Abstract: This invention provides a novel crystalline form of N-[3-(4-[(2S,3R)2-2-[4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl]-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]4-oxoazetidin-1-yl]phenyl]propyl)methanesulfonamide. The compound is useful for lowering plasma cholesterol levels, particularly LDL cholesterol, and for treating mixed hyperlipidemia.
TITLE OF THE INVENTION
ANTI-HYPERCHOLESTEROLEMIC COMPOUND

BACKGROUND OF THE INVENTION

The instant invention relates to a crystalline form of $N$-[3-(4-[{(25^1,3i?)\-2-}\{4-[3,4-
dihydroxy-3-(hydroxymethyl)butyl]phenyl \}-3-\{(35)-3-(4-fluorophenyl)-3\-hydroxypropyl]4-
oxaoazetidin-1-yl}phenyl]propylmethanesulfonamide, and its use alone or in combination with
other active agents to treat hypercholesterolemia and for preventing, halting or slowing the
progression of atherosclerosis and related conditions and disease events.

It has been clear for several decades that elevated blood cholesterol is a major risk
factor for coronary heart disease (CHD), and many studies have shown that the risk of CHD
events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering
armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid
sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol.
Unfortunately, all of these treatments have limited efficacy or tolerability, or both. Substantial
reductions in LDL (low density lipoprotein) cholesterol accompanied by increases in HDL (high
density lipoprotein) cholesterol could be achieved by the combination of a lipid-lowering diet
and a bile acid sequestrant, with or without the addition of nicotinic acid. However, this therapy
is not easy to administer or tolerate and was therefore often unsuccessful except in specialist lipid
clinics. The fibrates produce a moderate reduction in LDL cholesterol accompanied by increased
HDL cholesterol and a substantial reduction in triglycerides, and because they are well tolerated
these drugs have been more widely used. Probucol produces only a small reduction in LDL
cholesterol and also reduces HDL cholesterol, which, because of the strong inverse relationship
between HDL cholesterol level and CHD risk, is generally considered undesirable. With the
introduction of lovastatin, the first inhibitor of HMG-CoA reductase to become available for
prescription in 1987, for the first time physicians were able to obtain large reductions in plasma
cholesterol with very few adverse effects.

Studies have unequivocally demonstrated that lovastatin, simvastatin and
pravastatin, all members of the HMG-CoA reductase inhibitor class, slow the progression of
atherosclerotic lesions in the coronary and carotid arteries. Simvastatin and pravastatin have also
been shown to reduce the risk of coronary heart disease events, and in the case of simvastatin a
highly significant reduction in the risk of coronary death and total mortality has been shown by
the Scandinavian Simvastatin Survival Study. This study also provided some evidence for a
reduction in cerebrovascular events. Despite the substantial reduction in the risk of coronary
morbidity and mortality achieved by simvastatin, the risk is still substantial in the treated
patients. For example, in the Scandinavian Simvastatin Survival Study, the 42% reduction in the
risk of coronary death still left 5% of the treated patients to die of their disease over the course of
this 5 year study. Further reduction of risk is clearly needed.
A more recent class of anti-hyperlipidemic agents that has emerged includes inhibitors of cholesterol absorption. Ezetimibe, the first compound to receive regulatory approval in this class, is currently marketed in the U.S. under the tradename ZETIA®. Ezetimibe has the following chemical structure and is described in U.S. Patent No.'s Re. 37721 and 5,846,966:

Sugar-substituted 2-azetidinones, including glucuronidated analogs of the following general structure:

and methods for making them are disclosed in U.S. Patent No. 5,756,470, wherein Ar1 and Ar2 are unsubstituted or substituted aryl groups.


wherein, among other definitions, Ai, A3 and A4 can be
and wherein R.2 is -CH2OH, -CH2θC(O)-Ri, or -CO2R1; R.3 is -OH or -OC(O)Ri, and R.4 is -(CH2)kR5(CH2)i- where k and i are zero or integers of one or more, and k+i is an integer of 10 or less; and R.5 is a single bond, -CH=CH-, -OCH2-, carbonyl or -CH(OH).

US2002/0137689 A1 discloses hypolipidemic compounds of general formula

\[
\text{wherein, among other definitions, R}_{1}, \text{ R}_{2}, \text{ R}_{3}, \text{ R}_{4}, \text{ R}_{5}, \text{ R}_{6} \text{ independently of one another can be (C o-C3θ)-alkylene-(LAG), where one or more carbon atoms of the alkylene radical may be replaced by -0-, -C=O-, -CH=CH-, -C≡C-, -N((Ci-C6)-alkyl)-, -N((Ci-C6)-alkylphenyl) or -NH-; and (LAG) is a sugar residue, disugar residue, trisugar residue, tetrasugar residue; a sugar acid, or an amino sugar.}
\]

In the ongoing effort to discover novel treatments for hyperlipidemia and atherosclerotic process, the instant invention provides a novel crystalline form of the cholesterol absorption inhibitor \(N-[3-\{(4-\{(2S,3R)-2-\{(4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl\}-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl\}methanesulfonamide.\)

**DESCRIPTION OF THE FIGURES**

FIG. 1 is a characteristic X-ray powder diffraction (XRPD) pattern of the crystalline Form I of \(N-[3-(4-\{(2S,3R)-2-\{(4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl\}-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl\}methanesulfonamide.\)

FIG. 2 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum (13C-SSNMR) of crystalline Form I of \(N-[3-(4-\{(2S,3R)-2-\{(4-[4,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl\}-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl\}methanesulfonamide.\)
SUMMARY OF THE INVENTION

One object of the instant invention is to provide crystalline Form I of the cholesterol absorption inhibitor \( \mathcal{N}-[3-(4-((2\text{S}^\prime,3\text{R}^\prime)-2-\{4-[3,4\text{-dihydroxy-3-(hydroxymethyl)butyl]phenyl\}-3-[3\text{S}]-3-(4\text{-fluorophenyl})-3\text{-hydroxypropyl}\}-4\text{-oxoazetidin-1-yl}]phenyl)propyl]methanesulfonamide \) which has the following chemical structural formula:

![Chemical Structure](link)

**Compound A**

A second object of the instant invention is to provide a method for inhibiting cholesterol absorption comprising administering a therapeutically effective amount of Form I to a patient in need of such treatment. Another object is to provide a method for reducing plasma cholesterol levels, especially LDL-cholesterol, and treating hypercholesterolemia comprising administering a therapeutically effective amount of Form I.

As a further object, methods are provided for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of Form I to a patient who is at risk of developing atherosclerosis or who already has atherosclerotic disease. Another object of the present invention is the use of Form I for the manufacture of a medicament useful in treating, preventing or reducing the risk of developing these conditions. Other objects of this invention are to provide processes for making Form I and to provide novel pharmaceutical compositions comprising Form I.

Additional objects will be evident from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

For brevity, the compound \( \mathcal{N}-[3-(4-((2\text{S}^\prime,3\text{S}^\prime)-2-\{4-[3,4\text{-dihydroxy-3-(hydroxymethyl)butyl]phenyl\}-3-[3\text{S}]-3-(4\text{-fluorophenyl})-3\text{-hydroxypropyl}\}-4\text{-oxoazetidin-1-yl}]phenyl)propyl]methanesulfonamide \) may also be referred to herein as "Compound A." The anhydrous crystalline form of \( \mathcal{N}-[3-(4-((2\text{S},3\text{R})-2-\{4-[3,4\text{-dihydroxy-3-(hydroxymethyl)butyl]phenyl\}-3-[3\text{R}]-3-(4\text{-fluorophenyl})-3\text{-hydroxypropyl}\}-4\text{-oxoazetidin-1-yl}]phenyl)propyl]methanesulfonamide \) of the instant invention is referred to herein as "Form I."
Crystalline Form I was characterized by X-Ray Powder Diffraction (XRPD) and 13c Solid State Nuclear Magnetic Resonance (13c SSNMR), described as follows.

X-Ray Powder Diffraction Characterization of Form I:

X-ray diffraction patterns of Form I were measured using a Panalytical X'Pert Pro with a Cu LFF source (Cu K-alpha - wavelength = 1.54187) at a generator power of 40kV and 50 mA from 2-40 degrees 2-theta. Major peaks from FIG. I that characterize Form I are (wavelength CuKa): °2-theta 18.7, 19.3, 17.1, 22, 22.6, 6.2, 11.8, 12.4 and 13.4. In particular, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation containing at least one °2-theta value selected from the group consisting of 18.7, 19.3, 17.1, 22, 22.6, 6.2, 11.8, 12.4, and 13.4. More particularly, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation containing at least two °2-theta values selected from the group consisting of 18.7, 19.3, 17.1, 22, 22.6, 6.2, 11.8, 12.4, and 13.4. Even more particularly, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation containing at least three °2-theta values selected from the group consisting of 18.7, 19.3, 17.1, 22, 22.6, 6.2, 11.8, 12.4, and 13.4. Furthermore, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation containing °2-theta values 18.7, 19.3 and 17.1; or 22, 22.6 and 6.2; or 11.8, 12.4 and 13.4; or a combination of two or three these groupings. As used herein, °2-theta values are accurate within ±0.1, based on the experiments described in the Examples provided.

