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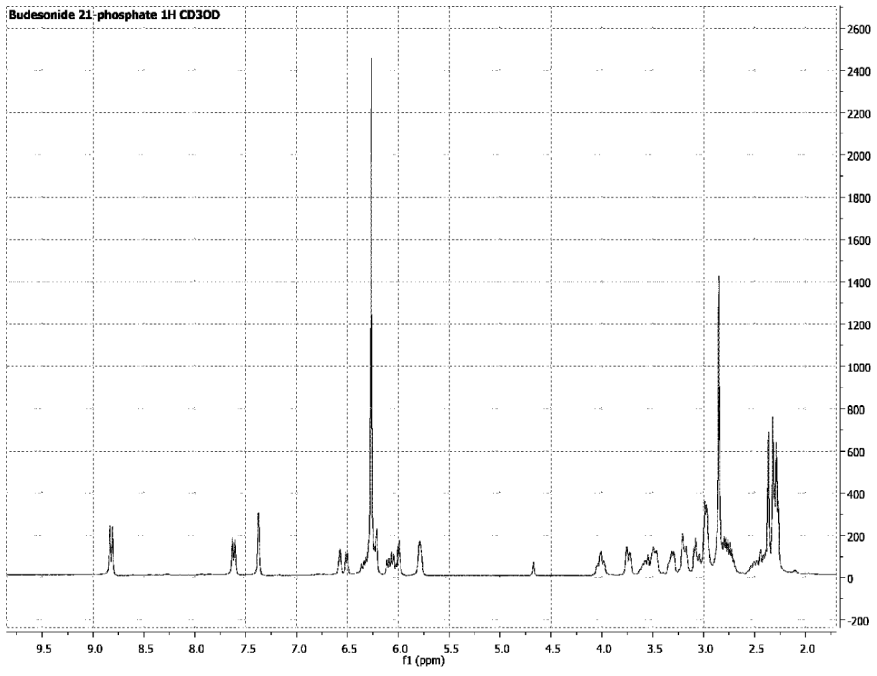
(54) Title: PROCESS FOR THE PREPARATION OF BUDESONIDE 21-PHOSPHATE

Figure 1



(57) Abstract: The present invention relates to a new process for the preparation of budesonide 21- phosphate and its disodium salt.

[Continued on next page]

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TITLE

PROCESS FOR THE PREPARATION OF BUDESONIDE 21-PHOSPHATE

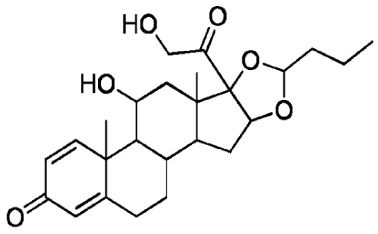
*****

TECHNICAL FIELD

The present invention relates to a new process for the preparation of budesonide 21-phosphate and its disodium salt

BACKGROUND OF THE INVENTION

Budesonide (Bud) (chemical name 11β,21-dihydroxy-16α,17α-(butylidenebis(oxy))pregna-1,4-diene-3,20-dione), is a glucocorticoid steroid for the treatment of asthma, chronic obstructive pulmonary disease (COPD), noninfectious rhinitis and Crohn disease, represented by Formula I.



FORMULA I

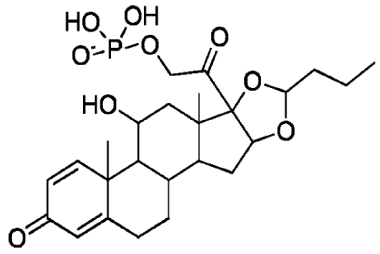
Budesonide has a logP of 3.2 and results practically insoluble in water (28 µg/mL) [Journal of Chemical and Engineering Data (2010), vol. 55, no. 1, pp. 578–582] at physiological pH in the intestinal region. It belongs to inhaled corticosteroids (ICS), a class of compounds that represents, by far, the most effective therapeutic tool used in the treatment of asthma, able to suppress and activate many genes relevant to elicit inflammation in asthmatic airways, even in very low doses.

Budesonide is virtually insoluble in water while it results readily soluble in alcohols. For this reason, hydroalcoholic solutions are usually prepared dissolving an adequate amount of active substance in solubilizers such as water-soluble alcohols. However,

the so prepared solutions have low stability because large amounts of budesonide are decomposed within a short time. Moreover, budesonide formulations have been prepared until now in the form of aqueous suspensions in which the solid phase tends in time to deposit onto the bottom of the container, thus requiring chemical additives or vigorous stirring. These are the reasons that make budesonide not suitable to be delivered by an electric nebulizer.

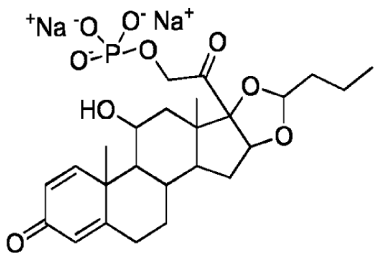
The 21-phosphate primary esters of several corticosteroids have been prepared and largely used as active ingredients for several pharmaceutical compositions. These molecules have valuable properties not possessed by the parent steroid; first, they are water soluble thus allowing the administration in aqueous solution.

Budesonide 21-phosphate (Formula II) has been used in some studies [Bioconjugate Chem. 2016, 27, 2081−2088; J. Am. Chem. Soc. 2016, 138, 1430−1445] where it is described as linker for targeted delivery of antibody-drug conjugates.



FORMULA II

Budesonide 21-phosphate disodium salt (Formula III) has been used in some studies for the preparation of liposomal glucocorticoids studied as antitumor agents [Journal of Steroid Biochemistry & Molecular Biology 111 (2008) 101–110; Journal of Controlled Release 127 (2008) 131–136].



FORMULA III

J. Am. Chem. Soc. 2016, 138, 1430−1445 473 describes the synthesis of Budesonide 21-phosphate starting from a stirred solution of budesonide in THF at −40 °C and reacting with diphosphoryl chloride. The reaction is quenched with water and treated with saturated sodium bicarbonate solution until pH ~ 8. The solution is subsequently made acidic using a 1 N HCl solution and extracted several times with ethyl acetate (3.55 g, 75%).

DEFINITIONS

Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this disclosure pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference; thus, the inclusion of such definitions herein should not be construed to represent a substantial difference over what is generally understood in the art.

The terms “approximately” and “about” herein refer to the range of the experimental error, which may occur in a measurement.

The term “room temperature” herein refers to a temperature between 15 °C and 25 °C.

The terms “comprising”, “having”, “including” and “containing” are to be construed open-ended terms (i.e. meaning “including, but not limited to”) and are to be

considered as providing support also for terms as “consist essentially of”, “consisting essentially of”, “consist of” or “consisting of”.

The terms “consist essentially of”, “consisting essentially of” are to be construed as semi-closed terms, meaning that no other ingredients which materially affects the basic and novel characteristics of the invention are included (optional excipients may thus included).

The terms “consists of”, “consisting of” are to be construed as closed terms.

The term “unknown impurity” refers to any unknown impurity present in Budesonide 21-phosphate disodium salt.

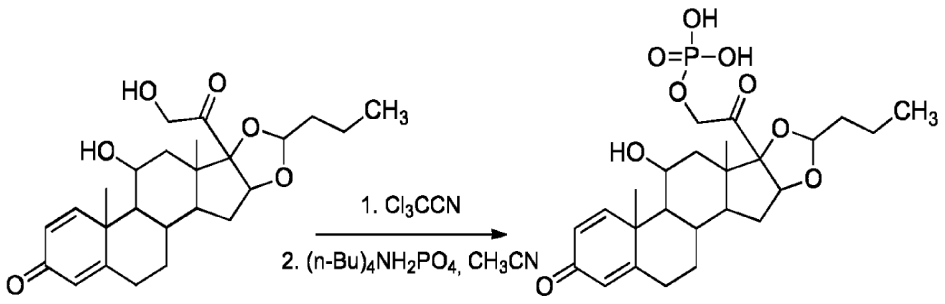
The term “area%” herein refers to area under the curve in the HPLC chromatogram.

References herein to percent (%) purity and impurity are based on area.

SUMMARY OF THE INVENTION

The invention relates to a novel and efficient process that leads to Budesonide 21-phosphate and its disodium salt, which is convenient for the industrial scale and provides the desired products in good yields.

The process of the invention is described in Scheme 1.



