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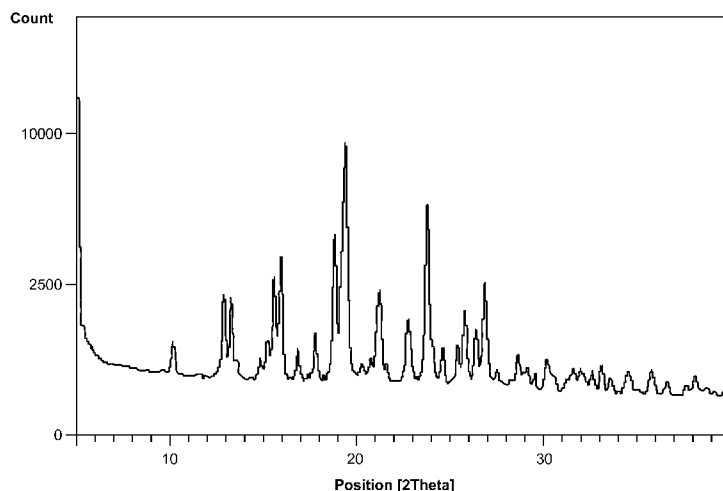


FIG. 1

(57) Abstract: Provided are certain solvates of 3-methoxy-N-[3-(2-methyl-2H-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide or a pharmaceutically acceptable salt thereof. Also provided are pharmaceutical compositions comprising such solvates and methods for their use.

**CRYSTALLINE FORMS OF CERTAIN 3-PHENYL-PYRAZOLE DERIVATIVES AS
MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE
TREATMENT OF DISORDERS RELATED THERETO**

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[0001] This application claims priority to U.S. Provisional Application No. 61/288,130, filed December 18, 2009, which is incorporated herein by reference.

[0002] Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein coupled receptors. Serotonin receptors are divided into seven subfamilies, referred to as 5-HT₁ through 5-HT₇, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT₂ subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. Certain phenyl-pyrazoles are modulators of 5-HT_{2A} serotonin receptor activity useful in the treatment of platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy, and the like.

[0003] Provided is 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate.

[0004] Also provided is (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate.

[0005] Also provided are pharmaceutical compositions comprising one or more pharmaceutically acceptable diluents and a therapeutically effective amount of at least one solvate described herein.

[0006] Also provided are processes for preparing the solvates described herein as well as solvates prepared by the processes.

[0007] Also provided are pharmaceutical compositions prepared by formulating a therapeutically effective amount of at least one solvate described herein with one or more pharmaceutically acceptable carrier to provide the pharmaceutical composition.

[0008] Also provided are methods for modulating the activity of a 5-HT_{2A} serotonin receptor in an individual by administering a pharmaceutical compositions prepared by formulating a therapeutically effective amount of at least one solvate described herein with one or more pharmaceutically acceptable carrier to provide the pharmaceutical composition.

[0009] Also provided are methods for treating a 5-HT_{2A} mediated disorder in an individual by administering a pharmaceutical compositions prepared by formulating a therapeutically effective amount of at least one solvate described herein with one or more pharmaceutically acceptable carrier to provide the pharmaceutical composition.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1 shows powder X-ray diffraction pattern of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate.

[0011] Figure 2 shows differential scanning calorimetry (DSC) and thermogravimetric analyses (TGA) plots for 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate.

[0012] Figure 3 shows representative DSC and TGA plots for (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate.

[0013] Figure 4 shows a proton NMR of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate.

[0014] For clarity and consistency, the following definitions will be used throughout this document.

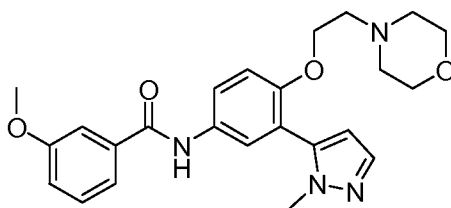
[0015] "Polymorphism" is defined as in the International Conference on Harmonization (ICH) Guideline Q6A Guideline: Specifications for New Drug Substances and Products: Chemical Substances, October 1999 and refers to the occurrence of different solid forms of the same drug substance. Polymorphs can be unsolvated or solvated, such as hydrated, crystal forms. Unsolvated crystal forms are crystals that do not have solvent incorporated within the crystal structure and include anhydrous crystal forms or anhydrites. Solvated crystal forms, or solvates, are crystalline solid adducts containing either stoichiometric or nonstoichiometric amounts of solvent molecules incorporated within the crystal structure. If the incorporated solvent is water, the solvates are also commonly known as hydrates. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice.

[0016] "Pharmaceutically acceptable salt" refers to a pharmaceutically acceptable organic or inorganic acid or base salt. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulinate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate,

hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, 5 einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0017] In addition, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable 10 addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[0018] The term “3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide” refers to a chemical entity with the following structure:



[0019] As used herein, the term “treating” refers to, for example, preventing, inhibiting, as well as ameliorating a disease, condition or disorder in an individual.

[0020] As used herein, the term “individual” or “patient,” used interchangeably, refers to 20 any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[0021] As used herein, the phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, 25 medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an 30 individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology) such as stabilizing viral load in the case of a viral infection; and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as lowering viral load in the case of a viral infection.

5 [0022] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. subcombination. All combinations of the embodiments pertaining to
10 hydrates, as well as all combinations of uses and medical indications described herein, are specifically embraced by the present invention just as if each and every combination was individually explicitly recited. In addition, all subcombinations of the hydrates listed in the embodiments are also specifically embraced by the present invention just as if each and every subcombination of hydrates and subcombination of uses and medical indications was individually
15 and explicitly recited herein.

[0023] Provided is 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate contains water ranging from about 3.5% to about 4.2%, such as about 3.8%, by weight, as measured by TGA.

20 [0024] Provided is (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate contains ethanol ranging from about 5.0% to about 6.0%, such as about 5.3%, by weight, as measured by TGA.

25 [0025] The solvates described herein may be identified by one or more solid state analytical methods. For example, the solvates may be characterized according to one or more of, e.g., X-ray diffraction, unit cell constants, Fourier transform infrared spectroscopy, differential scanning calorimetry curve data, solid state nuclear magnetic resonance spectroscopy, and Raman spectroscopy.

30 [0026] A sample is considered to be a solvate if it is characterized as such by at least one of the methods described herein, regardless of any inconsistent or contradictory results obtained by any of the other methods described above. In addition, a sample is considered to be a solvate if it is characterized as such by at least one of the above methods under a particular set of experimental conditions, regardless of any inconsistent or contradictory results obtained by the
35 same method under a different set of experimental conditions.

[0027] In some embodiments, the solvates described herein may be characterized according to differential scanning calorimetry curve data (DSC). For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by plus or minus about 4 °C.

[0028] In some embodiments, the solvates may be characterized according to melting point. For example, also provided is 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate having a melting endotherm with an onset of about 105±4°C, as measured by differential scanning calorimetry.

[0029] Also provided is an embodiment of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate having a melting endotherm with an onset of about 170±4°C, as measured by differential scanning calorimetry.

[0030] In some embodiments, the thermogravimetric analysis profile of the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate is substantially as shown in Figure 2 wherein by “substantially” is meant that the reported TGA features can vary by about ±5°C.

[0031] In some embodiments, the thermogravimetric analysis profile of the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate is substantially as shown in Figure 3 wherein by “substantially” is meant that the reported TGA features can vary by about ±5°C.

[0032] In some embodiments, the solvates described herein may be characterized according to X-ray powder diffraction. The intensity in the X-ray powder diffraction diagram of different batches of the solvates described herein may vary, because of preferred orientation or even variable hydration. Furthermore, in the X-ray powder diffraction diagram of the solvates described herein, there can be differences in the measured peaks, due to the difference of the measuring instruments and testing conditions during the X-ray diffraction measurement. But notwithstanding experimental and machine errors, and principles such as preferred orientation, one skilled in the art can find sufficient information in the XRPD data provided herein to identify a specific crystalline form. In other words, not all of the data are necessary to identify the crystalline form.

[0033] Owing to natural deviations in the samples or in the measuring method, the 2θ values of the peaks can be stated with an accuracy of +/- 0.2000 degrees 2θ. However, it is common to see some measurement variations in reported data due to, for example, instrumental variations and environmental disturbances, such as preferred orientation, sample surface and inter-apparatus variability, and thus even the same forms of a compound may not exhibit the same exact

5 XRPD data (in terms of D-spacing and peak intensity) all the time. Thus, even when the specific numerical values are not identical in every measurement, if the overall pattern is reproduced and the peak locations and relative peak intensities are sufficiently similar, one of skill in the art, using known and accepted techniques for such evaluation, can conclude that all of the obtained data demonstrate a single crystalline form.

[0034] For example, also provided is an embodiment of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate with an XRPD, measured with CuK α radiation, having peaks chosen from those having about the following values: 5.0998, 18.7064, 19.1157, 19.3029, and 23.6567. Again, those multiple peaks are sufficient but not
10 necessary to identify that specific crystalline embodiment.

[0035] Also provided is an embodiment of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate with an XRPD, measured with CuK α radiation, having peaks chosen from those having about the following values: 5.0998, 12.7991, 15.4771, 15.8201, 18.7064, 19.1157, 19.3029, 21.1196, 23.6567, and 26.7255. Again, those
15 multiple peaks are sufficient but not necessary to identify that specific crystalline embodiment.

[0036] Also provided is an embodiment of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate with an XRPD, measured with CuK α radiation, having one or more peaks chosen from those set forth in Table 1 below. Again, those multiple peaks are sufficient but not necessary to identify that specific crystalline embodiment.

