

POLYMORPHIC FORM OF N-[(R)-2,3-DIHYDROXY-PROPOXY]-3,4-DIFLUORO-2-(2-FLUORO-4-IODOPHENYLAMINO)-BENZAMIDE

FIELD OF THE INVENTION

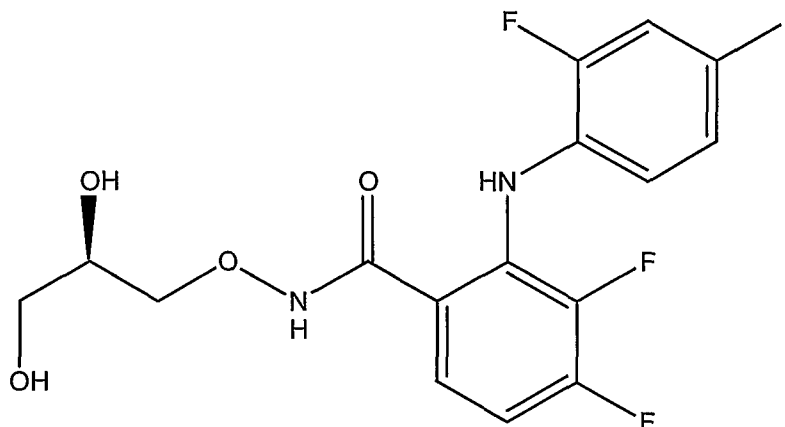
This invention provides a novel polymorphic form IV of *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide, as well as methods of preparing the polymorphic form, as well as pharmaceutical compositions and methods of treatment utilizing the polymorphic form.

BACKGROUND OF THE INVENTION

N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide is described in WO 2002006213 A2 (Barrett et al.) and EP 1262176 A1 (Baragi et al.).

SUMMARY OF THE INVENTION

This invention comprises a novel crystalline polymorph of *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide, having the formula:



that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ at approximately 4.6, 7.2, 14.6, 19.9, 23.2 and 26.5.

This crystalline polymorph of *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide may be further characterized as exhibiting an X-ray powder diffraction pattern having peaks expressed in degrees 2θ at approximately 4.6, 7.2, 14.6, 19.1, 19.9, 20.7, 22.0, 22.2, 23.2, 23.6, 23.9, 25.0, 26.5, 28.1, 28.3, 30.0, 30.4, 32.7, 33.0, 34.1, 36.6, 40.1, 42.1, 43.4 and 44.6.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a Powder X-ray Diffractogram of Form IV *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to 4,000 cps)

DETAILED DESCRIPTION OF THE INVENTION

Additionally, the invention provides a method of treating a proliferative disease in a patient in need thereof comprising administering a pharmaceutically or therapeutically effective amount of this polymorphic form IV of *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide.

The invention also provides the use of a pharmaceutically or therapeutically effective amount of this novel polymorphic form IV of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide for the manufacture of a medicament for the treatment of a proliferative disease.

5 Furthermore, the invention provides methods of treating cancer, restenosis, psoriasis, autoimmune disease, atherosclerosis, osteoarthritis, rheumatoid arthritis, heart failure, chronic pain, and neuropathic pain in a patient in need thereof comprising administering a therapeutically effective amount of polymorphic form IV of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide.

10 Melanomas which may be treated with the methods herein include superficial spreading melanoma, also known as the Clark melanocytic nevus, nodular melanoma, lentigo maligna melanoma (also sometimes called Hutchinson's melanotic freckle), acral lentiginous melanoma, ocular melanomas, including conjunctiva melanoma and uveal (choroidal) melanoma, and less common melanomas, such as malignant melanomas of the oral and
15 genital regions, such as vulval melanoma, and mucosal melanomas, including anorectal melanomas.

The invention also provides the use of a pharmaceutically or therapeutically effective amount of this novel polymorphic form IV of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide for the manufacture of a medicament for the treatment
20 of cancer, restenosis, psoriasis, autoimmune disease, atherosclerosis, osteoarthritis, rheumatoid arthritis, heart failure, chronic pain, and neuropathic pain.