Scheme 1

Scheme 1 shows the one-pot process for the preparation of Budesonide 21-phosphate characterized by a phosphorylation with tetrabutylammonium dihydrogen phosphate and trichloroacetonitrile.

Preferably, the final product is isolated as disodium salt.

Conversely, the process described in the prior art involves the use of diphosphoryl chloride as a phosphorylating agent. The latter reacts with water to produce HCl and H_3PO_4. This makes it necessary to preserve both the reactive and the reaction mixture from contact with moisture. The known process requires more careful preparation of the reaction mixture and, therefore, more expensive chemical procedures.

Furthermore, the diphosphoryl chloride gives rise in the phosphorylation process to a strongly exothermic reaction which requires operating temperatures of −40 °C. To guarantee this condition, expensive experimental methodologies are required both from an energy point of view and from the specialized personnel employed.

The process of the present invention is a notable improvement with respect to the prior art because the reaction takes place under very mild conditions and at room temperature. Therefore, it is more manageable, less expensive and safer. Furthermore, under such experimental conditions, no strong acids are produced.

DESCRIPTION OF THE FIGURES

Figure 1 shows ^{1}H-NMR (500 MHz; CD_3OD-d_4) spectrum of Budesonide 21-phosphate.

Figure 2 shows ^{13}C-NMR (126 MHz; CD_3OD-d_4) spectrum of Budesonide 21-phosphate.

Figure 3 shows ^{1}H-NMR (500 MHz; CD_3OD-d_4) spectrum of Budesonide 21-phosphate disodium salt.

Figure 4 shows ^{13}C-NMR (126 MHz; CD_3OD-d_4) spectrum of Budesonide 21-phosphate disodium salt.

Figure 5 shows ESI-MS spectrum of Budesonide 21-phosphate.

Figure 6 shows the FT-IR spectrum of Budesonide 21-phosphate.

Figure 7 shows the FT-IR spectrum of Budesonide 21-phosphate disodium salt.

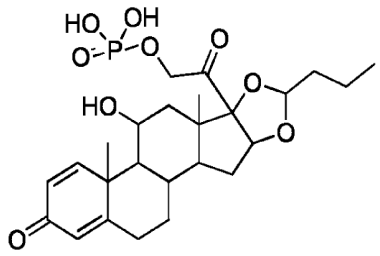
Figure 8 shows the X-Ray Powder Diffraction spectrum of Budesonide 21-phosphate.

Figure 9 shows the X-Ray Powder Diffraction spectrum of Budesonide 21-phosphate disodium salt.

Figure 10 shows UV spectrum of budesonide 21 phosphate disodium salt.

DETAILED DESCRIPTION OF THE INVENTION

According to a first aspect, the present invention relates to a new process for preparing budesonide 21-phosphate of formula (II)



(II)

which comprises the steps of:

a) reacting budesonide with tetrabutylammonium dihydrogen phosphate and trichloroacetonitrile to obtain the compound of formula (II);

b) optionally, salifying the compound of formula (II) with NaOH to form the corresponding disodium salt.

Advantageously, the one-pot procedure by tetrabutylammonium dihydrogen phosphate and trichloroacetonitrile provides the budesonide 21-phosphate in improved yield (83%).

In one preferred embodiment, the step a) is performed in an aprotic solvent, preferably selected from acetonitrile, acetone, ethyl acetate, dichloromethane, or chloroform. More preferably, acetonitrile.

In another embodiment, the step a) is performed at room temperature.

According to a preferred embodiment of the process of the invention, budesonide 21-phosphate is isolated by crystallization. The useful solvents for said crystallization are ethyl acetate, n-hexane. More preferably, ethyl acetate.

In one preferred embodiment, the pH of step b) is from 7 to 9.

In another embodiment, the process further comprises the step of isolating the disodium salt.

Budesonide 21-phosphate disodium salt has a much higher water solubility than Budesonide and Budesonide 21-phosphate. Its solubility can be defined "freely soluble in water (100 - 1000 mg / mL)" and is equal to 110 mg / ml.

At the concentration of use (0.25 mg ml - 4.0 mg ml), it is rapidly soluble and remains stable at room temperature for long periods of time (12 months) without yellowing or precipitating.

According to a preferred embodiment of the process of the invention, the isolation step of disodium salt is carried out by adding anti-solvent selected from methanol or ethanol.

According to a preferred embodiment of the process of the invention, the isolation step of the disodium salt is carried out by treatment with an opportune solvent. The

useful solvents for said process are diethyl ether, ethyl acetate, or n-hexane. More preferably, diethyl ether.

According to a second aspect, the present invention relates to budesonide 21-phosphate disodium salt having an amount of any single unknown impurity equal to or lower than 0.10% (by area%) or having an amount of the qualified impurities budesonide (I) or budesonide 21-phosphate (II) equal to or lower than 0.2% (by area%).

According to a third aspect thereof, the present invention relates to budesonide 21-phosphate disodium salt having a purity equal to or greater than 98% by area%.

Purity was assessed through the HPLC method of the European Pharmacopoeia 1075 – Budesonide - related substance.

Budesonide 21-phosphate disodium salt contains only the process impurities, namely budesonide (RRT of 17.8 min) and budesonide 21-phosphate (RRT of 4.3 min), the RRT being measured using the same HPLC method of the European Pharmacopoeia.

CHEMISTRY

Materials and Methods

All the commercial products have been purchased from Merck-Sigma Aldrich. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on an Agilent INOVA spectrometer; chemical shifts were referenced to the residual solvent signal (CD_3OD: δ_H = 3.31, δ_C = 49.0). ESI-MS spectrum was recorded on a LTQ Orbitrap XL™ Fourier transform mass spectrometer (FTMS) equipped with an ESI ION MAX™ (Thermo Fisher, San José, USA). X-ray powder diffraction (XRPD) was performed using a Panalytical X'pert PRO diffractometer. Intensity profiles were collected in the 2θ range of 4–40° using Ni-filtered CuKα radiation (λ = 1.5406 Å) at 40 kV and 30

mA, with a step size 0.02°, at a scanning time of 120 s/step. The diffraction patterns were processed using the Highscore Plus suite. IR spectra were recorded on Thermo Nicolet 5700 FT-IR spectrometer. Thermo Fisher GENESYS™ 40/50 Vis/UV-Vis Spectrophotometers.

EXAMPLE 1

Preparation of budesonide 21-phosphate

To a solution of budesonide (200 mg, 0.46 mmol) in acetonitrile (1 mL), trichloroacetonitrile (220 mL, 2.20 mmol) is added, followed by dropwise addition of tetrabutylammonium dihydrogen phosphate (625 mg, 1.84 mmol) in acetonitrile (2 mL). The reaction mixture was monitored by TLC using $CHCl_3$/MeOH/CH_3COOH (8 mL/2 mL/150 mL) as eluent mixture. The reaction mixture is stirred at room temperature for 24 hours. The reaction was treated with 1 N NaOH and extracted with ethyl acetate. The aqueous phase was made acidic using a 1 N HCl solution and extracted several times with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated to give 195 mg of budesonide 21-phosphate (yield 83%). M.P. 219-221 °C LRMS (ES) $(M + H)^+$: calcd, 510.5; found, 511.2.

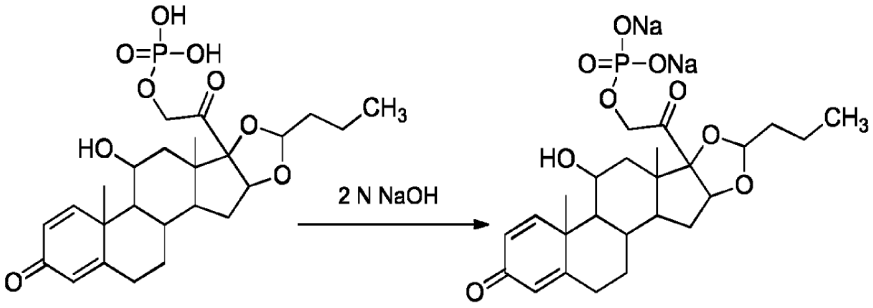
^1H NMR (500 MHz, CD_3OD-d_4) δ 7.47 (d, J = 10.1 Hz, 1H), 6.26 (d, J = 10.1 Hz, 1H), 6.01 (s, 1H), 5.18 (dd, J = 13.1, 6.2 Hz, 1H), 4.96 – 4.83 (m, 2H), 4.72-4.62 (m, 2H), 4.41 (d, J = 3.5 Hz, 1H), 2.64 (dt, J = 13.0, 6.7 Hz, 1H), 2.37 (d, J = 11.0 Hz, 1H), 2.24 – 2.09 (m, 3H), 1.94 (dd, J = 17.8, 9.7 Hz, 1H), 1.70 (dd, J = 14.1, 6.6 Hz, 1H), 1.60 (dd, J = 12.1, 7.0 Hz, 3H), 1.51 – 1.39 (m, 4H), 1.04 – 0.89 (m, 7H).

