

SALTS OF ISOBUTYRIC ACID (1 R*, 2R*, 4R*)-2-(2-{ [3-(4,7-DIMETHOXY-1H-BENZOIMIDAZOL-2-YL)-PROPYL]-METHYL-AMINO}-ETHYL)-5-PHENYL-BICYCLO[2.2.2]OCT-5-EN-2-YL

Salt Forms

The invention relates to novel crystalline salt forms of isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester (hereinafter also referred to as "COMPOUND") or enantiomers thereof, processes for the preparation thereof, pharmaceutical compositions containing said crystalline salt forms, and their use as calcium channel blockers in the treatment or prevention of chronic stable angina, hypertension, ischemia (renal and cardiac), cardiac arrhythmias including atrial fibrillation, cardiac hypertrophy, or congestive heart failure. Said crystalline salt forms of the present invention may also be used, alone or in pharmaceutical compositions, for the treatment of renal diseases, diabetes and its complications, hyperaldosteronism, epilepsy, neuropathic pain, or cancer in humans and other mammals.

Background of the Invention

Many cardiovascular disorders have been associated with a 'calcium overload' resulting from an abnormal elevated calcium influx through the plasma membrane of cardiac and vascular smooth muscle cells. There are 3 major pathways through which extracellular calcium can enter these cells: 1) receptor-activated calcium channels, 2) ligand-gated calcium channels and 3) voltage-operated calcium channels (VOCs).

VOCs have been classified into 6 main categories: L (Long-lasting), T (Transient), N (Neuronal), P (Purkinje cells), Q (after P) and R (Remaining or Resistant).

L-type calcium channels are responsible for the inward movement of calcium that initiates contraction in cardiac and smooth muscle cells suggesting a putative application for blockers of these channels in the cardiovascular field. In this view, L-type calcium channel blockers have been used in clinic since the early 60s and are now recommended as a first line of treatment for systolic-diastolic hypertension and angina pectoris.

T-type calcium channels are found in various tissues such as coronary and peripheral vasculature, sinoatrial node and Purkinje fibres, brain, adrenal glands and in the kidney. This broad distribution suggests a T-type channel blocker to have a putative cardiovascular protection, to have an effect on sleep disorders, mood disorders, depression, migraine, hyperaldosteroneemia, preterm labor, urinary incontinence, brain aging or neurodegenerative disorders such as Alzheimers disease.

Mibefradil (Posicor®), the first L-type and T-type calcium channels blocker demonstrated a superior effect over calcium channel blockers, which target the L channel predominantly.

Mibefradil was used for the treatment of hypertension and angina without showing negative side-effects often seen by L channel blockers like inotropy, reflex tachycardia, vasoconstrictive hormone release or peripheral edema. Additionally, mibefradil showed a potentially cardioprotective effect (Villame, Cardiovascular Drugs and Therapy 15, 41-28, 2001; Ramires, J Mol Cell Cardiol **1998**, 30, 475-83), a renal protective effect (Honda, Hypertension 19, 2031-37, 2001), and showed a positive effect in the treatment of heart failure (Clozel, Proceedings Association American Physicians **1999**, 111, 429-37).

Despite the enormous demand for a compound of this profile, mibefradil was withdrawn from the market in 1998 (one year after its launch), due to unacceptable CYP 3A4 drug interactions. Moreover, ECG abnormalities (i.e. QT prolongations) and interaction with the MDR-1 mediated digoxin efflux were also reported (du Souich, Clin Pharmacol Ther 67, 249-57, 2000; Wandel, Drug Metab Dispos **2000**, 28, 895-8).

It has now been found that crystalline salt forms of COMPOUND (isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester) may under certain conditions be found. Said crystalline salt forms of COMPOUND are novel and may have advantageous properties, especially compared to the free base (WO2008/132679) or the di-hydrochloride salt of COMPOUND. Such advantages may include better flow properties, better solubility, less hygroscopicity, better reproducibility in manufacturing (for example better filtration parameters, better reproducibility of formation, better sedimentation), defined morphology and/or better long term stability.

Description of the Figures

Fig. 1 shows the X-ray powder diffraction diagram of the di-hydrochloric acid salt of COMPOUND in a crystalline form as obtained from Reference Example S1. The X-ray diffraction diagram measured with method 1 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (2θ) (selected peaks from the range 2-40°, 2theta with relative intensity larger than 10% are reported): 3.02° (100%), 9.19° (88%), 9.77° (81%), 10.81° (16%), 12.50° (19%), 12.94° (21%), 13.15° (30%), 14.30° (26%), 14.62° (24%), 15.36° (66%), 16.14° (37%), 17.08° (73%), 18.12° (76%), 19.46° (45%), 19.71° (40%), 20.54° (35%), 20.92° (31%), 21.17° (29%), 21.56° (41%), 22.47° (29%), 22.90° (22%), 23.99° (24%), 25.41° (52%), 26.05° (31%), 26.90° (32%), 27.28° (24%), and 28.45° (37%).

Fig. 2 shows the X-ray powder diffraction diagram of the di-methylsulfonic acid salt of COMPOUND in a crystalline form as obtained from Example S2. The X-ray diffraction

diagram measured with method 1 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 2-40° 2theta with relative intensity larger than 10% are reported): 3.97° (100%), 7.21° (42%), 10.00° (39%), 14.09° (40%), 14.45° (29%), 15.99° (55%), 16.38° (22%), 17.16° (51%), 18.12° (44%), 18.34° (53%), 18.60° (19%), 19.38° (25%), 20.62° (35%), 21.02° (74%), 21.79° (18%), 22.24° (25%), 26.66° (30%), and 27.63° (29%).

Fig. 3 shows the X-ray powder diffraction diagram of the di-toluenesulfonic acid salt of COMPOUND in a crystalline form as obtained from Example S3. The X-ray diffraction diagram measured with method 1 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 2-40° 2theta with relative intensity larger than 10% are reported): 4.35° (31%), 5.79° (100%), 7.43° (16%), 8.62° (17%), 10.93° (19%), 11.51° (31%), 13.98° (34%), 15.81° (26%), 18.06° (30%), 19.00° (20%), 19.39° (21%), 19.84° (31%), 20.30° (25%), and 25.51° (20%).

Fig. 4 shows the X-ray powder diffraction diagram of the sulfuric acid salt of COMPOUND in a crystalline form as obtained from Example S4. The X-ray diffraction diagram measured with method 1 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 2-30° 2theta with relative intensity larger than 10% are reported): 2.85° (100%), 8.50° (21%), 9.50° (28%), 11.78° (85%), 13.26° (41%), 13.69° (51%), 14.19° (82%), 15.78° (40%), 16.47° (39%), 17.12° (38%), 18.91° (40%), 19.48° (43%), 26.77° (65%), and 27.24° (63%).

Fig. 5 shows the X-ray powder diffraction diagram of the di-maleic acid salt of COMPOUND in a crystalline form as obtained from Example S5. The X-ray diffraction diagram measured with method 1 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 2-40° 2theta with relative intensity larger than 10% are reported): 5.07° (26%), 8.19° (12%), 10.15° (93%), 15.26° (39%), 17.20° (12%), 17.61° (18%), 20.39° (100%), 20.88° (12%), 22.63° (47%), 23.93° (43%), 24.27° (26%), 24.51° (13%), 24.73° (17%), 25.61° (21%), 29.42° (25%), and 32.93° (16%),

Fig. 6 shows the X-ray powder diffraction diagram of the sesqui-fumaric acid salt of COMPOUND in a crystalline form as obtained from Example S6. The X-ray diffraction diagram measured with method 1 shows peaks having a relative intensity, as compared to

the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2θ (selected peaks from the range $2-40^\circ$ 2θ with relative intensity larger than 10% are reported): 5.27° (57%), 8.05° (100%), 12.93° (18%), 15.20° (10%), 15.50° (20%), 19.45° (14%), 20.31° (31%), 20.61° (62%), 21.11° (27%), 22.77° (15%), 25.42° (11%), 26.22° (11%), and 31.27° (21%).

Fig. 7 shows the X-ray powder diffraction diagram of the di-hydrobromic acid salt of COMPOUND in a crystalline form as obtained from Example S7. The X-ray diffraction diagram measured with method 1 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2θ (selected peaks from the range $2-40^\circ$ 2θ with relative intensity larger than 10% are reported): 3.1° (59%), 6.2° (28%), 9.3° (18%), 14.4° (11%), 15.6° (100%), 17.3° (33%), 18.1° (15%), 19.4° (20%), 20.0° (37%), 21.4° (14%), 22.8° (16%), and 34.8° (43%).

Fig. 8 shows the X-ray powder diffraction diagram of the sesqui-naphthalene-1,5-disulfonic acid salt of COMPOUND in a crystalline form as obtained from the general procedure for salt formation. The X-ray diffraction diagram measured with method 2 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2θ (selected peaks from the range $8-26.5^\circ$ 2θ with relative intensity larger than 10% are reported): 9.9° (40%), 10.4° (18%), 12.8° (42%), 14.2° (100%), 15.0° (73%), 18.3° (68%), 19° (54%), 20.1° (39%), 20.6° (48%), 21.3° (83%), 23.8° (13%), 24.9° (14%), and 26.2° (22%).

Fig. 9 shows the X-ray powder diffraction diagram of the di-benzenesulfonic acid salt of COMPOUND in a crystalline form as obtained from the general procedure for salt formation. The X-ray diffraction diagram measured with method 2 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2θ (selected peaks from the range $8-26.5^\circ$ 2θ with relative intensity larger than 10% are reported): 8.1° (16%), 8.5° (18%), 10.9° (20%), 11.4° (16%), 12.3° (20%), 12.6° (37%), 12.9° (22%), 13.4° (55%), 14.6° (32%), 15.3° (37%), 16.1° (27%), 17.5° (71%), 17.9° (37%), 19.1° (22%), 19.4° (25%), 20.1° (46%), 21.3° (91%), 21.8° (46%), 22.7° (100%), 23.6° (18%), 24.5° (20%), and 25.5° (21%).