Additionally a listing of peaks below 28 degrees 2-theta are listed below in Table 1 with heights, d-spacings and relative intensity (Rel. Int.):
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.9</td>
<td>837.12</td>
<td>45.684</td>
<td>16.34</td>
</tr>
<tr>
<td>2</td>
<td>6.2</td>
<td>275.91</td>
<td>14.184</td>
<td>5.39</td>
</tr>
<tr>
<td>3</td>
<td>10.6</td>
<td>190.88</td>
<td>8.314</td>
<td>3.73</td>
</tr>
<tr>
<td>4</td>
<td>11.8</td>
<td>232.03</td>
<td>7.533</td>
<td>4.53</td>
</tr>
<tr>
<td>5</td>
<td>12.4</td>
<td>360.17</td>
<td>7.113</td>
<td>7.03</td>
</tr>
<tr>
<td>6</td>
<td>13.4</td>
<td>974.11</td>
<td>6.629</td>
<td>19.02</td>
</tr>
<tr>
<td>7</td>
<td>14.9</td>
<td>267.22</td>
<td>5.965</td>
<td>5.22</td>
</tr>
<tr>
<td>8</td>
<td>17.1</td>
<td>1965.4</td>
<td>5.185</td>
<td>38.37</td>
</tr>
<tr>
<td>9</td>
<td>17.2</td>
<td>1643.25</td>
<td>5.150</td>
<td>32.08</td>
</tr>
<tr>
<td>10</td>
<td>18.3</td>
<td>722.45</td>
<td>4.846</td>
<td>14.1</td>
</tr>
<tr>
<td>11</td>
<td>18.7</td>
<td>5122.09</td>
<td>4.745</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>19.0</td>
<td>772.64</td>
<td>4.678</td>
<td>15.08</td>
</tr>
<tr>
<td>13</td>
<td>19.3</td>
<td>2059.88</td>
<td>4.594</td>
<td>40.22</td>
</tr>
<tr>
<td>14</td>
<td>20.1</td>
<td>643.54</td>
<td>4.427</td>
<td>12.56</td>
</tr>
<tr>
<td>15</td>
<td>20.4</td>
<td>1005.27</td>
<td>4.351</td>
<td>19.63</td>
</tr>
<tr>
<td>16</td>
<td>22.0</td>
<td>1575.3</td>
<td>4.034</td>
<td>30.75</td>
</tr>
<tr>
<td>17</td>
<td>22.6</td>
<td>1262.84</td>
<td>3.938</td>
<td>24.65</td>
</tr>
<tr>
<td>18</td>
<td>25.0</td>
<td>681.32</td>
<td>3.561</td>
<td>13.3</td>
</tr>
<tr>
<td>19</td>
<td>25.8</td>
<td>203.65</td>
<td>3.449</td>
<td>3.98</td>
</tr>
<tr>
<td>20</td>
<td>26.3</td>
<td>1281.01</td>
<td>3.388</td>
<td>25.01</td>
</tr>
<tr>
<td>21</td>
<td>26.6</td>
<td>818.66</td>
<td>3.351</td>
<td>15.98</td>
</tr>
<tr>
<td>22</td>
<td>27.6</td>
<td>377.75</td>
<td>3.234</td>
<td>7.37</td>
</tr>
</tbody>
</table>

Crystalline Form I of \(N\-[3-(4-\{(25,3i?)-2-\{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl\}]phenyl\}]-3-\{(35)-3-(4-fluorophenyl)\}-3-hydroxypropyl\}-4-o xoazetidin-1-yl]phenyl]propyl\]methanesulfonamide can also be characterized by the X-ray powder diffraction pattern of Figure 1.

Additionally, a sample of crystalline Form I was ground in a mortar and pestle for 1 minute with the application of slight pressure. This sample was sieved through a 200 mesh screen. The sample was then subjected to x-ray diffraction and the peaks recorded. The grinding of a sample will somewhat help alleviate the problem of inaccurate relative intensities due to preferred orientation. The positions of peaks with relative intensities above 14% (°2-theta) with and without grinding are listed below in Table 2.
Accordingly, Form I can also be characterized by having an XRPD pattern obtained from ground Form I using CuKa radiation containing at least one °2-theta value selected from those listed in Table 2. More particularly, Form I can be characterized by having an XRPD pattern obtained from ground Form I using CuKa radiation containing at least two °2-theta values selected from those listed in Table 2. Even more particularly, Form I can be characterized by having an XRPD pattern obtained from ground Form I using CuKa radiation containing at least three °2-theta values selected from those listed in Table 2. Furthermore, Form I can be characterized by having an XRPD pattern obtained from ground Form I using CuKa radiation containing °2-theta values 18.7, 19.3 and 17.1; or 22, 22.6 and 13.4; or 18.3, 19.0 and 20.4; or a combination of two or three of these groupings.

d-Spacings, distances between peaks and distances between d-spacings are also listed below in Table 3 for Form I. The peak at 18.7° 2-theta is taken as reference for these calculations.

### TABLE 2

<table>
<thead>
<tr>
<th>Pos. [°2Theta]</th>
<th>Unground Rel. Int. [%]</th>
<th>Ground Rel. Int. [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.4</td>
<td>19.02</td>
<td>48.42</td>
</tr>
<tr>
<td>17.1</td>
<td>38.37</td>
<td>64.89</td>
</tr>
<tr>
<td>18.3</td>
<td>14.1</td>
<td>34.24</td>
</tr>
<tr>
<td>18.7</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>19.0</td>
<td>15.08</td>
<td>35.32</td>
</tr>
<tr>
<td>19.3</td>
<td>40.22</td>
<td>98.12</td>
</tr>
<tr>
<td>20.4</td>
<td>19.63</td>
<td>34.59</td>
</tr>
<tr>
<td>22.0</td>
<td>30.75</td>
<td>44.74</td>
</tr>
<tr>
<td>22.6</td>
<td>24.65</td>
<td>48.36</td>
</tr>
<tr>
<td>26.3</td>
<td>25.01</td>
<td>28.02</td>
</tr>
<tr>
<td>26.6</td>
<td>15.98</td>
<td>30.74</td>
</tr>
</tbody>
</table>

### TABLE 3

<table>
<thead>
<tr>
<th>Pos. [°2Theta]</th>
<th>d-spacing</th>
<th>Distance between peaks</th>
<th>Distance between d-spacings</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.4</td>
<td>6.629</td>
<td>-5.3</td>
<td>1.883</td>
</tr>
<tr>
<td>17.1</td>
<td>5.185</td>
<td>-1.6</td>
<td>0.439</td>
</tr>
<tr>
<td>18.3</td>
<td>4.846</td>
<td>-0.4</td>
<td>0.101</td>
</tr>
<tr>
<td>18.7</td>
<td>4.745</td>
<td>0.0</td>
<td>0.000</td>
</tr>
<tr>
<td>19.0</td>
<td>4.678</td>
<td>0.3</td>
<td>-0.068</td>
</tr>
<tr>
<td>19.3</td>
<td>4.594</td>
<td>0.6</td>
<td>-0.151</td>
</tr>
<tr>
<td>20.4</td>
<td>4.351</td>
<td>1.7</td>
<td>-0.394</td>
</tr>
<tr>
<td>22.0</td>
<td>4.034</td>
<td>3.3</td>
<td>-0.712</td>
</tr>
<tr>
<td>22.6</td>
<td>3.938</td>
<td>3.9</td>
<td>-0.808</td>
</tr>
</tbody>
</table>
Accordingly, Form I can also be characterized by having an XRPD pattern obtained using CuKa radiation having at least one distance between d-spacings listed in Table 3 using 18.7° 2-theta as reference. More particularly, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation having at least two distances between d-spacings listed in Table 3 using 18.7° 2-theta as reference. Even more particularly, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation having at least three distances between d-spacings listed in Table 3 using 18.7° 2-theta as reference. Furthermore, Form I can alternatively be characterized by having an XRPD pattern obtained using CuKa radiation having the following distances between d-spacings using 18.7° 2-theta as reference: 0.000, -0.151 and 0.439; or -0.712, -0.808 and 1.883; or 0.101, -0.068 and -0.394; or a combination of two or three of these groupings.

Form I can also be characterized by having an XRPD pattern obtained using CuKa radiation having at least one distance between peaks listed in Table 3 using 18.7° 2-theta as reference. More particularly, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation having at least two distances between peaks listed in Table 3 using 18.7° 2-theta as reference. Even more particularly, Form I can be characterized by having an XRPD pattern obtained using CuKa radiation having at least three distances between peaks listed in Table 3 using 18.7° 2-theta as reference. Furthermore, Form I can alternatively be characterized by having an XRPD pattern obtained using CuKa radiation having the following distances between peaks using 18.7° 2-theta as reference: 0.0, 0.6 and -1.6; or 3.3, 3.9 and -5.3; or 0.3, 1.7 and -0.4; or a combination of two or three of these groupings.

13C-SSNMR Characterization of Form I:

In addition to the X-ray powder diffraction patterns described above, crystalline Form I was further characterized by solid-state carbon-13 nuclear magnetic resonance (13C-SSNMR) spectra. The solid-state carbon-13 NMR spectra were obtained on a Bruker DSX 500WB NMR system using a Bruker 4 mm H/X/Y CPMAS probe. The carbon-13 NMR spectra utilized proton/carbon-13 cross-polarization magic-angle spinning with variable-amplitude cross polarization, total sideband suppression, and SPINAL decoupling at 100kHz. The samples were spun at 10.0 kHz, and a total of 4096 scans were collected with a recycle delay of 10 seconds. A line broadening of 10 Hz was applied to the spectra before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 p.p.m.) as a secondary reference.

Crystalline Form I exhibited characteristic signals by 13C-SSNMR with chemical shift values of 28.8, 34.2, 43.4, 58.3, 74.8, 113.9, 129.9, 136.2, 146.5 and 168.3 parts per million.
In particular, Form I can be characterized by having at least one chemical shift value obtained by 13C-SSNMR selected from the group consisting of 28.8, 34.2, 43.4, 58.3, 74.8, 113.9, 129.9, 136.2, 146.5 and 168.3 ppm. More particularly, Form I can be characterized by having at least two chemical shift values obtained by 13C-SSNMR selected from the group consisting of 28.8, 34.2, 43.4, 58.3, 74.8, 113.9, 129.9, 136.2, 146.5 and 168.3 ppm. Even more particularly, Form I can be characterized by having at least three chemical shift values obtained by 13C-SSNMR selected from the group consisting of 28.8, 34.2, 43.4, 58.3, 74.8, 113.9, 129.9, 136.2, 146.5 and 168.3 ppm. Furthermore, Form I can be characterized by 13C-SSNMR signals with chemical shift values of 28.8, 136.2, 43.4 and 74.8 p.p.m.; or 129.9, 58.3, and 168.3 p.p.m.; or 34.2, 113.9 and 146.5 p.p.m.; or a combination of two or three of these groupings.

