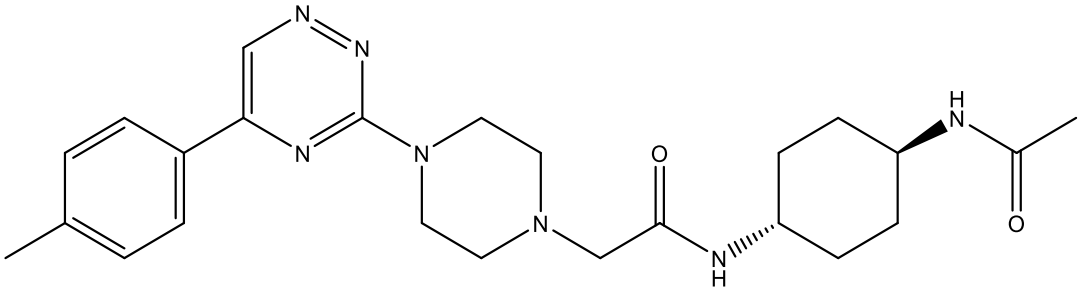
CLAIMS

What is claimed is:

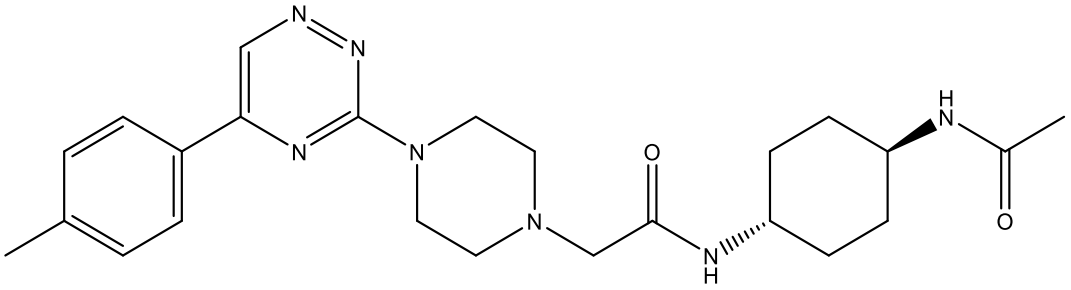
1. A pharmaceutical composition comprising a salt of a compound having the formula:



3-[4-[[trans-4-(acetoamino)cyclohexyl]carbamoylmethyl]piperazin-1-yl]-5-(p-tolyl)-1,2,4-triazine,

and one or more excipients, wherein the pharmaceutical composition avoids inducing disproportionation of the salt of the compound.

2. A pharmaceutical composition comprising a salt of a compound having the formula:



3-[4-[[trans-4-(acetoamino)cyclohexyl]carbamoylmethyl]piperazin-1-yl]-5-(p-tolyl)-1,2,4-triazine,

and one or more excipients, wherein the pharmaceutical composition has a dissolution profile such that more than 70% of the compound is dissolved in 15 minutes in an *in vitro* dissolution test of the pharmaceutical composition using USP Apparatus 2 Paddle Method at 50 rpm in a dissolution medium of water at 37° C.

3. The pharmaceutical composition of any one of claims 1 to 2, comprising from about 0.5 milligrams to about 500 milligrams of the compound, or preferably from about 5 milligrams to about 150 milligrams of the compound.

4. The pharmaceutical composition of any one of claims 1 to 3, wherein the pharmaceutical composition comprises:

   a) about 30 wt% to about 60 or 99 wt% of lactose, mannitol, or a combination thereof;

   b) about 25 wt% to about 50 or 99 wt% of microcrystalline cellulose;

   c) about 1 wt% to about 10 wt% of polyvinylpyrrolidone, pregelatinized starch, or a combination thereof; and

   d) about 1 wt% to about 10 wt% of talc, glyceryl dibehenate, colloidal silicone dioxide, or a combination of two or more thereof.

5. The pharmaceutical composition of any one of claims 1 to 4, wherein the compound is more soluble in water than the same compound in an equivalent pharmaceutical composition comprising a calcium salt, a sodium salt or magnesium salt, wherein the pharmaceutical composition avoids disproportionation in excess of 10% when stored at 25 ºC and 60% relative humidity for 6 months in a closed container, preferably wherein the pharmaceutical composition avoids disproportionation in excess of 5% when stored at 25 ºC and 60% relative humidity for 6 months in a closed container, or more preferably wherein the pharmaceutical composition avoids disproportionation in excess of 1% of the salt when stored at 25 ºC and 60% relative humidity for 6 months in a closed container when stored at 25 ºC and 60% relative humidity for 6 months in a closed container, and wherein after storage at 25ºC and 60% relative humidity for 6 months in a closed container, the pharmaceutical composition has a dissolution profile such that more than 70% of the compound is dissolved in 15 minutes in an *in vitro* dissolution test of the pharmaceutical composition using USP Apparatus 2 Paddle Method at 50 rpm in a dissolution medium of water at 37° C.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises from about 5 milligrams to about 20 milligrams of the compound, preferably from about 10 milligrams to about 15 milligrams of the compound, or more preferably about 12.5 milligrams of the compound.

