(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 August 2017 (17.08.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/137784 A1

(51) International Patent Classification:
C07D 277/40 (2006.01)

(21) International Application Number:
PCT/HU2016/050045

(22) International Filing Date:
22 September 2016 (22.09.2016)

(25) Filing Language: Hungarian

(26) Publication Language: English

(30) Priority Data:
P1600087 10 February 2016 (10.02.2016) HU

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: METHOD FOR THE PRODUCTION OF MORPHOLOGICALLY HOMOGENOUS MIRABEGRON AND MIRABEGRON MONOHYDROCHLORIDE

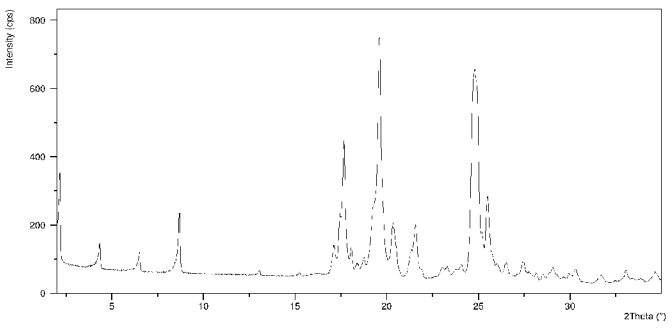

Figure 1

(57) Abstract: The object of the present invention relates to a method for the production of formula 1 (*R*)-2- (2-aminothiazole-4-yl)-4'-[2-[(2-hydroxy-2-phenyl)ethylamino]ethyl]acetanilide (mirabegron) and formula 1c mirabegron monohydrochloride, as well as the intermediates used during the method.

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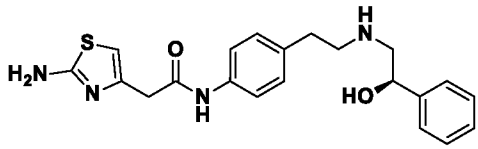
Method for the production of morphologically homogenous mirabegron and mirabegron monohydrochloride

The object of the invention

The object of the present invention relates to a method for the production of formula **1** (*R*)-2-(2-aminothiazole-4-yl)-4'-[2-[(2-hydroxy-2-phenyl)ethylamino]ethyl]acetanilide (mirabegron)



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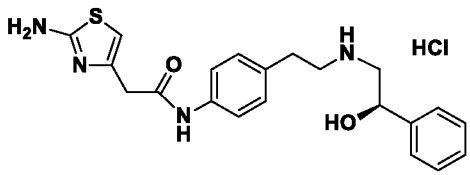
and formula **1c** mirabegron monohydrochloride



1c

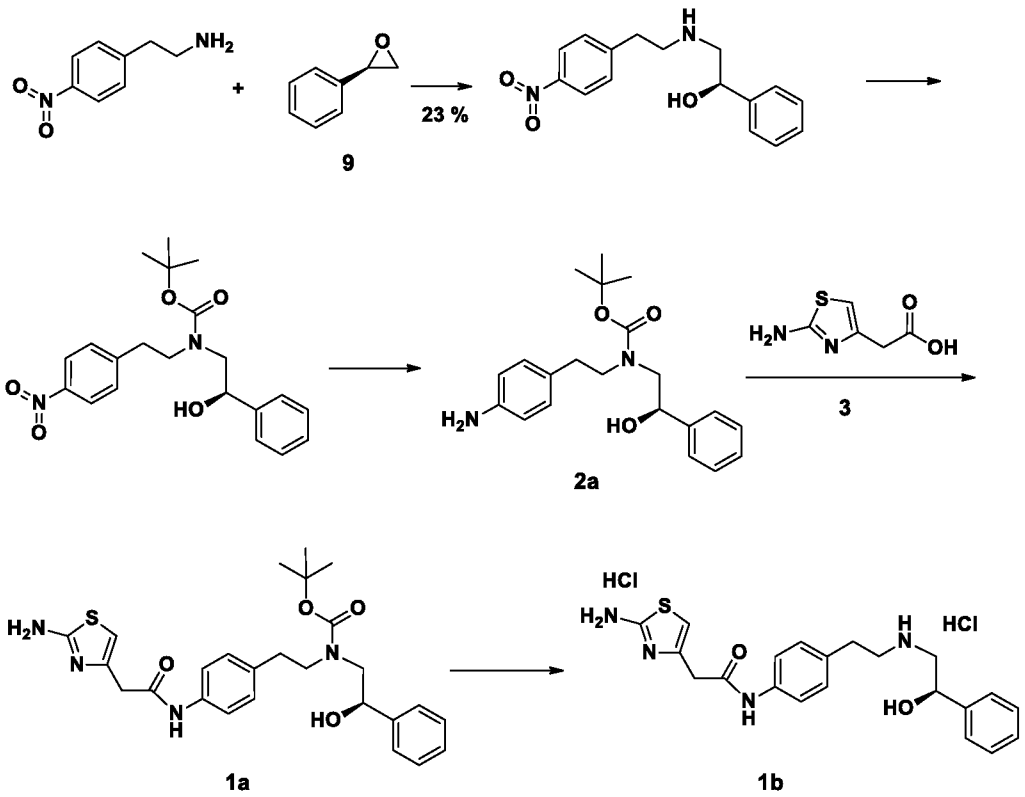
as well as the intermediates used during the method.

The state of the art

Formula **1** mirabegron is a selective β_3 agonist, an active substance used for the treatment of overactive bladder syndrome.

The known forms of synthesis usually have many steps, and are not advantageous methods from the points of view of technology and economy.

International patent application with publication number WO 99020607 presents the production of formula **1b** mirabegron dihydrochloride salt according to the following reaction scheme.



Reaction scheme 1

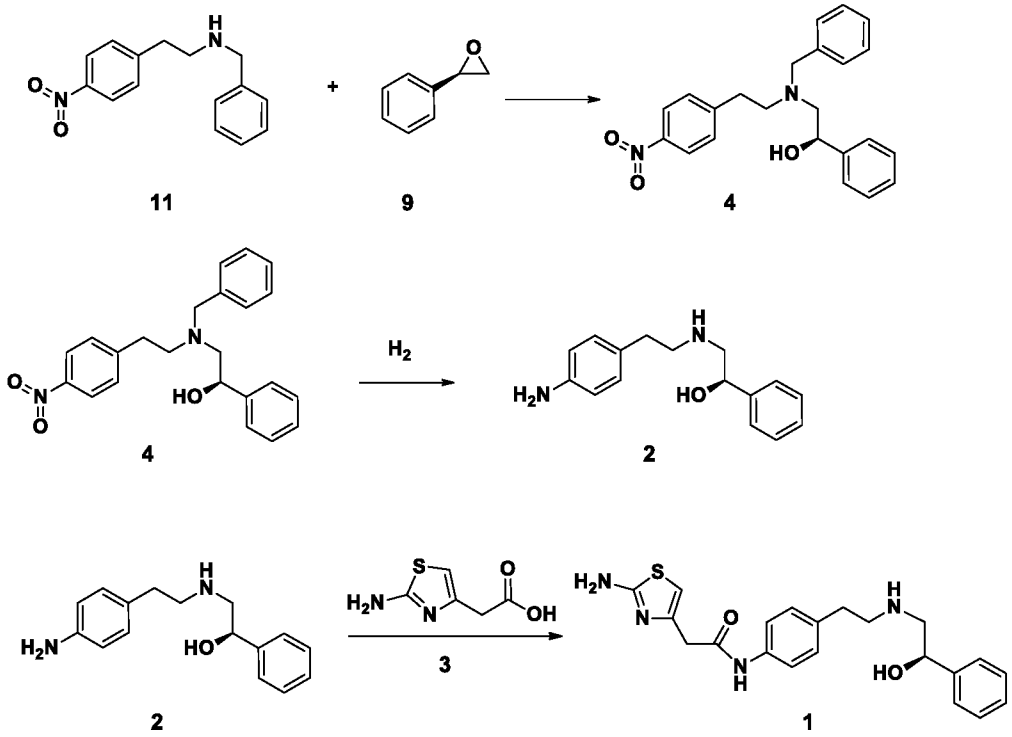
One of the key steps of the method is the reaction of 4-nitrophenethylamine with formula **9** optically active styrene oxide. This reaction is not selective, several products are produced, the material must be isolated and purified chromatographically, which is not economical on the