Fig. 10 shows the X-ray powder diffraction diagram of the di-ethanesulfonic acid salt of COMPOUND in a crystalline form as obtained from the general procedure for salt formation. The X-ray diffraction diagram measured with method 2 shows peaks having a relative

intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2θ (selected peaks from the range $8-26.5^\circ$ 2θ with relative intensity larger than 10% are reported): 9.6° (25%), 9.9° (21%), 10.5° (23.3%), 11.2° (27%), 11.9° (17%), 12.9° (48%),
 5 14.5° (53%), 15.0° (40%), 15.7° (100%), 16.5° (65%), 17.0° (40%), 17.7° (49%), 19.0° (67%), 19.7° (69%), 20.4° (68%), 21.5° (55%), 22.6° (67%), and 23.3° (47%).

Fig. 11 shows the X-ray powder diffraction diagram of the di-naphthalene-2-sulfonic acid salt of COMPOUND in a crystalline form as obtained from the general procedure for salt formation. The X-ray diffraction diagram measured with method 2 shows peaks having a
 10 relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2θ (selected peaks from the range $8-26.5^\circ$ 2θ with relative intensity larger than 10% are reported): 9.8° (98%), 11.2° (45%), 11.8° (24%), 13.7° (20%), 14.6° (33%), 15.6° (100%), 16.9° (90%), 19.4° (96%), 22.4° (45%), and 23.9° (23%).

15 In the X-ray diffraction diagrams of Fig. 1 to Fig 11 the angle of refraction 2θ (2θ) is plotted on the horizontal axis and the counts on the vertical axis.

Detailed Description of the Invention

1) The invention relates to a crystalline salt, especially an essentially pure crystalline salt, of
 20 COMPOUND (isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester); wherein said crystalline salt consists of:

- 1 equivalent of COMPOUND;
- an acid component consisting of 1 to 2 equivalents of an acid selected from the group
 25 consisting of hydrobromic acid, sulfuric acid, maleic acid, fumaric acid, methanesulfonic acid, para-toluenesulfonic acid, benzenesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, and ethanesulfonic acid; and
- 0 to 5 equivalents of water.

2) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment
 30 1), wherein COMPOUND is enantiomerically enriched isobutyric acid (1R,2R,4R)-2-(2-([3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester.

3) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment
 1), wherein COMPOUND is enantiomerically enriched isobutyric acid (1S,2S,4S)-2-(2-([3-

(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester.

4) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 1), wherein COMPOUND is isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester in enantiomerically enriched form having negative optical rotation.

5) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 4), wherein said crystalline salt contains 0 to 3 (especially 0.5 to 3, notably 1 to 2) equivalents of water.

6) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 4), wherein said crystalline salt contains 0 equivalents of water.

7) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 6), wherein the acid component of said crystalline salt consists of 1 or 2 (especially 2) equivalents of hydrobromic acid, 1 or 2 equivalents of sulfuric acid, 1 or 2 (especially 2) equivalents of maleic acid, 1 to 2 (especially 1.5) equivalents of fumaric acid, 1 or 2 (especially 2) equivalents of methanesulfonic acid, 1 or 2 (especially 2) equivalents of para-toluenesulfonic acid, 1 or 2 (especially 2) equivalents of benzenesulfonic acid, 1 to 2 (especially 1.5) equivalents of naphthalene-1,5-disulfonic acid, 1 or 2 (especially 2) equivalents of naphthalene-2-sulfonic acid, or 1 or 2 (especially 2) equivalents of ethanesulfonic acid.

In a sub-embodiment, the acid component of said crystalline salt preferably consists of 2 equivalents of hydrobromic acid, 1 or 2 equivalents of sulfuric acid, 2 equivalents of maleic acid, 1 to 2 (especially 1.5) equivalents of fumaric acid, 2 equivalents of methanesulfonic acid, 2 equivalents of para-toluenesulfonic acid, or 2 equivalents of benzenesulfonic acid. In another sub-embodiment, the acid component of said crystalline salt preferably consists of 1 or 2 (especially 2) equivalents of maleic acid, or 1 to 2 (especially 1.5) equivalents of fumaric acid.

8) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2 equivalents of hydrobromic acid. A sub-embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 5) or 7), wherein the acid component of said crystalline salt consists of 2 equivalents of hydrobromic acid; and wherein said crystalline salt contains about 3 equivalents of water.

9) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 1 or 2 equivalents of sulfuric acid.

5 10) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2 equivalents of maleic acid.

11) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 1 to 2 (especially 1.5) equivalents of fumaric acid.

10 12) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2 equivalents of methanesulfonic acid.

13) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2
15 equivalents of para-toluenesulfonic acid.

14) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2 equivalents of benzenesulfonic acid.

15) Another embodiment relates to a crystalline salt of COMPOUND according to any one of
20 embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 1 to 2 (especially 1.5) equivalents of naphthalene-1,5-disulfonic acid.

16) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2 equivalents of naphthalene-2-sulfonic acid.

25 17) Another embodiment relates to a crystalline salt of COMPOUND according to any one of embodiments 1) to 7), wherein the acid component of said crystalline salt consists of 2 equivalents of ethanesulfonic acid.

18) Another embodiment relates to a crystalline salt, especially an essentially pure crystalline salt, of COMPOUND according to embodiment 1) or 10), wherein said crystalline salt
30 consists of:

- 1 equivalent of COMPOUND, or of enantiomerically enriched COMPOUND as defined in any one of embodiments 2) to 4);
- 2 equivalents of maleic acid; and

- 0 equivalents of water.

19) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 10) or 18), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 10.15° , 20.39° , and 22.63° .

- 5 20) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 10) or 18), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 5.07° , 8.19° , 10.15° , 15.26° , 17.61° , 20.39° , 22.63° , 23.93° , 24.27° , and 25.61° .

- 10 21) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 10) or 18), which essentially shows the X-ray powder diffraction pattern as depicted in Fig.5.

22) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 10) or 18) to 21), which has a melting point of about 147°C as determined by differential scanning calorimetry using the method as described herein.

- 15 23) In another embodiment the present invention relates to a crystalline salt according to any one of embodiments 10) or 18) to 22), obtainable by:

1. refluxing a solution of COMPOUND (682 g, 84% w/w, 1.05 mol) in EtOAc (6.3 L, 11 volumes);
- 20 2. adding maleic acid (256 g, 2.2 mol, 2.1 eq) dissolved in MeOH (630 mL, 1.1 volumes);
3. stirring the resulting mixture under reflux for 15 minutes and cooling to $65\text{--}68^\circ\text{C}$ within 30 minutes;
4. optional seeding with 0.04% w/w of seeding crystals;
5. cooling the mixture to 40°C within 3 hours;
- 25 6. cooling the mixture to 20°C within 1 hour;
7. filtering the solid under 0.2 bar of nitrogen and rinsing the solid with EtOAc (1500 mL 2.6 volumes); and
8. drying the solid under 1 atmosphere of nitrogen for 24 hours.

- 30 24) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 8), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.3° , 15.6° , and 17.3° .

25) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 8) or 24), characterised by the presence of peaks in the X-ray powder diffraction

diagram at the following angles of refraction 2θ : 6.2, 9.3°, 15.6°, 17.3°, 18.1°, 19.4°, 20.0°, and 22.8°.

26) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 8), 24) or 25), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 7.

27) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 11), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 5.27°, 8.05°, and 20.61°.

28) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 11) or 27), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 5.27°, 8.05°, 12.93°, 19.45°, 20.61°, 21.11° and 31.27°.

29) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 11), 27) or 28), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 6.

30) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 11), or 27) to 29), which has a melting point of about 180°C as determined by differential scanning calorimetry using the method as described herein.

31) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 12), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 7.21° and 10.00°.

32) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 12) or 31), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 3.97°, 7.21°, 10.00°, 15.99°, 17.16°, and 21.02°.

33) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 12), 31) or 32), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 2.

34) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 13), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 5.79° and 19.84°.

35) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 13) or 34), characterised by the presence of peaks in the X-ray powder

diffraction diagram at the following angles of refraction 2θ : 4.35° , 5.79° , 10.93° , 13.98° , 15.81° and 19.84° .

36) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 13), 34) or 35), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 3.

37) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 14), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 13.4° , 17.5° , and 21.3° .

38) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 14) or 37), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 12.6° , 13.4° , 14.7° , 17.5° , 21.3° , and 22.7° .

39) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 14), 37) or 38), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 9.

40) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 15), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.9° , 14.2° , and 21.3° .

41) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 15) or 40), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.9° , 12.9° , 14.2° , 20.1° , 20.6° , and 21.3° .

42) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 15), 40) or 41), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 8.

43) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 16), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.8° , 11.2° , and 15.6° .

44) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 16) or 43), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.8° , 11.2° , 15.6° , 22.4° , and 23.9° .

45) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 16), 43) or 44), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 11.

5 46) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 17), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 11.2° , 15.7° , and 20.4° .

10 47) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 17) or 46), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 11.2° , 14.5° , 15.7° , 17.7° , 20.4° , and 22.6° .

48) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 17), 46) or 47), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 10.

15 49) The invention further relates to a crystalline salt, especially an essentially pure crystalline salt, of COMPOUND (isobutyric acid (1R*,2R*,4R*)-2-(2-[[3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino]-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester); wherein said crystalline salt consists of:

- 1 equivalent of COMPOUND;
- an acid component consisting of about 1 equivalent of sulfuric acid; and
- 20 • about 6 equivalents of water.

50) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 49), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 11.78° , 13.69° , and 14.19° .

25 51) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 49) or 50), characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 2.85° , 8.50° , 9.50° , 11.78° , 13.26° , 13.69° , and 14.19° .

