

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
29 December 2005 (29.12.2005)

PCT

(10) International Publication Number  
**WO 2005/123706 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 279/12**

(21) International Application Number:  
PCT/US2005/020065

(22) International Filing Date: 7 June 2005 (07.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/577,784 8 June 2004 (08.06.2004) US

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(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ,  
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL,  
SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,  
VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,  
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,  
GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: CRYSTALLINE POLYMORPHS OF (3S)-N-HYDROXY-4-({4-[(4-HYDROXY-2-BUTYNYL)OXY]PHENYL}SUL-  
FONYL)-2,2-DIMETHYL-3-THIOMORPHOLINE CARBOXAMIDE

(57) Abstract: ABSTRACT This invention relates to crystalline polymorphs of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-bu-  
tynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide, and preparation and uses thereof.



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CRYSTALLINE POLYMORPHS OF (3S)-N-HYDROXY-4-({4-[(4-HYDROXY-2-BUTYNYL)OXY]PHENYL}SULFONYL)-2,2-DIMETHYL-3-THIOMORPHOLINE CARBOXAMIDE

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FIELD OF THE INVENTION

This invention relates to crystalline polymorphs of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyryl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide (apratat), an inhibitor of TNF- $\alpha$  converting enzyme (TACE).

10

BACKGROUND OF THE INVENTION

TNF- $\alpha$  converting enzyme (TACE) catalyzes the formation of TNF- $\alpha$  from membrane bound TNF- $\alpha$  precursor protein. TNF- $\alpha$  is a pro-inflammatory cytokine that is believed to have a role in rheumatoid arthritis [Shire, M. G.; Muller, G. W. *Exp. Opin. Ther. Patents* **1998**, 8(5), 531; Grossman, J. M.; Brahn, E. J. *Women's Health* **1997**, 6(6), 627; Isomaki, P.; Punnonen, J. *Ann. Med.* **1997**, 29, 499; Camussi, G.; Lupia, E. *Drugs*, **1998**, 55(5), 613], Crohn's disease [Van Assche, G.; Rutgeerts, P.; *Exp. Opin. Invest. Drugs*, **2000**, 9, 103; Rutgeerts, P.; Baert, F. *Drugs of Today*, **2000**, 36(Suppl. G, Doctor in Focus), 59], psoriatic arthritis [Kreuger, G.; Callis, K.; *Archives of Dermatology*, **2004**, 140, 218], psoriasis [Kristensen, M.; Chu, C. Q.; Eedy, D. J.; et al.; *Clin. Exp. Immunol.*, **1993**, 94, 354], vasculitis [Lorenz, H.-M.; Kalden, J. R.; *Arthritis Res.*, **2002**, 4(suppl 3), S17], ankylosing spondylitis [Wendling, D.; Toussiot, E.; *Exp. Opin. Pharmacotherapy*, **2004**, 5, 1497], septic shock [Mathison, et. al. *J. Clin. Invest.* **1988**, 81, 1925; Miethke, et. al. *J. Exp. Med.* **1992**, 175, 91; Robertshaw, H. J.; Brennan, F. M.; *Br. J. Anaesth.*, **2005**, 94, 222], graft rejection [Piguet, P. F.; Grau, G. E.; et al. *J. Exp. Med.* **1987**, 166, 1280], cachexia [Beutler, B.; Cerami, A. *Ann. Rev. Biochem.* **1988**, 57, 505], anorexia, inflammation [Ksontini, R.; MacKay, S. L. D.; Moldawer, L. L. *Arch. Surg.* **1998**, 133, 558], congestive heart failure [Packer, M. *Circulation*, **1995**, 92(6), 1379; Ferrari, R.; Bachetti, T.; et. al. *Circulation*, **1995**, 92(6), 1479; Feldman, A. M.; Combes, A.; Wagner, D.; *J. Am. Coll. Cardiol.*, **2003**, 35, 537; Mamoru, S.; Iwasaka, J.; Nakamura, M.; et al.; *Eur. J. Heart Failure*, **2004**, 6, 869], post-ischaemic reperfusion injury [Gilles, S.; Zahler, S.; Welsch, U.; et al.; *Cardiovascular Res.*, **2003**, 60, 608], inflammatory disease of the central nervous system [Moro, M. A.; Hurtado, O.;

Cardenas, A; et al.; *Neurosignals*, **2003**, 12, 53], inflammatory bowel disease and ulcerative colitis [Colon, A. L.; Menchen, L. A.; Hurtado, O.; De Cristobal, J.; Lizasoain, I.; Leza, J. C.; Lorenzo, P.; Moro, M. A.; *Cytokine*, **2001**, 16, 220; Kirkegaard, T.; Pedersen, G.; Saermark, T.; Brynskov, J.; *Clin. Exp. Immunol.*; **2004**, 135, 146], insulin

5 resistance and diabetes [Hotamisligil, G. S.; Shargill, N. S.; Spiegelman, B. M.; *et. al. Science*, **1993**, 259, 87; Hotamisligil, G. S.; Spiegelman, B. M.; *Diabetes*, **1994**, 43, 1271; Morimoto, Y.; Nishikawa, K.; Ohashi, M. *Life Sci.*, **1997**, 61, 795], chronic obstructive pulmonary disease (COPD) and asthma [Trifilieff, A.; Walker, C.; Keller, T.; Kottirsch; Neumann, U.; *Brit. J. Pharmacol.*, **2002**, 135, 1655], stroke [Wang, X.;

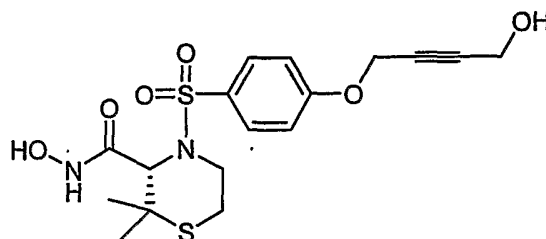
10 Feuerstein, G. Z.; Xu, L.; et al.; *Mol. Pharmacol.*, **2004**, 65, 890; Wang, X.; Xu, L.; Feuerstein, G. Z.; et al. *Circulation*, **2003**, 108 (17 Supp.), iv-103; Hallenback, J. M.; *Nature Medicine*, **2002**, 8, 1363.], pneumococcal meningitis [Meli, D. N.; Loeffler, J. M.; Baumann, P. et al.; *J. Neuroimmunology*, **2004**, 151, 6], tumor metastasis [Nelson, A. R.; Fingleton, B.; Rothenberg, M. L.; et al.; *J. Clin. Oncol.*, **2000**, 18, 1135], multiple

15 sclerosis [Clements, J. M.; Cossins, J. A.; Wells, G. M.; et al.; *J. Neuroimmunol.*, **1997**, 74, 85]] and HIV infection [Peterson, P. K.; Gekker, G.; *et. al. J. Clin. Invest.* **1992**, 89, 574; Pallares-Trujillo, J.; Lopez-Soriano, F. J. Argiles, J. M. *Med. Res. Reviews*, **1995**, 15 (6), 533], in addition to its well-documented antitumor properties [Old, L. *Science*, **1985**, 230, 630]. For example, research with anti-TNF- $\alpha$  antibodies and transgenic

20 animals has demonstrated that blocking the formation of TNF- $\alpha$  inhibits the progression of arthritis [Rankin, E.C.; Choy, E.H.; Kassimos, D.; Kingsley, G.H.; Sopwith, A.M.; Isenberg, D.A.; Panayi, G.S. *Br. J. Rheumatol.* **1995**, 34, 334; *Pharmaprojects*, **1996**, Therapeutic Updates 17 (Oct.), au197-M2Z]. This observation has been extended to humans as well ["TNF- $\alpha$  in Human Diseases", *Current Pharmaceutical Design*, **1996**, 2,

25 662].

