(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 3487835 B1**

(19) NO

NORGE

(51) Int Cl.

C07C 227/34 (2006.01)
C07C 229/34 (2006.01)

Patentstyret

(45)	Oversettelse publisert	2020.08.03
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2020.04.08
(86)	Europeisk søknadsnr	17754393.1
(86)	Europeisk innleveringsdag	2017.07.20
(87)	Den europeiske søknadens Publiseringsdato	2019.05.29
(30)	Prioritet	2016.07.22, FR, 1657054
(84)	Utpekte stater	AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR
(73)	Innehaver	Université de Rouen, 1, rue Thomas Becket, 76130 Mont-Saint-Aignan, Frankrike
(72)	Oppfinner	COQUEREL, Gérard, 158 route de Maromme, 76130 Mont Saint Aignan, Frankrike MAHIEUX, Julien, Grand'Route 2, 1612 Ecoteaux, Sveits GENDRON, François-Xavier, 30 bis Allée des Tisserands, 76190 Autretot, Frankrike
(74)	Fullmektig	BRYN AARFLOT AS, Stortingsgata 8, 0161 OSLO, Norge

(54) Benevnelse **METHOD FOR THE RESOLUTION OF BACLOFEN SALTS**

(56) Anførte publikasjoner

WO-A1-2011/073300
US-A- 6 022 409
WO-A1-97/22579
MAZZENGA G C ET AL: "The transdermal delivery of zwitterionic drugs I: the solubility of zwitterion salts", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 16, no. 1-2, 1 juin 1991 (1991-06-01) , pages 77-88, XP025567249, ISSN: 0168-3659, DOI: 10.1016/0168-3659(91)90032-9 [extrait le 1991-06-01]

Vedlagt foreligger en oversettelse av patentkravene til norsk. I hht patentloven § 66i gjelder patentvernet i Norge bare så langt som det er samsvar mellom oversettelsen og teksten på behandlingsspråket. I saker om gyldighet av patentet skal kun teksten på behandlingsspråket legges til grunn for avgjørelsen. Patentdokument utgitt av EPO er tilgjengelig via Espacenet (http://worldwide.espacenet.com), eller via søkemotoren på vår hjemmeside her: https://search.patentstyret.no/

METHOD FOR THE RESOLUTION OF BACLOFEN SALTS

TECHNICAL FIELD

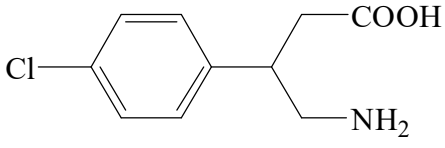
The present invention relates to the field of resolving chiral compounds existing in the form of two optical antipodes (enantiomers), such as baclofen. “The transdermal delivery of zwitterionic drugs I: the solubility of zwitterion salts”, JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 16, no. 1-2, (1991-06-01), pages 77-88, discloses the maleate salt of racemic baclofen.

More particularly, the invention relates to the preparation of the pure (R)(-)-baclofen and S(+)-baclofen enantiomers, the chemical name of which is (R)-4-amino-3-(4-chlorophenyl)butanoic acid and (S)-4-amino-3-(4-chlorophenyl)butanoic acid and the hydrogen maleate salt thereof.

Most especially, the present invention relates to the resolution of the hydrogen maleate salts of racemic baclofen by preferential crystallization and especially via the AS3PC (auto-seeded programmed polythermic preferential crystallization) process or the ASPreCISE (auto-seeded preferential crystallization induced by solvent evaporation) process.

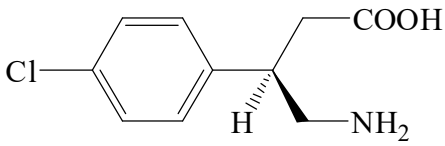
BACKGROUND OF THE INVENTION

Racemic baclofen is represented by the general formula (I) below:



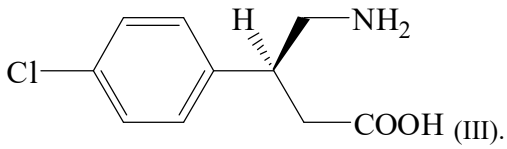
(I).

The pure (R)(-)-baclofen enantiomer is represented by the general formula (II) below:



(II).

The pure (S)(-)-baclofen enantiomer is represented by the general formula (III) below:



(III).

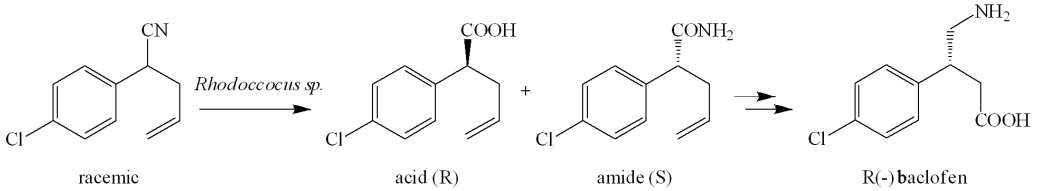
Baclofen, also known under the name Lioresal, is a medicament used as a muscle relaxant for treating the painful cramps accompanying multiple sclerosis and certain paralyses.

In France, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) [National Agency for the Safety of Drugs and Health Products] recently granted a temporary recommendation for use of baclofen for the treatment of alcohol dependency.

In its current therapeutic use, this molecule is administered in the form of a racemic mixture. Since the R(-) enantiomer is three times more active than the S(+) enantiomer, it appears advantageous, especially for long treatments, to prescribe only the more active R(-) absolute configuration. As such, there will be fewer side products in the body and the dosage can be reduced while maintaining the benefit of the activity.

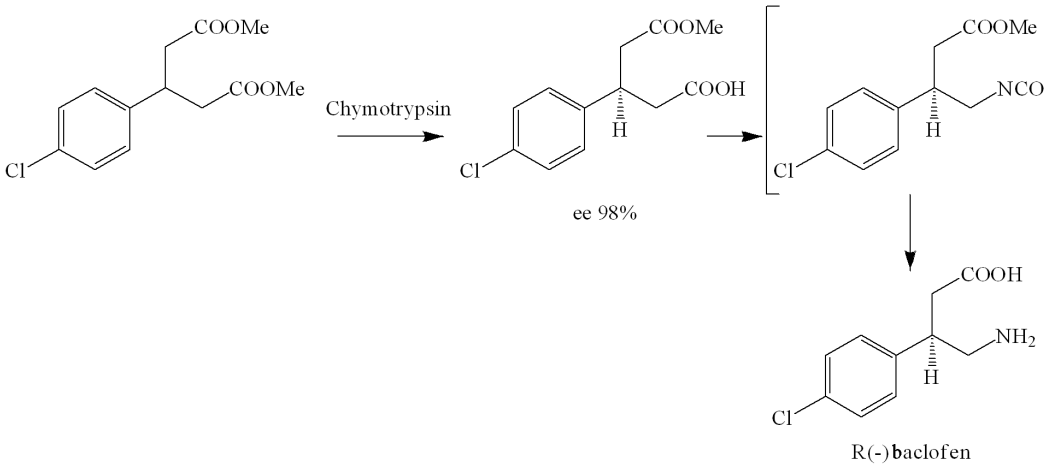
To produce the R(-) form, the methods described in the literature involve either an asymmetric synthesis starting with a racemic mixture or a prochiral compound with catalysts, or an enantioselective synthesis starting with a chiral reagent.