Below is a listing of peaks from 13C-SSNMR for Form I with their relative intensities:

<table>
<thead>
<tr>
<th>Peak [ppm]</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.86</td>
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</tr>
<tr>
<td>35.66</td>
<td>85.51</td>
</tr>
<tr>
<td>43.44</td>
<td>72.48</td>
</tr>
<tr>
<td>74.88</td>
<td>67.85</td>
</tr>
<tr>
<td>1139.99</td>
<td>66.20</td>
</tr>
<tr>
<td>1288.66</td>
<td>63.87</td>
</tr>
<tr>
<td>58.33</td>
<td>63.61</td>
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<tr>
<td>700.99</td>
<td>62.38</td>
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<td>34.22</td>
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<td>422.33</td>
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<td>1133.99</td>
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<td>600.77</td>
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<td>266.88</td>
<td>46.62</td>
</tr>
<tr>
<td>1466.55</td>
<td>46.02</td>
</tr>
<tr>
<td>333.66</td>
<td>44.25</td>
</tr>
<tr>
<td>4311.55</td>
<td>42.45</td>
</tr>
<tr>
<td>599.88</td>
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<td>1144.35</td>
<td>41.34</td>
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<td>1337.44</td>
<td>41.04</td>
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<td>655.22</td>
<td>39.62</td>
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<td>1118.77</td>
<td>39.58</td>
</tr>
<tr>
<td>132.5</td>
<td>38.87</td>
</tr>
</tbody>
</table>
Crystalline Form I of $\text{N-[3-(4-\{(2S,3')\text{-2-\{4-\{3,4-dihydroxy-3-(hydroxymethyl)butyl\}phenyl\}-3-\{(3S)-3-(4-fluorophenyl)-3-hydroxypropyl\}-4-oxoazetidin-1-yl\}phenyl\}propyl\}methanesulfonamide}$ can also be characterized by the solid-state 13C-SSNMR CPMAS nuclear magnetic resonance spectrum of FIG. 2.

In addition, crystalline Form I can be characterized by 13C-SSNMR having chemical shift differences between the lowest ppm resonance and other resonances using 26.8 ppm as the lowest reference resonance. For example, Form I can be characterized by 13C-SSNMR having chemical shift differences between the lowest ppm resonance and other resonances as follows: 2.0, 7.4, 16.6, 31.5, 48.0, 87.1, 103.1, 109.4, 119.7, and 141.5. In particular, Form I can be characterized by having at least one chemical shift difference between the lowest ppm resonance and other resonances, using 26.8 ppm as the lowest reference resonance, selected from the group consisting of 2.0, 7.4, 16.6, 31.5, 48.0, 87.1, 103.1, 109.4, 119.7 and 141.5. More particularly, Form I can be characterized by having at least two chemical shift differences between the lowest ppm resonance and other resonances, using 26.8 ppm as the lowest reference resonance, selected from the group consisting of 2.0, 7.4, 16.6, 31.5, 48.0, 87.1, 103.1, 109.4, 119.7 and 141.5. Even more particularly, Form I can be characterized by having at least three chemical shift differences between the lowest ppm resonance and other resonances, using 26.8 ppm as the lowest reference resonance, selected from the group consisting of 2.0, 7.4, 16.6, 31.5, 48.0, 87.1, 103.1, 109.4, 119.7 and 141.5. Furthermore, Form I can be characterized by 13C-SSNMR having chemical shift differences between the lowest ppm resonance and other resonances as follows: 2.0, 109.4, 26.8 and 48.0; or 103.1, 31.5 and 141.5; or 7.4, 87.1 and 119.7; or a combination of two or three of these groupings.

The instant invention is further related to a process for preparing a crystal form of $\text{N-[3-(4-\{(2S,3')\text{-2-\{4-\{3,4-dihydroxy-3-(hydroxymethyl)butyl\}phenyl\}-3-\{(3S)-3-(4-fluorophenyl)-3-hydroxypropyl\}-4-oxoazetidin-1-yl\}phenyl\}propyl\}methanesulfonamide}$ comprising:

a) adding a solvent to $\text{N-[3-(4-\{(2S,3')\text{-2-\{4-\{3,4-dihydroxy-3-(hydroxymethyl)butyl\}phenyl\}-3-\{(3S)-3-(4-fluorophenyl)-3-hydroxypropyl\}-4-oxoazetidin-1-yl\}phenyl\}propyl\}methanesulfonamide}$ to create a slurry, and
b) filtering the slurry to obtain a crystal form of JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide.

In a second embodiment of the instant invention, the process further comprises:

a) filtering the slurry to obtain solids, and

b) drying the solids to obtain a crystal form of JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide.

In a third embodiment of the instant invention, the process for preparing a crystal form of JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide comprises:

a) adding a solvent to JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide,

b) filtering to obtain filtrate solutions, and
c) evaporating the filtrate solutions to obtain a crystal form of JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide.

In a further embodiment of the third embodiment, the process further comprises, in step b, filtering at about 55-75°C.

In a fourth embodiment, the process comprises:

a) adding a solvent to JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide,

b) filtering to obtain filtrate solutions,
c) cooling the filtrate solutions,
d) drying the filtrate solutions to obtain a crystal form of JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide.

In a fifth embodiment, the process comprises:

a) adding a solvent to JV-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl}propyl]methanesulfonamide,

b) filtering to obtain filtrate solutions,
c) adding antisolvent to the filtrate solutions,
d) drying to obtain a crystal form of N-[3-(4-{(2S,3R)-3-{4-hydroxypropyl}phenyl}-4-oxoazetidin-1-yl]phenyl)propyl]methanesulfonamide.

In a further embodiment of the fifth embodiment, after step c, supernatant is removed.

The instant invention is also directed to a process for preparing a crystal form of 7V-[3-(4-{(2S,3R)-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl}-3-(35)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl]methanesulfonamide comprising:

a) adding a transesterification catalyst to a solution of 3-[4-{(2S,3R)-3-{(3S)-2-(4-fluorophenyl)propyl} -1-(4-[3-{(methylsulfonyl)amino]propyl} ]phenyl)-4-oxoazetidin-2-yl]phenyl]-1,1-bis(hydroxymethyl)propyl acetate in an alcohol;

b) adding solvent to obtain a slurry;

c) filtering to obtain a solution;

d) adding seed to obtain the crystal form.

In a further embodiment, the alcohol is methanol or ethanol. In a further embodiment, the solvent is IPA. In a further embodiment of the above process, the transesterification catalyst is TMSOK.

The instant invention is also directed to a pharmaceutical composition comprising about 5 mg to about 150 mg of crystal form of N-[3-(4-{(2S,3Rf)-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl} ]-3-(35)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl]methanesulfonamide, about 30 to about 150 mg of microcrystalline cellulose, about 30 mg to about 150 mg of lactose monohydrate, about 0.5 to about 20 mg of croscarmellose sodium, about 0.1 to about 10 mg of sodium lauryl sulfate, about 0.1 to about 10 mg of magnesium stearate, and about 0.1 to about 10 mg of sodium stearyl fumarate. In a further embodiment, the composition comprises about 10 mg to about 100 mg of crystal form of N-[3-(4-{(25,33)-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl} ]-3-(35)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl]methanesulfonamide, about 40 to about 140 mg of microcrystalline cellulose, about 40 mg to about 140 mg of lactose monohydrate, about 2 to about 15 mg of croscarmellose sodium, about 0.5 to about 5 mg of sodium lauryl sulfate, about 0.5 to about 5 mg of magnesium stearate, and about 0.5 to about 5 mg of sodium stearyl fumarate.

In the instant invention, the term "solvent" refers to broad range of organic solvents known to those skilled in the art. In one embodiment, the solvent system is selected from the group consisting of alcohols, amines, arenes, and halogenated alkanes. Examples of solvents that may be used in the process of the instant invention include, but are not limited to, 1,2-Dichloroethane, Acetonitrile, Nitromethane, iPrOAc in 1,2-dimethoxyethane, Cyclohexane.
in Ethyl Acetate, Cyclohexane in Ethanol, Cyclohexane in 2-Propanol, Ethyl Acetate: Heptanes, MIBK (methyl iso-butyl ketone), Water in 1,2- Dichloroethane, Cyclohexane in 1,2-Dimethoxyethane and the like. In an embodiment, the solvent may be selected from Water in 1,2- Dichloroethane, 1,2- Dichloroethane, Acetonitrile, Nitromethane, iPrOAc in 1,2-dimethoxyethane, Cyclohexane in Ethyl Acetate, Cyclohexane in Ethanol, Cyclohexane in 2-Propanol, Ethyl Acetate: Heptanes, and Cyclohexane in 1,2- Dimethoxyethane. In an embodiment, the solvent may be selected from 100% 1,2-dichloroethane.

In the instant application, known antisolvents may be utilized. In an embodiment of the invention, the antisolvent is selected from water or heptanes. In an embodiment, the solvent and antisolvent system may be selected from

a) water in 1,2-dichloroethane and water,
b) Water in Ethanol and water,
c) THF in 1-Propanol and heptanes,
d) THF in Toluene and heptanes,
e) THF in Ethanol and heptanes,
f) iPrOAc in 2-Propanol and heptanes,
g) Butyronitrile and heptanes,
h) iPrOAc in Ethanol and heptanes,
i) Cyclohexane in Ethyl Acetate and heptanes,
j) Cyclohexane in Ethanol and heptanes, or
k) Cyclohexane in 2-Propanol and heptanes.

In the instant invention, a transesterification catalyst is used. Transesterification is the process of exchanging the alkoxy group of an ester compound by another alcohol. These reactions are often catalyzed by the addition of an acid or base. As used herein, the term "acid" refers to organic or inorganic acids. Examples of an organic acid include, but are not limited to, carboxylic acids such as stearic acid, acetic acid, formic acid, propionic acid, butyric acid, and the like. Examples of inorganic acid include, but are not limited to, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, boric acid, and the like. As used herein, the term "base" refers to an organic base, an inorganic base, and the like. Examples of a base include, but are not limited to, TMSOK, K2CO3, Cs2CC>3, Li2CO3, Na2CO3, KOH, LiOH, NaOH, CsOH, K3PO4, KF, Et3N and other tertiary amines, diisopropylamine and other secondary amines, and butylamine and other primary amines. In an embodiment of the instant invention, the base is TMSOK.

As used herein, the term "alcohol" is any organic compound in which a hydroxyl group (-OH) is bound to a carbon atom of an alkyl or substituted alkyl group. In an embodiment, the alcohol is selected from methanol, ethanol, propanol, isopropyl alcohol, and tert-butyl alcohol. In another embodiment, the alcohol is methanol or ethanol.
The term "patient" includes mammals, especially humans, who use the instant active agent for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of cholesterol absorption.

The term "therapeutically effective amount" is intended to mean that amount of a pharmaceutical drug that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. Particularly, the dosage a patient receives can be selected so as to achieve the amount of LDL cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing the compound of the instant invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition.