(3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide (apratatstat) is a potent, reversible, and competitive inhibitor of TACE in vitro having the structure below:



Apratastat inhibits TNF- $\alpha$  secretion by human synovium tissue explants from patients suffering from rheumatoid arthritis and is a potent TNF- $\alpha$  inhibitor in murine and primate lipopolysaccharide (LPS) models. These data demonstrate that apratastat has the potential for treating and/or inhibiting disease states mediated by TACE. The preparation of apratastat was first disclosed in U.S. Patent No. 6,225,311, the entire disclosure of which is hereby incorporated by reference.

It is well known that the crystalline polymorph form of a particular drug is often an important determinant of the drug's ease of preparation, stability, solubility, storage stability, ease of formulation and *in vivo* pharmacology. Polymorphic forms occur where the same composition of matter crystallizes in a different lattice arrangement resulting in different thermodynamic properties and stabilities specific to the particular polymorph form. In cases where two or more polymorph substances can be produced, it is desirable to have a method to make polymorphs in pure form. In deciding which polymorph is preferable, the numerous properties of the polymorphs must be compared and the preferred polymorph chosen based on the many physical property variables. It is entirely possible that one polymorph form can be preferable in some circumstances where certain aspects such as ease of preparation, stability, etc. are deemed to be critical. In other situations, a different polymorph may be preferred, for example, for greater solubility and/or superior pharmacokinetics.

Because improved drug formulations showing, for example, better bioavailability or better stability are consistently sought, there is an ongoing need for new or purer polymorphic forms of drug molecules. The polymorphs of apratastat described herein help meet these and other needs.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a powder X-ray diffraction pattern of apratastat polymorph form A.

Figure 2 depicts an attenuated total reflection infrared spectrum of apratastat polymorph form A.

Figure 3 depicts Raman spectra of apratastat polymorph forms A, C and D and an amorphous form of apratastat.

Figure 4 depicts a powder X-ray diffraction pattern of apratastat polymorph form B.

Figure 5 depicts an attenuated total reflection infrared spectrum of apratastat polymorph form C.

Figure 6 depicts a powder X-ray diffraction pattern of apratastat polymorph form C.

Figure 7 depicts an attenuated total reflection infrared spectrum of apratastat polymorph form D.

Figure 8 depicts a powder X-ray diffraction pattern of apratastat polymorph form D.

5 Figure 9 depicts an attenuated total reflection infrared spectrum of an amorphous form of apratastat.

Figure 10 depicts a differential scanning calorimetry profile of a sample of apratastat polymorph form A.

10 Figure 11 depicts a powder X-ray diffraction pattern of an apratastat sample prepared by the evaporative crystallization method described in Example 7.

Figure 12 depicts a differential scanning calorimetry profile of the sample from Figure 11.

#### SUMMARY OF THE INVENTION

15 The present invention provides crystalline polymorphs of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyryl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide (apratastat) characterized by the powder X-ray diffraction data, IR data, and Raman spectroscopy data provided herein. Compositions containing the polymorphs of apratastat are also provided. The invention further provides methods of preparing the  
20 apratastat polymorphs.

Methods of treating or inhibiting diseases or disorders mediated by TACE are also provided by the present invention, comprising administering to a mammal a therapeutically effective amount of a composition containing a polymorph of apratastat as described herein. The invention further provides methods of alleviating a symptom of  
25 a disease or disorder mediated by TNF- $\alpha$  comprising administering to a mammal a therapeutically effective amount of a composition containing a polymorph of apratastat as described herein.

#### DETAILED DESCRIPTION OF THE INVENTION

30 The invention provides crystalline polymorphs of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyryl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide (apratastat) which can be identified by one or more solid state analytical methods.

One polymorph (form A) can be identified by its powder X-ray diffraction pattern, for example, as shown in Figure 1. Powder X-ray diffraction data consistent with form A is provided in Table 1 below.

5

**Table 1**

Degree (2 $\theta$ )	Intensity
6.8	58.6
7.5	7827.4
9.8	968.1
12.2	882.2
13.7	1058.2
14.1	521.5
14.7	1395.2
14.9	256.2
15.3	80.1
16.5	1387.6
17.8	669.9
18.9	65.2
19.6	2304.3
20.1	85.1
21.0	593.3
21.6	1599.8
22.2	364.5
22.7	1523.9
23.3	523.8
23.4	313.6
24.5	740.8
24.7	2384.0
25.6	1325.3
26.2	2530.8
27.5	576.7
28.0	643.8
28.6	90.5

29.0	131.0
29.7	1871.3
30.3	355.5
30.6	372.5
31.1	493.3
31.5	180.5
32.0	203.1
32.7	199.1
33.5	376.1
34.2	340.6
35.0	184.6
35.8	614.9
36.8	253.9
37.2	357.8
37.8	535.2
38.2	258.7
38.9	478.5
39.1	375.7
39.4	233.1
39.9	207.4

Polymorph form A of apratastat is characterized as having peaks in its powder X-ray diffraction pattern at diffraction angle  $2\theta$  of about  $7.5^\circ$ ,  $19.6^\circ$ ,  $24.7^\circ$ , and  $26.2^\circ$ . Form A may be further characterized as having peaks at diffraction angle  $2\theta$  of about  $14.7^\circ$ ,  $16.5^\circ$ ,  $21.6^\circ$ ,  $22.7^\circ$ ,  $25.6^\circ$  and  $29.7^\circ$ . Due to variations in sample preparation and instrument configurations, all reported powder X-ray diffraction peaks may vary by plus or minus  $0.2^\circ$ .

Form A can also be identified by its infrared (IR) spectrum, for example, as shown in Figure 2. Form A can be characterized as having one or more bands in its IR spectrum at about  $3380\text{ cm}^{-1}$ ,  $3220\text{ cm}^{-1}$ ,  $2970\text{ cm}^{-1}$ ,  $2930\text{ cm}^{-1}$ ,  $1680\text{ cm}^{-1}$ ,  $1650\text{ cm}^{-1}$ ,  $1590\text{ cm}^{-1}$ ,  $1580\text{ cm}^{-1}$ ,  $1500\text{ cm}^{-1}$ ,  $1450\text{ cm}^{-1}$ ,  $1370\text{ cm}^{-1}$ ,  $1330\text{ cm}^{-1}$ ,  $1300\text{ cm}^{-1}$ ,  $1250\text{ cm}^{-1}$ ,  $1150\text{ cm}^{-1}$ ,  $1090\text{ cm}^{-1}$ , and  $1050\text{ cm}^{-1}$ . Due to variations in sample preparation and instrument configurations, all IR bands may vary by as much as plus or

minus  $15\text{ cm}^{-1}$  (e.g., plus or minus  $15\text{ cm}^{-1}$ , plus or minus  $10\text{ cm}^{-1}$ , or plus or minus  $5\text{ cm}^{-1}$ ). Form A can further be identified by its Raman spectrum, for example, as shown in Figure 3.