^{13}C NMR (126 MHz, CD_3OD-d_4): δ 210.89, 209.55, 188.85, 174.28, 159.86, 127.84, 122.55, 109.41, 105.45, 99.88, 98.97, 84.01, 82.92, 70.53, 70.48, 69.96, 69.68, 57.17, 57.08, 54.22, 51.33, 47.07, 45.98, 45.94, 41.34, 40.97, 38.27, 36.17, 35.50,

35.35, 34.34, 33.83, 33.01, 32.47, 31.75, 21.55, 18.44, 17.98, 17.82, 17.54, 14.40, 14.26.

EXAMPLE 2

Preparation of budesonide 21-phosphate disodium salt



Budesonide 21-phosphate (100 mg, 0,196 mmol) was suspended in water (10 mL) and titrated with 2N NaOH to pH 7.94, obtaining a completely clear solution. Then the solvent was removed, and the residue was treated with methanol (5 mL) keeping the suspension at the boiling point of the solvent for 30 min. After cooling, the insoluble solid was filtered off and the solvent was removed in vacuo. The residue was then treated with diethyl ether affording budesonide 21-phosphate disodium salt as a white solid (86 mg, yield 79%), M.P. 245-246 °C.

^{1}H NMR (500 MHz, CD_3OD-d_4) δ 7.47 (d, J = 10.1 Hz, 1H), 6.26 (d, J = 10.1 Hz, 1H), 6.01 (s, 1H), 5.18 (dd, J = 13.1, 6.2 Hz, 1H), 4.96 – 4.83 (m, 2H), 4.72-4.62 (m, 2H), 4.41 (d, J = 3.5 Hz, 1H), 2.64 (dt, J = 13.0, 6.7 Hz, 1H), 2.37 (d, J = 11.0 Hz, 1H), 2.24 – 2.09 (m, 3H), 1.94 (dd, J = 17.8, 9.7 Hz, 1H), 1.70 (dd, J = 14.1, 6.6 Hz, 1H), 1.60 (dd, J = 12.1, 7.0 Hz, 3H), 1.51 – 1.39 (m, 4H), 1.04 – 0.89 (m, 7H).

^{13}C NMR (126 MHz, CD_3OD-d_4): δ 210.89, 209.55, 188.85, 174.28, 159.86, 127.84, 122.55, 109.41, 105.45, 99.88, 98.97, 84.01, 82.92, 70.53, 70.48, 69.96, 69.68, 57.17, 57.08, 54.22, 51.33, 47.07, 45.98, 45.94, 41.34, 40.97, 38.27, 36.17, 35.50,

35.35, 34.34, 33.83, 33.01, 32.47, 31.75, 21.55, 18.44, 17.98, 17.82, 17.54, 14.40, 14.26.

STABILITY TESTING

According to ICH guidelines (STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2) Current Step 4 version dated 6 February 2003), studies on budesonide 21-phosphate disodium salt were conducted at 25°C/60% RH (relative humidity) and 30°C/65% RH for a period of 12 months (m). Accelerated tests were also conducted under conditions of 40°C/75% RH for 6 months (m), as shown in the following Tables.

ICH study at 25°C and 60% RH

	Specification	**Time 0**	**Time 3 m**	**Time 6 m**	**Time 9 m**	**Time 12 m**
Title	95.0 – 105.0 %	98.22%	98.10%	98.08%	97.85%	97.45%
known impurities	≤0.2%	0.14 %	0.14 %	0.14 %	0.15 %	0.15 %
unknown impurities	≤0.1%	0.05 %	0.05 %	0.05 %	0.08 %	0.08 %

ICH study at 30°C and 65% RH

	Specification	**Time 0**	**Time 3 m**	**Time 6 m**	**Time 9 m**	**Time 12 m**
Title	95.0 – 105.0 %	98.22%	97.50%	97.28%	97.00%	94.55%
known impurities	≤0.2%	0.14 %	0.20 %	0.25 %	0.25 %	0.30 %
unknown impurities	≤0.1%	0.05 %	0.15 %	0.15 %	0.40 %	0.40 %

ICH study at 40°C and 75% RH

	Specification	**Time 0**	**Time 3 m**	**Time 6 m**
Title	95.0 – 105.0 %	98.22%	96.50%	93.28%
known impurities	≤0.2%	0.14 %	0.30 %	0.45 %
unknown impurities	≤0.1%	< 0.05 %	2.45 %	2.80 %

Formulation studies

The following formulations were prepared to test the stability of the budesonide 21-phosphate disodium salt in aqueous solution.

Budesonide disodium phosfate			
Ingredient	**Formula I**	**Formula II**	**Function**
Active substance			
Budesonide (disodium phosphate)	0.25 mg	4.0 mg	Active substance
Excipients			
Disodium edetate	0.10 mg	0	Chelating agent
Sodium chloride	8.50 mg	3.0	Tonicity agent
Citric acid, anhydrous	0.28 mg	0	Buffering agent
Sodium citrate tribasic dihydrate	0.50 mg	10.0	Buffering agent
Water for injections	q. s. to 1.00 ml	q. s. to 1.00 ml	Solvent
HCl	q. s. to pH 4.5	q. s. to pH 7.75	

The same formulations were tested according to ICH guidelines in the stability studies at 25°C and 40°C and the results are reported below.

ICH study at 25°C and 60% RH FORMULA I

	Specification	**Time 0**	**Time 3 m**	**Time 6 m**	**Time 9 m**	**Time 12 m**
Aspect	Clear solution free from visible particles	Compliant	Compliant	Compliant	Compliant	Compliant
Title	95.0 – 105.0 %	100.5%	100.2%	100.2%	100.0	99.8%
known impurities	≤0.2%	0.10 %	0.10 %	0.10 %	0.15 %	0.15 %
unknown impurities	≤0.1%	0.05 %	0.05 %	0.05 %	0.10 %	0.10 %
pH	4.0 – 5.0	4.5	4.5	4.5	4.5	4.5

ICH study at 40°C and 75% RH FORMULA I

	Specification	Time 0	Time 3 m	Time 6 m
Aspect	Clear solution free from visible particles	Compliant	Compliant	Compliant
Title	95.0 – 105.0 %	100.5%	100.2%	100.2%
known impurities	≤0.2%	0.10 %	0.15 %	0.20 %
unknown impurities	≤0.1%	< 0.05 %	0.1 %	0.1 %
pH	4.0 – 5.0	4.5	4.5	4.5

ICH study at 25°C and 60% RH FORMULA II

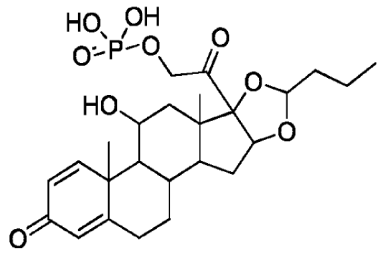
	Specification	Time 0	Time 3 m	Time 6 m	Time 9 m	Time 12 m
Aspect	Clear solution free from visible particles	Compliant	Compliant	Compliant	Compliant	Compliant
Title	95.0 – 105.0 %	101.2%	101.2%	101.0%	100.6%	99.8%
known impurities	≤0.2%	0.10 %	0.10 %	0.10 %	0.10 %	0.20 %
unknown impurities	≤0.1%	0.05 %	0.05 %	0.10 %	0.10 %	0.10 %
pH	7.25 – 8.25	7.75	7.75	7.75	7.75	7.75

ICH study at 40°C and 75% RH FORMULA II

	Specification	Time 0	Time 3 m	Time 6 m
Aspect	Clear solution free from visible particles	Compliant	Compliant	Compliant
Title	95.0 – 105.0 %	101.2%	100.5%	99.6 %
known impurities	≤0.2%	0.10 %	0.20 %	0.20 %
unknown impurities	≤0.1%	0.05 %	0.10 %	0.10 %
pH	7.25 – 8.25	7.75	7.80	7.90

CLAIMS

1. A process for preparing budesonide 21-phosphate of formula (II)



(II)

which comprises the steps of:

a) reacting budesonide with tetrabutylammonium dihydrogen phosphate and trichloroacetonitrile to obtain the compound of formula (II);

b) optionally, salifying the compound of formula (II) with NaOH to form the corresponding disodium salt.

