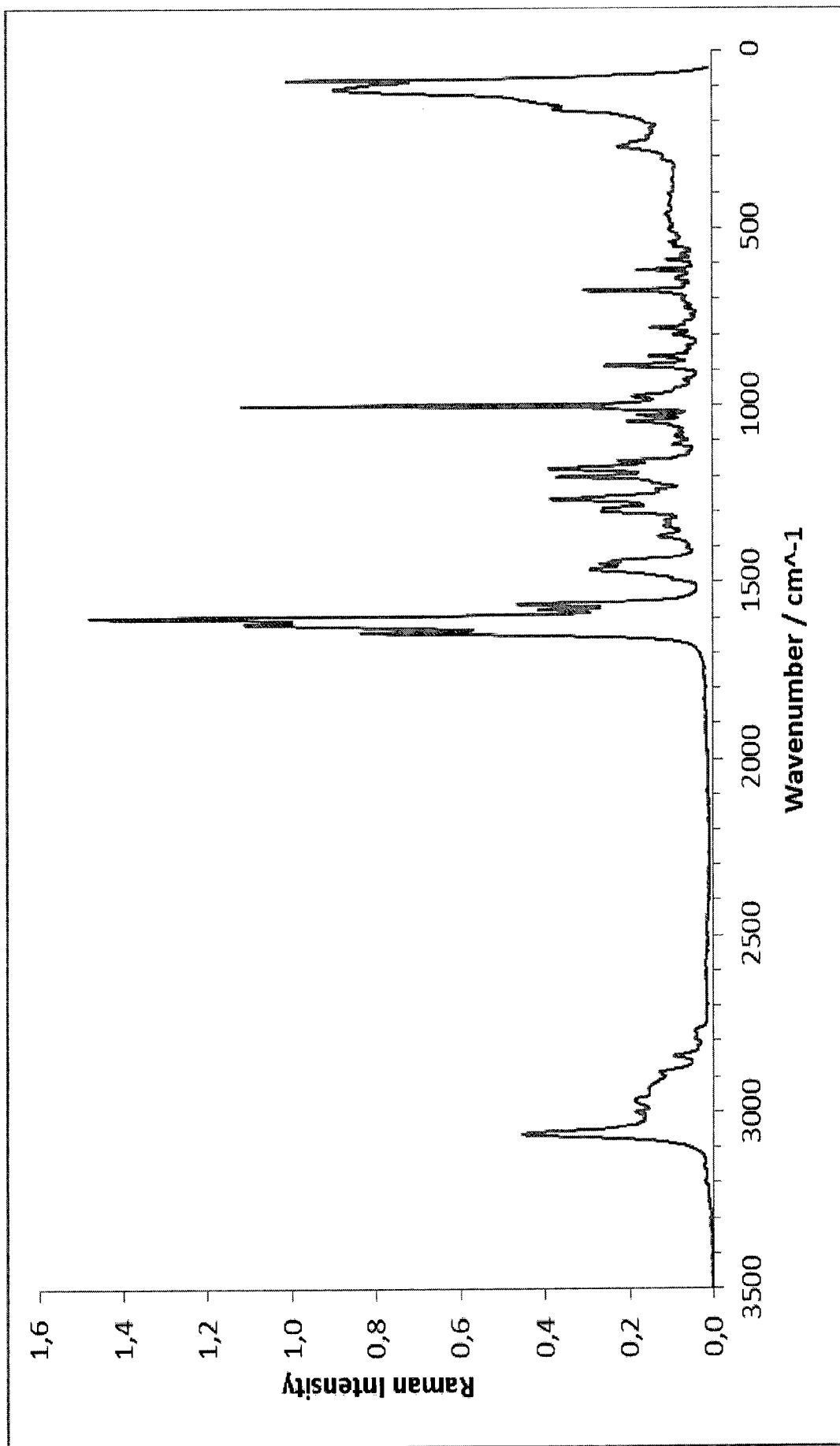