Table 1. PXRD Peaks

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.0998	16685.21	0.1338	17.32837	100.00
10.1034	502.62	0.1171	8.75519	3.01
12.7991	1743.46	0.1506	6.91662	10.45
13.2049	1636.11	0.1338	6.70497	9.81
13.4980	294.04	0.1004	6.56007	1.76
14.7576	235.93	0.1004	6.00284	1.41
15.0902	586.25	0.0836	5.87129	3.51
15.4771	2317.73	0.1338	5.72535	13.89
15.8201	3116.02	0.1673	5.60201	18.68
16.7468	417.97	0.1171	5.29402	2.51
17.6943	789.80	0.1338	5.01264	4.73
18.7064	3916.41	0.1506	4.74364	23.47
19.1157	4737.16	0.0669	4.64298	28.39
19.3029	8968.85	0.1506	4.59837	53.75

Table 1. PXRD Peaks

Pos. [$^{\circ}$ 2Th.]	Height [cts]	FWHM [$^{\circ}$ 2Th.]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
20.2058	232.91	0.1673	4.39490	1.40
20.6138	326.86	0.1171	4.30881	1.96
21.1196	1942.76	0.2676	4.20677	11.64
22.6440	1152.76	0.1506	3.92689	6.91
23.6567	5478.93	0.2007	3.76103	32.84
24.4655	505.78	0.1338	3.63850	3.03
25.2482	568.85	0.1171	3.52745	3.41
25.6649	1398.90	0.1840	3.47111	8.38
26.1913	838.97	0.1840	3.40253	5.03
26.7255	2159.11	0.1506	3.33573	12.94
27.3900	169.35	0.1338	3.25628	1.01
28.4861	412.85	0.1673	3.13344	2.47
29.0404	243.67	0.1673	3.07488	1.46
29.4217	135.96	0.1338	3.03588	0.81
30.0303	374.65	0.2342	2.97573	2.25
30.4984	153.30	0.1004	2.93112	0.92
31.4985	232.22	0.2007	2.84030	1.39
31.8583	235.44	0.1338	2.80904	1.41
32.4897	198.24	0.1338	2.75588	1.19
32.9338	269.98	0.1171	2.71973	1.62
33.4436	128.77	0.1673	2.67942	0.77
34.3265	212.68	0.2342	2.61250	1.27
35.7053	208.51	0.2676	2.51472	1.25
36.5207	92.02	0.2007	2.46042	0.55
37.9565	182.89	0.2342	2.37059	1.10

[0037] In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate contains no more than about 50% of any other polymorphic forms. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate contains no more than about 10% of any other polymorphic forms. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate contains no more than about 5% of any other polymorphic forms. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-

3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate contains no more than about 1% of any other polymorphic forms.

[0038] In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate has a chemical purity of greater than about 95%. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate has a chemical purity of greater than about 98%. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate has a chemical purity of greater than about 99%.

[0039] In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate contains no more than about 50% of any other polymorphic forms. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate contains no more than about 10% of any other polymorphic forms. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate contains no more than about 5% of any other polymorphic forms. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate contains no more than about 1% of any other polymorphic forms.

[0040] In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate has a chemical purity of greater than about 95%. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate has a chemical purity of greater than about 98%. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate has a chemical purity of greater than about 99%.

[0041] Also provided is a method for the preparation of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate or a pharmaceutically acceptable salt thereof.

[0042] 3-Methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate can be prepared by any of the suitable procedures in the art for preparing crystalline polymorphs. In some embodiments, 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate can be prepared by a process comprising:

adding aqueous base to a solution of 4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium chloride; and

collecting the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate.

[0043] In some embodiments, the aqueous base comprises aqueous sodium hydroxide. In some embodiments, the aqueous base comprises 1 N sodium hydroxide. In some embodiments, aqueous base is added until the mixture has a pH of ~8. In some embodiments, the 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate is collected by filtration.

[0044] In some embodiments, the method for the preparation of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate comprises:

adding ethanol and oxalic acid to 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide; and

collecting the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate.

[0045] In some embodiments, the ethanol comprises 95% aqueous ethanol. In some embodiments, less than an equivalent, such as about 0.5 equivalent, of oxalic acid is used. In some embodiments, the (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate is collected by filtration.

[0046] Also provided is a product of any of the methods of preparation described herein.

[0047] In some embodiments, the solvates described herein further comprises a detectable amount of at least one organic solvent. In some embodiments, the at least one organic solvent corresponds to a solvent used during the preparation of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide or a pharmaceutically acceptable salt thereof.

[0048] Provided are compositions comprising at least one solvate described herein. In some embodiments, the compositions described herein comprise at least about 1, about 5, about 10, about 20, about 30, or about 40% by weight of at least one solvate described herein. In some embodiments, the compositions described herein comprise at least about 1, about 5, about 10, about 20, about 30, or about 40% by weight of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate. In some embodiments, the compositions described herein comprise at least about 1, about 5, about 10, about 20, about 30, or about 40% by weight of a hydrate of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate.

[0049] In some embodiments, the solvates described herein have activity as 5-HT_{2A} receptor modulators. Accordingly, the solvates described herein may be used in methods of

modulating the 5-HT_{2A} receptor by contacting the receptor with at least one solvate described herein. In some embodiments, at least one solvate described herein can be used to modulate 5-HT_{2A} receptors in an individual in need of such modulation by administering a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

5 **[0050]** Also provided are methods of treating diseases associated with the 5-HT_{2A} receptor in an individual (e.g., patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of at least one solvate described herein or a pharmaceutical composition thereof. Example diseases can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the 5-HT_{2A} receptor.

10 **[0051]** Example diseases include platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic
15 schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy, and the like.

[0052] Also provided are methods of treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation comprising administering to a patient in need thereof a therapeutically effective amount of at least one solvate
20 described herein or a pharmaceutical composition thereof.

[0053] Also provided are methods of treating a condition associated with platelet aggregation comprising administering to a patient in need thereof a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0054] Also provided are methods of reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to a patient in need
25 thereof a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0055] Also provided are methods of reducing the risk of blood clot formation in an individual suffering from atrial fibrillation comprising administering to a patient a therapeutically
30 effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0056] Also provided are methods of treating a sleep disorder comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0057] Also provided are methods of treating a dyssomnia comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

5 [0058] Also provided are methods of treating a parasomnia comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0059] Also provided are methods of treating a diabetic-related disorder comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

10 [0060] Also provided are methods of treating progressive multifocal leukoencephalopathy comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0061] Also provided are methods of treating hypertension comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a
15 pharmaceutical composition thereof.

[0062] Also provided are methods of treating pain comprising administering to a patient a therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0063] In some embodiments, the above methods further comprise the step of identifying
20 a patient, where the patient is in need of treatment for the particular disease being treated, wherein the identifying step is performed prior to administration to the patient of the therapeutically effective amount of at least one solvate described herein or a pharmaceutical composition thereof.

[0064] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method of treatment of the human or animal body by therapy.

25 [0065] Also provided is a pharmaceutical composition comprising at least one solvate described herein and at least one pharmaceutically acceptable carrier for use in a method of treatment of the human or animal body by therapy.

[0066] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method of treatment of a 5HT_{2A}-related disorder.

30 [0067] Also provided is at least one solvate described herein or a pharmaceutical composition thereof in a method of treatment of platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder,
35 organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic

schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders or progressive multifocal leukoencephalopathy.

[0068] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method of treatment of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke or atrial fibrillation.

[0069] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating a condition associated with platelet aggregation.

[0070] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery.

[0071] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation.

[0072] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating a sleep disorder.

[0073] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating a parasomnia.

[0074] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating a dyssomnia.

[0075] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating a diabetic-related disorder.

[0076] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating progressive multifocal.

[0077] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating hypertension.

[0078] Also provided is at least one solvate described herein or a pharmaceutical composition thereof for use in a method for treating pain.

[0079] Also provided is at least one solvate described herein for the manufacture of a medicament for treating a 5HT_{2A}-related disorder.

[0080] Also provided is at least one solvate described herein for the manufacture of a medicament for treating platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis,

psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy.

5 [0081] Also provided is at least one solvate described herein for the manufacture of a medicament for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

[0082] Also provided is at least one solvate described herein for the manufacture of a medicament for treating condition associated with platelet aggregation.

10 [0083] Also provided is at least one solvate described herein for the manufacture of a medicament for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual.

[0084] Also provided is at least one solvate described herein for the manufacture of a medicament for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation.

15 [0085] Also provided is at least one solvate described herein for the manufacture of a medicament for treating a sleep disorder.

[0086] Also provided is at least one solvate described herein for the manufacture of a medicament for treating a dyssomnia.

20 [0087] Also provided is at least one solvate described herein for the manufacture of a medicament for treating a parasomnia.

[0088] Also provided is at least one solvate described herein for the manufacture of a medicament for treating a diabetic-related disorder.

[0089] Also provided is at least one solvate described herein for the manufacture of a medicament for treating progressive multifocal leukoencephalopathy.

25 [0090] Also provided is at least one solvate described herein for the manufacture of a medicament for treating hypertension.

[0091] Also provided is at least one solvate described herein for the manufacture of a medicament for treating pain.

30 [0092] In addition to the foregoing beneficial uses for the modulators of 5-HT_{2A} receptor activity disclosed herein, the solvates disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

Antiplatelet Therapies (Conditions related to platelet aggregation):

[0093] Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

5 [0094] In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

10 [0095] A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

[0096] Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

15 [0097] Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

20 [0098] Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

[0099] Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

25 [00100] Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the
30 heart and traveling to the brain (embolism).

[00101] 5-HT_{2A} receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see Satimura, K, et al., Clin Cardiol 2002 Jan.
35 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost 1991 Sep 2;66(3):355-60).

