Abstract: The present invention relates to 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, its salt forms, and novel polymorphic forms of these salts.

Fig. 1

(54) Title: SALT FORMS OF 3-CYCLOPROPYLCARBONYL-3,6-DIAZABICYCLO[3.1.1]HEPTANE

Compound A, hemigalactarate monohydrate

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(I))

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
SALT FORMS OF 3 - CYCLOPROPYLCARBONYL - 3 , 6 - DIAZABICYCLO [3.1.1] HEPTANE

Field of the Invention

The present invention relates to 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, its salt forms, and novel polymorphic forms of these salts. The present invention also includes pharmaceutical compositions of these salt forms as well as methods for treating a wide variety of conditions and disorders.

Background of the Invention

The compound, 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane (Compound A), is a neuronal nicotinic receptor (NNR) agonist with selectivity for α4β2* (a432-containing) and α6β2* (a632-containing) NNRs. Compound A demonstrates efficacy in, among other things, preventing full onset of abnormal involuntary movements (AIMs) and also in attenuating existing AIMs in preclinical rodent models of levodopa-induced dyskinesias (LIDs). Compound A reduces LIDs in non-human primates (macaques) and does not impede general activity or levodopa's (L-dopa's) effect on motor deficits. Compound A exhibits neuroprotective effects against MPP+ toxicity in primary cultures of rat dopamine neurons.

3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane has the following structural formula:

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   N
  /|
 / |
HN O
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The commercial development of a drug candidate, such as 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, involves many steps, including the development of a cost effective synthetic method that is adaptable to a large scale manufacturing process. Commercial development also involves research regarding salt forms of the drug substance that exhibit suitable purity, chemical stability, pharmaceutical properties, and characteristics that facilitate convenient handling and processing. Furthermore, compositions containing the drug substance should have adequate shelf life. That is, they should not exhibit significant changes in physicochemical characteristics such as, but not limited to, chemical composition, water content, density, hygroscopicity, and solubility upon storage over an appreciable period of time. Additionally, reproducible and constant plasma concentration profiles of drug upon administration to a patient are also important factors.

Solid salt forms are generally preferred for oral formulations due to their tendency to exhibit these properties in a preferential way; and in the case of basic drugs such as 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, acid addition salts are often the
preferred salt form. Salt forms, however, vary greatly in their ability to impart these properties, and such properties cannot be predicted with accuracy. For example, some salts are solids at ambient temperatures, while other salts are liquids, viscous oils, or gums at ambient temperatures. Furthermore, some salt forms are stable to heat and light under extreme conditions and others readily decompose under much milder conditions. Thus, the development of a suitable acid addition salt form of a basic drug for use in a pharmaceutical composition is a highly unpredictable process.

One synthesis of Compound A is disclosed in PCT Application No. PCT/US2010/058836 (WO 2011/071758), which is incorporated by reference. Syntheses of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.0]heptane, which are scalable to a large-scale production, however, are desirable. Furthermore, there is a need for salt forms that display improved properties, including purity, stability, solubility, and bioavailability. Preferential characteristics of these novel salt forms include those that would increase the ease or efficiency of manufacture of the active ingredient and its formulation into a commercial product. Lastly, there is a need for stable polymorphic forms of these salts that increase the ease or efficiency of manufacture of the active ingredient and its formulation into a commercially viable product.

Summary of the Invention

One aspect of the present invention is an acid addition salt of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.0]heptane. In certain embodiments, the acid is selected from hydrochloric, p-toluenesulfonic, L-aspartic, maleic, L-glutamic, 1-hydroxy-2-naphthoic (namely, xinafoate), fumaric, galactaric, hippuric, L-mandelic, succinic, adipic, or (+)-camphoric. In preferred embodiments, the acid addition salt is a p-toluenesulfonate, maleate, galactarate, benzoate, hippurate, xinafoate, or (+)-camphorate. In still more preferred embodiments, the salt is a galactarate, benzoate, hippurate, or xinafoate.

Another aspect of the present invention includes 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.0]heptane hemigalactarate monohydrate.

Another aspect of the present invention includes an acid addition salt of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.0]heptane, wherein the salt is crystalline.

One aspect of the present invention is a method, use, compound for use, or use for preparation of a medicament for treating or preventing one or more disease or disorder. In one embodiment, the disease or disorder is one or more of Parkinsonism, Parkinson's Disease, abnormal involuntary movements, dyskinesia, and L-dopa induced dyskinesia. In one embodiment, a patient in need thereof is undergoing existing therapy that includes a dosing regimen of L-dopa. In a further embodiment, there is a synergism with administration of Compound A, such that the patient is able to either reduce the dose, or alter the time course, or otherwise modify the existing dosing regimen of L-dopa therapy. Thus, one
aspect of the present invention includes treating L-dopa induced dyskinesia without inhibiting the anti-parkisonian activity of the L-dopa. Another aspect includes retarding Parkinson's Disease progression so as to provide a lower dose of L-dope or a later on time course of dosing thereby delaying onset of L-dopa induced dyskinesia. Compound A attenuates abnormal involuntary movements and L-dopa induced dyskinesias. Such forms another aspect of the present invention. Yet another aspect of the present invention includes the reduction of L-dopa induced dyskinesia without impeding the L-dopa effect on motor deficits. Compound A is neuroprotective.

One aspect of the present invention includes a novel synthetic method for the manufacture of Compound A. Further, the present invention includes one or more novel intermediates useful in the synthetic method.

Other aspects and embodiments of the present invention will be described herein. The scope of the present invention includes combinations of aspects, embodiments, and preferences.

**Brief Description of the Figures**

Figure 1 illustrates the crystal structure for Compound A, hemigalactarate monohydrate.

Figure 2 illustrates the crystal structure with a numbering scheme employed.

Figure 3 illustrates a TGA/DSC of Compound A hemigalactarate monohydrate salt.

Figure 4 illustrates a GVS of Compound A hemigalactarate monohydrate salt.

Figure 5 illustrates an XRPD pattern for Compound A hemigalactarate monohydrate salt before and after storage at 40°C/75% RH and GVS.

Figure 6 illustrates an XRPD of Compound A xinafoate salt.

Figure 7 illustrates a TGA/DSC of Compound A xinafoate salt.

Figure 8 illustrates a GVS of Compound A xinafoate salt.

Figure 9 illustrates an XRPD of Compound A benzoate salt.

Figure 10 illustrates a TGA/DSC of Compound A benzoate salt.

Figure 11 illustrates a GVS of Compound A benzoate salt.

Figure 12 illustrates a high resolution VT-XRPD of Compound A benzoate salt.

Figure 13 illustrates an XRPD of Compound A hippurate salt.

Figure 14 illustrates a TGA/DSC of Compound A hippurate salt.

Figure 15 illustrates a GVS of Compound A hippurate salt.

Figure 16 illustrates a high resolution VT-XRPD of Compound A hippurate salt.

Figure 17 illustrates an XRPD of Compound A hemigalactarate salt for polymorphism assessment.

Figure 18 illustrates an XRPD of Compound A benzoate salt for polymorphism assessment.
Figure 19 illustrates an XRPD of Compound A hippurate salt for polymorphism assessment.

Figure 20 illustrates an XRPD of Compound A xinafoate salt for polymorphism assessment.

Figure 21 illustrates an XRPD for Compound A (+)-camphorate salt.

Figure 22 illustrates a TGA/DSC for Compound A (+)-camphorate salt.

Figure 23 illustrates an XRPD for Compound A tosylate salt.

Figure 24 illustrates a TGA/DSC for Compound A tosylate salt.

Figure 25 illustrates an XRPD for Compound A maleate salt, using 0.5 eq acid. The sample deliquesced so TGA and DSC were not measured.

Figure 26 illustrates an XRPD for Compound A maleate salt, using 1 eq acid.

Figure 27 illustrates a TGA/DSC for Compound A maleate salt, using 1 eq acid.

Figure 28 illustrates an XRPD for Compound A L-mandelate salt.

Figure 29 illustrates a TGA/DSC for Compound A L-mandelate salt.

Figure 30 illustrates Compound A's ability to decrease AIMs in parkinsonian rats.

Figure 31 illustrates Compound A's ability to decrease LIDs in non-human primates.

Figure 32 illustrates Compound A's ability to increase good quality on-time during L-dopa treatment.

**Detailed Description**

**Definitions**

The following definitions are meant to clarify, but not limit, the terms defined. If a particular term used herein is not specifically defined, such term should not be considered indefinite. Rather, terms are used within their accepted meanings.

3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane may also be referred to as 3,6-diazabicyclo[3.1.1]heptan-3-yl(cyclopropyl)methanone, or, potentially, still other chemical names, depending upon the naming convention used. The choice of naming convention should not affect the scope of the present invention. As noted herein, the structure of the compound is:

![Chemical Structure]

, and may also be referred to herein as Compound A for ease of reference.

The phrase "compound of the present invention" as used herein refers to 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or an acid addition salt thereof. The acid is selected from hydrochloric, p-toluenesulfonic, L-aspartic, maleic, L-glutamic, 1-hydroxy-2-
naphthoic (namely, xinafoate), fumaric, galactaric, hippuric, L-mandelic, succinic, adipic, or (+)-camphoric. In preferred embodiments, the acid addition salt is a p-toluenesulfonate, maleate, galactarate, benzoate, hippurate, xinafoate, or (+)-camphorate. In still more preferred embodiments, the salt is a galactarate, benzoate, hippurate, or xinafoate.

The phrase "compound of the present invention" includes a hydrated or a solvated salt form.

Further, as used herein, the term "compound" may be used to mean the free base form, or alternatively, a salt form of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, depending on the context, which will be readily apparent.

As used herein, the term "pharmaceutically acceptable" refers to carrier(s), diluent(s), excipient(s) or salt forms that are compatible with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

As used herein, the term "pharmaceutical composition" refers to a compound of the present invention optionally admixed with one or more pharmaceutically acceptable carriers, diluents, excipients, or adjuvants. Pharmaceutical compositions preferably exhibit a degree of stability to environmental conditions so as to make them suitable for manufacturing and commercialization purposes.

As used herein, the terms "effective amount," "therapeutic amount," or "effective dose" refer to an amount of active ingredient sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of a disorder. Prevention of a disorder may be manifested by delaying or preventing the progression of the disorder, as well as delaying or preventing the onset of the symptoms associated with the disorder. Treatment of the disorder may be manifested by a decrease or elimination of symptoms, inhibition or reversal of the progression of the disorder, as well as any other contribution to the well being of the patient.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. Typically, to be administered in an effective dose, compounds are required to be administered in an amount of less than 5 mg/kg of patient weight. Often, the compounds may be administered in an amount from less than about 1 mg/kg patient weight to less than about 100 µg/kg of patient weight, and occasionally between about 10 µg/kg to less than about 100 µg/kg of patient weight. The foregoing effective doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24 h period. For human patients, the effective dose of the compounds may require administering the compound in an amount of at least about 1mg/24 hr/patient, but not more than about 1000 mg/24 hr/patient, and often not more than about 500 mg/24 hr/patient. Potential doses may be in the range of 500 µg to 2 mg,
as free base equivalents.

As used herein, the phrase "substantially crystalline" includes greater than 20%, preferably greater than 30%, and more preferably greater than 40% (e.g. greater than any of 50, 60, 70, 80, or 90%) crystalline.

The term "stability" as defined herein includes chemical stability and solid state stability, where the phrase "chemical stability" includes the potential to store salts of the invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents, excipients, or adjuvants, such as in an oral dosage form, such as a tablet, capsule, or the like, under normal storage conditions, with an insignificant degree of chemical degradation or decomposition, and the phrase "solid state stability", includes the potential to store salts of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents, excipients, or adjuvants, such as in an oral dosage form, such as a tablet, capsule, or the like, under normal storage conditions, with an insignificant degree of solid state transformation, such as crystallization, recrystallization, solid state phase transition, hydration, dehydration, solvation, or desolvation.

Examples of "normal storage conditions" include one or more of temperatures of between -80 °C and 50 °C, preferably between 0 °C and 40 °C and more preferably ambient temperatures, such as 15 °C to 30 °C, pressures of between 0.1 and 2 bars, preferably at atmospheric pressure, relative humidity of between 5 and 95%, preferably 10 to 60%, and exposure to 460 lux or less of UV/visible light, for prolonged periods, such as greater than or equal to six months. Under such conditions, salts of the invention may be found to be less than 5%, more preferably less than 2%, and especially less than 1%, chemically degraded or decomposed, or solid state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature, pressure, and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g., a temperature of 50 °C and a pressure of 0.1 bar).

Compounds

One embodiment of the present invention includes 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane (Formula I) or a pharmaceutically acceptable salt thereof.
One embodiment includes use of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof in the manufacture of a medicament.

One embodiment of the present invention includes a method for the treatment or prevention of a variety of disorders and dysfunctions, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof.

More specifically, the disorder or dysfunction may be selected from the group consisting of CNS disorders, including AIMS and LIDs, or other disorders described in further detail herein. Another embodiment of the present invention includes compounds that have utility as diagnostic agents and in receptor binding studies as described herein.

