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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

EISAI CO., LTD., EISAI INC., and NOVARTIS PHARMA AG,

Plaintiffs,

v.

ALKEM LABORATORIES LTD. and ASCEND LABORATORIES, LLC,

Defendants.

Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

(Filed Electronically)

Plaintiffs Eisai Co., Ltd. and Eisai Inc. (collectively, "Eisai") and Novartis Pharma AG ("Novartis," and together with Eisai, "Plaintiffs"), for their Complaint against Defendants Alkem Laboratories Ltd. ("Alkem Labs") and Ascend Laboratories, LLC ("Ascend Labs," and together with Alkem Labs, "Alkem"), hereby allege as follows:

THE PARTIES

1. Plaintiff Eisai Co., Ltd. is a Japanese corporation having a principal place of business at 6-10 Koishikawa 4-chrome, Bunkyo-ku, Tokyo 112-8088, Japan.

2. Plaintiff Eisai Inc. is a Delaware corporation having a principal place of business at 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677.

3. Plaintiff Novartis is a Swiss corporation having a principal place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

4. Upon information and belief, Defendant Alkem Labs is an Indian corporation having a place of business at Devashish Building, Alkem House, Senapati Bapat Road, Lower Parel, Mumbai, 400013, Maharashtra, India.

5. Upon information and belief, Defendant Alkem Labs, itself and through its wholly owned subsidiaries and agents, develops, manufactures, markets, sells, and/or imports generic pharmaceutical versions of branded products throughout the United States, including in this Judicial District.

6. Upon information and belief, Defendant Ascend Labs is a New Jersey corporation having a place of business at 339 Jefferson Road, Suite 101, Parsippany, NJ 07054. Upon information and belief, Defendant Ascend Labs is a wholly owned subsidiary of Alkem Labs acting as an agent of Alkem Labs with respect to Abbreviated New Drug Application ("ANDA") No. 213410.

7. Upon information and belief, Defendant Ascend Labs, itself and through its wholly owned subsidiaries and agents, develops, manufactures, markets, sells, and/or imports generic pharmaceutical versions of branded products throughout the United States, including in this Judicial District.

8. Upon information and belief, Defendant Ascend Labs assisted in the preparation and submission of ANDA No. 213410, which was done at the direction of, under the control of, in concert with, and for the direct benefit of Defendant Alkem Labs.

NATURE OF THE ACTION

9. This is a civil action concerning the infringement of United States Patent No. 6,740,669 ("the '669 patent" or "the patent-in-suit"). This action arises under the Patent Laws of the United States, 35 U.S.C. §§ 100 *et seq*.

JURISDICTION AND VENUE

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over Alkem Labs and Ascend Labs by virtue of, *inter alia*, the fact that they have committed, aided, abetted, contributed to, and/or participated in the commission of the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including by sending written notification of Alkem's ANDA No. 213410 and its accompanying certification under 21 U.S.C. § 505(j)(2)(A)(vii)(IV) by overnight mail ("Alkem's Notice Letter") to Eisai Inc. in New Jersey. This Court has personal jurisdiction over Alkem Labs and Ascend Labs for the additional reasons set forth below and for other reasons that will be presented to the Court if jurisdiction is challenged.

12. This Court has personal jurisdiction over Alkem Labs for the additional reasons that, *inter alia*, Alkem Labs (1) has substantial, continuous, and systematic contacts with

this State, including by virtue of incorporating at least one subsidiary company in this State, Ascend Labs; (2) intends to market, sell, and/or distribute generic pharmaceutical drug products to residents of this State, including the generic product that is the subject of ANDA No. 213410, through its New Jersey subsidiary, Ascend Labs; and (3) enjoys substantial income from sales of its generic pharmaceutical products in this State.

13. This Court also has personal jurisdiction over Alkem Labs because it has previously been sued in this District and has not challenged personal jurisdiction and has affirmatively availed itself of the jurisdiction of this Court by filing claims and counterclaims in this District. *See, e.g.*, *Janssen Pharms, Inc. v. Alkem Laboratories, Ltd.*, 13 -7803 (D.N.J. Dec. 23, 2013).

14. This Court has personal jurisdiction over Ascend Labs for the additional reasons that, *inter alia*, Ascend Labs (1) is incorporated under the laws of New Jersey; (2) maintains its principal place of business in New Jersey; (3) has purposefully availed itself of the privilege of doing business in New Jersey; and (4) intends to market, sell, and/or distribute generic pharmaceutical drug products to residents of New Jersey, including the generic product that is the subject of ANDA No. 213410.

15. This Court also has personal jurisdiction over Ascend Labs because it has been sued previously in this District and has not challenged personal jurisdiction, and has affirmatively availed itself of the jurisdiction of this Court by litigating in this District. *See, e.g.*, *AstraZeneca AB, et al. v. Alkem Labs. Ltd., et al.*, 15-cv-6609 (D.N.J. Nov. 9, 2015).

16. Alternatively, should the Court find that the above facts do not establish personal jurisdiction over Alkem Labs in this action, this Court may exercise jurisdiction over Alkem Labs pursuant to Fed. R. Civ. P. 4(k)(2) because (a) Plaintiffs' claims arise under federal

law; (b) Alkem Labs is a foreign defendant not subject to personal jurisdiction in the courts of any state; and (c) Alkem Labs has sufficient contacts with the United States as a whole, including, but not limited to, submitting various ANDAs to the FDA, and manufacturing and selling active pharmaceutical ingredients that are used in pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Alkem Labs satisfies due process.

17. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

18. On May 25, 2004, the '669 patent, titled "Crystal Modification of 1-(2,6-Difluorobenzyl)-1H-1,2,3-Triazole-4-Carboxamide and its Use as Antiepileptic," was duly and legally issued. A copy of the '669 patent is attached as Exhibit A.

