(12) STANDARD PATENT (11) Application No. **AU 2004274139 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
amino]-methyl}-1-methyl-1H-ben midazol-5-carbonyl)-pyridine-2-3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylziyl-amino]-propionic acid ethyl ester methane sulphonate and use thereof as a medicament

(51) International Patent Classification(s)
A61P 7/02 (2006.01) ***C07D 401/12*** (2006.01)
A61K 31/4439 (2006.01)

(21) Application No: **2004274139** (22) Date of Filing: **2004.08.24**

(87) WIPO No: **WO05/028468**

(30) Priority Data

(31) Number	(32) Date	(33) Country
103 39 862.7	**2003.08.29**	**DE**

(43) Publication Date: **2005.03.31**
(44) Accepted Journal Date: **2010.05.13**

(71) Applicant(s)
Boehringer Ingelheim International GmbH

(72) Inventor(s)
Sobotta, Rainer;Sieger, Peter;Schmid, Rolf

(74) Agent / Attorney
Davies Collison Cave, 1 Nicholson Street, Melbourne, VIC, 3000

(56) Related Art
J Med Chem 45(9) (2002) pp 1757-1766

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
31. März 2005 (31.03.2005)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2005/028468 A1

(51) Internationale Patentklassifikation[7]: C07D 401/12, A61K 31/4439, A61P 7/02

(21) Internationales Aktenzeichen: PCT/EP2004/009432

(22) Internationales Anmeldedatum:
24. August 2004 (24.08.2004)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
103 39 862.7 29. August 2003 (29.08.2003) DE

(71) Anmelder *(nur für AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 INGELHEIM (DE).

(71) Anmelder *(nur für DE)*: **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Strasse 173, 55216 INGELHEIM (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder *(nur für US)*: **SOBOTTA, Rainer** [DE/DE]; Ludwig-Richter-Str. 6, 55218 INGELHEIM (DE). **SIEGER, Peter** [DE/DE]; Klingenäcker 7, 88441 MITTELBIBERACH (DE). **SCHMID, Rolf** [DE/DE]; Talstrasse 37, 88487 BALTRINGEN (DE).

(74) Gemeinsamer Vertreter: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**; Binger Strasse 173, 55216 INGELHEIM (DE).

(81) Bestimmungsstaaten *(soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDINE-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER METHANE SULPHONATE AND USE THEREOF AS A MEDICAMENT

(54) Bezeichnung: 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONSÄURE-ETHYLESTER -METHANSULFONAT UND DESSEN VERWENDUNG ALS ARZNEIMITTEL

(57) Abstract: The invention relates to the compound 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazol-5-carbonyl)-pyridine-2-yl-amino]-propionic acid-ethyl ester methane sulphonate in crystal modifications I and II and also as a hemihyrate in addition to the use thereof as a medicament.

(57) Zusammenfassung: Gegenstand der vorliegenden Erfindung ist die Verbindung 3-[(2-{[4-(Hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionsäure-ethylester - Methansulfonat in den Kristallmodifikationen I und II sowie als Hemihydrat und deren Verwendung als Arzneimittel.

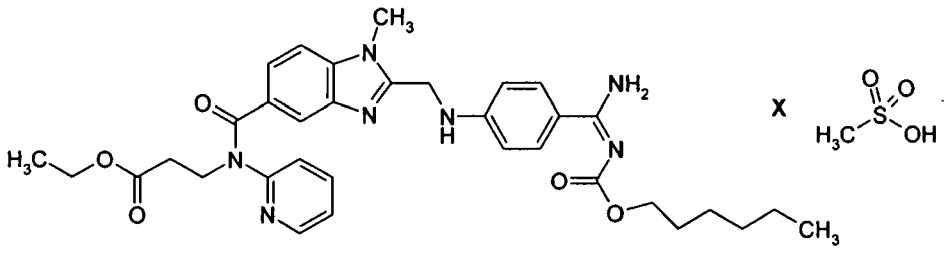
WO 2005/028468 A1

85068pct

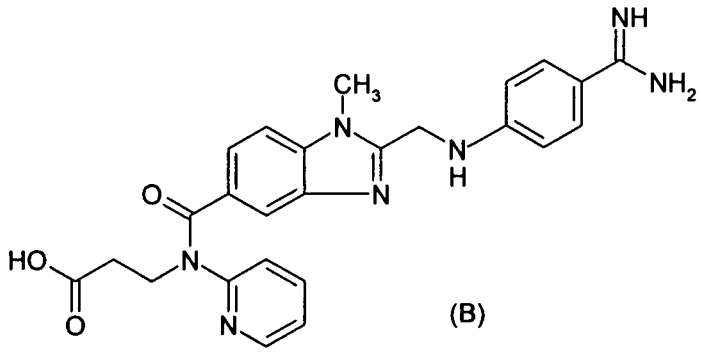
3-[(2-{[4-(Hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazol-5-carbonyl)-pyridine-2-yl-amino]-propionic acid ethyl ester methane sulphonate and use thereof as a medicament

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 present invention advantageously provides 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 present invention advantageously relates to 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 pharmaceutical composition it is essential that the active substance contained therein is in a uniform crystalline modification to ensure reliable bioavailability.