The compound of the instant invention is a cholesterol absorption inhibitor and is useful for reducing plasma cholesterol levels, particularly reducing plasma LDL cholesterol levels, when used either alone or in combination with another active agent, such as an anti-atherosclerotic agent, and more particularly a cholesterol biosynthesis inhibitor, for example an HMG-CoA reductase inhibitor. Thus the instant invention provides methods for inhibiting cholesterol absorption and for treating lipid disorders including hypercholesterolemia comprising administering a therapeutically effective amount of Form I to a patient in need of such treatment. The term hypercholesterolemia includes but is not limited to homozygous familial hypercholesterolemia (HoFH) and heterozygous familial hypercholesterolemia (HeFH) and therefore Form I can be used treat HoHF and HeHF patients. Form I can also be used for the treatment of mixed hyperlipidemia which is characterized by an elevated LDL cholesterol level and elevated triglycerides level along with an undesirably low HDL cholesterol level. Form I can also be used to treat or prevent sitosterolemia and/or to lower the concentration of one or more sterols other than cholesterol in the plasma or tissue of a patient.
Further provided are methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of Form I to a patient who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease including restenosis following revascularization procedures, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease including multi-infarct dementia, and peripheral vessel disease including erectile dysfunction are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

Form I may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of Form I to a patient at risk for such an event. The patient may or may not have atherosclerotic disease at the time of administration, or may be at risk for developing it.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III),
JAMA, 2001; 285 pp.2486-2497. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

The oral dosage amount of Form I is from about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg of body weight per day. For an average body weight of 70 kg, the dosage level may be from about 1 mg to about 1000 mg of drug per day, and more particularly from about 1 mg to 250 mg per day. However, dosage amounts will vary depending on factors as noted above. Although the active drug of the present invention may be administered in divided doses, for example from two to four times daily, a single daily dose of the active drug is preferred. As examples, the daily dosage amount may be selected from, but not limited to, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 200 mg and 250 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, caplets, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred, and particularly solid oral formulations such as tablets.

Administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time controlled-release and delayed-release (such enteric coated) pharmaceutical dosage forms. Additional suitable pharmaceutical compositions for use with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders,
lubricants, disintegrating agents and coloring and flavoring agents can also be incorporated into
the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole
(BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid,
calcium metabisulphite, hydroquinone, and 7-hydroxycoumarin, particularly BHA, propyl gallate
and combinations thereof, can also be added to stabilize the dosage forms. When Form I is
formulated together with an HMG-CoA reductase inhibitor such as simvastatin, the use of at
least one stabilizing agent is preferred in the composition, particularly BHA or a combination of
BHA with propyl gallate. Other suitable components include gelatin, sweeteners, natural and
synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene
glycol, waxes and the like.

An example of a suitable pharmaceutical composition is one comprised of Form I,
microcrystalline cellulose, lactose (particularly lactose monohydrate), croscarmellose sodium,
and magnesium stearate, with or without the inclusion of sodium lauryl sulfate. The drug load
(\% by weight of Form I based on total weight of the tablet without external surface coatings) in a
single tablet can range for example from 1\% to 35\%. Examples of drug load include but are not
limited to 1\%, 10 \%, 25\% and 35\%.

The instant invention also encompasses a process for preparing a pharmaceutical
composition comprising combining Form I with a pharmaceutically acceptable carrier. Also
encompassed is the pharmaceutical composition which is made by combining Form I with a
pharmaceutically acceptable carrier.

One or more additional active agents may be administered in combination with
Form I, and therefore an embodiment of the instant invention encompasses a drug combination.
The drug combination encompasses a single dosage formulation comprised of Form I and an
additional active agent or agents, as well as administration of each of Form I and the additional
active agent or agents in separate dosage formulations, which allows for concurrent or sequential
administration of the active agents. The additional active agent or agents can be lipid modifying
agents, particularly a cholesterol biosynthesis inhibitor such as an HMG-CoA reductase inhibitor,
or agents having other pharmaceutical activities, or agents that have both lipid-modifying effects
and other pharmaceutical activities. Examples of HMG-CoA reductase inhibitors useful for this
purpose include statins in their lactonized or dihydroxy open acid forms and pharmaceutically
acceptable salts and esters thereof, including but not limited to lovastatin (MEVACOR®; see US
Patent No. 4,342,767); simvastatin (ZOCOR®; see US Patent No. 4,444,784); dihydroxy open-
acid simvastatin, particularly the ammonium or calcium salts thereof; pravastatin, particularly the
sodium salt thereof (PRAVACOL®; see US Patent No. 4,346,227); fluvastatin particularly the
sodium salt thereof (LESCOL®; see US Patent No. 5,354,772); atorvastatin, particularly the
calcium salt thereof (LIPITOR®; see US Patent No. 5,273,995); rosuvastatin (CRESTOR®; see
US Patent No. 5,260,440); and pitavastatin also referred to as NK-104 (see PCT international
Examples of additional active agents which may be employed include but are not limited to one or more of FLAP inhibitors; 5-lipoxygenase inhibitors; additional cholesterol absorption inhibitors such as ezetimibe (ZETIA®), described in U.S. Patent No.’s Re. 37721 and 5,846,966; cholesterol ester transfer protein (CETP) inhibitors, for example JTT-705; HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors); acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-I and -2; microsomal triglyceride transfer protein (MTP) inhibitors; niacin; niacin receptor agonists such as acipimox and acifran, as well as niacin receptor partial agonists; niacin in combination with a DP receptor antagonist; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPARγ) agonists including the compounds commonly referred to as glitazones for example pioglitazone and rosiglitazone and, including those compounds included within the structural class known as thiazolidinediones as well as those PPARγ agonists outside the thiazolidinedione structural class; PPARα agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual α/γ agonists; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril; calcium channel blockers such as nifedipine and diltiazam; endothelial antagonists; agents that enhance ABC1 gene expression; FXR ligands including both inhibitors and agonists; and LXR ligands including both inhibitors and agonists of all sub-types of this receptor, e.g. LXRα and LXRβ; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors such as celecoxib and valdecoxib. Additionally, Form I can be used in combination with PCSK9 antagonists; antisense; Apo-AI, Apo-AI variants such as Apo-AI Milano, or Apo-AI mimetics such as D4F; an HDL selective delipidation process; anti-hypertensive agents such as renin inhibitors and angiotensin II antagonists; anti-diabetic agents such as DPP-IV inhibitors, including e.g., JANUVIA and JANUMET; anti-obesity agents such as CB1 inverse agonists; and 11βHSD1 inhibitors.

Form I can also be used in combination with a nucleic acid molecule inhibitor that targets NPC1L1 or other protein sequences involved in hyperlipidemia. A polynucleotide-based gene expression inhibitor comprises any polynucleotide containing a sequence whose presence or expression in a cell causes the degradation of or inhibits the function, transcription, or translation of a gene in a sequence-specific manner. Polynucleotide-based expression inhibitors may be selected from the group comprising: siRNA, microRNA, interfering RNA or RNAi, dsRNA,
ribozymes, antisense polynucleotides, and DNA expression cassettes encoding siRNA, microRNA, dsRNA, ribozymes or antisense nucleic acids. RNAi molecules are polynucleotides or polynucleotide analogs that, when delivered to a cell, inhibit RNA function through RNA interference. Small RNAi molecules include RNA molecules less that about 50 nucleotides in length and include siRNA and miRNA. siRNA comprises a double stranded structure typically containing 15-50 base pairs and preferably 19-25 base pairs and having a nucleotide sequence identical or nearly identical to an expressed target gene or RNA within the cell. An siRNA may be composed of two annealed polynucleotides or a single polynucleotide that forms a hairpin structure. MicroRNAs (miRNAs) are small noncoding polynucleotides, about 22 nucleotides long, that direct destruction or translational repression of their mRNA targets. Antisense polynucleotides comprise sequence that is complimentary to a gene or mRNA. Antisense polynucleotides include, but are not limited to: morpholinos, 2'-O-methyl polynucleotides, DNA, RNA and the like. The polynucleotide-based expression inhibitor may be polymerized in vitro, recombinant, contain chimeric sequences, or derivatives of these groups. The polynucleotide-based expression inhibitor may contain ribonucleotides, deoxyribonucleotides, synthetic nucleotides, or any suitable combination such that the target RNA and/or gene is inhibited.

Form I could also be used in combination with peptide inhibitors and antibody molecule antagonists such as a PCSK9-specific antagonist. A PCSK9-specific antagonist can be any binding molecule with specificity for PCSK9 protein including, but not limited to, antibody molecules as described below, any PCSK9-specific binding structure, any polypeptide or nucleic acid structure that specifically binds PCSK9, and any of the foregoing incorporated into various protein scaffolds; including but not limited to, various non-antibody-based scaffolds, and various structures capable of affording selective binding to PCSK9 including but not limited to small modular immunopharmaceuticals (or "SMIPs"); see, Haan & Maggos, 2004 Biocentury Jan 26; Immunity proteins (see, e.g., Chak et al., 1996 Proc. Natl. Acad. Sci. USA 93:6437-6442); cytochrome b562 (see Ku and Schultz, 1995 Proc. Natl. Acad. Sci. USA 92:6552-6556); the peptide D2p8 (see Barthe et al., 2000 Protein Sci. 9:942-955); avimers (Avidia; see Silverman et al., 2005 Nat. Biotechnol. 23:1556-1561); DARPins (Molecular Partners; see Binz et al., 2003 J. Mol. Biol. 332:489-503; and Forrer et al., 2003 FEBS Lett. 539:2-6); Tetranectins (see, Kastrup et al., 1998 Acta. Crystallogr. D. Biol. Crystallogr. 54:757-766); Adnectins (Adnexus; see, Xu et al., 2002 Chem. Biol. 9:933-942), Anticalins (Pieris; see Vogt & Skerra, 2004 Chembiochem. 5:191-199; Beste et al., 1999 Proc. Natl. Acad. Sci. USA 96:1898-1903; Lamia & Erdmann, 2003 J. Mol. Biol. 329:381-388; and Lamia & Erdmann, 2004 Protein Expr. Purif. 33:39-47); A-domain proteins (see North & Blacklow, 1999 Biochemistry 38:3926-3935), Lipocalins (see Schlehuber & Skerra, 2005 Drug Discov. Today 10:23-33); Repeat-motif proteins such as Ankyrin repeat proteins (see Sedgwick & Smerdon, 1999 Trends Biochem. Sci. 24:3 11-3 16; Mosavi et al., 2002 Proc. Natl. Acad. Sci. USA 99:16029-16034; and Binz et al., 2004 Nat.
A therapeutically or prophylactically effective amount, as appropriate, of Form I can be used for the preparation of a medicament useful for inhibiting cholesterol absorption, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of cholesterol absorption, such as treating lipid disorders, preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 5 mg to about 1000 mg of Form I. The medicament comprised of Form I may also be prepared with one or more additional active agents, such as those described supra.

\[ \text{V-[3-(4-((2S,3R)-2-[(3,4-dihydroxy-3-(hydroxymethyl)buryl]phenyl)-3-(35)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazetidin-1-yl]phenyl})propyl\]methanesulfonamide was determined to inhibit cholesterol absorption employing the Cholesterol Absorption Assay in Mice, below. This assay involves comparing a test compound to ezetimibe with respect to their ability to inhibit cholesterol absorption in mice. Both ezetimibe and the tested compound inhibited cholesterol absorption by >90% at the highest dose tested. The tested compound had an ID 50 < 1 mg/kg.