7. The pharmaceutical composition of claim 6, wherein the pharmaceutical composition comprises:

a) about 1 wt% to about 8 wt% of the compound;
b) about 50 wt% to about 60 wt% of lactose, mannitol, or a combination thereof;
c) about 25 wt% to about 40 wt% of microcrystalline cellulose;
d) about 1 wt% to about 10 wt% of polyvinylpyrrolidone, pregelatinized starch, or a combination thereof; and
e) about 1 wt% to about 10 wt% of talc, glyceryl dibehenate, colloidal silicone dioxide, or a combination of two or more thereof;

preferably wherein the pharmaceutical composition comprises between 3 wt% and 8 wt% of stearic acid, more preferably about 5 wt% stearic acid.

8. The pharmaceutical composition of any one of claims 1 to 7, wherein the pharmaceutical composition comprises from about 15 milligrams to about 35 milligrams of the compound, preferably from about 20 milligrams to about 30 milligrams of the compound, or more preferably about 25 milligrams of the compound.

9. The pharmaceutical composition of claim 8 wherein the pharmaceutical composition comprises:
a) about 5 wt% to about 15 wt% of the compound;
b) about 30 wt% to about 50 wt% of mannitol;
c) about 30 wt% to about 50 wt% of microcrystalline cellulose;
d) about 1 wt% to about 10 wt% of pregelatinized starch; and
e) about 1 wt% to about 5 wt% of glyceryl dibehenate, colloidal silicone dioxide, or a combination thereof;

preferably wherein the pharmaceutical composition comprises between 3 wt% and 8 wt% of stearic acid, more preferably about 5 wt% stearic acid.

10. The pharmaceutical composition of any one of claims 1 to 9, wherein the pharmaceutical composition comprises from about 80 milligrams to about 120 grams of the compound, preferably from about 95 milligrams to about 105 milligrams of the compound, or more preferably about 100 milligrams of the compound.

11. The pharmaceutical composition of claim 10, wherein the pharmaceutical composition comprises:

a) about 30 wt% to about 40 wt% of the compound;

b) about 20 wt% to about 30 wt% of mannitol;

c) about 20 wt% to about 40 wt% of microcrystalline cellulose;

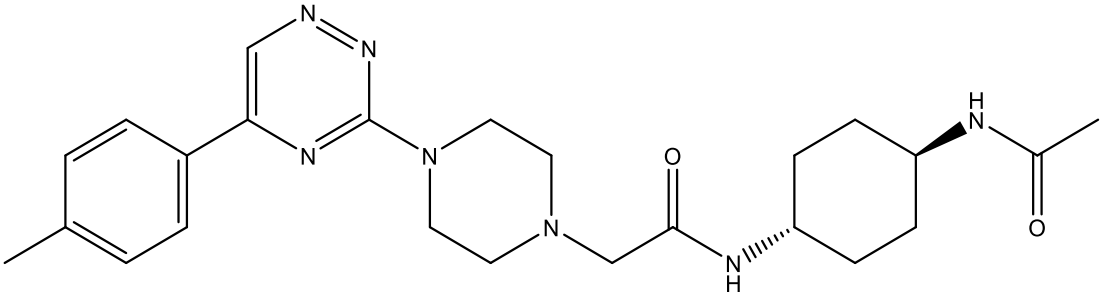
d) about 1 wt% to about 10 wt% of pregelatinized starch;

e) about 1 wt% to about 5 wt% of glyceryl dibehenate, colloidal silicone dioxide, or a combination thereof;

preferably wherein the pharmaceutical composition comprises between 3 wt% and 8 wt% of stearic acid, more preferably about 5 wt% stearic acid.

12. The pharmaceutical composition of any one of claims 1 to 11, wherein the pharmaceutical composition is a tablet, preferably wherein the tablet comprises a coating, more preferably wherein the coating comprises hydroxypropylmethyl cellulose, polyvinyl alcohol, or a combination thereof.