ACTS GIVING RISE TO THIS ACTION

COUNT I – INFRINGEMENT OF U.S. PATENT NO. 6,740,669

19. Plaintiffs re-allege paragraphs 1-18 as if fully set forth herein.

20. Novartis owns the patent-in-suit. Eisai holds an exclusive license to the patent-in-suit in the United States and holds New Drug Application ("NDA") No. 201367 for an oral suspension containing 40 mg/mL of the active pharmaceutical ingredient rufinamide. Eisai markets and sells this oral suspension in the United States under the brand name "Banzel®."

21. Pursuant to 21 U.S.C. § 355(b)(1), the '669 patent is listed in the FDA's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book") as covering the oral suspension form of Banzel® or its use.

22. Upon information and belief, Alkem submitted ANDA No. 213410 to the FDA under 21 U.S.C. § 355(j). Upon information and belief, Alkem's ANDA No. 213410 seeks FDA approval to engage in the commercial manufacture, use, offer for sale, or sale of an oral

suspension containing 40 mg/mL of rufinamide ("the Alkem Generic Product") prior to the expiration of the patent-in-suit.

23. Upon information and belief, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Alkem certified in ANDA No. 213410 that the claims of the patent-in-suit are invalid, unenforceable, or would not be infringed by the commercial manufacture, use, offer for sale, or sale of the Alkem Generic Product.

24. Upon information and belief, by filing ANDA No. 213410, Alkem has represented to the FDA that the Alkem Generic Product has the same active ingredient as the oral suspension form of Banzel® and has the same or substantially the same proposed labeling as the oral suspension form of Banzel®.

25. Plaintiffs received written notification of Alkem's ANDA No. 213410 and its accompanying certification under 21 U.S.C. § 505(j)(2)(A)(vii)(IV) by overnight mail dated May 15, 2019 ("Alkem's Notice Letter").

26. This action was commenced within 45 days of Plaintiffs receiving Alkem's Notice Letter.

27. Alkem's submission of ANDA No. 213410 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '669 patent under 35 U.S.C. § 271(e)(2)(A).

28. Upon information and belief, the commercial manufacture, use, offer for sale, sale, or import of the Alkem Generic Product, if approved by the FDA, prior to the expiration of the '669 patent, for use in accordance with its proposed labeling would infringe and/or induce and/or contribute to the infringement of the '669 patent.

29. Plaintiffs are entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Alkem's ANDA No. 213410 be a date that is not earlier than the expiration of the '669 patent, or any later expiration of exclusivity for the '669 patent to which Plaintiffs are or become entitled.

30. Plaintiffs will be irreparably harmed by Alkem's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

31. Upon information and belief, Alkem was aware of the existence of the '669 patent and was aware that the filing of its ANDA and certification with respect to the '669 patent constituted an act of infringement of that patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs request that:

A. A Judgment be entered that Alkem infringes one or more claims of the '669 patent by submitting ANDA No. 213410;

B. A Judgment be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Alkem's ANDA No. 213410 shall not be a date that is earlier than the latest expiration date of the patent-in-suit, including any applicable exclusivities or extensions;

C. A Judgment be entered that Alkem, its officers, agents, servants and employees, and those persons acting in concert, participation, or in privity with any of them, and their successors or assigns, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing into the United States the Alkem Generic Product and any other product that infringes or induces or contributes to the

infringement of one or more claims of the ’669 patent prior their expiration, including any exclusivities or extensions to which Plaintiffs are or become entitled;

D. Plaintiffs be awarded the attorney fees, costs and expenses that they incur in prosecuting this action; and

E. Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: June 27, 2019

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Eisai Co., Ltd., et al. v. Alkem Laboratories Ltd., et al.* (D. Del. June 26, 2019) is related to the matter in controversy because the matter in controversy involves the same plaintiffs, the same defendants, and the same patent.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: June 27, 2019

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EXHIBIT A

US006740669B1

(12) **United States Patent**
Portmann et al.

(10) **Patent No.: US 6,740,669 B1**
(45) **Date of Patent: May 25, 2004**

(54) **CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC**

(75) Inventors: **Robert Portmann**, Pratteln (CH); **Urs Christoph Hofmeier**, St. Pantaleon (CH); **Andreas Burkhard**, Basel (CH); **Walter Scherrer**, Rheinfelden (CH); **Martin Szelagiewicz**, Münchenstein (CH)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 801 days.

(21) Appl. No.: **09/125,329**

(22) PCT Filed: **Jun. 8, 1998**

(86) PCT No.: **PCT/EP98/03427**

§ 371 (c)(1),
(2), (4) Date: **Sep. 8, 1998**

(87) PCT Pub. No.: **WO98/56772**

PCT Pub. Date: **Dec. 17, 1998**

(30) **Foreign Application Priority Data**

Jun. 10, 1997 (CH) 1404/97

(51) **Int. Cl.**[7] **A61K 31/4192**; C07D 249/04
(52) **U.S. Cl.** **514/359**; 548/255
(58) **Field of Search** 514/359; 548/255

(56) **References Cited**

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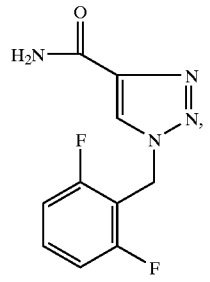
Primary Examiner—Patricia L. Morris
(74) *Attorney, Agent, or Firm*—Joseph J. Borovian