industrial scale and is difficult to carry out in the case of a larger batch size. Due to both the low yield and the high price of active styrene oxide, it is not suitable for the industrial production of mirabegron. Also, the use of protective groups results in extra reaction steps.

The key step in the method used in Chinese patent application number CN 103896872 is the styrene oxide reaction depicted in reaction scheme 1, the disadvantage of which is that the reaction of formula **9** styrene oxide with a primary amine results in three different products in comparable amounts, among which the desired product is difficult to extract and difficult to purify. Therefore waste is produced from a significant part of the expensive styrene oxide.

In several patent applications – WO 2003037881, CN 104016943, CN 104016877 – the mirabegron is produced starting from mandelic acid or mandelic acid ester instead of styrene oxide.

According to the method published in Chinese patent application number CN 103387500 formula **9** optically active styrene oxide is used to produce formula **4** (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol. The aforementioned formula **9** styrene oxide is an exceptionally expensive reagent. The isomer compounds produced during ring opening appear as potential contaminants in the reaction series, and so also contaminate the final product, to varying extents (reaction scheme 2).



Reaction scheme 2

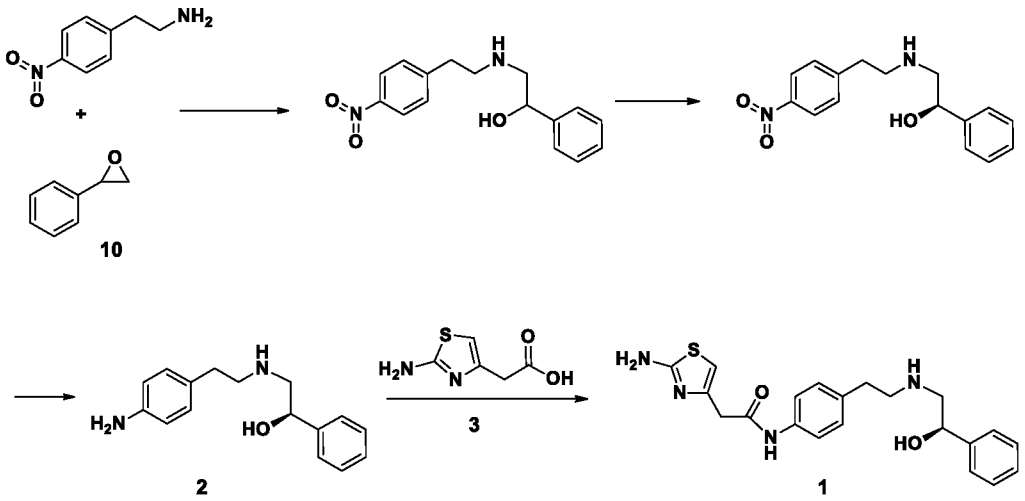
Indian patent application number 3843/CHE/2012 describes a form of mirabegron hydrochloride characterised by powder x-ray also presumably containing water (referred to as form R), as well as an isopropyl acetate solvate of mirabegron containing a base (referred to as form S). No mention is made of the precise stoichiometry nor of how homogenous these compositions are.

Mirabegron monohydrochloride and its production are described international patent application publication number WO 2014132270.

Several forms of mirabegron synthesis are discussed in the publication entitled "Practical synthesis of Mirabegron" (*J. Chem. Pharm. Res.* **2015**, *7*, 1473-1478), none of the methods published in it provide yealds or advantages that could be realistically implemented on the industrial scale.

According to the method published in Chinese patent application number CN 104876890 (reaction scheme 3) the product obtained by the reaction of 4-nitro phenethyl amine and the

formula **10** racemic styrene oxide are resolved, then following hydrogenation the formula **2** key intermediate (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol is obtained. The disadvantage of the method is that only 20-25% of the desired product is produced in the primary amine and styrene oxide reaction, burdened by a large amount of contaminant.