2. The process according to claim 1, characterized in that the step a) is performed in an aprotic solvent, preferably selected from acetonitrile, acetone, ethyl acetate, dichloromethane, or chloroform; more preferably, acetonitrile.

3. The process according to claim 1 or 2, characterized in that the step a) is performed at room temperature.

4. The process according to any one of the preceding claims, characterized in that the pH of step b) is from 7 to 9.

5. The process according to any one of the preceding claims, characterized in that further comprising a step of isolating the compound of formula (II), preferably by crystallization; more preferably from ethyl acetate.

6. The process according to any one of the preceding claims, characterized in that further comprising a step of isolating the disodium salt of the compound of formula (II).
7. The process according to claim 6, wherein the isolation step is carried out by adding an anti-solvent selected from methanol or ethanol.
8. The process according to claim 6 or 7, wherein the isolation step is carried out by treatment with an opportune solvent, preferably diethyl ether, ethyl acetate, or n-hexane; more preferably, diethyl ether.
9. Budesonide 21-phosphate disodium salt having an amount of any single unknown impurity equal to or lower than 0.10% by area% or having an amount of the qualified impurities budesonide (I) or budesonide 21-phosphate (II) equal to or lower than 0.2% by area%.
10. Budesonide 21-phosphate disodium salt having a purity equal to or greater than 98% by area%.