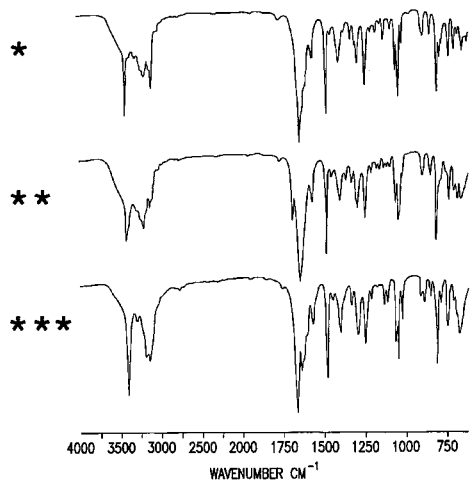
(57) **ABSTRACT**

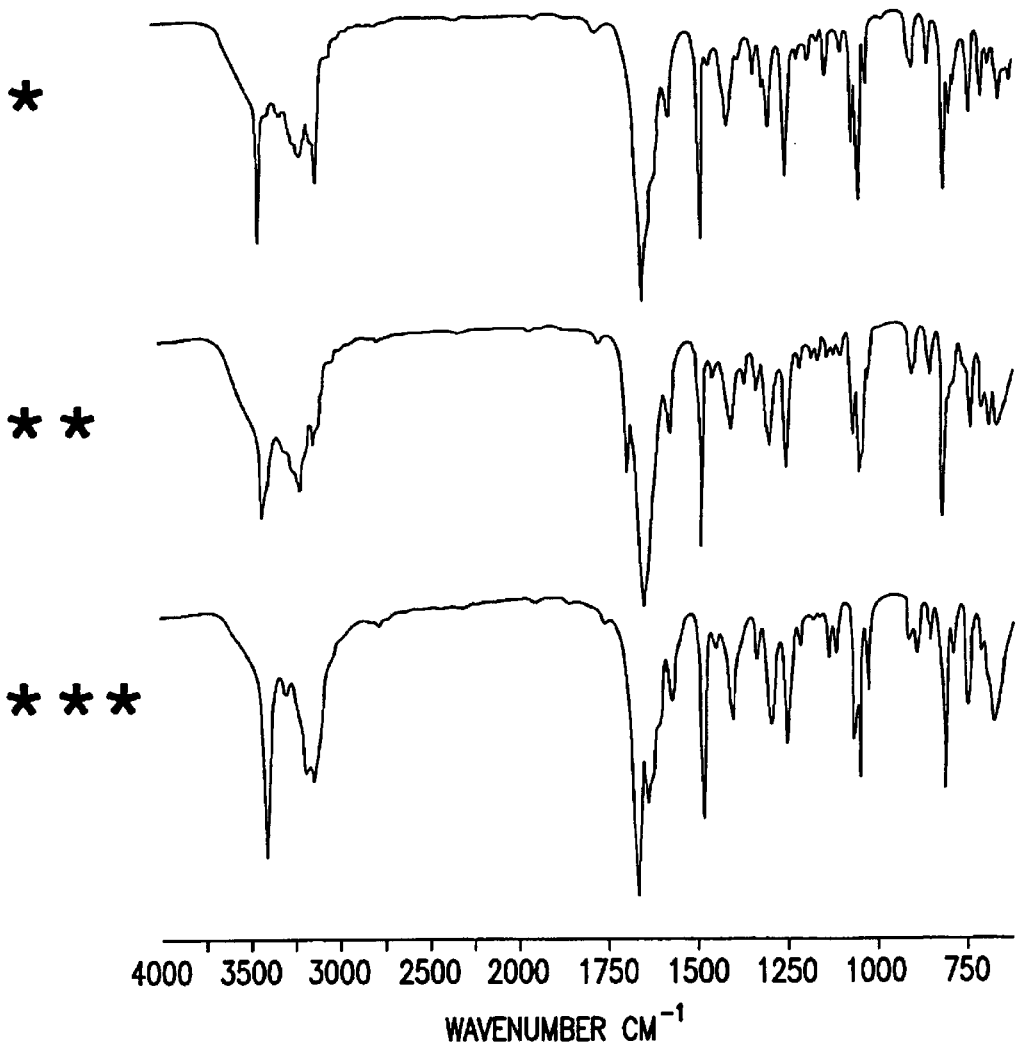
The invention relates to the novel modification A or A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



its use and pharmaceutical preparations comprising this crystal modification.

21 Claims, 2 Drawing Sheets

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4000 3500 3000 2500 2000 1750 1500 1250 1000 750
WAVENUMBER CM-1