Apratasat polymorph form A can be prepared, for example, by recrystallizing  
5 apratastat (made, for example, according to the procedure set forth in U.S. Patent No. 6,225,311, which is incorporated by reference herein in its entirety) from a suitable solvent or solvent mixture. Weight ratios of the total solvent to the amount of apratastat can be, for example, about 5:1, about 4:1, about 3:1, about 2:1, or about 1:1. Examples of suitable solvents include alcohols such as methanol, ethanol, n-propanol, isopropanol,  
10 and mixtures thereof. Water may be added as a co-solvent to any of the aforementioned alcohols to form a solvent mixture, e.g., methanol/water, ethanol/water, n-propanol/water, or isopropanol/water mixtures. The apratastat solution or suspension may be heated for a time sufficient to produce form A. For example, the solution or suspension may be heated to a temperature between about  $25\text{ }^{\circ}\text{C}$  and the reflux temperature of the solvent or solvent mixture. For an isopropanol or isopropanol/water solution, suitable  
15 temperatures may range from about  $25\text{ }^{\circ}\text{C}$  to about  $80\text{ }^{\circ}\text{C}$  (e.g., about  $30\text{ }^{\circ}\text{C}$  to about  $80\text{ }^{\circ}\text{C}$ , or about  $50\text{ }^{\circ}\text{C}$  to about  $75\text{ }^{\circ}\text{C}$ ). After heating, the solution may optionally be cooled to a temperature at or below  $25\text{ }^{\circ}\text{C}$  (e.g., about  $-5\text{ }^{\circ}\text{C}$  to about  $25\text{ }^{\circ}\text{C}$ , about  $0\text{ }^{\circ}\text{C}$  to about  $20\text{ }^{\circ}\text{C}$ , about  $0\text{ }^{\circ}\text{C}$  to about  $15\text{ }^{\circ}\text{C}$ , or about  $0\text{ }^{\circ}\text{C}$  to about  $10\text{ }^{\circ}\text{C}$ ). Form A seed  
20 crystals, obtained from a previous preparation, may optionally be added during the cooling process. Additional water may be added to facilitate precipitation of the polymorph form A. Alternatively, an alcohol solution of apratastat may be slowly evaporated at or near ambient temperature (e.g.,  $20\text{--}25\text{ }^{\circ}\text{C}$ ) to form a slurry, which can then be filtered and dried to yield the desired polymorph. In addition to the parameters  
25 described above, those of skill in the art of will readily recognize other suitable recrystallization conditions that can yield essentially the same results.

If apratastat polymorph form A is placed in a low-moisture environment (for example, about 4-5% relative humidity) at or near room temperature, a portion or all of the polymorph may convert to a new form (form B), which can be identified by its powder  
30 X-ray diffraction pattern as shown in Figure 4. Powder X-ray diffraction data consistent with form B is provided in Table 2 below.

Table 2



Degree (2 $\theta$ )	Intensity
7.6	9466.6
9.8	678.8
10.4	271.0
11.1	113.4
11.3	113.9
12.2	394.2
13.5	457.0
13.7	963.2
14.1	964.1
14.7	1115.6
15.1	685.3
15.6	201.7
16.6	887.0
17.9	546.5
19.0	248.3
19.5	1427.2
20.3	333.2
20.8	147.9
21.2	138.6
21.8	841.2
22.2	456.1
22.9	1251.3
23.3	680.5
24.6	771.1
24.8	776.0
25.7	729.0
26.4	1469.9
27.0	127.4
27.5	233.5
28.2	585.3
29.0	196.4

29.2	86.4
29.8	1031.8
30.4	498.2
30.8	351.1
31.3	193.5
31.6	130.8
33.0	269.0
33.4	87.3
33.8	128.7
34.3	146.7
35.1	145.5
36.0	391.7
36.9	129.2
37.6	279.4
38.3	968.6
39.0	208.9
39.2	307.8
39.6	337.0

Polymorph form B of apratastat is characterized as having peaks in its powder X-ray diffraction pattern at diffraction angle  $2\theta$  of, for example, about  $7.6^\circ$ ,  $19.5^\circ$ ,  $22.9^\circ$ , and  $26.4^\circ$ . The powder X-ray diffraction pattern for form B contains several peaks not  
5 present in that of form A, for example, peaks at  $10.4^\circ$ ,  $11.1^\circ$  and  $11.3^\circ$ . Due to variations in sample preparation and instrument configurations, all reported powder X-ray diffraction peaks may vary by plus or minus  $0.2^\circ$ .

Polymorph form B is likely also an anhydrous form of apratastat. The powder X-ray diffraction data for forms A and B are similar, and no significant differences are  
10 expected in the physical properties (e.g., solubility) of form A and form B. Form B can convert back to form A under ambient conditions with little or no energy input. Form B disappears upon mild heating (e.g., at or above about  $35^\circ\text{C}$ ) under ambient humidity levels.

A third anhydrous crystalline polymorph of apratastat (form C) can form when  
15 apratastat is heated at or near about  $120^\circ\text{C}$ , but not exceeding about  $145^\circ\text{C}$ . Form C

can be identified by its IR spectrum, for example, as shown in Figure 5, and its Raman spectrum, for example, as shown in Figure 3. Form C can also be identified by its powder X-ray diffraction pattern as shown in Figure 6 and in Table 3 below.

5

**Table 3**

<b>Degree (2<math>\theta</math>)</b>	<b>Intensity</b>
6.1	71.0
7.5	472.3
8.9	84.9
9.9	208.1
10.4	131.2
10.9	44.9
11.3	137.3
12.1	47.4
13.1	192.4
13.4	599.5
13.6	284.6
14.1	196.6
14.7	449.6
15.1	109.1
15.5	691.4
16.3	74.7
16.5	116.3
17.0	86.4
17.8	476.1
16.4	69.4
19.1	285.9
19.5	190.5
19.8	390.7
20.3	232.4
20.5	107.3
21.0	185.0
21.8	606.6

22.2	250.1
22.9	281.0
23.3	344.4
24.4	182.1
24.7	320.7
25.4	174.7
25.8	135.5
26.2	61.1
26.5	160.8
27.0	302.3
27.4	142.4
27.9	80.6
28.4	215.2
29.3	176.9
30.0	268.7
30.5	256.0
30.7	171.1
31.3	151.1
32.0	94.7
32.3	57.8
33.1	104.0
33.4	75.6
33.7	54.9
34.6	207.9
35.2	105.0
35.9	114.6
36.4	89.6
37.0	85.4
37.7	77.5
38.2	81.9
38.8	106.3
39.2	86.8

39.5	59.2
39.9	45.6

Polymorph form C of apratastat is characterized as having peaks in its powder X-ray diffraction pattern at diffraction angle  $2\theta$  of, for example, about  $7.5^\circ$ ,  $13.4^\circ$ ,  $15.5^\circ$ ,  $17.8^\circ$ , and  $21.8^\circ$ . Due to variations in sample preparation and instrument configurations, all reported powder X-ray diffraction peaks may vary by plus or minus  $0.2^\circ$ .

A fourth anhydrous crystalline polymorph of apratastat (form D) can form when apratastat is heated above about  $120^\circ\text{C}$ , but not exceeding about  $155^\circ\text{C}$ . Form D can be identified by its IR spectrum, for example, as shown in Figure 7, as well as its Raman spectrum, as shown in Figure 3. Powder X-ray diffraction data consistent with form D is provided in Figure 8 and in Table 4 below.

Table 4

Degree ( $2\theta$ )	Intensity
8.3	647.8
9.2	49.9
9.5	175.9
10.1	128.7
10.7	26.9
11.1	29.6
12.4	106.7
12.6	147.5
12.8	232.2
13.5	437.5
13.6	540.2
13.9	643.1
14.1	225.6
14.5	28.3
14.8	145.5
15.1	156.0
15.5	334.7
15.8	258.8

16.1	107.2
16.4	207.9
16.6	69.9
17.0	124.7
17.2	443.2
17.8	119.0
18.5	948.7
19.0	659.8
19.5	429.6
19.8	87.8
20.3	346.4
20.6	1115.6
21.2	578.3
21.6	205.7
21.8	122.1
22.3	102.9
22.8	82.9
23.6	56.1
24.4	227.1
24.9	783.1
25.4	225.0
25.8	142.6
26.2	118.7
26.7	237.7
27.0	112.1
27.6	148.1
28.0	217.8
28.5	677.1
28.8	191.5
29.1	121.3
29.6	53.2
30.0	198.9

30.7	85.7
31.4	84.9
32.0	106.9
32.3	132.7
32.9	220.0
33.7	71.6
34.0	103.3
34.4	153.8
34.9	279.6
35.8	99.7
36.4	108.8
36.7	134.1
37.6	158.4
38.0	167.5
38.3	66.4
38.6	117.0
39.0	109.5
39.3	113.8

Polymorph form D of apratastat is characterized as having peaks in its powder X-ray diffraction pattern at diffraction angle  $2\theta$  of, for example, about  $8.3^\circ$ ,  $18.5^\circ$ ,  $19.0^\circ$ ,  $20.6^\circ$ ,  $24.9^\circ$ , and  $28.5^\circ$ . Due to variations in sample preparation and instrument configurations, all reported powder X-ray diffraction peaks may vary by plus or minus  $0.2^\circ$ .