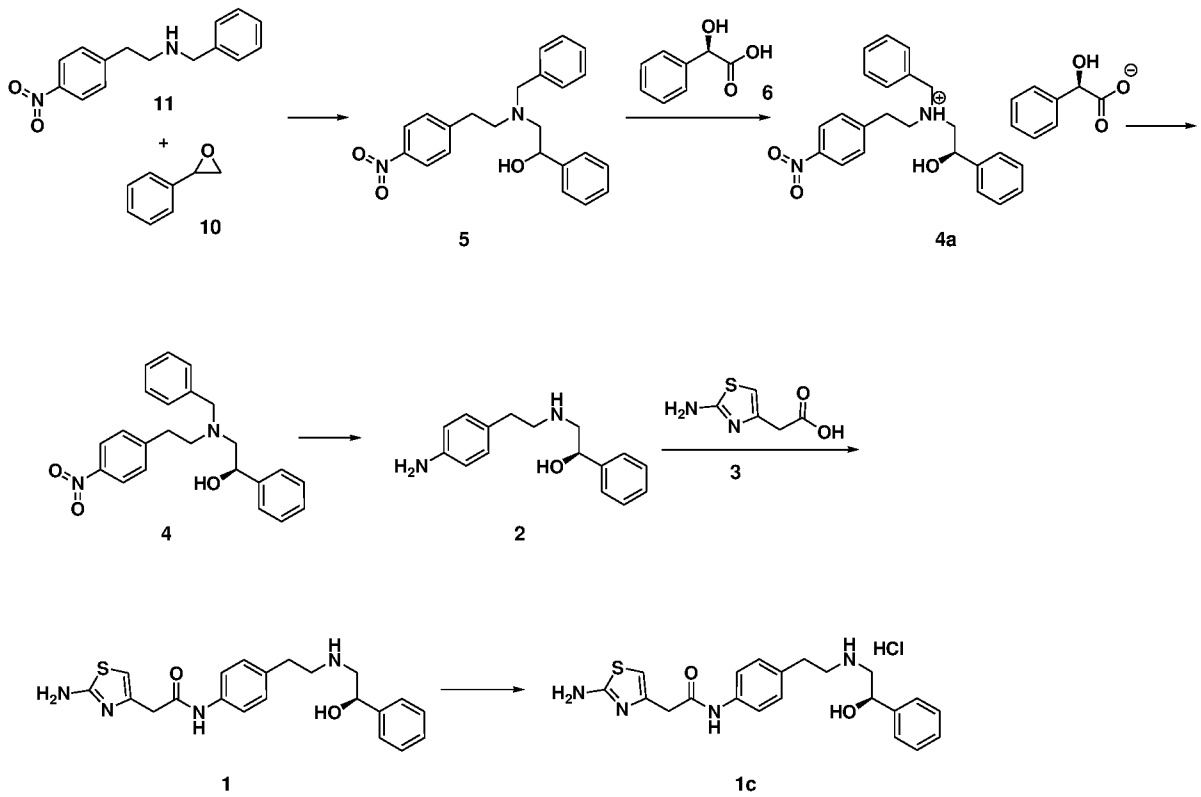
Reaction scheme 3

Brief summary of the invention

When elaborating the method according to the invention the objective was to elaborate a novel synthetic method for the production of formula **1** mirabegron that can be carried out in a way that is simpler and more economic than previous methods, that provides a better yield, uses easily accessible reagents, that is free of toxic auxiliary substances, that is implementable under normal reaction conditions, that progresses through crystalline and easily purified intermediates in the critical steps, that results in an easily separable final product and that can be implemented to advantage at industrial scales.

During the research work in connection with the invention it was surprising to find that if the synthesis series presented in the following reaction scheme 4 is implemented, in other words if formula **5** racemic 2-(benzyl(4-nitro phenethyl)amino)-1-phenylethanol is produced from formula

11 *N*-benzyl-4-nitro phenethyl-amine and formula **10** racemic styrene oxide then if this is resolved with formula **6** (*R*)-mandelic acid to produce the formula **4a** (*R*)-mandelic acid salt of formula **4** (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol, then by freeing the base from the **4a** salt the desired, optically active formula **4** compound is obtained, with the catalytic hydrogenation of which the formula **2** amino-ethanol is obtained, following this, by reacting the formula **2** amino-ethanol with the formula **3** 2-aminothiazolyl acetic acid, the formula **1** mirabegron is produced, then from this, optionally, the formula **1c** mirabegron hydrochloride is produced, then the set objective may be achieved.



Reaction scheme 4

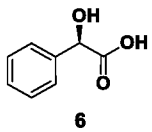
It is especially surprising that during the resolving process carried out at 40-50 °C with mandelic acid in the presence of ethyl acetate in a single crystallization step, without further purification a diastereomer salt is obtained where with great selectivity the salt precipitated contains 98.9% of

the desired enantiomer, in other words very great enantiomer purification takes place. This is not expected even in the light of that stated in the literature (see F. Faigl, E. Fogassy, M. Nógrádi, E. Pálovics, J. Schindler, *Tetrahedron: Asymmetry, 2008, 19, 519-536*).

The object of the invention relates to the production of formula **1** mirabegron. It is characteristic of the method that by reacting formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol in a solvent with mandelic acid, or by reacting the salt of the formula **5** compound with mandelic acid salt formula **4** (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is produced, then in one step the formula **4** compound is transformed into formula **2** (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol, then by reacting the formula **2** compound with formula **3** 2-aminothiazolyl acetic acid the formula **1** mirabegron base is produced.

In the case of a preferable embodiment of the method according to the invention the transformation of compound **4** into compound **2** is preferably performed with catalytic hydrogenation.

In the case of another preferable embodiment of the method according to the invention formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is reacted with formula **6** *(R)*-mandelic acid,



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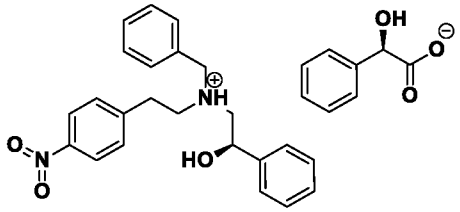
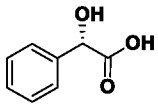
or the salt of the formula **5** compound is reacted with formula **6** *(R)*-mandelic acid salt, and from the crystalized formula **4a** (*R*)-mandelic acid salt



4a

the optically active formula **4** base is released in a known way.

In the case of a further preferable embodiment of the method according to the invention formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is reacted with formula **7** *(S)*-mandelic acid,



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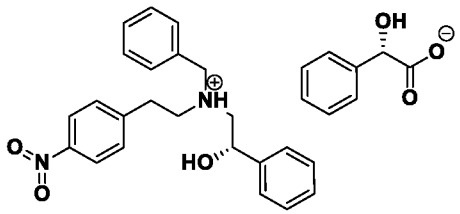
or a salt of the formula **5** compound is reacted with a salt of formula **7** *(S)*-mandelic acid, and after removing the crystalizing formula **8a** *(S)*-mandelic acid salt



8a

the desired formula **4** compound is extracted from the supernatant, which is purified if necessary.

In the case of a further preferable embodiment of the method according to the invention the salt of the formula **5** compound is hydrochloride, hydrobromide, sulphate or dihydrogen phosphate salt, or a salt formed with organic acids, including acetic acid, propionic acid, benzoic acid, preferably hydrochloride or acetate salt.

In the case of a further preferable embodiment of the method according to the invention the salt of the formula **6** or **7** mandelic acid is sodium, potassium or ammonium salt, preferably sodium salt.

In the case of a further preferable embodiment of the method according to the invention the solvent used for resolving is a straight or branched chain alcohol with C_1-C_6 carbon atoms, preferably an aliphatic alcohol with C_1-C_4 carbon atoms, esters of carboxylic acids with C_1-C_4 carbon atoms formed with alcohols with C_1-C_4 carbon atoms, acetonitrile, tetrahydrofuran, dioxane, toluene, t-butyl methyl ether, diisopropyl ether, water or any mixture of two or more of these.

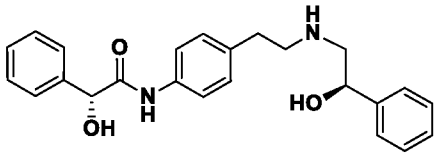
In the case of a further preferable embodiment of the method according to the invention the solvent used for resolving is acetonitrile, isopropyl acetate or ethyl acetate, preferably ethyl acetate.

In the case of a further preferable embodiment of the method according to the invention the temperature used during resolving is 40-50 °C, preferably 43-45 °C.

In the case of a further preferable embodiment of the method according to the invention during resolving the ratio of the formula **6** or **7** mandelic acid with respect to compound **5** is 0.1–1 mole-equivalent, preferably 0.5-1.0 mole-equivalent, most preferably 0.6-0.8 mole-equivalent.

In the case of a further preferable embodiment of the method according to the invention the temperature range used for the crystallization of the formula **4a** and **8a** salts is -50 °C – +120 °C, preferably - 20 °C – +60 °C.

The invention also relates to mirabegron produced with one of the above methods which contains a maximum of 0.15 mass%, preferably a maximum of 0.05 mass% of the formula **12**



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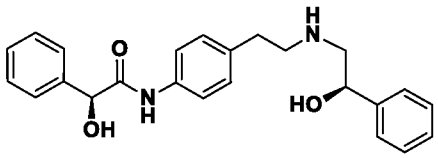
or formula **13**



13

contaminants.

