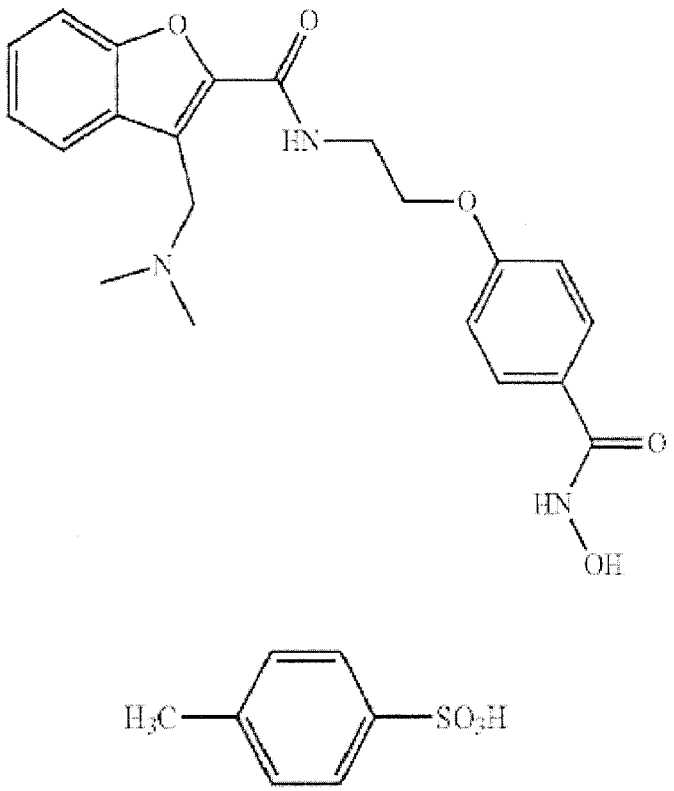
# NOVEL ABEXINOSTATE SALT, ASSOCIATED CRYSTALLINE FORM, PREPARATION METHOD THEREOF AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

The present invention relates to *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)-benzofuran-2-ylcarbonylamino]ethoxy}benzamide tosylate, or a solvate thereof.

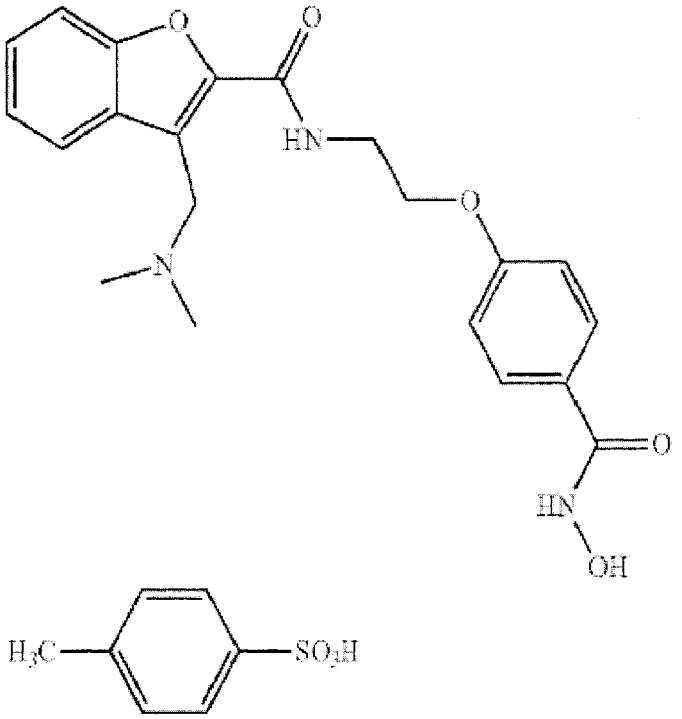
The present invention also relates to a crystalline form I of abexinostat tosylate of formula (II):




having an X-ray powder diffraction diagram having the following diffraction lines (Bragg's angle 2 theta, expressed in degrees ±0.2°): 6.50, 9.94, 11.35, 12.33, 14.08, 18.95, 21.08, and 27.05.

The present invention also relates to a crystalline form I of abexinostat tosylate of formula (II):

(II)

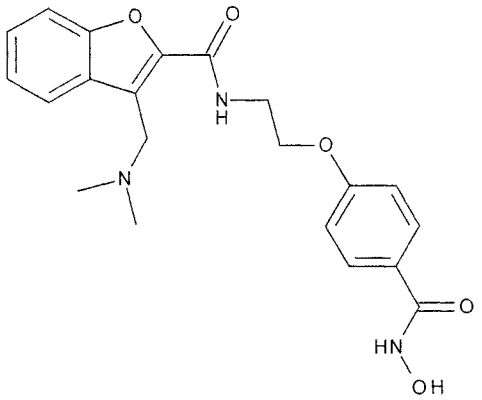


having a Raman spectrum having peaks at the positions 940 $cm^{-1}$, 1088 $cm^{-1}$, 1132 $cm^{-1}$, 1242 $cm^{-1}$, 1360 $cm^{-1}$, and 1608 $cm^{-1}$.