For example, it is possible to use enzymatic catalysts, such as bacteria of the *Rhodococcus sp.* type, as described in M.X. Wang, S.M. Zhao, Tetrahedron Lett. 2002, 43, 6617-6620, to access R(-)-baclofen according to the following scheme:

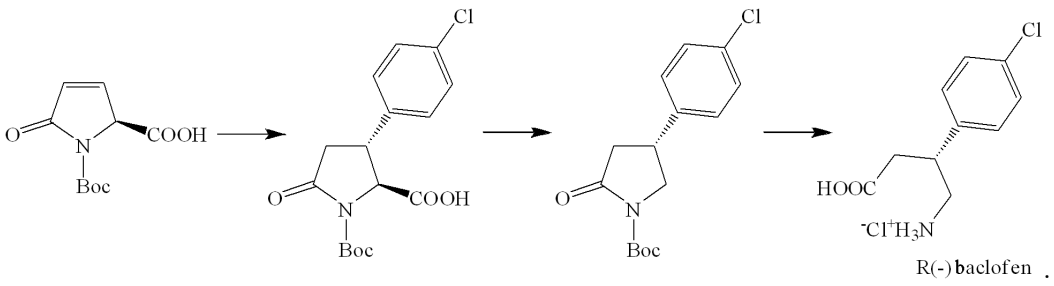


.

The article *Canadian Journal of Chemistry*, **1994**, 72(11), 2312-2317 also discloses a route for the asymmetric synthesis of R(-)-baclofen involving desymmetrization of a prochiral glutarate with chymotrypsin according to the following scheme:



Finally, patent application WO 94/02443 describes an enantioselective synthesis of R(-)-baclofen starting with an S-pyroglutamic acid derivative according to the following scheme:



However, these methods involve reagents that are expensive and difficult to implement industrially. Furthermore, the final yield of R(-)-baclofen is relatively low. In addition, due to the number of synthetic steps, the final product is contaminated with impurities that must be removed via purification steps so as to obtain a product that is pure enough to be administered as a medicament.

In this context, the inventors developed a process for separating the baclofen enantiomers starting with a racemic mixture. This process is advantageously industrially implementable and does not require the use of chiral derivatives. Furthermore, the steps of the process of the present invention are easy to perform and there is no loss of starting material by virtue of the successive recyclings.

This aim is achieved by means of the application of the process of preferential

crystallization to racemic baclofen in salt form. Thus, the invention relates most particularly to the application, to a racemic baclofen hydrogen maleate salt, of resolution via preferential crystallization of each of its enantiomers, making it possible to obtain the R(-)-baclofen eutomer in an enantiomerically and chemically pure form.

The racemic baclofen hydrogen maleate salt may be resolved via any type of preferential crystallization, especially the most advantageous, i.e. auto-seeded processes.

In particular, the AS3PC preferential crystallization process has been the subject of an entirely novel development excluding the constraining use of crystallization seeds (i.e. without seeding). This process is described, for example, in the following patents and patent applications: FR 2 710 337, WO 95/08522, EP 0 720 595 and US 6 022 409 and in G. Coquerel, *Preferential Crystallization* in *Topics in Current Chemistry, Novel Optical Resolution Technologies, Springer, Berlin, Heidelberg, Eds. K. Sakai, N. Hirayama and R. Tamura*, 2007, *269*, 1-51. This process is named AS3PC, meaning Auto-Seeded Programmed Polythermic Preferential Crystallization.

Another auto-seeded preferential crystallization process is described in patent application WO 2011/07330. This process is known by the abbreviation ASPreCISE meaning Auto-Seeded PREferential Crystallization Induced by Solvent Evaporation.

Preferential crystallization processes are based on the alternating stereoselective crystallization of the two (R) and (S) enantiomers, of the same racemic chemical species crystallizing in conglomerate form, in a medium which may be a solvent or a mixture of solvents or a set of constituents including the solvent(s), and for a given temperature range ΔT. Within this temperature range, this racemic mixture, which is in thermodynamic equilibrium with its saturated solution, is constituted of two types of crystals each containing only molecules of the same absolute configuration.

Knowledge of these (R)-enantiomer - (S)-enantiomer - solvent heterogeneous equilibria provides data that are exploited for performing efficient resolution by preferential crystallization.

The studies conducted by the Applicant show that racemic baclofen does not crystallize in the form of a conglomerate. This means that neither the preferential crystallization process

AS3PC or ASPreCISE nor any other preferential crystallization process can be applied.

In the perspective of implementing such a process, the search for a baclofen salt allowing chiral discrimination was performed by addition of a coformer, such as an acid, a base or an alkali metal. The full list of the various coformers tested is presented in Table 1 below:

5

Coformers: acids, bases or alkali metals (the compounds in **bold** are those for which a new phase is observed, the new phase being a co-crystal comprising baclofen and the coformer)		
4-nitrobenzoic acid	cholic acid	adipic acid
3,4-dichlorobenzoic acid	3-bromo-4-nitrobenzoic acid	4-hydroxybenzenesulfonic acid
4-fluoro-3-nitrobenzoic acid	3-fluoro-4-nitrobenzoic acid	dichloroacetic acid
2-chloro-4-nitrobenzoic acid	2,5-dinitrobenzoic acid	tetrafluoroboric acid
2,4-dihydroxybenzoic acid	3-methoxy-4-nitrobenzoic acid	trifluoromethanesulfonic acid
4-hydroxybenzoic acid	2-chloro-3,5-dinitrobenzoic acid	acetic acid
4-chloro-3,5-dinitrobenzoic acid	2-methyl-3,5-dinitrobenzoic acid	2,4-diaminobenzenesulfonic acid
3,5-dinitro-4-toluic acid	3,5-dinitrosalicylic acid	**methanesulfonic acid**
4-methyl-3-nitrobenzoic acid	3-bromo-5-nitrobenzoic acid	4-nitrobenzenesulfonic acid
3-nitro-5-(trifluoromethyl)benzoic acid	salicylic acid	**trichloroacetic acid**
3,4-dinitrobenzoic acid	hydrocinnamic acid	**benzenesulfonic acid**
citraconic acid	5-chloro-2-nitrobenzoic acid	3,5-diamino-2,4,6-trimethylbenzenesulfonic acid
3,5-dinitrobenzoic acid	2,5-dichlorobenzoic acid	**1,2-phenylenediacetic acid**
o-toluic acid	fumaric acid	2,5-diaminobenzenesulfonic acid
3-nitrobenzoic acid	2-phenylbutyric acid	bromoacetic acid
4-chloro-3-nitrobenzoic acid	2-tetrahydrofolic acid	ethanesulfonic acid
3-methyl-4-nitrobenzoic acid	*trans*-3,4-dimethoxycinnamic acid	methanesulfonic acid
oxalic acid	3-phenylbutyric acid	**methoxyacetic acid**
methylsulfamic acid	**4-chlorobenzenesulfonic acid**	hexamethylenetetramine
stearic acid	butylethylhydroxypropionic acid	diphenylamine
undecanedioic acid	*trans*-cinnamic acid	tetrahydrofurfurylamine
cis,cis-muconic acid	glutaric acid	tert-butylamine
2,4-diaminobenzenesulfonic acid	isophthalic acid	benzylamine
glycolic acid	itaconic acid	n-butylamine