30 52) Another embodiment relates to a crystalline salt of COMPOUND according to embodiment 49), 50) or 51), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 4.

For avoidance of any doubt, whenever one of the above embodiments, especially one of embodiments 19), 20), 24), 25), 27), 28), 31), 32), 34), 35), 37), 38), 40), 41), 43), 44), 46), 47), 50) and 51), refers to "peaks in the X-ray powder diffraction diagram at the following

angles of refraction 2θ ", said X-ray powder diffraction diagram is obtained by using Cu K α 1 radiation ($\lambda = 1.5406 \text{ \AA}$); and it should be understood that the accuracy of the 2θ values as provided herein is in the range of ± 0.1 - 0.2° . Notably, when specifying an angle of refraction 2θ for a peak in the invention embodiments and the claims, the 2θ value given is to be understood as an interval from said value minus 0.2° to said value plus 0.2° ($2\theta \pm 0.2^\circ$); and preferably from said value minus 0.1° to said value plus 0.1° ($2\theta \pm 0.1^\circ$).

For avoidance of any doubt, the relative configuration of stereoisomers is denoted as follows: isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester denominates

- 10 isobutyric acid (1R,2R,4R)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester, or
isobutyric acid (1S,2S,4S)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester,
or mixtures of these two enantiomers such as for example the racemate.

- 15 Encompassed in the scope of the present invention are the crystalline salt forms of COMPOUND, i.e. isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester, described herein; wherein COMPOUND may be in racemic form; in enantiomerically enriched form of the enantiomer of absolute configuration (1R,2R,4R); in enantiomerically enriched form of the enantiomer of absolute configuration (1S,2S,4S); or in form of any mixture of these two enantiomers. Preferred is the enantiomerically enriched form having negative optical rotation as determined using the method as described herein.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

- 25 The term "enantiomerically enriched" is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the COMPOUND are present in form of one enantiomer of the COMPOUND.

- 30 The term "essentially pure" is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the crystals of a COMPOUND are present in a crystalline form according to the present invention, especially in a single crystalline form of the present invention.

When defining the presence of peak in e.g. an X-ray powder diffraction diagram, a common approach is to do this in terms of the S/N ratio (S = signal, N = noise). According to this

definition, when stating that a peak has to be present in an X-ray powder diffraction diagram, it is understood that the peak in the X-ray powder diffraction diagram is defined by having an S/N ratio (S = signal, N = noise) of greater than x (x being a numerical value greater than 1), usually greater than 2, especially greater than 3.

- 5 In the context with stating that the crystalline form essentially shows an X-ray powder diffraction pattern as depicted in Fig. 1 to Fig. 11, respectively, the term "essentially" means that at least the major peaks of the diagram depicted in said figures, i.e. those having a relative intensity of more than 10%, especially more than 20%, as compared to the most intense peak in the diagram, have to be present. However, the person skilled in the art of
10 X-ray powder diffraction will recognize that relative intensities in X-ray powder diffraction diagrams may be subject to strong intensity variations due to preferred orientation effects.

Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In
15 the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C. Room temperature means a temperature of about 25 °C. When in the current application the term n equivalent(s) is used wherein n is a number, it is meant and within the scope of the current
20 application that n is referring to about the number n, preferably n is referring to the exact number n.

The crystalline salts, especially the essentially pure crystalline salts, of COMPOUND according to any one of embodiments 1) to 51) can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

- 25 The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the crystalline forms of the present invention, optionally in combination with other therapeutically valuable substances, into a
30 galenical administration form together with suitable, non-toxic, inert, pharmaceutically acceptable solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The crystalline salts, especially the essentially pure crystalline salts, of COMPOUND according to any one of embodiments 1) to 51) may be used as single component or as mixtures with other crystalline forms or the amorphous form of COMPOUND.

The crystalline salts, especially the essentially pure crystalline salts, of COMPOUND according to any one of embodiments 1) to 51) are useful in the preparation of a medicament and/or are suitable

- for the treatment or prevention of chronic stable angina, hypertension, ischemia (renal and cardiac), cardiac arrhythmias including atrial fibrillation, cardiac hypertrophy, or congestive heart failure.

The crystalline salts, especially the essentially pure crystalline salts, of COMPOUND according to any one of embodiments 1) to 51) are further also useful in the preparation of a medicament and/or are suitable for the following disease groups alone or in any combination:

- for the treatment of renal diseases, diabetes and its complications, hyperaldosteronism, epilepsy, neuropathic pain, or cancer in humans and other mammals;
- for use as anti-fibrillatory agent, anti-asthmatic agent, anti-atherosclerotic agent, additive to cardioplegic solutions for pulmonary bypasses, adjunct to thrombolytic therapy, as antiaggregant agent, or as agent for the treatment of unstable angina;
- for the treatment or prophylaxis of hypertension, especially portal hypertension, hypertension secondary to treatment with erythropoietin and low renin hypertension;
- for use in hypoxic or ischemic diseases, or as anti ischemic agent for the treatment of e.g. cardiac, renal and cerebral ischemia and reperfusion (e.g. occurring after cardiopulmonary bypass surgery), coronary and cerebral vasospasm and the like, therapy for peripheral vascular diseases (e.g. Raynaud's disease, intermittent claudication, Takayashus disease), sickle cell disease including initiation and/or evolution of the pain crisis;
- for the treatment or prophylaxis of disorders related to renal, glomerular and mesangial cell function, including acute and chronic renal failure, diabetic nephropathy, hypertension-induced nephropathy, glomerular injury, renal damage related to age or dialysis, nephrosclerosis, nephrotoxicity related to imaging and contrast agent and to cyclosporine, renal ischemia, primary vesicoureteral reflux, or glomerulosclerosis;
- for use in therapy for myocardial infarction, treatment of cardiac hypertrophy, primary and secondary pulmonary hypertension, therapy for congestive heart failure including inhibition of fibrosis, inhibition of left ventricular dilatation, remodelling and dysfunction, or restenosis following angioplasty or stenting;
- for the treatment of endotoxemia or endotoxin shock, or hemorrhagic shock;
- for the treatment of sexual dysfunction in both men (erectile dysfunction e.g. due to diabetes mellitus, spinal cord injury, radical prostatectomy, psychogenic etiology and other causes) and women by improving blood flow to the genitalia, especially corpus cavernosum;

- for the prevention and/or reduction of cancer or end-organ damage associated with cell proliferation;
- for therapy of metabolic disorders or chronic inflammatory diseases, insulin-dependent and non insulin-dependent diabetes mellitus and their complications (e.g. neuropathy, retinopathy), hyperaldosteronism, bone remodelling, psoriasis, arthritis, rheumatoid arthritis, osteoarthritis sarcoidosis, or eczematous dermatitis;
- for the treatment of hepatotoxicity and sudden death, early and advanced liver disease and injury including attendant complication (e.g. hepatotoxicity, fibrosis, cirrhosis), deleterious consequences of tumors such as hypertension resulting from hemangiopericytoma, spastic diseases of the urinary tract and/or bladder, hepatorenal syndrome, immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia, fibrosis associated with renal dysfunction and hepatotoxicity;
- for use in gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer inflammatory bowel disease and ischemic bowel disease, gall bladder or bile duct-based diseases such as cholangitis, pancreatitis, regulation of cell growth, benign prostatic hypertrophy, or transplantation, or for use as anti-diarrheal agent;
- for the treatment of disorders involving bronchoconstriction or disorders of chronic or acute inflammation such as obstructive pulmonary disease and adult distress syndrome;
- for the alleviation of pain including neuropathic pain, peripheral pain and pain associated with cancer such as pain associated with prostate cancer or bone-cancer;
- for the treatment of central nervous system vascular disorders such as stroke, transient ischemic attacks, migraine and subarachnoid hemorrhage, central nervous system behavioural disorders, treatment of dementia including Alzheimer's dementia, senile dementia and vascular dementia, epilepsy, or sleep disorders; or
- for reduction of general morbidity and/or mortality as a result of above utilities.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a crystalline salt, especially of an essentially pure crystalline salt, of COMPOUND according to any one of embodiments 1) to 51).

Furthermore, the crystalline salts, especially the essentially pure crystalline salts, of COMPOUND according to any one of embodiments 1) to 51) may also be used favourably in combination with one or more agents selected from lipid lowering agents such as statins, anticoagulants such as coumarins, antithrombotic agents such as clopidogrel, β -blockers, and other cardioprotective agents.

The present invention also relates to a process for the preparation of COMPOUND in racemic and enantiomerically enriched form, and to processes for the preparation and characterization of crystalline salts of COMPOUND according to any one of embodiments 1) to 51), said processes are described in the experimental part below.

5

Experimental Part

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius. If not stated otherwise percentages are given by weight.