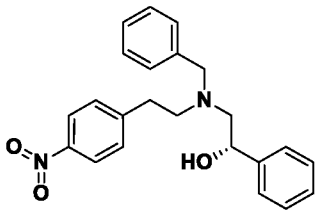
The invention also relates to the use of the formula **12** or **13** compounds as analytical comparison substances for the classification of the mirabegron active substance or preparation.

The invention also relates to formula **1** mirabegron which contains a maximum of 0.15 mass%, preferably a maximum of 0.05 mass% of the formula **12** or **13** contaminants.

The invention also relates to formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol.

The invention also relates to formula **4a** (*R*)-mandelic acid salt.

The invention also relates to formula **8** (*S*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol



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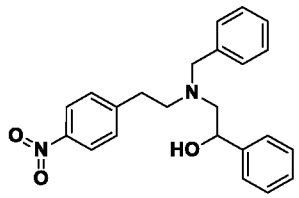
and to formula **8a** (*S*)-mandelic acid salt.

Detailed description of the invention

The process of our method was summarised in the above reaction scheme 4.

In the first step the key intermediate formula **5** racemic 2-(benzyl(4-nitro phenethyl)amino)-1-phenylethanol, a new compound not yet described in the literature,



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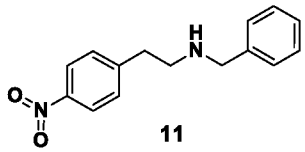
is produced from the known and readily available **11** *N*-benzyl-4-nitro phenethyl-amine



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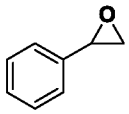
and the cheap and readily available **10** racemic styrene oxide



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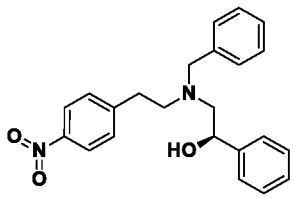
In the second step by resolving the formula **5** racemic compound the formula **4** (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is produced.



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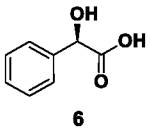
The resolving may be performed using optically active acids by forming a diastereomeric salt pair, in this method the resolving was preferably performed with formula 6 (*R*)-mandelic acid,



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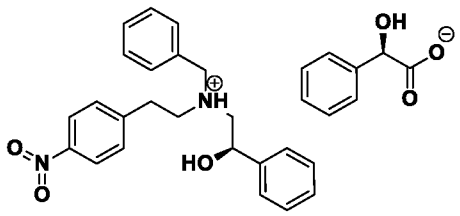
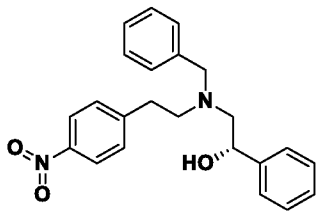
during which the formula **4a** (*R*)-mandelic acid salt of the desired formula **4** isomer



4a

precipitated in crystalline form from the system, with a good yield and with high optical purity, in other words with a low degree of formula **8** enantiomer contamination



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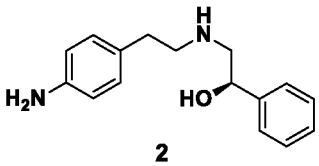
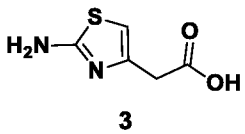
Then by freeing the base from the **4a** salt the desired optically active formula **4** compound was obtained.

In the third step of the method by the catalytic hydrogenation of the formula **4** compound the formula **2** (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol was obtained.



2

In the last step during the production of mirabegron the formula **2** compound was reacted with formula **3** 2-aminothiazolyl acetic acid.

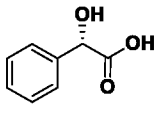


3

It is exceptionally important to use the purest possible chemical and optical form of the above formula **2** compound in the reaction, as the contaminants of the latter determine the purity of the

final product. In this method the formula **2** amino-ethanol is obtained with 99.7% or higher HPLC purity.

As an alternative to the above resolving step the method may also involve reacting the formula **5** compound with formula **7** (*S*)-mandelic acid,



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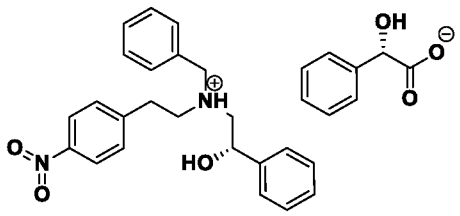
then after removing the formula **8a** diastereomeric salt



8a

the desired formula **4** compound is extracted from the mother liquor, which is purified if necessary.

The optical rotation of the above formula **8** compound is $[\alpha]_{D,25}$ = + 22.7 ° (c:1, ethanol).

The characteristics of the formula **8a** diastereomeric salt determined using structure testing methods are the following:

^{1}HNMR (a600, DMSO-d_6): 8.07 (d, J=8.7 Hz, 2H); 7.42 (~dd, 2H); 7.34 (~t, 2H); 7.33 (~d, 2H); 7.28 (m, 3H); 7.26 (~d, 2H); 7.23 (m, 1H); 7.22 (m, 2H); 7.20 (m, 1H); 7.16 (~dd, 2H); 5.01 (s, 1H); 4.68 (dd, J1=7.3 Hz, J2=5.6 Hz, 1H); 3.76 (d, J=13.9 Hz, 1H); 3.69 (d, J=13.9 Hz, 1H); 2.83 (~t, 2H); 2.74 (~t, 2H); 2.70 (dd, J1=13.2 Hz, J2=7.3 Hz, 1H); 2.65 (dd, J1=13.2 Hz, J2=5.6 Hz, 1H)

CNMR (a600, DMSO-d_6): 174.33; 149.48; 145.95; 144.88; 140.51; 139.32; 130.23; 128.87; 128.31; 128.18; 128.04; 127.81; 126.99; 126.93; 126.83; 126.40; 123.37; 72.59; 70.86; 61.88; 58.25; 55.09; 32.52

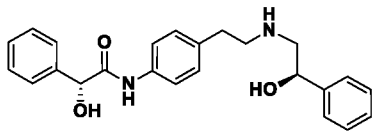
The method may also involve reacting a chosen salt of formula **6** or **7** mandelic acid with a salt of the formula **5** compound, then after removing any salt produced due to metathesis the formula **4a** or **8a** diastereomeric salt is crystalized. In this case the salt of formula **6** or **7** mandelic acid is any chosen alkali metal salt or ammonium salt, preferably sodium, potassium or ammonium salt, preferably sodium salt. The salt of the formula **5** compound is any chosen salt formed with a hydrogen halide, preferably hydrochloride or a salt formed with any univalent organic acid, preferably acetate, or a salt formed with a univalent or multivalent inorganic acid, preferably sulphate, dihydrogen phosphate.

Examples of univalent organic acids include acetic acid, propionic acid and benzoic acid. The salt of the formula **5** compound is preferably hydrochloride or acetate salt.