pimelic acid	malonic acid	ethylenediamine
tetradecanedioic acid	n-butyric acid	N,N'-dibenzylethylenediamine
mucic acid	*p*-tolylacetic acid	ethanolamine
suberic acid	propionic acid	ammonia
sebacic acid	**1H-benzimidazole-2-sulfonic acid**	triethanolamine
dodecanedioic acid	1-naphthalenesulfonic acid	potassium hydroxide
uric acid	**3-pyridinesulfonic acid**	calcium hydroxide
succinic acid	chloroacetic acid	magnesium hydroxide
boric acid	**1-hydroxy-2-naphthoic acid**	aluminum hydroxide
p-toluenesulfonic acid monohydrate	1-propanesulfonic acid	strontium hydroxide
citric acid	iodoacetic acid	lithium hydroxide monohydrate
nitric acid	**hydrochloric acid**	sodium hydroxide
sulfuric acid	bromic acid	rubidium formate hydrate
phosphoric acid	hydriodic acid	trifluoroacetic acid
sulfamic acid	perchloric acid	pyrophosphoric acid

Table 1

However, entirely unexpectedly, the Applicant has found that baclofen forms with maleic acid a salt which crystallizes without formation of a solvate in the majority of the usual solvents and without formation of a eutectic mixture in molten medium. This saline derivative also has the advantage of being a pharmaceutically acceptable and inexpensive salt. Surprisingly, this salt shows virtually total chiral discrimination at room temperature but no chiral discrimination at high temperature. This property was used to resolve the racemic mixture with an optimum yield by repeated application of preferential crystallization. Furthermore, the resolution process may be performed in water using AS3PC auto-seeded resolution for greater ease of exploitation at the industrial scale.

DESCRIPTION OF THE INVENTION

One subject of the present invention is a racemic baclofen hydrogen maleate (Bahma) salt with a melting/decomposition point of 164±1°C.

Another subject of the invention is the use of the racemic baclofen hydrogen maleate salt for resolving the (S) and (R) enantiomers of baclofen.

A subject of the present invention is also a process for resolving the (S) and (R) enantiomers of baclofen, in which racemic baclofen is transformed into the racemic baclofen hydrogen maleate salt in the presence of maleic acid and in which said salt is resolved by preferential crystallization to separate the two (S) and (R) enantiomers.

A subject of the present invention is also a process for the enantiomeric purification of baclofen hydrogen maleate salts, comprising the recrystallization of baclofen hydrogen maleate salts in a solvent.

DETAILED DESCRIPTION

The racemic baclofen hydrogen maleate salt that is the subject of the present invention has a melting/decomposition point of 164±1°C. The melting/decomposition point is measured by differential scanning calorimetry (DSC) according to the method described below. The term “Bahma” used in the present patent application denotes “baclofen hydrogen maleate”.

The melting/decomposition point corresponds to the melting point of the Bahma salt which is followed or accompanied by decomposition of the Bahma salt. Specifically, the Bahma salt may undergo one or more decomposition reactions, for example the formation of maleic anhydride or the esterification of baclofen or another decomposition reaction.

Said salt corresponds to the formula $[C_{10}H_{13}ClNO_2]^+,[C_4H_3O_4]^-$. Thus, the amine function of baclofen is protonated and there is only one baclofen molecule and only one hydrogen maleate molecule in the asymmetric unit. The molar mass of the salt is 329.73 $g.mol^{-1}$.

Said salt may especially be obtained by dissolving a racemic mixture of baclofen and of maleic acid in stoichiometric proportions in a solvent or a mixture of solvents.

The salification reaction may especially be performed in a solvent chosen from acetone, water, methanol, a water/n-propanol azeotrope and mixtures thereof.

In order to ensure good crystallization, it is advantageous to dissolve the baclofen and the

maleic acid in the smallest possible volume of solvent. Furthermore, to achieve a homogeneous solution, the mixture may be heated.

After dissolution of the solids, the solution is allowed to return to room temperature and the crystals form by evaporation of the solvent within a few days.

The single crystals obtained have a characteristic facies with zones of total reflection, along the axis of longest development of the crystal, as shown in Figure 1.

The (R) and (S) salts of baclofen hydrogen maleate of the present invention exhibit a total solid solution at high temperature, especially at a temperature above 150°C. Specifically, the phase diagram of the two enantiomers of Figure 2 shows that there is a single one-phase domain, i.e. a total solid solution, above 150°C. Below this temperature, which corresponds exactly to the maximum critical demixing point in the solid state of the racemic mixture, there is chiral discrimination in the solid state, which becomes increasingly amplified as the temperature is lowered.

Unexpectedly, Figure 2 also shows that there is virtually total chiral discrimination at a temperature of less than or equal to 70°C. Thus, below 70°C, the one-phase domain is very low in composition, i.e. less than <1% of the other enantiomer, on each side of the binary phase diagram. This large demixing gap offers very substantial chiral discrimination in the solid state which may be exploited to perform resolution by preferential crystallization or preparative enantiomeric purification, i.e. without loss of enantiomeric excess.

This behavior was all the less anticipated since baclofen and maleic acid offer multiple possibilities for directed hydrogen bonds that are sparingly favorable to the formation of a solid solution. This very rare case of total solid solution with demixing in the solid state differs from the more conventional cases of conglomerates with partial solid solution, the phase diagram of which is represented in Figure 3.

It should be noted that many baclofen salts other than Bahma were studied (cf. Table 1 above). However, their binary phase diagrams, similar to that shown in Figure 4, do not present a total solid solution or chiral discrimination, which does not make it possible to envisage resolution

by preferential crystallization.

Thus, owing to its specific behavior, baclofen hydrogen maleate is, in principle, entirely suitable for use in resolving the (S) and (R) enantiomers of baclofen.

A subject of the invention is also a process for resolving the (S) and (R) enantiomers of baclofen, in which racemic baclofen is transformed into racemic baclofen hydrogen maleate salt in the presence of maleic acid. The racemic Bahma salt obtained is then resolved by preferential crystallization to separate the two (S) and (R) enantiomers.

Resolution of the racemic Bahma salt may especially be performed by auto-seeded preferential crystallization (AS3PC or ASPreCISE) or by seeded preferential crystallization, preferably by auto-seeded preferential crystallization.

According to a particular embodiment of the process of the present invention, the preferential crystallization is performed with a solvent chosen from an alcoholic solvent, an aqueous solution, an acidic aqueous solution and mixtures thereof.

Examples of alcoholic solvents that may be used are methanol, ethanol, n-propanol and mixtures thereof, in particular n-propanol.

According to a particular embodiment, the solvent is an azeotropic mixture of n-propanol and water.

According to a preferred embodiment, the preferential crystallization is performed with an acidic aqueous solution, the acid being chosen from hydrochloric acid, acetic acid, nitric acid, preferably an aqueous hydrochloric acid solution, more preferentially an aqueous 2 mol/L hydrochloric acid solution.

Indeed, the solubility of Bahma in an acidified aqueous solution is greater than that of Bahma in water or in an azeotropic mixture of n-propanol and water. This better solubility makes it possible to increase the productivity of the preferential crystallization.

According to a particular embodiment, the preferential crystallization is auto-seeded and comprises the following steps:

a) a volume V of a saturated solution of racemic Bahma salt in a solvent is prepared at

a temperature T_L;

b) at least 5% by weight of the first Bahma enantiomer to be recovered relative to the weight of the racemic Bahma salt is added;

c) the mixture is heated to a temperature $T_B = T_L + \Delta T$;

d) a cooling programming law is applied to the mixture from T_B to T_F, T_F being below T_B, such that the mixture maintains a low supersaturation which favors the growth of the first Bahma enantiomer present in the form of crystals, while prohibiting the spontaneous nucleation of the second Bahma enantiomer dissolved in the solution;

e) the crystals of the first Bahma enantiomer are harvested at the temperature T_F;

f) substantially the same mass of racemic Bahma salt as the mass of the harvest made in the preceding step is added to the mixture, the difference is made up with solvent to reach the volume V and the new combined mixture is brought to the temperature T_B;

g) the temperature T_B is maintained for a time t so as to allow the system to return to thermodynamic equilibrium;

h) the same cooling programming law as in step (d) is applied to the mixture prepared in step (g) containing the second Bahma enantiomer, so that the mixture maintains a low supersaturation during the crystallization so as to promote the growth of the second Bahma enantiomer present in the form of crystals while at the same time prohibiting the spontaneous nucleation of the first Bahma enantiomer present in the solution;

i) the crystals of the second Bahma enantiomer are harvested at the temperature T_F;

j) substantially the same mass of racemic Bahma salt as the mass of the harvest made in the preceding step is added to the mixture, the difference is made up with solvent to reach the volume V and the new combined mixture is brought to the temperature T_B;

k) the temperature T_B is maintained for a time t so as to allow the system to return to thermodynamic equilibrium;

l) steps (d) to (k) are repeated to successively obtain one and then the other of the two enantiomers.

In the above process, the solvent is as described previously, especially an azeotropic mixture of n-propanol and water or an acidic aqueous solution. The volume V of solvent used to obtain a saturated solution is determined as a function of the amount of racemic Bahma salt to be resolved and of the solubility of the racemic Bahma salt in the chosen solvent.

In step (b) of the above process, the amount of the first Bahma enantiomer added is at least 5% by weight relative to the weight of the racemic Bahma salt dissolved in the solvent, in particular from 5% to 15% by weight, more particularly from 5% to 10% by weight.

In step (c) of the above process, the temperature T_L corresponds to the temperature of dissolution of the racemic mixture alone in the solvent according to step (a). According to a particular embodiment, the temperature T_L ranges from 30 to 70°C; preferably, T_L ranges from 40 to 60°C and more preferentially T_L is 50°C.

In step (c) of the above process, the temperature T_B corresponds to a temperature slightly above the dissolution temperature of the racemic mixture T_L. Thus, the temperature $T_B = T_L + \Delta T$ in which ΔT ranges from 1°C to 10°C, in particular from 2°C to 7°C, more particularly from 3°C to 5°C.

Advantageously, in steps (d) and (h) of the above process, a stirring speed that increases slightly as a function of time is adapted throughout the duration of the crystal growth so that it is slow enough to favor growth of the first or the second Bahma enantiomer, while avoiding the generation of uncontrolled nucleation and attrition of crystals.

In the above process, the temperature T_F depends on the amount of racemic Bahma salt that it is desired to resolve. According to a particular embodiment, the temperature T_F ranges from 20 to 40°C; preferably, T_F ranges from 25 to 35°C; more preferentially, T_F is 30°C.

In the above process, the time t depends on the amount of racemic Bahma salt that it is desired to resolve. According to a particular embodiment, the time t is greater than 20 min, preferably from 25 min to 45 min, and more preferentially t is 30 min.

In steps (e) and (i) of the above process, the crystals of the first Bahma enantiomer and the crystals of the second Bahma enantiomer are harvested by filtration or centrifugation.

The crystals of the first Bahma enantiomer and the crystals of the second Bahma enantiomer obtained via the process that is the subject of the present invention may especially have an enantiomeric excess of greater than 80%. Said crystals may be recrystallized to obtain an enantiomeric excess of close to 100%, especially according to the enantiomeric purification process according to the invention described below. A suitable solvent for the recrystallization is a solvent chosen from acetone, water, methanol, the water/n-propanol azeotrope and mixtures thereof.