One embodiment of the present invention includes a pharmaceutical composition comprising a therapeutically effective amount of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carrier. Another embodiment of the present invention includes the use of a pharmaceutical composition of the present invention in the manufacture of a medicament for treatment of central nervous system disorders and dysfunctions. Another embodiment of the present invention includes 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof with reference to any one of the Examples. Another embodiment of the present invention includes 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance. Another embodiment of the present invention includes 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof for to modulate an NNR in a subject in need thereof. Another embodiment of the present invention includes 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of conditions or disorders mediated by one or more NNRs. Another embodiment of the present invention includes use of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use of modulating one or more NNRs in a subject in need thereof. Another embodiment of the present invention includes use of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of conditions or disorders mediated by one or more NNRs. Another embodiment of the present invention includes a method of modulating one or more NNRs in a subject in need thereof through the administration of 3-
cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by deuterium or tritium, or the replacement of a carbon atom by $^{13}$C or $^{14}$C, or the replacement of a nitrogen atom by $^{15}$N, or the replacement of an oxygen atom with $^{17}$O or $^{18}$O are within the scope of the invention. Such isotopically labeled compounds are useful as research or diagnostic tools.

As noted herein, the present invention includes specific representative compounds, which are identified herein with particularity. The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

In all of the examples described below, protecting groups for sensitive or reactive groups are employed wherever necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts, *Protecting Groups in Organic Synthesis, 3rd Edition*, John Wiley & Sons, New York (1999)). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of the present invention.

The present invention also provides a method for the synthesis of compounds useful as intermediates.

**General Synthetic Methods**

The manner in which Compound A can be synthesized can vary. In one approach, Compound A can be prepared via the coupling of a 3,6-diazabicyclo[3.1.1]heptane in which the 6-position nitrogen atom has been protected (to prevent reaction with acylating agents) with a suitable cyclopropylcarbonyl derivative (such as cyclopropylmethanoyl chloride), followed by removal of the protecting group (typically with acid). Cyclopropylmethanoyl chloride may be prepared by treatment of the cyclopropylcarboxylic acid with, among other reagents, thionyl chloride or oxalyl chloride.

The synthesis of a suitably protected 3,6-diazabicyclo[3.1.1]heptane, 6-(tert-butoxy carbonyl)-3,6-diazabicyclo[3.1.1]heptane, is disclosed in WO 2005/108402 to Pinna, et al. (incorporated by reference with regard to such synthetic teaching). Those skilled in the art of organic synthesis will recognize that other suitably protected 3,6-diazabicyclo[3.1.1]heptanes can also be used to prepare Compound A (see, for example, T.
Another means of making Compound A is to couple a suitable 6-protected-3,6-diazabicyclo[3.1.1]heptane with a cyclopropylcarboxylic acid, followed by removal of the protecting group. This approach typically requires the use of a suitable activating agent, such as N,N’-dicyclohexylcarbodiimide (DCC), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), O-(benzotriazol-1-yl)-N,N,N',N'-bis(tetramethylene)uronium hexafluorophosphate (HBPyU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), or (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (EDCI) with 1-hydroxybenzotriazole (HOBt). Other activating agents are well known to those skilled in the art, for example, see Kiso and Yajima, Peptides, pp 39-91, Academic Press, San Diego, CA (1995).

**Scheme 1: Synthesis of Compound A**

![Scheme 1](image)

Bn = benzyl; Ms = methanesulfonyl; DMF = dimethylformamide; THF = tetrahydrofuran; TEA = triethylamine; DCM = dichloromethane; NMP = N-methyl-2-pyrrolidone.

Alternatively, and advantageously, Compound A can be made using a reaction sequence similar to that shown in Scheme 1. This approach involves a ring closing process in which the anion of cyclopropylcarboxamide is reacted with a bis-electrophile, such as intermediate 6, decreasing the overall length of the synthesis compared with previously described syntheses (for instance, WO 201 1/071758). A specific example of this approach to the synthesis of Compound A is given in the Examples Section and summarized in Scheme 1. However, the reagents used to accomplish the transformations of this approach can vary. For instance, a variety of alcohols can be used the esterification reaction,
providing a variety of diester products (an example being diester 3). The physical properties of particular diesters may provide advantages in purification or handling. Likewise, a variety of amines and solvents can be utilized in the ring closure of the 4-membered (azetidine) ring, a particular amine/solvent mixture providing advantages in either reactivity or product purity (including stereochemical purity). The reduction of the dialkyl azetidinyl-2,4-dicarboxylate (intermediate 4, for example) to the corresponding dialcohol (such as dialcohol 5) can be accomplished by a variety of reagents (e.g., borohydride and aluminumhydride reagents) in a variety of solvents. It is important to choose a reducing reagent that preserves the cis relative stereochemistry around the azetidine ring. Conversion of the dialcohol into a suitable bis-electrophile can be accomplished by a variety of reagents known to those of skill in the art. Reactions for converting alcohols to the corresponding halides (e.g., chlorides, bromides, iodides), as well as those for converting alcohols to sulfonates, phosphates, and the like, are all well known in the chemical literature. The closure of the 6-membered (piperidine) ring with cyclopropylcarboxamide can also be accomplished with a variety of reagents, including a variety of bases for production of the anion and a variety of solvents. Finally, the deprotection of the azetidinyl nitrogen can be accomplished by a variety of conditions, depending on the nature of the protecting group.

Those skilled in the art of organic synthesis will appreciate that there are multiple means of producing Compound A in which one or more atoms are labeled with a radioisotope appropriate to various uses. For example, coupling of $^{11}$C-labeled cyclopropylcarboxylic acid with 6-(tert-butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptane, using one of the activating agents listed above, will produce 3-$^{11}$C-labeled-cyclopropylcarboxyl-6-(tert-butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptanes. Subsequent removal of the tert-butoxycarbonyl protecting group, as described above will produce a compound suitable for use in positron emission tomography. Likewise, coupling of $^3$H- or $^{14}$C-labeled cyclopropylcarboxylic acid with 6-(tert-butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptanes, followed by removal of the protecting group as described above will produce an isotopically modified Compound A, suitable for use in receptor binding and metabolism studies or as an alternative therapeutic compound.

As mentioned hereinabove, solid salt forms are generally preferred for oral formulations due to their tendency to exhibit these properties in a preferential way; and in the case of basic drugs, such as 3-cyclopropylcarboxyl-3,6-diazabicyclo[3.1.1]heptane, acid addition salts are often the preferred salt form.

Different salt forms vary greatly in their ability to impart these properties, and such properties cannot be predicted with accuracy. For example, some salts are solids at ambient temperatures, while other salts are liquids, viscous oils, or gums at ambient temperatures. Furthermore, some salt forms are stable to heat and light under extreme
conditions and others readily decompose under much milder conditions. Thus, the development of a suitable acid addition salt form of a basic drug for use in a pharmaceutical composition is a highly unpredictable process. There is a need for salt forms that display improved properties, including purity, stability, solubility, and bioavailability. Preferential characteristics of these novel salt forms include those that would increase the ease or efficiency of manufacture of the active ingredient and its formulation into a commercial product. Lastly, there is a need for stable polymorphic forms of these salts that allows for an increased ease or efficiency of manufacture of the active ingredient and its formulation into a commercially product.

The degree (%) of crystallinity may be determined by the skilled person using x-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used. For compounds of the current invention, it has been found to be possible to produce salts in forms which are substantially crystalline.

Several of these crystalline salts demonstrated stability that is sufficient to establish their promise in the production of pharmaceutical preparations. Such stability can be demonstrated in a variety of ways. Propensity to gain and release atmospheric moisture can be assessed by dynamic vapor sorption (DVS). Stability to elevated temperatures and humidity can be studied by storing the solid salts at 40°C/75% RH for up to eight days, and then re-examining each by weight, appearance under the microscope, and XRPD.

Polymorphs

The compounds of the present invention may crystallize in more than one form, a characteristic known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of the present invention. Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as XRPD patterns (diffractograms), solubility in various solvents, and melting point.

The present invention includes various polymorphic forms of the salt forms of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, including hydrates and solvates of the salts. Such polymorphic forms are characterized by their x-ray powder diffraction (XRPD) patterns (diffractograms).

As noted, the salt forms of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane may exist in solvated, for example hydrated, as well as unsolvated forms. The present invention encompasses all such forms.

The present invention also includes isotopically labeled compounds wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from
the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, and oxygen, such as $^2\text{H}$, $^3\text{H}$, $^{13}\text{C}$, $^{14}\text{C}$, $^{15}\text{N}$, $^{16}\text{O}$, and $^{17}\text{O}$. Such isotopically labeld compounds are useful as research or diagnostic tools.

5 **Pharmaceutical Compositions**

Although it is possible to administer the compounds of the present invention in the form of a bulk active chemical, it is preferred to administer the compound in the form of a pharmaceutical composition or formulation. Thus, one aspect of the present invention includes pharmaceutical compositions comprising the compound of the present invention and one or more pharmaceutically acceptable carriers, diluents, or excipients. Another aspect of the invention provides a process for the preparation of a pharmaceutical composition, including admixing the compound of the present invention with one or more pharmaceutically acceptable carriers, diluents or excipients.

The manner in which the compounds of the present invention are administered can vary. The compounds of the present invention are preferably administered orally. Preferred pharmaceutical compositions for oral administration include tablets, capsules, caplets, syrups, solutions, and suspensions. The pharmaceutical compositions of the present invention may be provided in modified release dosage forms such as time-release tablet and capsule formulations.

The pharmaceutical compositions can also be administered via injection, namely, intravenously, intramuscularly, subcutaneously, intraperitoneally, intrarterially, intrathecally, and intracerebroventricularly. Intravenous administration is a preferred method of injection. Suitable carriers for injection are well known to those of skill in the art and include 5% dextrose solutions, saline, and phosphate buffered saline.

The formulations may also be administered using other means, for example, rectal administration. Formulations useful for rectal administration, such as suppositories, are well known to those of skill in the art. The compounds can also be administered by inhalation, for example, in the form of an aerosol; topically, such as, in lotion form; transdermally, such as, using a transdermal patch (for example, by using technology that is commercially available from Novartis and Alza Corporation), by powder injection, or by buccal, sublingual, or intranasal absorption.

Pharmaceutical compositions may be formulated in unit dose form, or in multiple or subunit doses.

The administration of the pharmaceutical compositions described herein can be intermittent, or at a gradual, continuous, constant or controlled rate. The pharmaceutical compositions may be administered to a warm-blooded animal, for example, a mammal such as a mouse, rat, cat, rabbit, dog, pig, cow, or monkey; but advantageously is administered to
a human being. In addition, the time of day and the number of times per day that the
pharmaceutical composition is administered can vary.

The compounds of the present invention may be used in the treatment of a variety
of disorders and conditions and, as such, may be used in combination with a variety of other
suitable therapeutic agents useful in the treatment or prophylaxis of those disorders or
conditions. Thus, one embodiment of the present invention includes the administration of
the compound of the present invention in combination with other therapeutic compounds.
For example, the compound of the present invention can be used in combination with other
NNR ligands (such as varenicline), antioxidants (such as free radical scavenging agents),
antibacterial agents (such as penicillin antibiotics), antiviral agents (such as nucleoside
analogs, like zidovudine and acyclovir), anticoagulants (such as warfarin), anti-inflammatory
agents (such as NSAIDs), anti-pyretics, analgesics, anesthetics (such as used in surgery),
acetylcholinesterase inhibitors (such as donepezil and galantamine), antipsychotics (such as
haloperidol, clozapine, olanzapine, and quetiapine), immuno-suppressants (such as
cyclosporin and methotrexate), neuroprotective agents (such as A$_2$A inhibitors and caffeine),
blood-brain barrier permeability enhancers, steroids (such as steroid hormones),
corticosteroids (such as dexamethasone, predisone, and hydrocortisone), vitamins,
minerals, nutraceuticals, anti-depressants (such as imipramine, fluoxetine, paroxetine,
estcitalopram, sertraline, venlafaxine, and duloxetine), anti-convulsants (such as
prazosin and sildenafil), mood stabilizers (such as valproate and aripiprazole), anti-cancer
drugs (such as anti-proliferatives), antihypertensive agents (such as atenolol, clonidine,
amlopidine, verapamil, and olmesartan), laxatives, stool softeners, diuretics (such as
furosemide), anti-spasmodics (such as dicyclomine), anti-dyskinetic agents, and anti-ulcer
medications (such as esomeprazole). One preferred use of the compounds of the present
invention is the treatment and prevention of Parkinson's Disease, AIMS, and LIDs, and thus
compounds of the present invention may be used in combination with pharmaceutical agents
used to treat Parkinson's Disease, AIMS, and LIDs. Such agents include NNR agonists
($\alpha4\beta2$, $\alpha7$, etc.), dopamine precursors (such as levodopa-carbidopa, levodopa-benserazide,
and duodopa), dopamine agonists (such as bromocriptine, cabergoline, lisuride, pergolide,
pramipexole, popinrole, talipoxeole, rotigotine, and apomorphine), dopa carboxylase
inhibitors, MAO-B inhibitors (such as selegiline, rasagoline, and safinamide), COMT
inhibitors (such as entacapone and tolcapone), antiglutamatergic agents (such as
amantadine), anticholinergic agents (such as trihexyphenidyl, benztrpine, and biperiden),
anti-dementia agents (such as rivastigmine, donepezil, galantamine, and memantine),
antipsychotic agents (such as quetiapine, clozapine, and resperdone), antiepileptic agents
(such as zonisamide), noradrenaline precursors (such as droidopa), mGluR4 agonists,
mGluR5 inhibitors, 5HT Α1B agonists, 5HT2A antagonists/inverse agonists, opioid antagonists (mu, delta, kappa), and AMPA receptor blockers. Such a combination of pharmacologically active agents may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compounds or agents and the relative timings of administration will be selected in order to achieve the desired therapeutic effect. The administration in combination of a compound of the present invention with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second. Such sequential administration may be close in time or remote in time.