In addition, the invention provides a method for treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of the polymorphic form described herein in combination with radiation therapy or at least one chemotherapeutic
25 agent.

The terms "treating" and "treatment" for purposes of the present invention refer to prophylaxis or prevention, inhibition, amelioration or elimination of a named condition once the condition has been established, as well as the inhibition or prevention of the physiological mechanisms that allow onset and progression of the condition to the point that symptoms or
30 manifestations of the condition become discoverable. The terms "pharmaceutically effective amount" or "therapeutically effective amount", or comparable terms, will be understood to be at least the minimum amount of active pharmacological agent or agents which will provide the onset of treatment or inhibition of a malady or physical condition described herein.

The disclosed compositions are useful as both prophylactic and therapeutic
35 treatments for diseases or conditions related to the hyperactivity of MEK, as well as diseases or conditions modulated by the MEK cascade. Examples include, but are not limited to, stroke, septic shock, heart failure, osteoarthritis, rheumatoid arthritis, organ transplant

rejection, and a variety of tumors such as ovarian, lung, pancreatic, brain, prostatic, and colorectal.

The invention further relates to a method for treating proliferative diseases; such as cancer, restenosis, psoriasis, autoimmune disease, and atherosclerosis. Other aspects of the invention include methods for treating MEK-related (including ras-related) cancers, whether solid or hematopoietic. Examples of cancers include brain, breast, lung, such as non-small cell lung, ovarian, pancreatic, prostate, renal, colorectal, cervical, acute leukemia, and gastric cancer. Further aspects of the invention include methods for treating or reducing the symptoms of xenograft (cell(s), skin, limb, organ or bone marrow transplant) rejection, osteoarthritis, rheumatoid arthritis, cystic fibrosis, complications of diabetes (including diabetic retinopathy and diabetic nephropathy), hepatomegaly, cardiomegaly, stroke (such as acute focal ischemic stroke and global cerebral ischemia), heart failure, septic shock, asthma, Alzheimer's disease, and chronic or neuropathic pain. Compounds of the invention are also useful as antiviral agents for treating viral infections such as HIV, hepatitis (B) virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). These methods include the step of administering to a patient in need of such treatment, or suffering from such a disease or condition, a therapeutically effective amount of a disclosed compound, including crystal forms, or pharmaceutical composition thereof.

The term "chronic pain" for purposes of the present invention includes, but is not limited to, neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism. Chronic pain is associated with numerous conditions including, but not limited to, inflammation, arthritis, and post-operative pain.

As used herein, the term "neuropathic pain" is associated with numerous conditions which include, but are not limited to, inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and nerve injury between the peripheral nervous system and the central nervous system.

The invention also features methods of combination therapy, such as a method for treating cancer, wherein the method further includes providing to a recipient a pharmaceutically effective amount of polymorphic form IV of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in combination with radiation therapy or chemotherapy, for example, with mitotic inhibitors such as a taxane or a vinca alkaloid. Examples of mitotic inhibitors include paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine. Other therapeutic combinations include a MEK inhibitor of the invention and an anticancer agent such as cisplatin, 5-fluorouracil or 5-fluoro-2-4(1H,3H)-pyrimidinedione (5FU), flutamide, and gemcitabine.

The chemotherapy or radiation therapy may be administered before, concurrently, or after the administration of a disclosed compound according to the needs of the patient.

Those skilled in the art will be able to determine, according to known methods, the appropriate therapeutically-effective amount or dosage of a compound of the present invention to administer to a patient, taking into account factors such as age, weight, general health, the compound administered, the route of administration, the type of pain or condition requiring treatment, and the presence of other medications. In general, an effective amount or a therapeutically-effective amount of this polymorphic form IV of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide will be between about 0.1 and about 1000 mg/kg per day, preferably between about 1 and about 300 mg/kg body weight, and daily dosages will be between about 1 and about 500 mg for an adult subject of normal weight, preferably between about 1 mg and 50 mg. As determined by a medical professional, a daily dose range for an adult human may be between about 1 mg and about 20 mg, in a single dosage or in divided doses. Commercially available capsules or other formulations (such as liquids and film-coated tablets) of, for example, 0.25 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

Pharmaceutically useful formulations utilizing *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical composition comprising a pharmaceutically effective amount of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide and a pharmaceutically acceptable carrier. In making the compositions of the present invention, the active ingredient, *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide, will usually be mixed with a carrier, or diluted by a carrier or enclosed within a carrier. Dosage unit forms or pharmaceutical compositions include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses.