According to a second embodiment, the preferential crystallization is seeded and comprises the following steps:

a) a first homogeneous solution is prepared, composed of the racemic Bahma salt, of an excess of the first Bahma enantiomer to be recovered and of a solvent, the figurative point I of which, defined by the concentration and temperature variables T_I ($T_I > T_{HOMO}$), is within the one-phase domain composed of the under-saturated solution;

b) a cooling programming law is applied to the one-phase mixture;

c) when the mixture reaches a temperature below the temperature T_{HOMO}, the solution is seeded with enantiomerically pure seeds of the first Bahma enantiomer to be recovered;

d) a stirring speed that increases slightly as a function of time is adapted throughout the crystal growth so that it is slow enough to favor growth of the first Bahma enantiomer;

e) the crystals of the first Bahma enantiomer are harvested;

f) the same mass of racemic Bahma salt as the mass of the harvest made in the preceding step is added to the mixture, and the new combined mixture is brought to the temperature T_I ($T_I > T_{HOMO}$), the point I' being within the one-phase domain;

g) the same cooling programming law as in step (b) is applied to the one-phase mixture prepared in step (f) containing the second enantiomer, so that the mixture maintains a low supersaturation during the crystallization so as to promote growth of the second Bahma enantiomer during seeding;

h) when the mixture reaches a temperature below the temperature T_{HOMO}, the solution is seeded with enantiomerically pure seeds of the second Bahma enantiomer;

i) a stirring speed that increases slightly as a function of time is adapted throughout the crystal growth of the preceding step, so that it is slow enough to favor growth of this second Bahma enantiomer;

j) the crystals of the second Bahma enantiomer are harvested;

k) the same mass of racemic Bahma salt as the mass of the harvest made in the preceding step is added to the mixture, to obtain a solution whose composition is identical to that of the initial solution;

l) steps (b) to (k) are repeated to successively obtain one and then the other of the two enantiomers.

A subject of the present invention is also a process for the enantiomeric purification of Bahma salts, comprising the recrystallization of Bahma salts in a solvent. The solvent may especially be chosen from acetone, water, methanol, a water/n-propanol azeotrope and mixtures thereof.

The enantiomeric purification process of the present invention may especially be performed after the process for resolving the baclofen enantiomers according to the present invention described above.

The enantiomeric purification process of the present invention is based on the exploitation of the ternary phase diagram comprising the domain of the solid solutions and the solubilities of the system {Solvent - Bahma (R) enantiomer - Bahma (S) enantiomer}, represented in Figure 7.

This figure shows an isothermal and isobaric section of the ternary phase diagram between the salts of the two Bahma enantiomers and a solvent, the chosen temperature allowing high chiral discrimination between the two enantiomers. Starting with a mixture of salts of Bahma (R) and (S) enantiomers of known composition I, which may especially be a mixture of (R) and (S) enantiomers obtained during the preferential crystallization process according to the present invention, and by adding solvent, various domains constituted of phases each having a different composition and a different nature are traversed:

I → H_0: three-phase domain constituted of the two Bahma enantiomers in solid form (ssR and ssS) and of the saturated racemic solution (r.s.s.);

H_0 → G: two-phase domain constituted of a salt enriched in the Bahma (R) enantiomer (ssR) in solid form and of its saturated solution (sat.sol.), the proportion of crystals of Bahma (R) enantiomer decreasing throughout the segment [H_0G], the point H_0 being the point that is the richest in crystals of Bahma (R) enantiomer;

G → F: one-phase domain constituted of an under-saturated solution (U.S.S.).

Thus, by precisely knowing the initial composition of the mixture **I** and its mass, the solid solution domains and the solubility of the racemic mixture, the composition of the point **H_0** can be determined with precision, which makes it possible, by filtration, to separate the salt enriched in the Bahma (R) enantiomer in solid form, represented by the point **P_0**, from the saturated racemic solution **L_0**. This point **H_0** is reached by adding a volume **V_{H0}** of solvent or a mass **m_{H0}** of solvent to the mixture **I**.

It is also possible to add a volume of solvent **V_{H1}** slightly greater than **V_{H0}** ($V_{H1} = V_{H0} + \Delta V$) or a mass of solvent **m_{H1}** slightly greater than **m_{H0}** ($m_{H1} = m_{H0} + \Delta m$) so as to reach the composition point **H_1**. After filtration, the salt enriched in the Bahma (R) enantiomer in solid form, represented by the point **P_1**, is separated from the saturated racemic solution **L_1**. The addition of this amount of solvent **V_{H1}** or **m_{H1}** makes it possible to obtain a salt comprising a higher proportion of Bahma (R) enantiomer than that obtained by adding an amount of solvent **V_{H0}** or **m_{H0}**. On the other hand, the yield of salt enriched by adding an amount of solvent **V_{H1}** or **m_{H1}** is lower than that obtained by adding an amount of solvent **V_{H0}** or **m_{H0}** since a larger amount of Bahma (R) enantiomer remains dissolved in the saturated solution. The lower the amount of solvent **ΔV** or **Δm**, the more limited the amount of Bahma (R) enantiomer which remains dissolved in the saturated solution.

Figure 7 illustrates the enantiomeric purification process for a mixture initially enriched in Bahma (R) enantiomer, but the process may be applied symmetrically to a mixture enriched in Bahma (S) enantiomer.

Thus, according to a preferred embodiment, the process for the enantiomeric purification of the Bahma salt according to the present invention comprises the following steps:

a) providing a solid mixture of Bahma (R) and (S) enantiomers of known composition represented by the point **I** on the isothermal and isobaric section of the ternary phase diagram between the two Bahma enantiomers and a solvent;

b) adding an amount of solvent so as to pass into the two-phase domain constituted of a salt enriched in a Bahma enantiomer in solid form and of its saturated solution of said ternary phase diagram;

c) filtering the mixture obtained in step b) to obtain the salt enriched in a Bahma enantiomer.

Preferably, the amount of solvent added in step b) is the volume $\mathbf{V_{H0}}$ or the mass $\mathbf{m_{H0}}$ of solvent which makes it possible to reach the point $\mathbf{H_0}$ on said phase diagram, said point $\mathbf{H_0}$ corresponding to the intersection of the curve passing between point **I** and point **F**, point F being the peak of the phase diagram corresponding to the pure solvent, and of the curve $\mathbf{P_0}$-$\mathbf{L_0}$ (i.e. the conode) delimiting the three-phase domain from the two-phase domain of the salt enriched in Bahma enantiomer that it is desired to obtain.

Preferably, the amount of solvent added in step b) is the volume $\mathbf{V_{H1}} = \mathbf{V_{H0}} + \mathbf{\Delta V}$ or the mass $\mathbf{m_{H1}} = \mathbf{m_{H0}} + \mathbf{\Delta m}$ of solvent that makes it possible to reach the point $\mathbf{H_1}$ on said phase diagram, said point $\mathbf{H_1}$ corresponding to the intersection of the curve passing between point **I** and point **F**, point F being the peak of the phase diagram corresponding to the pure solvent, and of the curve $\mathbf{P_1}$-$\mathbf{L_1}$ (i.e. the conode).

The Bahma salts obtained via the resolution process of the present invention and/or the enantiomeric purification process of the present invention may be transformed into baclofen or into a baclofen salt other than the Bahma salt without racemization, i.e. without loss of enantiomeric excess. The transformation of Bahma salts into baclofen may especially be performed by adding a base.