Figure 1

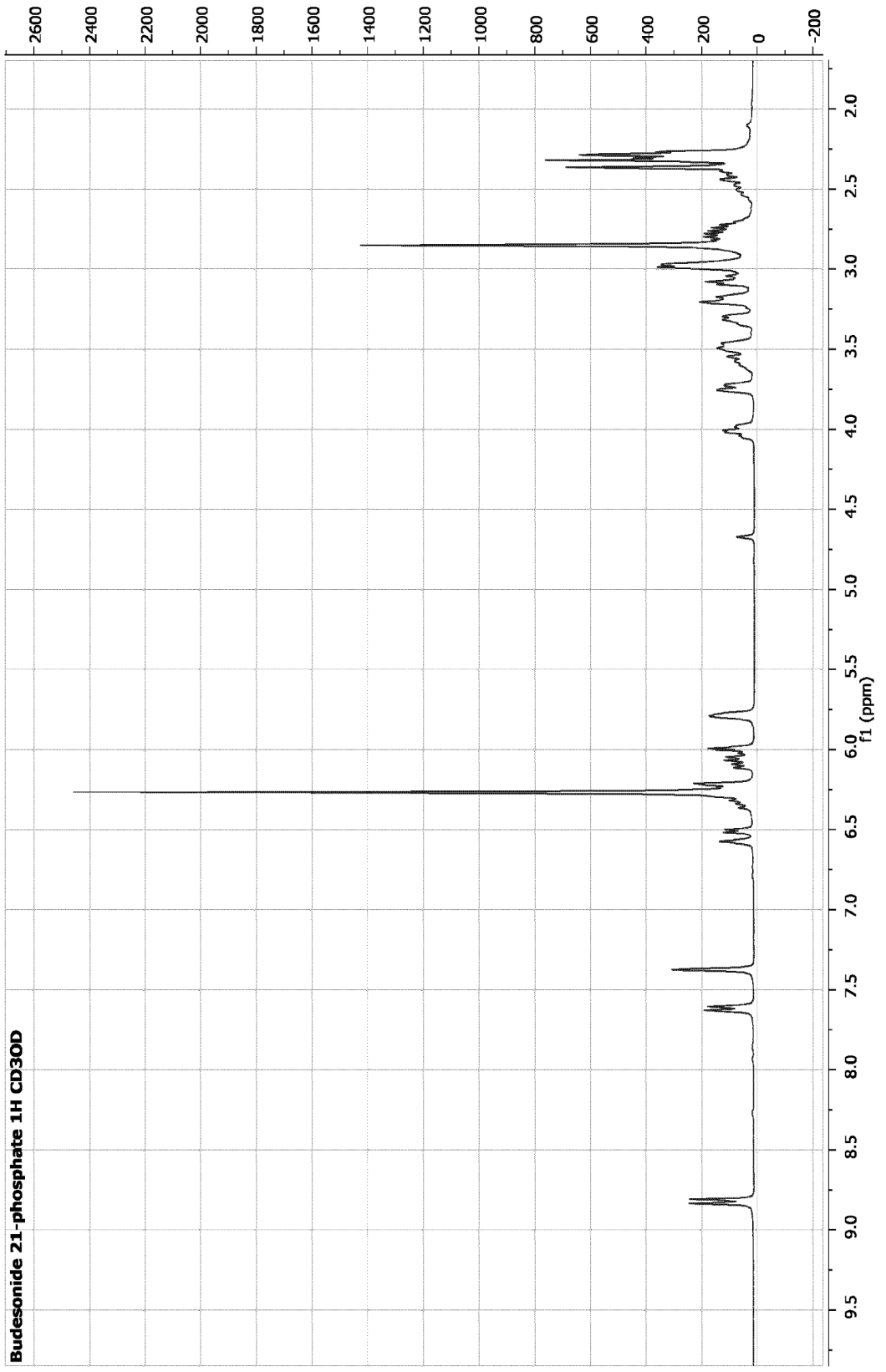


Figure 2

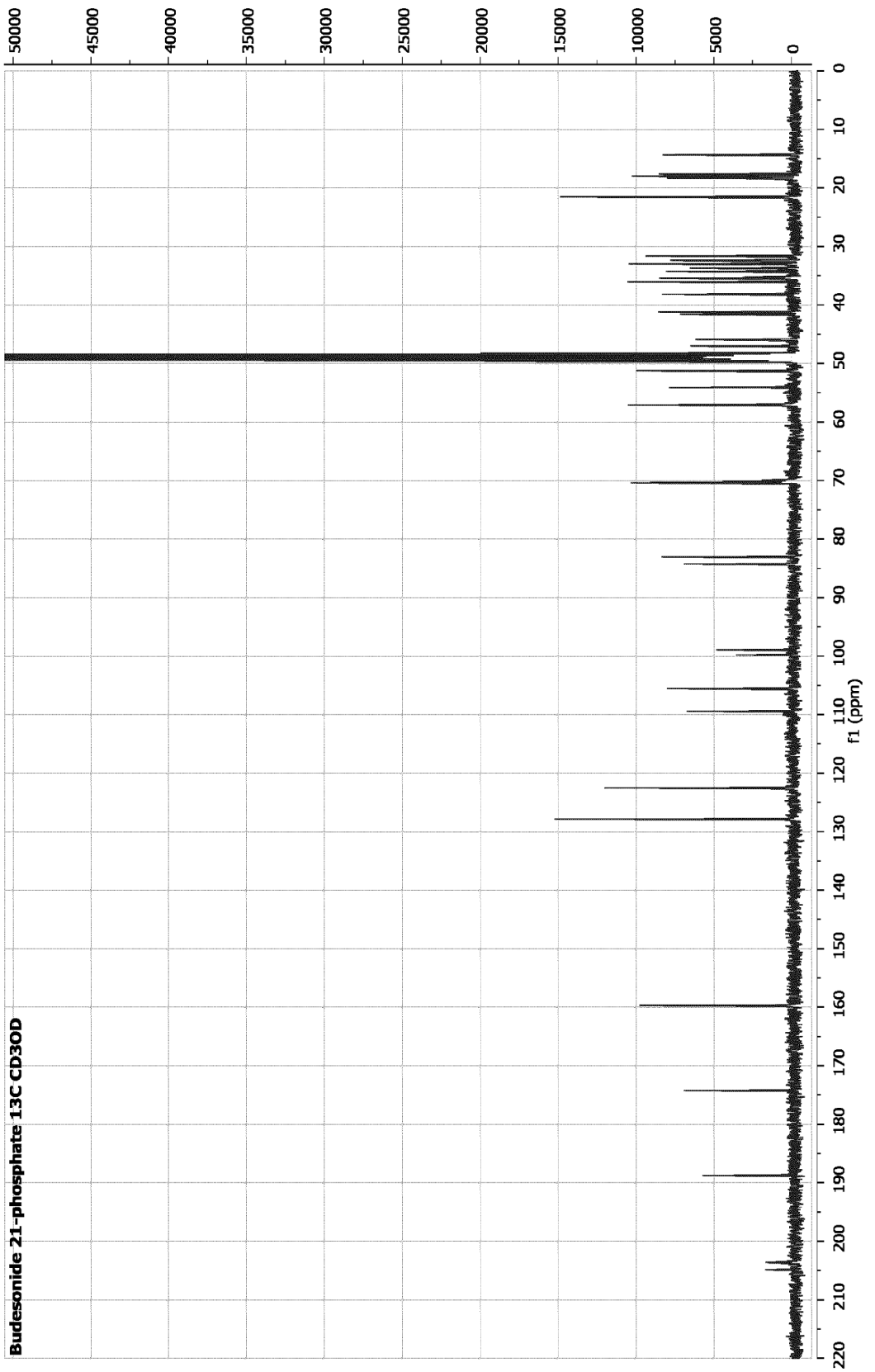


Figure 3

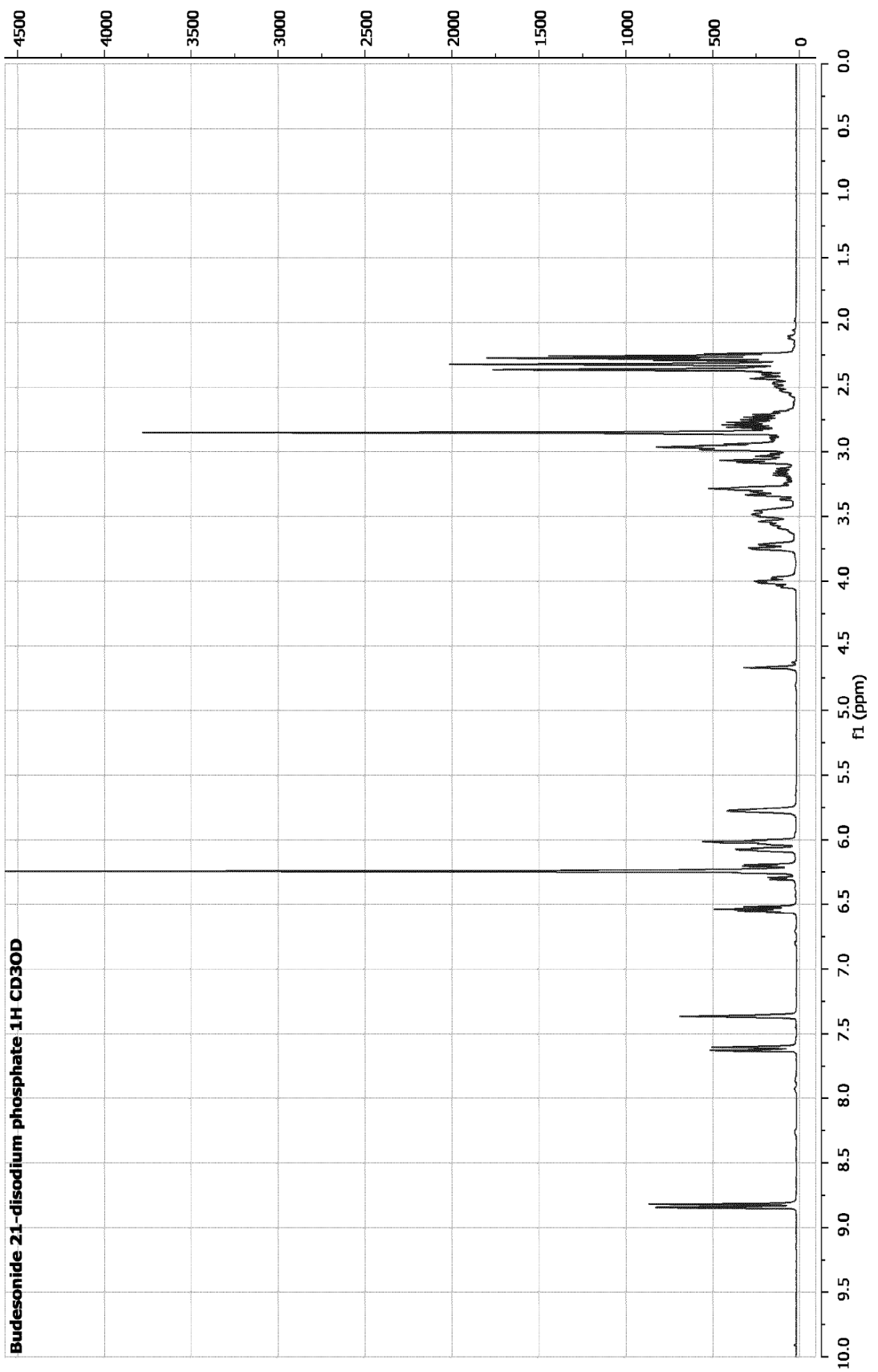


Figure 4

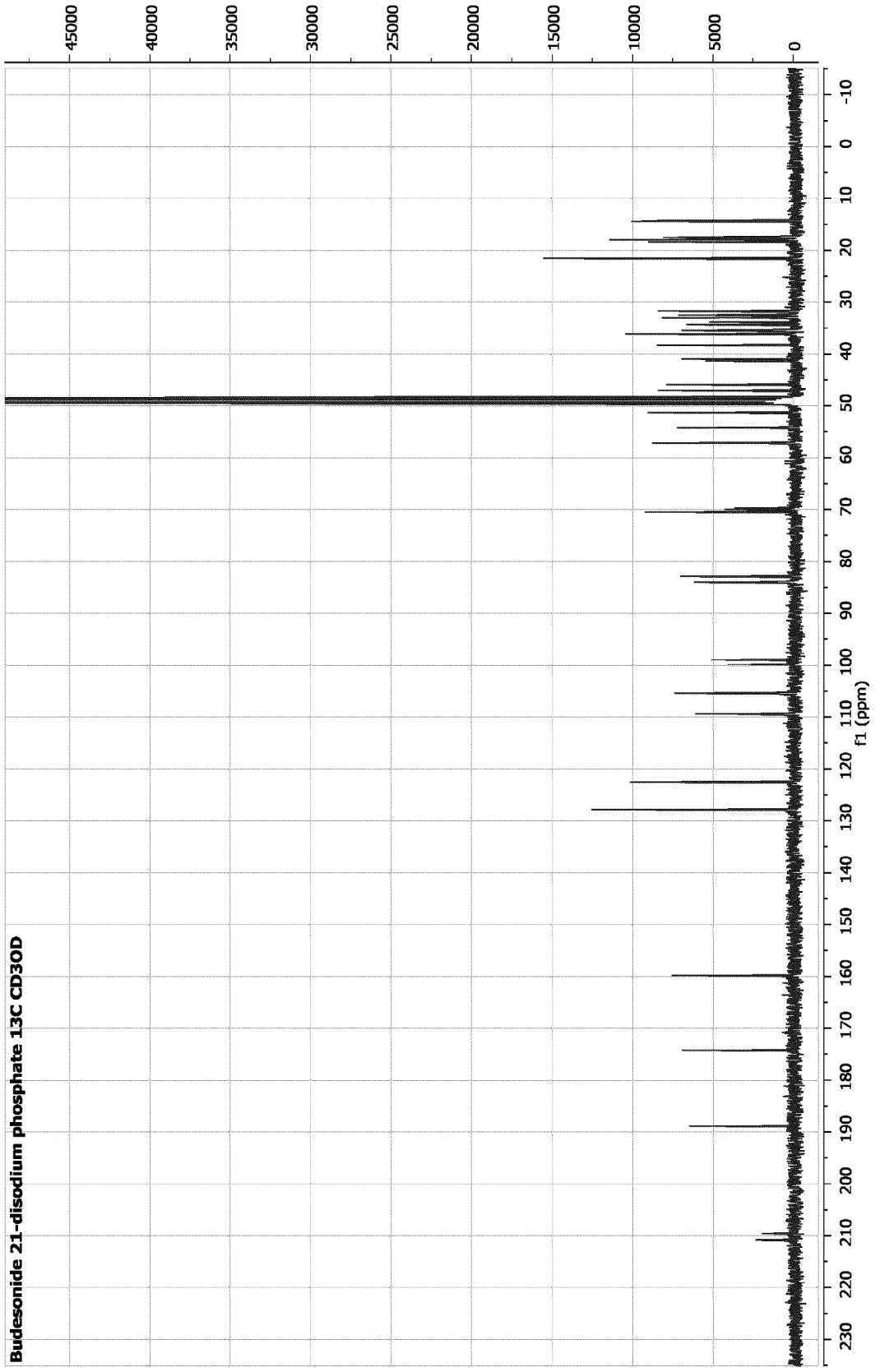
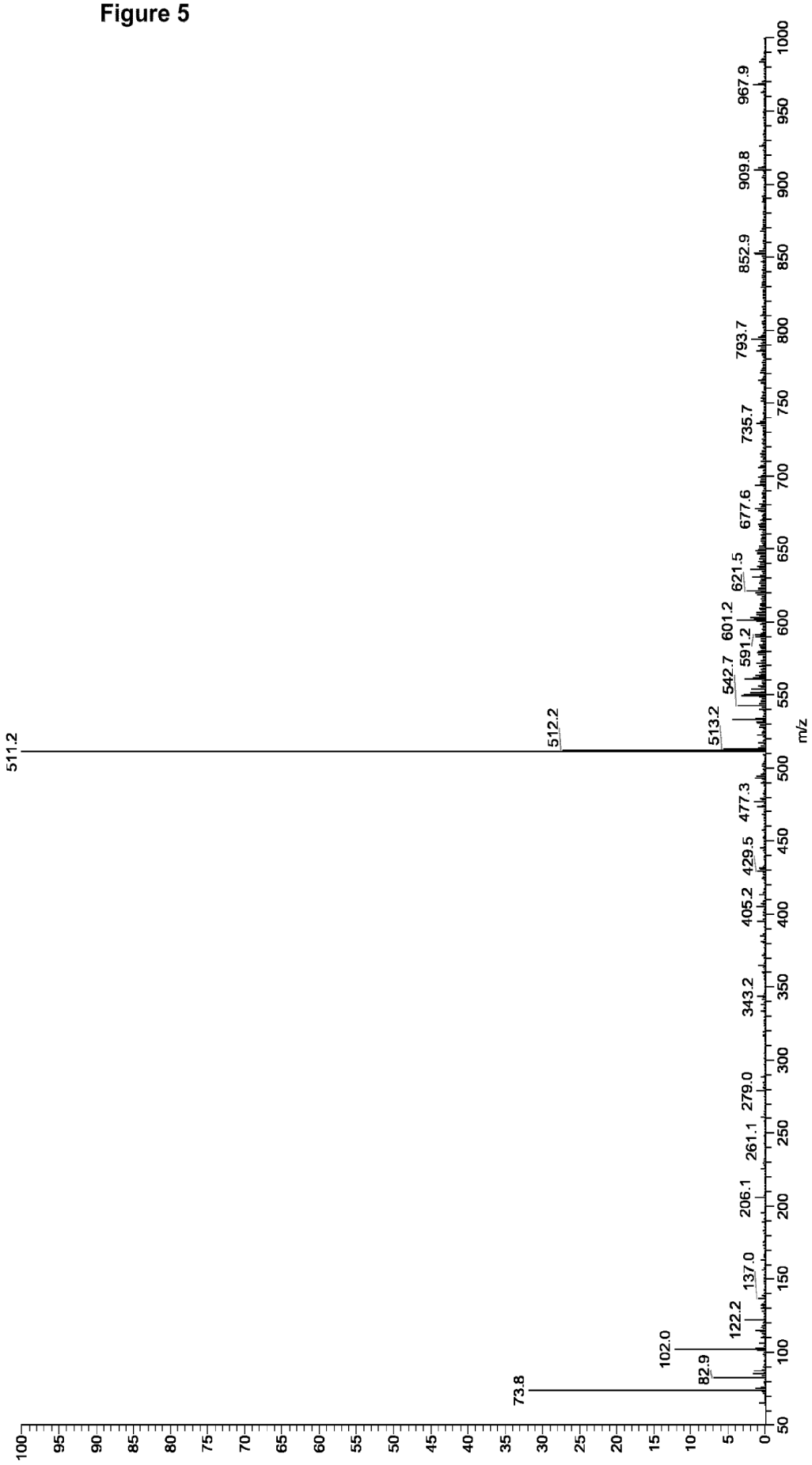