FIG. 1

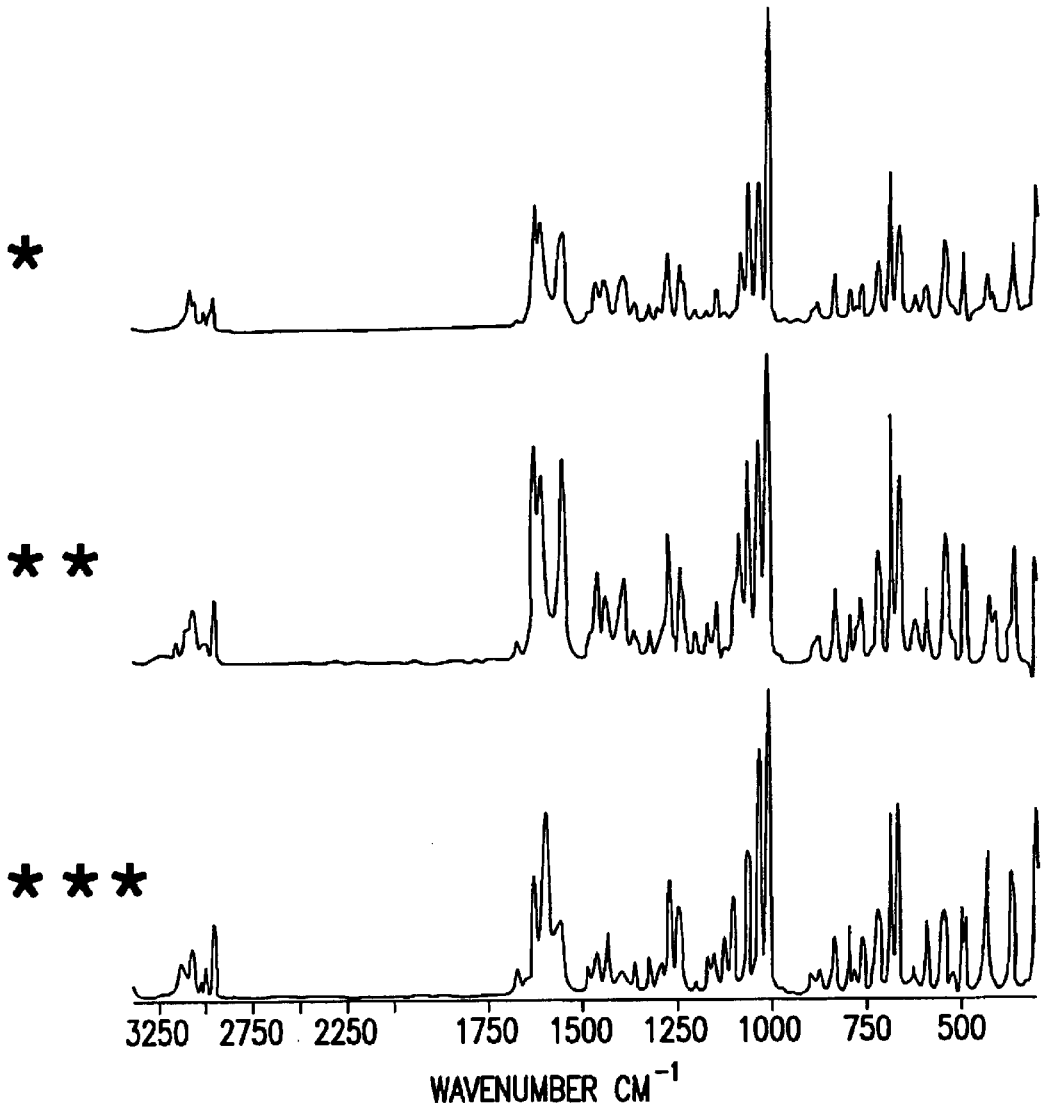
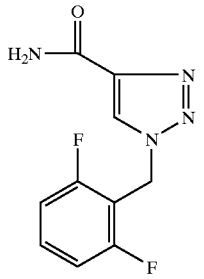


FIG.2

CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

BACKGROUND OF THE INVENTION

The compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



is described in the European Patent Application with the Publication No. 0 199 262 A2 (EP 199262), for example in Example 4. Valuable pharmacological properties are attributed to this compound; thus, it can be used, for example, as an antiepileptic. The compound 1-(2,6-difluorobenyl)-1H-1,2,3-triazole-4-carboxamide is obtained according to EP 199262, starting from 2,6-difluorobenzyl azide via the formation of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid, the procedure being analogous to Example 2.

EP 199262 provides no information at all about possible crystal modifications obtained. If the method according to the Example 4 is used in conjunction with Example 2, the crude 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide product obtained is finally crystallized from ethanol. However, EP 199262 gives no indication that such recrystallization is specifically to be applied, or on particular conditions that might be adopted. It has now surprisingly been found that the different crystal modifications (polymorphism) characterized below can be prepared by choice of specialty selected process conditions, for example through the choice of an appropriate solvent for the recrystallization or the duration of the recrystallization.

DESCRIPTION OF THE INVENTION

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be obtained in the novel crystal modifications A, A', B and C. These crystal modifications differ with respect to their thermodynamic stability, in their physical parameters, such as the absorption pattern of IR and Raman spectra, in X-ray structure investigations and in their preparation processes.

The invention relates to the novel crystal modifications A and A' preparation and use in pharmaceutical preparations comprising the crystal modifications.

The modification A', compared with A, has defects in the crystal lattice. These are detectable, for example, by X-ray analysis, e.g. by smaller line spacings with otherwise predominantly identical lines or bands.

The novel crystal modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide melts at 242° C. (239–245° C.).

In the FT infrared (FT-IR) spectrum (KBr pellet—transmission method), modification A or A' differs from

modifications B and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3412 cm^{-1} and 3092 cm^{-1} [cf. FIG. **1**], which are not present in the Fr-IR spectra of the modifications B and C. In the range 4000–600 cm^{-1}, inter alia the following bands are obtained for modification A: 3412, 3189, 3092, 1634, 1560, 1473, 1397, 1325, 1300, 1284, 1235, 1125, 1053, 1036, 1014, 885, 840, 799, 781, 723, 688 and 640 cm^{-1}. For example, the apparatus IFS 88 (Bruker) can be used for the recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder—reflection method 180°), the modification A or A' differs from modifications B and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the band at 1080 cm^{-1} [cf. FIG. **2**], which is not present in the Raman spectra of the modifications B and C. In the range 3400–300 cm^{-1}, inter alia the following bands are obtained for the modification A: 3093, 2972, 1628, 1614, 1558, 1465, 1446, 1393, 1279, 1245, 1147, 1080, 1061, 1036, 1014, 840, 724, 691, 667, 550, 499, 437 and 368 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for the recording of each of the FT Raman spectra.