Apratastat can also exist in an amorphous form. For example, prolonged and/or intense heating (e.g., at or above about  $155^\circ\text{C}$ ), or heating in the presence of oxygen can facilitate formation of the amorphous form of apratastat. An IR spectrum of a representative amorphous form of apratastat is shown in Figure 9, and a representative Raman spectrum is shown in Figure 3.

Differential scanning calorimetry (DSC) experiments on apratastat polymorph A have revealed three endotherms at about  $121^\circ\text{C}$ ,  $144^\circ\text{C}$  and  $154^\circ\text{C}$  (Figure 10). It is believed that the endotherm at about  $144^\circ\text{C}$  is related to the transformation from form C to amorphous and/or to form D, and the  $154^\circ\text{C}$  endotherm is the melting event of form

D. The broad endotherm which generally occurs between about 100 °C and about 125 °C (which sometimes appears as an exo-endotherm) is thought to be related to the transformation of A to other forms. All three endotherms do not always appear in DSC experiments, however, and the extent of the transformation from form A to forms B, C or  
5 D, or the amorphous state appears to depend on many parameters, such as humidity, ambient oxygen levels, temperature, intensity of heating, heating scheme, and sample history and characteristics (e.g., moisture content and particle size). The DSC experiments indicate that upon heating, the first crystalline transformation tends to be to form C whether in an inert atmosphere or with a limited amount of oxygen present, but  
10 form C generally does not exist at temperatures higher than about 145 °C. If the transformation to form D does occur, it tends to prevail over the transformation to form C at higher temperatures and longer heating times. Form D generally does not exist at temperatures higher than about 155 °C.

As described in U.S. Patent No. 6,225,311, apratastat is an inhibitor of matrix  
15 metalloproteinase (MMP) and TACE enzymes. Apratastat is therefore useful in the treatment or prevention of disorders mediated by one or more of the MMP enzymes and/or TACE, such as arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease, septic shock, congestive heart failure and HIV infection and for the alleviation of symptoms  
20 thereof. Apratastat is also useful in treating or inhibiting pathological changes mediated by MMP enzymes such as atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic  
25 arthritis, corneal ulceration, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the central nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of  
30 prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection and for the alleviation of symptoms thereof. Accordingly, polymorphs of apratastat and compositions containing such polymorphs can be used to treat or prevent these



diseases and disorders. Methods of treatment include identifying a mammal having a disease or disorder mediated by TNF- $\alpha$ , and providing to the mammal a composition containing a therapeutically effective amount of a polymorph of apratastat as described herein.

5           In further embodiments, the methods are provided for alleviating a symptom of a disease or disorder mediated by TNF- $\alpha$ . In some embodiments, the methods include identifying a mammal having a symptom of a disease or disorder mediated by TNF- $\alpha$ , and providing to the mammal an amount of a composition containing a polymorph of apratastat as described herein effective to ameliorate (*i.e.*, lessen the severity of) the  
10       symptom.

          The present invention provides pharmaceutical compositions comprising at least one polymorph according to the invention and one or more pharmaceutically acceptable carriers, excipients, or diluents. In some embodiments, the composition contains at least about 50% to at least about 99% by weight of a single polymorph (*e.g.*, at least about  
15       50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%). Examples of suitable carriers are well known to those skilled in the art and are prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in *Remington's Pharmaceutical Sciences*, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985), which is incorporated herein  
20       by reference in its entirety. Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable. Supplementary active ingredients can also be incorporated into the compositions.

          The compositions of the invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid  
25       carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or encapsulating materials. The compositions may be formulated in conventional manner, for example, in a manner similar to that used for known antiinflammatory agents. Oral formulations may comprise any conventionally  
30       used oral form, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. In powders, the carrier is a finely divided solid, which is an admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable

proportions and compacted in the shape and size desired. The powders and tablets may contain up to 99% of the active ingredient.

Capsules may contain mixtures of the polymorph with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch),  
5 sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc.

Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including  
10 surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol,  
15 dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes and ion exchange resins. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters,  
20 colliodol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or fruit juice, containing appropriate solubilizers or emulsifiers as needed.

25 Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The polymorphs of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a mixture of both, or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers,  
30 preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as described above, e.g. cellulose derivatives, such as a sodium carboxymethyl cellulose

solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration may be in either liquid or solid form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form may contain from about 1 mg/kg to about 250 mg/kg, and may given in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that the effective dosage may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. In therapeutic application, compositions of the present invention are provided to a patient already suffering from a disease in an amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically

effective amount". The dosage to be used in the treatment of a specific case must be subjectively determined by the attending physician. The variables involved include the specific condition and the size, age and response pattern of the patient.

5 In some cases it may be desirable to administer the compositions directly to the airways in the form of an aerosol. For administration by intranasal or intrabrochial inhalation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution.

10 The polymorphs according to the invention or compositions containing the polymorphs may be administered parenterally or intraperitoneally. Solutions or suspensions of these compositions may be prepared in water suitably mixed with a surfactant such as hydroxyl-propylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to inhibit the growth of microorganisms.

15 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the  
20 contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

25 The polymorphs of this invention may be administered transdermally, i.e., administered across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compositions in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal). Topical formulations that deliver the compositions through the epidermis may be useful for localized treatment of  
30 inflammation and arthritis.

Transdermal administration may be accomplished through the use of a transdermal patch containing the active composition and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic

absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream, such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The polymorphs of this invention may be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

Lipid formulations or nanocapsules may be used to introduce the compositions of the present invention into host cells either *in vitro* or *in vivo*. Lipid formulations and nanocapsules may be prepared by methods known in the art.

In order to increase the effectiveness of the compositions of the present invention, it may be desirable to combine these compositions with other agents effective in the treatment of the target disease. For inflammatory diseases, other agents effective in their treatment, and particularly in the treatment of rheumatoid arthritis, may be administered with the compounds of the present invention. The other agents may be administered at the same time or at different times than the compositions of the present invention.

## EXAMPLES

The following examples are presented to illustrate certain embodiments of the present invention, but should not be construed as limiting the scope of this invention.

### Example 1: Preparation of polymorph form A

Crude (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyryl)oxy]phenyl)sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide (105 g) was added to a mixture of 368 mL of isopropanol and 158 mL of water. The mixture was warmed to 51-55 °C until all solids

had dissolved and a clear solution was obtained. Water (1.2 L) was added slowly over 1 hour, maintaining the temperature between 51 and 55 °C. The solution was stirred at 51-55 °C for 3 hours, then allowed to cool gradually to 22-24 °C and stirred for an additional 12-16 hours. The solution was then cooled to 5-10 °C and stirred for 1 hour.

- 5 The precipitated solids were filtered and dried in an oven at 50 °C for 72 hours under vacuum to yield 93 g product (85% yield). LC area % 99.3, KF 1.0%, IPA 0.5%; DSC:  $T_{\text{apex}}$  145°C;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  1.45 (d, 6H), 2.52 (m, 1H), 3.07 (m, 2H), 3.9 (m, 2H), 4.14 (s, 2H), 4.37 (s, 2H), 7.12 (d, 2H), 7.71 (d, 2H); HPLC: area 99 %, strength 98 %.

10 **Example 2:** Determination of powder X-ray diffraction patterns

X-ray diffraction data (e.g., Figures 1, 4, 6 and 8) were collected using a Philips X'Pert PW-3040-MPD X-ray diffractometer (Philips, Bothell, WA) set at 40 kV and 40 mA. Data was collected as a continuous scan at 0.02°/sec. between 4° to 40°.

15 **Example 3:** Determination of IR spectra

IR data (e.g., Figures 2, 5, 7 and 9) were collected using a Digilab Excalibur FTS-4000 with Durasampl IR II ATR (Digilab, Randolph, MA) operated at 4  $\text{cm}^{-1}$  resolution and 16 scans between 500-4000  $\text{cm}^{-1}$ . All samples were run in attenuated total reflection (ATR) mode.