Figure 5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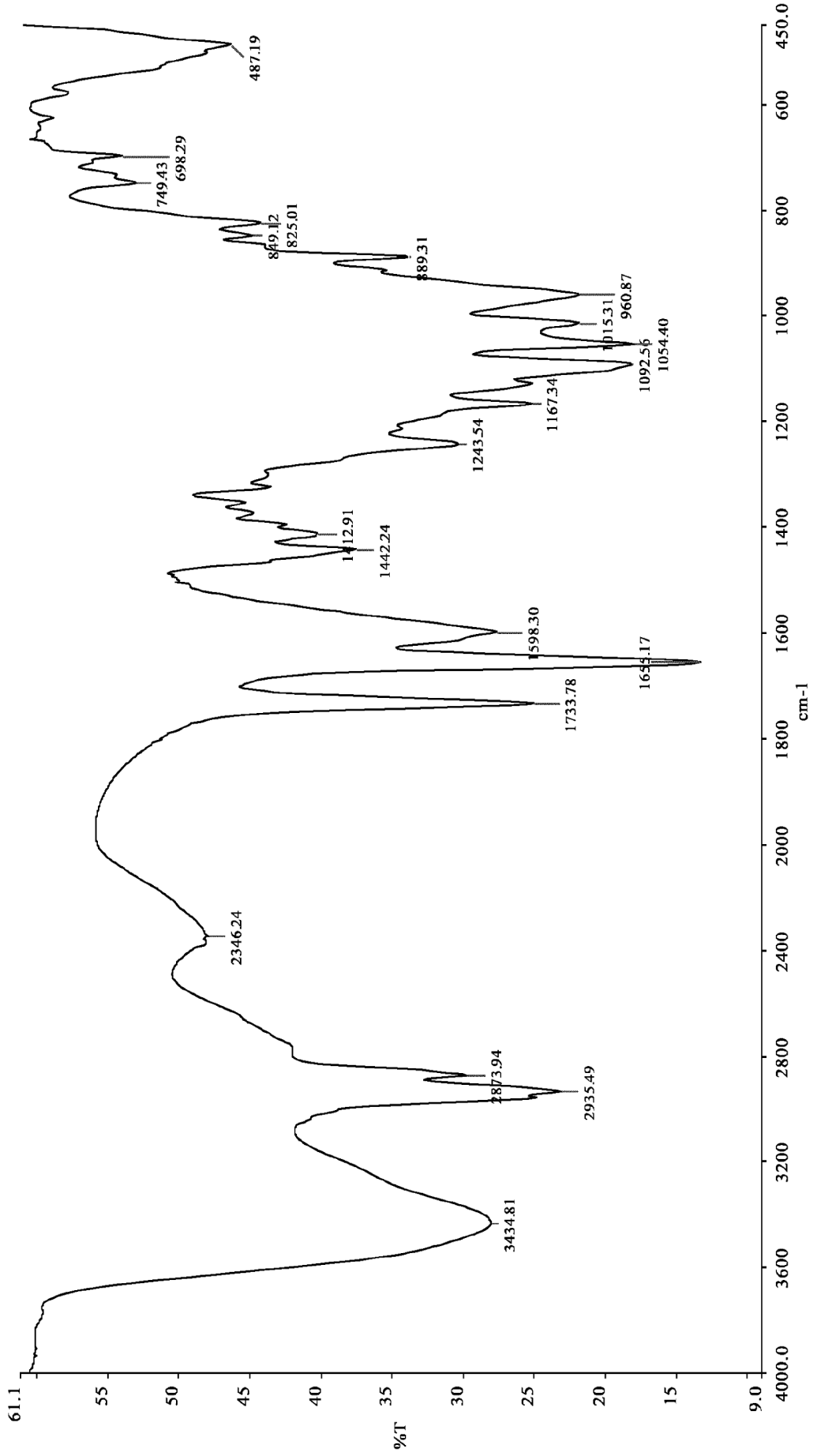
542.7
591.2
601.2
621.5
677.6
735.7
793.7
852.9
909.8
967.9
477.3
429.5
405.2
343.2
279.0
261.1
206.1
137.0
122.2
102.0
82.9
73.8
m/z