Dosage unit forms can be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be

maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

- 5 Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

- 10 Specific examples of oral formulations in hard gelatin capsules may include dosages, for example, from 0.1 mg to 50 mg per capsule. The compositions may include the active drug substance, *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide form IV, a diluent, such as microcrystalline cellulose, and a disintegrant, such as croscarmellose sodium. The composition may also contain a lubricant, such as stearic acid or magnesium stearate.

- 15 Examples of these oral formulations in hard gelatin capsules include those in which the active drug substance comprises from about 0.1-20% of the formulation, by weight, a diluent comprises from about 75-95%, a disintegrant comprises from about 3-7% and, optionally, a lubricant comprises from about 0.1-2%.

- 20 A 0.25 mg capsule may contain from about 0.15 to about 0.25 % *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide form IV, by weight, from about 93-95% microcrystalline cellulose, from about 4-6% croscarmellose sodium and, optionally, from about 0.5-1.5% magnesium stearate.

- 25 A 1 mg capsule may contain from about 0.7 to about 0.85 % *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide form IV, by weight, from about 92.5-95% microcrystalline cellulose, from about 4-6% croscarmellose sodium and, optionally, from about 0.5-1.5% magnesium stearate.

- 30 A 5 mg capsule may contain from about 4% to about 6 % *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide form IV, by weight, from about 87-93% microcrystalline cellulose, from about 4-6% croscarmellose sodium and, optionally, from about 0.5-1.5% magnesium stearate.

- A 25 mg capsule may contain from about 14% to about 17 % *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide form IV, by weight, from about 76-83% microcrystalline cellulose, from about 4-6% croscarmellose sodium and, optionally, from about 0.5-1.5% magnesium stearate.

- 35 Hard gelatin capsule oral formulation of the type just described may be prepared by methods known in the art. An example includes blending and milling the active drug agent with the desired amount of disintegrant, such as croscarmellose sodium, and half the desired

amount of diluent, such as microcrystalline cellulose. The second half of the diluent may then be milled and blended with the first mixture of active agent, diluent and disintegrant and the resulting composition blended. An optional lubricant, such as magnesium stearate, may then be added with additional blending. The total composition may then be measured and placed in hard gelatin capsules. Alternatively, the dry composition may be pressed into slugs using a tablet press, followed by additional milling of the resulting slugs. This final mixture may then be divided into the appropriate dosages and sealed in hard gelatin capsules.

It will be understood that *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide can be readily prepared by methods known in the art. For instance, it may be prepared as described in the methods of WO 2002006213 A2 (Barrett et al.) beginning with the reaction of 2-Fluoro-4-iodo-phenylamine (Registry No. 367-25-9) and 2,3,4-Trifluoro-benzoic acid (Registry No. 61079-72-9) in the presence of an organic base, such as lithium diisopropylamide, to form 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid, which can then be reacted with (*R*)-*O*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine. The resulting product can be hydrolysed with aqueous acid to provide *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide.