20

**Example 4:** Determination of Raman spectra

- Raman spectral data (e.g., Figure 3) were collected using PhAT Systems Optical Spectrophotometer (Kaiser Optical Systems, Inc., (Ann Arbor, MI) including a 785 nm Invictus NIR diode laser, a Raman RXN f/1.8 holographic imaging spectrograph with a 25 1024 CCD detector, and a PhAT probe. The sample was centered in the laser beam for measurement and scanned with an exposure time of 1 minute. Data was collected at 100-1800  $\text{cm}^{-1}$  with a wavenumber resolution of 3.8  $\text{cm}^{-1}$ .

**Example 5:** DSC measurement

- 30 DSC data (e.g., Figure 10) were collected using a TA Instruments DSC 2920 Differential Scanning Calorimeter (TA Instruments, New Castle, DE). Measurements were carried out in both closed pan and open pan modes on about 5-35 mg samples. The heating profile was from 25 °C to 170 °C at 5 °C/min., or 25 °C to 120 °C at

5 °C/min. with a ten minute holding time at 120 °C, 25 °C to 135 °C at 5 °C/min. with a five minute holding time at 135 °C, or 25 °C to 150 °C at 5 °C/min. with a one minute holding time at 150 °C.

5 **Example 6: Formation of polymorph forms C and D**

A micronized sample of apratastat polymorph form A was subjected to three separate DSC experiments performed in the open pan mode as described in Example 5 above using the 120 °C, 135 °C, and 150 °C heating profiles. Each sample was cooled to ambient temperature and then recovered for powder X-ray diffraction (XRD) analysis as described in Example 2. A summary of the XRD results are shown in Table 5 below.

**Table 5**

120 °C	135 °C	150 °C
Form C	Form C	Amorphous

15 A milled sample of apratastat polymorph form A was subjected to similar DSC conditions. A summary of the XRD results are shown in Table 6 below.

**Table 6**

120 °C	135 °C	150 °C
Form C + D	Form C + D	Form D

20 **Example 7: Evaporative crystallization method**

1.5 g of apratastat was dissolved in 20 mL isopropanol with stirring at 30 °C. The solution was distilled at 30 °C and 150 mm Hg vacuum to remove 12 mL isopropanol. The resulting solution was subjected to slow evaporation at 23 °C without stirring over 2 days to obtain a thick slurry. The slurry was filtered and the solid dried at 50 °C under vacuum to obtain 1.38 g of product.

Powder XRD data was collected using a Rigaku Miniflex Diffraction System (Rigaku MSC Inc., The Woodlands, TX) equipped with a Ni K $\beta$  filter. The powder samples were deposited on a zero-background polished silicon sample holder. A normal focus copper x-ray tube was operated at 30kV and 15 mA, and sample

scanning was at 0.02 degree/step from 3.00° to 40.00° at 2 $\theta$ . XRD data consistent with the product is provided in Figure 11 and in Table 7 below.

**Table 7**

<b>Degree (2<math>\theta</math>)</b>	<b>Intensity</b>
7.4	16090
9.7	302
12.1	500
13.6	558
14.0	266
14.8	1436
16.4	680
17.7	588
19.5	740
21.0	644
21.6	894
22.6	1099
23.2	260
24.3	741
24.6	1793
25.6	621
26.1	1943
27.5	184
27.9	1117
29.6	1458
29.9	780
33.3	585
35.8	454
37.6	2684

5

The XRD data for this form differ from that of polymorph form A at least by the presence of the peak at 37.6° and the relative attenuation of the peak at 27.5°.



DSC data was collected for the product using a Q1000 DSC (TA Instruments, New Castle, DE). About 1-5 mg of sample was used in a hermetically sealed aluminum pan (no pin-hole). The sample was heated from 40 °C-200 °C at a ramp rate of 10 °C/min. The DSC profile (Figure 12) indicates two endotherms, one at about 127 °C and another at about 145 °C.

It is intended that each of the patents, applications, and printed publications including books mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

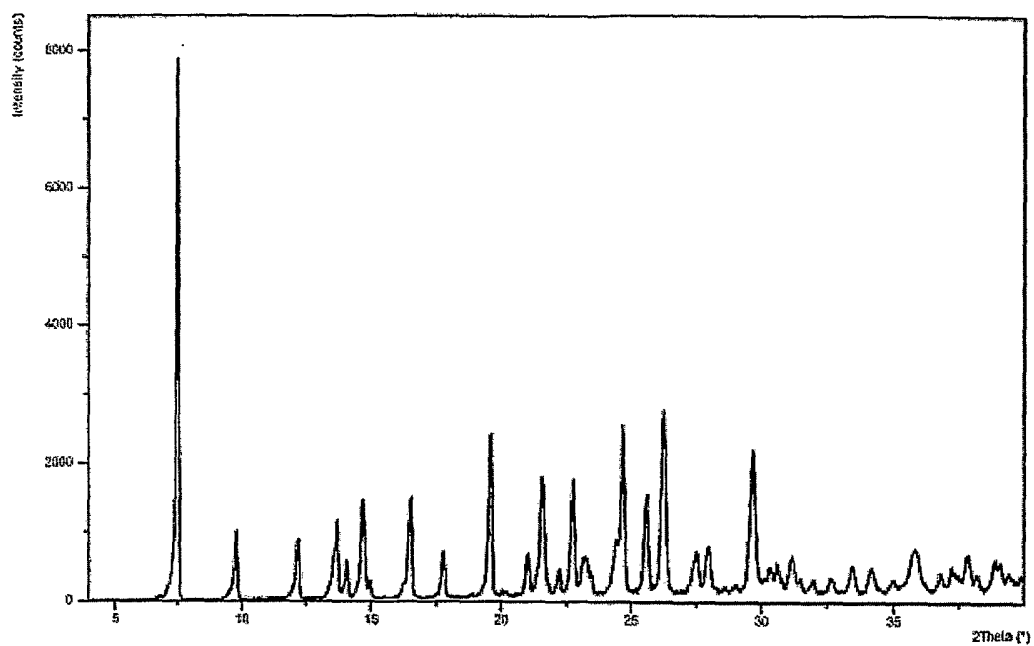
**What is claimed is:**

1. A crystalline polymorph of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyryl)oxy] phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide having a powder X-ray diffraction pattern comprising peaks at diffraction angle  $2\theta$  of about  $7.5^\circ$ ,  $19.6^\circ$ ,  $24.7^\circ$  and  $26.2^\circ$ .
2. The polymorph of claim 1, wherein the X-ray powder diffraction pattern further comprises peaks at diffraction angle  $2\theta$  of about  $14.7^\circ$ ,  $16.5^\circ$ ,  $21.6^\circ$ ,  $22.7^\circ$ ,  $25.6^\circ$  and  $29.7^\circ$ .
3. The polymorph of claim 1 having a powder X-ray diffraction pattern substantially as shown in Figure 1.
4. The polymorph of claim 1 having an attenuated total reflection infrared spectrum substantially as shown in Figure 2.
5. A pharmaceutical composition comprising the polymorph of claim 1 and at least one pharmaceutically acceptable carrier.
6. A method of preparing the polymorph of claim 1, comprising combining (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyryl)oxy] phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide with a solvent comprising an alcohol to form a mixture, wherein the mixture is maintained at a temperature between about  $30^\circ\text{C}$  and about  $80^\circ\text{C}$  for a time and under conditions suitable for forming the polymorph.
7. The method of claim 6, wherein the alcohol is selected from the group consisting of methanol, ethanol, n-propanol, and isopropanol.
8. The method of claim 7, wherein the alcohol is isopropanol.
9. The method of claim 6, wherein the solvent further comprises water.