**Cholesterol Absorption Assay in Mice:** C57BL/6 male mice (n = 6/group), aged 10-14 weeks, were dosed orally with 0.2 ml 0.25% methyl cellulose solution with or without test compound or ezetimibe (0.12-10 mg/kg). Thirty minutes later all of the mice were dosed orally with 0.2 ml INTRALIPID™ containing 2 μCi [3H]-cholesterol per mouse. Five hours later, the animals were euthanized, and liver and blood were collected. Cholesterol counts in liver and plasma were determined, and percent inhibition of cholesterol absorption was calculated.

A variety of chromatographic techniques may be employed in the preparation of Form I. These techniques include, but are not limited to: High Performance Liquid Chromatography (HPLC) including normal- reversed- and chiral-phase; Medium Pressure Liquid Chromatography (MPLC), Super Critical Fluid Chromatography; preparative Thin Layer Chromatography (prep TLC); Gas Chromatography (GC); flash chromatography with silica gel or reversed-phase silica gel; ion-exchange chromatography; and radial chromatography. All temperatures are degrees Celsius unless otherwise noted. Degrees Celsius may be noted in the examples as "C" without the degree symbol (e.g. 50°C) or "°C" with a degree symbol (e.g. 50°C).

Some abbreviations used herein include:

- **Ac:** Acyl (CH₃C(O)-)
- **Aq.:** Aqueous
- **Bn:** Benzyl
Example 1
Preparation of N-prop-2-yn-1-ylmethanesulfonamide (i-1):

Methanesulfonyl chloride (1.40 mL, 18.1 mmol) was added dropwise to a stirred solution of propargylamine (1.00 g, 18.1 mmol) and dimethylaminopyridine (44.0 mg, 0.36
mmol) in pyridine (10 mL) at 0°C. After aging for approximately 15 h, the reaction mixture was poured into 1N HCl and extracted twice with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, brine, dried (MgSO₄), filtered and concentrated in vacuo, to afford the title compound i-1. Crude i-1 crystallized on standing and was used without further purification. ¹HNMR (500 MHz, CDCl₃) δ: 4.92 (br s, 1H), 3.99 (dd, J = 2.3, 6.2 Hz, 2H), 3.11 (s, 3H), 2.70 (br t, J = 2.3 Hz).

Example 2
Preparation of 5-ethynyl-2,2-dimethyl-L-3-dioxan-5-yl acetate (i-6):

![Chemical structure of i-6]

To a dry 250mL roundbottom flask was charged with a 0.5M solution of ethynylmagnesium bromide in THF (115mL, 57.7mmol) under nitrogen atmosphere. The resulting solution was cooled to 0°C in an ice bath. To the cooled solution was added slowly a solution of 2,2-dimethyl-L-3-dioxan-5-one (5g, 38.44mmol) in 50mL dry THF. The ice bath was removed and the resulting reaction mixture was stirred at ambient temperature for 1.5hrs. The reaction mixture was quenched with sat. aq. NH₄Cl (50mL) and then extracted with ethyl acetate (100mL). The organic layer was dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude intermediate.

The crude intermediate was dissolved in CH₂Cl₂ (100mL) under nitrogen atmosphere. To the resulting solution was added simultaneously by syringe acetic anhydride (4.34mL, 46mmol) and TEA (6.4mL, 46mmol). To the reaction mixture was added DMAP (0.56g, 4.6mmol). The reaction mixture was stirred for 3hrs at room temperature at which time the reaction was quenched by the addition of IN aq. HCl (100mL). The reaction mixture was transferred to separately funnel and the organic layer was separated. The organic layer was washed with aq. NaHCO₃ (100mL), water (50mL), brine, dried, filtered and the solvent removed under vacuum to afford the title compound (i-6) which was used without further purification. ¹HNMR (500 MHz, CDCl₃) δ: 4.14 (d, J = 12.6, 2H) 4.07 (d, J = 12.6 Hz, 2H), 2.65 (s, IH), 2.12 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H).

Example 3
The compounds (3R,4S)-3-[(35)-3-(4-fluorophenyl)-3'-hydroxypropyl]-4-(4-hydroxyphenyl)-1-(4-iodophenyl)azetidin-2-one Q-T and (l-7a) were prepared according to

**Preparation of 4-[(2S,3R)-3-f(3S)-3-(acetyloxy)-3-(4-fluorophenyl)propyl-1-(4-iodophenyl)-4-oxoazetidin-2-yl]phenyl acetate (i-8):**

To a solution of (1S)-l-(4-fluorophenyl)-3-[(2S,3R)-2-(4-hydroxyphenyl)-l-(4-iodophenyl)-4-oxoazetidin-3-yl]propyl acetate (i-7a) (2g, 3.58 mmol) (prepared according to Burnett, D. S.; Caplen, M. A.; Domalski, M. S.; Browne, M. E.; Davis, H. R. Jr.; Clader, J. W. Bioorg. Med. Chem. Lett. (2002), 12, 311) in CH₂Cl₂ (25 mL) under nitrogen atmosphere was added acetic anhydride (0.4 mL, 4.30 mmol), triethylamine (0.75 mL, 5.38 mmol) and DMAP. The reaction mixture was stirred at RT for 1 hr and the solvent removed under vacuum. The residue was purified by MPLC (silica column) with stepwise gradient elution; (0 - 100% EtOAc/hexanes as eluent) to afford the title compound (i-8). m/z (ES) (M-OAc)+. ¹HNMR (500 MHz, CDCl₃) δ: 7.57 (d, J = 8.6, IH) 7.38-7.26 (m, 5H), 7.22 (br d, J = 7.1 Hz, 2H), 7.14 (d, J = 8.5 Hz, IH), 7.08-7.02 (m, 3H), 5.74 (t, J = 6.7 Hz, IH), 4.62 (d, J = 2.3 Hz, IH), 3.10 (dt, J = 2.3, 7.8 Hz, IH), 2.34 (s, 3H), 2.08 (s, 3H), 2.09-2.03 (m, 2H), 1.94-1.86 (m, 2H).
Example 4
Preparation of amorphous \( N\)-r3-f4-(f2S.3i?V2-(4-r3.4-dihydroxy-3-
(hydroxymethylbutylphenyl)-3-[3S]-3-(4-fluorophenyl)propyl]-4-hydroxypropyl]-4-oxoazetidin-1-
\( \alpha \)phenylpropylmethanesulfonamide (referred to herein as Compound \( A \))

Step A: Preparation of \( 4\)-r2S.3R)-3-[3S]-3-(acetyloxy]-3-(4-fluorophenyl)propyl]-1-(A-
(3-r(methylsulfonyl)aminolprop-1-yn-1-yl)phenyl)-4-oxoazetidin-2-yl phenyl acetate

\[
\begin{align*}
\text{OAc} & \quad \text{OAc} \\
\text{F} & \quad \text{N} \\
\text{H} & \quad \text{SO} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

Dichlorobis(triphenylphosphine)palladium(II) (1.27 g, 1.68 mmol) and copper(I) iodide (632 mg, 3.32 mmol) were added to a solution of i-8 (10.0 g, 16.6 mmol) and i-1 (3.34 g, 25.0 mmol) in triethylamine (16.2 mL, 116.34 mmol) and DMF (150 mL). The reaction mixture was saturated with nitrogen and stirred at room temperature. After 2h, the reaction mixture was partitioned between 400mL EtOAc and 250mL water. The organic layer was washed with water (150mL), brine (150mL), dried (\( \text{MgSO}_4 \)), filtered and concentrated \textit{in vacuo}. Purification of the crude residue by MPLC (silica column) with stepwise gradient elution; (0 - 100% EtOAc/hexanes as eluent) afforded the title compound, \textit{mlz} (ES) 629 (M+Na)^+ , 547 (M-OAc)^+. 

\(^1\)HNMR (500 MHz, \( \text{CDCl}_3 \)) \( \delta \): 7.35 (d, \( J = 8.4 \text{ Hz, IH} \)), 7.28 (dd, \( J = 6.4, 8.4 \text{ Hz, IH} \)), 7.19 (d, \( J = 8.5 \text{ Hz, IH} \)), 7.12 (d, \( J = 8.5 \text{ Hz, IH} \)), 7.08 (d, \( J = 8.3 \text{ Hz, IH} \)), 7.02 (dd, \( J = 6.5, 8.6 \text{ Hz, IH} \)), 5.72 (t, \( 6.6 \text{ Hz, IH} \)), 4.60 (d, \( J = 2.3 \text{ Hz, IH} \)), 4.21-4.16 (m, IH), 4.15 (overlapped dd, \( J = 7.1, 11 \text{ Hz, IH} \)), 3.15-3.12 (m, 2H), 3.09-3.04 (m, IH), 2.96 (s, 3H), 2.58 (t, \( 7.6 \text{ Hz, 2H} \)), 2.30 (s, 3H), 2.07 (overlapped s, 3H), 2.09-2.03 (m, 2H), 1.90-1.83 (m, 4H).
Step B: Preparation of 4-U2S. 3R)-3-(3S)-3-(acetyloxy)-3-(4-fluorophenyl)propyl-1-(4-
{3-I methylsulfonyl}amino-propyl)phenyl)-4-oxoazetidin-2-ylphenyl acetate

A mixture of the intermediate from Step A (8.5 g, 14 mmol) and 10% palladium on activated carbon (2.2 g) in ethanol (100 mL) and EtOAc (150 mL) was hydrogenated at atmospheric pressure. After 15 h, the reaction mixture was filtered through MgSO4 and filter aid and the filtered catalyst washed several times with EtOAc. The filtrate was concentrated in vacuo to afford the title compound which was used without further purification. m/z (ES) 663 (M+Na)+, 551 (M-OAc)+.