[00102] 5-HT_{2A} inverse agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications (see Br. Med. J. 298: 424 – 430, 1989), Arterial thrombosis (see, Pawlak, D. et al. Thrombosis Research 90: 259 – 270, 1998), atherosclerosis (see, Hayashi, T. et al. Atherosclerosis 168: 23 – 31, 2003), vasoconstriction, caused by serotonin (see, Fujiwara, T. and Chiba, S. Journal of Cardiovascular Pharmacology 26: 503 – 510, 1995), restenosis of arteries following angioplasty or stent placement (see, Fujita, M. et al. Am Heart J. 145:e16 2003). It can also be used alone or in combination with thrombolytic therapy, for example, tPA (see, Yamashita, T. et al. Haemostasis 30:321 – 332, 2000), to provide cardioprotection following MI or postischemic myocardial dysfunction (see, Muto, T. et al. Mol. Cell. Biochem. 272: 119-132, 2005) or protection from ischemic injury during percutaneous coronary intervention (see, Horibe, E. Circulation Research 68: 68 – 72, 2004), and the like, including complications resulting therefrom.

[00103] 5-HT_{2A} inverse antagonists can increase circulating adiponectin in patients, suggesting that they would also be useful in protecting patients against indications that are linked to adiponectin, for example, myocardial ischemia reperfusion injury and atherosclerosis (see Nomura, Shosaku, et al. Blood Coagulation and Fibrinolysis 2005, **16**, 423-428).

[00104] The solvates disclosed herein may provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, also provided are methods for reducing platelet aggregation in a patient in need thereof comprising administering to the patient at least one solvate disclosed herein or a pharmaceutical composition thereof. Also provided are methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof.

[00105] Also provided are methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof at a time where such risk exists.

Asthma

[00106] 5-HT (5-hydroxytryptamine) has been linked to the pathophysiology of acute asthma (see Cazzola, M. and Matera, M.G., TIPS, 2000, 21, 13; and De Bie, J.J. et al., British J. Pharm., 1998, 124, 857-864). The solvates described herein may be useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, also provided are methods for treating asthma in a patient in need of the treatment, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof. Also provided are methods for treating a symptom

of asthma in a patient in need of the treatment, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof.

Agitation

5 **[00107]** Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. *J Am Geriatr Soc* 34(10): 711-721).

10 **[00108]** Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 15 11(suppl 2):S45-S50).

[00109] An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia; of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

20 **[00110]** Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia.

[00111] Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., *J Clin Psychiatry* 1999 Feb., 60(2):107-115; and Street, J.S., et al., 25 *Arch Gen Psychiatry* 2000 Oct., 57(10):968-976).

[00112] The solvates described herein may be useful for treating agitation and symptoms thereof. Thus, provided are methods for treating agitation in a patient in need of such treatment comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof. In some embodiments, the agitation is due to a psychiatric disorder other than 30 dementia. Also provided are methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimers disease, Lewy Body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that 35 affect blood vessels, including, without limitation, stroke and multi-infarct dementia. Also provided are methods for treating agitation or a symptom thereof in a patient in need of such treatment, where

the patient is a cognitively intact elderly patient, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof.

Add-On therapy to Haloperidol in the treatment of schizophrenia and other disorders:

[00113] Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (*See*, American Statistical and Diagnostic Handbook).

[00114] Haloperidol (Haldol) is a potent dopamine D₂ receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In some embodiments, adding a 5-HT_{2A} inverse agonist concomitantly with Haldol may provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

[00115] Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5-HT_{2A} inverse agonists disclosed herein with haloperidol also may provide benefits in these indications.

[00116] Also provided are methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient a dopamine D₂ receptor antagonist and at least one solvate described herein or a pharmaceutical composition thereof.

[00117] Also provided are methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising

administering to the patient haloperidol and at least one solvate described herein or a pharmaceutical composition thereof.

[00118] Also provided are methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient a dopamine D₂ receptor antagonist and at least one solvate described herein or a pharmaceutical composition thereof.

[00119] Also provided are methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient haloperidol and at least one solvate described herein or a pharmaceutical composition thereof.

[00120] Also provided are methods for treating schizophrenia in a patient in need of the treatment comprising administering to the patient a dopamine D₂ receptor antagonist and at least one solvate described herein or a pharmaceutical composition thereof. Preferably, the dopamine D₂ receptor antagonist is haloperidol.

[00121] The administration of the dopamine D₂ receptor antagonist can be concomitant with administration of the at least one solvate described herein or a pharmaceutical composition thereof, or they can be administered at different times. Those of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious reduction or elimination of deleterious haloperidol effects. In some embodiments, haloperidol and the at least one solvate described herein or a pharmaceutical composition thereof are administered in a single dosage form, and in other embodiments, they are administered in separate dosage forms.

[00122] Also provided are methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from schizophrenia, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof.

Sleep disorders

[00123] It is reported in the National Sleep Foundation's 2002 Sleep In America Poll, more than one-half of the adults surveyed (58%) report having experienced one or more symptoms of insomnia at least a few nights a week in the past year. Additionally, about three in ten (35%) say they have experienced insomnia-like symptoms every night or almost every night.

[00124] The normal sleep cycle and sleep architecture can be disrupted by a variety of organic causes as well as environmental influences. According to the International Classification of Sleep Disorders, there are over 80 recognized sleep disorders. Of these, at least one solvate described herein or a pharmaceutical composition thereof may be effective, for example, in any one or more of the following sleep disorders (ICSD – International Classification of Sleep Disorders: Diagnostic and

Coding Manual. *Diagnostic Classification Steering Committee*, American Sleep Disorders Association, 1990):

DYSSOMNIAS

Intrinsic Sleep Disorders:

- 5 **[00125]** Psychophysiological insomnia, Sleep state misperception, Idiopathic insomnia, Obstructive sleep apnea syndrome, Central sleep apnea syndrome, Central alveolar hypoventilation syndrome, Periodic limb movement disorder, Restless leg syndrome and Intrinsic sleep disorder NOS.

Extrinsic Sleep Disorders:

- 10 **[00126]** Inadequate sleep hygiene, Environmental sleep disorder, Altitude insomnia, Adjustment sleep disorder, Insufficient sleep syndrome, Limit-setting sleep disorder, SleepOnset association disorder, Nocturnal eating (drinking) syndrome, Hypnotic dependent sleep disorder, Stimulant-dependent sleep disorder, Alcohol-dependent sleep disorder, Toxin-induced sleep disorder and Extrinsic sleep disorder NOS.

15 Circadian Rhythm Sleep Disorders:

- [00127]** Time zone change (jet lag) syndrome, Shift work sleep disorder, Irregular sleep-wake pattern, Delayed sleep phase syndrome, Advanced sleep phase syndrome, Non-24-hour sleep-wake disorder and Circadian rhythm sleep disorder NOS.

PARASOMNIAS

20 Arousal Disorders:

Confusional arousals, Sleepwalking and Sleep terrors.

Sleep-Wake Transition Disorders:

Rhythmic movement disorder, Sleep starts, Sleep talking and Nocturnal leg cramps.

SLEEP DISORDERS ASSOCIATED WITH MEDICAL/PSYCHIATRIC DISORDERS

25 Associated with Mental Disorders:

Psychoses, Mood disorders, Anxiety disorders, Panic disorders and Alcoholism.

Associated with Neurological Disorders:

Cerebral degenerative disorders, Dementia, Parkinsonism, Fatal familial insomnia, Sleep-related epilepsy, Electrical status epilepticus of sleep and Sleep-related headaches.

30 Associated with Other Medical Disorders:

Sleeping sickness, Nocturnal cardiac ischemia, Chronic obstructive pulmonary disease, Sleep-related asthma, Sleep-related gastroesophageal reflux, Peptic ulcer disease, Fibrositis syndrome, Osteoarthritis, Rheumatoid arthritis, Fibromyalgia and Post-surgical.

- [00128]** The effects of sleep deprivation are more than excessive daytime sleepiness.

- 35 Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses (National Institutes of Health, National Heart, Lung, and Blood Institute, *Insomnia Facts Sheet*, Oct.

1995). Preliminary evidence suggests that having a sleep disorder that causes significant loss of sleep may contribute to increased susceptibility to infections due to immunosuppression, cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction, compromised glucose tolerance, increased obesity and metabolic syndrome. The solvates described herein may be useful to prevent or alleviate these complications by improving sleep quality.

[00129] The most common class of medications for the majority of sleep disorders are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on Sleeping Pills and Insomnia in 1984 have developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over drug misuse, dependency, withdrawal and rebound insomnia. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia, which is more effective and/or has fewer side effects than those currently used. In addition, benzodiazepines are used to induce sleep, but have little to no effect on the maintenance of sleep, sleep consolidation or slow wave sleep. Therefore, sleep maintenance disorders are not currently well treated.

[00130] Clinical studies with agents of a similar mechanism of action as those described herein have demonstrated significant improvements on objective and subjective sleep parameters in normal, healthy volunteers as well as patients with sleep disorders and mood disorders [Sharpley AL, et al. Slow Wave Sleep in Humans: Role of 5-HT_{2A} and 5HT_{2C} Receptors. *Neuropharmacology*, 1994, Vol. 33(3/4):467-71; Winokur A, et al. Acute Effects of Mirtazapine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study. *Soc of Biol Psych*, 2000, Vol. 48:75-78; and Landolt HP, et al. Serotonin-2 Receptors and Human Sleep: Effect of Selective Antagonist on EEG Power Spectra. *Neuropsychopharmacology*, 1999, Vol. 21(3):455-66].

[00131] Some sleep disorders are sometimes found in conjunction with other conditions and accordingly those conditions may be treatable by at least one solvate described herein or a pharmaceutical composition thereof. For example, but not limited to, patients suffering from mood disorders typically suffer from a sleep disorder that may be treatable by at least one solvate described herein or a pharmaceutical composition thereof. Having one pharmacological agent which treats two or more existing or potential conditions may be more cost effective, may lead to better compliance and may have fewer side effects than taking two or more agents.

[00132] Also provided are methods for treating Sleep Disorders. Also provided are pharmaceutical agent, which may be useful in treating two or more conditions wherein one of the conditions is a sleep disorder. The solvates described herein may be used alone or in combination with a mild sleep inducer (i.e. antihistamine).

Sleep Architecture:

[00133] Sleep comprises two physiological states: Non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep consists of four stages, each of which is characterized by progressively slower brain wave patterns, with the slower patterns indicating deeper sleep. So called delta sleep, stages 3 and 4 of NREM sleep, is the deepest and most refreshing type of sleep. Many patients with sleep disorders are unable to adequately achieve the restorative sleep of stages 3 and 4. In clinical terms, patients' sleep patterns are described as fragmented, meaning the patient spends a lot of time alternating between stages 1 and 2 (semi-wakefulness) and being awake and very little time in deep sleep. As used herein, the term "fragmented sleep architecture" means an individual, such as a sleep disorder patient, spends the majority of their sleep time in NREM sleep stages 1 and 2, lighter periods of sleep from which the individual can be easily aroused to a Waking state by limited external stimuli. As a result, the individual cycles through frequent bouts of light sleep interrupted by frequent awakenings throughout the sleep period. Many sleep disorders are characterized by a fragmented sleep architecture. For example, many elderly patients with sleep complaints have difficulty achieving long bouts of deep refreshing sleep (NREM stages 3 and 4) and instead spend the majority of their sleep time in NREM sleep stages 1 and 2.

[00134] In contrast to fragmented sleep architecture, as used herein the term "sleep consolidation" means a state in which the number of NREM sleep bouts, particularly Stages 3 and 4, and the length of those sleep bouts are increased, while the number and length of waking bouts are decreased. In essence, the architecture of the sleep disorder patient is consolidated to a sleeping state with increased periods of sleep and fewer awakenings during the night and more time is spent in slow wave sleep (Stages 3 and 4) with fewer oscillation Stage 1 and 2 sleep. The solvates described herein may be effective in consolidating sleep patterns so that the patient with previously fragmented sleep can now achieve restorative, delta-wave sleep for longer, more consistent periods of time.

[00135] As sleep moves from stage 1 into later stages, heart rate and blood pressure drop, metabolic rate and glucose consumption fall, and muscles relax. In normal sleep architecture, NREM sleep makes up about 75% of total sleep time; stage 1 accounting for 5-10% of total sleep time, stage 2 for about 45-50%, stage 3 approximately 12%, and stage 4 13-15%. About 90 minutes after sleep onset, NREM sleep gives way to the first REM sleep episode of the night. REM makes up approximately 25% of total sleep time. In contrast to NREM sleep, REM sleep is characterized by high pulse, respiration, and blood pressure, as well as other physiological patterns similar to those seen in the active waking stage. Hence, REM sleep is also known as "paradoxical sleep." Sleep onset occurs during NREM sleep and takes 10-20 minutes in healthy young adults. The four stages of NREM sleep together with a REM phase form one complete sleep cycle that is repeated throughout the duration of sleep, usually four or five times. The cyclical nature of sleep is regular and reliable; a REM period occurs about every 90 minutes during the night. However, the first REM period tends to be the shortest, often lasting less than 10 minutes, whereas the later REM periods may last up to 40

minutes. With aging, the time between retiring and sleep onset increases and the total amount of night-time sleep decreases because of changes in sleep architecture that impair sleep maintenance as well as sleep quality. Both NREM (particularly stages 3 and 4) and REM sleep are reduced. However, stage 1 NREM sleep, which is the lightest sleep, increases with age.

5 [00136] As used herein, the term "delta power" means a measure of the duration of EEG activity in the 0.5 to 3.5 Hz range during NREM sleep and is thought to be a measure of deeper, more refreshing sleep. Delta power is hypothesized to be a measure of a theoretical process called Process S and is thought to be inversely related to the amount of sleep an individual experiences during a given sleep period. Sleep is controlled by homeostatic mechanisms; therefore, the less one sleeps
10 the greater the drive to sleep. It is believed that Process S builds throughout the wake period and is discharged most efficiently during delta power sleep. Delta power is a measure of the magnitude of Process S prior to the sleep period. The longer one stays awake, the greater Process S or drive to sleep and thus the greater the delta power during NREM sleep. However, individuals with sleep disorders have difficulty achieving and maintaining delta wave sleep, and thus have a
15 large build-up of Process S with limited ability to discharge this buildup during sleep. 5-HT_{2A} agonists tested preclinically and clinically mimic the effect of sleep deprivation on delta power, suggesting that subjects with sleep disorders treated with a 5-HT_{2A} inverse agonist or antagonist will be able to achieve deeper more refreshing sleep. These same effects have not been observed with currently marketed pharmacotherapies. In addition, currently marketed pharmacotherapies
20 for sleep have side effects such as hangover effects or addiction that are associated with the GABA receptor. 5-HT_{2A} inverse agonists do not target the GABA receptor and so these side effects are not a concern.

Subjective and objective determinations of sleep disorders:

[00137] There are a number of ways to determine whether the onset, duration or quality of
25 sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods involve the observation of the patient by another during sleep, e.g., how long it takes the patient to fall asleep, how many times does the patient wake up during the night, how restless is the patient during sleep, etc. Another method is to objectively measure the stages of sleep using polysomnography.

30 [00138] Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of EEG activity, electroculographic activity and electromyographic activity, as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) and sleep consolidation (percent of sleeping
35 time spent in delta-wave or restorative sleep) which may be an indication of the quality of sleep.

[00139] There are five distinct sleep stages, which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific EEG waveforms (sleep spindles and K complexes), occupies about 50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep and delta-wave sleep) are the deepest levels of sleep and occupy about 10-20% of sleep time. REM sleep, during which the majority of vivid dreams occur, occupies about 20-25% of total sleep.

[00140] These sleep stages have a characteristic temporal organization across the night. NREM stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase in duration in response to sleep deprivation. REM sleep occurs cyclically through the night. Alternating with NREM sleep about every 80-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and depth deteriorate across the adult age range. This deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

[00141] In addition, the solvates described herein may be useful for the treatment of the sleep disorders characterized by excessive daytime sleepiness such as narcolepsy. Inverse agonists at the serotonin 5-HT_{2A} receptor improve the quality of sleep at nighttime which can decrease excessive daytime sleepiness.

[00142] Also provided is the therapeutic use of at least one solvate described herein or a pharmaceutical composition thereof for the treatment of Sleep Disorders. The solvates described herein are potent inverse agonists at the serotonin 5-HT_{2A} receptor and may be effective in the treatment of Sleep Disorders by promoting one or more of the following: reducing the sleep onset latency period (measure of sleep induction), reducing the number of nighttime awakenings, and prolonging the amount of time in delta-wave sleep (measure of sleep quality enhancement and sleep consolidation) without effecting REM sleep. In addition, the solvates described herein can be effective either as a monotherapy or in combination with sleep inducing agents, for example but not limited to, antihistamines.

Diabetic-Related Pathologies:

[00143] Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), increased plasma serotonin concentration in diabetic patients has also been implicated to play a role in disease progression (Pietraszek, M.H., et al. *Thrombosis Res.* 1992, 66(6), 765-74; and Andrzejewska-Buczko J, et al., *Klin Oczna.* 1996; 98(2), 101-4).

Serotonin is believed to play a role in vasospasm and increased platelet aggregability. Improving microvascular blood flow is able to benefit diabetic complications.

[00144] A recent study by Cameron and Cotter in *Naunyn Schmiedebergs Arch Pharmacol.* 2003 Jun; 367(6):607-14, used a 5-HT_{2A} antagonist experimental drug AT-1015, and other non-specific 5-HT_{2A} antagonists including ritanserlin and sarpogrelate. These studies found that all three drugs were able to produce a marked correction (82.6-99.7%) of a 19.8% sciatic motor conduction deficit in diabetic rats. Similarly, 44.7% and 14.9% reductions in sciatic endoneurial blood flow and saphenous sensory conduction velocity were completely reversed.

[00145] In a separate patient study, sarogrelate was evaluated for the prevention of the development or progression of diabetic nephropathy (Takahashi, T., et al., *Diabetes Res Clin Pract.* 2002 Nov; 58(2):123-9). In the trial of 24 months of treatment, sarpogrelate significantly reduced urinary albumin excretion level.

Glaucoma

[00146] Topical ocular administration of 5-HT₂ receptor antagonists result in a decrease in intra ocular pressure (IOP) in monkeys (Chang et al., *J. Ocul Pharmacol* 1:137-147 (1985)) and humans (Mastropasqua et al., *Acta Ophthalmol Scand Suppl* 224:24-25 (1997)) indicating utility for similar compounds such as 5-HT_{2A} inverse agonists in the treatment of ocular hypertension associated with glaucoma. The 5-HT₂ receptor antagonist ketanserin (Mastropasqua supra) and sarpogrelate (Takenaka et al., *Investig Ophthalmol Vis Sci* 36:S734 (1995)) have been shown to significantly lower IOP in glaucoma patients.

Progressive Multifocal Leukoencephalopathy

[00147] Progressive multifocal leukoencephalopathy (PML) is a lethal demyelinating disease caused by an opportunistic viral infection of oligodendrocytes in immunocompromised patients. The causative agent is JC virus, a ubiquitous papovavirus that infects the majority of the population before adulthood and establishes a latent infection in the kidney. In immunocompromised hosts, the virus can reactivate and productively infect oligodendrocytes. This previously rare condition, until 1984 reported primarily in persons with underlying lymphoproliferative disorders, is now more common because it occurs in 4% of patients with AIDS. Patients usually present with relentlessly progressive focal neurologic defects, such as hemiparesis or visual field deficits, or with alterations in mental status. On brain MRI, one or more white matter lesions are present; they are hyperintense on T2-weighted images and hypointense on T1-weighted images. There is no mass effect, and contrast enhancement is rare. Diagnosis can be confirmed by brain biopsy, with demonstration of virus by *in situ* hybridization or immunocytochemistry. Polymerase chain reaction amplification of JC virus sequences from the CSF can confirm diagnosis without the need for biopsy [see, e.g., Antinori et al., *Neurology* (1997) 48:687-694; Berger and Major, *Seminars in Neurology* (1999) 19:193-200; and

Portegies, et al., *Eur. J. Neurol.* (2004) 11:297-304]. Currently, there is no effective therapy. Survival after diagnosis is about 3 to 5 months in AIDS patients.