During the reaction of the formula **5** compound with both the formula **6** *(R)*-mandelic acid, and with the formula **7** (*S*)-mandelic acid the solvent used may be a straight or branched chain alcohol with C_1-C_6 carbon atoms, preferably an aliphatic alcohol with C_1-C_4 carbon atoms, esters of carboxylic acids with C_1-C_4 carbon atoms formed with alcohols with C_1-C_4 carbon atoms, acetonitrile, tetrahydrofuran, dioxane, toluene, t-butyl methyl ether, diisopropyl ether, water or any mixture of two or more of the above solvents. A preferably used solvent may be acetonitrile, isopropyl acetate and ethyl acetate, most preferably ethyl acetate.

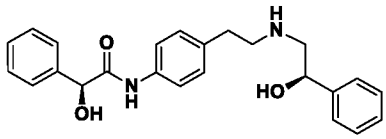
The ratio of the formula **6** or **7** mandelic acid used with respect to compound **5** is 0.1–1 mole-equivalent, preferably 0.5-1.0 mole-equivalent, most preferably 0.6-0.8 mole-equivalent. Optionally, in addition to formula **6** or **7** mandelic acid other achiral acids may also be used, in a 0-0.9 mole-equivalent amount, preferably in a 0-0.5 mole-equivalent amount, and most preferably in a 0.2-0.4 mole-equivalent amount. The latter achiral acids may be organic acids with a low number of carbon atoms, preferably formic acid, acetic acid, propionic acid, most preferably acetic acid. The temperature range used for the crystallization of the formula **4a** and **8a** salts is -50 °C – +120 °C, preferably - 20 °C – +100 °C, most preferably - 20 °C – +60 °C.

The formula **12**



12

and the formula **13** compounds



13

may appear in the mirabegron obtained according to the method as potential contaminants, the identification of these in the mirabegron is a task belonging to the knowledge of a person skilled in the art. The formula **12** and **13** compounds may be used as analytical standards.

During our experiments we found that when resolving with other chiral acids the enantiomer purification does not meet expectations, and the handling of the diastereomeric salt becomes difficult. In an unexpected way it was found that when crystalizing the diastereomeric mandelic acid salt with a suitable solvent, in an appropriate temperature range, a material that is easy to handle and that has high enantiomer purity was obtained.

During our method the formula **1c** monohydrochloride salt was produced in a known way using hydrochloric acid from the formula **1** mirabegron base, all the characteristic x-ray powder diffraction peaks of which (with relative intensity greater than 1%) measured with CuK_α x-rays can be found in the following Table 1. The most characteristic peaks of the formula 1c compound are the following: 2θ (±0.2° 2θ): 2.15; 4.33; 8.68; 17.66; 19.59; 21.57; 24.77; 25.47; and the even more characteristic peaks are the following: 2θ (±0.2° 2θ): 2.15; 19.59; 24.77; 25.47.

The characteristic x-ray powder diffractogram of formula **1c** mirabegron monohydrochloride can be seen in Figure 1, and the signals with 1% or higher intensity have been summarised in the following Table 1.

Table 1

The position and relative intensities of the x-ray diffraction peaks characteristic of formula **1c** mirabegron monohydrochloride (≥ 1%)

Peak	**2θ (°)**	**d (Å)**	**Relative intensity (%)**
1	2.15	41.09	17
2	4.33	20,40	5
3	6.51	13.58	4
4	8.68	10.19	11
5	13.04	6.79	1
6	17.11	5.18	7
7	17.66	5.02	28
8	18.06	4.91	4
9	18.37	4.83	1
10	18.72	4.74	4
11	19.59	4.53	89
12	20.32	4.37	13
13	21.57	4.12	16
14	23.02	3.86	3
15	24.04	3.70	3
16	24.77	3.59	100
17	25.47	3.50	31
18	26.53	3.36	5
19	27.39	3.26	11
20	28.52	3.13	1
21	29.05	3.07	6
22	30.31	2.95	5
23	31.69	2.82	3

Peak	2θ (°)	d (Å)	Relative intensity (%)
24	32.97	2.72	8
25	34.66	2.59	7

The x-ray powder diffraction data disclosed in the present application were obtained under the following measuring conditions:

Device: PANalytical Empyrean x-ray powder diffractometer

Measurement alignment: Transmission

X-ray tube

Type: Empyrean long fine focussing, high resolution tube

Anode: Cu

Wavelength: Kα (1,541874 Å)

Focus: line focus

Source-side optical elements

Divergence slit: Fixed slit 1/2 °

Mirror: Focussing elliptical mirror

Soller slit: 0.04 rad

Diffusion inhibitor slit: Fixed slit 1/2 °

Diffracted side optical elements

Diffusion inhibitor slit: Programmable slit in fixed mode: 1/2 °

Soller slit: 0.04 rad

Sample table

Type: Reflection-transmission, with rotatable sample holders

Sample rotation speed: 1 rotation/second

Direct beam catcher

("beam knife"): Transmission

Detector

Type:	PIXcel 3D 1×1 area detector
Operation mode:	Scanning line detector (1D) operation mode
Active detector window size:	3.3473°
Sample preparation:	samples placed between two Mylar sheets, without pulverisation

Measurement conditions

Temperature:	room temperature
Accelerating voltage:	45 kV
Anode heating current:	40 mA
Scanning method:	continuous (θ/θ) scanning
Measurement range:	2.0000 – 34.9964° 2θ
Step width:	0.0131° 2θ
Step duration:	109.650 seconds
No of measurement cycles:	1
Measurement duration:	~20 minutes

The characteristic DSC curve of formula **1c** mirabegron monohydrochloride can be seen in Figure 2.

The conditions of the differential scanning calorimetry (DSC) measurement were the following:

Device:	TA Instruments Discovery DSC differential scanning calorimeter
Atmosphere:	flowing N_2 (50 mL/minute)

Sampling frequency:	0.1 seconds/point	
Temperature program:	30 °C – 235 °C	10 °C/minute
Cell:	Hermetically sealed Al	

The advantage of the method according to the invention is that by using simple crystallization steps, without the use of toxic solvents, reagents, auxiliary substances, the desired product is obtained in an environmentally friendly, effective and economic way that may be easily implemented at industrial scales.

The advantage of the resolving method according to the invention is that under the conditions used a product is obtained with good yield that has exceptionally high chemical and optical purity in one crystallization step, due to which the final product mirabegron, and the mirabegron monohydrochloride salt is also pure.

The further details of the solution according to the invention are presented in the following examples without restricting the scope of protection of the invention in any way to these examples.

Example 1

The production of formula 5 2-(benzyl(4-nitro phenethyl)amino)-1-phenylethanol

10.24 g (40 mmol) of formula **11** *N*-benzyl-4-nitro phenethyl-amine is dissolved in 120 ml of butanol, 6.24 g (52 mmol) of formula **10** racemic styrene oxide is added, then the mixture is mixed at reflux temperature until the initial compound **11** is used up. The reaction mixture is cooled, mixed at a temperature of 4-5 °C, the precipitated substance is filtered and then washed twice on the filter with butanol. 8.14 g (21.6 mmol; 54 %) of crystalline material is obtained. Mp.: 60-62 °C.

^{1}H-NMR (DMSO-d_6; 600 MHz): 8.07 (d, J=8.6 Hz, 2H); 7.33 (d, J=8.6 Hz, 2H); 7.28 (~t, 2H); 7.25 (~d, 2H); 7.23 (~t, 1H); 7.21 (~t, 2H); 7.19 (m, 1H); 7.16 (~dd, 2H); 5.00 (br d, J=3.1 Hz, 1H); 4.68 (m, 1H); 3.75 (d, J=13.8 Hz, 1H); 3.68 (d, J=13.8 Hz, 1H); 2.82 (~t, 2H); 2.73 (~t, 2H); 2.69 (dd, J_1=13.2 Hz, J_2=7.3 Hz, 1H); 2.64 (dd, J_1=13.2 Hz, J_2=5.6 Hz, 1H).

Example 2

The production of formula 4a (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol (*R*)-mandelate

21.3 g (0.14 mol) of formula **6** (*R*)-(-)-mandelic acid, then 3.72 g (0.062 mol) of 99% acetic acid is added to a solution of 75.2 g (0.20 mol) of formula **5** 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol with 310 ml of ethyl acetate at 45℃. The mixture obtained is mixed for 1 hour, then the suspension is cooled down to 0℃ and then mixed for a further 3 hours. The crystalline material is filtered out and then washed with a cold ethyl acetate–DIPE (1:1) mixture. After drying 48.3 g (0.091 mol; 91% calculating using half of the initial racemate) of the white crystalline title material is obtained. (*S*)-isomer: 1.1 %.

IR (KBr): 3426; 3062; 1598; 1518; 1494; 1453; 1392; 1348; 1317; 1185; 1085; 1061; 746; 735; 698

^{1}HNMR (a600, DMSO-d_6): 8.07 (d, J=8.6 Hz, 2H); 7.42 (~dd, 2H); 7.34 (~t, 2H); 7.34 (~d, 2H); 7.29 (m, 3H); 7.26 (~d, 2H); 7.23 (m, 1H); 7.22 (m, 2H); 7.20 (m, 1H); 7.17 (~dd, 2H); 5.01 (s, 1H); 4.68 (~t, 1H); 3.76 (d, J=13.8 Hz, 1H); 3.69 (d, J=13.8 Hz, 1H); 2.83 (~t, 2H); 2.74 (~t, 2H); 2.70 (dd, J1=13.2 Hz, J2=7.4 Hz, 1H); 2.65 (dd, J1=13.2 Hz, J2=5.5 Hz, 1H)

CNMR (a600, DMSO-d_6): 174.33; 149.48; 145.95; 144.87; 140.51; 139.31; 130.23; 128.88; 128.32; 128.19; 128.04; 127.81; 126.99; 126.93; 126.84; 126.40; 123.37; 72.60; 70.86; 61.88; 58.26; 55.09; 32.52

Example 3

The production of formula 4 (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol

15.9 g (30.0 mmol) of the formula **4a** diastereomeric salt obtained in example 2 is suspended in 150 ml of ethyl acetate, then mixed with 50 ml of an aqueous solution of NaOH, then after the phases have separated, the organic phase is washed, dried, then finally evaporated. 11.4 g of light beige material is obtained.

Example 4

The production of formula 2 (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol

28.2 g (75 mmol) of formula **4a** (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is suspended in 280 ml of methanol, then 1.13 g of 10% palladium-on-carbon is added, then hydrogenated at room temperature. The catalyst is filtered out, and the methanolic solvent is evaporated. Methanol and diisopropyl ether are added to the residue. The suspension is mixed for 1 hour at an internal temperature of 50 °C, then cooled to room temperature. The substance is filtered out and washed with diisopropyl ether. After drying 16.77 g of formula **2** white crystalline material is obtained. Mp.: 101-103 °C. This is suspended in water, then mixed for 3 hours after adding triethylamine. The material is filtered out and washed with water. After drying 16.14 g (63 mmol, 84%) of white crystalline material according to the title is obtained. Mp.: 102-103 °C.

Example 5

The production of formula 1c (*R*)-2-(2-aminothiazole-4-yl)-4'-[2-[(2-hydroxy-2-phenyl)ethylamino]ethyl] acetanilide monohydrochloride (mirabegron monohydrochloride)

15.0 g (37.8 mmol) of mirabegron base (**1**) obtained in a known way (EP 1440969) from the material **2** obtained in example 4 is heated to a temperature of 75 °C in 210 ml of 2-propanol, then 6.80 ml (37.5 mmol) of a 5.52 molar HCl/2-propanol solution is added. After mixing for 15 minutes the crystalline mixture obtained is cooled to room temperature, the precipitate is filtered. After drying 16.15 g (37.3 mmol; 99 %) title material is obtained. Mp. 221-223 °C. (Figures 1 and 2)

Element analysis

Calculated: C 58.26%, H 5.82%, N 12.94%, S 7.40%, Cl 8.19%.

Measured: C 58.11%, H 5.78%, N 12.86%, S 7.41%, Cl 8.20%.

Example 6

The production of the contaminant formula 12 (2*R*)-hydroxy-2-phenylacetyl-4'-[2-[(2*R*)-hydroxy-2-phenyl)ethylamino]ethyl]acetanilide

0.77 g (3 mmol) of (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol (**2**) is suspended in 9 ml of water, then 1.5 ml of 2.02 M hydrochloric acid and 0.46 g (3 mmol) of (*R*)-mandelic acid (**6**) are added while mixing. After a short mixing 0.63 g of EDC hydrochloride is added and then the mixture is stirred at room temperature. The precipitated hydrochloride of the title material is filtered, washed with water, then after drying it is recrystallized from hydrous ethanol.

^{1}H-NMR (DMSO-d_6; 600 MHz): 10.02 (s, 1H); 8.99 (br, 2H); 7.66 (d, J=8.6 Hz, 2H); 7.51 (~d, 2H); 7.39 (m, 4H); 7.35 (~t, 2H); 7.31 (m, 1H); 7.28 (~t, 1H); 7.17 (d, J=8.6 Hz, 2H); 6.45 (d, J=4.9 Hz, 1H); 6.21 (br d, J=4.1 Hz, 1H); 5.11 (d, J=4.9 Hz, 1H); 4.97 (m, 1H); 3.15 (m, 1H); 3.14 (m, 2H); 3.01 (dd, J_1=12.5 Hz, J_2=10.6 Hz, 1H); 2.94 (m, 2H).

Example 7

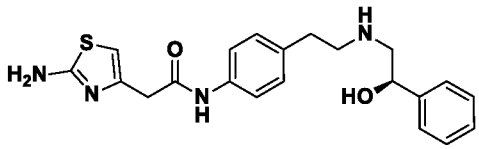
The production of the contaminant formula 13 (2*S*)-hydroxy-2-phenylacetyl-4'-[2-[(2*R*)-hydroxy-2-phenyl)ethylamino]ethyl]acetanilide

0.77 g (3 mmol) of (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol (**2**) is suspended in 9 ml of water, then 1.5 ml of 2.02 M hydrochloric acid and 0.46 g (3 mmol) of (*S*)-mandelic acid (**7**) are added while mixing. After a short mixing 0.63 g of EDC hydrochloride is added and then the mixture is stirred at room temperature. The precipitated hydrochloride of the title material is filtered, washed with water, then after drying it is recrystallized from hydrous ethanol.