Step C: Preparation of (15)-1-(4-fluorophenyl)-3-IY3i?. 4^l-r4-{3-
[(methylsulfonyl)amino1propyl]phenyl)-2-oxo-4-{{[trifluoromethyl]-
sulfonyl]oxy}phenyl}azetidin-3-Ypropyl acetate

Guanidine hydrochloride (1.34 g, 13.93 mmol) was added to a mixture of the intermediate from Step B, (8.5 g, 13.93 mmol) and triethylamine (1.95 mL, 13.93 mmol) in methanol (150 mL). After 3 h, the solvent was removed under vacuum and the residue was dissolved in EtOAc (200 mL) / water (100 mL) and 2N aq. HCl. The mixture was transferred to a separatory funnel and the layers separated. The organic layer was washed with brine (100 mL), dried (MgSO4), filtered and concentrated in vacuo to afford a clear oil.

The crude intermediate was dissolved in methylene chloride (100 mL) and to the solution was added (bis(trifluoromethylsulfonyl)amino pyridine (8.14 g, 13.93 mmol), triethylamine (1.95 mL, 13.93 mmol), DMAP (~100 mg, catalytic). The resulting solution was stirred for 2 h at room temperature. The reaction was quenched with IN aq. HCl and the organic
layer was separated. The organic extract was washed with brine, dried (MgSO₄) and
concentrated in vacuo. Purification of the crude residue by MPLC (silica column) with stepwise
gradient elution (0 - 100% EtOAc/hexanes as eluent) afforded the title compound, \textit{mlz} (ES) 723
(M+Na)⁺, 641 (M-OAc)⁺.

**Step D:**

Preparation of (1S)-3-r(2S,3R)-2-f4-(\{5-(acetyloxyV2,2-dimethyl-1,3-dioxan-5-yl\}ethynyl \{phenyl\}- 1-(4-\{3-[\{\{methylsulfonyl\}aminolpropyUphenyl\}-4-
oxoazetidin-3-yl\}l-(4-1IuOrOPhCnVl)PrOPyl acetate:

![Chemical Structure](image)

To an oven dried flask 25OmL flask was added CuI (300 mg, 1.44 mmol),
tetrabutylammonium iodide (TBAI, 1.58g, 4.28 mmol). The charged flask was set under
nitrogen atmosphere and a solution of the intermediate from Step C, (3.5 g, 4.28 mmol) in 30mL
anhydrous DMF was added to the flask. A solution of 5-ethynyl-2,2-dimethyl-1,3-dioxan-5-yl
acetate (i-6) (1.70 g, 8.56 mmol) in DMF (20 mL) was added to the mixture. The flask was then
equipped with a condensor, and the mixture was evacuated and set under nitrogen several times
to de-gas the solvent. Solid Pd(PPh₃)₄ (3.32 g, 3 mmol) was then added to the reaction followed
by TEA (4.2 mL, 30 mmol). The reaction mixture was heated to 70°C for 2 hours during which
time the reaction mixture became dark brown in color. The reaction was removed from the
heating bath, cooled and partitioned with EtOAc (25OmL) and IN aq. HCl (100 mL). The
organic layer was washed with water (10OmL), brine (75mL), dried over magnesium sulfate,
filtered and concentrated under vacuum. The residue was purified by MPLC (silica column) with
stepwise gradient elution; (0 - 100% EtOAc/hexanes as eluent) to afford the title compound, \textit{mlz}
(ES) 689 (M-OAc)⁺. ¹H NMR (500 MHz, CD₃OD) δ: 7.44 (d, J = 8.3 Hz, 1H), 7.38-7.32 (m,
4H), 7.16 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.06 (t, J = 8.6 Hz, 2H), 5.70 (app t, 6.3
Hz, 1H).20 (s, 3H), 3.10-3.05 (m, 1H), 3.02 (d, J = 7.0 Hz, 2H), 2.89 (s, 3H), 2.60 (t, 7.4 Hz,
2H), 2.10 (s, 3H), 2.04 (s, 3H), 1.78 (t, J = 7.6, 3H), 1.47 (s, 3H), 1.39 (s, 3H).
Step E: Preparation of riSV3-r(2S,3RV2-r4-(2-r5-racetyloxy)-2,2-dimethyl-13-dioxan-5-yl[ethyl]phenyl)-1-(4-{3-[2-(me-thylsulfonyl)amino]propyl}phenyl)4-oxoazetidin-3-yll-l-f4-fluorophenyl)propyl acetate:

A roundbottom flask was charged with 10% Pd-C (500mg) and 300mg 20% Pd(OH)$_2$-C. EtOAc (~2mL) was added to cover the solid catalyst mixture. To this mixture was added a solution of the intermediate from Step D, (1.5g, 2.0 mmol) in ethanol (40mL) and ethyl acetate (2 mL). The resulting suspension set under hydrogen atmosphere and stirred vigorously for 1 hr. The catalysts were filtered, solids washed with ethanol and the solvent was removed under vacuum to obtain partially hydrogenated intermediate. The reaction procedure was repeated as above. A roundbottom flask was charged with 10% Pd-C (500mg) and 300mg 20% Pd(OH)$_2$-C. EtOAc (~2mL) was added to cover the solid catalyst mixture. To this mixture was added a solution of the intermediate from above in ethanol (40mL) and ethyl acetate (2 mL). The resulting suspension set under hydrogen atmosphere and stirred vigorously for 2 hours. The catalyst was filtered through filter aid and MgSO$_4$ and washed with EtOH/EtOAc. The filtrate was concentrated in vacuo to afford the title compound which was used without further purification. m/z (ES) 692 (M-OAc)$^+$. $^1$HNMR (500 MHz, CD$_3$OD) δ: 7.31-7.24 (m, 6H), 7.21-7.17 (m, 3H), 7.08-7.02 (m, 3H), 5.72 (app t, 6.7 Hz, IH) 4.60 (d, J = 2.1 Hz, IH), 4.20 (app t, J = 6.5, IH), 4.02 (d, J = 12.4 Hz, 2H), 3.90 (d, J = 12.2 Hz, 2H), 3.13 (q, J = 6.7 Hz, 2H), 3.06 (dt, J = 2.2, 7.6 Hz, IH), 2.94 (s, 3H), 2.60 (app q, 7.4 Hz, 4H), 2.35-2.29 (m, 2H), 2.08 (s, 3H), 2.03 (s, 3H), 1.83-1.90 (m, 3H), 1.45 (s, 3H), 1.40 (s, 3H).
Step F: Preparation of 3-{4-r(2S,3R V3-rG SV3-(acetyloxy)-3-(4-fluorophenylpropyll-1- \(4-\{3-[\text{N-methylsulfonyl}diamo] \text{propyl}\text{[phenyl}\text{V4-oxoazetidin-2-yl]}\text{phenyl}\})-1,1-\text{bisOivdroxymethyl}} \text{propyl acetate}

To a solution of the intermediate of step E (1.5 g, 2 mmol) in THF/water (16mL/4mL) was added TFA (1 mL). The reaction mixture was stirred at RT for 16hr. To the reaction mixture was added 100mL toluene and the water was removed under vacuum with water bath temperature of 40°C. The residue was treated twice with 100mL toluene followed by azeotropic removal of water. The solvent was completely removed under vacuum. The crude product was purified by MPLC (silica column) with stepwise gradient elution (50 - 100% EtOAc/hexanes as eluent). Mixed fractions were also isolated and were further purified by prep TLC eluting with CH\(_2\)Cl\(_2\)/MeOH (95/5). The purified fractions were combined to afford the title compound. mlz (ES) 653 (M-OAc)\(^+\).

Step G: Preparation of \(N\{3-\{4-(25.31?2-V2-\{4-r3,4-dihydroxy-3-\text{hydroxymethyl} \text{butylphenyl}\})-3\{3,5\}-3-(4-fluorophenyl)-4-\text{hydroxypropyl}\}-4\text{-oxoazetidin-1-yl} \text{phenylpropyl}^{-}\text{mesulfonamide}

To a solution of the intermediate from Step F, (1.05g, 1.47 mmol) in methanol (2.5 mL) was added potassium cyanide (100 mg, 1.58 mmol) and the resulting solution stirred at 50°C for 2 hours. The solution was concentrated and the residue purified by preparative TLC
plate eluting with methanol/dichloromethane (10/90) to afford the title compound. This product
was further purified by MPLC (silica column) with stepwise gradient elution; (5 - 10%
EtOH/EtOAc as eluent) to afford the title compound as a white solid. 1H NMR (500 MHz, CD3OD) δ: 7.35-7.31 (m, 2H), 7.28-7.234 (m, 4H), 7.18
(d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 7.03 (app, t, J = 8.6 Hz, 2H), 4.79 (br d, J = 2.1 Hz, 
IH), 4.60 (br dd, J = 5.1, 6.60 Hz, IH), 3.53 (s, 4H), 3.09-3.03 (m, IH), 3.02 (t, J = 6.8 Hz, 2H), 2.88 (s, 3H), 2.73-2.67 (m, 2H), 2.61 (t, 7.6 Hz, 2H), 1.97-1.83 (m, 3H), 1.81-1.73 (m, 3H).

Example 5
Procedures for the crystallization of amorphous iV-[3-(4-[(2S',3i?)-2-[(4-[3,4-dihydroxy-3-
[4i-hydroxyethyl]phenyl]-3-[3S]-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazetidin-1-

The starting material Compound A for these experiments was an amorphous solid
which had been purified by chromatography over silica gel using mixtures of dichloromethane:

Ethanol as eluent and was >99% pure by HPLC assay.

When a % range appears for a solvent system below, it indicates that the
experiment was run more than once, employing a 20% incremental v/v change for the solvent
system in each experiment. For example, "0-40% (v/v) Water in 1,2- Dichloroethane" indicates
that three experiments were performed using: 0% water, 100% dichloroethane; 20% water, 80%
dichloroethane; and 40% water, 60% dichloroethane.

A- Slurry process.

