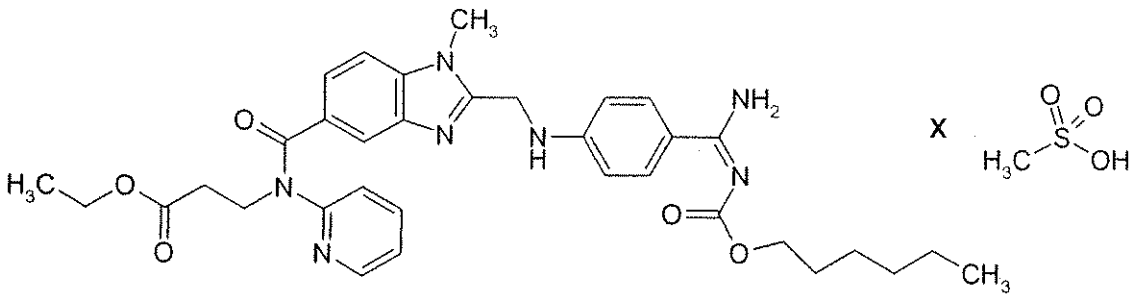
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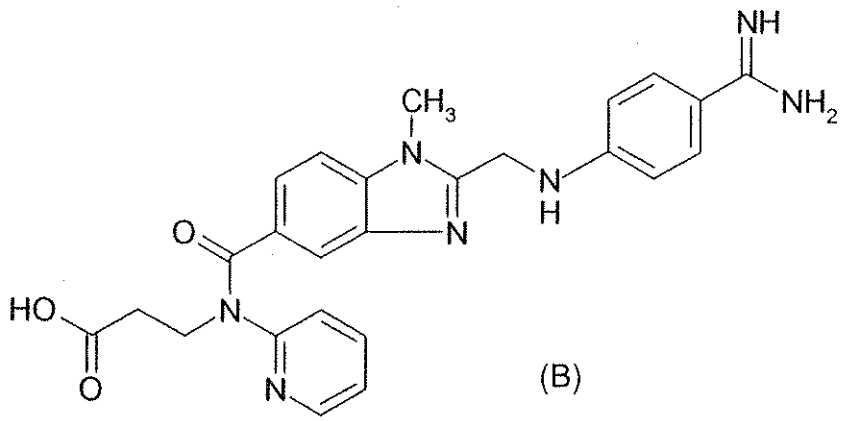
3-[(2-{[4-(Hexyloxycarbonylamino-imino-methyl)-phenyl amino]-methyl}-1-methyl-1*H*-benzimidazol-5-carbonyl)-pyridine-2-yl-amino]-propionic acid ethyl ester methane sulphonate and use thereof as a medicament

The present invention relates to the compound ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate of formula A and the use thereof as a pharmaceutical composition.

Formula A:



The base of the compound of formula A is already known from WO 98/37075, in which compounds with a thrombin-inhibiting effect and a thrombin time-prolonging activity are disclosed, under the name 1-methyl-2-[*N*-[4-(*N*-n-hexyloxycarbonyl-amidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide. The compound of formula I is a double prodrug of the compound



(B)

i.e. the compound of formula A (BIBR 1048 MS) is only converted into the actual effective compound, namely the compound of formula B, in the body. The main fields of application of the compound of chemical formula A are the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke.

The above-mentioned pharmacologically beneficial properties of the disubstituted bicyclic heterocycles disclosed in the prior art are the main prerequisite for effective use of the compounds as pharmaceutical compositions. An active substance must, however, also meet other requirements in order to be capable of being used as pharmaceutical compositions. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restricted thereto, examples of these parameters are the stability of effect of the starting substance under different ambient conditions, stability in the course of the preparation of the pharmaceutical formulation and stability in the final compositions of the pharmaceutical preparation. The pharmaceutical active substance used to prepare the pharmaceutical compositions should therefore have high stability, which should also be guaranteed even under different environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the active substance itself, breakdown products thereof, for example. In such cases the content of active substance found in the pharmaceutical formulations might be less than specified.