^{1}H-NMR (DMSO-d_6; 600 MHz): 10.01 (s, 1H); 8.99 (br, 2H); 7.66 (d, J=8.5 Hz, 2H); 7.51 (~d, 2H); 7.38 (m, 4H); 7.35 (~t, 2H); 7.31 (m, 1H); 7.28 (~t, 1H); 7.17 (d, J=8.5 Hz, 2H); 6.45 (d, J=4.7 Hz, 1H); 6.19 (br, 1H); 5.11 (d, J=4.7 Hz, 1H); 4.96 (m, 1H); 3.13 (m, 3H); 3.00 (m, 1H); 2.93 (m, 2H).

Claims

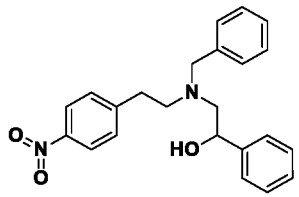
1. Method for the production of formula **1** mirabegron,



1

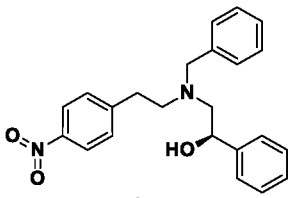
characterised by that

by reacting formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol



5

in a solvent with mandelic acid, or by reacting the salt of the formula **5** compound with mandelic acid salt formula **4** (*R*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is produced



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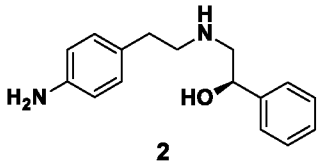
,

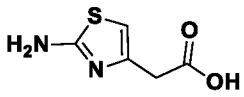
then in one step the formula **4** compound is transformed into formula **2** (*R*)-2-(4-amino phenethyl)amino-1-phenylethanol



2 ,

then by reacting the formula **2** compound

with formula **3** 2-aminothiazolyl acetic acid

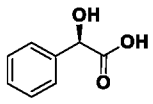


3

the formula **1** mirabegron base is produced.

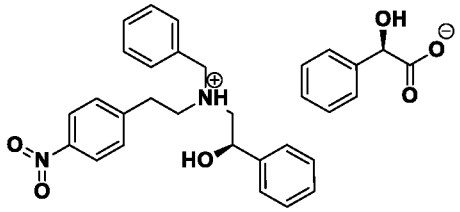
2. The method according to claim 1, characterised by that the transformation of compound **4** into compound **2** is preferably performed with catalytic hydrogenation.

3. The method according to claim 1 or 2, characterised by that formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is reacted with formula **6** *(R)*-mandelic acid



6

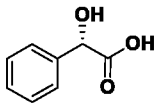
or the salt of the formula **5** compound is reacted with formula **6** *(R)*-mandelic acid salt, and from the crystalized formula **4a** (*R*)-mandelic acid salt



4a

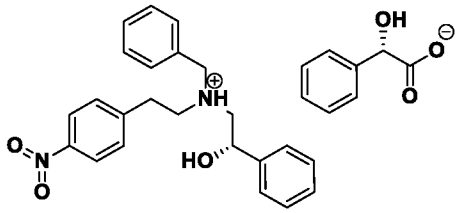
the optically active formula **4** base is released in a known way.

4. The method according to claim 1 or 2, characterised by that formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol is reacted with formula **7** *(S)*-mandelic acid



7

or a salt of the formula **5** compound is reacted with a salt of formula **7** *(S)*-mandelic acid, and after removing the crystalizing formula **8a** *(S)*-mandelic acid salt



8a

the desired formula **4** compound is obtained from the mother liquor, which is purified if necessary.

5. The method according to any of claims 1 to 4, characterised by that the salt of the formula **5** compound is hydrochloride, hydrobromide, sulphate, dihydrogen phosphate salt, or a salt formed with organic acids, including acetic acid, propionic acid, benzoic acid, preferably hydrochloride or acetate salt.

6. The method according to any of claims 1 to 5, characterised by that the salt of the formula **6** or **7** mandelic acid is sodium, potassium or ammonium salt, preferably sodium salt..

7. The method according to any of claims 1 to 6, characterised by that the solvent used for resolving is a straight or branched chain alcohol with C_1-C_6 carbon atoms, preferably an aliphatic alcohol with C_1-C_4 carbon atoms, esters of carboxylic acids with C_1-C_4 carbon atoms formed with alcohols with C_1-C_4 carbon atoms, acetonitrile, tetrahydrofuran, dioxane, toluene, t-butyl methyl ether, diisopropyl ether, water or any mixture of two or more of these.

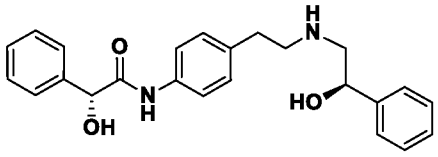
8. The method according to any of claims 1 to 6, characterised by that the solvent used for resolving is acetonitrile, isopropyl acetate or ethyl acetate, preferably ethyl acetate.

9. The method according to any of claims 1 to 8, characterised by that the temperature used during resolving is 40-50 °C, preferably 43-45 °C.

10. The method according to any of claims 1 to 9, characterised by that during resolving the ratio of the formula **6** or **7** mandelic acid with respect to compound **5** is 0.1–1 mole-equivalent, preferably 0.5-1.0 mole-equivalent, most preferably 0.6-0.8 mole-equivalent.

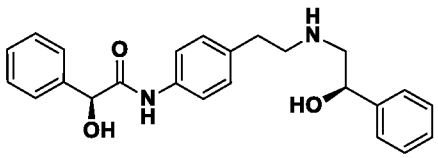
11. The method according to any of claims 1 to 10, characterised by that the temperature range used for the crystallization of the formula **4a** and **8a** salts is -50 °C – +120 °C, preferably - 20 °C – +60 °C.

12. Mirabegron produced with any of the methods according to claims 1 to 11, which contains a maximum of 0.15 mass%, preferably a maximum of 0.05 mass% of the formula **12**



12

or formula **13**



13

contaminants.

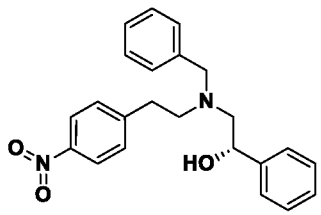
13. The use of the formula **12** or **13** compounds as analytical comparison substances for the classification of the mirabegron active substance or preparation.

14. The formula **1** mirabegron which contains a maximum of 0.15 mass%, preferably a maximum of 0.05 mass% of the formula **12** or **13** contaminants.

15. The formula **5** racemic 2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol.

16. The formula **4a** (*R*)-mandelic acid salt.

17. The formula **8** (*S*)-2-[benzyl(4-nitro phenethyl)amino]-1-phenylethanol



8

and formula **8a** (*S*)-mandelic acid salt.