Using the Pow dernium, a powder dispensing robot, 1Omg +/- 1.0mg of
Compound A (amorphous solid) was dispensed into each well of a 96-well plate. A magnetic stir
bar was added to each well. 900 μl of solvent was dispensed into each well. The 96-well plate
was capped and the system was equilibrated at 65°C for 2 hours. The system was then filtered
hot at 65°C. The remaining solids were dried and analyzed by XRPD.

Preferred solvent compositions to obtain the crystalline phase:
100% (v) 1,2- Dichloroethane
100% (v) Acetonitrile
100% (v) Nitromethane
80% (v/v) iPrOAc in 1,2-dimethoxyethane
20% (v/v) Cyclohexane in Ethyl Acetate
80% (v/v) Cyclohexane in Ethanol
80% (v/v) Cyclohexane in 2-Propanol
3:1 (v/v) Ethyl Acetate: Heptanes
100% (v/v) MIBK (methyl iso-butyl ketone)

- 30 -
B- Evaporation process.

Using the Powdernium, a powder dispensing robot, 10mg +/- 1.0mg of Compound A (amorphous solid) was dispensed into each well of a 96-well plate. A magnetic stir bar was added to each well. 900 µl of solvent was dispensed into each well. The 96-well plate was capped and the system was equilibrated at 65°C for 2 hours. The system was then filtered hot at 65°C. 200 µl of each of the filtrate solutions were transferred into a new 96-well plate. This plate was left uncapped and allowed to evaporate at room temperature until dry. The remaining solids were dried and analyzed by XRPD.

Preferred solvent composition to obtain the crystalline phase:

100% 1,2-dichloroethane.

C- Cooling process.

Using the Powdernium, a powder dispensing robot, 10mg +/- 1.0mg of Compound A (amorphous solid) was dispensed into each well of a 96-well plate. A magnetic stir bar was added to each well. 900 µl of solvent was dispensed into each well. The 96-well plate was capped and the system was equilibrated at 65°C for 2 hours. The system was then filtered hot at 65°C. 200 µl of each of the filtrate solutions were transferred into a new 96-well plate. This plate was cooled with a cubic cool down temperature gradient of 65°C-10°C over 8 hours. The plate was equilibrated at 10°C for 2 hours and then the supernatant was removed from the plate. The following day, the plate was wicked to dry the remaining solvent and the solid residues were analyzed by XRPD.

Preferred solvent compositions to obtain the crystalline phase:

0-40% (v/v) Water in 1,2- Dichloroethane.

100% (v) 1,2- Dichloroethane
100% (v) Acetonitrile
100% (v) Nitromethane
80% (v/v) iPrOAc in 1,2-dimethoxyethane
40% (v/v) Cyclohexane in Ethyl Acetate
40-80% (v/v) Cyclohexane in Ethanol
60-80% (v/v) Cyclohexane in 2-Propanol
3:1 (v/v) Ethyl Acetate: Heptanes
40% (v/v) Cyclohexane in 1,2- Dimethoxyethane

D- Precipitation process:

Using the Powdernium, a powder dispensing robot, 10mg +/- 1.0mg of Compound A (amorphous solid) was dispensed into each well of a 96-well plate. A magnetic stir
bar was added to each well. 900 µl of solvent was dispensed into each well. The 96-well plate was capped and the system was equilibrated at 65°C for 2 hours. The system was then filtered hot at 65°C. 100 µl of each of the filtrate solutions were transferred into a new 96-well plate containing 200 µl of antisolvent in each well. The plate was equilibrated for 2 hours and then the supernatant was removed from the plate. The following day, the plate was wicked to dry the remaining solvent and the solid residues were analyzed by XRPD.

Preferred solvent compositions to obtain the crystalline phase:
- 0-20% (v/v) water in 1,2-dichloroethane (100 µl). Antisolvent: 200 µl of water.
- 20% (v/v) Water in Ethanol (100 µl). Antisolvent: 200 µl of water.
- 0-60% (v/v) THF in 1-Propanol (100 µl). Antisolvent: 200 µl of heptanes.
- 80% (v/v) THF in Toluene (100 µl). Antisolvent: 200 µl of heptanes.
- 0-60% (v/v) THF in Ethanol (100 µl). Antisolvent: 200 µl of heptanes.
- 20-100% (v/v) iPrOAc in 2-Propanol (100 µl). Antisolvent: 200 µl of heptanes.
- 100% (v) Butyronitrile (100 µl). Antisolvent: 200 µl of heptanes.
- 60% (v) iPrOAc in Ethanol (100 µl). Antisolvent: 200 µl of heptanes.
- 0-40% (v/v) Cyclohexane in Ethyl Acetate (100 µl). Antisolvent: 200 µl of heptanes.
- 20-40% (v/v) Cyclohexane in Ethanol (100 µl). Antisolvent: 200 µl of heptanes.
- 20% (v/v) Cyclohexane in 2-Propanol (100 µl). Antisolvent: 200 µl of heptanes.

**Example 6**

Procedure for the 60mg scale-Up Experiments for preparing Crystalline Form I

A- Precipitation experiment.

60 mg of the starting material, Compound A amorphous solid, was manually weighed in a glass vial. 2 ml of MIBK were manually dispensed into the vial. The vial was capped and equilibrated for one hour at 65°C.

The vial was removed from the oven and 500 µl of the supernatant was added to 1 ml of room temperature heptanes (anti-solvent). A white precipitate formed. The solids were isolated by vacuum filtration over a glass frit and analyzed.

B- Cooling experiment.

60 mg of the starting material, Compound A amorphous solid, was manually weighed in a glass vial. 2 ml of 1,2-dichloroethane were manually dispensed into the vial. The vial was capped and equilibrated for one hour at 65°C.

A slow cubic cool down from 65-10°C was completed over 10 hours. The mixture was held at 10°C for two hours and then warmed to 20°C. The solids were isolated by vacuum filtration over a glass frit and analyzed.

Results:
The scale-up experiments were analyzed by XRPD. The experiments generated crystalline material of Form I which appeared to be the same crystalline form as each other by XRPD. The scale-up experiments were successful in reproducing a crystalline phase of Compound A identified by the screen.

In the following examples, degrees Celsius may be represented as °C or °C (for example 50°C or 50°C).

Example 7

Crystallization with Unmilled Seed

Following the procedures described in Examples 1-4, but in Example 4, Step G, replacing the 1 eq of KCN at 50°C, with a catalytic amount of potassium trimethylsilanolate (TMSOK), as the transesterification catalyst, at room temperature, produces Compound A. Simple alcohols were chosen as solvents. Reaction rates are dependent on the size of the alcohol, and thus the use of smaller alcohols, which speed up the reaction, also allows for a reduction in the amount of the reagent. While other smaller alcohols such as EtOH may be used, the reaction is fastest in methanol (5 to 10 volumes) and requires only 10 mol% of TMSOK to drive the reaction to >99% completion in 1 hour at 20°C (2 hours at 10°C).

PROCEDURE (DEPROTECTION AND CRUDE CRYSTALLIZATION FROM IPA/HEPTANE).

<table>
<thead>
<tr>
<th>Reagent</th>
<th>MW</th>
<th>Amount</th>
<th>Eq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diacetate</td>
<td>712.7</td>
<td>3.8 Kg</td>
<td>1</td>
</tr>
<tr>
<td>TMSOK</td>
<td>128.29</td>
<td>69 g</td>
<td>0.1</td>
</tr>
<tr>
<td>MeOH</td>
<td>32</td>
<td>52 L</td>
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</tr>
<tr>
<td>HCl 37%</td>
<td>36.45</td>
<td>50 mL</td>
<td>0.1</td>
</tr>
<tr>
<td>IPA</td>
<td>60</td>
<td>110 L</td>
<td></td>
</tr>
<tr>
<td>Heptane</td>
<td>100</td>
<td>15 L</td>
<td></td>
</tr>
</tbody>
</table>

As described in Example 4, Step G, a solution of diacetate in methanol was filtered through a 1 μm line filter into a 100 L round bottom flask. The solution was cooled to 12°C and TMSOK was added in two portions (pH=8). No exotherm was observed. The reaction was monitored by HPLC until <1% of monoacetate was observed by HPLC (2 hours). Assay yield was 91% (3050g). The temperature was kept constant throughout the reaction and the pH stayed also constant. The reaction was quenched by acidification with 50 mL of cone. HCl (pH=5 after addition). The solution was concentrated to 30 L and solvent switched to IPA by flushing a total of 110 L of IPA at constant volume. GC assay showed <0.1% MeOH and
KF=335 ppm. A slurry was obtained after the solvent switch. The batch was heated up to 63C. The thin slurry obtained was line filtered while hot to remove KCl. After the filtration, temperature was brought back to 60C to obtain a clear solution, cooled down to 58C and seeded at this point with 30g of Form I. The batch was then cooled down at 5C/hour until it reached room temperature and then aged overnight at 20C. Concentration of Form I in the MLs was 18 mg/g. A total of 15 L of heptane were charged over 1 hour and the batched aged for two more hours. Concentration of Form I in the MLs was 9.2 mg/g (it would reach 5 mg/g if aged longer). The solids were filtered off and washed with 2/1 v/v IPA/heptane (18L total volume). The solids were dried in the filter pot under nitrogen stream.

Solids obtained: 2750g; 90 wt%; 80.7% yield from the diacetate; 90.1% yield for the crystallization.

PROCEDURE (PURE CRYSTALLIZATION FROM CH3CN/IPAC).

<table>
<thead>
<tr>
<th>Reagent</th>
<th>MW</th>
<th>Amount</th>
<th>Eq</th>
<th>Density/Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form I</td>
<td>628.75</td>
<td>2.7 Kg</td>
<td>1</td>
<td>90 wt%</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>41</td>
<td>11.9 L</td>
<td></td>
<td></td>
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<tr>
<td>IPAc</td>
<td>102</td>
<td>7.1 L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The solids previously isolated were charged into a 75 L round bottom flask, suspended in 11.9 L of acetonitrile and heated up to 56C until a clear solution was obtained. This solution was line filtered through a 1 µm filter into a 50 L round bottom flask. The temperature was brought back up to 52C, cooled down to 49C and seeded with 40g of Form I. The mixture was cooled down at 3C/hour to room temperature and aged overnight at 20C. Assay showed 21.8 mg/ml of Form I in the MLs. 7.1 L of IPAc were charged over 1h and the mixture aged for another 2 hours. Assay of the MLs showed 11.6 mg/ml. The slurry was filtered and washed with 4.8 L of CH₃CN/IPAc (5/3 v/v) followed by 4.8 L of IPAc. Solids were dried overnight in the filter pot under nitrogen stream.