Figure 6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889.31
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1015.31
1054.40
1092.56
1167.34
1243.54
1412.91
1442.24
1598.30
1655.17
1733.78
2346.24
2873.94
2935.49
3434.81
%T
cm-1
61.1
55
50
45
40
35
30
25
20
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3200
2800
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2000
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1600
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1200
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800
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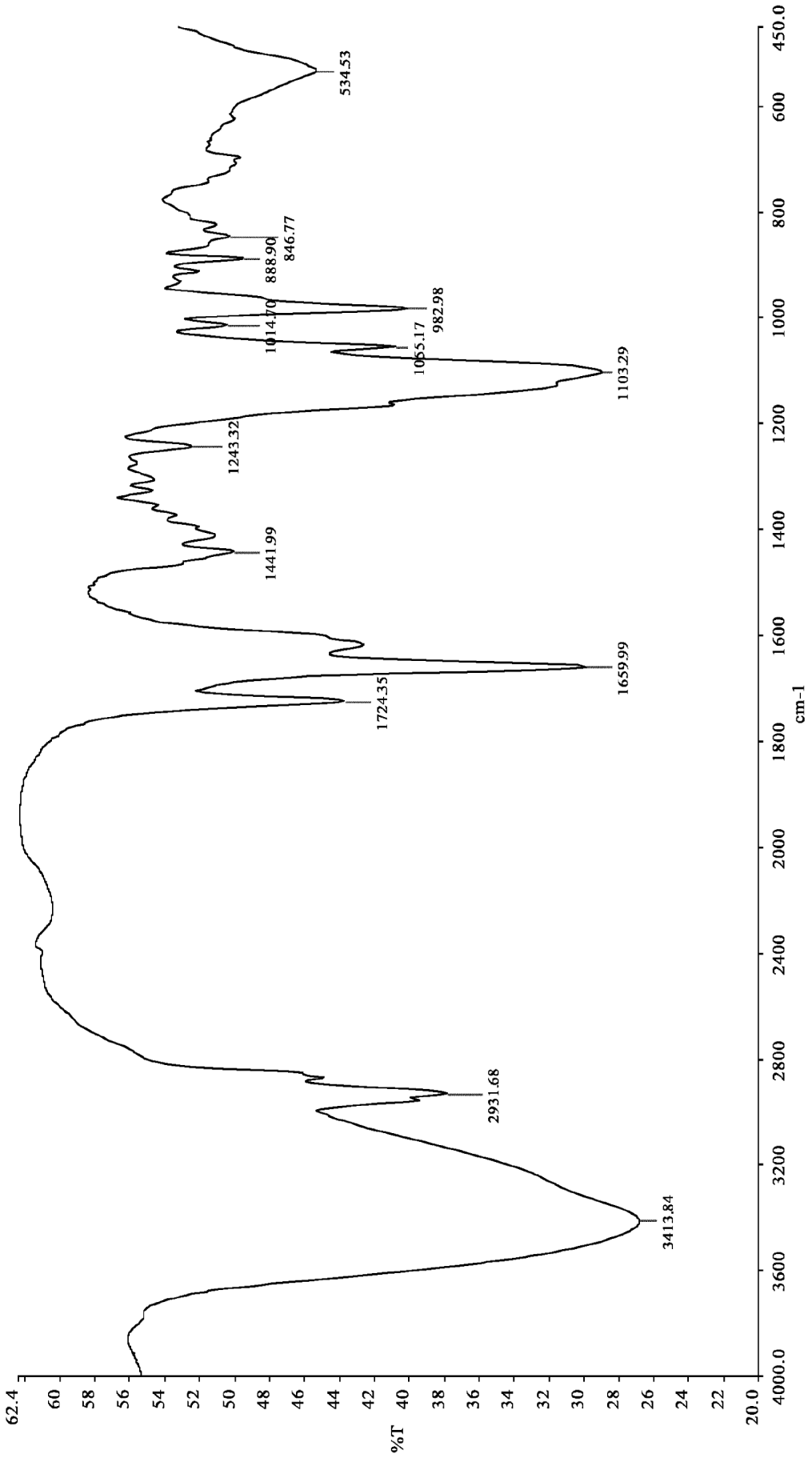
450.0

Figure 7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3413.84
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cm-1
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1800
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1400
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1000
800
600
450.0
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60
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Figure 8