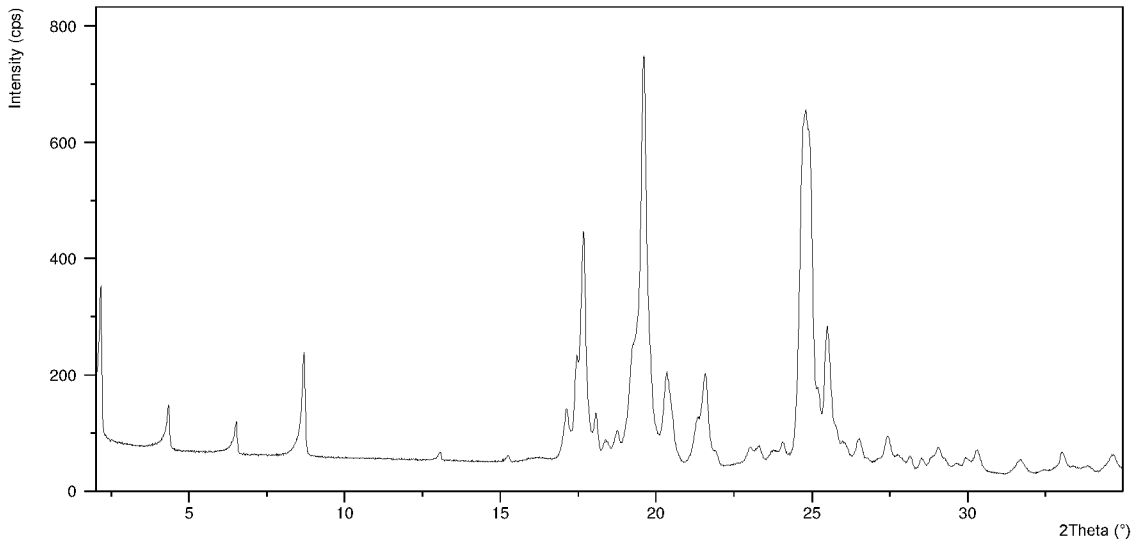


Figure 1

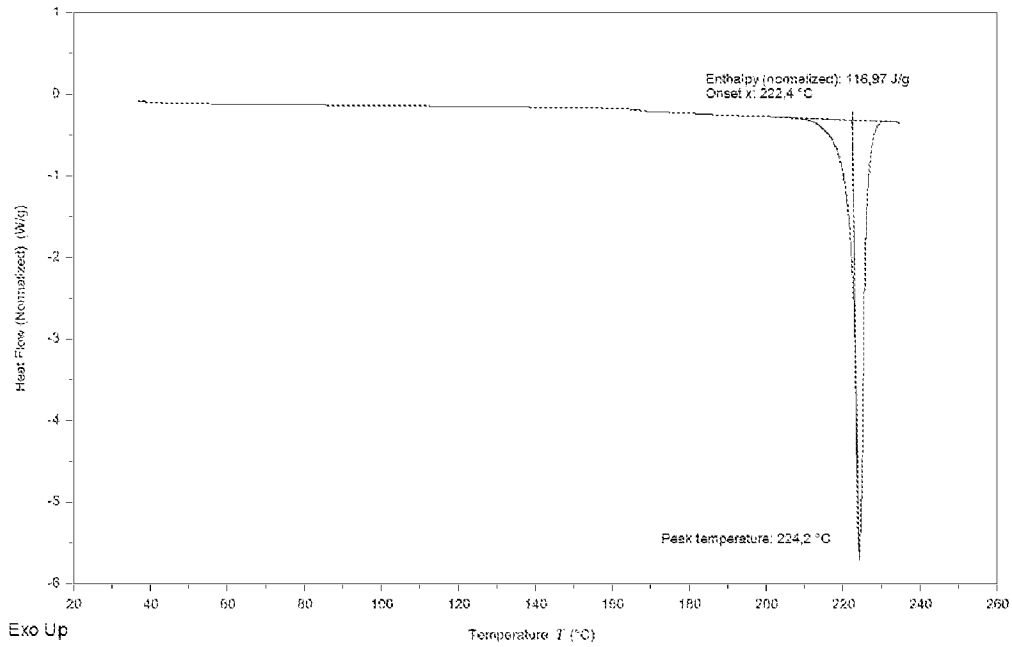


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2016/050045

A. CLASSIFICATION OF SUBJECT MATTER
C07D277/40 (2015.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic databases consulted during the international search (name of database and, where practicable, search terms used)
Epodoc, WPI, Registry, Caplus, X-Full

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim no.
	CN 104876890 A (Humanwell Healthcare Co., Ltd) (02.09.2015)	
X	fig. on p. 5; examples 1-20	12, 14
Y	fig. on p. 5; examples 1-20	1-11, 13, 15-17
Y	CN 103387500 A (Shanghai Institute of Pharmaceutical Industry) (13.11.2013) examples	1-11, 13, 15-17
Y	GB 1544872 A (Sterling Drug Inc) (25.04.1979) example 21	1-11, 13, 15-17
Y	WO 2014/132270 A2 (MSN Laboratories Ltd.) (04.09.2014) p. 14-15, figs, examples 8-9	1-11, 13, 15-17
A	WO 99/20607 A1 (Yamanouchi Pharma Co Ltd) (29.04.1999) the whole document	1-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25/01/2017	30/01/2017
Name and mailing address of the ISA/ Visegrad Patent Institute/Branch Office HU H-1081 Budapest, II. János Pál pápa tér 7., Hungary Facsimile No.	Authorized officer Attila Koncz Telephone No. +36-1-4745981

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2016/050045

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Invention 1 (claims 1-14, 16): process for the preparation of mirabegron (compound **1**) *consisting of* the following steps:

a) preparation of compounds **4/4a** (*R*-) from racemic compound **5** via resolution [separation from compound **8** (*S*-)] *then*
b) preparation of compound **2** from compounds **4/4a** (*R*-) through reduction and debenzylation *then*
c) preparation of mirabegron (**1**) from compounds **2** and **3**.

Invention 2 (claims 15, 17): compounds **5**, **4a** and **8/8a** (*S*-).

For reasons see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Unity (Continuation of Box III.)

Unity of invention is present in the context of intermediate (the term "intermediate" means intermediate or starting compound) and final products where the conditions (A) **and** (B) are fulfilled:

(A) the intermediate and final products have the same **essential** structural element, in that:
- the *basic chemical structures* of the intermediate and the final products are the same,
OR
- the chemical structures of the 2 products are technically closely interrelated, the intermediate incorporating an **essential** structural element into the final product,

AND

(B) the intermediate and final products are *technically* interrelated, this meaning that the final product
- is manufactured *directly* from the intermediate
OR
- is separated from it by a small number of intermediates all containing the same **essential** structural element.

Mirabegron was first described in **WO 99/20607 (D5)** encompassed by formula (I) as β_3 adrenergic receptor activators which can be used as antidiabetics. In the compounds of formula (I) of **D5** the essential structural element is -NH-CO-X-(B) corresponding to a derivative of compound **3** of the present application. However, this group is missing from intermediates **5**, **4a** and **8/8a** (*S*-).
Therefore, the *basic chemical structures* of the intermediate (i.e. compounds **5**, **4a**, **8/8a** (*S*-)) and the final product (compound **1**) are not the same. Further, mirabegron is *not directly* manufactured from these intermediates.

Consequently, unity does not exist between *Inventions 1-2*.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU2016/050045

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