10. The method of claim 6, wherein the mixture is maintained at a temperature between about 50 °C and about 60 °C.
11. The method of claim 6, further comprising the steps of adding water to the mixture to form a precipitate and collecting the precipitate.
12. A method of treating or inhibiting a disease or disorder mediated by TNF- $\alpha$  in a mammal, said method comprising providing to the mammal a therapeutically effective amount of a polymorph of claim 1.
13. The method of claim 12 wherein the disease or disorder is rheumatoid arthritis, graft rejection, cachexia, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.
14. A method of alleviating a symptom of a disease or disorder mediated by TNF-  $\alpha$  in a mammal, said method comprising providing to the mammal a therapeutically effective amount of a polymorph of claim 1.
15. The method of claim 14 wherein the disease or disorder is rheumatoid arthritis, graft rejection, cachexia, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.
16. A crystalline polymorph of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyne)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide having a powder X-ray diffraction pattern substantially as shown in Figure 4.
17. A crystalline polymorph of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butyne)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide having a powder X-ray diffraction pattern substantially as shown in Figure 6.

18. A crystalline polymorph of (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide having a powder X-ray diffraction pattern substantially as shown in Figure 8.

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**Figure 1**

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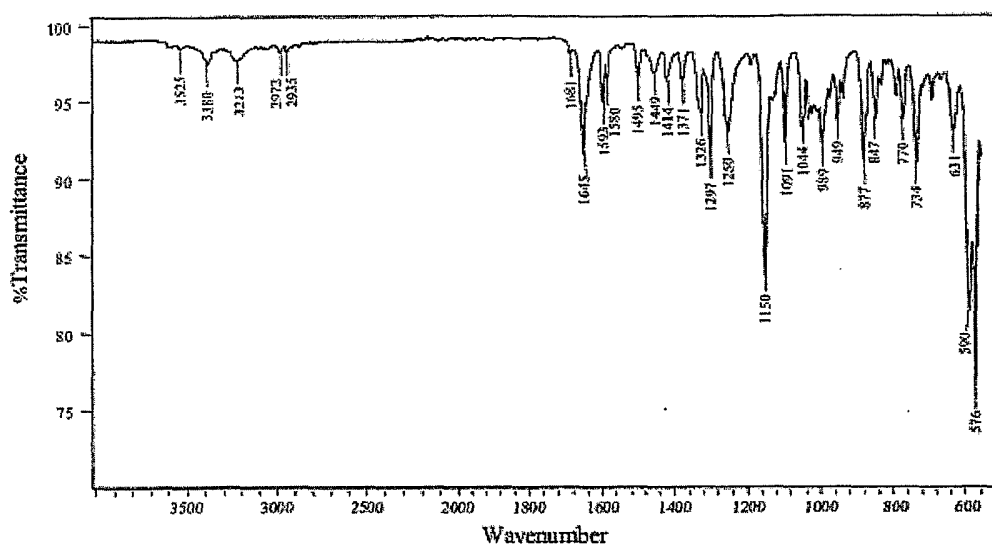
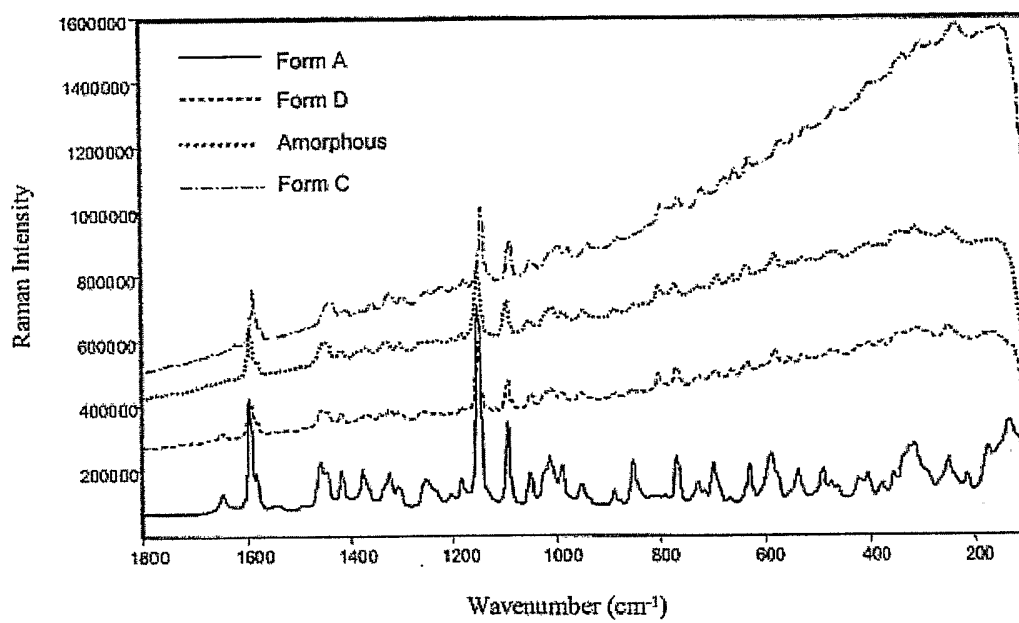


Figure 2

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**Figure 3**

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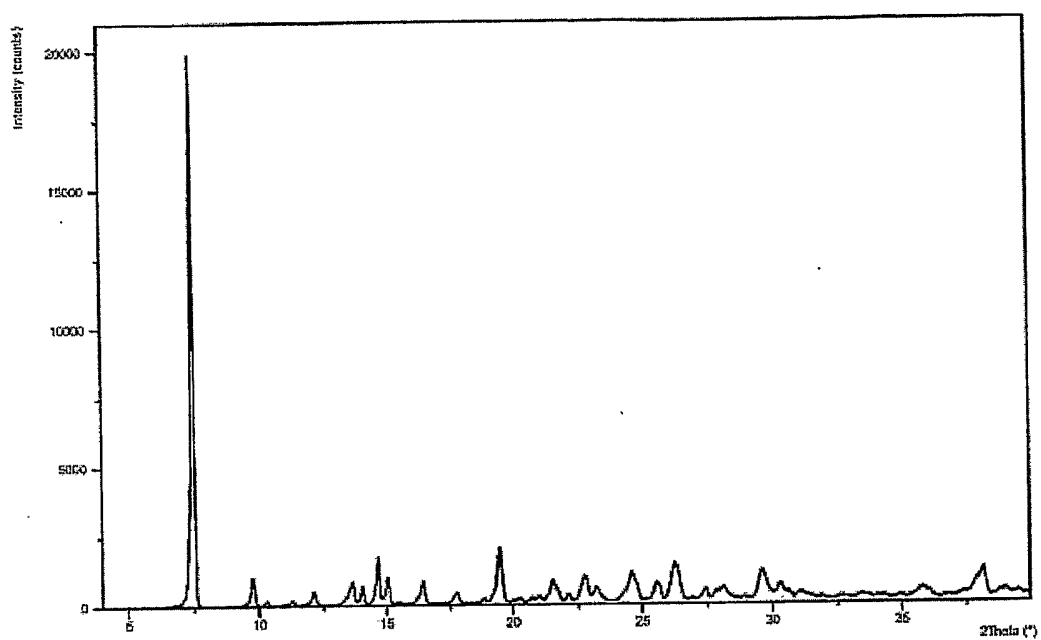