[00148] JC virus enters cells by receptor-mediated clathrin-dependent endocytosis. Binding of JC virus to human glial cells (*e.g.*, oligodendrocytes) induces an intracellular signal that is critical for entry and infection by a ligand-inducible clathrin-dependent mechanism [Querbes et al., *J Virology* (2004) 78:250-256]. Recently, 5-HT_{2A} was shown to be the receptor on human glial cells mediating infectious entry of JC virus by clathrin-dependent endocytosis [Elphick et al., *Science* (2004) 306:1380-1383]. 5-HT_{2A} antagonists, including ketanserin and ritanserin, inhibited JC virus infection of human glial cells. Ketanserin and ritanserin have inverse agonist activity at 5-HT_{2A}.

[00149] 5-HT_{2A} antagonists including inverse agonists have been contemplated to be useful in the treatment of PML [Elphick et al., *Science* (2004) 306:1380-1383]. Prophylactic treatment of HIV-infected patients with 5-HT_{2A} antagonists is envisioned to prevent the spread of JC virus to the central nervous system and the development of PML. Aggressive therapeutic treatment of patients with PML is envisioned to reduce viral spread within the central nervous system and prevent additional episodes of demyelination.

[00150] Also provided are methods for treating progressive multifocal leukoencephalopathy in a patient in need of such treatment, comprising administering to the patient at least one solvate described herein or a pharmaceutical composition thereof.

Hypertension

[00151] Serotonin has been observed to play an important role in the regulation of vascular tone, vasoconstriction, and pulmonary hypertension (see, Deuchar, G. et al. *Pulm. Pharmacol. Ther.* 18(1):23-31. 2005; and Marcos, E. et al. *Circ. Res.* 94(9):1263-70 2004). Ketanserin, a 5-HT_{2A} inverse agonist, have been demonstrated to protect against circulatory shocks, intracranial hypertension, and cerebral ischemia during heatstroke (see, Chang, C. et al. *Shock* 24(4): 336-340 2005); and to stabilize blood pressure in spontaneously hypertensive rats (see, Miao, C. *Clin. Exp. Pharmacol. Physiol.* 30(3): 189-193). Mainserin, a 5-HT_{2A} inverse agonist, has been shown to prevent DOCA-salt induced hypertension in rats (see, Silva, A. *Eur. J. Pharmacol.* 518(2-3): 152-7 2005).

Pain

[00152] 5-HT_{2A} inverse agonists are also effective for the treatment of pain. Sarpogrelate has been observed to provide a significant analgesic effect both on thermal induced pain in rats after intraperitoneal administration and on inflammatory pain in rats after either intrathecal or intraperitoneal administration (see, Nishiyama, T. *Eur. J. Pharmacol.* 516:18-22 2005). This same 5-HT_{2A} inverse agonist in humans has been shown to be an effective treatment for lower back

pain, leg pain and numbness associated with sciatica brought on by lumbar disc herniation (see, Kanayama, M. et al. J. Neurosurg: Spine 2:441-446 2005).

[00153] Also provided are pharmaceutical compositions comprising at least one solvate described herein and one or more pharmaceutically acceptable carriers.

5 **[00154]** In some embodiments, the at least one solvate is administered as a raw or pure chemical.

[00155] Also provided are pharmaceutical compositions comprising 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate and one or more pharmaceutically acceptable carriers.

10 **[00156]** Also provided are pharmaceutical compositions comprising (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate and one or more pharmaceutically acceptable carriers.

[00157] Also provided is a method of producing a pharmaceutical composition comprising admixing at least one solvate described herein and a pharmaceutically acceptable carrier.

15 **[00158]** Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

[00159] Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid
20 preparations. Parenteral dosage forms may be prepared by dissolving at least one solvate described herein in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

[00160] Pharmaceutical compositions may be formulated using techniques well known to
30 those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Ed., 2000, Lippincott Williams & Wilkins, (Editors: Gennaro, A. R., et al.). The carrier(s) is be "acceptable" in the sense of being compatible with the other ingredients of the for compositions and not overly deleterious to the recipient thereof.

[00161] Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug.

Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

[00162] The solvates described herein, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

[00163] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient.

Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethylcellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

[00164] The solvates described herein can be used as active ingredients in pharmaceutical compositions, specifically as 5-HT_{2A} receptor modulators. By the term “active ingredient” is defined in the context of a “pharmaceutical composition” and shall mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an “inactive ingredient” which would generally be recognized as providing no pharmaceutical benefit.

[00165] The dose when using the solvates described herein can vary within wide limits, as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the solvates described herein. Representative doses include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg, and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

[00166] The amount of active ingredient required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, or whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the solvates described herein and as part of a drug combination. The dosage regimen for treating a disease condition with the solvates described herein is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods described herein.

[00167] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are

administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

5 **[00168]** The solvates described herein can be administrated in a wide variety of oral and parenteral dosage forms.

10 **[00169]** For preparing pharmaceutical compositions from the solvates described herein, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

15 **[00170]** In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

20 **[00171]** In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desire shape and size.

25 **[00172]** The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

30 **[00173]** For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

35 **[00174]** Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

40 **[00175]** Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid

preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00176] The solvates described herein may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptically isolating the sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

[00177] Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

[00178] Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

[00179] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[00180] For topical administration to the epidermis the solvates described herein may be formulated as ointments, creams or lotions, or as a transdermal patch.

[00181] Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

[00182] Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

5 [00183] Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

10 [00184] Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the solvates described herein or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered
15 inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the solvates described herein as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the solvates described herein in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the
20 bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

[00185] In formulations intended for administration to the respiratory tract, including
25 intranasal formulations, the solvates described herein will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

[00186] Alternatively the active ingredients may be provided in the form of a dry powder,
30 for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethylcellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

35 [00187] The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active

component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

5 [00188] In some embodiments, tablets or capsules for oral administration and liquids for intravenous administration are used.

[00189] While the solvates described herein can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), they can also be used in combination with other pharmaceutical agents (i.e., combination-therapy) for the treatment of the
10 diseases/conditions/disorders described herein. Accordingly, also provided are methods of treatment of 5-HT_{2A} serotonin receptor mediated disorders comprising administering to an individual in need of such treatment a therapeutically-effective amount of at least one solvate described herein in combination with one or more additional pharmaceutical agent as described herein.

15 [00190] Suitable pharmaceutical agents that can be used in combination with the solvates described herein include other antiplatelet, antithrombotic or anticoagulant drugs, anti-arrhythmic agents, Cholesteryl ester transfer protein (CETP) inhibitors, Niacin or niacin analogs, Adenosine or adenosine analogs, Nitroglycerin or nitrates, prothrombolytic agents, and the like. Other pharmaceutical agents, including the agents set forth *infra*, are well known or will be readily
20 apparent in light of the instant disclosure, to one of ordinary skill in the art.

[00191] The solvates described herein can also be used in combination with other antiplatelet, antithrombotic or anticoagulant drugs such as thrombin inhibitors, platelet aggregation inhibitors such as aspirin, clopidogrel (Plavix®), ticlopidine or CS-747 {i.e., acetic acid 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl
25 ester and its active metabolite R-99224, (Z)-2-[1-[2-cyclopropyl-1(*S*)-(2-fluorophenyl)-2-oxoethyl]-4(*R*)-sulfanylpiperidin-3-ylidene]acetic acid}, abciximab (ReoPro®), eptifibatide (Integrilin®), tirofiban (Aggrastat®), warfarin, low molecular weight heparins (such as LOVENOX), GPIIb/GPIIIa blockers, PAI-1 inhibitors such as XR-330 [i.e., (3*Z*,6*Z*)-3-Benzylidene-6-(4-methoxybenzylidene)-1-methylpiperazine-2,5-dione] and T-686 [i.e., 3(*E*)-
30 Benzylidene-4(*E*)-(3,4,5-trimethoxybenzylidene)pyrrolidine-2,5-dione], inhibitors of α -2-antiplasmin such as anti- α -2-antiplasmin antibody and thromboxane receptor antagonists (such as ifetroban), prostacyclin mimetics, phosphodiesterase (PDE) inhibitors, such as dipyridamole (Persantine®) or cilostazol, PDE inhibitors in combination with thromboxane receptor antagonists/thromboxane A synthetase inhibitors (such as picotamide), serotonin-2-receptor
35 antagonists (such as ketanserin), fibrinogen receptor antagonists, hypolipidemic agents, such as

HMG-CoA reductase inhibitors, e.g., pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, AZ4522, and itavastatin (Nissan/Kowa); microsomal triglyceride transport protein inhibitors (such as disclosed in U.S. Pat. Nos. 5,739,135, 5,712,279 and 5,760,246), antihypertensive agents such as angiotensin-converting enzyme inhibitors (e.g., captopril, lisinopril or fosinopril); angiotensin-II receptor antagonists (e.g., irbesartan, losartan or valsartan); and/or ACE/NEP inhibitors (e.g., omapatrilat and gemopatrilat); β -blockers (such as propranolol, nadolol and carvedilol), PDE inhibitors in combination with aspirin, ifetroban, picotamide, ketanserin, or clopidogrel (Plavix®) and the like.

[00192] The solvates described herein can also be used in combination with anti-arrhythmic agents such as for atrial fibrillation, for example, amiodarone or dofetilide.

[00193] The solvates described herein can also be used in combination with Cholesteryl ester transfer protein (CETP) inhibitors for dislipidemia and atherosclerosis, Niacin or niacin analogs for dislipidemia and atherosclerosis, Adenosine or adenosine analogs for vasodilation, Nitroglycerin or nitrates for vasodilation.

[00194] The solvates described herein can be used in combination with prothrombolytic agents, such as tissue plasminogen activator (natural or recombinant), streptokinase, reteplase, activase, lanoteplase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, and the like. The solvates described herein may also be used in combination with β -adrenergic agonists such as albuterol, terbutaline, formoterol, salmeterol, bitolterol, pilbuterol, or fenoterol; anticholinergics such as ipratropium bromide; anti-inflammatory corticosteroids such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide or dexamethasone; and anti-inflammatory agents such as cromolyn, nedocromil, theophylline, zileuton, zafirlukast, monteleukast and pranleukast.

[00195] Suitable pharmaceutical agents that can be used in combination with solvates described herein include antiretrovirals [see, e.g., Turpin, *Expert Rev Anti Infect Ther* (2003) 1:97-128]. Some embodiments include methods of treatment of progressive multifocal leukoencephalopathy as described herein comprising administering to an individual in need of such treatment a therapeutically effective amount or dose of at least one solvate described herein in combination with at least one pharmaceutical agent selected from nucleoside reverse transcriptase inhibitors (for example, Retrovir®, Epivir®, Combivir®, Hivid®, Videx®, Trizvir®, Zerit®, Ziagen®, Vired®, Emtricitabine, DAPD, and the like), non-nucleoside reverse transcriptase inhibitors (for example, Virammune®, Rescriptor®, Sustiva®, GW687, DPC083, TMC 125, Emivirine, Capravirine, BMS 561390, UC-781 and other oxathiin carboxyanilides, SJ-3366, Alkenyldiarylmethane (ADAM), Tivirapine, Calanolide A, HBY097, Loviride, HEPT Family

Derivatives, TIBO Derivatives, and the like), protease inhibitors (for example, Fortovase[®], Invirase[®], Novir[®], Crixivan[®], Viracep[®], Ageberase[®], Kaletra[®], Atazanavir, Tipranavir, DMP450, and the like), inhibitors of HIV-cell interaction (for example, soluble CD4, toxin-conjugated CD4, monoclonal antibodies to CD4 or gp120, PRO 542, dextran sulfate, Rersobene, FP-23199, 5 Cyanovirin-N, Zintevir (T30177, AR177), L-chicoric acid and derivatives, and the like), coreceptor inhibitors ligands (for example, R5, X4, modified ligands (R5), modified ligands (X4), and the like), coreceptor inhibitors X4 (for example, T22, T134, ALX40-4C, AMD3100, bycyclam derivatives, and the like), coreceptor inhibitors R5 (for example, TAK-779, SCH-C (SCH-351125), SCH-D (SCH-350634), NSC 651016, ONO Pharmaceutical, Merck, and the like), 10 fusion inhibitors (for example, Fuzeon[®] (T-20, DP 178, enfuvritide) trimeris, T-1249, TMC125, and the like), integrase inhibitors (for example, 5CITEP, L731,988, L708,906, L-870,812, S-1360, and the like), NCp7 nucleocapsid Zn finger inhibitors (for example, NOBA, DIBA, dithianes, PD-161374, pyridinioalkanoyl thioesters (PATES), azodicarbonamide (ADA), cyclic 2,2 dithio bisbenzamide, and the like), RNase H inhibitors (for example, BBHN, CPHM PD-26388, and the 15 like), Tat inhibitors (for example, dominant negative mutants, Ro24-7429, Ro5-3335, and the like), Rev inhibitors (for example, dominant negative mutants, Leptomycin B, PKF050-638, and the like), transcriptional inhibitors (for example, Temacrazine, K-12 and K-37, EM2487, and the like), inhibitors of HIV assembly/maturation (for example, CAP-1 and CAP-2, and the like), and pharmaceutical agents directed to cellular anti-HIV targets (for example, LB6-B275 and 20 HRM1275, Cdk9 inhibitors, and the like).

[00196] In a certain embodiment, a solvates described herein can be used in conjunction with highly active antiretroviral therapy (HAART). When antiretroviral drugs are used in combinations of three or four drugs, this treatment is called HAART [*see, e.g., Portegies, et al., Eur. J. Neurol.* (2004) 11:297-304].

25 **[00197]** In some embodiment, the combination of a solvate described herein and pharmaceutical agent can be prepared by mixing the respective active components either all together or independently with a pharmaceutically acceptable carrier, excipient, binder, diluent, etc. as described herein, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition(s). When a solvate described herein is administered as a combination 30 therapy with another active compound each can be formulated as separate pharmaceutical compositions given at the same time or at different times. Alternatively, in some embodiments, pharmaceutical compositions comprise at least one solvate described herein and the pharmaceutical agent(s) as a single pharmaceutical composition.

[00198] In some embodiments, a method of producing a pharmaceutical composition for 35 "combination-therapy" comprises admixing at least one solvate described herein, together with at

least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

[00199] It is noted that when the 5-HT_{2A} receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as 5-HT_{2A} receptor modulators, for the treatment of a 5-HT_{2A} mediated disease or disorder in domestic animals (e.g., cats and dogs) and in other livestock animals (e.g., such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such solvates described herein in such settings.

[00200] For the avoidance of any doubt, it is understood that those embodiments which refer to methods of treatment or other uses of the solvates described herein further embrace pharmaceutical compositions comprising the solvates described herein, as well as combinations of other pharmaceutical agents with solvates and pharmaceutical compositions described herein.

[00201] The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

EXAMPLE 1

4-(2-(4-(3-Methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium chloride

[00202] Anhydrous 4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium chloride can be prepared as described in WO 2007/136689.

[00203] A slurry of anhydrous 4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium chloride in water was stirred at ambient/stir plate temperature (about 26-28° C) for ~3 days. The anhydrous form was recovered.

EXAMPLE 2

3-Methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate

[00204] 100 mg of 4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium chloride were added to 3 mL of H₂O in a 4 mL vial. The solution was stirred until it became clear. 225 µL of 1 N NaOH was added to the vial to reach a

pH of ~8. A white precipitate formed. The solution was stirred for 1 hour at room temperature. The crystalline materials formed on the side of the vial were scraped off, and the solution was filtered using centrifuge tube filters. The material was dried overnight in the hood.

[00205] The sample was characterized by an X'Pert PRO MPD powder diffractometer (PANalytical, Inc.; EQ0233) with a Cu source set at 45 kV and 40 mA, Cu(K α) radiation and an X'Celerator detector. Briefly, samples were added to a sample holder and smoothed flat with a spatula and weigh paper. While the samples were spinning, X-ray diffractograms were obtained by a 12-minute scan over the (2 θ) range 5-40°.

[00206] Figure 1 shows the PXRD pattern of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate and Table 1 above shows a list of peaks of PXRD pattern of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate collected by X'Pert HighScore software.

[00207] Differential scanning calorimetry (DSC) studies were conducted using a TA Instruments, Q2000 (EQ0090 or EQ1980) at heating rate 10°C/min from ~25° C to ~270° C. The instruments were calibrated by the vendor for temperature and energy using the melting point and enthalpy of fusion of an indium standard. Thermal events (desolvation, melting, etc.) were evaluated using Universal Analysis 2000 software, version 4.1D, Build 4.1.0.16.

[00208] Thermogravimetric analyses (TGA) were conducted using a TA Instruments TGA Q500 (EQ0089) or Q5000 (EQ1982) at heating rate 10°C/min. The instruments were calibrated by the vendor for temperature using Alumel and Nickel standards (Curie points) and for weight using a standard weight. Thermal events such as weight-loss are calculated using the Universal Analysis 2000 software, version 4.1D, Build 4.1.0.16.

[00209] The DSC and TGA plots of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate are shown in Figure 2. The TGA thermogram shows that the onset of weight loss event occurred at ~ 41° C at 10° C/min. The weight loss of 3.8% as shown on the TGA thermogram suggests about one mole of H₂O was loss (theoretical value is 4.0%). The DSC thermogram shows a broad endotherm peak at between 50 ~ 90° C that is consistent with the loss of H₂O from dehydration. The DSC thermogram also shows an apparent recrystallization exotherm after the dehydration, and a melting endotherm with an onset of ~105° C.

EXAMPLE 3

(4-(2-(4-(3-Methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium Carboxyformate Ethanol Solvate

[00210] To a 1-liter jacketed reactor equipped with an overhead stirrer, nitrogen inlet and bottom drain valve was charged, *N*-(4-hydroxy-3-(1-methyl-1*H*-pyrazol-5-yl)phenyl)-

methoxybenzamide (35.0 g, 108 mmol), ethyl hydroxymorpholine (29.8 g, 227 mmol) and triphenylphosphine (59.6 g, 227 mmol). The reaction was cooled to -8 °C (jacket) and diisopropyl azodicarboxylate (46.0 g, 227 mmol) was added at -6 to 5 °C, over 30 min. The reaction was then allowed to warm to 25 °C and stirred for approximately 3 days. The reaction was cooled again to -5 °C and ethyl hydroxymorpholine (0.1 eq.), triphenylphosphine (0.1 eq.) and diisopropyl azodicarboxylate (0.1 eq.) were added. After 25 min, the reaction was warmed to 25 °C. The reaction mixture was divided in seven aliquots, approximately equal by weight. One such aliquot was concentrated, the residue was taken up in ethanol (95%) and oxalic acid (1.46 g, 0.5 eq.) was added. The mixture was stirred overnight at 20-25 °C during which time a precipitate formed. The mixture was filtered at room temperature for 1.5 h and the solid was dried to give the title compound (5.49 g).

[00211] Representative DSC and TGA plots of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate are shown in Figure 3. The TGA thermogram of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate shows two primary weight loss events occurred prior to the degradation of the free base. The first weight loss event is consistent with the loss of approximately 0.59 moles of ethanol; the second weight loss event suggests about 0.5 moles of oxalic acid was lost.

[00212] A proton NMR of (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium carboxyformate ethanol solvate is shown in Figure 4.

[00213] Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

What is claimed is:

1. A solvate of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide or a pharmaceutically acceptable salt thereof that is 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide hydrate.
5
2. A solvate of 3-methoxy-*N*-[3-(2-methyl-2*H*-pyrazol-3-yl)-4-(2-morpholin-4-yl-ethoxy)-phenyl]-benzamide or a pharmaceutically acceptable salt thereof that is (4-(2-(4-(3-methoxybenzamido)-2-(1-methyl-1*H*-pyrazol-5-yl)phenoxy)ethyl)morpholin-4-ium
10 carboxyformate ethanol solvate.
3. A pharmaceutical composition comprising at least one solvate of claim 1 and at least one pharmaceutically acceptable carrier.
- 15 4. A pharmaceutical composition comprising at least one solvate of claim 2 and at least one pharmaceutically acceptable carrier.
5. A method of treating a 5HT_{2A}-related disorder comprising administering to a patient in need thereof a therapeutically effective amount of at least one solvate of claim 1 or claim 2.
20
6. The method according to claim 5 wherein the 5HT_{2A}-related disorder is selected from platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la
25 Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders and progressive multifocal leukoencephalopathy.
7. The method according to claim 6 wherein the 5HT_{2A}-related disorder is a condition
30 associated with platelet aggregation.
8. A method of treating a 5HT_{2A}-related disorder comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 3 or 4.

9. The method according to claim 8 wherein the 5HT_{2A}-related disorder is selected from platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la
5 Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders and progressive multifocal leukoencephalopathy.

10. The method according to claim 9 wherein the 5HT_{2A}-related disorder is a condition
10 associated with platelet aggregation.

11. The solvate of claim 1 or 2 for use in a method of treatment of the human or animal body by therapy.

12. The pharmaceutical composition of claim 3 or 4 for use in a method of treatment of the
15 human or animal body by therapy.

13. The solvate of claim 1 or 2 for use in a method of treatment of a 5HT_{2A}-related disorder.

14. The solvate of claim 1 or 2 for use in a method of treatment of platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute
25 schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders or progressive multifocal leukoencephalopathy.

15. The solvate of claim 1 or 2 for use in a method for treating a condition associated with platelet aggregation.

30

16. The pharmaceutical composition of claim 3 or 4 for use in a method of treatment of a 5HT_{2A}-related disorder.

17. The pharmaceutical composition of claim 3 or 4 for use in a method of treatment of
35 platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack,

angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders or progressive multifocal leukoencephalopathy.

18. The pharmaceutical composition of claim 3 or 4 for use in a method for treating a condition associated with platelet aggregation.

10 19. Use of the solvate of claim 1 or 2 for the manufacture of a medicament for treating a 5HT_{2A}-related disorder.

20. The use according to claim 19, wherein said 5HT_{2A}-related disorder is selected from platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders and progressive multifocal leukoencephalopathy.

20

21. The use according to claim 20, wherein said 5HT_{2A}-related disorder is a condition associated with platelet aggregation.

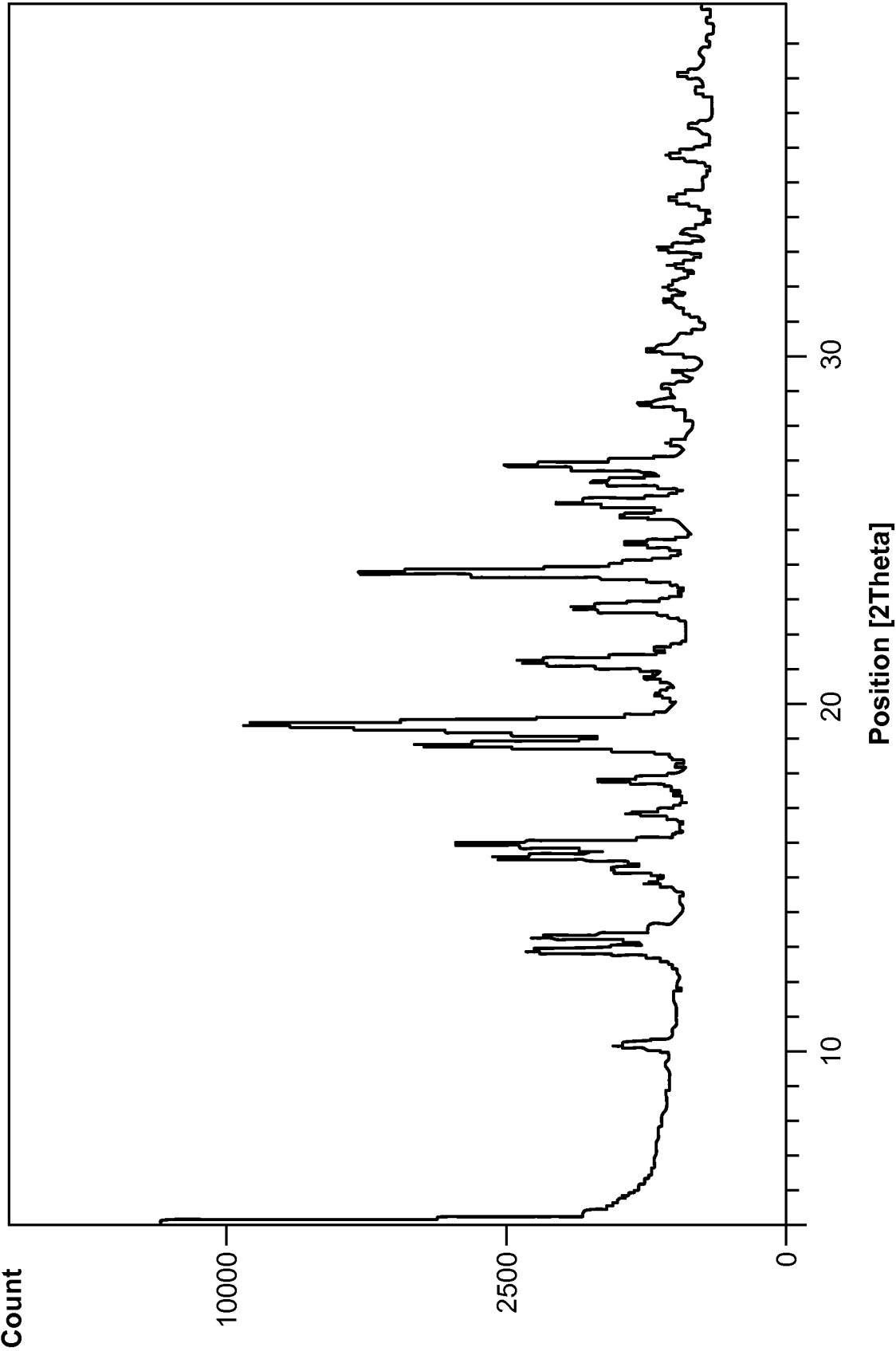


FIG. 1

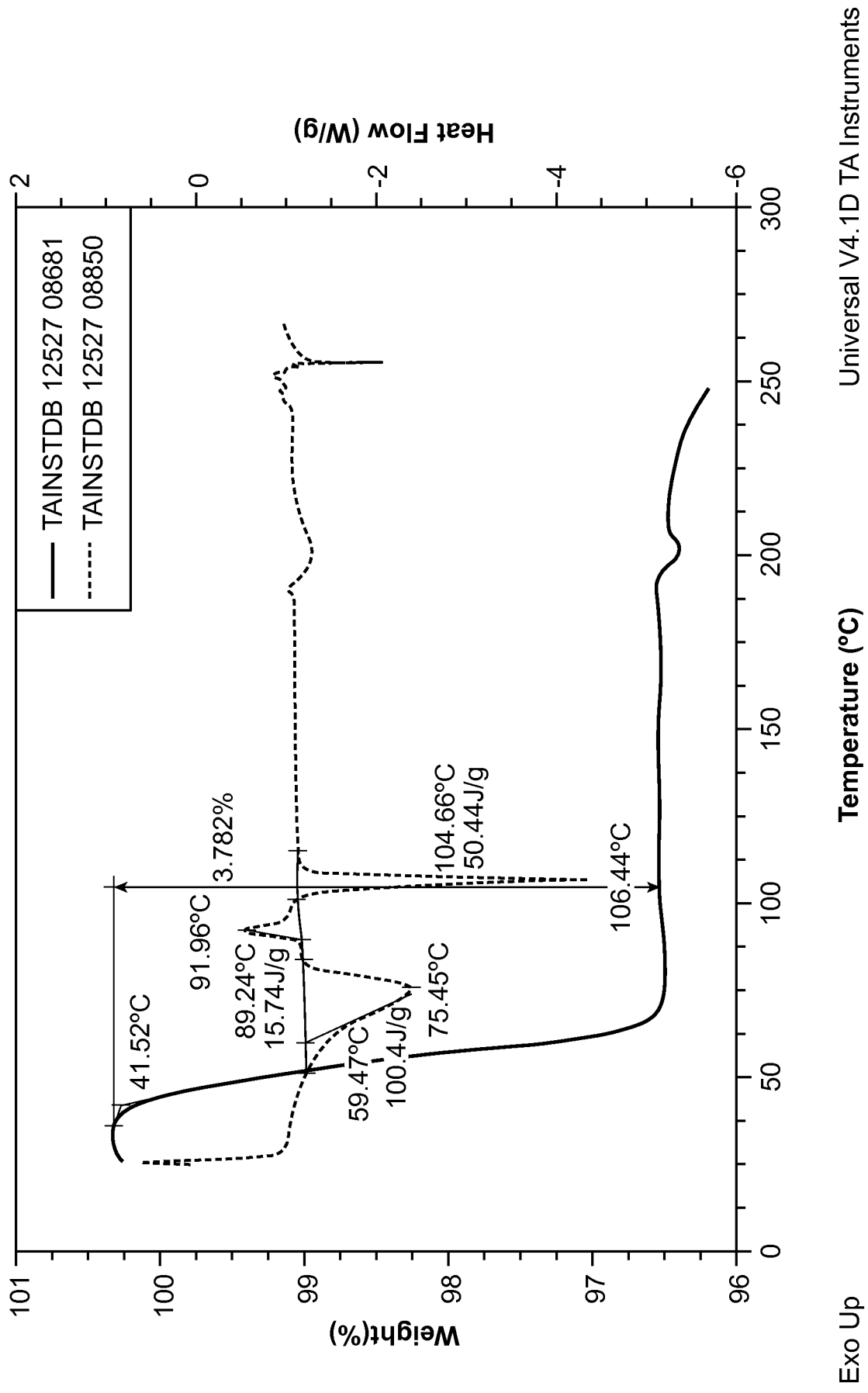


FIG. 2

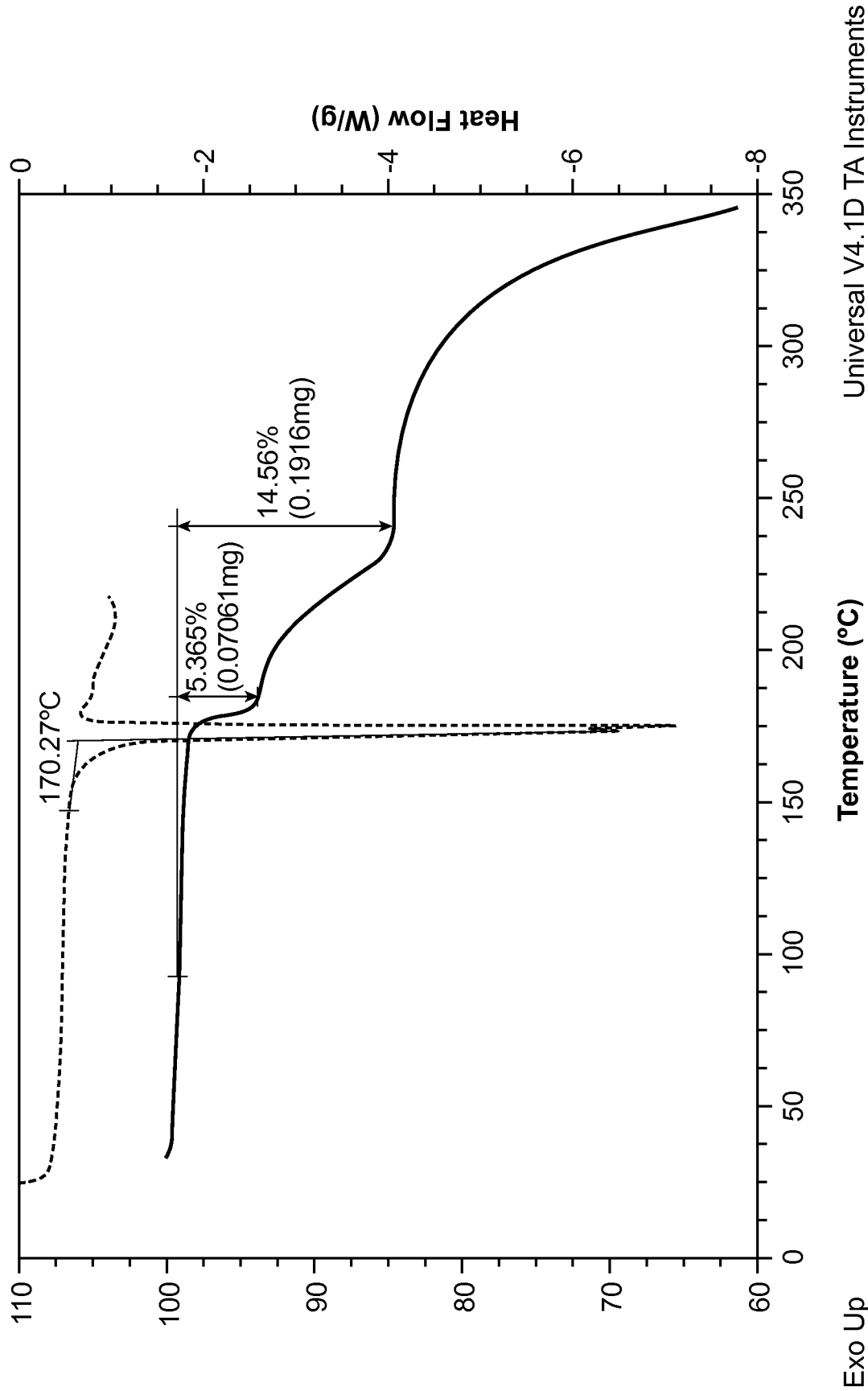


FIG. 3

4 / 4

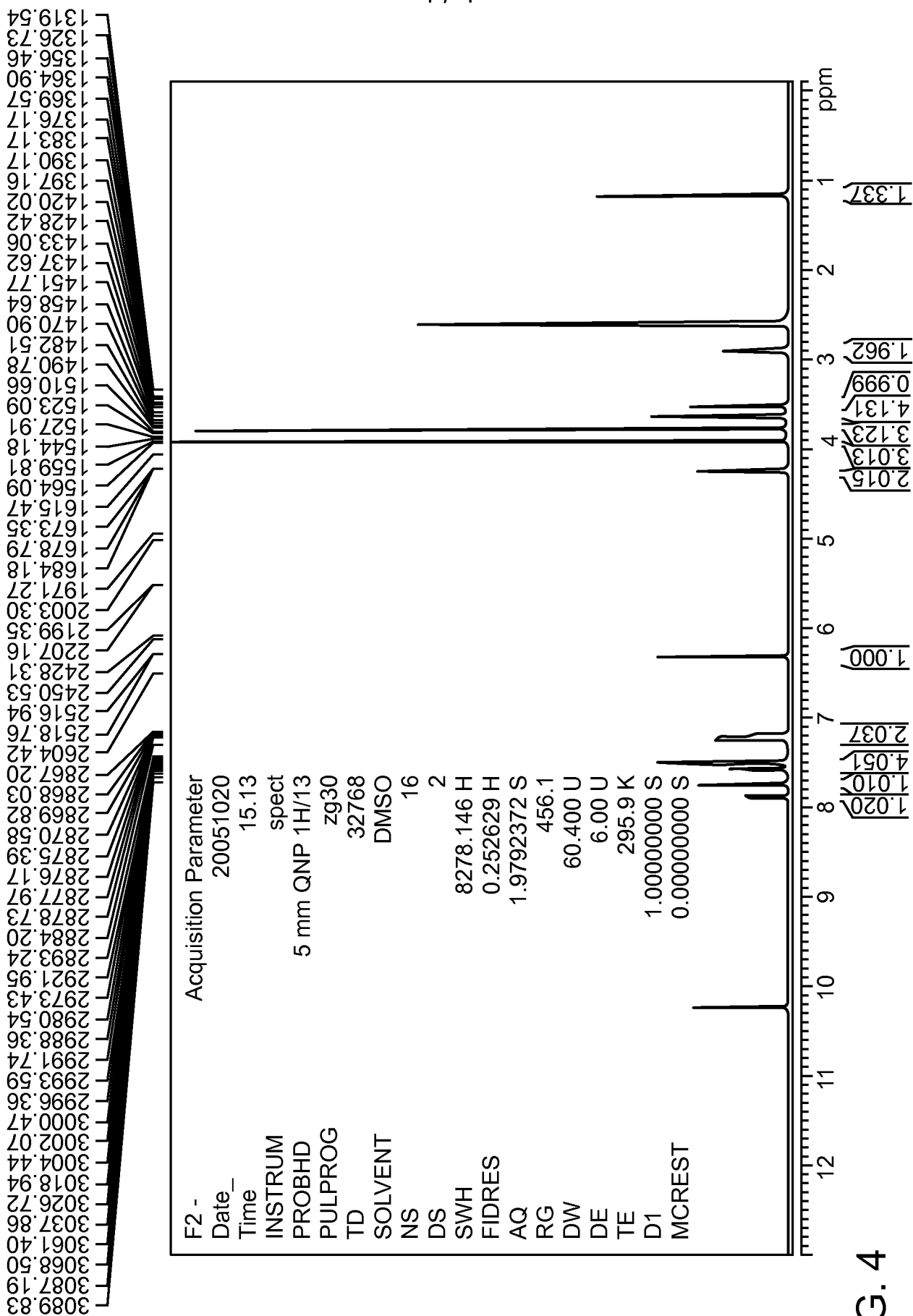


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/060848

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D231/12	A61K31/415
	A61P11/06	A61P7/02
ADD.	A61P25/18	A61P25/30
		A61P9/10
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/244086 A1 (TEEGARDEN BRADLEY [US] ET AL) 18 October 2007 (2007-10-18) page 34; compound 733 page 35, paragraph 381 claims 27-33	1-21
A	WO 2007/136689 A2 (ARENA PHARM INC [US]; GHARBAOUI TAWFIK [US]; SENGUPTA DIPANJAN [US]; K) 29 November 2007 (2007-11-29) examples 6,12	1,3,5-21
☐ Further documents are listed in the continuation of Box C. ☒ See patent family 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 "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
5 April 2011		13/04/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/060848

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/060848

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007244086	A1	18-10-2007	AR 051675 A1 31-01-2007
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			EP 2018372 A2 28-01-2009
			JP 2009537544 T 29-10-2009
			KR 20090009244 A 22-01-2009
			US 2010234380 A1 16-09-2010

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 3(completely); 5-21(partially)

hydrates of
3-methoxy-N-[3-(2-methyl-2H-pyrazol-3-yl)-4-(2.morpholin-4-y
l-ethoxy)-phenyl]benzamide and its salts

2. claims: 2, 4(completely); 5-21(partially)

ethanol solvate of
3-methoxy-N-[3-(2-methyl-2H-pyrazol-3-yl)-4-(2.morpholin-4-y
l-ethoxy)-phenyl]benzamide and its salts