Abbreviations as used herein and in the description above:

10	aq.	aqueous
	ca.	about
	CC	column chromatography on silica gel
	DCM	dichloromethane
	DIPA	diisopropyl-amine
15	DIPEA	diisopropyl-ethylamine, Hünig's base, ethyl-diisopropylamine
		DMAP
		4-dimethylamino-pyridine
	DMF	dimethylformamide
	DSC	differential scanning calorimetry
	eq.	equivalent(s)
20	Et ₂ O	diethyl ether
	EtOAc	ethyl acetate
	EtOH	ethanol
	Fig.	figure
	h	hour(s)
25	¹ H-NMR	hydrogen-1 nuclear magnetic resonance
	Hept	heptane
	Hex	hexane
	HOBt	1-hydroxybenzotriazole
	MEK	2-butanone
30	MeCN	acetonitrile
	MeOH	methanol
	NEt ₃	triethylamine
	Pd/C	palladium on carbon
	2-PrOH	isopropanol
35	Red-Al	sodium-bis(2-methoxyethoxy)aluminumhydride

RH	relative humidity
rt	room temperature
rpm	rotations per minute
sat.	saturated
5 TBME	<i>tert</i> -butyl methyl ether
tert.	tertiary
THF	tetrahydrofuran
TsOH	para (p)-toluene sulfonic acid
XRPD	X-ray powder diffraction

10 X-ray powder diffraction analysis (XRPD):

Method 1: X-ray powder diffraction patterns were collected on a Bruker D8 Advance X-ray diffractometer equipped with a LynxEye detector with 3° window operated with Cu K α -radiation in reflection geometry (Bragg-Brentano). Typically, the X-ray tube was run at 40kV/40mA. A step size of 0.02° (2 θ) and a step time of 37 sec over a scanning range of 2 -
15 50° in 2theta (2 θ) were applied. The divergence slit was set to variable V12 or V20, dependent on sample holder depth. The powder (about 15 mg for 0.1 mm depth and about 80 mg for 1 mm depth) was slightly pressed into a silicon single crystal sample holder with depth of 0.1 mm or 1 mm and samples were rotated in their own plane during the measurement. Selected samples were covered with Kapton foil. Diffraction data are reported
20 using Cu K α 1 (λ = 1.5406 Å), after the K α 2 component has been stripped using the instrument evaluation software (EVA). In addition, the background signal has been removed using the instrument evaluation software (EVA), for samples that were covered by Kapton during data acquisition. The accuracy of the 2 θ values as provided herein is in the range of +/- 0.1-0.2° as it is generally the case for conventionally recorded X-ray powder diffraction
25 patterns.

Method 2: X-ray powder diffraction patterns were collected on a Bruker D8 HTS X-ray diffractometer equipped with a GADDS HiStar detector operated with Cu K α -radiation in reflection geometry. Typically, the X-ray tube was run at 40kV/40mA. The instrument is performance checked using a certified Corundum standard (NIST 1976). Samples run under
30 ambient conditions were prepared as flat plate specimens using powder as received. Approximately 3 mg of the sample was gently pressed on a microscopy slide. The data were collected over an angular range of 7.6° to 26.7° 2 θ in 1 frame with an acquisition time of 180second. Diffraction data are reported without K α 2 component stripping and the background signal has been removed using the instrument evaluation software (EVA). The

accuracy of the 2θ values as provided herein is in the range of ± 0.1 - 0.2° as it is generally the case for conventionally recorded X-ray powder diffraction patterns.

Melting points were measured on a Buchi B-540 apparatus and are not corrected; or were measured, if explicitly stated, by differential scanning calorimetry (DSC):

- 5 DSC data were collected on a Perkin Elmer DSC7. Typically 2-3 mg of sample, previously stored open under dry nitrogen for 16 hours, were heated in a closed gold pan at $20^\circ\text{C min}^{-1}$ from -20°C to 200°C . Melting points are reported as peak temperatures.

Optical rotations were measured on a Jasco P-1030 apparatus at room temperature using the D-line of sodium ($\lambda = 589 \text{ nm}$).

- 10 $^1\text{H-NMR}$ were measured on a Bruker Avance 400 (400 MHz); chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, hex = hexet, sept = septuplet, m = multiplet, dm = doublet of multiplet, br = broad, coupling constants are given in Hz). NMR assays were measured using hydroquinone dimethylether as internal standard.

- 15 Hygroscopicity was assessed through scanned gravimetric vapour sorption measurements on a SPS11-100m (Projekt Messtechnik, Ulm, Germany) (scan rate was 5% relative humidity change per hour, cycle started at 50% relative humidity followed by a scan to dryness and an upwards scan to 95% relative humidity). Classification was done according to the European Pharmacopea Technical Guide (1999 edition) (e.g. slightly hygroscopic: increase in mass is less than 2% and equal to or greater than 0.2% mass/mass). The mass change between 20 40% relative humidity and 80% relative humidity in the upwards scan was considered.

- LC-MS were run using the following conditions: Finnigan Navigator with HP 1100 Binary Pump and DAD, column: 4.6x50 mm, Zorbax SB-AQ, 5 μm , 120 $\text{\AA}$, gradient: 5-95% acetonitrile in water, 1 min, with 0.04% trifluoroacetic acid, flow: 4.5 mL/min, t_R is given in 25 min.

- Compounds are purified by preparative HPLC (column: X-terra RP18, 50x19 mm, 5 μm , gradient: 10-95% acetonitrile in water containing 0.5 % of formic acid) or by column chromatography on silica gel. Racemates can be separated into their enantiomers by preparative HPLC (preferred conditions: Daicel, ChiralCel OD 20x250 mm, 10 μm , 4% 30 ethanol in hexane, flow 10-20 mL/min).

I. Preparation and characterization of COMPOUND

The preparation of COMPOUND is known from WO2008/132679:

Preparation of intermediates

General procedures for the preparation of key intermediates K:

- 5 Key intermediates K1A and K2A which are bicyclo[2.2.2]oct-5-en-2-yl or bicyclo[3.2.2]non-8-en-6-yl derivatives are obtained as a mixture between the major racemate having the relative configuration (R^*, R^*, R^*) (i.e. the bridge $-(CH_2)_2-$ of the cyclohexene moiety is *cis* to the group $-OR^2$ being hydroxy) and the minor racemate having the relative configuration (R^*, S^*, R^*) (i.e. the bridge $-(CH_2)_2-$ of the cyclohexene moiety is *trans* to the group $-OR^2$ being hydroxy). The
- 10 major and the minor racemates can be separated as described for key intermediate K1A in procedure A1.5. The major racemate is isolated and used in the preparation of the examples below.

K1A: rac-(1R*,2R*,4R*)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester

- 15 K1A.1 (Procedure A1.1): rac-(1R*,4R*)-Bicyclo[2.2.2]octane-2,5-dione

25 mL of 2-(trimethylsilyloxy)-1,3-cyclohexadiene and 13 mL of α -acetoxyacrylonitrile were mixed and heated at 150°C in a closed vessel for 22 h. The obtained dark orange viscous oil was dissolved in 200 mL of MeOH. After dropwise addition of a solution of 2.2 g of sodium methoxide in 150 mL of MeOH the reaction mixture was stirred for 3 h at rt, poured into

20 ice/water and extracted with DCM. The organic phases were concentrated in vacuo and the crude residue was purified by CC with EtOAc-Hept (1:2) to yield 7.9 g of rac-(1R*,4R*)-bicyclo[2.2.2]octane-2,5-dione.

LC-MS: t_R = 0.44 min.

K1A.2 (Procedure A1.2): rac-(1R*,4R*)-Spiro[bicyclo[2.2.2]octane-2,2'-[1,3]dioxolan]-5-one

- 25 To 4.0 g of rac-(1R*,4R*)-bicyclo[2.2.2]octane-2,5-dione (intermediate K1A.1), dissolved in 120 mL of toluene, 1.7 mL of ethylene glycol and 0.27 g of TsOH were added and the solution was heated under vigorous stirring to reflux for 3.5 h. The reaction mixture was cooled to rt, quenched with saturated aq. $NaHCO_3$, extracted with Et_2O , and the organic phase was evaporated. The crude product was purified by CC with Hex-EtOAc (7:3) to yield
- 30 2.41 g of rac-(1R*,4R*)-spiro[bicyclo[2.2.2]octane-2,2'-[1,3]dioxolan]-5-one as yellow oil.

LC-MS: t_R = 0.64 min; $[M+H+CH_3CN]^+$: 224.35.

K1A.3 (Procedure A1.3): Mixture of rac-(7R*,8R*,10R*)- and rac-(7R*,8S*,10R*)-7,10-(1,2-Ethylen)-8-phenyl-1,4-dioxo-spiro[4.5]decan-8-ol

To a solution of 2.41 g of rac-(1R*,4R*)-spiro[bicyclo[2.2.2]octane-2,2'-[1,3]dioxolan]-5-one (intermediate K1A.2) in 80 mL Et₂O, 14.5 mL phenylmagnesium bromide solution (1M in Et₂O) was added dropwise over 10 min. The reaction mixture was stirred for 4 h at rt. Then, the mixture was quenched carefully with ice, 8 mL 2N HCl were added and the phases were separated. The organic phase was evaporated and the crude product was purified by CC with Hept-EtOAc (7:3) to give 0.37 g of 7,10-(1,2-ethylen)-8-phenyl-1,4-dioxo-spiro[4.5]decan-8-ol as colorless oil. (Separation of the diastereomers by CC is possible but was not performed here.)

LC-MS: t_R = 0.84 min; $[M-H_2O+H]^+$: 243.34.

K1A.4 (Procedure A1.4): rac-(1R*,4R*)-5-Phenyl-bicyclo[2.2.2]oct-5-en-2-one

To a solution of 0.54 g of 7,10-(1,2-ethylen)-8-phenyl-1,4-dioxo-spiro[4.5]decan-8-ol (intermediate K1A.3) in 20 mL acetone was added 200 mg of TsOH and then the mixture was stirred for 2 d at rt. The reaction mixture was quenched with sat. aq. NaHCO₃, extracted with EtOAc and the organic phase was evaporated. The crude product was purified by CC with Hept-EtOAc (7:3) to give 0.34 g of rac-(1R*,4R*)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-one as colorless oil.

LC-MS: t_R = 0.93 min; $[M+H+CH_3CN]^+$: 240.11.

K1A.5 (Procedure A1.5): rac-(1R*,2R*,4R*)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester and rac-(1R*,2S*,4R*)-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester

To a solution of 0.51 mL of DIPA in 0.5 mL THF 2.2 mL of n-butyllithium (1.6M in Hex) were added dropwise at -20°C. After 10 min, 0.5 mL of toluene were added and the solution was stirred for 30 min. The mixture was cooled to -50°C, 0.73 mL of *tert.*-butyl acetate were added and stirring was continued for 1 h at -50°C. Then 0.32 g of rac-(1R*,4R*)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-one (intermediate K1A.4) dissolved in 1 mL of THF was added and the solution was stirred at -50 to -20°C over 2.5 h. The reaction mixture was poured on ice/aq. HCl, the organic phase was separated, washed and evaporated. The crude reaction product was purified by CC with Hept-EtOAc (9:1) to yield 0.30 g of the major racemate, rac-(1R*,2R*,4R*)-2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester, as white solid and 0.07 g of the minor racemate, rac-(1R*,2S*,4R*)-2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester, as colorless oil.

