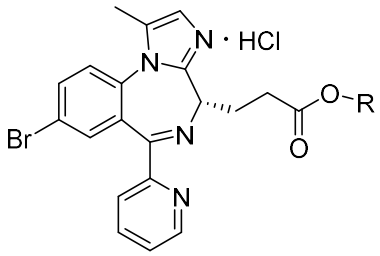
What is claimed is:

1. A crystalline form of the hydrochloride of a benzodiazepine derivative of Formula I ~~or its ethanolate~~,



Formula I

wherein R~~is methyl or ethyl; wherein when R is methyl, the crystal form has the following cell parameters: a=7.6929(6) Å, b=11.9174(10) Å, c=13.2096(11) Å, α= 90°, β= 96.904(1)°, γ=90°; and when R is ethyl, the crystal form has the following cell parameters: a=7.3774(1) Å, b=12.7332(2) Å, c=27.1779(4) Å, α= 90°, β= 90°, γ=90°~~ is ethyl, and it has an X-ray powder diffraction pattern with the following 2θ values measured using CuKα radiation: about 6.87, 7.38, 9.53, 13.65, 18.71, 22.13, 22.67, 25.10, 27.25, 29.30±0.2 degrees.

~~2. The crystal form according to claim 1, wherein R is methyl, and its crystal form has a structure substantially as shown in FIG. 1, or may be characterized by one or more parameters substantially as shown in Tables 1-6; and wherein R is ethyl, and its crystal form has a structure substantially as shown in FIG. 2, or may be characterized by one or more parameters substantially as shown in Tables 7-12.~~

~~3. The crystal form according to claim 1, wherein R is methyl, and the compound of Formula I has a content of chloride ion of 6.71-7.52% (w/w); and wherein R is ethyl, and the compound of Formula I has a content of chloride ion of 6.51-7.31% (w/w).~~

~~4. The crystal form according to claim 1, wherein R is methyl, and it has an X-ray powder diffraction pattern with the following 2θ values measured using CuKα radiation: about 6.81, 8.93, 13.39, 19.38, 21.23, 22.42, 24.20, 27.31±0.2 degrees; or the X-ray powder diffraction pattern shows the following 2θ values measured using CuKα radiation: about 8.11, 9.86, 14.73, 17.47, 23.03, 25.94, 28.31±0.2 degrees; or the crystal form has an X-ray powder diffraction pattern substantially as shown in FIG.~~

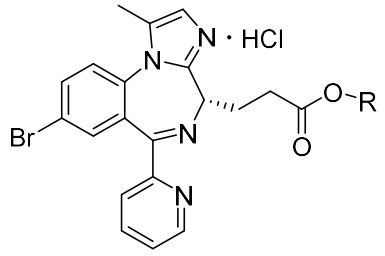
~~3.~~

~~5. The crystal form according to claim 1, wherein R is methyl, and it has an X-ray powder diffraction pattern with the following 2θ values measured using CuKα radiation: about 6.80, 8.93, 9.87, 13.37, 14.69, 19.36, 20.76, 21.25, 22.19, 22.38, 23.06, 24.21, 25.93, 27.73±0.2 degrees; or the X-ray powder diffraction pattern shows the following 2θ values measured using CuKα radiation: about 16.14, 17.48, 20.02, 25.17, 26.36, 28.30, 34.13±0.2 degrees; or the crystal form has an X-ray powder diffraction pattern substantially as shown in FIG. 4.~~

~~6~~2. The crystal form according to claim 1, wherein ~~R is ethyl, and it has an X-ray powder diffraction pattern with the following 2θ values measured using CuKα radiation: about 6.87, 7.38, 9.53, 13.65, 18.71, 22.13, 22.67, 25.10, 27.25, 29.30±0.2 degrees; or~~ the X-ray powder diffraction pattern shows the following 2θ values measured using CuKα radiation: about 14.96, 15.43, 20.23, 20.67, 21.13, 23.52, 28.22, 31.26±0.2 degrees~~; or the crystal form has an X-ray powder diffraction pattern substantially as shown in any one of FIGs. 5-8~~.

3. The crystal form according to claim 1 or 2, wherein the crystal form has an X-ray powder diffraction pattern substantially as shown in any one of FIGs. 5-8.

~~7~~4. ~~The~~ A crystalline form ~~according to claim 1~~of the hydrochloride of a benzodiazepine derivative of Formula I,



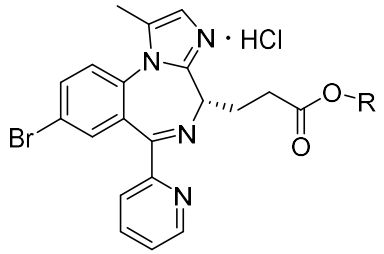
Formula I

~~,~~ wherein R is ethyl, and ~~it~~ the crystal form has an X-ray powder diffraction pattern with the following 2θ values measured using CuKα radiation: about 7.41, 9.24, 12.71, 13.64, 15.06, 18.30, 18.72, 21.59, 22.18, 25.74±0.2 degrees~~; or the X-ray powder diffraction pattern shows the following 2θ values measured using CuKα radiation: about 9.52, 11.69, 20.90, 22.60, 23.65, 24.26, 26.40, 28.43, 29.35±0.2 degrees; or the crystal form has an X-ray powder diffraction pattern substantially as shown in FIG. 9~~.