The novel modification A has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å, 2.81 Å [cf. Table 1]. The measurement can be carried out, for example, in transmission geometry on an FR 552 Guinier camera from Enraf-Nonius, Deft (The Netherlands), using copper $K\alpha_1$ radiation (wavelength λ=1.54060 Å). The patterns recorded on X-ray film were measured using an LS-18 line scanner from Johannsson, Täby (Sweden) and evaluated using the Scanpi software (P. E. Werner, University of Stockholm).

Characteristic for the novel modification A is the thermogram in differential scanning calorimetry. It has an endothermic peak in the range from 230° C. to 260° C. The peak temperature is 239–245° C., and the endothermic signal is 209 J/g+/−10 J/g. The measurement was carried out on a Perkin Elmer DSC 7 in a closed pan with a heating rate of 20 K/minute. The typical sample quantity is about 4 mg. As a typical distinguishing feature compared with the modifications B and C, the thermogram of the modification A has no further thermal signal.

Crystals of the modfication A' have the same crystal structure as modification A. They differ from the modification A in the X-ray powder pattern in that they have slightly smaller line spacings between specific pairs of lines. These are the pairs of lines with the following interplanar spacings: 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å, 3.19 Å and 3.15 Å.

In the FT-IR spectrum (KBr pellet—transmission method), the modification B differs from the modification A or A' and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic is a band at 1678 cm^{-1} [cf. FIG. **1**], which is not to be observed in the corresponding spectra of the modifications A and C. In the range 4000–600 cm^{-1}, inter alia the following bands are obtained for the modification B: 3404, 3199, 3125, 1678, 1635, 1560, 1475, 1393, 1357, 1322, 1286, 1237, 1051, 1036, 1028, 889, 837, 800, 719, 667 and 645 cm^{-1}. For example, the apparatus IFS 85 (Bruker) can be used for recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder—reflection method 180°), the modification B differs from the modifications A or A' and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3166 cm^{-1} and 1086 cm^{-1} [cf. FIG. **2**], which are

not present in the Raman spectra of the modifications A and C. In the range 3400–300 cm^{-1}, inter alia the following bands are obtained for the modification B: 3166, 3089, 2970, 1678, 1628, 1614, 1559, 1464, 1441, 1391, 1275, 1244, 1147, 1086, 1062, 1036, 1014, 839, 773, 724, 690, 668, 595, 549, 500, 493, 430 and 365 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for recording of each of the Fr Raman spectra.

The modification B has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 11.0 Å, 8.3 Å, 5.18 Å, 4.88 Å, 4.80 Å, 4.42 Å, 4.33 Å, 4.19 Å, 4.12 Å, 3.81 Å, 3.50 Å, 3.41 Å, 3.36 Å, 3.32 Å, 3.28 Å, 3.24 Å, 3.05 Å, 2.83 Å [cf. Table 1].

In the thermogram in differential scanning calorimetry, the modification B has, in addition to an endothermic signal in the range from 230° C. to 260° C. (peak temperature 239–245° C.), a weak thermal signal at 205° C. (180–220° C.) as a typical distinguishing feature compared with the modifications A or A' and C.

In the FT-IR spectrum (KBr pellet—transmission method), the modification C differs from the modifications A or A' and B predominantly in the shape and in the relative intensity of many bands. Particularly characteristic is a band at 3137 cm^{-1} [cf. FIG. **11**], which is not to be observed in the corresponding spectra of the modifications A and B.

In the range 4000–600 cm^{-1}, inter alia the following bands are obtained for the modification C: 3396, 3287, 3137, 1657, 1631, 1602, 1559, 1475, 1392, 1323, 1287, 1237, 1122, 1104, 1047, 1035, 1012, 876, 839, 797, 773, 729 and 653 cm^{-1}. For example, the apparatus IFS 85 (Bruker) can be used for recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder—reflection method 180°), the modification C differs from the modifications A or A' and B predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3137 cm^{-1} and 1602 cm^{-1} [cf. FIG. **2**], which are not present in the Raman spectra of the modifications A and B. In the range 3400–300 cm^{-1}, inter alia the following bands are obtained for the modification C: 3137, 3080, 3012, 2971, 1673, 1629, 1602, 1561, 1436, 1271, 1248, 1105, 1065, 1035, 1013, 839, 800, 767, 726, 690, 672, 593, 549, 500, 492, 435 and 370 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for recording of each of the FT Raman spectra.

The modification C has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 9.0 Å, 4.73 Å, 4.65 Å, 3.75 Å, 3.54 Å, 3.42 Å, 325 Å [cf. Table 1]. In the thermogram in differential scanning calorimetry, the modification C has, in addition to an endothermic signal in the range of 230° C. to 260° C. (peak temperature 239–245° C.), a very broad, weak, exothermic signal in the region of 180° C. compared with the modifications A or A' and B.