LC-MS (major racemate): t_R = 1.06 min; $[M-(CH_3)_3-H_2O+H]^+$: 241.11.

LC-MS (minor racemate): t_R = 1.05 min; $[M+H]^+$: 315.18.

K1A.6: (1S,2S,4S)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester and (1R,2R,4R)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester

rac-(1R*,2R*,4R*)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester was separated into the respective enantiomers using prep. chiral HPLC (column: Daicel ChiralPak AD-H, 20x250 mm, 5 μ m; Hex/ EtOH 95:5, flow 16 mL/min)

Chiral analytic HPLC (Daicel ChiralPak AD-H, 4.6x250 mm, 5 μ m; Hex/ EtOH 95:5, flow 0.8 mL/min):

(1R,2R,4R)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester:

Enantiomer A: t_R = 6.70 min.

(1S,2S,4S)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester:

Enantiomer B: t_R = 7.93 min.

BB. [3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amine

BB.1 3,6-Dimethoxy-benzene-1,2-diamine

3,6-Dimethoxy-benzene-1,2-diamine was synthesized by dissolving 6.0 g of 1,4-dimethoxy-2,3-dinitro-benzene (Eur.J.Org.Chem. 2006, 2786-2794) in 220 mL EtOH, evacuating 3 times with N₂ and adding 600 mg of 10wt% Pd/C. The reaction was stirred under a H₂ atmosphere (balloon). Another 300 mg of 10wt% Pd/C were added after 2 days and the mixture was stirred for another 24 h. Filtration over a pad of celite and washing with EtOH and EtOAc yielded after concentration in vacuo 4.3 g of 3,6-dimethoxy-benzene-1,2-diamine as black solid.

LC-MS: t_R = 0.48 min; [M+H]⁺: 169.09.

BB.2 [3-(2-Amino-3,6-dimethoxy-phenylcarbamoyl)-propyl]-methyl-carbamic acid benzyl ester

To a solution of 3.1 g of 4-(benzyloxycarbonyl-methyl-amino)-butyric acid in 80 mL DCM were added 6.5 mL of DIPEA, 1.8 g of HOBt, 2.6 g of EDC and 154 mg of DMAP. After stirring for 10 min, 2.1 g of 3,6-dimethoxy-benzene-1,2-diamine, dissolved in 20 mL DCM, were added and the mixture was stirred at rt overnight. The reaction was quenched with sat. aq. NaHCO₃, the phases were separated and the organic phase was washed with brine, dried over MgSO₄ and concentrated in vacuo to yield the crude title compound as black oil.

LC-MS: t_R = 0.88 min; [M+H]⁺: 402.06.

BB.3 [3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-carbamic acid benzyl ester

To a mixture of the above crude 3-(2-amino-3,6-dimethoxy-phenylcarbamoyl)-propyl]-methyl-carbamic acid benzyl ester in 16 mL toluene were added 4 mL of DMF and 1.9 g of TsOH

and the reaction was heated to 150°C for 2 h in the microwave. Sat. aq. NaHCO₃ was added and the phases were separated. The organic phase was washed with brine, dried over MgSO₄, concentrated in vacuo, filtered over a short pad of silica gel with EtOAc and concentrated again. Purification by CC with EtOAc yielded 2.7 g of 3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-carbamic acid benzyl ester as brown resin.

LC-MS: t_R = 0.85 min; [M+H]⁺: 384.62.

BB.4 [3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amine

A solution of 2.6 g of 3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-carbamic acid benzyl ester in 60 mL EtOH was evacuated 3 times with N₂ before 260 mg of 10 wt% Pd/C were added. The reaction mixture was then stirred under a H₂ atmosphere (balloon) for 5 h at rt. Filtration over a pad of celite and washing with EtOH yielded after concentration in vacuo 1.7 g of 3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amine as brown foam.

LC-MS: t_R = 0.57 min; [M+H]⁺: 250.13.

Preparation of COMPOUND

Reference Example 1A: rac-Isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester

1.1 (Procedure P1.1): rac-(1R*,2R*,4R*)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid

To a solution of 4.0 g of rac-(1R*,2R*,4R*)-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester in 25 mL EtOH were added 2.1 g of LiOH.H₂O, 8 mL H₂O and 22 mL MeOH. The reaction mixture was stirred at rt for 3 d and then concentrated. The residue was partitioned between water and Et₂O. The aq. layer was separated and acidified with 1N HCl resulting in the formation of a white solid. The solid was filtrated, washed with 5 mL aq. HCl and dried in vacuo to obtain 3.2 g of rac-(1R*,2R*,4R*)-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid as white solid.

LC-MS: t_R = 0.86 min; [M-H₂O+H]⁺: 241.28.

1.2 (Procedure P1.2): rac-(1R*,2R*,4R*)-N-[3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-2-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-N-methyl-acetamide

To a solution of 280 mg of rac-(1R*,2R*,4R*)-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid in 7 mL THF were added 0.58 mL of DIPEA, 175 mg of HOBt and 250 mg of EDC at rt. After stirring for 10 min, 270 mg of 3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amine were added and the reaction mixture was stirred at rt overnight. The

reaction mixture was quenched with sat. aq. NaHCO₃, the phases were separated and the organic phase was washed with water and brine, dried over MgSO₄ and concentrated in vacuo. Purification by CC using EtOAc-MeOH (5:1 to 2:1) yielded 475 mg of rac-(1R*,2R*,4R*)-N-[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-2-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-N-methyl-acetamide as white foam.

LC-MS: t_R = 0.91 min; [M+H]⁺: 490.06.

1.3 (Procedure P1.3): rac-(1R*,2R*,4R*)-2-(2-{[3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-ol

To a solution of 310 mg of rac-(1R*,2R*,4R*)-N-[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-2-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-N-methyl-acetamide in 8 mL toluene were added dropwise 0.77 mL of a Red-Al solution (65% in toluene) at 0°C. After stirring for 10 min at 0°C, the cooling bath was removed and stirring was continued for 3 h at rt. The reaction mixture was then carefully poured onto a mixture of 1M NaOH/ice and stirred for 10 min. The aq. phase was extracted with toluene, the combined organic phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by CC using EtOAc-MeOH (2:1) yielded 230 mg of rac-(1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-ol as white foam.

LC-MS: t_R = 0.79 min; [M+H]⁺: 476.13.

1.4: rac-Isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester

To a solution of 199 mg of rac-(1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-ol in 4 mL DCM were added 0.2 mL of NEt₃ and 0.1 mL of isobutyrylchloride at 0°C. The reaction mixture was stirred overnight allowing the temperature to reach slowly rt. The reaction was quenched with sat. aq. NaHCO₃, the phases were separated and the water phase was re-extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was redissolved in 3 mL EtOAc, silica gel and 1.5 mL MeOH were added and the mixture was stirred vigorously for 7 d. The mixture was filtered, thoroughly washed with EtOAc-MeOH (2:1) and evaporated. Purification by CC using EtOAc-MeOH (5:1 to 3:1 + 0.1% NEt₃) yielded 186 mg of rac-isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester as beige foam.

LC-MS: t_R = 0.90 min; [M+H]⁺: 546.23.

Reference Example 2A: Isobutyric acid (1S,2S,4S)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester

2.1: (1S,2S,4S)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid

- 5 Prepared according to procedure P1.1 in Reference Example 1A using enantiomer B of rac-(1R*,2R*,4R*)-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester (see K1A.6).

LC-MS: t_R = 0.91 min; $[M-H_2O+H]^+$: 241.10.

2.2: (1S,2S,4S)-2-(2-([3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-ol

10

Prepared according to procedures P1.2 to P1.3 in Reference Example 1A using the above (2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid.

LC-MS: t_R = 0.78 min; $[M+H]^+$: 476.09.

2.3: Isobutyric acid (1S,2S,4S)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester

15

Prepared according to procedure P1.4 in Reference Example 1A using the above 2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-ol.

LC-MS: t_R = 0.89 min; $[M+H]^+$: 546.19.

- 20 **Reference Example 3A: Isobutyric acid (1R,2R,4R)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester**

3.1: (1R,2R,4R)-(2-Hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid

- 25 Prepared according to procedure P1.1 in Reference Example 1 using enantiomer A of rac-(1R*,2R*,4R*)-(2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid tert.-butyl ester (see K1A.6).

LC-MS: t_R = 0.91 min; $[M-H_2O+H]^+$: 241.16.

3.2: (1R,2R,4R)-2-(2-([3-(4,7-Dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-ol

- 30 Prepared according to procedures P1.2 to P1.3 in Reference Example 1 using the above (2-hydroxy-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl)-acetic acid.

LC-MS: t_R = 0.79 min; $[M+H]^+$: 476.09.

3.3: Isobutyric acid (1R,2R,4R)-2-(2-([3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester

Prepared according to procedure P1.4 in Reference Example 1A using the above 2-(2-([3-(4,7-dimethoxy-1H-benzimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-

5 bicyclo[2.2.2]oct-5-en-2-ol.

LC-MS: t_R = 0.89 min; $[M+H]^+$: 546.11.

Optical rotation: α_D (c = 10 mg/mL EtOH) = -21.5°.