The invention will now be illustrated by the nonlimiting examples that follow.

FIGURES

Figure 1 is an optical microscopy image of a single crystal with an enantiomeric excess of 98.6% derived from a racemic salt of Bahma prepared in example 1.

Figure 2 is the binary phase diagram of Bahma obtained by differential scanning calorimetry (DSC) (the liquidus curve is not present, given that the Bahma salt decomposes during or after melting).

Figure 3 is a theoretical binary phase diagram of a conglomerate having a partial solid solution.

Figure 4 is a theoretical binary phase diagram of a baclofen salt other than the Bahma salt with the usual presence of a stoichiometric racemic compound.

Figure 5 represents the calibration curve plotted by varying the concentration (C) of a pure Bahma enantiomer and by measuring the specific optical rotation (α) at a wavelength of 365 nm in the water/n-propanol azeotrope at 25°C.

Figure 6 represents the XRD diffractogram calculated and measured for the racemic salt of Bahma of example 1.

Figure 7 represents the ternary isobaric isotherm of the system {Bahma (R) enantiomer - Bahma (S) enantiomer - Solvent} illustrating the enantiomeric purification process of the present invention.

Figure 8 is a comparison of the diffractograms, obtained by x-ray diffraction analysis, of the B form of (R)(-)-baclofen and of Test 1 of example 5.

Figure 9 corresponds to the ^{1}H NMR spectrum of Test 1 of example 5 in deuterated DMSO.

Figure 10 is a comparison of the diffractograms, obtained by x-ray diffraction analysis, of the B form of (R)(-)-baclofen and of Test 2 of example 5.

Figure 11 corresponds to the ^{1}H NMR spectrum of Test 2 of example 5 in deuterated DMSO.

Figure 12 is a comparison of the diffractograms, obtained by x-ray diffraction analysis,

of the B form of (R)(-)-baclofen and of Test 3 of example 5.

Figure 13 corresponds to the ^{1}H NMR spectrum of Test 3 of example 5 in deuterated DMSO.

Figure 14 corresponds to the ^{1}H NMR spectrum of the baclofen hydrogen maleate salt in deuterated water.

Figure 15 corresponds to the ^{1}H NMR spectrum of baclofen in deuterated water.

Figure 16 corresponds to the ^{1}H NMR spectrum of maleic acid in deuterated water.

ANALYTICAL TECHNIQUES

Determination of the melting/decomposition point and production of the binary phase diagram by differential scanning calorimetry (DSC)

The differential scanning calorimetry measurements were taken in the following manner:

- DSC 204 F1 Netzsch equipped with an Intracooler
- aluminum crucible, closed aluminum lid
- Atmosphere: helium
- Heating rate: 5K. min^{-1}
- Data processing: Netzsch Proteus Thermal Analysis software (v.4.8.4)

Following the DSC and chiral HPLC analyses performed on single crystals obtained at 20 and 70°C (98.3%ee at 70°C and 98.8%ee at 20°C), the binary phase diagram of Figure 1 was established. The enantiomeric excess (%ee) was determined by chiral HPLC according to the method described below.

Determination of the enantiomeric excess (%ee) by chiral HPLC

The chromatographic method originates from that described in Hefnawy, M., Aboul-Enein, H. *Talanta*, **2003**, vol. 61, No. 5, pages 667-673.

The enantiomeric excesses were determined by chiral HPLC chromatography using a

Chirobiotic T column (length 15 cm, inside diameter 4.6 mm, 5 µm particles) mounted on a Spectra System HPLC chain equipped with an AS sample changer, a P1000 pump and a UV1000 detector. The experimental conditions were:

- Solvent: isocratic mixture of methanol, water, acetic acid and triethylamine in 98:2:0.1:0.1 proportions;
- Flow rate: 1 $ml.min^{-1}$;
- Detector: $\lambda = 226$ nm;
- Volume injected: 10 µL

Determination of the enantiomeric excess (%ee) by polarimetry

Between each preferential crystallization, the enantiomeric excesses (%ee) of the precipitates and of the solution were also determined by polarimetry. This technique is faster than chiral HPLC analysis and thus makes it possible to check the correct progress of the resolution process so as to adjust the parameters accordingly (amount of solvent and of racemic Bahma salt to be compensated for before the start of a crystallization).

These analyses were performed on a Perkin-Elmer Model 341 polarimeter equipped with a thermostatically regulated 10 cm measuring cell allowing analysis at various wavelengths. The measurements were taken at 25°C and the samples were dissolved in the water/n-propanol azeotrope (43.29 mol%). The table below gives the specific optical rotation (α) of a pure Bahma enantiomer at various wavelengths (λ).

λ (nm)	α (°)
365	**-0.35**
589	-0.11
578	-0.08
546	-0.1
436	-0.19

The wavelength of 365 nm was retained since it had the best deviation of polarized light (-0.35°).

Figure 5 shows the calibration curve which was plotted by varying the concentration of the pure Bahma enantiomer and by measuring the specific optical rotation at a wavelength of 365 nm. The values are reported in the table below.

C (g/dL)	α (°)
2.20	-0.34
1.65	-0.26
1.24	-0.22
0.93	-0.16
0.70	-0.12
0.00	0

It was then possible to deduce the specific optical rotation value for Bahma via the following formula:

$$\alpha = [\alpha]_{365nm}^{25°C} * l * C$$

in which:

α is the optical rotation of the sample in degrees (°);

C is the concentration of the sample in $g.dL^{-1}$;

l is the length of the analysis cell in dm;

$[\alpha]_{365nm}^{25°C}$ is the specific optical rotation of Bahma at 25°C and at 365 nm in the solvent used, expressed in $°.dL.g^{-1}.dm^{-1}$.

The specific optical rotation of Bahma under these conditions is $0.1642°dL.g^{-1}.dm^{-1}$.

Analysis by single-crystal x-ray diffraction

The single crystal chosen was bonded to the end of a glass rod and mounted on a goniometric head of the Brüker SMART APEX diffractometer equipped with a two-dimensional detector. Three sets of measurements were recorded (in total 1800 images (frames)) corresponding to 3 ω scans (incrementation of 0.3°), for four different values of ϕ.

The elemental lattice parameters and the orientation matrix were determined using the

SMART program. The data integrations and the refinement of the lattice parameters were performed using the SAINT program. The intensities were corrected for the Lorentz polarization factor and for absorption by the SAINT and SADABS programs to obtain the F_O^2.(hkl). The WinGX program was used for determination of the space group, the resolution of the structure and its refinement.