The absorption of moisture reduces the content of pharmaceutically active substance as a result of the increased weight caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, e.g. by the addition of suitable drying agents or by storing the drug in an environment where it is protected from moisture. In addition, the uptake of moisture may reduce the content of pharmaceutically active substance during manufacture if the pharmaceutical substance is exposed to the environment without being protected from moisture in any way. Preferably, therefore, a pharmaceutically active substance should be only slightly hygroscopic.

As the crystal modification of an active substance is important to the reproducible

active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances characterised by only slight polymorphism are preferred.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions) it is essential that the active substance should be sufficiently soluble in physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible.

Detailed Description of the Invention

The problem outlined above is solved by the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate salt of formula A.

In fact, it has been found, surprisingly, that crystalline modification I of this salt can be prepared by the process described in Example 1 and crystalline modification II of this salt can be prepared by the processes described in Examples 2 to 4, selectively and uniformly in each case.

Moreover, under certain conditions of synthesis as described for example in Example 5, a hydrate form may be obtained, the water content of which indicates a hemihydrate.

For use of the pharmaceuticai composition it is essential that the active substance contained therein is in a uniform crystalline modification to ensure reliable bioavailability.

The disclosed methanesulphonate is characterised in all three crystalline modifications by good crystallinity and low amorphisation during grinding and compression. Moreover, it is non-hygroscopic in all three crystalline modifications and dissolves very easily in physiologically acceptable acid aqueous media.

The crystalline forms of the methanesulphonate of the compound ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate as disclosed herein are characterised by a melting point of $T_{m.p..}$ = 180 $\pm$ 3°C (form I), $T_{m.p..}$ = 190 $\pm$ 3°C (form il) or $T_{m.p..}$ = 120 $\pm$ 5°C (hemihydrate) (determined by DSC = Differential Scanning Calorimetry; evaluation by peal maximum; heating rate: 10°C/min). The values shown were determined using a DSC 821^e made by Messrs Mettler Toledo.

The disclosure therefore relates to the three above-mentioned polymorphic forms of the salt ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate, preferably in crystalline form, characterised by melting points of $T_{m.p..}$ = 180 $\pm$ 3°C, $T_{m.p..}$ = 190 $\pm$ 3°C or $T_{m.p..}$ = 120 $\pm$ 5°C (determined by DSC; evaluation by peak maximum; heating rate: 10°C/min). Polymorph I with a melting point of $T_{m.p..}$ = 180 $\pm$ 3°C is preferred.

Accordingly, in a first aspect, there is provided an Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate in

crystalline form, characterised by a melting point of $T_{m.p.}$ = 190 ± 3°C (form II) (determined by DSC; evaluation by peak maximum; heating rate: 10°C/min).

In a second aspect, there is provided a pharmaceutical composition, containing the salt ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate according to the first aspect, optionally together with one or more inert carriers and/or diluents.

In a third aspect, there is provided the use of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate according to the first aspect for preparing a pharmaceutical composition which is suitable for the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke.

The disclosure also relates to the methods of selectively producing the three polymorphic forms as well as the modifications which may be obtained by these methods.

In one embodiment, BIBR 1048 MS polymorph I is obtained by

a) slowly adding a solution of a slight deficiency (for example 0.98 equivalents) of methanesulphonic acid in acetone to a solution of BIBR 1048 base in acetone at a temperature of approx. 30°C to 36°C,
b) stirring the mixture for about 1 hour at a temperature of approx. 26°C to 33°C,
c) cooling it to approx. 17°C to 23°C and stirring for a further 40 to 80 minutes at this temperature,
d) suction filtering the precipitated crystals of BIBR 1048 MS form I and
e) drying the product thus obtained *in vacuo* for at least 4 hours at a maximum temperature of 50°C.