1H NMR (MeOD, 400 MHz) δ 7.39-7.37 (m, 2H), 7.30 (t, J = 6.4 Hz, 2H), 7.24-7.20 (m, 1H), 6.60 (s, 2 H), 6.43 (br d, J = 7.6 Hz, 1H), 3.91 (s, 6H), 3.27-3.23 (m, 1H), 3.18-3.15 (m, 1H),
10 2.87 (t, J = 7.6 Hz, 2H), 2.54 (sept, J = 7.0 Hz, 1H), 2.47-2.37 (m, 4H), 2.21 (s, 3H), 2.19-2.12 (m, 1H), 2.01-1.92 (m, 5H), 1.75-1.65 (m, 2H), 1.48-1.38 (m, 1H), 1.27-1.19 (m, 1H), 1.16 (d, J = 7.0 Hz, 6H).

Biological tests

***In vitro* assay L channel**

15 The L channel antagonistic activity (IC_{50} values) of Reference Examples 1A, 2A, and 3A is determined in accordance with the following experimental method.

Human embryonic kidney (HEK293) cells expressing the human $Ca_v1.2$ channel in addition to the auxiliary subunits β -2a and $\alpha_2\delta$ -1, are grown in culture medium (DMEM containing 10% heat-inactivated fetal calf serum (FCS), 100 U/ml penicillin, 100 μ g/ml streptomycin,
20 100 μ g/ml G418, 40 μ g/ml zeocin and 100 μ g/ml hygromycin). The cells are seeded at 20,000 cells/well into 384-well black clear bottom sterile plates (poly-L-lysine-coated, Becton Dickinson). The seeded plates are incubated overnight at 37°C in 5% CO_2 . The KCl solution is prepared as 80 mM stock solution in assay buffer (HBSS containing 0.1% BSA, 20 mM HEPES, 0.375g/l $NaHCO_3$, adjusted to pH 7.4 with NaOH) for use in the assay at a final
25 concentration of 20 mM. Antagonists are prepared as 10 mM stock solutions in DMSO, then diluted in 384w plates first in DMSO, then in assay buffer to obtain 3x stocks. On the day of the assay, 25 μ l of staining buffer (HBSS containing 20 mM HEPES, 0.375g/l $NaHCO_3$, and 3 μ M of the fluorescent calcium indicator fluo-4 AM (1 mM stock solution in DMSO, containing 10% pluronic) is added to each well of the seeded plate. The 384-well cell-plates
30 are incubated for 60 min at 37° C in 5% CO_2 followed by washing with 2 x 50 μ l per well using assay buffer leaving 50 μ l/well of this buffer for equilibration at room temperature (30-60 min). Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists are added to the plate in a volume of 25 μ l/well, incubated for 3 min and finally 25 μ l/well of KCl solution is added for cellular depolarization. Fluorescence is measured for each well at 2

second intervals for 8 minutes, and the area under the curve of each fluorescence peak is compared to the area of the fluorescence peak induced by 20 mM KCl with vehicle in place of antagonist. For each antagonist, the IC₅₀ value (the concentration (in nM) of compound needed to inhibit 50 % of the KCl-induced fluorescence response) up to 10µM is determined.

- 5 IC₅₀ values of reference example compounds 1A, 2A, and 3A have been measured and are in the range of 156 to 439 nM.

***In vitro* assay T channel:**

The T channel antagonistic activity (IC₅₀ values) of Reference Examples 1A, 2A, and 3A is determined in accordance with the following experimental method and data are shown in
10 Table 1.

- Human embryonic kidney (HEK293) cells expressing the human Ca_v3.1 Ca_v3.2 or Ca_v3.3 channel, respectively, are grown in culture medium (DMEM containing 10% heat-inactivated fetal calf serum (FCS), 100 U/ml penicillin, 100 µg/ml streptomycin and 1 mg/ml G418). The cells are seeded at 20.000 cells/well into 384-well black clear bottom sterile plates (poly-L-lysine-coated, Becton Dickinson). The seeded plates are incubated overnight at 37°C in 5%
15 CO₂. The Ca²⁺ solution is prepared as 100 mM stock solution in 100 mM tetraethylammoniumchloride (TEA-chloride), 50 mM HEPES, 2.5 mM CaCl₂, 5 mM KCl, 1 mM MgCl₂, adjusted to pH 7.2 with TEA-hydroxide, for use in the assay at a final concentration of 10 mM. Antagonists are prepared as 10 mM stock solutions in DMSO, then
20 diluted in 384w plates first in DMSO, then in 100 mM TEA-chloride, 50 mM HEPES, 2.5 mM CaCl₂, 5 mM KCl, 1 mM MgCl₂, adjusted to pH 7.2 with TEA-hydroxide, to obtain 9x stocks. On the day of the assay, 25 µl of staining buffer (HBSS containing 20 mM HEPES, 0.375g/l NaHCO₃ and 3 µM of the fluorescent calcium indicator fluo-4 AM (1 mM stock solution in DMSO, containing 10% pluronic) is added to each well of the seeded plate. The 384-well
25 cell-plates are incubated for 60 min at 37° C in 5% CO₂ followed by washing with 2 x 50µl per well using HBSS containing 0.1% BSA, 20 mM HEPES, 0.375g/l NaHCO₃, leaving 50 µl/well of this buffer for equilibration at room temperature (30-60 min). Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists are added to the plate in a volume of 6.25 µl/well, incubated for 3 min, and finally 6.25 µl/well of Ca²⁺ solution is added.
30 Fluorescence is measured for each well at 2 second intervals for 8 minutes, and the area under the curve of each fluorescence peak is compared to the area of the fluorescence peak induced by 10 mM Ca²⁺ with vehicle in place of antagonist. For each antagonist, the IC₅₀ value (the concentration (in nM) of compound needed to inhibit 50 % of the Ca²⁺-induced fluorescence response) up to 10µM is determined.

Table 1:

Compound of reference example	IC ₅₀	Compound of reference example	IC ₅₀
2A	778	3A	793

Effect on Isolated Hearts according to the Langendorff method (Lgdf)

The Reference Examples 1A, 2A, and 3A were tested for their potential to reduce blood pressure and their effect on the contractility of the heart muscle. EC₅₀ values on isolated mouse hearts were determined according to Literature (Doring HJ., The isolated perfused heart according to Langendorff technique--function--application, *Physiol. Bohemoslov.* **1990**, 39(6), 481-504; Kligfield P, Horner H, Brachfeld N., A model of graded ischemia in the isolated perfused rat heart, *J. Appl. Physiol.* **1976** Jun, 40(6), 1004-8).

- 10 The compound of reference example 1A has been measured using the procedure described above for the Langendorff experiment with an EC₅₀ of 5 nM.

15 II. Preparation of salt forms of COMPOUND

II.a) General procedure for salt formation with COMPOUND:

- 1 eq. of COMPOUND was dissolved in **SOLVENT1**. The solution was brought to 50°C. 2 Equivalents of acid dissolved in **SOLVENT2** was added. The mixture was stirred at 50°C for 5 min and the heating source was turned off. The mixture was allowed to cool to rt within 1 hour. If a precipitate was observed the mixture was filtered and the solid was isolated. In case that no solid was obtained the mixture was evaporated to dryness and 6 volumes of heptane were added. The mixture was heated to reflux, 3 volumes of EtOAc were added until all dissolved. In case that dissolution was not complete further 3 volumes EtOAc were added. If dissolution was still not complete, as less as possible MeOH was added until complete dissolution. The mixture was allowed to cool slowly to rt. At rt the vessel was scratched with a spatula and was further cooled to 0°C. The mixture was filtered and the solution was evaporated to dryness on the rotavapor.

The term "volumes" as used herein signifies 1L for 1kg of solid material.

SOLVENT1 = 8 volumes EtOAc for: benzensulfonic acid, benzoic acid, salicylic acid, saccharin, para-toluenesulfonic acid, malonic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, ethanesulfonic acid, malic acid, glycolic acid, ketoglutaric acid, and fumaric acid;

5 **SOLVENT1 = 1.8 volumes EtOAc** for: hydrobromic acid, and hydrochloric acid;

SOLVENT1 = 8 volumes acetone for: sulfuric acid, and phosphoric acid;

SOLVENT1 = 7 volumes acetone for: citric acid, succinic acid, and tartaric acid.

SOLVENT2 = 7 volumes EtOAc for: citric acid;

10 **SOLVENT2 = 3 volumes EtOAc** for: benzensulfonic acid, benzoic acid, methanesulfonic acid, salicylic acid, and saccharin (partially soluble);

SOLVENT2 = 3 volumes MeOH for: para-toluenesulfonic acid, malonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, malic acid, glycolic acid, ketoglutaric acid, and fumaric acid;

SOLVENT2 = 15 volumes acetone for: succinic acid;

15 **SOLVENT2 = 12 volumes EtOH** for: tartaric acid;

SOLVENT2 = water for: hydrobromic acid, hydrochloric acid, sulfuric acid, and phosphoric acid.

Results obtained using the general procedure described above are summarized in Tables 1 and 2. In case particular procedures have been used to prepare crystalline salt forms of
20 COMPOUND, such procedures are described in Reference Example S1 and the Examples S2 to S7 below.