The methanesulphonate according to the invention 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 according to the invention are characterised by a melting point of $T_{m.p.}$ = 180 ± 3°C (form I), $T_{m.p..}$ = 190 ± 3°C (form II) or $T_{m.p..}$ = 120 ± 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.

In a first aspect the present invention 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 ± 3°C, $T_{m.p..}$ = 190 ± 3°C or $T_{m.p..}$ = 120 ± 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 ± 3°C is preferred.

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

According to the invention 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.

According to the invention 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 it 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 least 4 hours at a maximum temperature of 50 °C.

According to the invention 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 another aspect, the present invention relates to 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 form II, optionally together with one or more inert carriers and/or diluents.

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

In another aspect, the present invention relates to a method for the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke, comprising administering to a subject in need thereof ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate form II.

In a further aspect, the present invention relates to a process for preparing a pharmaceutical composition of the invention, wherein 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 form II is incorporated in one more inert carriers and/or diluents.

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 invention 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.

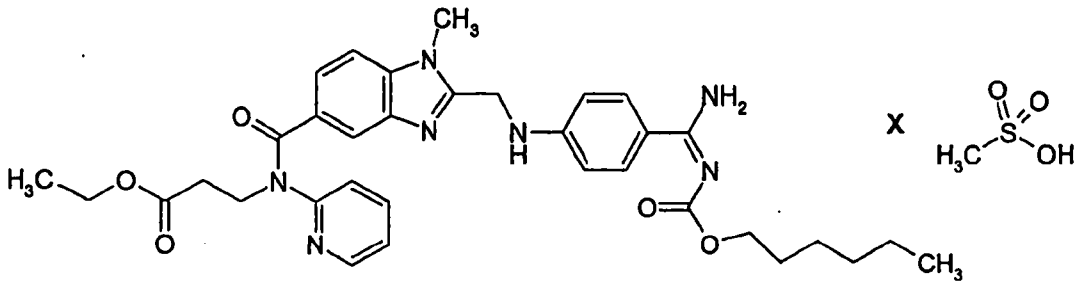
Figure 2 shows the thermoanalysis and measurement of the melting point (DSC) for the three crystalline forms of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

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



Formula A

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, wherein 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 form II according to claim 1, wherein

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 base in acetone at a temperature of approx. 40°C to 46°C,

b) the mixture is stirred for about 1 hour at a temperature of approx. 40°C to 46°C,

c) 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 suction filtered and

e) 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 form II according to claim 1, wherein

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) then cooled to approx. 15°C,

c) the precipitated crystals of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-

2004274139 13 Apr 2010

pyridin-2-yl-amino]-propionate methanesulphonate form II are suction filtered and

d) the product thus obtained is dried in vacuo for at least 4 hours at a maximum of 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 form II according to claim 1, wherein

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) 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

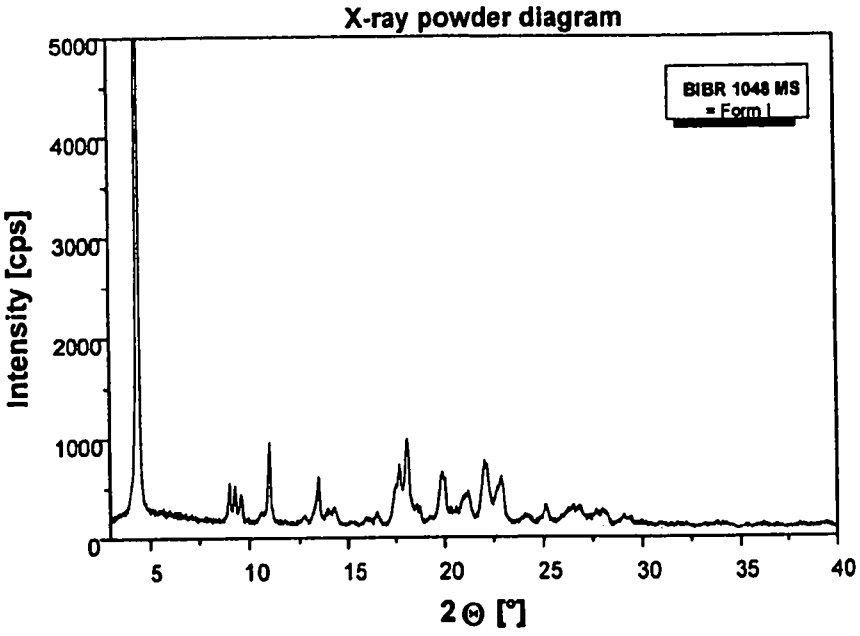
e) the product thus obtained is dried in vacuo for at least 4 hours at a maximum of 50°C.