TABLE 1

Characterization of the modifications A, B and C (X-ray powder patterns):

Modification A:		Modification B:		Modification C:	
d [Å]	Intensity	d [Å]	Intensity	d [Å]	Intensity
10.9	weak	11.0	medium	9.0	medium
10.5	medium	8.3	medium	7.0	weak
6.6	weak	8.1	very weak	5.49	weak
5.63	weak	5.68	very weak	5.11	very weak
5.25	weak	5.18	very strong	4.80	weak

TABLE 1-continued

Characterization of the modifications A, B and C (X-ray powder patterns):

Modification A:		Modification B:		Modification C:	
d [Å]	Intensity	d [Å]	Intensity	d [Å]	Intensity
5.14	medium	5.11	weak	4.73	strong
4.94	weak	4.88	medium	4.65	very strong
4.84	very strong	4.80	strong	4.47	very weak
4.55	strong	4.71	very weak	4.19	very weak
4.42	very weak	4.61	weak	4.11	very weak
4.34	medium	4.45	weak	3.98	very weak
4.23	very weak	4.42	strong	3.83	very weak
4.16	weak	4.33	very strong	3.75	strong
4.07	medium	4.19	medium	3.73	weak
4.01	weak	4.12	strong	3.54	medium
3.68	very weak	4.09	weak	3.50	weak
3.64	very weak	3.99	very weak	3.42	strong
3.60	weak	3.95	very weak	3.25	medium
3.56	weak	3.84	weak	2.88	very weak
3.51	medium	3.81	medium	2.80	very weak
3.48	medium	3.65	weak	2.74	very weak
3.38	very weak	3.61	very weak	2.67	very weak
3.25	strong	3.58	very weak	2.64	weak
3.19	medium	3.54	weak		
3.15	medium	3.50	medium		
3.11	weak	3.47	very weak		
3.07	medium	3.41	medium		
2.93	very weak	3.36	very strong		
2.87	very weak	3.32	strong		
2.81	medium	3.28	medium		
2.76	weak	3.24	medium		
2.73	very weak	3.10	weak		
2.68	weak	3.07	weak		
2.62	very weak	3.05	medium		
2.53	weak	2.93	weak		
2.43	weak	2.88	weak		
2.40	very weak	2.87	very weak		
		2.83	medium		
		2.66	weak		
		2.63	very weak		
		2.55	weak		
		2.50	weak		
		2.46	weak		
		2.44	weak		
		2.37	weak		
		2.35	weak		

Single Crystal X-ray Analysis

Crystal quality and unit cell of modifications A, B, and C were verified by Weissenberg and precession photographs. The intensities were measured on a four-axis Nonius CAD-4 diffractometer. The structures were solved with the SHELXS-97 and refined with the SHELXL-97 software.

Modification A

Space group: $Pna2_1$—orthorhombic

Cell dimensions:

a = 24.756 (5)Å	b = 23.069 (4)Å	c = 5.386 (1)Å
v = 3075.9 $Å^3$	Z = 12	D_x = 1.543 gcm^{-3}
v per formula:	V_z = 256.3 $Å^3$	

9011 unique reflections; 2479 thereof significant with $I>2\sigma$ (I). 557 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 3.65% (wR_2 for all 9011 reflections: 11.34%).

Modification B

Space group: $P^{-}1$—triclinic
Cell dimensions:

a = 5.326(1) Å	b = 11.976(2) Å	c = 17.355(3) Å
α = 107.22(3)°	β = 92.17(3)°	γ = 102.11(3)°
v = 1027.9 Å^3	Z = 4	D_x = 1.539 gcm^{-3}
v per formula	V_z = 257.0 Å^3	

4934 unique reflections; 834 thereof significant with I>2σ (I). 232 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 4.20% (wR_2 for all 4934 reflections: 7.93%).

Modification C

Space group: $P2_1/C$—monoclinic
Cell dimensions:

a = 10.982(2) Å	b = 5.350(1) Å β = 91.59(1)°	c = 17.945(3) Å
v = 1053.9 Å^3	Z = 4	D_x = 1.501 gcm^{-3}
v per formula:	V_z = 263.5 Å^3	

3073 unique reflections; 1071 thereof significant with I>2σ (I). 187 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 5,02% (wR_2 for all 3073 reflections: 14.55%). Modifications A, A', B and C have valuable pharmacological properties; in particular, they can be used for the treatment of epilepsy.

The modification A or A' has significant advantages compared with the modification B and compared with the modification C. Thus, for example, comprehensive thermodynamic investigations such as thermomicroscopy, X-ray powder diffractometry, DSC, solubility tests and other experiments, have shown that the modification A or A' surprisingly has substantially better thermodynamic stability than the modifications B and C. Modification C, which can be obtained only under specific conditions, is the least stable of the three modifications. The crystals of the modification C are converted into modification B at as low as room temperature within a few weeks. The modification C is converted either into the modification A or A' or into the modification B, depending on experimental conditions.

It is particularly important for a drug that its pharmaceutical formulation ensures high and reproducible stability over a long period. These preconditions are fulfilled by incorporation of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the crystal modification A or A', owing to its high thermodynamic stability. In particular, this is displayed in a solid pharmaceutical dosage form.

A constant stability also permits reproducible bioavailability of an active ingredient. If an active ingredient is subjected to a conversion process, this may readily also cause the bioavailability to fluctuate, which is undesirable. Accordingly, pharmaceutical active ingredients or polymorphic forms thereof which are of primary interest for pharmaceutical developments are those which exhibit high stability and do not have the above-mentioned disadvantages. The crystal modification A or A' fulfills these preconditions.

Furthermore, the modification A or A' has, for example, a slower dissolution rate in water or in gastric fluid (so-called "slow-release effect"). This effect can be utilized primarily for long-term therapy where a slow or delayed release is desired.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by the following absorptions in the infrared spectrum (KBr pellet—transmission method): bands at 3092 cm^{-1} and 3412 cm^{-1}.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by characteristic lines with interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.07 Å and 2.81 Å, determined by means of an X-ray powder pattern.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by the characteristic lines with interplanar spacings (d values) as shown in Table 1.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by an endothermic peak in the range from 230° C. to 260° C., the peak temperature being 239–245° C. and the endothermic signal being 209 J/g+/−10 J/g.

Furthermore, the invention relates to the crystal modification A' which, compared with modification A, has defects in the crystal lattice.

The invention relates to the modification A' which, compared with modification A, has smaller line spacings between the pairs of lines with interplanar spacings 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å and 3.19 Å and 3.15 Å.