Figure 4



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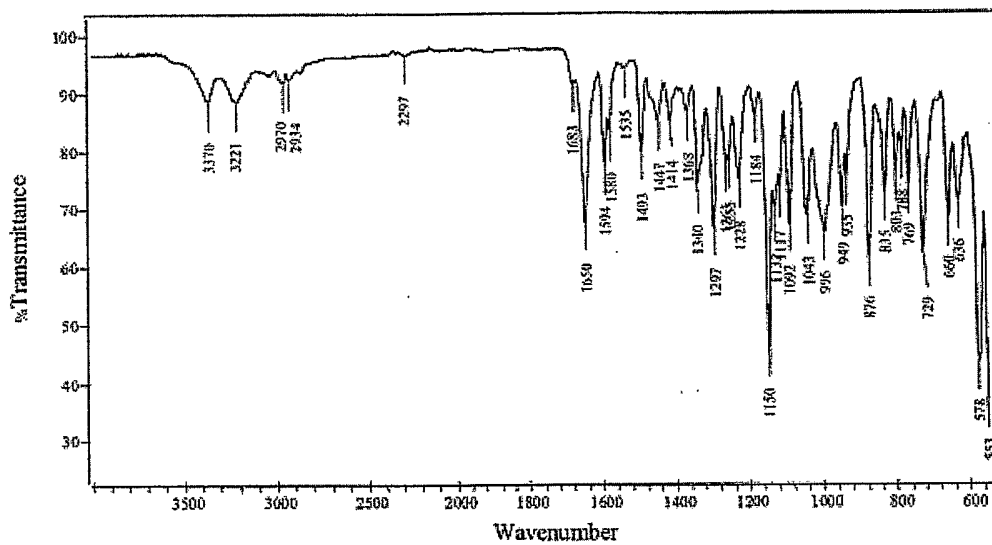


Figure 5

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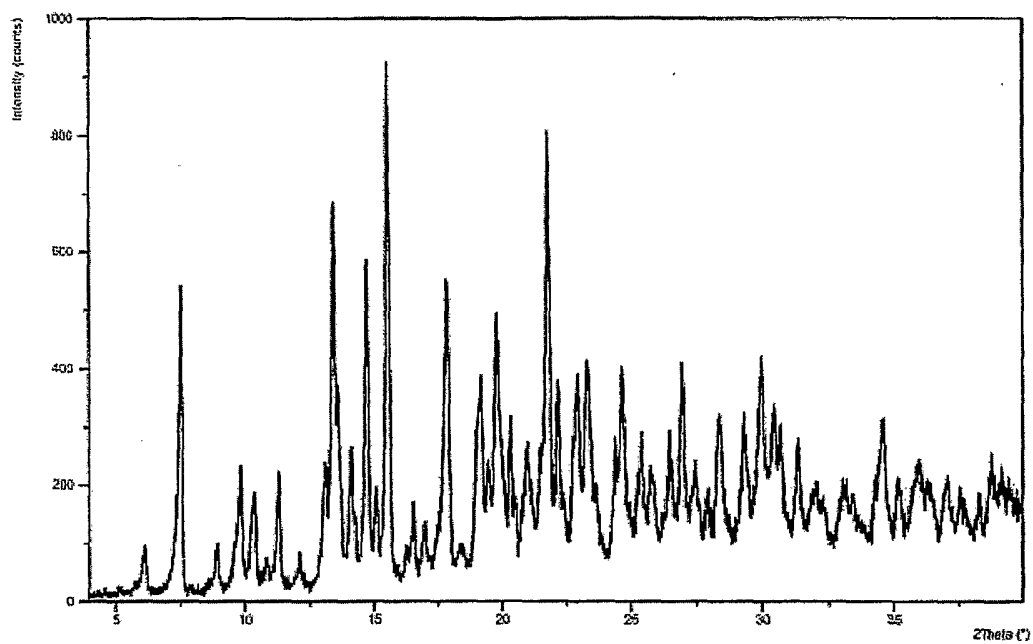


Figure 6

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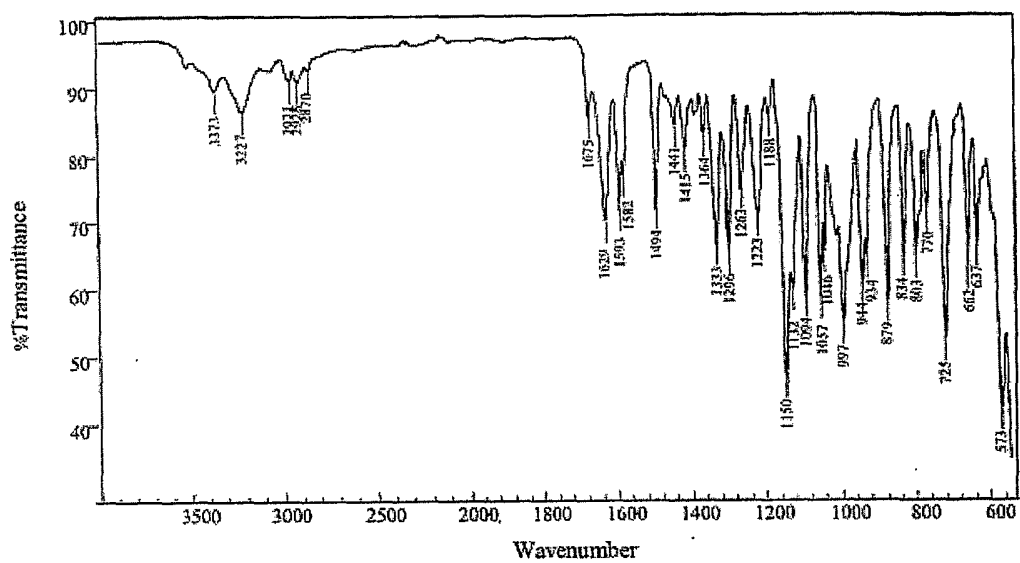


Figure 7

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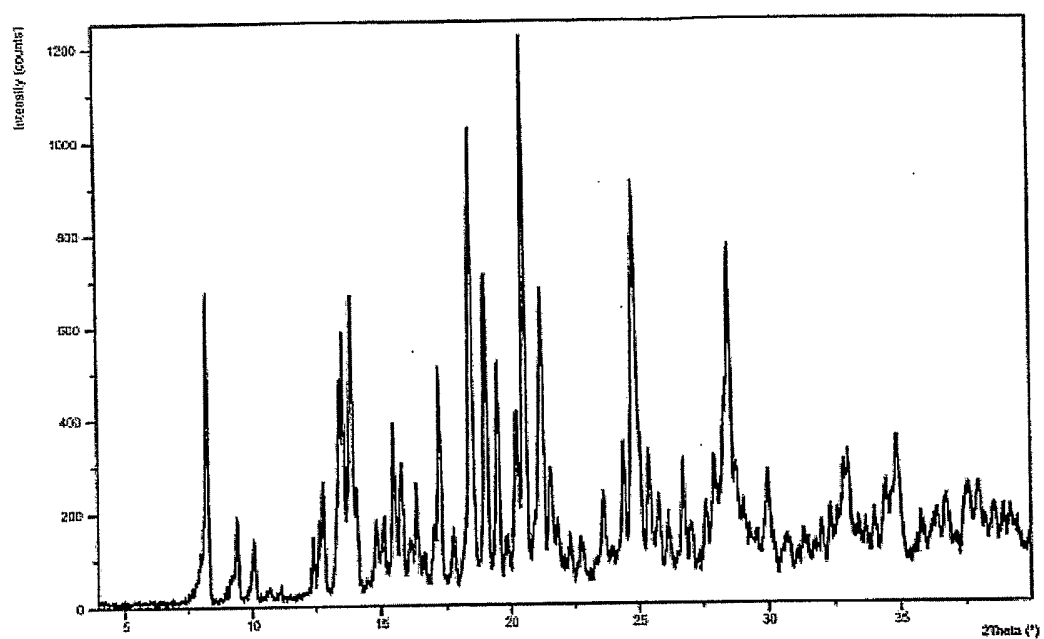