COMPARATIVE EXAMPLE 1

***N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form I)**

Step A: To a solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (39.3 g, 100.0 mmol) in dry tetrahydrofuran (500 mL, 0.2 M), under nitrogen atmosphere, was added (*R*)-*O*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (14.7 g, 100.0 mmol), followed by *N*-methymorpholine (27.5 mL, 0.25 mole). The orange-colored solution was cooled with an ice-water bath. Diphenylphosphinic chloride (22.9 mL, 0.12 mole) was added dropwise. Some solid formed. The mixture was warmed to ambient temperature and stirred for 18 hrs. Water was added to quench the reaction and the tetrahydrofuran was evaporated *in vacuo*. The remaining oil was dissolved in ethyl acetate (500 mL), washed with a mixture of saturated brine and saturated sodium bicarbonate (1:1) two times. The ethyl acetate was removed and the crude oily solid was purified by flash chromatography (silica gel, hexane-acetone / 2 : 1) to give *N*-[(*R*)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as an off-white solid after drying in a vacuum oven at 40 °C for 20 hrs: 41.7 g (79.8%), m.p. 124–125 °C. The impure fractions were combined and purified by a second column chromatography using the same condition to give a 2nd batch of 6.4 g (12.3%), mp 124–125 °C, total yield 48.1 g (92.1%). ¹H NMR (d⁶-DMSO): δ 11.9 (s, br, 1H), 8.7 (s, br, 1H), 7.6 (d, 1H, J=10.99 Hz), 7.4 (m, 2H), 7.2 (m, 1H), 6.7 (m, 1H), 4.2 (m, 1H), 4.0 (t, 1H, J1=8.3 Hz, J2=6.8 Hz), 3.8 (m, 2H), 3.7 (m, 1H), 1.3 (s, 3H), 1.2 (s, 3H); ¹⁹F NMR (d⁶-DMSO): δ -128.0, -133.1, -144.3; MS: 523 (M⁺+1).

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Step B: N-((R)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (22.3 g, 42.7 mmol) was suspended in methanol (223 mL, 10mL/g), and a solution of pTsOH·H₂O (4.1 g, 21.35 mmol) in water (22.3 mL) was added. The mixture was stirred at ambient temperature for 18 hrs, during which all solids dissolved to give a colorless, clear solution. The solution was concentrated and extracted with ethyl acetate (2 x 300 mL). The organic solution was washed with sodium bicarbonate, dried over MgSO₄. After filtration, the filtrate was concentrated, and co-evaporated with heptane to give a foaming solid. To this solid was added hexane-CH₂Cl₂ (1 : 1, 100 mL) and the mixture was stirred for 30 min. A white solid formed, which was filtered, washed with hexane. The solid was recrystallized from hexane-AcOEt to give N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as white crystals, 13.57 g (65.9%), after drying at 60 °C vacuum oven for 3 days. A second crop of 5.05 g was obtained from the mother liquor, after recrystallization from the same solvent system. The total yield was 18.62 g (90.4%); m.p. 89-90 °C (Form II of Compound B). The combined crystals were ground with a set of mortar and pestle to fine powder, and dried at 60 °C in a vacuum oven for 3 days: m.p. 117-118 °C (Form I of Compound B); $[\alpha]_D^{25} = -2.05^\circ$ (c=1.12, methanol); Analysis: Calcd. For: C₁₆H₁₄F₃I₂N₂O₄: C, 39.85; H, 2.93; N, 5.81; F, 11.82, I, 26.32. Found: C, 39.95; H, 2.76; N, 5.72; F, 11.71; I, 26.53. ¹NMR (400MHz, DMSO-d₆) δ 11.87 (s, 1H), 8.69 (s, 1H), 7.54 (dd, 1H, J=10.9, 1.5), 7.32-7.38 (m, 2H), 7.17 (dd, 1H, J=16.8, 9.0), 6.61-6.66 (cm, 1H), 4.82 (bs, 1H), 4.58 (bs, 1H), 3.84-3.85 (m, 1H), 3.71-3.64 (cm, 2H), 3.33 (2H, partially hidden by HDO).

COMPARATIVE EXAMPLE 2

N-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form II)

Step A: To a solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (2.25 g, 5.10 mmol) in dry tetrahydrofuran under nitrogen atmosphere, at -15°C was added diphenylphosphinic chloride (1.26 mL, 6.63 mole) dropwise. After stirring 20 min., N-methylmorpholine (0.70 mL, 6.375 mmol) was added and the reaction stirred an additional 20 min. (R)-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (0.748 g, 5.1 mmol) was added and the reaction stirred for 1 hour, at which point N-methylmorpholine (0.7 mL, 6.37 mmol) was added. The mixture was warmed to ambient temperature and stirred for 12 h. The reaction was concentrated in vacuo and then diluted with EtOAc. The organic layer was washed with saturated NaHCO₃ (2x), brine (1x), dried over Na₂SO₄, filtered and concentrated. The crude product was purified on SiO₂ using 4:1 hexane/EtOAc as elutant to provide 1.82g (68%) of a brownish red solid.