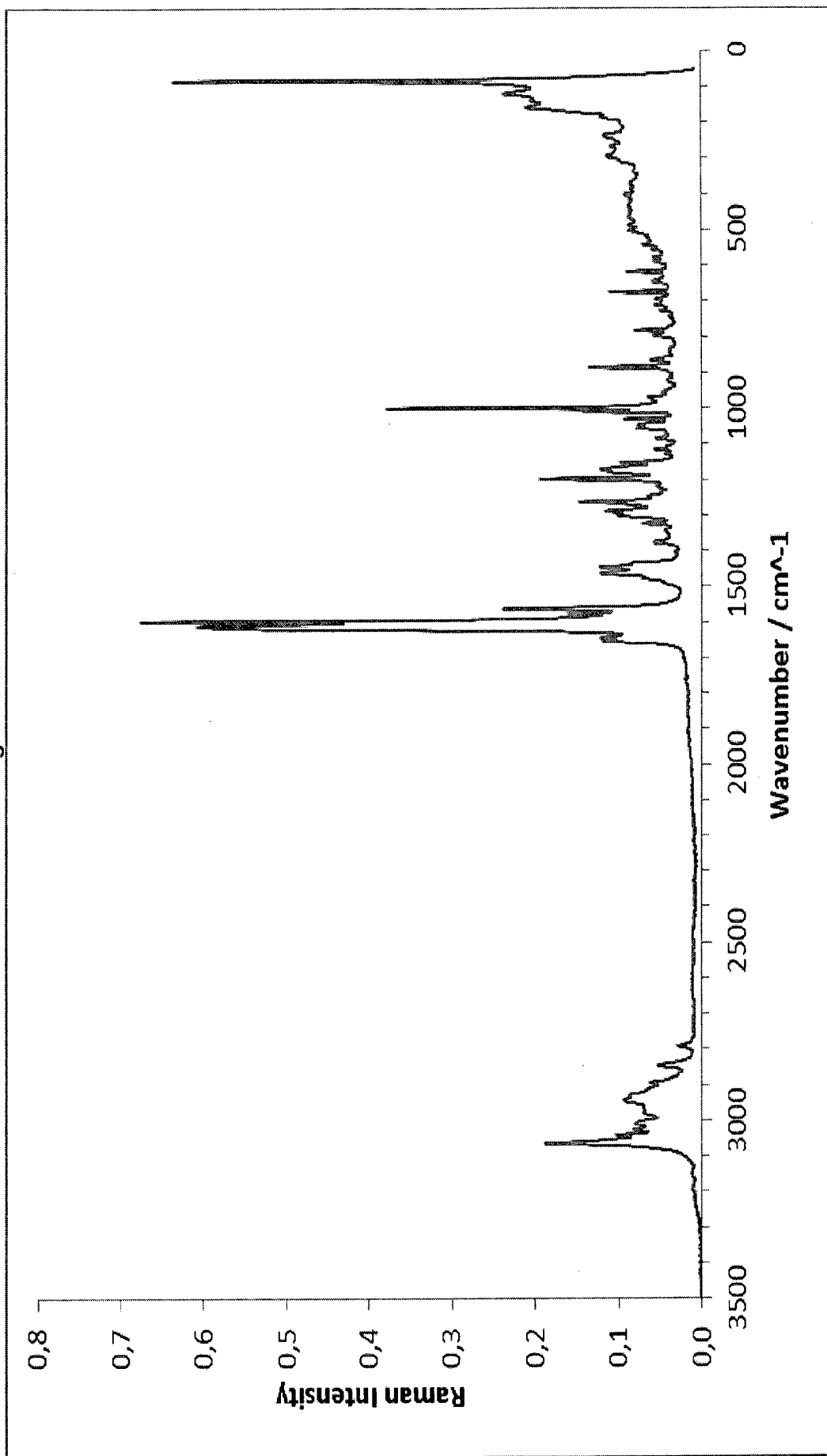Figure 1h