Figure 8

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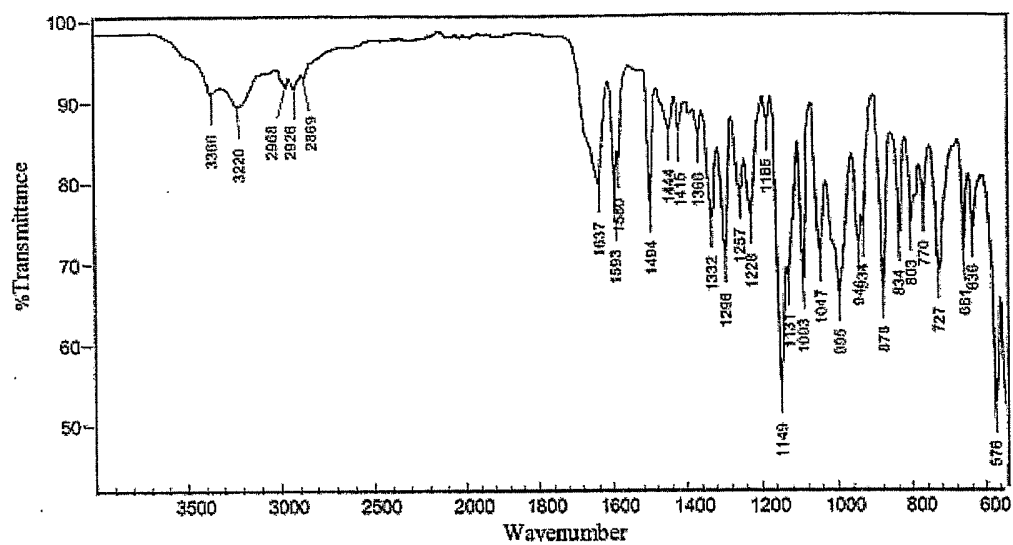


Figure 9

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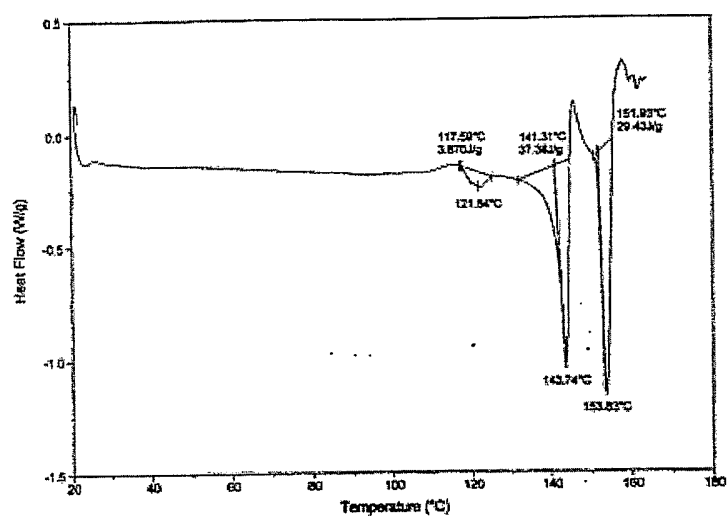


Figure 10

11/12

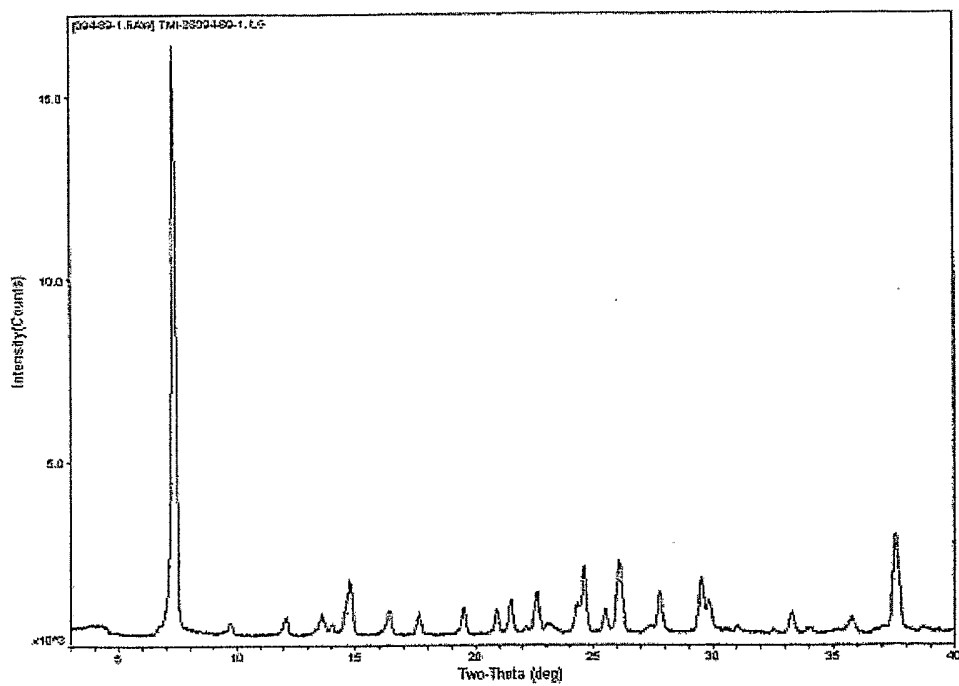


Figure 11

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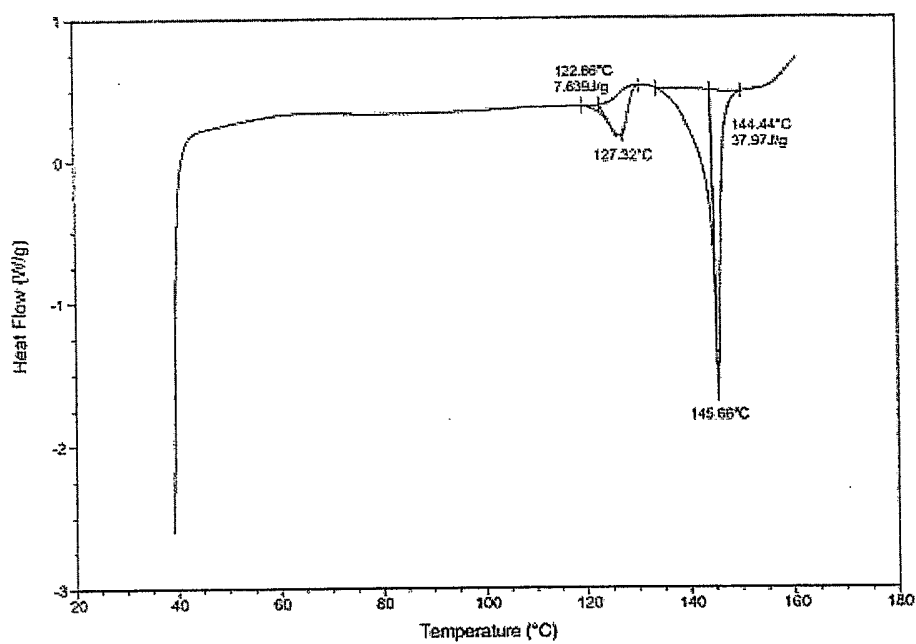


Figure 12



## INTERNATIONAL SEARCH REPORT

Inter

Application No

PCT/US2005/020065

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D279/12

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)

IPC 7 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 practical, 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.
A	WO 02/083112 A (AMERICAN DYANAMID COMPANY; FROST, PHILIP; LEVIN, JEREMY, IAN; WYETH HO) 24 October 2002 (2002-10-24) claim 8	1-18
X	US 6 225 311 B1 (LEVIN JEREMY I ET AL) 1 May 2001 (2001-05-01) cited in the application example 260	1-18
A	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS" TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1998, pages 163-208, XP001156954 ISSN: 0340-1022 the whole document	1-18
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
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- \*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
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- \* & \* document member of the same patent family

Date of the actual completion of the international search

26 October 2005

Date of mailing of the international search report

03/11/2005

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Authorized officer

Deutsch, W

# INTERNATIONAL SEARCH REPORT

Internat. Application No  
PCT/US2005/020065

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BRITAIN ET AL: "Polymorphism in Pharmaceutical Solids passage" 1999, POLYMORPHISM IN PHARMACEUTICAL SOLIDS, PAGE(S) 235-238 , XP002278123 the whole document -----</p>	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No  
PCT/US2005/020065

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 02083112	A	24-10-2002	BR	0208784 A	22-06-2004
			CA	2357110 A1	11-10-2002
US 6225311	B1	01-05-2001	US	2003008849 A1	09-01-2003