5. The crystal form according to claim 4, wherein the X-ray powder diffraction pattern further shows the following 2θ values measured using CuKα radiation: about 9.52, 11.69, 20.90, 22.60, 23.65, 24.26, 26.40, 28.43, 29.35±0.2 degrees.

6. The crystal for according to claim 4 or 5, wherein the crystal form has an X-ray powder diffraction pattern substantially as shown in FIG. 9.

~~8~~7. The crystalline form ~~according to claim 1~~ of the hydrochloride of a benzodiazepine derivative of Formula I,



Formula I

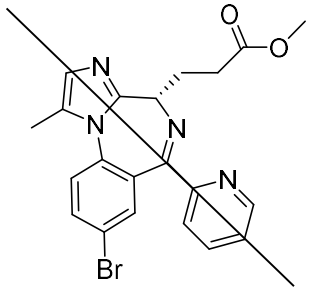
~~,~~ wherein R is ethyl, and ~~it~~ the crystal form has an X-ray powder diffraction pattern with the following 2θ values measured using CuKα radiation: about 6.84, 7.37, 9.53, 13.66, 22.63, 25.57, 29.28, 31.26±0.2 degrees~~; or the X-ray powder diffraction pattern shows the following 2θ values measured using CuKα radiation: about 15.43, 19.07, 22.16, 34.25±0.2 degrees; or the crystal form has an X-ray powder diffraction pattern substantially as shown in any one of FIGs. 10-13~~.

8. The crystal form according to claim 7, wherein the X-ray powder diffraction pattern further shows the following 2θ values measured using CuKα radiation: about 15.43, 19.07, 22.16, 34.25±0.2 degrees.

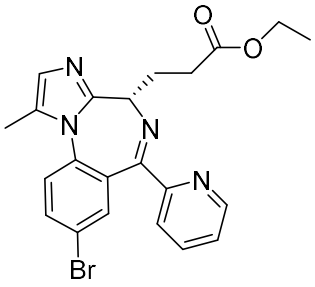
9. The crystal from according to claim 7 or 8, wherein the crystal form has an X-ray powder diffraction pattern substantially as shown in any one of FIGs. 10-13.

~~9~~10. A method for preparing the crystal form according to any one of claims 1 to ~~8~~9, comprising the following steps: dissolving the free base of the benzodiazepine derivative of the following Formula ~~II-1 or~~ II-2 in an organic solvent 1, adding HCl donor A wherein [H^+] is equimolar to the free base, to form a salt at a temperature of -20 to 60°C, after decolorizing the crude salt, crystallizing it in a crystallization

solvent 1 at a temperature of -60 to 80°C, to obtain the crystal form of the hydrochloride of the benzodiazepine derivative of Formula I-~~,~~



~~Formula II-1~~



Formula II-2

wherein the crystalline solvent 1 comprises methanol, ethanol, n-propanol, isopropanol, n-butanol, iso-butanol, ethyl ether, isopropyl ether, methyl tert-butyl ether, or a combination thereof.

~~10~~11. The method according to claim ~~9~~10, wherein the organic solvent 1 is an alcohol solvent, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol; an ester solvent, such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate; a ketone solvent, such as acetone and butanone; or a mixture thereof.

~~11~~12. The method according to claim ~~9~~10, wherein the HCl donor A is an amino acid hydrochloride, such as glycine hydrochloride, alanine hydrochloride, valine hydrochloride; a HCl-anhydrous alcohol solution, that is, an alcohol solution of dry HCl gas, such as dry HCl-methanol solution, dry HCl-ethanol solution, dry HCl-isopropanol solution; or a solution B that can generate HCl, such as acetyl chloride-methanol solution, acetyl chloride-ethanol solution, propionyl chloride-ethanol solution, acetyl chloride-isopropanol solution.

~~12~~13. The method according to claim ~~11~~12, wherein the HCl donor A is an amino acid hydrochloride, and the crystal form of the hydrochloride of the benzodiazepine derivative has an amount of amino acid of 0%-8% (w/w).

~~13~~14. The method according to claim ~~11~~12, wherein the HCl donor A is a HCl-anhydrous alcohol solution or a solution B that can generate HCl, and the ratio of amount of substance (molar ratio) of the free base of the benzodiazepine derivative to

the HCl donor A (calculated by [H^+]) is 1:0.4 - 1; the HCl donor A is an amino acid hydrochloride, and the ratio of amount of substance (molar ratio) of the free base of the benzodiazepine derivative to the amino acid hydrochloride is 1:1-10.

~~14~~15. The method according to claim ~~9~~10, wherein the temperature for forming a salt is -10 to 30°C, and the temperature for crystallizing is -20 to 60°C.

~~15. The method according to claim 9, wherein the crystallization solvent 1 comprises an alcohol solvent, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol; an ether solvent, such as ethyl ether, isopropyl ether, dioxane, methyl tert-butyl ether; an ester solvent, such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate; a ketone solvent, such as acetone and butanone; an alkane solvent, such as n-pentane, hexane, heptane, petroleum ether; a halogenated alkane, such as dichloromethane, chloroform, 1,2-dichloroethane; and a combination thereof.~~

16. A pharmaceutical composition comprising the crystal form according to any one of claims 1 to ~~8~~9, and a pharmaceutically acceptable excipient, carrier and/or other auxiliary materials.

17. The crystal form according to any one of claims 1 to ~~8~~–9 or the pharmaceutical composition according to claim 16 for use as intravenous anesthetics.

18. Use of the crystal form according to any one of claims 1 to ~~8~~–9 in manufacturing intravenous anesthetics.