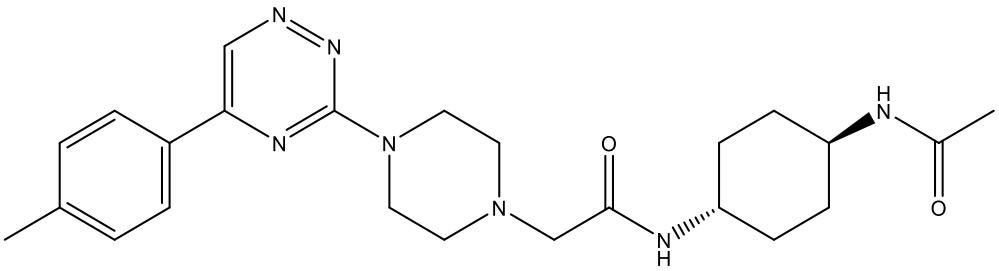
13. A process for making a pharmaceutical composition comprising a salt of a compound having the formula:



3-[4-[[trans-4-(acetoamino)cyclohexyl]carbamoylmethyl]piperazin-1-yl]-5-(p-tolyl)-1,2,4-triazine ,

and one or more excipients, wherein the pharmaceutical composition avoids inducing disproportionation of the salt of the compound and/or the pharmaceutical composition has a dissolution profile such that more than 70% of the compound is dissolved in 15 minutes in an *in vitro* dissolution test of the pharmaceutical composition using USP Apparatus 2 Paddle Method at 50 rpm in a dissolution medium of water at 37°C, comprising:

a) obtaining a salt of a compound having the formula:



3-[4-[[trans-4-(acetoamino)cyclohexyl]carbamoylmethyl]piperazin-1-yl]-5-(p-tolyl)-1,2,4-triazine ;

b) mixing the salt with one or more excipients to thereby produce the pharmaceutical composition; and

c) optionally tableting the pharmaceutical composition to produce tablet cores, preferably further comprising film-coating the tablet cores.

14. The process of claim 13 or 14, wherein step b) comprises:

i) blending the salt with one or more excipients; and

ii) roller compaction of the product of step i); and

iii) milling the product of step ii);

preferably wherein the one or more excipients of step i) comprises stearic acid, more preferably about 5 wt% stearic acid; and more preferably wherein step b) further comprises a step of blending the product of step iii) with one or more additional excipients, preferably wherein the one or more additional excipients comprise stearic acid.

15. The process of any one of claims 13 to 14, wherein the one or more excipients are selected from the group consisting of microcrystalline cellulose, lactose, mannitol, polyvinylpyrrolidone, colloidal silicone dioxide, pregelatinized starch, low-substituted hydroxypropyl cellulose, talc, glyceryl dibehenate, and stearic acid, preferably wherein the pharmaceutical composition comprises:

a) about 30 wt% to about 60 wt% of lactose, mannitol, or a combination thereof, preferably including between 20 wt% and 30 wt% of D-Mannitol, preferably wherein the D-Mannitol is mannitol 400DC;

b) about 25 wt% to about 50 wt% of microcrystalline cellulose, preferably between 20 wt% and 30 wt% of microcrystalline cellulose, preferably wherein the microcrystalline cellulose is microcrystalline cellulose 102;

c) about 1 wt% to about 10 wt% of polyvinylpyrrolidone, pregelatinized starch, or a combination thereof;

d) about 1 wt% to about 10 wt% of talc, glyceryl dibehenate, colloidal silicone dioxide, or a combination of two or more thereof; and

e) preferably between 3 wt% and 8 wt% of stearic acid, more preferably about 5 wt% stearic acid.

16. The pharmaceutical composition or process of any one of claims 1 to 15, wherein the salt of the compound is an anion salt, or preferably a halogen anion salt, or more preferably an HBr salt.

17. The pharmaceutical composition or process of any one of claims 1 to 16, wherein the one or more excipients do not comprise any of dicalcium phosphate, croscarmellose sodium, and magnesium stearate, carmellose calcium, sodium stearyl fumarate, calcium stearate, and anhydrous dibasic calcium phosphate, more preferably wherein the one or more excipients do not comprise a calcium salt, a magnesium salt or a sodium salt, more preferably wherein the one or more excipients do not comprise calcium, magnesium or sodium, even more preferably wherein the one or more excipients do not comprise a metal salt.

18. The pharmaceutical composition or process of any one of claims 1 to 17, wherein the salt of the compound is in crystalline form.

19. The pharmaceutical composition or process of any one of claims 1 to 17, wherein the salt of the compound is in amorphous form.

20. The composition of any one of claims 1 to 12 for use in treating hypertension and/or reducing blood pressure in a hypertensive subject.