Method of Treatment

3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing such, can be used for the prevention or treatment of various conditions or disorders for which other types of nicotinic compounds have been proposed or are shown to be useful as therapeutics, such as CNS disorders (including neurodegenerative disorders), inflammation, inflammatory response associated with bacterial and/or viral infection, pain, diabetes, metabolic syndrome, autoimmune disorders, dermatological conditions, addictions, obesity or other disorders described in further detail herein. This compound can also be used as a diagnostic agent in receptor binding studies (in vitro and in vivo). Such therapeutic and other teachings are described, for example, in references previously listed herein, including Williams et al., Drug News Perspec. 7(4): 205 (1994), Arneric et al., CNS Drug Rev. 1(1): 1-26 (1995), Arneric et al., Exp. Opin. Invest. Drugs 5(1): 79-100 (1996), Yang et al., Acta Pharmacol. Sin. 30(6): 740-751 (2009), Bencherif et al., J. Pharmacol. Exp. Ther. 279: 1413 (1996), Lippiello et al., J. Pharmacol. Exp. Ther. 279: 1422 (1996), Damaj et al., J. Pharmacol. Exp. Ther. 291: 390 (1999); Chiari et al., Anesthesiology 91: 1447 (1999), Lavand'homme and Eisenbach, Anesthesiology 91: 1455 (1999), Holladay et al., J. Med. Chem. 40(28): 4169-94 (1997), Bannon et al., Science 279: 77 (1998), PCT WO 94/08992, PCT WO 96/31475, PCT WO 96/40682, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., 5,604,231 to Smith et al. and 5,852,041 to Cosford et al.

CNS Disorders

The compounds and their pharmaceutical compositions are useful in the treatment or prevention of a variety of CNS disorders, including neurodegenerative disorders, neuropsychiatric disorders, neurologic disorders, and addictions. The compounds and their pharmaceutical compositions can be used to treat or prevent cognitive deficits and
dysfunctions, age-related and otherwise; attentional disorders and dementias, including those due to infectious agents or metabolic disturbances; to provide neuroprotection; to treat convulsions and multiple cerebral infarcts; to treat mood disorders, compulsions and addictive behaviors; to provide analgesia; to control inflammation, such as mediated by cytokines and nuclear factor kappa B; to treat inflammatory disorders; to provide pain relief; and to treat infections, as anti-infectious agents for treating bacterial, fungal, and viral infections. Among the disorders, diseases and conditions that the compounds and pharmaceutical compositions of the present invention can be used to treat or prevent are: age-associated memory impairment (AAMI), mild cognitive impairment (MCI), age-related cognitive decline (ARCD), pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Alzheimer's disease, cognitive impairment no dementia (CIND), Lewy body dementia, HIV-dementia, AIDS dementia complex, vascular dementia, Down syndrome, head trauma, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases, stroke, central ischemia, peripheral ischemia, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive dysfunction in schizophrenia, cognitive deficits in schizophrenia, Parkinsonism including Parkinson's disease, postencephalitic parkinsonism, parkinsonism-dementia of Gaum, frontotemporal dementia Parkinson's Type (FTDP), Pick's disease, Niemann-Pick's Disease, Huntington's Disease, Huntington's chorea, abnormal involuntary movements, dyskinesias, L-dopa induced dyskinesia, tardive dyskinesia, spastic dystonia, hyperkinesia, progressive supranuclear palsy, progressive supranuclear paresis, restless leg syndrome, Creutzfeld-Jakob disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), motor neuron diseases (MND), multiple system atrophy (MSA), corticobasal degeneration, Guillain-Barre Syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP), epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, mania, anxiety, depression, premenstrual dysphoria, panic disorders, bulimia, anorexia, narcolepsy, excessive daytime sleepiness, bipolar disorders, generalized anxiety disorder, obsessive compulsive disorder, rage outbursts, conduct disorder, oppositional defiant disorder, Tourette's syndrome, autism, drug and alcohol addiction, tobacco addiction, compulsive overeating and sexual dysfunction.

Cognitive impairments or dysfunctions may be associated with psychiatric disorders or conditions, such as schizophrenia and other psychotic disorders, including but not limited to psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, and psychotic disorders due to a general medical conditions, dementias and other cognitive disorders, including but not limited to mild cognitive impairment, pre-senile dementia, Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, age-related memory impairment, Lewy body
dementia, vascular dementia, AIDS dementia complex, dyslexia, Parkinsonism including Parkinson's disease, dyskinesias, levodopa-induced dyskinesias (LIDs), abnormal involuntary movements (AIMs), cognitive impairment and dementia of Parkinson's Disease, cognitive impairment of multiple sclerosis, cognitive impairment caused by traumatic brain injury, dementias due to other general medical conditions, anxiety disorders, including but not limited to panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder and generalized anxiety disorder due to a general medical condition, mood disorders, including but not limited to major depressive disorder, dysthymic disorder, bipolar depression, bipolar mania, bipolar I disorder, depression associated with manic, depressive or mixed episodes, bipolar II disorder, cyclothymic disorder, and mood disorders due to general medical conditions, sleep disorders, including but not limited to dyssomnia disorders, primary insomnia, primary hypersomnia, narcolepsy, parasomnia disorders, nightmare disorder, sleep terror disorder and sleepwalking disorder, mental retardation, learning disorders, motor skills disorders, communication disorders, pervasive developmental disorders, attention-deficit and disruptive behavior disorders, attention deficit disorder, attention deficit hyperactivity disorder, feeding and eating disorders of infancy, childhood, or adults, tic disorders, elimination disorders, substance-related disorders, including but not limited to substance dependence, substance abuse, substance intoxication, substance withdrawal, alcohol-related disorders, amphetamine or amphetamine-like-related disorders, caffeine-related disorders, cannabis-related disorders, cocaine-related disorders, hallucinogen-related disorders, inhalant-related disorders, nicotine-related disorders, opioid-related disorders, phencyclidine or phencyclidine-like-related disorders, and sedative-, hypnotic- or anxiolytic-related disorders, personality disorders, including but not limited to obsessive-compulsive personality disorder and impulse-control disorders. Cognitive performance may be assessed with a validated cognitive scale, such as, for example, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). One measure of the effectiveness of the compounds of the present invention in improving cognition may include measuring a patient's degree of change according to such a scale.

Regarding compulsions and addictive behaviors, the compounds of the present invention may be used as a therapy for nicotine addiction and for other brain-reward disorders, such as substance abuse including alcohol addiction, illicit and prescription drug addiction, eating disorders, including obesity, and behavioral addictions, such as gambling, or other similar behavioral manifestations of addiction.

The above conditions and disorders are discussed in further detail, for example, in the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders,
Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000. This Manual may also be referred to for greater detail on the symptoms and diagnostic features associated with substance use, abuse, and dependence. This Manual is updated and revised from time-to-time and the description of the diseases and conditions herein is intended to remain consistent with such revision.

Preferably, the treatment or prevention of diseases, disorders and conditions occurs without appreciable adverse side effects, including, for example, significant increases in blood pressure and heart rate, significant negative effects upon the gastro-intestinal tract, and significant effects upon skeletal muscle.

The compounds of the present invention, when employed in effective amounts, are believed to modulate the activity of the \( \alpha 4 \beta 2 \) and/or \( \alpha 6 \beta 2 \) NNRs without appreciable interaction with the nicotinic subtypes that characterize the human ganglia, as demonstrated by a lack of the ability to elicit nicotinic function in adrenal chromaffin tissue, or skeletal muscle, further demonstrated by a lack of the ability to elicit nicotinic function in cell preparations expressing muscle-type nicotinic receptors. Thus, these compounds are believed capable of treating or preventing diseases, disorders and conditions without eliciting significant side effects associated activity at ganglionic and neuromuscular sites. Thus, administration of the compounds is believed to provide a therapeutic window in which treatment of certain diseases, disorders and conditions is provided, and certain side effects are avoided. That is, an effective dose of the compound is believed sufficient to provide the desired effects upon the disease, disorder or condition, but is believed insufficient, namely is not at a high enough level, to provide undesirable side effects.

Thus, the present invention provides the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use in therapy, such as a therapy described above.

In yet another aspect the present invention provides the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a CNS disorder, such as a disorder, disease or condition described hereinabove.

**Inflammation**

The nervous system, primarily through the vagus nerve, is known to regulate the magnitude of the innate immune response by inhibiting the release of macrophage tumor necrosis factor (TNF). This physiological mechanism is known as the "cholinergic anti-inflammatory pathway" (see, for example, Tracey, "The Inflammatory Reflex," *Nature* 420: 853-9 (2002)). Excessive inflammation and tumor necrosis factor synthesis cause morbidity and even mortality in a variety of diseases. These diseases include, but are not limited to,
endotoxemia, rheumatoid arthritis, osteoarthritis, psoriasis, asthma, atherosclerosis,
idopathic pulmonary fibrosis, and inflammatory bowel disease.

Inflammatory conditions that can be treated or prevented by administering the
compounds described herein include, but are not limited to, chronic and acute inflammation,
psoriasis, endotoxemia, gout, acute pseudogout, acute gouty arthritis, arthritis, rheumatoid
arthritis, osteoarthritis, allograft rejection, chronic transplant rejection, asthma,
atherosclerosis, mononuclear-phagocyte dependent lung injury, idiopathic pulmonary
fibrosis, atopic dermatitis, chronic obstructive pulmonary disease, adult respiratory distress
syndrome, acute chest syndrome in sickle cell disease, inflammatory bowel disease, irritable
bowel syndrome, Crohn's disease, ulcers, ulcerative colitis, acute cholangitis, aphthous
stomatitis, cachexia, pockitis, glomerulonephritis, lupus nephritis, thrombosis, and graft vs.
host reaction.

**Inflammatory Response Associated with Bacterial and/or Viral Infection**

Many bacterial and/or viral infections are associated with side effects brought on by
the formation of toxins, and the body's natural response to the bacteria or virus and/or the
toxins. As discussed above, the body's response to infection often involves generating a
significant amount of TNF and/or other cytokines. The over-expression of these cytokines
can result in significant injury, such as septic shock (when the bacteria is sepsis), endotoxic
shock, urosepsis, viral pneumonitis and toxic shock syndrome.

Cytokine expression is mediated by NNRs, and can be inhibited by administering
agonists or partial agonists of these receptors. Those compounds described herein that are
agonists or partial agonists of these receptors can therefore be used to minimize the
inflammatory response associated with bacterial infection, as well as viral and fungal
infections. Examples of such bacterial infections include anthrax, botulism, and sepsis.

Some of these compounds may also have antimicrobial properties.

These compounds can also be used as adjunct therapy in combination with existing
therapies to manage bacterial, viral and fungal infections, such as antibiotics, antivirals and
antifungals. Antitoxins can also be used to bind to toxins produced by the infectious agents
and allow the bound toxins to pass through the body without generating an inflammatory
response. Examples of antitoxins are disclosed, for example, in U.S. Patent No. 6,310,043 to
Bundle et al. Other agents effective against bacterial and other toxins can be effective and
their therapeutic effect can be complemented by co-administration with the compounds
described herein.

**Pain**

The compounds can be administered to treat and/or prevent pain, including acute,
neurologic, inflammatory, neuropathic and chronic pain. The compounds can be used in
conjunction with opiates to minimize the likelihood of opiate addiction (e.g., morphine sparing
therapy). The analgesic activity of compounds described herein can be demonstrated in models of persistent inflammatory pain and of neuropathic pain, performed as described in U.S. Published Patent Application No. 20010056084 A1 (Allgeier et al.) (e.g., mechanical hyperalgesia in the complete Freund's adjuvant rat model of inflammatory pain and mechanical hyperalgesia in the mouse partial sciatic nerve ligation model of neuropathic pain).

The analgesic effect is suitable for treating pain of various genesis or etiology, in particular in treating inflammatory pain and associated hyperalgesia, neuropathic pain and associated hyperalgesia, chronic pain (e.g., severe chronic pain, post-operative pain and pain associated with various conditions including cancer, angina, renal or biliary colic, menstruation, migraine, and gout). Inflammatory pain may be of diverse genesis, including arthritis and rheumatoid disease, teno-synovitis and vasculitis. Neuropathic pain includes trigeminal or herpetic neuralgia, neuropathies such as diabetic neuropathy pain, causalgia, low back pain and deafferentation syndromes such as brachial plexus avulsion.

Other Disorders

In addition to treating CNS disorders, inflammation, and neovascularization, and pain, the compounds of the present invention can be also used to prevent or treat certain other conditions, diseases, and disorders in which NNRs play a role. Examples include autoimmune disorders such as lupus, disorders associated with cytokine release, cachexia secondary to infection (e.g., as occurs in AIDS, AIDS related complex and neoplasia), obesity, pemphitis, urinary incontinence, overactive bladder, diarrhea, constipation, retinal diseases, infectious diseases, myasthenia, Eaton-Lambert syndrome, hypertension, preeclampsia, osteoporosis, vasoconstriction, vasodilatation, cardiac arrhythmias, type I diabetes, type II diabetes, bulimia, anorexia and sexual dysfunction, as well as those indications set forth in published PCT application WO 98/25619. The compounds of this invention can also be administered to treat convulsions such as those that are symptomatic of epilepsy, and to treat conditions such as syphilis and Creutzfeld-Jakob disease. Lastly, the compounds of this invention may be used to treat a variety of dermatological disorders, including but not limited to psoriasis, dermatitis, acne, pustulosis, vitiligo, and the like.