Analysis by powder x-ray diffraction

The powder x-ray diffraction analyses were performed with a D8 Discover diffractometer (Brüker). The instrument is equipped with an x-ray tube containing a copper anticathode (40 kV, 40 mA, radiation Kα1 = 1.5406 Å, radiation Kα2 = 1.5444 Å) and is mounted with a Lynx eye angular detector. The analysis program used is a 3 to 30° sweep in 2θ in increments of 0.04° with 0.5 s/step and a rotation of 20 rpm (Phi spinner).

Determination of the solubility

The solubility of a Bahma salt in a given solvent was calculated, for a given temperature and in a given volume of solvent, via the following formula:

$$\frac{m_{Bahma}}{m_{Bahma} + (\rho_{solvent} \times V_{solvent})} \times 100$$

in which

m_{Bahma} is the mass of the Bahma salt introduced in grams to reach saturation;

$\rho_{solvent}$ is the density of the solvent in $g.mL^{-1}$; and

$V_{solvent}$ is the volume of the solvent in mL.

Experimental device for resolution by preferential crystallization

The crystallizations were performed in closed tubes (diameter 3 cm, length 9 cm). Stirring was performed by cruciform magnetic bars and the temperature control was provided by a Lauda ECO RE 415 programmable cryothermostat.

The entrainments were performed by means of the AS3PC process described in patent application WO 1995/008522.

In the course of the entrainments, samples of solutions (10 µL diluted in 1 mL of mobile phase) were collected so as to determine their enantiomeric excess by chromatography according to the method described above.

a) First crystallization

A volume V of 40 mL of saturated solution of racemic Bahma salt at 50°C (temperature T_L) in a solvent or a solvent mixture was prepared by filtration of a suspension at this same temperature after an equilibration time of several hours to reach saturation.

At least 5% by weight of excess of a pure Bahma enantiomer (Bahma-100%ee) relative to the weight of the racemic Bahma salt (rac. Bahma) introduced are added to this clear solution. The suspension obtained is then overheated slightly to a temperature $T_B = T_L + 3°C$. Thus, all the seeds of the enantiomer in deficit that might remain at T_L are necessarily dissolved. The starting system is thus a suspension of the enantiomer in excess. The liquid phase of the suspension is saturated in one enantiomer and slightly under-saturated in the other enantiomer. This system has the advantage of being at thermodynamic equilibrium.

A cooling temperature ramp is then applied to the system from T_B to T_F ($T_F < T_B$), the final temperature at which the system is rapidly filtered without waiting for the thermodynamic equilibrium to be established.

b) Following crystallizations

At the end of each entrainment, the suspensions were filtered through a sinter funnel. A sample of the filtrates (10 µL of filtrate diluted in 1 mL of mobile phase) was recovered for analysis of the %ee by chiral HPLC and the remainder was set aside to perform the following entrainment. The solid recovered was weighed and 15 mg were then dissolved in 1.5 mL of water/n-propanol azeotrope for analysis of the %ee by polarimetry and 10 µL of this solution were diluted in 1 mL of mobile phase for analysis of the %ee by chiral HPLC.

The filtrate recovered was compensated by adding a mass of racemic Bahma salt substantially equal to that of the crystals recovered in the preceding crystallization. The filtrate was also compensated for the losses of solvent by adding solvent to make up to 40 mL (initial volume of

solvent).

The system was then heated again to T_B at which point a new suspension was obtained. After 30 minutes of equilibration at this temperature, the same cooling program was applied, at the end of which a new filtration gives the opposite enantiomer to the preceding one. Successive recycling makes it possible to recover the same enantiomer as the starting one following the odd crystallizations, whereas the other enantiomer is systematically recovered for all the even crystallizations.

By successive recycling, it is then possible to preparatively resolve the two enantiomers of a racemic mixture.

EXAMPLES

Example 1: Preparation and characterization of Bahma salts

The Bahma salts (racemic or enantiomerically pure) used in the process of the present invention were prepared by evaporation of a suspension of baclofen (racemic or enantiomerically pure) and of maleic acid (1:1 stoichiometric mixture) in acetone.

The single crystals of Bahma salt for the x-ray diffraction analysis were obtained by dissolving 50 mg of racemic Bahma salt in a given volume of solvent: water, methanol or water/n-propanol azeotrope (to achieve a homogeneous solution, the mixture may be heated). After dissolution of the solids, a temperature may be imposed on the solution or it is left at room temperature (about 20°C). The salt crystals highly enriched in Bahma form by evaporation of the solvent or solvent mixture after a few days for the slowest evaporations; single crystals were thus obtained by evaporation of solutions left at 20, 50 and 70°C.

These single crystals were studied by x-ray diffraction to determine their complete structure. The crystallographic data for a single crystal obtained at 20°C are reported in table 1.

System	Monoclinic
Space group	$P2_1$ (No. 4)
a/Å	5.728(1)
b/Å	13.774(1)
c/Å	9.618(9)
α/°	90
β/°	106.628(1)
γ/°	90
Volume/Å^3	727.2(2)
Final R_1 ($I > 2\sigma(I)$)	0.0287
Final $wR(F^2)$ ($I > 2\sigma(I)$)	0.0812
Final R_1	0.0294
Final $wR(F^2)$	0.0817
Flack parameter	-0.02(5)

$$R_1 = \Sigma \left(||F_O| - |F_C|| \right) / \Sigma |F_O|$$

$$wR(F^2) = [\Sigma [w (F_O^2 - F_C^2)^2] / \Sigma [w (F_O^2)^2]]^{1/2}$$

Table 1

The space group, the number of molecules in the asymmetric unit, the absence of disorder and the value of the Flack parameter indicate virtually total chiral discrimination in the solid state at room temperature. These observations were correlated by identical behavior up to at least 70°C.

Table 2 below shows the reduced coordinates of the atoms other than hydrogen ($\times 10^4$) and the isotropic agitation factor U_{eq} (Å^2 x 10^3).

Atom	x	y	z	U_{eq}
C(1)	-5631(3)	8817(1)	-938(2)	33(1)
C(2)	-3549(3)	9419(1)	-1112(2)	35(1)
C(3)	-3199(3)	10379(1)	-272(2)	31(1)
C(4)	-1434(3)	10998(1)	-828(2)	36(1)
C(5)	-2316(3)	10237(1)	1357(2)	30(1)
C(6)	-80(3)	9806(1)	2015(2)	37(1)
C(7)	739(3)	9687(1)	3512(2)	39(1)
C(8)	-725(4)	9994(1)	4340(2)	39(1)
C(9)	-2951(3)	10412(1)	3718(2)	41(1)
C(10)	-3730(3)	10535(1)	2229(2)	35(1)
Cl(1)	289(1)	9851(1)	6215(1)	58(1)
N(1)	-1225(3)	12006(1)	-269(2)	38(1)
O(1)	-7139(2)	9107(1)	-380(2)	46(1)
O(2)	-5825(2)	7935(1)	-1485(1)	39(1)
C(1A)	2665(3)	2546(1)	3835(2)	35(1)
O(1A)	2173(2)	2425(1)	2502(1)	41(1)
O(2A)	4794(3)	2762(2)	4591(2)	67(1)
C(2A)	683(3)	2437(1)	4532(2)	35(1)

C(3A)	787(3)	2427(2)	5927(2)	37(1)
C(4A)	2891(4)	2502(2)	7252(2)	40(1)
O(3A)	5022(3)	2668(2)	7127(2)	62(1)
O(4A)	2565(3)	2399(1)	8443(2)	60(1)

Table 2

Table 3 below shows the reduced coordinates of the hydrogen atoms ($x10^4$) and the isotropic agitation factor U_{eq} ($Å^2 \times 10^3$).