The present invention also relates to a pharmaceutical composition comprising as active ingredient the crystalline form I of abexinostat tosylate as described herein, in combination with one or more pharmaceutically acceptable excipients.

The present invention also relates to a process for the preparation of crystalline form I of abexinostat tosylate as described herein, wherein the abexinostat is crystallised in the presence of para-toluenesulphonic acid in a polar medium.

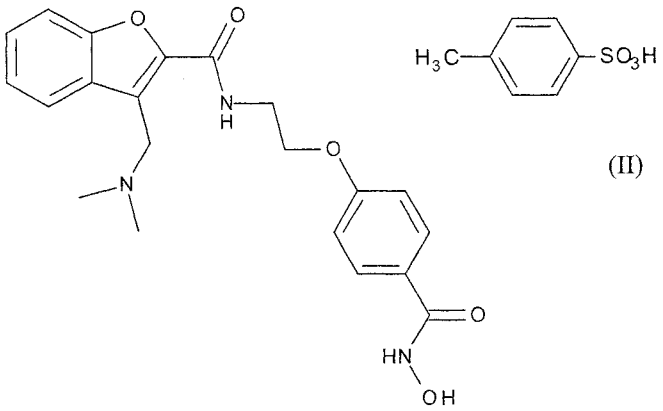
Alternatively, the subject-matter of the invention relates to a tosylate salt of abexinostate of formula (I):



(I).

(I)

More particularly, the invention is directed to the salt of formula (II):

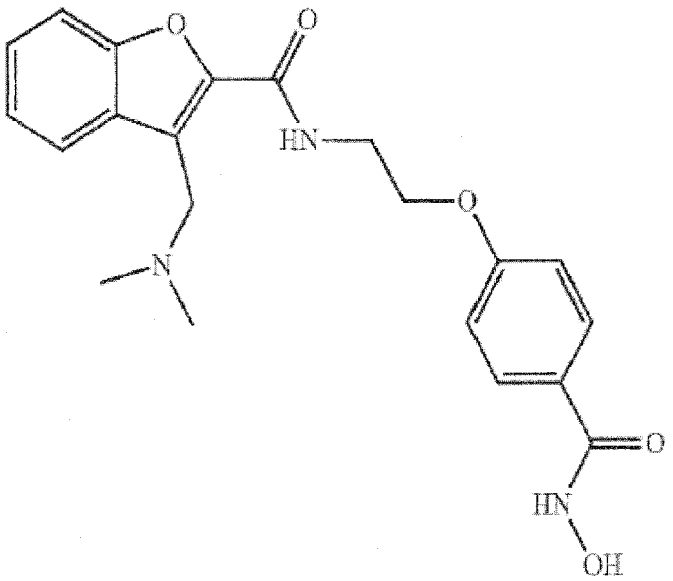


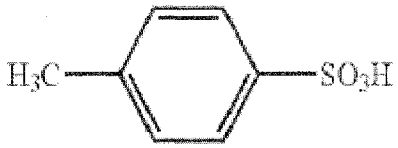
(II)

The present invention relates also to the crystalline form I of *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide tosylate, to the preparation method thereof and also to the pharmaceutical compositions containing same.

**CLAIMS:**

1. A crystalline form I of abexinostat tosylate of formula (II):





having an X-ray powder diffraction diagram having the following diffraction lines (Bragg's angle 2 theta, expressed in degrees ±0.2°): 6.50, 9.94, 11.35, 12.33, 14.08, 18.95, 21.08, and 27.05.

2. The crystalline form according to claim 1, wherein the crystalline form has an X-ray powder diffraction diagram having the following diffraction lines (Bragg's angle 2 theta, expressed in degrees ±0.2°): 6.50, 9.94, 11.35, 12.33, 14.08, 18.95, 19.61, 19.96, 21.08, 22.82, 23.61, and 27.05.