In another embodiment, BIBR 1048 MS polymorph II is obtained by

a) slowly adding a solution of a slight deficiency (for example 0.98 equivalents) of methanesulphonic acid in acetone to a solution of BIBR 1048 base in acetone at a temperature of approx. 40°C to 46°C,
b) optionally inoculating it with BIBR 1048 polymorph II crystals,
c) stirring the mixture for about 1 hour at a temperature of approx. 40°C to 46°C,
d) cooling to approx. 17°C to 23°C and stirring for a further 40 to 80 minutes at this temperature,
e) suction filtering the precipitated crystals of BIBR 1048 MS form II and
f) drying the product thus obtained *in vacuo* for at least 4 hours at a maximum temperature of 50°C;

or by

a) heating a suspension of BIBR 1048 MS polymorph I in acetone to 45°C to 50°C for approx. 4 hours with stirring,
b) optionally i) inoculating with BIBR 1048 polymorph II crystals, or
ii) inoculating with BIBR 1048 polymorph II crystals and additionally adding a small amount of BIBR 1048 base,
c) then cooling to approx. 15°C,

d) suction filtering the precipitated crystals of BIBR 1048 MS form II and

e) drying the product thus obtained *in vacuo* for at least 4 hours at a maximum temperature of 50°C;

or by

a) placing BIBR 1048 MS polymorph I in acetone and
b) optionally i) inoculating with a small amount of BIBR 1048 polymorph II, or

ii) inoculating with BIBR 1048 polymorph II crystals and additionally adding a small amount of BIBR 1048 base,

c) heating the mixture thus obtained to 40°C to 46°C for at least one hour with stirring,
d) then cooling to approx. 17°C to 23°C and stirring for a further 40 to 80 minutes at this temperature,
e) separating off the precipitated crystals of BIBR 1048 MS form II and
f) drying the product thus obtained *in vacuo* for at ieast 4 hours at a maximum temperature of 50°C.

In a further embodiment, BIBR 1048 MS hemihydrate is obtained by

a) slowly adding a solution of one equivalent of methanesulphonic acid in ethyl acetate to a solution of BIBR 1048 base in a mixture of 90% aqueous ethanol and ethyl acetate in a ratio by volume of approx. 2:5 at a temperature of approx. 35°C to 40°C,
b) optionally adding more ethyl acetate as a diluent at the start of the crystallisation of the product,
c) stirring for approx. another 30 minutes at approx. 35°C to 40°C,
d) then stirring for a further 30 minutes at ambient temperature,
e) suction filtering the precipitate of BIBR 1048 MS hemihydrate and
f) drying at approx. 40°C in a circulating air drying cupboard.

In a fourth aspect, there is provided a process for preparing a pharmaceutical composition according to the second aspect, characterised in that by a non-chemical method the salt ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-

amino]-propionate-methanesulphonate according to the first aspect is incorporated in one or more inert carriers and/or diluents.

In a fifth aspect, there is provided a process for preparing Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, characterised in that

a) a solution of a slight deficiency of methanesulphonic acid in acetone is slowly added to a solution of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate base in acetone at a temperature of approx. 40°C to 46°C,
b) the mixture is optionally inoculated with Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals,
c) it is then stirred for about 1 hour at a temperature of approx. 40°C to 46°C,
d) cooled to approx. 17°C to 23°C and stirred for a further 40 to 80 minutes at this temperature,
e) the precipitated crystals of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II are suction filtered and
f) the product thus obtained is dried in vacuo for at least 4 hours at a maximum of 50°C.

In a sixth aspect, there is provided a process for preparing Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, characterised in that

a) a suspension of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-

phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph I in acetone is heated to 45°C to 50°C for approx. 4 hours with stirring,

b) optionally i) inoculated Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals, or
ii) inoculated with Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals and additionally a small amount of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate base is added,

c) then cooled to approx. 15 °C,

d) the precipitated crystals of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II are suction filtered and

e) the product thus obtained is dried in vacuo for at least 4 hours at a maximum 50°C.

In a seventh aspect, there is provided a process for preparing Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, characterised in that

a) Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph I is placed in acetone and

b) optionally i) inoculated with a small amount of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, or

ii) inoculated with Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals and additionally a small amount of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate base is added,

b) the mixture thus obtained is heated to 40°C to 46°C for at least one hour with stirring,

c) then cooled to approx. 17°C to 23°C and stirred for a further 40 to 80 minutes at this temperature,

d) the precipitated crystals of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II are separated off and

e) the product thus obtained is dried in vacuo for at least 4 hours at a maximum 50°C.