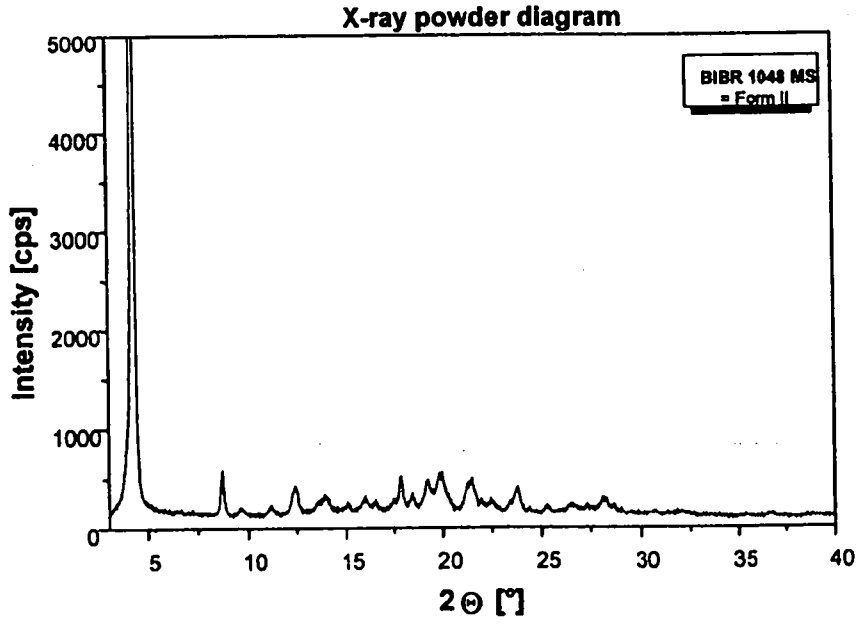
8. A method for the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke, comprising administering to a subject in need thereof ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate according to claim 1.

9. 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, substantially as hereinbefore described with reference to any one of the examples.

10. Process according to any one of claims 4 to 7, substantially as hereinbefore described with reference to any one of the examples.

Figure 1:





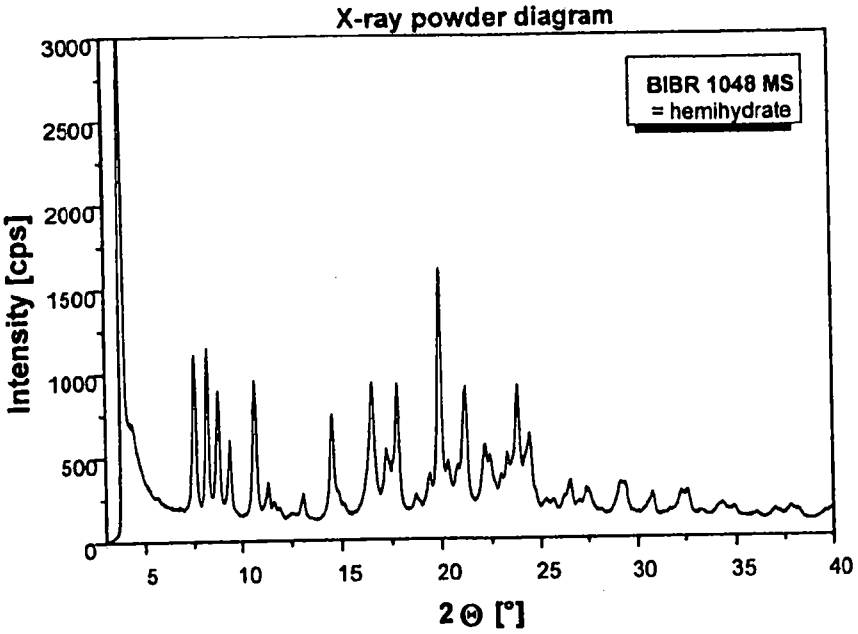


Figure 2: