1,3,4-thiadiazol-2-yloxy)-1-azatricyclo [3.3.1.1^{3,7}] decane dihydrogen citrate (Compound A) solid recovered from a suspension having a water activity of 0.05.

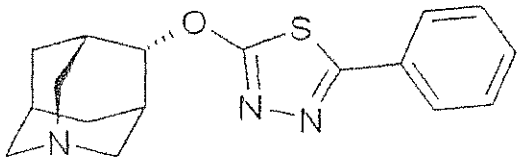
Figure 4(f) illustrates the X-ray powder diffraction pattern for a formulation consisting of substantially pure crystalline anhydrous *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}] decane dihydrogen citrate (Compound A).

SUMMARY ~~OF THE INVENTION~~

The compounds of the '336 publication were subjected to a thorough salt screening to determine primary compounds of interest. In the process of testing the salt compositions, the dihydrogen citrate anhydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo [3.3.1.1^{3,7}]decane was identified as a compound of particular interest due to favorable solid state properties, pharmaceutical properties, and manufacturing properties. In view of these favorable characteristics, *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo [3.3.1.1^{3,7}]decane dihydrogen citrate was selected for additional analysis, including polymorph screening and polymorph analysis. Accordingly, the current invention is directed to the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo [3.3.1.1^{3,7}]decane dihydrogen citrate and related methods and processes thereof.

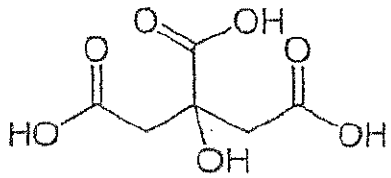
In a first aspect, there is provided a crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-

azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate, wherin the *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane is represented by formula (I)



(I);

and wherein the dihydrogen citrate is represented by formula (II)



(2)

(II).

In a second aspect, there is provided a crystalline monohydrate as defined herein for use in treating or preventing conditions,

disorders, or deficits modulated by α7 nicotinic acetylcholine receptors, α4β2 nicotinic acetylcholine receptors, or both α7 and α4β2 nicotinic acetylcholine receptors wherein the condition, disorder, or deficit is selected from the group consisting of a memory disorder, cognitive disorder, neurodegeneration, and neurodevelopmental disorder.

In a third aspect, there is provided a crystalline monohydrate as defined herein for use of treating or preventing a condition or

disorder selected from the group consisting of infertility, lack of circulation, need for new blood vessel growth associated with wound healing, need for new blood vessel growth associated with vascularization of skin grafts, ischemia, inflammation, arthritis and related disorders, wound healing, and complications associated with diabetes.

In a fourth aspect, there is provided a process for preparing a crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate, the process comprising the steps of:

(a) dissolving *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane in at least one solvent at a temperature ranging from approximately 65° C to approximately 85° C;

(b) adjusting the temperature of the solution to a temperature ranging from approximately 55° C to approximately 75° C;

(c) adding at least one additional solvent to the solution and mixing;

(d) adjusting the temperature of the solutions to a temperature ranging from approximately 30° C to approximately 50° C;

(e) adding at least one additional solvent to the solution;

(f) maintaining the slurry at a temperature ranging from approximately 30° C to approximately 50° C;

(g) adjusting the temperature of the slurry to a temperature ranging from approximately -5° C to approximately 15° C;

(h) mixing the slurry for at least one hour; and

(i) recovering the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate.

In a fifth aspect, there is provided a process for preparing a crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate the process comprising the steps of:

(a) dissolving *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane in approximately 4 volumes of 2-propanol and approximately 1 volume of water at a temperature of approximately 75° C;

(b) adjusting the temperature of the solution to a temperature ranging from approximately 65° C;

(c) adding approximately 6 volumes of 2-propanol to the solution and mixing;

(d) adjusting the temperature to approximately 40° C;

(e) adding approximately 5 volumes of 2-propanol to the solution;

(f) maintaining the slurry at a temperature of approximately 40° C;

(g) adjusting the temperature of the slurry to a temperature of approximately 5° C;

(h) mixing the slurry; and

(i) recovering the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane.

In a sixth aspect, there is provided a process for preparing a crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate, the process comprising the steps of:

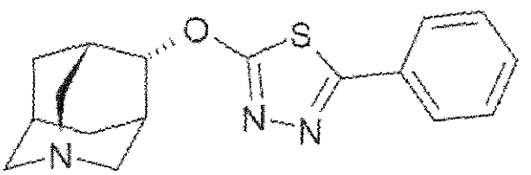
(a) contacting anhydrous *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate with a solvent in a reaction vessel;

(b) sealing the reaction vessel and protecting the suspension from light at ambient conditions; and

(c) recovering the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane.

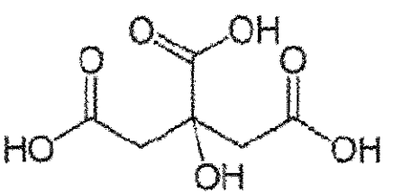
In a seventh aspect, there is provided a pharmaceutical composition comprising the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate as an active ingredient and a pharmaceutically acceptable carrier, diluent, or excipient.

One embodiment of the ~~invention~~disclosure relates to the crystalline salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane having formula (I)



(I);

wherein the salt comprises dihydrogen citrate having formula (II)



(II)

In an additional embodiment, the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate has a purity of at least 90% of the monohydrate form and not greater than 10% of the non-monohydrate form. In yet an additional embodiment, the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate has a purity of at least 95% of the monohydrate form and not greater than 5% of the non-monohydrate form. In still yet a further additional embodiment, the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate has a purity of at least 97% and not greater than 3% of the non-monohydrate form.

In a further embodiment, the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate demonstrates at least one characteristic peak in the powder X-ray diffraction pattern at values in degrees two theta of 8.4 ± 0.20, 11.3 ± 0.20, 14.2 ± 0.20, 15.5 ± 0.20, 16.4 ± 0.20, 16.6 ± 0.20, 17.2 ± 0.20, 19.7 ± 0.20, 20.7 ± 0.20, 21.0 ± 0.20, 21.2 ± 0.20, 21.6 ± 0.20, 24.8 ± 0.20, and 26.9 ± 0.20.

In yet another embodiment, the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate of claim 1, has unit cell parameters wherein a is about 6.52 Å, b is about 20.99 Å, c is about 16.83 Å, α is about 90.0°, β is about 93.75°, γ is about 90.0°, the volume is about 2297.52 Å^3, and Z is about 4.

In another embodiment, the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate exhibits non-hygroscopic qualities when evaluated by dynamic moisture sorption gravimetry, having a weight loss of less than approximately 0.2% from relative humidities of 0% to 90%.

Another embodiment of the ~~invention~~disclosure relates to pharmaceutical compositions comprising compounds of the ~~invention~~disclosure. Such compositions can be administered in accordance with a methods of the ~~invention~~disclosure, typically as part of a therapeutic regimen for treatment or prevention of conditions and disorders related to nAChR activity, and more particularly α7 nAChR activity, α4β2 nAChR activity, or both α7 nAChR activity and α4β2 nAChR activity.

Yet another embodiment of the ~~invention~~disclosure relates to a method of modulating both α7 and α4β2 nAChR activity. The method is useful for treating, preventing or both treating and preventing conditions and disorders related to both α7 and α4β2 nAChR activity, particularly in mammals.

A further embodiment of the ~~invention~~disclosure relates to a method of selectively modulating nAChR activity, for example α7 nAChR activity. The method is useful for treating, preventing or both treating and preventing conditions and disorders related to α7 nAChR activity in mammals. A method of selectively modulating α4β2 nAChR activity also is contemplated.

Such methods are useful for conditions and disorders related to attention deficit disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), schizophrenia, mild cognitive impairment, age-associated memory impairment (AAMI), senile dementia, AIDS dementia, Pick's disease, dementia associated with Lewy bodies, dementia associated with Down's syndrome, schizophrenia, smoking cessation, nicotinic withdrawal syndrome, amyotrophic lateral sclerosis, Huntington's disease, diminished CNS function associated with traumatic brain injury, acute pain, post-surgical pain, chronic pain, inflammatory pain, neuropathic pain, infertility, lack of circulation, need for new blood vessel growth associated with wound healing, more particularly circulation around a vascular occlusion, need for new blood vessel growth associated with vascularization of skin grafts, ischemia, inflammation, sepsis, wound healing, and other complications associated with diabetes, among other systemic and neuroimmunomodulatory activities.

An additional embodiment of the ~~invention~~disclosure relates to a method for producing the crystalline monohydrate salt of the current ~~invention~~disclosure, using a dihydrogen citrate anhydrate salt as the starting material. Specifically, the process for preparing a crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.$1^{3,7}$]decane dihydrogen citrate the process comprises the steps of: (a) dissolving *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.$1^{3,7}$]decane in at least one solvent at a temperature ranging from approximately 65° C to approximately 85° C; (b) adjusting the temperature of the solution to a temperature ranging from approximately 55° C to approximately 75° C over a period of at least thirty minutes; (c) adding at least one additional solvent to the solution and mixing for a period of at least thirty minutes; (d) adjusting the temperature of the solutions to a temperature ranging

Further, step (i) may comprise recovering the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo [3.3.1.1^{3,7}] decane dihydrogen citrate by filtration.

In another embodiment, the current ~~invention~~disclosure comprises a process for preparing a crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate the process comprising the steps of: (a) dissolving *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane in approximately 4 volumes of 2-propanol and approximately 1 volume of water at a temperature of approximately 75° C; (b) adjusting the temperature of the solution to a temperature ranging from approximately 65° C over a period of at least thirty minutes; (c) adding approximately 6 volumes of 2-propanol to the solution and mixing for a period of at least thirty minutes; (d) adjusting the temperature to approximately 40° C over a period greater than two hours; (e) adding approximately 5 volumes of 2-propanol to the solution over a period of not less than three hours; (f) maintaining the slurry at a temperature of approximately 40° C for a period of at least one hour; (g) adjusting the temperature of the slurry to a temperature of approximately 5° C; (h) mixing the slurry for at least one hour; and (i) recovering the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane.

In an alternative embodiment, the current ~~invention~~disclosure also comprises a process for preparing a crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate, the process comprising the steps of: (a) contacting anhydrous *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate with a solvent in a reaction vessel; (b) sealing the reaction vessel and protecting the suspension from light at ambient conditions; and; and (c) recovering the crystalline monohydrate salt of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane.

According to this method, the solvent of step (a) may comprise water. Additionally, the amount of anhydrous *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate may comprise approximately 100 mg to approximately 300 mg, and the amount of water may comprise approximately 0.1 mL to approximately 2.0 mL. In a further preferred embodiment, the amount of anhydrous *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane dihydrogen citrate comprises approximately 150 mg to approximately 250 mg, and wherein the amount of water comprises approximately 0.8 mL to approximately 1.2 mL. One skilled in the art

will also appreciate that the solvent of step (a) may comprise a mixture of an organic solvent and water. Moreover, the organic solvent may comprise methanol, ethanol, 2-propanol, butanol, butanol acetonitrile, acetone, formamide, dimethyl formamide, toluene, benzene, anisole, ethyl acetate, isopropyl acetate, tetrahydrofuran, 1,4-dioxane, methyl tert-butyl ether, dichloromethane, chloroform, hexanes, n-heptane, 2-butanone, dimethyl sulfoxide, nitromethane, 1-methyl-2-pyrrolidone, triethylamine, tributylamine, triflourotoluene, and mixtures thereof.

In a further alternative embodiment, the current ~~invention~~disclosure comprises a *pharmaceutical composition comprising the crystalline monohydrate salt of (4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.$1^{3,7}$]decane dihydrogen citrate as an active ingredient and a pharmaceutically acceptable carrier, diluent, or excipient. In a preferred embodiment of the pharmaceutical composition, the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.$1^{3,7}$]decane dihydrogen citrate is present in an amount ranging from approximately 0.1% to approximately 99.9% by weight based on the total weight of the composition. In this embodiment, the pharmaceutical composition comprising the crystalline monohydrate of *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.$1^{3,7}$]decane dihydrogen citrate demonstrates at least one characteristic peak in the powder X-ray diffraction pattern at values in degrees two theta of 8.4 ± 0.20, 11.3 ± 0.20, 14.2 ± 0.20, 15.5 ± 0.20, 16.4 ± 0.20, 16.6 ± 0.20, 17.2 ± 0.20, 19.7 ± 0.20, 20.7 ± 0.20, 21.0 ± 0.20, 21.2 ± 0.20, 21.6 ± 0.20, 24.8 ± 0.20, and 26.9 ± 0.20.

DETAILED DESCRIPTION OF THE INVENTION

The compound *(4s)*-4-(5-phenyl-1,3,4-thiadiazol-2-yloxy)-1-azatricyclo [3.3.1.$1^{3,7}$] decane is known to exist in multiple salt forms, as reported in the co-pending '336 publication. One of the salt forms, the dihydrogen citrate salt, was identified as a primary compound of interest, due to several observed benefits associated with the compound. Specifically, the dihydrogen citrate anhydrate exhibited favorable solid state properties including high crystallinity, acceptable melting point, non-hygroscopicity, and the ability to avoid exhibiting complex polymorphisms. In addition, the dihydrogen citrate anhydrate salt showed beneficial pharmaceutical properties, including a solid state stability in the form of stability at 40° C and 75% relative humidity for 12 weeks, stability when exposed to a UV/Visible ICH Type I light source, and stability when exposed to