The crystalline forms of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate - methanesulphonate according to the disclosure were investigated in more detail by x-ray powder diffraction. The diagrams obtained are shown in Figure 1.

Tables 1 to 3 that follow list the data obtained in this analysis:

Table 1: X-ray powder reflections and intensities (standardised) of the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate – methanesulphonate (form I)

2 Θ [°]	d_{hkl} value [Å]	intensity [%]
4.4	20.1	100
8.94	9.90	5
9.23	9.57	4
9.55	9.26	4
10.55	8.38	2
10.95	8.08	11
12.73	6.95	1
13.46	6.57	7
13.95	6.34	3
14.26	6.21	2
15.17	5.84	1
15.93	5.56	1
16.46	5.38	1
17.66	5.02	8
18.07	4.91	13
18.60	4.77	2
19.89	4.46	6
20.28	4.38	2
20.54	4.32	2

2 Θ [°]	d_{hkl} value [Å]	intensity [%]
21.12	4.20	4
22.06	4.03	8
22.85	3.89	6
24.12	3.69	1
25.10	3.54	3
25.99	3.43	1
26.52	3.36	2
26.83	3.32	2
27.16	3.28	1
27.64	3.22	2
28.09	3.17	2
29.08	3.07	1
29.26	3.05	1
29.94	2.98	1
31.88	2.80	1
34.37	2.61	1
36.21	2.48	1
38.26	2.35	1
39.47	2.28	1
39.98	2.25	1

Table 2: X-ray powder reflections and intensities (standardised) of the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate – methanesulphonate (form II)

2 Θ [°]	d_{hkl} value [Å]	intensity [%]
4.3	20.4	100
8.72	10.1	3
9.68	9.13	1
11.15	7.93	1
12.42	7.12	2
13.59	6.51	1
13.95	6.34	1
15.11	5.86	1
15.97	5.55	1
16.52	5.36	1
17.45	5.08	1
17.86	4.96	2
18.45	4.81	1
19.22	4.61	2
19.89	4.46	2
21.46	4.14	2
21.98	4.04	1
22.48	3.95	1
23.75	3.74	1
25.29	3.52	1
28.17	3.17	1
28.59	3.12	1

Table 3: X-ray powder reflections and intensities (standardised) of the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate – methanesulphonate (hemihydrate)

2 Θ [°]	d_{hkl} value [Å]	Intensity [%]
3.9	22.8	100
4.4	20.1	10
5.64	15.7	2
7.57	11.8	16
8.25	10.7	17
8.77	10.1	12
9.34	9.46	7
10.69	8.27	13
11.33	7.80	3
11.66	7.58	1
11.96	7.39	1
13.04	6.78	3
14.54	6.09	11
15.16	5.84	1
16.56	5.35	13
17.27	5.13	6
17.78	4.98	12
18.75	4.73	1
19.41	4.57	3
19.95	4.45	24
20.38	4.35	4

2 Θ [°]	d_{hkl} value [Å]	intensity [%]
20.84	4.26	4
21.21	4.19	12
22.22	4.00	6
22.46	3.96	5
23.05	3.85	3
23.40	3.80	4
23.85	3.73	12
24.44	3.64	7
25.30	3.52	1
25.63	3.47	1
26.22	3.40	2
26.52	3.36	3
27.06	3.29	1
27.45	3.25	2
29.27	3.05	3
30.78	2.90	2
32.32	2.77	2
32.59	2.75	2
34.31	2.61	1
34.91	2.57	1
36.04	2.49	1
37.00	2.43	1
37.84	2.38	1
38.13	2.36	1

In the preceding Tables 1 to 3 the value "2 Θ [°]" denotes the angle of diffraction in degrees and the value "d_{hkl} [Å]" denotes the specified distances in Å between the lattice planes.

The x-ray powder diagrams were recorded, within the scope of the present invention, using a Bruker D8 Advanced diffractometer fitted with a location-sensitive detector (OED) and a Cu anode as the x-ray source (CuK_{α_1} radiation, λ = 1.5406 Å, 40 kV, 40 mA).