Diagnostic Uses

The compounds can be used in diagnostic compositions, such as probes, particularly when they are modified to include appropriate labels. The probes can be used, for example, to determine the relative number and/or function of specific receptors, particularly the α4β2* and/or α6-containing receptor subtypes. For this purpose the compounds of the present invention most preferably are labeled with a radioactive isotopic moiety such as 11C, which can be detected using positron emission tomography (PET). A high specific activity is
desired to visualize the selected receptor subtypes at non-saturating concentrations. The administered doses typically are below the toxic range and provide high contrast images. The compounds are expected to be capable of administration in non-toxic levels. Determination of dose is carried out in a manner known to one skilled in the art of radiolabel imaging. See, for example, U.S. Patent No. 5,969,144 to London et al.

The compounds can be administered using known techniques. See, for example, U.S. Patent No. 5,969,144 to London et al., as noted. The compounds can be administered in formulation compositions that incorporate other ingredients, such as those types of ingredients that are useful in formulating a diagnostic composition. Compounds useful in accordance with carrying out the present invention most preferably are employed in forms of high purity. See, U.S. Patent No. 5,853,696 to Elmalch et al.

After the compounds are administered to a subject (e.g., a human subject), the presence of that compound within the subject can be imaged and quantified by appropriate techniques in order to indicate the presence, quantity, and functionality of selected NNR subtypes. In addition to humans, the compounds can also be administered to animals, such as mice, rats, dogs, and monkeys. PET imaging can be carried out using any appropriate technique and apparatus. See Villemagne et al., in: Arneric et al. (Eds.) Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities, 235-250 (1998) and U.S. Patent No. 5,853,696 to Elmalch et al., each herein incorporated by reference, for a disclosure of representative imaging techniques.

The radiolabeled compounds bind with high affinity to selective NNR subtypes (e.g., \( \alpha 4\beta 2^* \) and/or \( \alpha 6 \)-containing) and preferably exhibit negligible non-specific binding to other nicotinic cholinergic receptor subtypes (e.g., those receptor subtypes associated with muscle and ganglia). As such, the compounds can be used as agents for noninvasive imaging of nicotinic cholinergic receptor subtypes within the body of a subject, particularly within the brain for diagnosis associated with a variety of CNS diseases and disorders.

In one aspect, the diagnostic compositions can be used in a method to diagnose disease in a subject, such as a human patient. The method involves administering to that patient a detectably labeled compound as described herein, and detecting the binding of that compound to selected NNR subtypes (e.g., \( \alpha 4\beta 2^* \) and/or \( \alpha 6 \)-containing receptor subtypes). Those skilled in the art of using diagnostic tools, such as PET, can use the radiolabeled compounds described herein to diagnose a wide variety of conditions and disorders, including conditions and disorders associated with dysfunction of the central and autonomic nervous systems. Such disorders include a wide variety of CNS diseases and disorders, including Alzheimer's disease, Parkinson's disease, and schizophrenia. These and other
representative diseases and disorders that can be evaluated include those that are set forth in U.S. Patent No. 5,952,339 to Benchert et al.

In another aspect, the diagnostic compositions can be used in a method to monitor selective nicotinic receptor subtypes of a subject, such as a human patient. The method involves administering a detectably labeled compound as described herein to that patient and detecting the binding of that compound to selected nicotinic receptor subtypes namely, the α4β2* and/or a6-containing receptor subtypes.

Receptor Binding

The compounds of this invention can be used as reference ligands in binding assays for compounds which bind to NNR subtypes, particularly the α4β2* and/or a6-containing receptor subtypes. For this purpose the compounds of this invention are preferably labeled with a radioactive isotopic moiety such as ³H, or ¹⁴C.

EXAMPLES

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, all parts and percentages are by weight, unless otherwise noted.

Example 1: Instrumentation and experimental protocols for characterization of salt forms of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane

X-Ray Powder Diffraction (XRPD)

X-Ray Powder Diffraction patterns were collected on a Bruker AXS C2 GADDS diffractometer using CuKa radiation (40 kV, 40 mA), automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. X-ray optics consists of a single Gobel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence (i.e. the effective size of the X-ray beam on the sample) was approximately 4 mm. A Θ-Θ continuous scan mode was employed with a sample - detector distance of 20 cm which gives an effective 20 range of 3.2° - 29.7°. Typically the sample would be exposed to the X-ray beam for 120 seconds. Samples run under ambient conditions were prepared as flat plate specimens using powder as received without grinding. Approximately 1-2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Samples run under non-ambient conditions were mounted on a silicon wafer with heat-conducting compound. The sample was then heated to the appropriate temperature at ca. 10°C/min and subsequently held isothermally for about 5 min before data collection was initiated. Peak positions are reported as °2Θ with an accuracy of ± 0.1°.

Single Crystal XRD (SXD)

Data were collected on a Bruker AXS 1K SMART CCD diffractometer equipped with an Oxford Cryosystems Cryostream cooling device. Structures were solved using either the
SHELXS or SHELXD programs and refined with the SHELXL program as part of the Bruker AXS SHELXTL suite. Unless otherwise stated, hydrogen atoms attached to carbon were placed geometrically and allowed to refine with a riding isotropic displacement parameter. Hydrogen atoms attached to a heteroatom were located in a difference Fourier synthesis and were allowed to refine freely with an isotropic displacement parameter.

Nuclear Magnetic Resonance (NMR) Spectrometry

NMR spectra were collected on either a Varian Unity 300 MHz instrument or a Bruker 400MHz instrument equipped with an auto-sampler and controlled by a DRX400 console. Automated experiments were acquired using ICONNMR v4.0.4 (build 1) running with Topspin v 1.3 (patch level 8) using the standard Bruker loaded experiments. For non-routine spectroscopy, data were acquired through the use of Topspin alone.

Melting Point

A Fisher-Johns hot stage melting point apparatus was used, at a setting corresponding to a heating rate of about 5°C per min.

Differential Scanning Calorimetry (DSC)

DSC data were collected on a TA Instruments Q1000 or a Mettler DSC 823e equipped with a 50 position auto-sampler. The instrument was calibrated for energy and temperature calibration using certified indium. Typically 0.5-1.5 mg of each sample, in a pin-holed aluminium pan, was heated at 10 °C/min from 25°C to 175-200°C. A nitrogen purge at 30 mL/min was maintained over the sample.

Thermo-Gravimetric Analysis (TGA)

TGA data were collected on a TA Instruments Q500 TGA equipped with a 16 position auto-sampler or a Mettler TGA/SDTA 851e equipped with a 34 position auto sampler. TA Instruments Q500: The instrument was temperature calibrated using certified Alumel. Typically 5-10 mg of each sample was loaded onto a pre-tared platinum crucible and aluminium DSC pan, and was heated at 10°C/min from ambient temperature to 350°C. A nitrogen purge at 60 mL/min was maintained over the sample. Mettler TGA/SDTA 851e: The instrument was temperature calibrated using certified indium. Typically 5-1.0 mg of each sample was loaded onto a pre-tared aluminum crucible and was heated at 10°C/min from ambient temperature to 350°C. A nitrogen purge at 50 mL/min was maintained over the sample.

Polarized Light Microscopy (PLM)

Samples were studied on a Leica LM/DM polarized light microscope with a digital video camera for image capture. A small amount of each sample was placed on a glass slide, mounted in immersion oil and covered with a glass slip, the individual particles being separated as well as possible. The sample was viewed with appropriate magnification and partially polarized light, coupled to a λ false-color filter.
Hot Stage Microscopy (HSM)

Hot Stage Microscopy was carried out using a Leica LM/DM polarized light microscope combined with a Mettler-Toledo MTFP82HT hot-stage and a digital video camera for image capture. A small amount of each sample was placed onto a glass slide with individual particles separated as well as possible. The sample was viewed with appropriate magnification and partially polarized light, coupled to a λ false-color filter, whilst being heated from ambient temperature typically at 10°C/min.

Dynamic Vapor Sorption (DVS)

Sorption isotherms were determined using a SMS DVS Intrinsic moisture sorption analyzer controlled by SMS Analysis suite software. The sample temperature was maintained at 25°C by the instrument controls. The humidity was controlled by mixing streams of dry and wet nitrogen, with a total flow rate of 200 mL/min. The relative humidity was measured by a calibrated Rotronic probe (dynamic range of 1.0-100 %RH), located near the sample. The weight change, (mass relaxation) of the sample as a function of % RH was constantly monitored by the microbalance (accuracy ±0.005 mg).

Typically a 5-20 mg sample was placed on the tared mesh stainless steel basket under ambient conditions. The sample was loaded and unloaded at 40% RH and 25°C (typical ambient conditions). A moisture sorption isotherm was performed as outlined below (2 scans giving 1 complete cycle). The standard isotherm was performed at 25°C at 10% RH intervals over a 0-90% RH range.

DVS Generic method parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorption - Scan 1</td>
<td>40 – 90</td>
</tr>
<tr>
<td>Desorption / Adsorption - Scan 2</td>
<td>90 - Dry, Dry - 40</td>
</tr>
<tr>
<td>Intervals (% RH)</td>
<td>10</td>
</tr>
<tr>
<td>Number of Scans</td>
<td>2</td>
</tr>
<tr>
<td>Flow rate (mL/min)</td>
<td>200</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>25</td>
</tr>
<tr>
<td>Stability (°C/min)</td>
<td>0.2</td>
</tr>
<tr>
<td>Sorption Time (hours)</td>
<td>6 hour time out</td>
</tr>
</tbody>
</table>

Samples were recovered after completion of the isotherm and re-analyzed by XRPD.

Water Determination by Karl Fischer (KF)

The water content of each sample was measured on a Mettler Toledo DL39 Coulometer using Hydranal Coulomat AG reagent and an argon purge. Weighed solid samples were introduced into the vessel on a platinum TGA pan which was connected to a subaseal to avoid water ingress. Approx 10 mg of sample was used per titration and duplicate determinations were made.
Thermodynamic Aqueous Solubility by HPLC

Aqueous solubility was determined by suspending sufficient compound in water to give a maximum final concentration of ≥10 mg/mL of the parent free-form of the compound. The suspension was equilibrated at 25°C for 24 h, and then the pH was measured. The suspension was then filtered through a glass fiber C filter into a 96 well plate. The filtrate was then diluted by a factor of 101. Quantitation was by HPLC with reference to a standard solution of approximately 0.1 mg/mL in DMSO. Different volumes of the standard, diluted and undiluted sample solutions were injected. The solubility was calculated using the peak areas determined by integration of the peak found at the same retention time as the principal peak in the standard injection. If there was sufficient solid in the filter plate, the XRPD was collected.

HPLC method parameters for thermodynamic aqueous solubility method

<table>
<thead>
<tr>
<th>Type of method:</th>
<th>Reverse phase with gradient elution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Phenomenex Luna, C18 (2) 5 μm, 50 x 4.6 mm</td>
</tr>
<tr>
<td>Column Temperature (°C):</td>
<td>25</td>
</tr>
<tr>
<td>Standard Injections (μL):</td>
<td>1, 2, 3, 5, 7, 10</td>
</tr>
<tr>
<td>Test Injections (μL):</td>
<td>1, 2, 3, 10, 20, 50</td>
</tr>
<tr>
<td>Detection: Wavelength, Bandwidth (nm):</td>
<td>260, 80</td>
</tr>
<tr>
<td>Flow Rate (mL/min):</td>
<td>2</td>
</tr>
<tr>
<td>Phase A:</td>
<td>0.1% TFA in water</td>
</tr>
<tr>
<td>Phase B:</td>
<td>0.085% TFA in acetonitrile</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timetable:</th>
<th>Time (min)</th>
<th>% Phase A</th>
<th>% Phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>95</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>80</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>5</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>3.3</td>
<td>5</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>95</td>
<td>5</td>
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</tr>
<tr>
<td>4.4</td>
<td>95</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Analysis was performed on an Agilent HP1 100 series system equipped with a diode array detector and using ChemStation software vB.02.01-SR1.

Chemical Purity by HPLC

Purity analysis was performed on an Agilent HP1 100 series system equipped with a diode array detector and using ChemStation software vB.02.01-SR1.

HPLC method parameters for chemical purity determination

<table>
<thead>
<tr>
<th>Sample Preparation</th>
<th>0.5 mg/mL in acetonitrile:water 1:1 (v/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Phenomenex Luna C18 (2), 150 x 4.6 mm, 5 μm</td>
</tr>
<tr>
<td>Column Temperature (°C):</td>
<td>25</td>
</tr>
<tr>
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</tr>
<tr>
<td>Detection: Wavelength, Bandwidth (nm):</td>
<td>255,90</td>
</tr>
<tr>
<td>Flow Rate (mL/min):</td>
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</tr>
</tbody>
</table>
**Ion Chromatography**

Data were collected on a Metrohm 761 Advanced Compact IC (for cations) and a Metrohm 861 Advanced Compact IC (for anions) using IC Net software v2.3. Samples were prepared as 1000 ppm stocks in DMSO. Samples were diluted to 100 ppm with DMSO prior to testing. Quantification was achieved by comparison with standard solutions of known concentration of the ion being analyzed.

**Ion Chromatography method for anions**

<table>
<thead>
<tr>
<th>Type of method</th>
<th>Anion exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Metrosep A Supp 5 – 250 (4.0 x 250 mm)</td>
</tr>
<tr>
<td>Column Temperature (°C):</td>
<td>Ambient</td>
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<tr>
<td>Injection (μL):</td>
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</tr>
<tr>
<td>Detection:</td>
<td>Conductivity detector</td>
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<tr>
<td>Flow Rate (mL/min):</td>
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</tr>
<tr>
<td>Eluent:</td>
<td>3.2 mM sodium carbonate, 1.0 mM sodium hydrogen carbonate in water</td>
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**Ion Chromatography method for cations**

<table>
<thead>
<tr>
<th>Type of method</th>
<th>Cation exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
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<tr>
<td>Column Temperature (°C):</td>
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<td>Injection (μL):</td>
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<tr>
<td>Detection:</td>
<td>Conductivity detector</td>
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<tr>
<td>Eluent:</td>
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</table>

**pKa Determination and Prediction**

Data were collected on a Sirius GlpKa instrument with a D-PAS attachment. Measurements were made at 25°C in aqueous solution by UV and in methanol water mixtures by potentiometry. The titration media was ionic-strength adjusted (ISA) with 0.15 M KCl (aq). The values found in the methanol water mixtures were corrected to 0% co-solvent via Yasuda-Shedlovskey extrapolation. The data were refined using Refinement Pro software v1.0. Prediction of pKa values was made using ACD pKa prediction software v9.

**Log P Determination**

Data were collected by potentiometric titration on a Sirius GlpKa instrument using three
ratios of octanohionic-strength adjusted (ISA) water to generate Log P, Log P_{ion}, and Log D values. The data were refined using Refinement Pro software v 1.0. Prediction of Log P values was made using ACD v9 and Syracuse KOWWIN v 1.67 software.

**Example 2. Synthesis of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane**

(Compound A)

A three-neck flask, equipped with a mechanical stirrer, two reflux condensers, a cold finger, a temperature probe, a nitrogen inlet and an exhaust outlet (leading to a aqueous sodium bisulfite/sodium hydroxide trap), was charged with glutaryl chloride (350 g, 2.07 mol) followed by bromine (160 mL, 3.12 mol). The resulting mixture was stirred under nitrogen and heated at gentle reflux, as the internal temperature gradually increased from 58°C to 91°C over a period of 7 h. During the heating period and as consumption/loss of bromine was observed, additional bromine was added twice (first 90 mL and later 120 mL). The reaction mixture was then allowed to gradually cool to ambient temperature while stirring under a nitrogen atmosphere overnight. Analysis of an aliquot of the reaction mixture quenched in methanol indicated complete conversion to dimethyl 2,4-dibromoglutarate (>98 % analyzed as the based on GCMS and LCMS). This 2,4-dibromoglutaril chloride was used without further purification in the next step.

A three-neck flask, equipped with a mechanical stirrer, a nitrogen inlet, an addition funnel and a temperature probe, was charged with anhydrous ether (7 L) followed by benzyl alcohol (493 g, 4.56 mol). The solution was stirred under nitrogen and cooled in an ice water bath until an internal temperature of 8°C was reached. Then 2,4-dibromoglutaril chloride was added through the addition funnel to the stirred solution (aided by an anhydrous ether rinse) over 1 to 1.5 h during which time a maximum observed exotherm of 12°C occurred. Following the addition, the reaction mixture was stirred on the cold bath for 1 h (internal temperature observed to be 12°C). The reaction mixture was then allowed to stir under a nitrogen atmosphere while gradually warming to ambient temperature overnight. Analysis of an aliquot of the reaction mixture diluted in methanol indicated complete consumption of 2,4-dibromoglutaril chloride (i.e., no dimethyl 2,4-dibromoglutarate was observed) based on LCMS. The reaction mixture was transferred to a separatory funnel (aided with an ether rinse) and the organic solution was washed twice with water, twice with 1 M aqueous sodium bisulfite, twice with saturated aqueous sodium bicarbonate (the second wash tested alkaline with pH paper) and finally once with saturated aqueous sodium chloride. The collected organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure affording intermediate dibenzyl 2,4-dibromoglutarate as a pale yellow oil (1.034 kg, quantitative crude yield) which was used directly in the next step without further purification. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.38 (s, 10H), 5.23 (s, 4H), 4.59-4.41 (m, 2H), 2.97-2.64 (m, 2H).
A three-neck flask, equipped with a mechanical stirrer, a nitrogen inlet, a temperature probe, an addition funnel and a reflux condenser, was charged with a solution of crude dibenzyl 2,4-dibromoglutarate (Intermediate 3) (1.034 kg, 2.199 mol) in dimethylformamide (2.93 L). The mixture was stirred under nitrogen at ambient temperature (internal temperature of 18°C) after which benzylamine (707 g, 720 ml, 6.60 mol) was added by addition funnel in one portion (< 5 min addition time), during which time an exotherm to a maximum temperature of 55-60°C was observed. Immediately following the complete addition, the reaction mixture was heated at 93-95°C for 4.5 h. LCMS analysis of an aliquot of the reaction mixture diluted in methanol indicated complete consumption of intermediate 3 and formation of product (in addition to its trans counterpart). The heating was stopped and the reaction mixture was allowed to gradually cool to ambient temperature under nitrogen overnight. The reaction solution was then poured into a stirred biphasic mixture of 1:1 ethyl acetate/hexanes (8 L) and water (6 L). After agitation, the organic and aqueous phases were separated. The collected organic phase was washed successively with water, saturated aqueous sodium bicarbonate (wash tested alkaline with pH paper) and saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure, providing 790 g of a dark colored oil. The crude material was loaded onto a silica gel plug (loading aided with a wash of a minimal amount of dichloromethane) after which elution with 15% ethyl acetate/hexanes was performed. Concentration of selected fractions under reduced pressure to give 543 g of dibenzyl N-benzylazetidine-2,4-dicarboxylate with a 82:17 ratio of cis (Intermediate 4):trans stereochemistry and an overall chemical purity of 92%. Crystallization from diethyl ether and air drying provided 310 g (36% overall yield from glutaryl chloride) of dibenzyl c/s-N-benzylazetidine-2,4-dicarboxylate (Intermediate 4) as a white solid (purity >96% based on LCMS). 1H NMR (CDCl3, 300 MHz); δ 7.30 (m, 10H), 5.07 (dd, 4H), 3.89 (s, 2H), 3.67 (dd, 2H), 2.55 (dd, 1H), 2.36 (dd, 1H); LCMS (m/z): 416 (M+1).

A three-neck flask, equipped with a mechanical stirrer, a temperature probe and a nitrogen inlet was charged with dibenzyl c/s-N-benzylazetidine-2,4-dicarboxylate (173 g, 416 mmol) followed by methanol (1.14 L) and tetrahydrofuran (560 mL). The resulting mixture was stirred at ambient temperature under nitrogen until homogeneity was obtained. The solution was then cooled in a dry ice/acetone bath until an internal temperature of -4°C was reached. Then sodium borohydride (79.0 g, 2.08 mol) was added in portions over 1-1.5 h, during which time a slight exotherm to a maximum temperature of 6°C was observed. Following the addition, the resulting mixture was stirred under nitrogen while gradually warming to ambient temperature overnight [Note: during warming, a secondary exotherm up to a maximum temperature of 27°C was observed and was controlled by the use of an ice bath]. LCMS analysis of an aliquot of the reaction mixture diluted in methanol indicated
consumption of stating material and formation of product (plus benzyl alcohol). The reaction mixture was then cooled in an ice water bath (internal temperature of 8°C) and quenched by the drop-wise addition of water (100 ml) via addition funnel. The resulting mixture was concentrated under reduced pressure to remove the bulk of volatiles. The remainder was partitioned between 10% methanol/dichloromethane (500 ml) and water (200 ml). After phase separation, the organic (upper layer) and aqueous phases were collected. The aqueous phase was again extracted with 10% methanol/dichloromethane (2 x 500 ml; organic layer is now the lower phase). Analysis of an aliquot of the aqueous phase at this stage shows no product present. The combined organic extracts were washed successively with water and saturated aqueous sodium chloride. Analysis of this aqueous (water plus saturated aequous sodium chloride) phase showed the presence of product (plus benzyl alcohol), so the aqueous phases were back-extracted with 10% methanol/dichloromethane (3 x). All the methanol/dichloromethane extracts were combined and dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, 177 g of a yellow colored oil was obtained. Further concentration of this residue under high vacuum in a water bath at 75°C was performed to remove the bulk of benzyl alcohol. After constant weight was observed, 100 g of an oil remained. This material was dissolved in dichloromethane and concentrated under reduced pressure giving a semisolid. The semisolid was twice suspended in hexanes and subsequently concentrated under reduced pressure. The remaining solid was suspended in hexanes (260 ml) and the resulting suspension was stirred overnight. The suspension was then filtered and the collected solids were washed with hexanes (2 x). LCMS analysis of a sample of the solid dissolved in methanol indicated a product purity of -90% (contaminated with benzyl alcohol). The solids were again suspended in hexanes (200 ml) and the suspension stirred (on rotovap) for 1 hour at 30°C. The suspension was filtered, and the collected solids were washed with additional hexanes (1 x). LCMS analysis of a sample of the solid dissolved in methanol indicated a product purity >96%. The solids were further air dried to constant weight, affording 81.9 g (95% yield) of c/s-N-benzyl-2,4-bis(hydroxymethyl)azetidine (intermediate 5) as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.28 (m, 5H), 4.24 (dd, 2H), 3.63 (s, 2H), 3.12 (dd, 4H), 3.05 (m, 2H), 2.00 (dd, 1H), 1.57 (dd, 1H); LCMS (m/z): 208 (M+1).

A three-neck flask, equipped with a mechanical stirrer, a temperature probe, a nitrogen inlet and an addition funnel, was charged with c/s-N-benzyl-2,4-bis(hydroxymethyl)azetidine (81.9 g, 395 mmol) followed by anhydrous dichloromethane (820 mL). The resulting solution was stirred under nitrogen, after which triethylamine (160 g, 220 mL, 1.58 mol) was added in one portion. The resulting solution was cooled in a dry ice/acetone bath until an internal temperature of -6°C was reached. Then methanesulfonyl chloride (109 g, 73.4 mL, 948 mmol) was added drop-wise by addition funnel over 45 min,
during which time an exotherm occurred up to a maximum observed temperature of 4°C. Following the addition, the reaction mixture was allowed to gradually warm to ambient temperature while stirring under nitrogen overnight. LCMS analysis of an aliquot of the reaction mixture diluted in acetonitrile indicated consumption of starting material and formation of product. To the reaction mixture was added water (250 mL) drop-wise followed by saturated aqueous sodium bicarbonate (250 mL). The resulting biphasic mixture was stirred vigorously for 20 min and transferred to a separatory funnel, aided by a dichloromethane rinse. The organic and aqueous phases were separated and the organic layer was then washed with saturated aqueous sodium chloride. After phase separation (slow), the organic layer was collected, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure, leaving 143 g (100% yield) of the bis-mesylate (Intermediate 6), as a brown colored oil, which was used without purification in the next step.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 7.33 (m, 5H), 3.97 (ddd, 4H), 3.74 (s, 2H), 3.44 (m, 2H), 2.92 (s, 6H), 2.28 (m, 1H), 1.91 (m, 1H); LCMS (m/z): 364 (M+1).

A three-neck flask, equipped with a mechanical stirrer, a temperature probe, a nitrogen inlet and a reflux condenser, was charged with cyclopropanecarboxamide (36.8 g, 432 mmol) under an atmosphere of nitrogen. Anhydrous 1-methyl-2-pyrrolidinone (N-methyl-2-pyrrolidone) (900 mL) was added and the resulting mixture was mechanically stirred under nitrogen while cooling in an ice water bath (internal temperature of 5°C). Then sodium hydride (39.4 g of a 60% dispersion in mineral oil, 980 mmol) was added in portions over 30 min, as the temperature varied between 5 and 12°C. The resulting mixture was stirred on the cold bath for an additional 10 min. The cold bath was allowed to warm to ambient temperature (over 30 min), at which point a slight exotherm (to a maximum temperature of 25°C) and gas evolution were observed. The resulting mixture was stirred at ambient temperature for an additional 50 min (no further gas evolution), after which a solution of the bis-mesylate (Intermediate 6) (143 g, 393 mmol) in anhydrous 1-methyl-2-pyrrolidinone (600 mL) was added to the suspension in one lot. The flask containing crude Intermediate 6 was rinsed with additional anhydrous 1-methyl-2-pyrrolidinone (2 x 100 mL), each rinse being added to the reaction suspension. The resulting mixture was then heated at 68°C for 3 h. LCMS analysis of an aliquot, withdrawn after 2 h of heating and quenched in moist acetonitrile, indicated that >96% of Intermediate 6 had been consumed and that desired product predominated. The reaction mixture was allowed to cool under nitrogen to ambient temperature overnight. The viscous solution was quenched, in an ice water bath cooling, by the addition of water (-10 mL) and diluted with methyl t-butyl ether (100 mL) and stirred for 10 min. The mixture was then transferred to a separatory funnel containing 5% aqueous sodium chloride (4.0 L) and 25% ethyl acetate/methyl t-butyl ether (3.0 L). The resulting mixture was agitated. After phase separation, the organic and aqueous layers
were drawn off. The aqueous phase was extracted with additional 25% ethyl acetate/methyl t-butyl ether (2 x 3.0 L). The combined organic extracts were washed with water (1 x 3.0 L) and then saturated aqueous sodium chloride (1 x 3.0 L). The organic phase was then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure, affording 86 g of brown colored oil. This residue was purified by silica gel chromatography, eluting initially with 0 to 40% ethyl acetate/hexanes and finally with 60 to 100% ethyl acetate/hexanes + 0.5% triethylamine. Concentration of selected fractions gave 56 g of 6-benzyl-3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane with HPLC purity of 78%. This was used in the next step without further purification.

A three-neck flask, equipped with a mechanical stirrer, a temperature probe, a reflux condenser and a nitrogen inlet, was charged with a solution of 6-benzyl-3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane (56 g of 78%, 220 mmol) in ethanol (200 proof, 670 ml) under nitrogen. Then 10% Pd/C (33.6 g, wet) was added followed by ammonium formate (82.6 g, 1.31 mol). The resulting mixture was rigorously stirred under a nitrogen atmosphere and gradually heated at 60 to 66°C for 6 h, an additional 20 g of 10% Pd/C and 60 g of ammonium formate being added after -3.5 h. The reaction was then heated (between 66°C and 71°C for 6 h) and periodically monitored by LCMS, as more reagents were added in several portions (total additional ammonium formate = 96 g; total additional 10% Pd/C = 21 g). An analysis of an aliquot of the reaction mixture then indicated consumption of starting material. Heating was stopped and the reaction mixture was allowed to gradually cool to ambient temperature under nitrogen overnight. The reaction mixture was then filtered through a bed of diatomaceous earth. The filter cake was subsequently washed with methanol (4 x), and the combined filtrates were concentrated under reduced pressure, providing 35 g of a pale yellow colored oil. The material was purified by silica gel chromatography, eluting with 0 to 60% DCMA80 in dichloromethane.

[Note: DCMA80 is a 80:18:2 mixture of dichloromethane, methanol, and aqueous ammonium hydroxide]. Selected fractions were combined and concentrated under reduced pressure, affording 9.2 g of a nearly white solid with HPLC purity of 97.7%. The purity of this material could be increased to 98.7% (HPLC) by trituration with methyl t-butyl ether. Less pure fractions from the chromatography were also concentrated, yielding an additional 11 g of material (~ 85% purity by HPLC). 1H NMR (D2O, 300 MHz): δ 4.02 (s, 2H), 3.73 (m, 2H), 3.64 (dd, 2H), 2.66 (m, 1H), 1.92 (m, 1H), 1.52 (d, 1H), 0.88 (m, 4H); LCMS (m/z): 167 (M+1).

Example 3: Synthesis of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane hemigalactarate monohydrate {3,6-diazabicyclo[3.1.1]heptan-3-yl(cyclopropyl)methanone hemigalactarate monohydrate}
A three neck round bottom flask, equipped with a mechanical stirrer, a temperature probe, a reflux condenser and a nitrogen inlet, was charged with 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane (132 g, 0.794 mol, representing multiple runs of the chemistry shown in Example 2) under nitrogen. Ethanol (200 proof, 925 ml) and water (110 ml) were added to the reaction flask, and the mixture was stirred at ambient temperature until solution was obtained. Then, galactaric acid (86.0 g, 0.397 mol) was added and the resulting mixture was heated at 50°C under nitrogen for 2 h. Heating was then stopped, and the resulting thick slurry was allowed to cool to ambient temperature while stirring under nitrogen overnight. The mixture was then cooled in an ice water bath to 0°C and suction filtered. The collected solids were air dried briefly and then dissolved in hot water (1000 ml; 60°C). The solution was filtered while hot to remove a small amount of insoluble material and then concentrated to near dryness. To this residue was added ethanol (200 proof, 800 ml), and the mixture was stirred at 50°C for 30 min and then cooled to 0°C in an ice water bath where it remained for 45 min. The slurry was filtered, and the collected solids were dried under vacuum overnight. Further drying of the solid was performed under vacuum at 56°C to constant weight (over a period of 4 h), giving 208 g (95% yield) of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane hemigalactarate monohydrate as a white solid (HPLC purity 99%). 1H NMR (D2O, 400 MHz): δ 4.39 (m, 2H), 4.20 (dd, 2H), 4.09 (s, 1H), 3.88 (d, 1H), 3.79 (s, 1H), 3.74 (d, 1H), 2.93 (m, 1H), 1.77 (m, 2H), 0.80 (m, 4H); LCMS (m/z): 167 (M+1); Karl Fischer analysis of the dried material indicated 6.5% water content (corresponds to monohydrate stoichiometry).

**Example 4: Synthesis of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane hydrochloride, using amide coupling procedure**

To tert-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (50 mg, 0.25 mmol) in a 25 ml round bottom flask were added cyclopropanecarboxylic acid (26 mg, 24 µL, 0.30 mmol), triethylamine (70 µL, 0.50 mmol), dichloromethane (5 ml) and O-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate (191 mg, 0.50 mmol). The reaction was stirred at ambient temperature for 2 h. Saturated ammonium chloride (5 ml) was added, and the reaction mixture was stirred for 30 min. The mixture was then passed through a phase extractor, and the solvent was removed under vacuum. The crude mixture was dissolved in 3 ml of ethyl acetate and concentrated HCl (1 ml) was added. This mixture was stirred for 2 h. The solvent was removed under vacuum, and the residue was passed through a silica-based cation exchange column, which was pre-washed with 2 ml of methanol followed by 2 ml of dichloromethane/methanol (1:1). The residue was taken up in 1 ml dichloromethane/methanol and passed through the column, eluting with 3 ml dichloromethane/methanol (1:1) followed by methanol/ammonia (7M). The eluates were concentrated, and the residue was purified by silica gel column chromatography, eluting with
a gradient of CMA90 (chloroform/methanol/aqueous ammonium hydroxide 90:9:1) in chloroform. Selected fractions were concentrated under vacuum, and the residue was combined with 1M hydrogen chloride in methanol (2 mL). The resulting mixture was filtered through a phase extractor (to remove any fine particles), and the solvent was removed under vacuum, leaving 3,6-diazabicyclo[3.1.1]heptan-3-yl(cyclopropyl)methanone hydrochloride, as an oil (14 mg, 27%). $^1$H NMR (CD$_3$OD, 400 MHz): δ 4.49 (m, 2H), 4.32 (dd, 2H), 4.01 (d, 1H), 3.88 (d, 1H), 3.06 (m, 1H), 1.94 (m, 2H), 0.93 (m, 4H). Note: While this material failed to crystallize, other samples of the hydrochloride salt were induced to crystallize (after trituration with acetone). The resulting solid is hygroscopic.

Example 5: Preparation of Additional Salts

Based upon measured pKa values, the following pharmaceutically acceptable acids were selected for inclusion in a salt selection study:
To a solution of 30.0 mg (0.165 mmol) of free base in the selected solvent at 50°C, the corresponding acid (0.5 equivalent or 1.1 equivalent depending on the number and strength of the acidic moieties of the acid) was added as a solution or suspension.

The mixture was stirred at 50°C for 1 h, then slowly cooled to 0°C overnight (0.1°C/min). The solids were filtered and analyzed. If no solid was produced, the corresponding solution was allowed to evaporate slowly at ambient conditions.

In the case of clear solutions, gums, or oils, these were cooled to -20°C, and allowed to evaporate slowly to encourage crystallization. Thereafter, anti-solvent (co-solvent; methyl...
t-butyl ether) was then added, if oils/gums would not crystallize; followed by trituration with acetone. With this added effort, many salts gave a precipitate when placed in isopropyl acetate (results shown in the two tables below).
<table>
<thead>
<tr>
<th>Acid</th>
<th>Eq.</th>
<th>At 50°C</th>
<th>At 0°C</th>
<th>XRPD</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Hydrochloric acid 37 wt% (12M)</td>
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<td>Gum</td>
<td>Gum</td>
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<td>1.1</td>
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<td>p-Toluene sulphonic acid, H2O</td>
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<td>Solid</td>
<td>Solid</td>
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<td>-</td>
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<tr>
<td>Methane sulphonic acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>-</td>
<td>Deliquesced within minutes after isolation</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>0.5</td>
<td>Solid</td>
<td>Solid</td>
<td>-</td>
<td>Deliquesced within minutes after isolation</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>-</td>
<td>Deliquesced within minutes after isolation</td>
</tr>
<tr>
<td>L-Aspartic acid</td>
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<td>Solid</td>
<td>Crystalline</td>
<td>L-Aspartic acid</td>
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<tr>
<td>L-Aspartic acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>L-Aspartic acid</td>
</tr>
<tr>
<td>Maleic acid</td>
<td>0.5</td>
<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>Same XRPD as TB-09-10</td>
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<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
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<td>1.1</td>
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<td>-</td>
<td>Deliquesced within minutes after isolation</td>
</tr>
<tr>
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<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>-</td>
</tr>
<tr>
<td>L-Glutamic acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>-</td>
</tr>
<tr>
<td>1-Hydroxy-2-Naphthoic acid (Xinofrate)</td>
<td>1.1</td>
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<td>Crystalline</td>
<td>-</td>
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<tr>
<td>L-Tartaric acid</td>
<td>0.5</td>
<td>Solid</td>
<td>Solid</td>
<td>-</td>
<td>Deliquesced within minutes after isolation</td>
</tr>
<tr>
<td>L-Tartaric acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>-</td>
<td>Deliquesced within minutes after isolation</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>0.5</td>
<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>-</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>Same XRPD as TB-09-17 with extra peaks</td>
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<tr>
<td>Galactaric acid (Mucic Acid)</td>
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<td>Solid</td>
<td>Solid</td>
<td>Crystalline</td>
<td>Same XRPD as hemigalactate ref.</td>
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<td>Galactaric acid (Mucic Acid)</td>
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<td>Citric acid</td>
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<tr>
<td>Citric acid</td>
<td>1.1</td>
<td>Solid</td>
<td>Solid</td>
<td>-</td>
<td>Deliquesced within minutes after isolation</td>
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<tr>
<td>D-Glucoronic acid</td>
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<td>Solid</td>
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<tr>
<td>Malic acid</td>
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<td>Gum</td>
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<td>Deliquesced within minutes after isolation</td>
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<td>Hippuric acid</td>
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<td>Solid</td>
<td>Crystalline</td>
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<tr>
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<td>Oil</td>
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<td>-</td>
</tr>
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</tr>
<tr>
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<td>Gum</td>
<td>Gum</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L-Ascorbic acid</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>Solid</td>
<td>Crystalline</td>
<td>-</td>
</tr>
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<td>Succinic acid</td>
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<td>-</td>
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<td>(+)-Camphoric acid</td>
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<td>Solid</td>
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Initially, a salt screen was performed using isopropyl acetate, however, for those experiments which produced non isolatable salts, a further salt screen was performed using isopropyl alcohol and 2-butanone (methyl ethyl ketone) (see the two tables below).

<table>
<thead>
<tr>
<th>Acid</th>
<th>Eq.</th>
<th>Observation at -20°C</th>
<th>Observation after slow evaporation</th>
<th>Observation after maturation in TBME</th>
<th>Observation after trituration with acetone</th>
<th>XRPD</th>
</tr>
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<td>Gum</td>
<td>Gum</td>
<td>Gum</td>
<td>-</td>
</tr>
<tr>
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<td>Gum</td>
<td>Solid</td>
<td>Amorphous</td>
</tr>
<tr>
<td>L-Lactic acid 85% aq solution</td>
<td>1.1</td>
<td>Gum</td>
<td>Gum</td>
<td>Gum</td>
<td>Clear solution</td>
<td>-</td>
</tr>
<tr>
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<td>Gum</td>
<td>Solid</td>
<td>Amorphous</td>
</tr>
<tr>
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<td>Clear solution</td>
<td>Gum</td>
<td>Gum</td>
<td>Gum</td>
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<tr>
<td>Acetic acid</td>
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<td>Gum</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>Crystalline</td>
</tr>
<tr>
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<td>Clear solution</td>
<td>Gum</td>
<td>Gum</td>
<td>Clear solution</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acid</th>
<th>Eq.</th>
<th>At 50°C</th>
<th>At 0°C</th>
<th>Observation after slow evaporation</th>
<th>Observation after trituration with acetone</th>
<th>XRPD</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Solid</td>
<td>-</td>
<td>-</td>
<td>Deliquesced on isolation</td>
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<td>Clear solution</td>
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<td>Gum</td>
<td>-</td>
</tr>
<tr>
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<td>Clear solution</td>
<td>Clear solution</td>
<td>Gum</td>
<td>Gum</td>
<td>-</td>
</tr>
<tr>
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<td>0.5</td>
<td>Clear solution</td>
<td>Clear solution</td>
<td>Solid after 1 month</td>
<td>-</td>
<td>Crystalline like free base + extra peaks</td>
</tr>
<tr>
<td>L-Glutamic acid</td>
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<td>Clear solution</td>
<td>Clear solution</td>
<td>Solid after 1 month</td>
<td>-</td>
<td>Crystalline</td>
</tr>
<tr>
<td>D-Glucuronic acid</td>
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<td>Oil</td>
<td>Oil</td>
<td>Gum</td>
<td>Solid</td>
<td>Amorphous</td>
</tr>
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<td>Clear solution</td>
<td>Clear solution</td>
<td>Gum</td>
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<td>-</td>
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<td>Clear solution</td>
<td>Gum</td>
<td>Clear solution</td>
<td>-</td>
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<tr>
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<td>Solid</td>
<td>-</td>
<td>-</td>
<td>Crystalline</td>
</tr>
<tr>
<td>Acid</td>
<td>Eq.</td>
<td>At 50°C</td>
<td>At 0°C</td>
<td>At -20°C</td>
<td>Observation after slow evaporation</td>
<td>Observation after anti-solvent addition/maturation</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----</td>
<td>----------</td>
<td>---------</td>
<td>----------</td>
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<tr>
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<td>Gum</td>
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<td>Clear solution</td>
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<td>Oil</td>
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<tr>
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<td>Oil</td>
<td>Gum</td>
<td>Gum</td>
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<tr>
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<td>Clear solution</td>
<td>Gum</td>
<td>Gum</td>
</tr>
<tr>
<td>4-hydroxybenzoic acid</td>
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<td>Solid</td>
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<td>Gum</td>
<td>Gum</td>
<td>Solid</td>
</tr>
</tbody>
</table>

All solids were filtered and analyzed by XRPD.

Figure 1 illustrates the crystal structure for Compound A, hemigaiaetarate monohydrate.

Figure 2 illustrates the crystal structure with a numbering scheme employed.

Figure 3 illustrates a TGA/DSC of Compound A hemigaalactarate monohydrate salt.

Figure 4 illustrates a GVS of Compound A hemigaalactarate monohydrate salt.

Figure 5 illustrates an XRPD pattern for Compound A hemigaalactarate monohydrate salt before and after storage at 40°C/75% RH and GVS.

Figure 8 illustrates an XRPD of Compound A xinafoate salt.

Figure 7 illustrates a TGA/DSC of Compound A xinafoate salt.

Figure 8 illustrates a GVS of Compound A xinafoate salt.

Figure 9 illustrates an XRPD of Compound A benzoate salt.

Figure 10 illustrates a TGA/DSC of Compound A benzoate salt.

Figure 11 illustrates a GVS of Compound A benzoate salt.

Figure 12 illustrates a high resolution VT-XRPD of Compound A benzoate salt.

Figure 13 illustrates an XRPD of Compound A hippurate salt.

Figure 14 illustrates a TGA/DSC of Compound A hippurate salt.

Figure 15 illustrates a GVS of Compound A hippurate salt.

Figure 16 illustrates a high resolution VT-XRPD of Compound A hippurate salt.

Figure 17 illustrates an XRPD of Compound A hemigaactarate salt for polymorphism assessment.

Figure 18 illustrates an XRPD of Compound A benzoate salt for polymorphism assessment.
Figure 19 illustrates an XRPD of Compound A hippurate salt for polymorphism assessment.

Figure 20 illustrates an XRPD of Compound A xinafoate salt for polymorphism assessment.

Figure 21 illustrates an XRPD for Compound A (+)-camphorate salt.

Figure 22 illustrates a TGA/DSC for Compound A (+)-camphorate salt.

Figure 23 illustrates an XRPD for Compound A tosylate salt.

Figure 24 illustrates a TGA/DSC for Compound A tosylate salt.

Figure 25 illustrates an XRPD for Compound A maleate salt, using 0.5 eq acid. The sample deliquesced so TGA and DSC were not measured.

Figure 26 illustrates an XRPD for Compound A maleate salt, using 1 eq acid.

Figure 27 illustrates a TGA/DSC for Compound A maleate salt, using 1 eq acid.

Figure 28 illustrates an XRPD for Compound A L-mandelate salt.

Figure 29 illustrates a TGA/DSC for Compound A L-mandelate salt.

Salts having acceptable physical characteristics for drug development include hydrochloride, p-toluenesulfonate, L-aspartate, maleate, L-glutamate, 1-hydroxy-2-naphtoate (xinafoate), fumarate, galactarate, hippurate, L-mandelate, succinate, adipate, or (+)-camphorate. Preferred salts include p-toluenesulfonate, maleate, galactarate, benzoate, hippurate, xinafoate, or (+)-camphorate.

The NMR spectra and melting points of several salts are given below. These data were obtained from the preliminary salt screen.

**Compound A p-toluenesulfonate:** $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 7.48 (d, 2H), 7.12 (d, 2H), 4.37 (m, 2H), 4.13 (dd, 2H), 3.79 (d, 1H), 3.70 (d, 1H), 2.81 (m, 1H), 2.29 (s, 3H), 1.87 (m, 1H), 1.75 (d, 1H), 0.81 (m, 4H); mp: 172°C.

**Compound A maleate:** $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 6.08 (s, 2H), 4.42 (m, 2H), 4.20 (dd, 2H), 3.84 (d, 1H), 3.78 (d, 1H), 2.88 (m, 1H), 1.94 (m, 1H), 1.82 (d, 1H), 0.85 (m, 4H); mp: 163°C.

**Compound A xinafoate:** $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 8.24 (m, 1H), 7.75 (m, 2H), 7.51 (dd, 1H), 7.41 (dd, 1H), 7.06 (d, 1H), 4.42 (m, 2H), 4.19 (m, 2H), 3.82 (dd, 2H), 2.91 (m, 1H), 1.93 (m, 1H), 1.79 (d, 1H), 0.84 (m, 4H).

**Compound A L-mandelate:** $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 7.41 (d, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 4.72 (s, 1H), 4.10 (m, 4H), 3.69 (dd, 2H), 2.72 (m, 1H), 1.91 (m, 1H), 1.62 (d, 1H), 0.82 (m, 4H); mp: 143°C.

**Compound A hippurate:** $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 7.92 (d, 2H), 7.57 (m, 3H), 4.01 (s, 2H), 3.88 (m, 4H), 3.60 (dd, 2H), 2.62 (m, 1H), 1.94 (m, 1H), 1.52 (d, 1H), 0.82 (m, 4H).
Compound A benzoate: $^1$H NMR ($d_6$-DMSO, 400 MHz): $\delta$ 7.92 (d, 2H), 7.54 (t, 1H), 7.44 (m, 2H), 3.95 (m, 2H), 3.84 (m, 2H), 3.56 (dd, 2H), 2.63 (m, 1H), 1.87 (m, 1H), 1.49 (d, 1H), 0.77 (m, 4H).

Compound A (+)-camphorate: $^1$H NMR ($d_6$-DMSO, 400 MHz): $\delta$ 3.94 (m, 2H), 3.70 (m, 2H), 3.56 (dd, 2H), 2.78 (t, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.75 (n, 1H), 1.44 (m, 2H), 1.23 (s, 3H), 1.16 (s, 3H), 0.82 (m, 7H); mp: 170d.

The syntheses of certain salts, identified in the salt screen, were scaled up as preferential. Those procedures, melting points, and solubility data are reported here.

Compound A xinafoate: 3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptanes (500 mg, 3.01 mmol) was dissolved in isopropyl acetate (5 mL) at 70°C. Xinafoic acid (626 mg, 3.31 mmol) was suspended in 98:2 isopropyl acetate/water (6.1 mL) at 60°C and added to the solution of free base. The resulting mixture was cooled slowly to 0°C, and the suspended solids were collected by suction filtration and dried under vacuum at ambient temperature for 5 h. An off-white powder was obtained (1.01 g, 95% yield). The sample exhibited a melting point of 177°C and an aqueous solubility of 2.6 mg/mL.

Compound A benzoate: 3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptanes (500 mg, 3.01 mmol) was dissolved in isopropyl acetate (5 mL) at 70°C. Benzoic acid (405 mg, 3.31 mmol) was dissolved in 98:2 isopropyl acetate/water (3.1 mL) at 60°C and added to the solution of free base. The resulting mixture was cooled slowly to 0°C, and the suspended solids were collected by suction filtration and dried under vacuum at ambient temperature for 5 h. A white powder was obtained (833 mg, 95% yield). The sample exhibited a melting point of 136°C and an aqueous solubility of >15 mg/mL.

Compound A hippurate: 3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptanes (500 mg, 3.01 mmol) was dissolved in isopropyl acetate (5 mL) at 70°C. Hippuric acid (596 mg, 3.31 mmol) was suspended in 98:2 isopropyl acetate/water (6.1 mL) at 60°C and added to the solution of free base. The resulting mixture was cooled slowly to 0°C, and the suspended solids were collected by suction filtration and dried under vacuum at ambient temperature for 5 h. An off-white powder was obtained (884 mg, 85% yield). The sample exhibited a melting point of 157°C and an aqueous solubility of >15 mg/mL.

**Example 6: Characterization of interactions at Nicotinic Acetylcholine Receptors**

**Cell lines**

SH-EP1/human $\alpha_4\beta_2$ (Eaton et al., 2003), SH-EP1/human $\alpha_4\beta_4$ (Gentry et al., 2003), SH-EP1/$\alpha_6\beta_3$$\beta_4$$\alpha_5$ (Grinevich et al., 2005), SH-EP1_hum $\alpha_6/\alpha_3/\beta_3$ (obtained from Paul Whiteaker, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, Arizona), TE671/RD and SH-SY5Y cell lines (obtained from Dr. Ron Lukas, Barrow
Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, Arizona) were maintained in proliferative growth phase in Dulbecco’s modified Eagle’s medium (Gibco/BRL) with 10% horse serum (Gibco BRL), 5% fetal bovine serum (HyClone, Logan UT), 1 mM sodium pyruvate, 4 mM L-glutamine. For maintenance of stable transfectants, the α4β2 and α4β4 cell media was supplemented with 0.25 mg/mL zeocin and 0.13 mg/mL hygromycin B. Selection was maintained for the α6β3γ4α5 cells with 0.25 mg/mL of zeocin, 0.13 mg/mL of hygromycin B, 0.4 mg/mL of geneticin, and 0.2 mg/mL of blasticidin.

Selection was maintained for the α6/α3β2β3 cells with 0.3 mg/mL zeocin and 0.3 mg/mL hygromycin B and 0.6 mg/mL G418 sulfate. HEK/human a7/RIC3 cells (obtained from J. Lindstrom, U. Pennsylvania, Philadelphia, Pennsylvania) were maintained in proliferative growth phase in Dulbecco’s modified Eagle’s medium (Gibco/BRL) with 10% fetal bovine serum (HyClone, Logan UT), 1 mM sodium pyruvate, 4 mM L-glutamine, 0.4 mg/mL geneticin; 0.2 mg/ml hygromycin B.

**Receptor Binding Assays**

**Preparation of membranes from rat tissues.** Rat cortices were obtained from Analytical Biological Services, Incorporated (ABS, Wilmington, Delaware). Tissues were dissected from female Sprague-Dawley rats, frozen and shipped on dry ice. Tissues were stored at -20 °C until needed for membrane preparation. Cortices from 10 rats were pooled and homogenized by Polytron (Kinematica GmbH, Switzerland) in 10 volumes (weight/volume) of ice-cold preparative buffer (KCl, 11 mM; KH₂PO₄, 6 mM; NaCl 137 mM; Na₂HPO₄ 8 mM; HEPES (free acid), 20 mM; iodoacetamide, 5 mM; EDTA, 1.5 mM; 0.1 mM PMSF pH 7.4).

The resulting homogenate was centrifuged at 40,000 g for 20 minutes at 4 °C and the resulting pellet was resuspended in 20 volumes of ice-cold water. After 60-minute incubation at 4 °C, a new pellet was collected by centrifugation at 40,000 g for 20 minutes at 4 °C. The final pellet was resuspended in preparative buffer and stored at -20 °C. On the day of the assay, tissue was thawed, centrifuged at 40,000 g for 20 minutes and then resuspended in PBS (Dulbecco’s Phosphate Buffered Saline, Life Technologies, pH 7.4) to a final concentration of 2-3 mg protein/mL. Protein concentrations were determined using the Pierce BCA Protein Assay kit (Pierce Biotechnology, Rockford, IL), with bovine serum albumin as the standard.

**Preparation of membranes from clonal cell lines.** Cells were harvested in ice-cold PBS, pH 7.4, then homogenized with a polytron (Brinkmann Instruments, Westbury, NY). Homogenenates were centrifuged at 40,000g for 20 minutes (4 °C). The pellet was resuspended in PBS and protein concentration determined using the Pierce BCA Protein Assay kit (Pierce Biotechnology, Rockford, IL).
Competition binding to receptors in membrane preparations. Binding to nicotinic receptors was assayed on membranes using standard methods adapted from published procedures (Lippiello and Fernandes, 1986; Davies et al., 1999). In brief, membranes were reconstituted from frozen stocks (approximately 0.2 mg protein) and incubated for 2 h on ice in 150 ml assay buffer (PBS) in the presence of competitor compound (0.001 nM to 100 mM) and radioligand. [3H]-nicotine (L-(-)[N-methyl-3H]-nicotine, 69.5 Ci/mmol, Perkin-Elmer Life Sciences) was used for human α4β2 binding studies. [3H]-epibatidine (52 Ci/mmol, Perkin-Elmer Life Sciences) was used for binding studies at the other receptor subtypes. Incubation was terminated by rapid filtration on a multimanifold tissue harvester (Brandel, Gaithersburg, MD) using GF/B filters presoaked in 0.33% polyethyleneimine (w/v) to reduce non-specific binding. Filters were washed 3 times and the radioactivity retained was determined by liquid scintillation counting.

Binding data analysis. Binding data were expressed as percent total control binding. Replicates for each point were averaged and plotted against the log of drug concentration. The IC_{50} (concentration of the compound that produces 50% inhibition of binding) was determined by least squares non-linear regression using GraphPad Prism software (GraphPAD, San Diego, CA). K was calculated using the Cheng-Prusoff equation (Cheng and Prusoff, 1973).

| TABLE 1 |
|------------------|------------------|------------------|------------------|------------------|
| STRUCTURE        | α6β3[4α5 K]      | α6ε3β3 K        | Human α4β2 K     | Rat α4β2 K       | Human α7 K       |
| ![Structure](image) | 140              | 20              | 3.0              | 2.3              | 620              |

Example 7: Summary of Pharmacology

In vitro pharmacology:

Compound A is a high affinity ligand for α6β2* and α4β2* NNRs, and demonstrates lower affinity for a7 NNRs. Compound A is a full agonist at all three subtypes and displays sufficient functional separation from muscle- and ganglion-type nicotinic receptors as well as non-target receptors. Compound A did not interact with any non-NNR receptors in a
Novascreen panel of > 60 targets. Compound A also exhibits robust desensitization of three \( \alpha_4 \beta_2 \) NNR subtypes known to be present in the striatum. Specifically, Compound A had DC_{50}s of 24 nm, 68 nm, and 42 nm at \((\alpha4)_2(\beta2)_2\) "high sensitivity", \((\alpha4)_2(\beta2)_2\) "low sensitivity", \((\alpha5(\alpha4))_2(\beta2)_2\) receptors respectively, with full inhibition (> 98% \( I_{\text{max}} \)) when administered 30 min prior to 10 \( \mu \)M acetylcholine at each. Desensitization is potentially relevant to efficacy in treating LIDs (see Bordia et al., J. Pharm. Exp. Ther. 327(1): 239-247 (2008)).

As preliminarily reported in WO 201 1/071758, Compound A produced extremely potent neuroprotective effects against MPP+ toxicity in primary cultures of rat dopamine neurons. Compound A was protective over a broad dose range (1 nM to 1 \( \mu \)M) when pre-incubated for either 24 or 48 hours before MPP+ exposure. When a 24 hour pre-incubation was used, the minimum effective dose was 10 nM, making Compound A as efficacious, and more potent than nicotine in this assay. The greater receptor selectivity and the greater neuroprotective potency of Compound A, compared with nicotine, may lead to better tolerability in long-term administration for disease modification in Parkinson's disease.

**In vivo pharmacology.**

Rat study: The ability of Compound A to reduce AIMs was determined in 6-OHDA-induced (hemi-) parkinsonian rats repeatedly administered L-dopa. Compound A was tested in both L-dopa naive (modeling prevention or delay in onset of LIDs) and L-dopa-primed (modeling treatment of existing LIDs) parkinsonian rats using a crossover design.

In the first phase of the crossover, Compound A was administered at 0.75 mg/kg/day via subcutaneous minipump for two weeks prior to L-dopa administration, then concurrently with L-dopa for an additional 3 weeks. Compound A prevented the full onset of LID at 0.75 mg/kg/day in L-dopa naive rats (34% decrease in AIMs, see Figure 30a) and the effect was maintained when the dose was dropped to 0.3 mg/kg/day for additional weeks.

Dosing groups were then crossed over so that animals that had been receiving vehicle in combination with L-dopa (L-dopa primed) were exposed to Compound A. Compound A produced a small but significant reduction (13%) in established LIDs after 2 weeks at 0.3 mg/kg/day via minipump. When the dose was increased to 0.7 mg/kg/day for an additional 2 weeks, the reduction increased to 21% (see Figure 30b). When the data was analyzed according to the severity of the lesion, Compound A reduced established AIMs in moderately lesioned animals by 36%.

Since drugs that reduce AIMs may worsen parkinsonism, the effect of Compound A was also tested on motor function in parkinsonian rats using the limb use asymmetry, or cylinder test, which is a sensitive measure of the degree of unilateral dopamine loss. The results show that Compound A does not worsen baseline motor function (off L-dopa) nor does it worsen the enhanced limb use with L-dopa treatment (see Figure 30c). Importantly,
compound a resulted in no detectable adverse effects (i.e., on body weight, body temperature, grooming, urination, defecation, secretion) during the course of the efficacy experiment.

Non-human primate study: To further assess the ability of Compound A to alleviate LIDs without reducing the anti-parkinsonian effect of L-dopa, an MPTP-lesioned cynomolgus macaque model of Parkinson's disease was employed. In this study, MPTP-lesioned cynomolgus macaques were treated, for two weeks, with a variable dose of L-dopa (20-35 mg/kg/day p.o. once daily in the morning) optimized for each animal to reverse parkinsonian symptoms but elicit marked-to-severe dyskinesia. For the following six weeks, animals continued to receive L-dopa, but also received (by oral gavage) either vehicle (once daily) or Compound A (twice daily, 8 hours apart, the morning treatment concurrent with L-dopa treatment). There were seven animals in each group (treatment and vehicle). Treatment animals received increasing doses of Compound A: two weeks at 0.03 mg/kg, followed by two weeks at 0.10 mg/kg; followed by two weeks at 0.30 mg/kg; b.i.d. On each of days 7, 13, 21, 28, 35, 42, 49 and 59, animals were assessed for "bad quality" on-time (marked-to-severe dyskinesia) and "good quality" on-time (no, mild, or moderate dyskinesia). This assessment period started with morning treatment and lasted 6 hours. During the two hour period between the end of the first hour and the end of the third hour, both dyskinesia severity and parkinsonian disability were assessed.

As shown in Figure 31a, Compound A significantly reduced LIDs. This effect was especially strong at the 0.10 mg/kg dose. As shown in Figures 31b and 31c, Compound A did not significantly alter either total on-time (total time when L-dopa's anti-parkinsonian effects are observed) or parkinsonian disability (the effectiveness of L-dopa treatment). As shown in Figure 32, Compound A significantly decreased the percent of bad quality on-time (time characterized by troubling dyskinesia) from 50-55% to approximately 30% and correspondingly increased the percent of good quality on-time (time without troubling dyskinesia) from 45-50% to approximately 70%. Total dyskinesias, as well as chorea and dystonia endpoints, were significantly decreased. Compound A was very well tolerated in the study, did not negatively impact the general motor activity of the animals, and did not counteract levodopa's effect on parkinsonism.

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are
provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.
What is claimed is:

1. An acid addition salt of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane.
2. An acid addition salt of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane wherein the acid is selected from hydrochloric, p-toluenesulfonic, L-aspartic, maleic, L-glutamic, 1-hydroxy-2-naphthoic, fumaric, galactaric, hippuric, L-mandelic, succinic, adipic, or (+)-camphoric.
3. The acid addition salt of Claim 2, wherein the salt is a p-toluenesulfonate, maleate, galactarate, benzoate, hippurate, xinafoate, or (+)-camphorate.
4. The acid addition salt of Claim 3, wherein the salt is a galactarate, benzoate, hippurate, or xinafoate.
5. 3-Cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane hemigalactarate monohydrate.
6. The acid addition salt of any one of claims 1-6, wherein the salt is crystalline.
7. A pharmaceutical composition comprising a compound according to any of Claims 1-6 and one or more pharmaceutically acceptable carrier, diluent, or excipient.
8. A method for the treatment or prevention of a disease or condition mediated by neuronal nicotinic receptors comprising the administration of a compound as claimed in any of claims 1-6.
9. Use of a compound as claimed in any of claims 1-6 for the preparation of a medicament for the treatment or prevention of a disease or condition mediated by neuronal nicotinic receptors.
10. A compound as claimed in claims 1-6 for use as an active therapeutic substance.
11. A compound as claimed in claims 1-6 for use in the treatment or prevention of a disease or condition mediated by neuronal nicotinic receptors.
12. The method, use, or compound of claim 8-11, wherein the neuronal nicotinic receptors are of the α4β2+ subtype.
13. The method, use, or compound of claim 8-11, wherein the neuronal nicotinic receptors are of the α6β2+ subtype.
14. The method, use, or compound of claim 8-11, wherein the neuronal nicotinic receptors are of both the α4β2+ and the α6β2+ subtypes.
15. The method, use, or compound of claim 8-11, wherein the disease or condition is a CNS disorder.
16. The method, use, or compound of claim 8-11, wherein the disease or condition is abnormal involuntary movements.
17. The method, use, or compound of claim 8-11, wherein the disease or condition is L-dopa induced dyskinesia.
18. The method, use, or compound of claim 8-11, wherein the disease or condition is
dyskinesia.

19. The method, use, or compound of claim 8 - 11, wherein the disease or condition is Parkinson's Disease.

20. The method, use, or compound of claim 19, wherein administration does not impede the effect of any existing therapy on motor deficit.

21. The method, use, or compound of claim 8 - 11, wherein the disease or condition is Parkinsonism.

22. The method, use, or compound of claim 8 - 11, wherein said method, use, or compound further comprises an existing administration of L-dopa.

23. The method, use, or compound of claim 22, wherein the L-dopa is provided at one or more of a lower dose or on a delayed time course of dosing over a pre-existing regimen.


25. The pharmaceutical composition of claim 7, wherein the composition is formulated for transdermal, intranasal, buccal, or sublingual administration.

26. A method for synthesis of 3-cyclopropylcarbonyl-3,6-diazabicyclo[3.1.1]heptane or a pharmaceutically acceptable salt thereof comprising reacting a cyclopropylcarboxamide nucleophile with an azetidenyl bis-electrophile to form a piperidine ring.

27. A compound

\[ \text{Bn-N} \quad \text{OMs} \quad \text{OMs} \]

28. The compound of claim 27 as a corresponding halide.
Compound A, hemigalactarate monohydrate

Fig. 1
Compound A, hemigalactarate monohydrate

Fig. 2
Fig. 3

1 equivalent of water for hemigalactarate = 6.1% w/w
XRPD patterns of hemigalactarate monohydrate before and after storage at 40°C/75%RH and GVS

- Post GVS
- After 1 week at 40°C/75%RH
- Reference material

Fig. 5
XRPD of benzoate

Fig. 9
TGA/DSC of benzoate

TB-776-26-01
02.12.2010 10:15:07

\[ \Delta_{\text{exo}} \]

\text{I\&TGA TB-776-26-01}
TGA TB-776-26-01, 11.0910 mg

\text{Step -3.2567 \%}
\text{-0.3612 mg}

\text{I\&DSC TB-776-26-01}
DSC TB-776-26-01, 2.2400 mg

\begin{align*}
\text{Integral} & \quad -81.55 \text{ ml} \\
\text{normalized} & \quad -36.41 \text{ lg}^{-1} \\
\text{Onset} & \quad 82.04 \, ^{\circ}\text{C} \\
\text{Peak} & \quad 93.54 \, ^{\circ}\text{C}
\end{align*}

\begin{align*}
\text{Integral} & \quad -242.67 \text{ ml} \\
\text{normalized} & \quad -108.33 \text{ lg}^{-1} \\
\text{Onset} & \quad 136.93 \, ^{\circ}\text{C} \\
\text{Peak} & \quad 136.17 \, ^{\circ}\text{C}
\end{align*}

\text{Fig. 10}

Lab: LabUser

STAR® SW 9.20
High resolution VT-XRPD of benzoate

Fig. 12
Fig. 13
VT-XRPD of hippurate

Fig. 16

File: TB-776-26-02 raw
Y + 10.0 mm-File: TB-776-26-02_100 °C.raw
Y + 20.0 mm-File: TB-776-26-02_100 °C.raw
Y + 30.0 mm-File: TB-776-26-02_140 °C.raw
Y + 40.0 mm-File: TB-776-26-02_160 °C.raw
Y + 50.0 mm-File: TB-776-26-02_200 °C.raw
XRPD of hippurate salt - polymorphism assessment

Fig. 19
The graph shows the XRPD (X-ray powder diffraction) data for xinafoate polymorphism assessment. The graph includes the following comparisons:

- After isolation (Pattern 1)
- Post GVS (Pattern 1)
- Post 40 °C/75%RH (Pattern 2)
- From THF (Pattern 2)
- From IPA (Pattern 2)
- From acetone (Pattern 2)
- From TBME (Pattern 1)
- From EtOH/water (Pattern 2)
- From Dioxane (Pattern 2)

The graph also includes annotations for different crystal orientations, such as 2-Theta-Scale and Y values for various crystal planes. The file references provided include:

- Y + 8.0 mm - File:TB-776-33-19_D8_01.raw
- Y + 16 mm - File:TB-776-33-21_D8_01.raw
- Y + 24.0 mm - File:TB-776-33-22_D8_01.raw
- Y + 32.0 mm - File:TB-776-33-23_D8_01.raw
- Y + 40.0 mm - File:TB-776-33-24_D8_01.raw
- Y + 48.0 mm - File:TB-776-26-03post4075_D8_01.raw
- Y + 56.0 mm - File:TB-776-26-03postGVS_D8_01.raw
- Y + 64.0 mm - File:TBTB-776-26-03_D8_01.raw

Fig. 20
Fig. 21

(+)-Camphorate salt

Lin (Counts)

2-Theta-Scale

0 4 10 20 30

0 1000 2000 3000

TB-776-09-37.raw
Camphorate salt

I&TGATB-776-09-37
TGA TB-776-09-37, 3.0200 mg

I&DSC TB-776-09-37
DSC TB-776-09-37, 2.0300 mg

Fig. 22
Fig. 23

XRPD of tosylate salt

2-Theta-Scale

Lin (Counts)
Maleate salt
(made using 0.5 eq acid)
Maleate salt
(made using 1 eq acid)
Fig. 30A

Compound A prevents full development of L-Dopa-induced AIMS in parkinsonian rats

Fig. 30B

Compound A reduces existing L-Dopa-induced AIMS in parkinsonian rats

Fig. 30C

Compound A does not worsen parkinsonism Off or On L-Dopa

% left limb

% contralateral limb use

OFF L-Dopa ON L-Dopa

Cpd A

Vehicle
Fig. 32
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INVENTION C07D487/08 A61K31/4985 A61P25/00

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  A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched:

Electronic database consulted during the international search (name of database and, where practicable, search terms used):

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance.

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“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.

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“A” document member of the same patent family.

Date of the actual completion of the international search: 14 August 2012

Date of mailing of the international search report: 23/08/2012

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