Solids obtained: 2150g; 90 wt%; 88% yield.

HPLC Conditions
Column: Symmetry C-18 5µm (Waters)
Flow Rate: 1 ml/min
Run Time: 10 min
Temp: 35 C
Solvents: A: Acetonitrile  B: 0.1% H₃PO₄ aq buffer.
Gradient:

<table>
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<tr>
<th>Time</th>
<th>%A</th>
<th>%B</th>
</tr>
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<tr>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

Ret times:
Form I: 3.3 min
Monoacetate: 4.1 min
Diacetate: 5.1 min
Methyl ester: 3.7 min

Column: Sunfire C18 5um
Flow Rate: 1 ml/min
Run Time: 43 min
Temp: 5 C
Solvents: A: Acetonitrile B: 0.1% H₃PO₄ aq buffer.

Gradient:

<table>
<thead>
<tr>
<th>Time</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33</td>
<td>67</td>
</tr>
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<td>25</td>
<td>33</td>
<td>67</td>
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<td>35</td>
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<tr>
<td>40</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>43</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

Ret times:
Form I: 21.4 min
Epi-OH: 22.5 min
Olefin: 22.5 min
Methyl ester: 32.0 min
Monoacetate: 33.5 min
Bissulfonamide: 37.1 min

¹H NMR (400 MHz, CD₃OD), δ (ppm): 1.70-2.0 (m, 8H), 2.55-2.65 (m, 2H), 2.65-2.75 (m, 2H), 2.89 (s, 3H), 3.00-3.10 (m, 3H), 3.54 (s, 4H), 4.58-4.65 (m, 1H), 4.78 (m, 1H), 4.8 (b, OH), 7.03 (d, J= 8.7 Hz, 1H), 7.05 (d, J= 8.7 Hz, 1H), 7.10 (d, J= 8.3 Hz, 2H), 7.19 (d, J= 8.3 Hz, 2H), 7.25 (d, J= 8.4 Hz, 2H), 7.28 (d, J= 8.4 Hz, 2H), 7.31 (d, J= 7.9 Hz, 2H), 7.33 (d, J= 7.9 Hz, 2H).
\(^{13}\)C NMR (100 MHz, CD\(_3\)OD) (ppm): 26.3, 30.0, 33.1, 33.3, 37.2, 37.7, 39.6, 43.5, 61.1, 62.1, 65.8, 73.8, 75.5, 116.1 (d, J=22.1 Hz), 118.5, 127.4, 128.9 (d, J=8.0 Hz), 130.2, 130.4, 136.8, 137.0, 138.9, 142.4 (d, J=2.5 Hz), 144.9, 163.5 (d, J=237.5 Hz), 169.9.

5 Crystallization Of Form I From EtOH-Water

Crude triacetate starting material (100g, 69.6 mmol) was dissolved in 400 mL of EtOH. To the resulting solution was added TMSOK (2.62g, 20.4 mmol) and the mixture was aged overnight at 21°C. Reaction was complete by LC assay after 16h age. The mixture was concentrated at reduced pressure and the resulting oil was chromatographed on silica gel using mixtures of dichloromethane and IPA as eluent. Chromatographic purification afforded 28.7g of an oily material (66% yield). This material was dissolved in 232 mL of EtOH and the resulting solution was warmed to 35°C. 464 mL of water were then added and the solution was warmed to 41°C. 150 mg of Form I seed were added. The mixture was cooled to 20°C over 3 hours and aged overnight at 20°C. Solids were filtered and washed with 150 mL of EtOH:H\(_2\)O 1:2 v/v. Obtained 25.0g of Form I of 98.7 wt%. Yield for the isolation was 87%.

Example 8

Crude Crystallization

Crude Compound A in dry MeCN (3 vol) was heated to 60°C and cooled to 45°C. The solution was seeded with 0.5 wt% Form I. Toluene (10 vol) was charged over 4 h at 45°C. The resulting slurry was cooled down to -10°C at a rate of 15°C/h. The resulting slurry was stirred at -10°C for 6-8 h. The solid was collected and washed with 3:10 MeCN/toluene and toluene and dried under nitrogen to afford crude Form I.

Example 9

The product, as described in Example 8, was treated with Ecosorb (a kind of charcoal) or silica gel either before or after crude crystallization in order to remove impurities. It was then dissolved in MeCN (5 vol.) at 55-60°C. The solution was cooled to 44-48°C, and seeded with 2.5 wt% media milled seed (typical size of seed is < 5 urn), charged as a slurry in 5/3
v/v toluene/MeCN. After aging the seed bed for 30-60 minutes, toluene (8.33 vol.) was charged over 10 hrs while maintaining the batch at 44-48°C. Following toluene addition, the batch was cooled slowly to 0°C over 6 hrs and aged at least 1 hr. The crystallized batch was then filtered and washed with 5/3 v/v toluene/MeCN and toluene. The washed cake was then dried under vacuum and nitrogen at 40°C.

Example 10
The following are examples of pharmaceutical formulations comprised of Form I.

Form I is formulated as either dry filled capsules or compressed tablets in doses that generally will range from 1 mg to 250 mg of Form I. More generally, the doses will be in the range of 2-100 mg. A typical capsule or tablet formulation contains Form I, microcrystalline cellulose (Avicel), lactose monohydrate, croscarmellose sodium, magnesium stearate and/or sodium stearyl fumarate, and may also contain sodium lauryl sulfate. The capsule formulations are transferred to hard gelatin capsules. Tablet formulations may be coated with a film coat containing lactose, hypromellose, triacetin, titanium dioxide, and ferric oxide.

The formulations are manufactured by first blending Form I with the excipients, then compressing the mixture into ribbons by roller compaction, and then milling the ribbons into granules. The granules are then lubricated and either filled into capsules or compressed into tablets. If tablets are selected, a film coat may be applied to the compressed tablets.

Exemplary formulation compositions that provide 10mg and 100mg dose of Form I are shown below. The examples provide the composition for uncoated compressed tablets which contain sodium lauryl sulfate as well as both magnesium stearate and sodium stearyl fumarate.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg/tablet</th>
<th>10mg potency</th>
<th>100mg potency</th>
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<tbody>
<tr>
<td>Form I</td>
<td>10.0</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>42.0</td>
<td>138.0</td>
<td></td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>42.0</td>
<td>138.0</td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>3.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>1.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
<td>1.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>100.0</strong></td>
<td><strong>400.0</strong></td>
<td></td>
</tr>
</tbody>
</table>

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes,
modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agent used in the instant invention as indicated above. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.
WHAT IS CLAIMED IS:

1. A crystalline Form I of \( N\)-[3-(4-{(25,3i?)\}-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl}-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl)methanesulfonamide characterized by \( ^{13}\text{C-SSNMR} \) having a chemical shift differences between the lowest ppm resonance and other resonances as follows: 2.0, 109.4, 26.8 and 48.0.

2. The crystalline Form I of claim 1 further characterized by \( ^{13}\text{C-SSNMR} \) having chemical shift differences between the lowest ppm resonance and other resonances as follows: 103.1, 31.5 and 141.5.

3. The crystalline Form I of claim 2 further characterized by \( ^{13}\text{C-SSNMR} \) having chemical shift differences between the lowest ppm resonance and other resonances as follows: 7.4, 87.1 and 119.7.

4. A crystalline Form I of \( N\)-[3-(4-{(25',3i?)\}-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl}-3-[(35)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl)methanesulfonamide characterized by \( ^{13}\text{C-SSNMR} \) having the following chemical shifts expressed in parts per million: 28.8, 136.2, 43.4 and 74.8.

5. A crystalline Form I of \( N\)-[3-(4-{(25,3i?)\}-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl}-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl)methanesulfonamide characterized by the solid-state \( ^{13}\text{C-SSNMR CPMAS} \) nuclear magnetic resonance spectrum of FIG. 2.

6. A crystalline Form I of \( N\)-[3-(4-{(25,3i?)\}-2-{4-[3,4-dihydroxy-3-(hydroxymethyl)butyl]phenyl}-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl]phenyl)propyl)methanesulfonamide characterized by diffraction peaks from X-ray powder diffraction pattern corresponding to peak reflections of 18.7, 19.3, 17.1 degrees 2-theta.

7. The crystalline Form I of claim 6 further characterized by diffraction peaks obtained from X-ray powder diffraction pattern corresponding to peak reflections of 22.0, 22.6, 6.2 degrees 2-theta.

8. The crystalline Form I of claim 6 further characterized by diffraction peaks obtained from X-ray powder diffraction pattern corresponding to peak reflections of 11.8, 12.4, 13.4 degrees 2-theta.
9. A crystalline Form I of \( N\{-3-(4\{(25,3i?)\}-2\{-4\{3,4\text{-dihydroxy-3-}
\text{(hydroxymethyl)butyl}\text{phenyl}\}\}-3\{-3\{(3\text{S})\}-3\{(4\text{-fluorophenyl})\}-3\text{-hydroxypropyl}\}-4\text{-oxoazetidin-
\text{yl}\text{phenyl}propyl\text{methanesulfonamide} \) characterized by the X-ray powder diffraction pattern of Figure 1.

10. A method of reducing plasma LDL-cholesterol levels comprising administering a therapeutically effective amount of the compound of claim 1 to a patient in need of such treatment.
FIGURE 1

1/2

XRPD

[Graph showing XRPD pattern with intensity on the y-axis and 2Theta on the x-axis]
2/2
SS-NMR

FIGURE 2
INTERNATIONAL SEARCH REPORT

International application No. PCT/US 08/04140

A CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01 N 43/00, A61 K 31/397 (2008.04)
USPC - 514/210 02
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)
USPC  514/210 02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC  514/210, 540/200 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST/USPT,PGPB,EPAB,JPAB, DialogWeb, Google Scholar
Search Terms Used sulfonamide oxazetidin, azetidinone, NMR, chemical shift, X-ray, powder diffraction, crystalline, cholesterol

C DOCUMENTS CONSIDERED TO BE RELEVANT

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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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I Further documents are listed in the continuation of Box C

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<th>Special categories of cited documents</th>
<th>T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle underlying the invention</th>
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<td>A document defining the general state of the art which is not considered to be of particular relevance</td>
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Date of the actual completion of the international search
11 June 2008 (11 06 2008)

Date of mailing of the international search report
20 JUN 2008

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