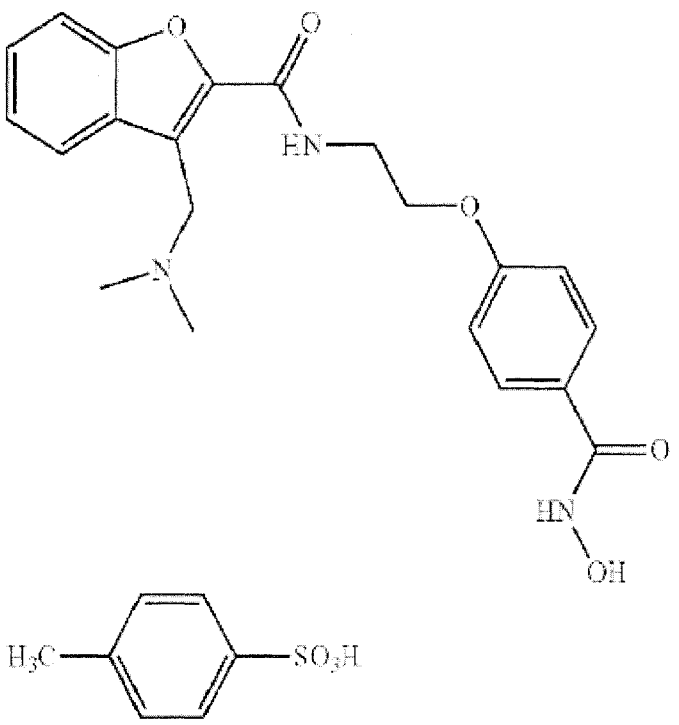
3. The crystalline form according to claim 1, wherein the crystalline form has the following X-ray powder diffraction diagram:

| Line no. | Angle 2-theta (degrees) | Interplanar distance (Å) |
|---|---|---|
| 1 | 6.50 | 13.581 |
| 2 | 9.94 | 8.894 |
| 3 | 11.35 | 7.789 |
| 4 | 12.33 | 7.173 |
| 5 | 14.08 | 6.285 |
| 6 | 18.95 | 4.683 |
| 7 | 19.61 | 4.526 |
| 8 | 19.96 | 4.449 |
| 9 | 21.08 | 4.215 |
| 10 | 22.82 | 3.897 |
| 11 | 23.61 | 3.768 |
| 12 | 27.05 | 3.296. |

4. The crystalline form according to claim 1, having a Raman spectrum having peaks at 940 $cm^{-1}$, 1088 $cm^{-1}$, 1132 $cm^{-1}$, 1242 $cm^{-1}$, 1360 $cm^{-1}$, and 1608 $cm^{-1}$.

5. A crystalline form I of abexinostat tosylate of formula (II):

(II)



having a Raman spectrum having peaks at the positions 940 $cm^{-1}$, 1088 $cm^{-1}$, 1132 $cm^{-1}$, 1242 $cm^{-1}$, 1360 $cm^{-1}$, and 1608 $cm^{-1}$.

6. The crystalline form according to claim 1, having a solid-state $^{13}C$ CP/MAS NMR spectrum having the following peaks (expressed in ppm ±0.2 ppm): 121.2 ppm, 122.1 ppm, 123.5 ppm, 126.0 ppm, 126.8 ppm, 128.2 ppm, 128.9 ppm, 143.4 ppm, 144.6 ppm, 153.8 ppm, 159 ppm, 161.2 ppm, and 162.1 ppm.

7. The crystalline form according to claim 6, wherein the crystalline form has a solid-state $^{13}C$ CP/MAS NMR spectrum having the following peaks (expressed in ppm ±0.2 ppm):

| Peak no. | Chemical shift (ppm) |
|---|---|
| 1 | 162.1 |
| 2 | 161.2 |
| 3 | 159.0 |
| 4 | 153.8 |
| 5 | 144.6 |
| 6 | 143.4 |
| 7 | 128.9 |
| 8 | 128.2 |
| 9 | 126.8 |
| 10 | 126.0 |
| 11 | 123.5 |
| 12 | 122.1 |
| 13 | 121.3 |
| 14 | 65.9 |
| 15 | 50.6 |
| 16 | 46.9 |
| 17 | 45.0 |
| 18 | 21.9. |

8. A pharmaceutical composition comprising as active ingredient the crystalline form I of abexinostat tosylate according to claim 1, in combination with one or more pharmaceutically acceptable excipients.

9. A process for the preparation of crystalline form I of abexinostat tosylate according to claim 1, wherein the abexinostat is crystallised in the presence of para-toluenesulphonic acid

in a polar medium.

10. The process according to claim 9, wherein the polar medium is composed of one or more solvents selected from water, alcohols, ketones and esters.

11. The process according to claim 10, wherein the polar medium is a binary mixture, one of the constituents of which is water.

12. The process according to claim 11, wherein the polar medium is a binary mixture selected from: acetone/water, ethanol/water, isopropanol/water and methyl ethyl ketone/water.