Table 1: Characterisation data for crystalline salt forms of COMPOUND gained according to the general procedure

Salt	Melting point/ ¹ H-NMR	XRPD
di-hydrobromic acid salt	Melting point at about 93°C. ¹H-NMR consistent with structure. The X-ray diffraction diagram measured with method 2 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 8-26.5° 2theta with relative intensity larger than 10% are reported): 9.1° (22%), 9.5° (62%), 12.3° (23%), 12.6° (27%), 14.1° (36%), 14.6° (18%), 15.3° (86%), 15.8° (49%), 17.0° (71%), 17.9° (100%), 19.1° (81%), 19.6° (67%), 20.2° (52%), 20.6° (44%), 21.1° (54%), 22.5° (35%), 23.6° (16%), 24.5° (48%), 25.0° (42%), 25.4° (28%), and 26.1° (43%). The above peaks correspond to Figure 7 measured for Example S7 below. A shift of 2theta of 0.2-0.3° may be explained by the use of method 1 for the measurement of the X-ray diffraction diagram in Example S7.	Crystalline, crystalline form identical to Example S7 below
sesqui-naphthalene-1,5-disulfonic acid salt	¹H-NMR (D6-DMSO, 400 MHz, only main peaks described) δ 8.88 (d, J = 9.2 Hz, 2.7 H, 1.5 molecules of naphthalene-1,5-disulfonic acid), 7.94 (d, J = 7.0 Hz, 2.7 H, 1.5 molecules of naphthalene-1,5-disulfonic acid), 7.47-7.25 (m, 8.6 H, 1.5 molecules of naphthalene-1,5-disulfonic acid + 5H), 6.99 (s, 2H), 6.54 (dd, J = 8.0 Hz, 1H), 3.94 (s, 6H), 3.24-3.03 (m, 8H), 2.72 (s, 3H), 2.56 (sept, J = 7.0 Hz, 1H), 1.14-1.06 (m, 6H).	Crystalline, see Fig. 8

di-benzensulfonic acid salt	¹H-NMR (MeOD, 400 MHz) δ 7.84-7.80 (m, 4H, 2 molecules of benzensulfonic acid), 7.45-7.38 (m, 8H, 2 molecules of benzensulfonic acid + 2H), 7.34-7.29 (m, 2H), 7.26-7.22 (m, 1H), 6.99 (s, 2H), 6.51 (br d, J = 6.4 Hz, 1H), 4.00 (s, 6H), 3.32-3.20 (m, 8H), 2.87 (s, 3H), 2.60 (sept, J = 7.0 Hz, 1H), 2.46-2.27 (m, 4H), 2.06-1.97 (m, 1H), 1.95-1.91 (m, 1H), 1.76-1.69 (m, 2H), 1.49-1.40 (m, 1H), 1.29-1.22 (m, 1H), 1.19 (d, J = 2.9 Hz, 3H), 1.18 (d, J = 2.9 Hz, 3H).	Crystalline, see Fig. 9
di-ethane sulfonic acid salt	¹H-NMR (MeOD, 400 MHz) δ 7.48-7.46 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.24 (m, 1H), 7.00 (s, 2H), 6.55 (dd, J = 7.0, 1.2 Hz, 1H), 4.01 (s, 6H), 3.22-3.15 (m, 8H), 2.87 (s, 3H), 2.79 (q, J = 7.8 Hz, 4 H, 2 molecules of ethane sulfonic acid), 2.62 (sept, J = 7.2 Hz, 1H), 2.50-2.29 (m, 4H), 2.07-1.94 (m, 2H), 1.80-1.71 (m, 2H), 1.50-1.41 (m, 1H), 1.29 (t, J = 7.8 Hz, 6H, 2 molecules of ethane sulfonic acid), 1.29-1.27 (m, 1H), 1.22 (d, J = 1.9 Hz, 3H), 1.19 (d, J = 2.4 Hz, 3H).	Crystalline, see Fig. 10
di-naphthalene-2-sulfonic acid salt	¹H-NMR (MeOD, 400 MHz) δ 8.34 (br s, 2H, 2 molecules of naphthalene-2-sulfonic acid), 7.91-7.85 (m, 8H, 2 molecule of acid), 7.57-7.51 (m, 4H, 2 molecules of naphthalene-2-sulfonic acid), 7.38-7.35 (m, 2H), 7.39-7.19 (m, 3H), 6.88 (s, 2H), 6.44 (br d, J = 7.2 Hz, 1H), 3.95 (s, 6H), 3.31-3.10 (m, 8H), 2.87 (s, 3H), 2.58 (sept, J = 7.0 Hz, 1H), 2.47-2.25 (m, 4H), 2.04-1.94 (m, 1H), 1.93-1.86 (m, 1H), 1.74-1.64 (m, 2H), 1.46-1.36 (m, 1H), 1.27-1.19 (m, 1H), 1.18 (d, J = 1.6 Hz, 3H), 1.16 (d, J = 2.4 Hz, 3H).	Crystalline, see Fig. 11

Table 2: Characterisation data for further salt forms of COMPOUND gained according to general procedure

Salt	Technique
di-benzoic acid salt	¹ H-NMR: Consistent with structure.
di-salicylic acid salt	¹ H-NMR: Consistent with structure.
di-saccharinate	¹ H-NMR: Consistent with structure.
di-malonic acid salt	¹ H-NMR: Consistent with structure.
di-malic acid salt	¹ H-NMR: Consistent with structure.
di-glycolic acid salt	¹ H-NMR: Consistent with structure.
di-ketoglutaric acid salt	¹ H-NMR: Consistent with structure.
di-phosphoric acid salt	Melting point at about 145°C. ¹ H-NMR consistent with structure.
di-citric acid salt	¹ H-NMR: Consistent with structure.
di-succinic acid salt	¹ H-NMR: Consistent with structure.
di-tartric acid salt	¹ H-NMR: Consistent with structure.

Reference Example S1: Preparation and characterization of the di-hydrochloric acid salt of COMPOUND

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7.598 mL aq. HCl (0.1N) was added to 200.7 mg COMPOUND resulting in a white suspension. 5 mL 2-PrOH were added and the obtained clear solution was evaporated to dryness under nitrogen. 4 mL TBME were added to the residue and the suspension was shaken with a temperature cycle (T1 = 20°C, T2 = 25°C, holding time 1 h, respectively; heating and cooling rate 5°C/h, 500 rpm). After 18 repetitions the suspension was filtered and the solid was dried in vacuum to yield 265 mg of the di-hydrochloric acid salt of COMPOUND.

Table S1: Characterisation data for the di-hydrochloric acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline. The di-hydrochloride salt of COMPOUND is characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2 θ : 9.19°, 9.77°, 15.36°, 16.14°, 17.08°, and 18.12° (especially characterised by 2 θ : 9.19°, 9.77°, and 18.12°).	see Fig. 1
Melting point	about 113°C	
¹ H-NMR	Consistent with structure.	
Elemental analysis	Consistent with di-hydrochloride salt	
Hygroscopicity	Slightly hygroscopic (mass change 0.5%)	

Example S2: Preparation and characterization of the di-methanesulfonic acid salt of COMPOUND

- 5 0.0476 mL Methanesulfonic acid was added to a clear solution of 199.7 mg of COMPOUND dissolved in 7 ml EtOAc. The clear solution was evaporated to dryness under nitrogen and the obtained residue was suspended and shaken in 4 mL of a EtOAc/heptane (1:3) mixture with a temperature cycle (T1 = 20°C, T2 = 25°C, holding time 1 h, respectively; heating and cooling rate 5°C/h, 500 rpm). After 18 repetitions the suspension was filtered and the solid
- 10 was dried in vacuum. The obtained solid was suspended and shaken in 1 mL TBME (temperature cycle: T1 = 20°C, T2 = 25°C, holding time 1 h, respectively; heating and cooling rate 5°C/h, 500 rpm). After 18 repetitions the suspension was filtered and the solid was dried in vacuum to yield the di-methanesulfonic acid salt of COMPOUND.

Table S2: Characterisation data for the di-methanesulfonic acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 2
¹ H-NMR	¹ H NMR (MeOD, 400 MHz) δ 7.48-7.46 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.23 (m, 1H), 7.00 (s, 2H), 6.57 (br d, J = 7.0 Hz, 1H), 4.01 (s, 6H), 3.35-3.20 (m, 8H), 2.89 (s, 3H), 2.71 (s, 6H, 2 molecules of methanesulfonic acid), 2.63 (sept, J = 7.2 Hz, 1H), 2.53-2.26 (m, 4H), 2.07-1.94 (m, 2H), 1.79-1.71 (m, 2H), 1.51-1.42 (m, 1H), 1.32-1.23 (m, 1H), 1.21 (d, J = 2.4 Hz, 3H), 1.20 (d, J = 1.8 Hz, 3H).	
Elemental analysis	Consistent with di-methanesulfonic acid salt.	

Example S3: Preparation and characterization of the di-para-toluenesulfonic acid salt of COMPOUND

- 5 199.7 mg of COMPOUND was dissolved in 7 mL EtOAc. 139.2 mg para-toluenesulfonic acid dissolved in 10 mL EtOAc was added. The clear solution was evaporated to dryness under nitrogen and the residue was suspended in 4 mL of a EtOAc/Hept (1:3) mixture, and shaken with a temperature cycle (temperature cycle: T1 = 20°C, T2 = 25°C, holding time 1 h, respectively; heating and cooling rate 5°C/h, 500 rpm). After 18 cycles the solvent was
- 10 evaporated under vacuum and the solid residue was suspended in 2 ml EtOAc. After brief sonication (3 min) the suspension was shaken with a temperature cycle (temperature cycle: T1 = 20°C, T2 = 25°C, holding time 1 h, respectively; heating and cooling rate 5°C/h, 500 rpm). After 18 repetitions the suspension was filtered and the solid was dried in vacuum to yield 173.8 mg of the di-para-toluenesulfonic acid salt of COMPOUND.

Table S3: Characterisation data for the di-para-toluenesulfonic acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 3
¹ H-NMR	¹ H NMR (MeOD, 400 MHz) δ 7.71-7.68 (m, 4H, 2 molecules of TsOH), 7.45-7.42 (m, 2H, 2 molecules of TsOH), 7.34-7.30 (m, 2H, 2 molecules of TsOH), 7.27-7.25 (m, 1H), 7.21-7.19 (m, 4H), 7.00 (s, 2H), 6.35 (br d, J = 8.0 Hz, 1H), 4.00 (s, 6H), 3.23-3.15 (m, 8H), 2.87 (s, 3H), 2.60 (sept, J = 7.0 Hz, 1H), 2.36 (s, 6H, 2 molecules of TsOH), 2.36-2.29 (m, 4H), 2.01-1.98 (m, 1H), 1.97-1.91 (m, 1H), 1.75-1.69 (m, 2H), 1.49-1.41 (m, 1H), 1.32-1.23 (m, 1H), 1.20 (d, J = 2.9 Hz, 3H), 1.17 (d, J = 2.9 Hz, 3H).	
Elemental analysis	Consistent with di-para-toluenesulfonic salt.	