The hydrate of the compound ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate –methanesulphonate according to the invention occurs in the form of the hemihydrate under standard conditions, from which water escapes at a temperature of about 120°C, parallel to the melting of this form.

Figure 2 shows the thermoanalysis of the three forms.

Experimental section

Example 1

Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form I (BIBR 1048 MS polymorph I)

52.6 kg of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (which has preferably been purified beforehand by recrystallisation from ethyl acetate) are placed in an agitator apparatus which has been rendered inert and then 293 kg acetone are added. The contents of the apparatus are heated to 40 to 46°C with stirring. After a clear solution has formed, the contents of the apparatus are filtered into a second agitator apparatus through a lens filter and then cooled to 30 to 36°C. 33 kg of acetone pre-cooled to 0 to 5°C, 7.9 kg of 99.5% methanesulphonic acid and for rinsing another 9 kg of acetone are placed in the suspended container of the second apparatus. The contents of the suspended container are added in metered amounts to the solution of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base at 26 to 36°C within 15 to 40 minutes. Then the mixture is stirred for 40 to 60 minutes at 26 to 33°C. It is then cooled to 17 to 23°C and stirred for a further 40 to 80 minutes. The crystal suspension is filtered through a filter dryer and washed with a total of 270 l of acetone. The product is dried in vacuo at a maximum of 50°C for at least 4 hours.

Yield: 54.5 – 59.4 kg; 90 – 98% of theory based on ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base

Example 2

BIBR 1048 MS polymorph II by conversion from BIBR 1048 MS polymorph I

4g BIBR 1048 MS polymorph I and 35 ml acetone are placed in a glass flask with stirrer and reflux condenser. The suspension is heated to 45 to 50°C with stirring and kept at this temperature for 4 hours. It is then cooled to 15°C and the crystals are suction filtered through a Büchner funnel, washed with 20 ml acetone and dried in vacuo at 45°C.

Note: The synthesis may also be carried out by inoculating with BIBR 1048 MS polymorph II. If the speed of conversion is low it may be accelerated by the addition of a small amount of BIBR 1048 base (for example, on an industrial scale, about 50 g BIBR 1048 base to roughly 90 kg BIBR 1048 MS polymorph I) in addition to the inoculation with BIBR 1048 MS polymorph II.

Example 3

Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II (BIBR 1048 MS polymorph II)

52.6 kg of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (which has preferably been purified beforehand by recrystallisation from ethyl acetate) are placed in an agitator apparatus which has been rendered inert and then 293 kg acetone are added. The contents of the apparatus are heated to 40 to 46°C with stirring. After a clear solution has formed, the contents of the apparatus are filtered into a second agitator apparatus through a lens filter. 33 kg of acetone pre-cooled to 0 to 5°C, 7.9 kg of 99.5% methanesulphonic acid and for rinsing another 9 kg of acetone are placed in the suspended container of the second apparatus. The contents of the suspended container are added in metered amounts to the solution of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base at 40 to 46°C within 15 to 40 minutes and inoculated with 10 g of BIBR 1048 MS polymorph II (prepared according to Examples 2, for example). Then the mixture is stirred for 40 to

60 minutes at 40 to 46°C. It is then cooled to 17 to 23°C and stirred for a further 40 to 80 minutes. The crystal suspension is filtered through a filter dryer and washed with a total of 270 l of acetone. The product is dried in vacuo at a maximum of 50°C for at least 4 hours.

Yield: 54.5 – 59.4 kg; 90 – 98% of theory based on ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base

Note: The synthesis may also be carried out without inoculation with BIBR 1048 MS polymorph II. However, the method using inoculation is preferred.

Example 4

BIBR 1048 MS polymorph II by conversion from BIBR 1048 MS polymorph I

30.7 kg BIBR 1048 MS polymorph I are placed in an agitator apparatus which has been rendered inert and then 199 kg of acetone are added. The contents of the apparatus are inoculated with 10 g BIBR 1048 MS polymorph II (e.g. prepared according to Example 2), heated to 40 to 46°C with stirring, and kept at this temperature for at least 1 hour. Then the mixture is cooled to 17 to 23°C and stirred for at least a further 40 to 80 minutes.