The invention relates to the essentially pure form of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide. The term "essentially pure form" means purity of >95%, in particular >98%, primarily >99%, based on the modification A or A'.

The invention relates to pharmaceutical preparations comprising the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide. The invention relates in particular to corresponding pharmaceutical preparations for the treatment of epilepsy and subindications thereof. The invention relates to the use of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide for the preparation of pharmaceutical preparations, in particular for the treatment of epilepsy and subindications thereof.

The novel modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be used, for example, in the form of pharmaceutical preparations which comprise a therapeutically effective amount of the active ingredient, if desired together with inorganic or organic, solid or liquid, pharmaceutically usable carriers, which are suitable for enteral, for example oral, or parenteral administration. Furthermore, the novel modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be used in the form of preparations which can be administered parenterally or of infusion solutions. The pharmaceutical preparations may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical preparations comprise from about 0.1% to 100%, in particular from about 1% to about 50%, of lyophilisates to about 100% of the active ingredient.

The invention also relates to the use of modification A or A' of 1-(2,6-difluorobeanzyl)-1H-1,2,3-triazole-4-

carboxamide as a drug, preferably in the form of pharmaceutical preparations. The dosage may depend on various factors, such as method of administration, species, age and/or individual condition. The doses to be administered daily are between about 0.25 and about 10 mg/kg in the case of oral administration, and preferably between about 20 mg and about 500 mg for warm-blooded species having a body weight of about 70 kg.

The preparation of modification A or A' is carried out, for example, as described in the embodiments below.

Preparation of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

EXAMPLE 1

A suspension of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate (about 62 parts by weight), methanol (475.2 parts by weight) and anhydrous ammonia (29.4 parts by weight) is stirred for about 24 hours at 50–55° C. in a closed vessel. The suspension is cooled to about 20° C. and stirred for about a further 2 hours. The product is isolated by filtration, washed with methanol (240 parts by weight) and dried at 40–60° C. in vacuo. Yield: 57.2 parts by weight= 98%. Modification A.

The starting compounds can be prepared, for example, as follows:

A mixture of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (167.1 parts by weight), methanol (552 parts by weight) and 96% sulfuric acid (35.7 parts by weight) is stirred for about 5 hours at 60–66° C. The suspension is cooled to about 20° C. and stirred for about a further 2 hours. The product is isolated by filtration and washed with methanol (198 parts by weight). A yield of about 160 parts by weight is obtained by drying at 40–60° C. in vacuo.

EXAMPLE 2

1 N sodium hydroxide solution (0.11 ml) is added to a mixture of 4-cyano-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole (2.20 g) and water (44 ml) at an external temperature of 95–100° C. while stirring. After 90 minutes, the suspension is cooled to 10° C. and the product is isolated by filtration, washed with water and dried at about 60° C. in vacuo. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is obtained in this manner, yield: 99.2% by weight, Modification A.

The starting material can be prepared, for example, as follows:

4-Cyano-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole

A mixture of 2,6-difluorobenzyl azide (34.2 g), 2-chloroacrylonitrile (17.73 g) and water (125 ml) is stirred for 24 hours at about 80° C. By increasing the external temperature to about 130° C., excess 2-chloroacrylonitrile is distilled off. The semisolid mixture is cooled to about 40° C., cyclohexane (50 ml) is added to the suspension and the mixture is brought to about 20° C. and stirred for about 2 hours. The product is isolated by filtration and washed with cyclohexane (75 ml) and then with water (50 ml). The moist product is mixed with water (100 ml), the suspension is filtered and the product is washed with water (50 ml) and dried at about 60° C. in vacuo. Yield: 38.04 g=86%.

Examples of the Recrystallization of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

EXAMPLE 3

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (75.0 g) is dissolved in formic acid (360 ml) at 50–55° C. by stirring. The solution is discharged in the course of 1 hour onto stirred methanol (375 ml) at about 20° C., a suspension-forming. After stirring has been continued for 2 hours at about 20° C., the product is isolated by filtration, washed with methanol (750 ml) and dried at about 60° C. in vacuo. Yield: 69.6 g=92.8%. Modification A.

EXAMPLE 4

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (22.86 kg) is dissolved in formic acid (111.6 kg) at 58–63° C. while stirring. The solution is discharged in the course of about 2 hours onto stirred methanol (131.9 l) at 20–25° C., after which washing with formic acid (7.6 kg) is carried out. A suspension forms. After stirring has been continued for at least 3 hours at about 20° C., the product is isolated by filtration and washed wit methanol (187.5 l). By drying in vacuo at about 60° C., the product is obtained as modification A in a yield of 93–94%.

EXAMPLE 5

1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (pure active ingredient, 4.0 g) is dissolved in 96% ethanol (500 ml, without denaturing agent) at about 80° C. while stirring. The solution is filtered into a suction bottle (1 liter) at about 20° C. (glass suction filter, pore size 10–20 μm), A suspension forming. After stifing has been continued for 5 minutes at about 20° C. and for 15 minutes at about 0° C., the product is isolated by filtration (about 0° to about 20° C.). The solvent-moist product (9.6 g) is investigated without subsequent drying. Modification A'.