Step B: N-((R)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (0.210 g, 0.40 mmol) was suspended in 10:1 methanol/H₂O and pTsOH·H₂O (0.008 g, 0.04 mmol) was added. The mixture was stirred at ambient

temperature for 18 hrs, during which all solids dissolved to give a colorless, clear solution. The solution was diluted with EtOAc. The organic solution was washed with sodium bicarbonate (2x), brine (1x) and dried over Na₂SO₄. After filtration, the filtrate was concentrated, and recrystallized from EtOAc and heptane. This solid was washed with
5 heptane-CH₂Cl₂ (1:1) and dried in vacuo at 60°C to give *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as a white solid, (0.136g, 70%). Product shrinks at 90.8°C, melts at 115-117°C. Analysis shows C 40.92, H 3.16, N 5.41, F 11.30, I 23.92 (6.75% EtOAc, 0.96 % heptane).

- N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-
10 benzamide form IV, can be prepared by a process comprising the steps of:
- a) entering an amount of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide into a volume of a C₁-C₄ lower alkanol and water, the amount of ethanol to water being at a ratio of from about 1:7 to about 1:13, at a temperature of from above about 30°C to about 40°C;
 - 15 b) stirring the components of step a) to create a mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in alkanol and water;
 - c) cooling the mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in alkanol and water to a temperature from about 20°C to
20 less than about 30°C;
 - d) separating the *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide from the alkanol and water.

Within the process parameters discussed above are the steps of preparing polymorphic form IV by:

- 25 a) entering an amount of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide into a volume of a C₁-C₄ lower alkanol and water, the amount of ethanol to water being at a ratio of from about 1:9 to about 1:11, at a temperature of from about 32°C to about 38°C;
- b) stirring the components of step a) to create a mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in alkanol and
30 water;
- c) cooling the mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in alkanol and water to a temperature from about 22°C to about 28°C;
- 35 d) separating the *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide from the alkanol and water.

C₁-C₄ lower alkanols which may be used in this process include methanol, ethanol, propanol, isopropanol, etc., with ethanol being a preferred alkanol. Within the processed described herein is a process in which from about 0.1 to about 5 kg of *N*-[(*R*)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide are mixed in an alkanol and
5 water mixture having a volume of from about 7.5 to about 15 liters.

EXAMPLE 1

N-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form IV)

To a flask containing 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (2.6
10 Kg, 6.6 mol) and *N,N'*-carbonyldiimidazole (1.1 Kg, 6.8 mol) under nitrogen atmosphere, was added 12 L of dry acetonitrile. After stirring at 22° ±5°C for about 90 minutes, a solution of (*R*)-*O*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine in toluene was added (8.5 L total volume, about 8 moles of amine). The solution was stirred for at least 6 hours at 22° ±5 C. Aqueous hydrochloric acid (9 L, 1.5 molar) was added, and after stirring for about 5
15 minutes, the layers were separated. Aqueous hydrochloric acid (9 L, 1.5 molar) was added to the remaining top layer, and after stirring for about 20 hours, the layers were separated. The remaining top layer was concentrated by vacuum distillation, and then diluted with 15 L toluene and 2 L ethanol. The mixture was warmed to 35 - 45°C and diluted with 20 L warm water, then cooled to 0 - 5°C. The product was collected by filtration and washed with 2 L
20 toluene. The product was recrystallized by dissolving in 12 L toluene and 2 L ethanol (50° ±5 C), adding 10 L water and cooling to 0 - 5°C. After collecting the product by filtration and washing with toluene, the product was dried in a vacuum oven resulting in 2.6 Kg of *N*-[(*R*)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide.

2.4 Kg of the above compound as a mixture of different crystalline forms was stirred
25 in a mixture of 10 L water and 1 L ethanol at 35± 5°C for 20-30 hours, then cooled to 25± 5°C. The product was collected by filtration and washed with 1 L of water, then dried in a vacuum oven at 65°C. This resulted in 2.3 Kg of material which was greater than 90% form IV. Note : DSC analysis shows an onset of melting at 110°C with only a small amount of the peak with an onset of melting at 117°C.