The crystal suspension is separated off using a horizontal centrifuge and washed with a total of 45 kg of acetone. The product is dried in a vacuum drying cupboard at a maximum temperature of 50°C for at least 4 hours.

Yield: 27.7 – 30.1 kg; 90 – 98% of theory).

Note: The synthesis may also be carried out without inoculation with BIBR 1048 MS polymorph II. However, the method using inoculation is preferred. If the speed of conversion is low a small amount of BIBR 1048 base (for example, about 50 g BIBR 1048 base to roughly 90 kg BIBR 1048 MS polymorph I) may be added, in addition to the inoculation with BIBR 1048 MS polymorph II.

Example 5

Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate-hemihydrate

A solution of 1.53 g (15.93 mmol) of methanesulphonic acid in 15 ml of ethyl acetate was added dropwise to a solution of 10.0 g (15.93 mmol) of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075) in 16.5 ml of 90% aqueous ethanol and 40 ml of ethyl acetate, with stirring, at 35-40°C. After a few minutes the product began to crystallise out and was diluted with 30 ml of ethyl acetate. It was stirred for another 30 minutes at 35-40°C and for a further 30 minutes at ambient temperature, then the precipitate was suction filtered, washed with approx. 20 ml of ethyl acetate and dried at 40°C in the circulating air drying cupboard.

Yield: 99% of theory

Brief description of the Figures

Figure 1 shows the X-ray powder diffractograms of the three crystalline forms of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate.

Figure 2 shows the thermoanalysis and measurement of the melting point (DSC) for the three crystalline forms of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate.

Patent Claims

1. Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate in crystalline form, characterised by a melting point of $T_{m.p.}$ = 190 ± 3°C (form II) (determined by DSC; evaluation by peak maximum; heating rate: 10°C/min).

2. Pharmaceutical composition, containing the salt ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate according to claim 1, optionally together with one or more inert carriers and/or diluents.

3. Use of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate according to claim 1 for preparing a pharmaceutical composition which is suitable for the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke.

4. Process for preparing a pharmaceutical composition according to claim 2,

characterised in that by a non-chemical method the salt ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate according to claim 1 is incorporated in one or more inert carriers and/or diluents.

5. Process for preparing Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, characterised in that

a) a solution of a slight deficiency of methanesulphonic acid in acetone is slowly added to a solution of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate base in acetone at a temperature of approx. 40 °C to 46 °C,
b) the mixture is optionally inoculated with Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals,
c) it is then stirred for about 1 hour at a temperature of approx. 40 °C to 46 °C,
d) cooled to approx. 17 °C to 23 °C and stirred for a further 40 to 80 minutes at this temperature,
e) the precipitated crystals of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II are suction filtered and
f) the product thus obtained is dried in vacuo for at least 4 hours at a maximum of 50 °C.

6. Process for preparing Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, characterised in that

a) a suspension of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph I in acetone is heated to 45 °C to 50 °C for approx. 4 hours with stirring,

b) optionally i) inoculated Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals, or

ii) inoculated with Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals and additionally a small amount of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate base is added,

c) then cooled to approx. 15 °C,

d) the precipitated crystals of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II are suction filtered and

e) the product thus obtained is dried in vacuo for at least 4 hours at a maximum 50 °C.

7. Process for preparing Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, characterised in that

a) Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph I is placed in acetone and

b) optionally i) inoculated with a small amount of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II, or

ii) inoculated with Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate polymorph II crystals and additionally a small amount of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate base is added,

c) the mixture thus obtained is heated to 40 °C to 46 °C for at least one hour with stirring,

d) then cooled to approx. 17 °C to 23 °C and stirred for a further 40 to 80 minutes at this temperature,

e) the precipitated crystals of Ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate-methanesulphonate form II are separated off and

f) the product thus obtained is dried in vacuo for at least 4 hours at a maximum 50 °C.