FORMULATION EXAMPLE 1

Film-coated tablets each containing, for example, 100, 200 or 400 mg of modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with the following composition per dosage unit:

	mg	mg	mg
Core material			
Active ingredient	100.00	200.00	400.00
Anhydrous, colloidal silica	0.88	1.75	3.5
Microcrystalline cellulose	36.62	73.25	146.50
Hydroxypropylmethyl-cellulose	5.00	10.00	20.00
Lactose	20.00	40.00	80.00
Magnesium stearate	2.00	4.00	8.00
Maize starch	10.00	20.00	40.00
Sodium carboxymethyl-cellulose	5.00	10.00	20.00
Sodium laurylsulfate	0.50	1.00	2.00
Film coat			
Hydroxypropylmethyl-cellulose	3.22	6.43	12.87
Red iron oxide	0.04	0.09	0.18
Polyethylene glycol 8000, flakes	0.58	1.16	2.32
Talc	2.33	4.66	9.31
Titanium dioxide	0.83	1.66	3.32

The active ingredient is granulated with demineralized water. Milled lactose, maize starch, Avicel PH 102, cellulose-HP-M-603 and sodium laurylsulfate are added to the above mixture and granulated with demineralized water.

The moist material is dried and milled. After the addition of the remaining ingredients, the homogeneous mixture is

compressed to give tablet cores having the stated active ingredient content.

The tablet cores are coated with the film coat which is formed from the appropriate ingredients, the latter being dissolved or being suspended in water or in small amounts of ethanol with 5% of isopropanol.

DESCRIPTION OF THE FIGURES

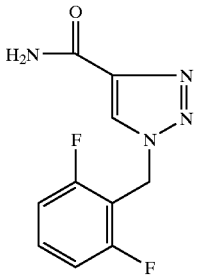
FIG. **1** shows the FT-IR spectra of the KBr pellets of modifications A, B and C.

FIG. **2** shows the FT-Raman spectra-of the powder of modification A, B and C.

In both Figures, the modification a is denoted by the symbol*, the modification b by the symbol** and the modification C by the symbol***.

What is claimed is:

1. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



characterized by characteristic lines at interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å, 2.81 Å, determined by means of an X-ray powder pattern.

2. The crystal modification according to claim **1**, characterized by an X-ray powder pattern having the following characteristic lines at interplanar spacings (d values) of 10.9 Å (weak), 10.5 Å (medium), 6.6 Å (weak), 5.63 Å (weak), 5.25 Å (weak), 5.14 Å (medium), 4.94 Å (weak), 4.84 Å (very strong), 4.55 Å (strong), 4.42 Å (very weak), 4.34 Å (medium), 4.23 Å (very weak), 4.16 Å (weak), 4.07 Å (medium), 4.01 Å (weak), 3.68 Å (very weak), 3.64 Å (very weak), 3.60 Å (weak), 3.56 Å (weak), 3.51 Å (medium), 3.48 Å (medium), 3.38 Å (very weak), 3.25 Å (strong), 3.19 Å (medium), 3.15 Å (medium), 3.11 Å (weak), 3.07 Å (medium), 2.93 Å (very weak), 2.87 Å (very weak), 2.81 Å (medium), 2.76 Å (weak), 2.73 Å (very weak), 2.68 Å (weak), 2.62 Å (very weak), 2.53 Å (weak), 2.43 Å (weak), 2.40 Å (very weak).

3. The crystal modification according to claim **1**, characterized by the following absorptions in the FT-IR spectrum (KBr pellet—transmission method) 3092 cm^{-1} and 3412 cm^{-1}.

4. The crystal modification according to claim **3**, characterized by the following absorptions in the FT-IR spectrum (KBr pellet—transmission method): 3412, 3189, 3092, 1634, 1560, 1473, 1397, 1325, 1300, 1284, 1235, 1125, 1053, 1036, 1014, 885, 840, 799, 781, 723, 688 and 640 cm^{-1}.

5. The crystal modification according to claim **1**, characterized by the following absorptions in the FT-Raman spectrum (powder—reflection method 180°): 3093, 2972, 1628, 1614, 1558, 1465, 1446, 1393, 1279, 1245, 1147, 1080, 1061, 1036, 1014, 840, 724, 691, 667, 550, 499, 437 and 368 cm^{-1}.

6. The crystal modification A according to claim **1**, characterized by an endothermic peak in the range from 230° C. to 260° C., the peak temperature being 239–245° C., and the endothermic signal being 209 J/g+/−10 J/g.

7. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **1** but has defects in the crystal lattice.

8. The crystal modification A' according to claim **7**, characterized by line spacings, smaller compared to modification A, between the pairs of lines at interplanar spacings 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å and 3.19 Å and 3.15 Å.

9. Modification A according to claim **1** in essentially pure form.

10. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by bands at 3412 cm^{-1} and 3092 cm^{-1} in the FT-IR spectrum.

11. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by bands at 1080 cm^{-1} in the FT-IR spectrum.

12. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **2** but has defects in the crystal lattice.

13. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **3** but has defects in the crystal lattice.

14. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **4** but has defects in the crystal lattice.

15. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **5** but has defects in the crystal lattice.

16. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **6** but has defects in the crystal lattice.

17. The crystal A' according to claim **7** in essentially pure form.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim **1**.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim **7**.

20. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **10** but has defects in the crystal lattice.

21. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim **11** but has defects in the crystal lattice.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,740,669 B1
APPLICATION NO. : 09/125329
DATED : May 25, 2004
INVENTOR(S) : Robert Portmann et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

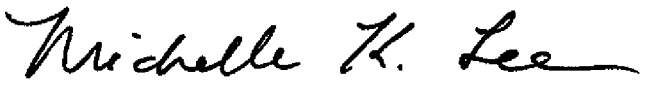
In the Claims

Column 10, line 22 (claim 11) change: "characterized by bands at 1080 cm^{-1} in the FT-IR spectrum."

to

-- characterized by bands at 1080 cm^{-1} in the FT-Raman spectrum. --

Signed and Sealed this
Seventh Day of October, 2014



Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office