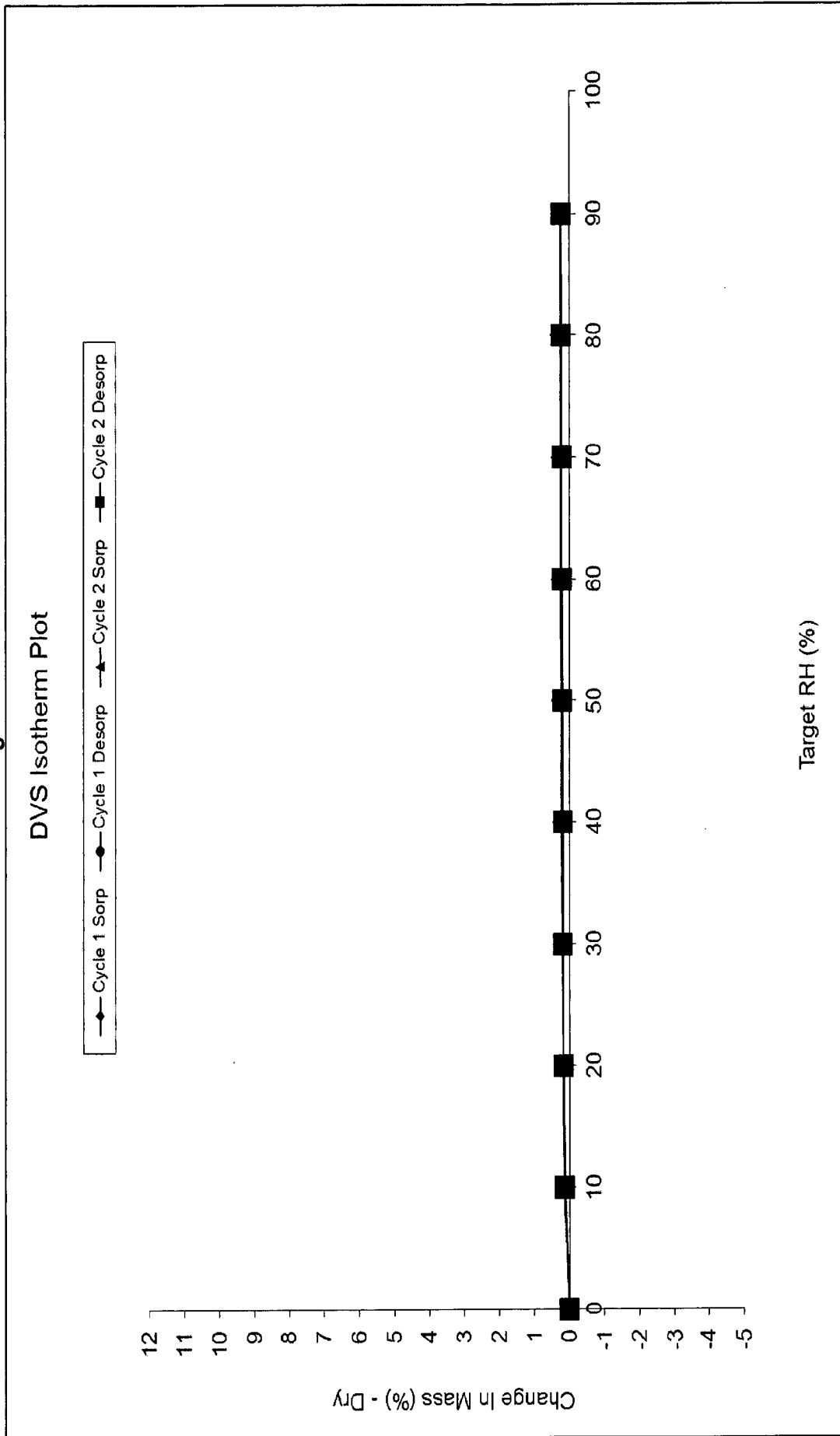**Figure 1i**

Figure 1j

Figure 1k

Figure 1l

Figure 2a

Figure 2b

Figure 2d

Figure 3a
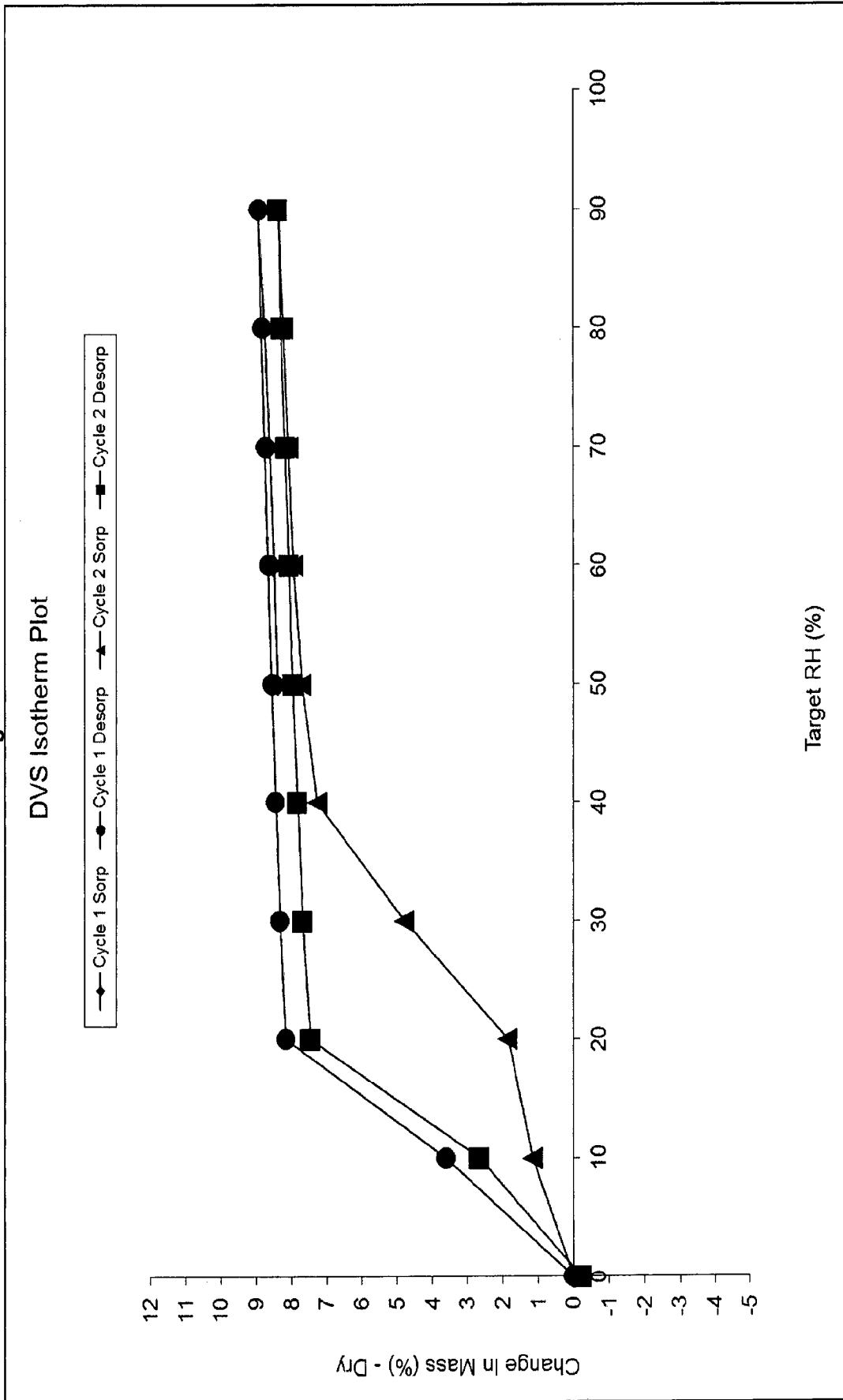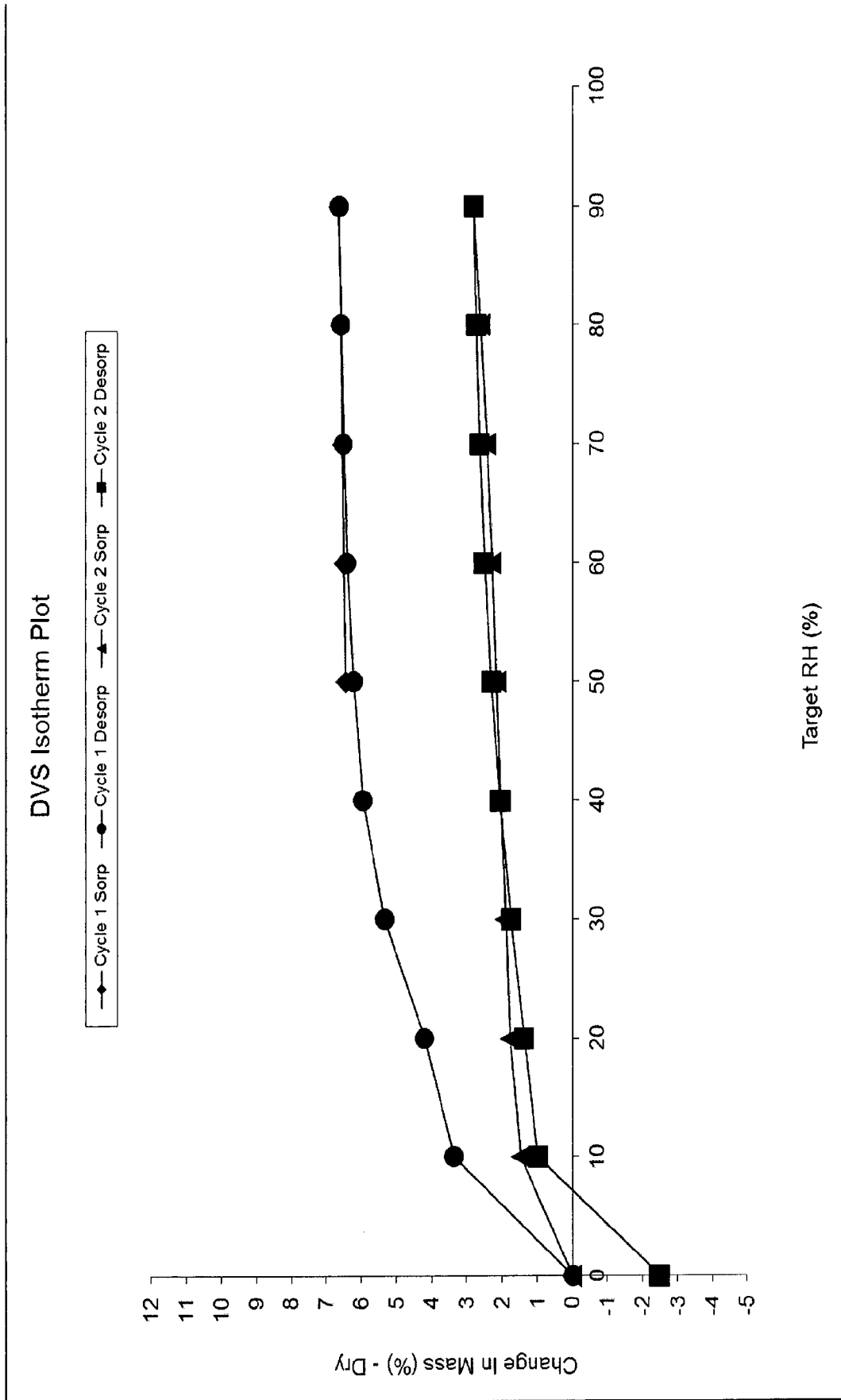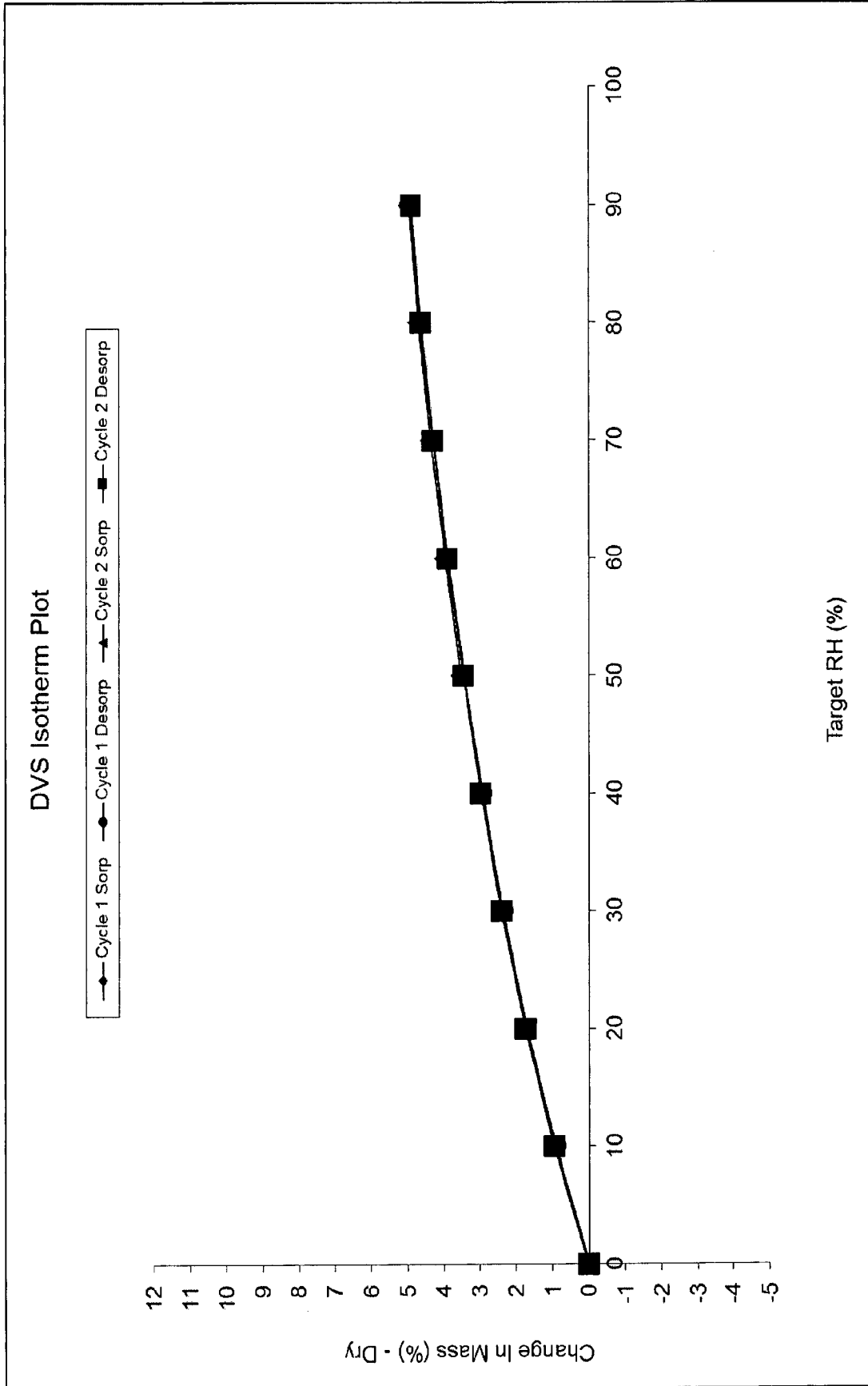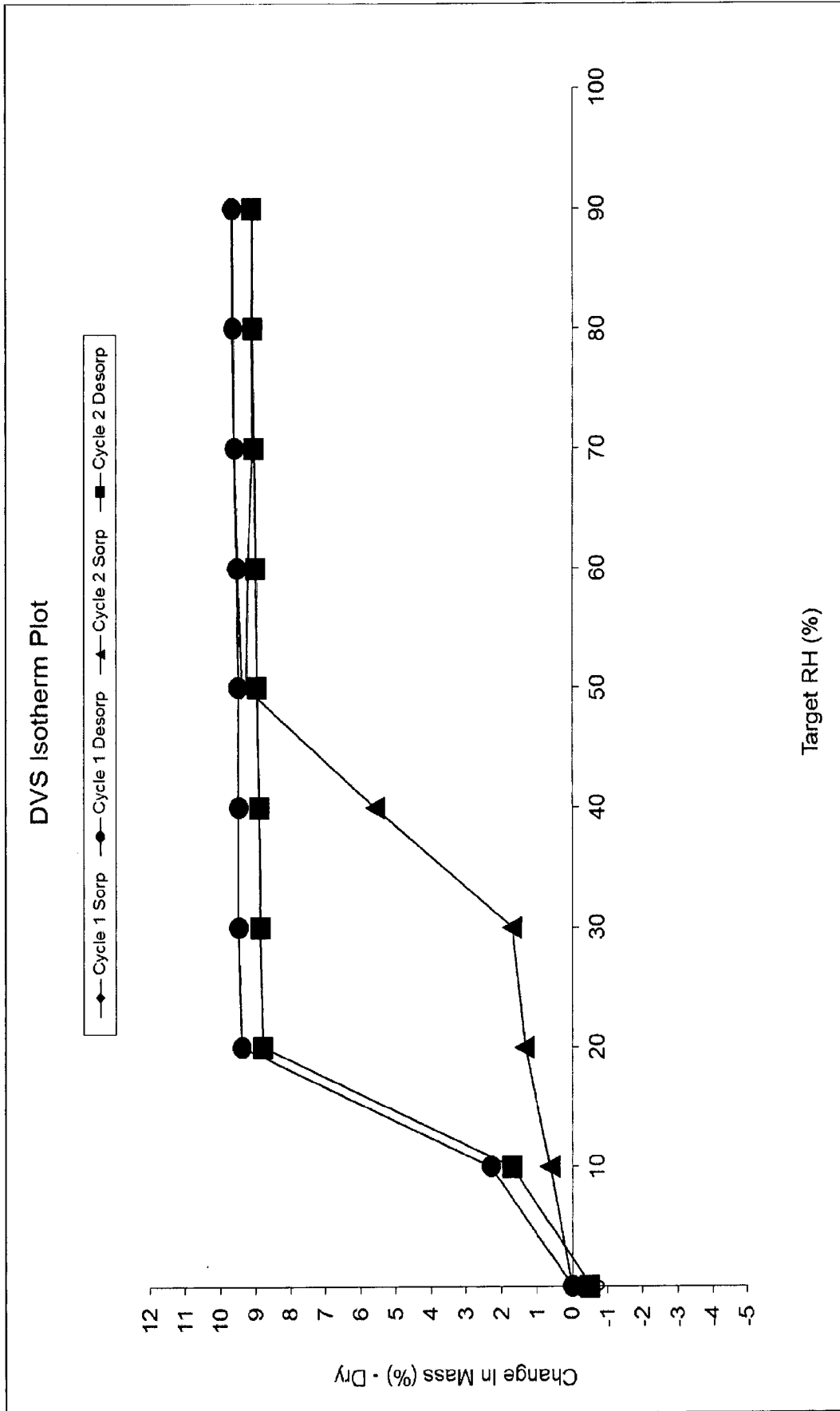
DVS Isotherm Plot

Figure 3b

DVS Isotherm Plot

Figure 3c

DVS Isotherm Plot

Figure 3d

DVS Isotherm Plot

Figure 3e

DVS Isotherm Plot

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/10   A61K31/438   A61P25/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/013343 A1 (GRUENENTHAL GMBH [DE]; LINZ KLAUS [DE]; ZEMOLKA SASKIA [DE]; NOLTE BER) 2 February 2012 (2012-02-02) cited in the application page 48 - page 50; claims 1,15 -----	1-13
A	WO 2006/108565 A1 (GRUENENTHAL GMBH [DE]; FRIDERICHS ELMAR [DE]; KOEGEL BABETTE-YVONNE [D) 19 October 2006 (2006-10-19) page 36; claim 8; example 50 -----	1-13

☐ Further documents are listed in the continuation of Box C.   ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 April 2014	22/04/2014

| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer Gettins, Marc |

Form PCT/ISA/210 (second sheet) (April 2005)

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Information on patent family members

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			SI	1868600 T1	31-08-2012
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