Example S4: Preparation and characterization of the sulfuric acid salt of COMPOUND

- 5 0.733 mL aqueous sulfuric acid (0.5M) was added to a solution of 200.2 mg COMPOUND in 10 mL MEK resulting in a clear solution. After 2 days the obtained suspension was filtered and the solid was dried in vacuum for 1h yielding the mono-sulfuric acid salt of COMPOUND containing about 6 equivalents of water.

Table S4: Characterisation data for the di-sulfuric acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 4
Elemental analysis	Consistent with mono-sulfuric acid salt (about 1.1 equivalents H ₂ SO ₄ found). Contains about 6 equivalents of water.	

Example S5: Preparation and characterization of the di-maleic acid salt of COMPOUND

Maleic acid (256 g, 2.2 mol, 2.1 eq), dissolved in MeOH (630 mL, 1.1 volumes) was added to a refluxing solution of COMPOUND (682 g, 84% w/w (NMR assay), 1.05 mol) in EtOAc (6.3 L, 11 volumes). The resulting mixture was stirred under reflux for 15 minutes and was then cooled to 65-68°C within 30 minutes and seeded with 0.04% w/w of seeding crystals of di-maleic acid salt of COMPOUND (Seeding crystals were obtained after careful crystallisation using the same protocol.). The mixture was then cooled from 65-68°C to 40°C within 3 h. The obtained suspension was then cooled down to 20°C over 1 h, filtered under 0.2 bar of nitrogen and rinsed with EtOAc (1500 mL 2.6 volumes). The obtained white solid was then dried under 1 atmosphere of nitrogen for 24 hours to yield 715 g (88%) of the di-maleic acid salt of COMPOUND.

Table S5: Characterisation data for the di-maleic acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 5
DSC	Melt endotherm with melting point at about 147°C	
¹ H-NMR	¹ H NMR (MeOD, 400 MHz) δ 7.31-7.21 (m, 5H), 6.68 (s, 2 H), 6.38 (br d, J = 5.8 Hz, 1H), 6.27 (s, 4H, 2 molecules of maleic acid), 3.88 (s, 6H), 3.32-3.10 (m, 8H), 2.86 (s, 3H), 2.60 (sept, J = 7.0 Hz, 1H), 2.52-2.45 (m, 2H), 2.29-2.23 (m, 2H), 2.06-2.02 (m, 1H), 1.96 (dd, J = 14.2, 2.4 Hz, 1H), 1.76-1.69 (m, 2H), 1.48-1.39 (m, 1H), 1.29-1.21 (m, 1H), 1.19 (d, J = 2.5 Hz, 3H), 1.18 (d, J = 2.5 Hz, 3H).	
Elemental analysis	Consistent with di-maleic acid salt.	
Hygroscopicity	Non hygroscopic (mass change 0.1%)	

Example S6: Preparation of the sesqui-fumarate salt of COMPOUND

199.5 mg of COMPOUND were dissolved in 5 mL EtOAc. A clear solution of 85.4 mg fumaric acid in 5 mL THF was slowly added. The obtained clear solution was concentrated to 3 mL solution under nitrogen resulting in precipitation. The mixture was filtered and the solid was dried in vacuum. The obtained solid was the sesqui-fumaric acid salt of COMPOUND.

Table S6: Characterisation data for the sesqui-fumaric acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 6
DSC	Melt endotherm with melting point at about 180°C	
¹ H-NMR	¹ H NMR (MeOD, 400 MHz) δ 7.25-7.20 (m, 5H), 6.73 (s, 3 H, 1.5 molecule of fumaric acid), 6.59 (s, 2H), 6.35 (dd, J = 7.1, 1.6 Hz, 1H), 3.86 (s, 6H), 3.29-3.22 (m, 4H), 3.22-3.18 (m, 1H), 3.15-3.11 (m, 3H), 2.85 (s, 3H), 2.60 (sept, J = 7.0 Hz, 1H), 2.53-2.46 (m, 2H), 2.28-2.21 (m, 2H), 2.07-1.98 (m, 1H), 1.96 (dd, J = 14.0, 2.8 Hz, 1H), 1.76-1.69 (m, 2H), 1.48-1.39 (m, 1H), 1.29-1.21 (m, 1H), 1.19 (d, J = 2.8 Hz, 3H), 1.18 (d, J = 2.8 Hz, 3H).	
Elemental analysis	Consistent with sesqui-fumaric acid salt.	
Hygroscopicity	Non hygroscopic (mass change 0.1%)	

Example S7: Preparation of the di-hydrobromic acid salt of COMPOUND

0.3665 mL of aqueous 2 molar hydrobromic acid was slowly added to a solution of 199.8 mg COMPOUND in 0.4 ml THF and the obtained suspension was heated (heat gun). The clear solution was cooled to r.t. resulting in a precipitation. 3 mL THF was added, the suspension
5 was shaken, filtered and the solid was vacuum dried (1h, 3 mbar).. The obtained solid was the di-hydrobromic acid salt of COMPOUND containing about 3 equivalents of water.

Table S7: Characterisation data for the di-hydrobromic acid salt of COMPOUND

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 7
DSC	2 broad endotherms with peaks at about 99 and 117°C	
Elemental analysis	Consistent with di-hydrobromic acid salt. Contains about 3 equivalents of water.	
Hygroscopicity	Non hygroscopic (mass change 0.1%)	

Claims

1. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester; wherein said crystalline salt consists of:
- 5 • 1 equivalent of isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester;
- an acid component consisting of 1 to 2 equivalents of an acid selected from the group consisting of hydrobromic acid, sulfuric acid, maleic acid, fumaric acid,
- 10 methanesulfonic acid, para-toluenesulfonic acid, benzenesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, and ethanesulfonic acid; and
- 0 to 5 equivalents of water.
2. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 1, wherein the compound is enantiomerically enriched isobutyric acid (1R,2R,4R)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester.
- 15
3. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claims 1 or 2, wherein the acid component of said crystalline salt consists of 1 or 2 equivalents of hydrobromic acid, 1 or 2 equivalents of sulfuric acid, 1 or 2 equivalents of maleic acid, 1 to 2 equivalents of fumaric acid, 1 or 2 equivalents of methanesulfonic acid, 1 or 2 equivalents of para-toluenesulfonic acid, 1 or 2 equivalents of benzenesulfonic acid, 1 to 2 equivalents of naphthalene-1,5-disulfonic acid, 1 or 2 equivalents of naphthalene-2-sulfonic acid, or 1 or 2 equivalents of ethanesulfonic acid.
- 20
4. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 3, wherein the acid component of said crystalline salt consists of 2 equivalents of hydrobromic acid, 2 equivalents of maleic acid, or 1.5 equivalents of fumaric acid.
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5. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 4, wherein said crystalline salt consists of:

- 1 equivalent of compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester;
- 2 equivalents of maleic acid; and
- 0 equivalents of water.

6. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 5, characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 10.15°, 20.39°, and 22.63°; wherein said X-ray powder diffraction diagram is obtained by using Cu K α 1 radiation; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

7. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 5, characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 5.07°, 8.19°, 10.15°, 15.26°, 17.61°, 20.39°, 22.63°, 23.93°, 24.27°, and 25.61°; wherein said X-ray powder diffraction diagram is obtained by using Cu K α 1 radiation; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

8. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 5, which essentially shows the X-ray powder diffraction pattern as depicted in Fig.5.

9. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 5, which has a melting point of about 147°C as determined by differential scanning calorimetry using the method as described herein.

10. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 5, obtainable by:

1. refluxing a solution of COMPOUND (682 g, 84% w/w, 1.05 mol) in EtOAc (6.3 L, 11 volumes);
2. adding maleic acid (256 g, 2.2 mol, 2.1 eq) dissolved in MeOH (630 mL, 1.1 volumes);
3. stirring the resulting mixture under reflux for 15 minutes and cooling to 65-68°C within 30 minutes;
4. optional seeding with 0.04% w/w of seeding crystals;
5. cooling the mixture to 40°C within 3 hours;
6. cooling the mixture to 20°C within 1 hour;
7. filtering the solid under 0.2 bar of nitrogen and rinsing the solid with EtOAc (1500 mL 2.6 volumes); and
8. drying the solid under 1 atmosphere of nitrogen for 24 hours.

11. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 4, wherein the acid component of said crystalline salt consists of 1.5 equivalents of fumaric acid.

12. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 11, characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 5.27°, 8.05°, and 20.61°; wherein said X-ray powder diffraction diagram is obtained by using Cu K α 1 radiation; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

13. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 4, wherein the acid component of said crystalline salt consists of 2 equivalents of hydrobromic acid.

14. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-{[3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino}-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to claim 13, characterised by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.3°, 15.6°, and 17.3°; wherein said X-ray powder diffraction diagram is obtained by using Cu K α 1 radiation; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

15. A pharmaceutical composition comprising a crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

5 16. A crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 14, or a pharmaceutical composition according to claim 15, for use as a medicament.

10 17. Use of a crystalline salt of the compound isobutyric acid (1R*,2R*,4R*)-2-(2-([3-(4,7-dimethoxy-1H-benzoimidazol-2-yl)-propyl]-methyl-amino)-ethyl)-5-phenyl-bicyclo[2.2.2]oct-5-en-2-yl ester according to any one of claims 1 to 14 for the preparation of a pharmaceutical composition for the treatment or prevention of chronic stable angina, hypertension, ischemia (renal and cardiac), cardiac arrhythmias including atrial fibrillation, cardiac hypertrophy, or congestive heart failure.