30 X-ray diffraction patterns of the crystal form of the present invention were measured on a Rigaku Ultima + diffractometer with CuK_α radiation.

Equipment

Rigaku Ultima + Diffractometer with an IBM-compatible interface equipped with 6 position autosampler, software = RigMeas v2.0 (Rigaku, December 1995) and JADE 3.1
35 (Materials Data, Inc.).

CuK_α radiation (40 mA, 40 kV, λ = 1.5419 Å). Slits I and II at 0.5°, slit III at 0.3°.

Methodology

Continuous $\theta/2\theta$ coupled scan: 3.00° to 45.00° in 2θ , scan rate of $0.2^\circ/\text{min}$: 15.0 sec/ 0.05° step.

5 Sample tapped out of vial and pressed onto zero-background silicon in aluminum holder. Sample width 5 mm.

Samples were stored and run at room temperature.

Samples were spun at 40 rpm around vertical axis during data collection.

10 Table 1 lists the X-ray powder diffraction pattern for crystalline Form IV of Compound A, expressed in terms of the 2-theta (" 2θ "), d-spacings or d(A), and relative intensities by peak area with a relative intensity of $>10\%$ measured on a Rigaku Ultima + diffractometer with CuK_α radiation.

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TABLE 1

	2-Theta	d(A)	Relative Intensity Area %
5	4.577	19.2922	34.8
	7.245	12.1910	16.1
	14.584	6.0686	23.0
	19.091	4.6449	14.5
	19.894	4.4592	14.1
10	20.697	4.2881	16.4
	21.964	4.0434	43.3
	22.245	3.9931	76.5
	23.157	3.8378	100.0
	23.648	3.7592	52.9
15	23.884	3.7226	33.2
	25.006	3.5580	54.7
	26.491	3.3619	57.8
	26.905	3.3110	12.8
	28.103	3.1726	23.4
20	28.296	3.1514	17.2
	29.962	2.9798	13.8
	30.393	2.9385	29.9
	32.653	2.7402	23.1
	33.008	2.7115	25.2
25	34.054	2.6305	20.6
	36.593	2.4536	12.6
	40.093	2.2471	13.8
	42.098	2.1446	20.5
	43.360	2.0851	11.3
30	44.554	2.0320	14.7

WHAT IS CLAIMED:

1. A crystalline polymorph of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ at approximately 4.6, 7.2, 14.6, 19.9, 23.2 and 26.5.
2. A crystalline polymorph of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide of Claim 1 that exhibits an X-ray powder diffraction pattern having peaks expressed in degrees 2θ at approximately 4.6, 7.2, 14.6, 19.1, 19.9, 20.7, 22.0, 22.2, 23.2, 23.6, 23.9, 25.0, 26.5, 28.1, 28.3, 30.0, 30.4, 32.7, 33.0, 34.1, 36.6, 40.1, 42.1, 43.4 and 44.6.
3. A process for making *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide form IV, the process comprising the steps of:
 - a) entering an amount of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide into a volume of ethanol and water, the amount of ethanol to water being at a ratio of from about 1:7 to about 1:13, at a temperature of from about 30°C to about 40°C;
 - b) stirring the the components of step a) to create a mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in ethanol and water;
 - c) cooling the mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in ethanol and water to a temperature from about 20°C to less than about 30°C;
 - d) separating the *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide from the ethanol and water.
4. A product comprising a polymorphic form of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide prepared by the process steps of:
 - a) stirring an amount of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in a volume of ethanol and water, the ethanol and water being in a ratio of from about 1:7 to about 1:13, at a temperature of from above about 30°C to about 40°C;
 - b) stirring the components of step a) for a period of from about 10 to about 48 hours to form a mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in ethanol and water;
 - b) cooling the mixture of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide in ethanol and water to a temperature of between about 20°C to less than about 30°C; and

c) separating the *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide from the ethanol and water.

5. A pharmaceutical formulation comprising a pharmaceutically effective amount of *N*-[(*R*)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide
- 5 form IV and a pharmaceutically acceptable carrier.