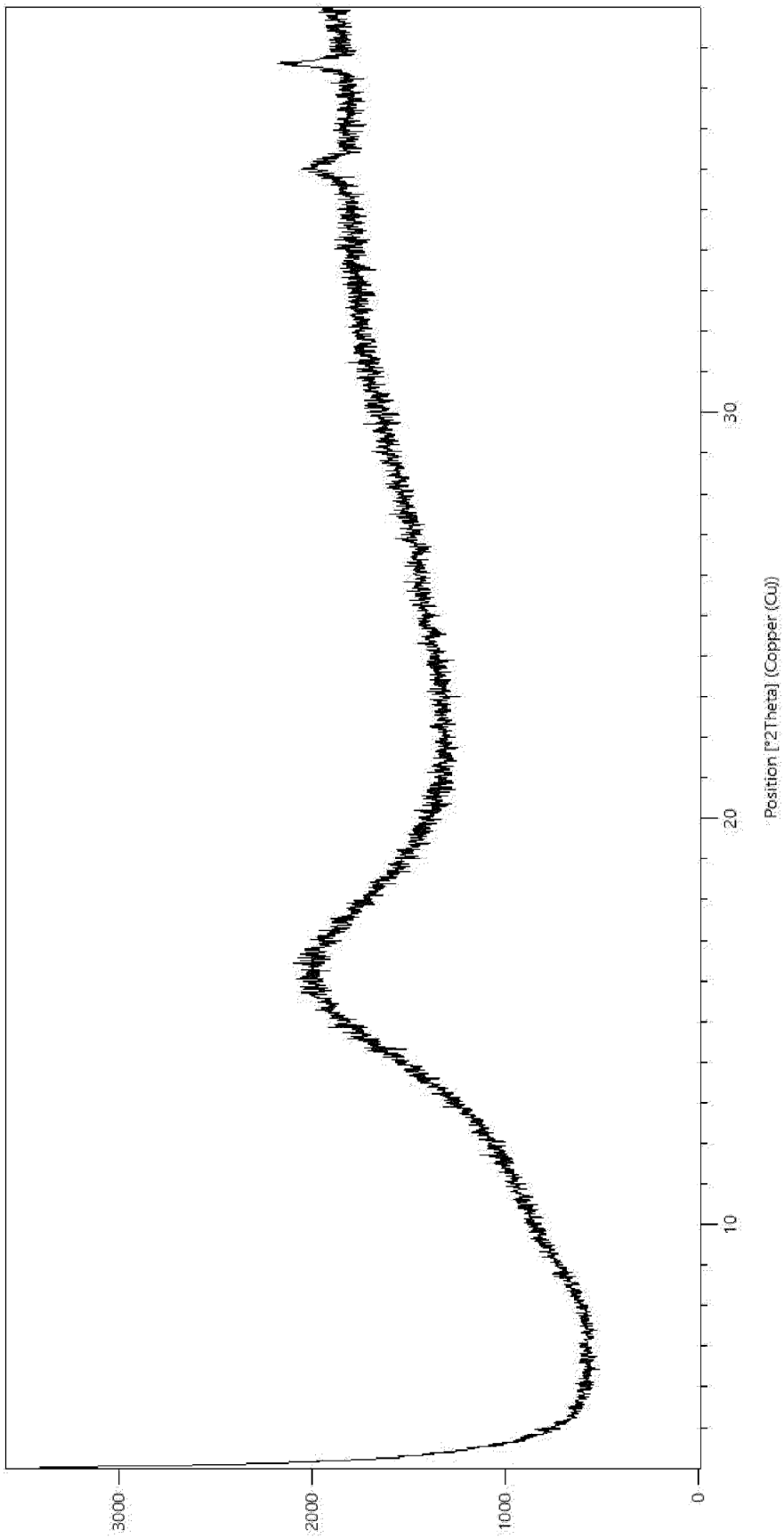


Figure 9

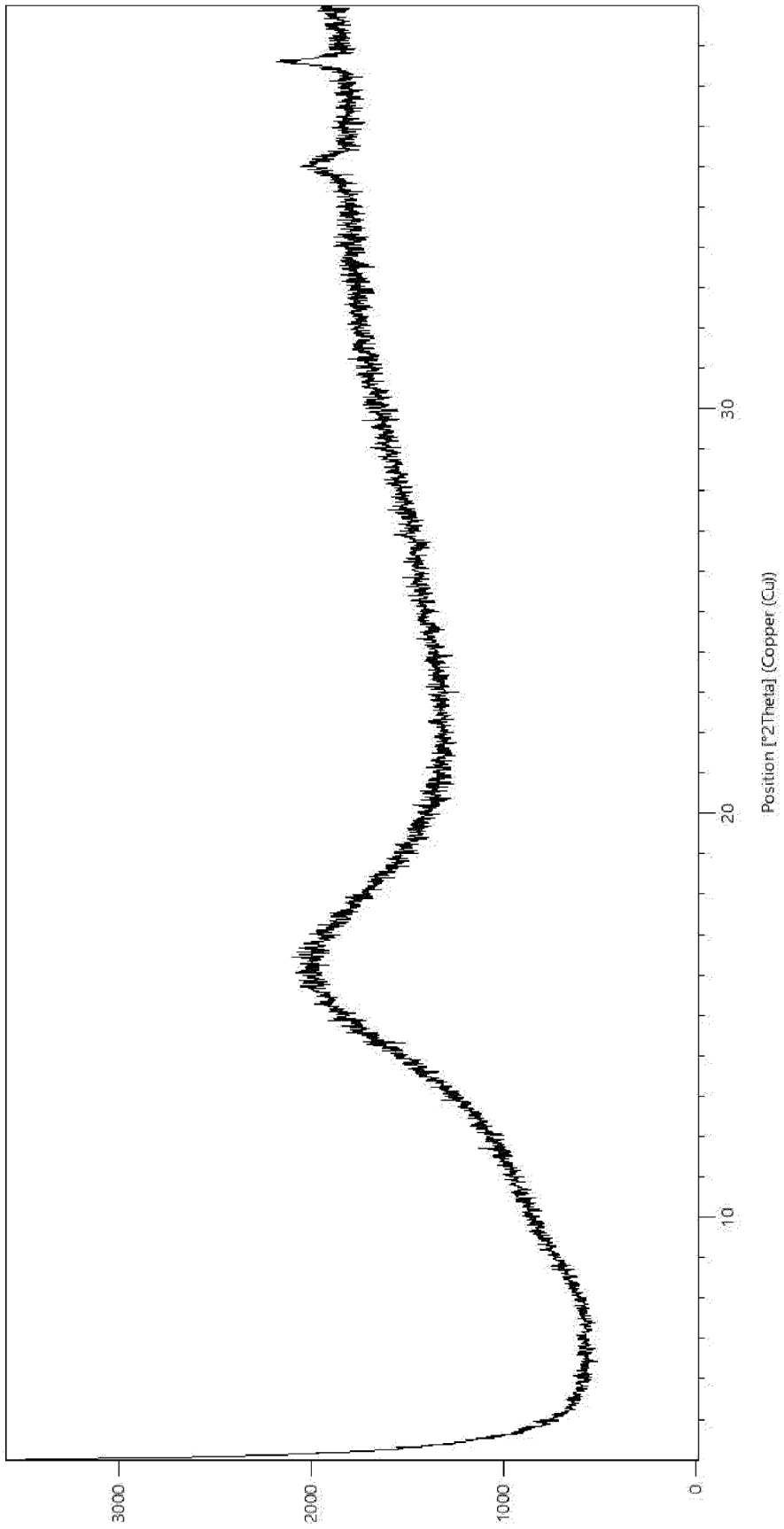
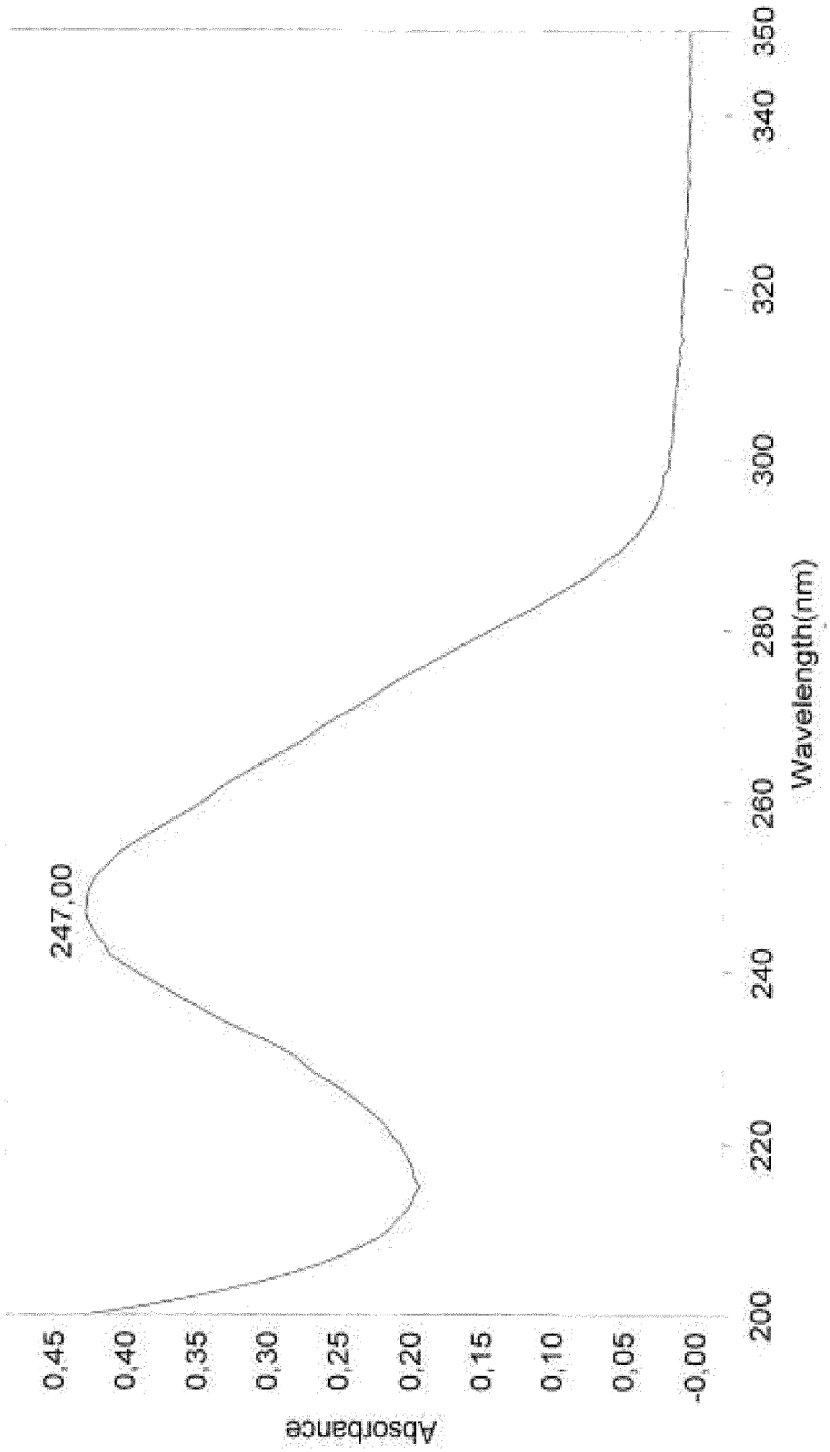


Figure 10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0,20
0,15
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0,05
-0,00
Absorbance
200
220
240
260
280
300
320
340
350
Wavelength(nm)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/070381

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J71/00
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)
C07J

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEFFREY C. KERN ET AL: "Discovery of Pyrophosphate Diesters as Tunable, Soluble, and Bioorthogonal Linkers for Site-Specific Antibody?Drug Conjugates", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 138, no. 4, 25 January 2016 (2016-01-25), pages 1430-1445, XP055577573, ISSN: 0002-7863, DOI: 10.1021/jacs.5b12547	9,10
Y	page 1441 compound 20	1-8
Y	US 2017/283446 A1 (FAN PINGCHEN [US] ET AL) 5 October 2017 (2017-10-05) paragraph [0181] page 24	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2022	28/10/2022

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/070381

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		ZA 201806632 B	28-04-2022