Atom	x	y	z	U_{eq}
H(2A)	-3817	9558	-2133	41
H(2B)	-2063	9042	-787	41
H(3)	-4770	10714	-506	38
H(4A)	161	10697	-542	43
H(4B)	-1985	11014	-1880	43
H(6)	883	9593	1445	44
H(7)	2245	9406	3947	47
H(9)	-3924	10610	4290	49
H(10)	-5231	10823	1806	42
H(1A)	-2693	12278	-496	56
H(1B)	-260	12345	-665	56
H(1C)	-598	11999	690	56
H(2)	-4657	7823	-1791	58
H(2A1)	-867	2364	3894	42
H(3A)	-713	2362	6108	44
H(3A1)	4939	2737	6267	93

Table 3

Table 4 below shows the calculated and measured position and intensity of the characteristic XRD peaks for the racemic Bahma salt. The corresponding XRD diffractograms are shown in Figure 6.

Miller indices			**Calculated Bahma**			**Measured Bahma**			
h	**k**	**l**	**2θ/deg**	**d/Å**	**I/rel.**	**2θ/deg**	**d/Å**	**Intensity (counts)**	**Intensity (I/Io %)**
0	0	1	9.59	9.22	2.41	9.58	9.223	344	1.8
0	1	1	11.54	7.66	2.72	11.51	7.679	1116	5.8
0	2	0	12.83	6.89	5.77	12.81	6.904	2266	11.8
0	2	1	16.04	5.52	4.96	16.03	5.525	2047	10.6
1	0	0	16.12	5.49	5.4				
-1	0	1	16.24	5.45	54.44	16.21	5.462	8893	46.2
1	1	0	17.36	5.1	33.95	17.35	5.108	6557	34
-1	1	1	17.47	5.07	19.97	17.45	5.078	3944	20.5

0	1	2	20.3	4.37	6.49	20.28	4.375	1874	9.7
1	2	0	20.66	4.3	51.05	20.64	4.3	8915	46.3
-1	2	1	20.75	4.28	44.13	20.7	4.288	8204	42.6
1	0	1	21.04	4.22	3.14	21.02	4.224	1696	8.8
0	3	1	21.59	4.11	22.72	21.56	4.119	5218	27.1
1	1	1	22.02	4.03	29.17	21.99	4.039	6216	32.3
-1	1	2	22.28	3.99	17.94	22.24	3.993	2895	15
0	2	2	23.2	3.83	2.46	23.16	3.837	1381	7.2
1	2	1	24.72	3.6	14.87	24.69	3.603	3047	15.8
-1	2	2	24.95	3.57	13.08	24.92	3.57	2218	11.5
1	3	0	25.24	3.53	78.2	25.22	3.528	9331	48.4
-1	3	1	25.32	3.51	7.46				
0	4	0	25.82	3.45	100	25.79	3.452	19184	100
0	3	2	27.38	3.25	11.56	27.35	3.258	2470	12.8
0	4	1	27.61	3.23	34.09	27.57	3.233	5707	29.6
1	0	2	28.6	3.12	2.89	28.55	3.124	1238	6.4
1	3	1	28.7	3.11	6.3	28.68	3.11	1618	8.4
-1	3	2	28.9	3.09	4.41	28.87	3.09	1396	7.2
-1	0	3	28.93	3.08	2.51				
1	1	2	29.34	3.04	27.72	29.29	3.047	5113	26.5
-1	1	3	29.66	3.01	4.39				
0	1	3	29.77	3	17.51	29.71	3.005	3125	16.2

Table 4

Example 2: Resolution in the n-propanol/water azeotropic mixture by auto-seeded preferential crystallization

The solubility of the racemic Bahma salt at various temperatures was determined in the n-propanol/water azeotropic mixture (ρ = 0.870 g.mL^{-1}). The calculated values are presented in the table below.

Temperature	Solubility
20°C	1.49%
35°C	2.80%
50°C	4.81%

Several entrainments were performed in this solvent using a saturated racemic solution at 50°C and following the experimental device described previously.

- 1st series:

Initial system:	**40 mL saturated at 50°C (1.7583 g of rac. Bahma in 34.796 g of solvent) and 0.2505 g of Bahma-100%ee**				
	Temperature (°C)	**Time (min)**	**Solution**	**Crude harvests**	
			ee (%)	**Mass (g)**	**ee (%)**
Test 1	53	0	-4.71		
	50	6	-4.44		
	45	16	-0.40		
	40	26	4.54		
	35	36	11.69		
	32.5	41	15.30		
	30	46	19.92	**0.6682 g**	**-91.08**
4h at 53°C			**Compensation 0.6895 g of rac. Bahma and 2 mL of solvent**		
Test 2	53	0	6.43		
	35	36	-9.89		
	30	46	-18.08	**0.6587 g**	**+84.29**
12h at 53°C			**Compensation 0.6718 g of rac. Bahma and 2 mL of solvent**		
Test 3	53	0	-5.47		
	35	36	-3.37		
	30	46	10.02	**0.4971 g**	**-91.03**
2h at 53°C			**Compensation 0.4955 g of rac. Bahma and 2 mL of solvent**		
Test 4	53	0	5.14		
	35	36	-2.38		
	30	46	-11.27	**0.4156 g**	**+82.72**
1h at 53°C			**Compensation 0.4153 g of rac. Bahma**		

Test 5	53	0	-3.07		
	35	36	12.84		
	30	46	20.93	**0.5608 g**	**-93.78**
30 min at 53°C			**Compensation 0.555 g of rac. Bahma and 1.5 mL of solvent**		
Test 6	53	0	9.76		
	35	36	-5.35		
	30	46	-13.76	**0.5339 g**	**+96.59**

- 2nd series:

Initial system:	**40 mL saturated at 50°C (1.7583 g of rac. Bahma in 34.796 g of solvent) and 0.2445 g de Bahma-100%ee**				
	Temperature (°C)	**Time (min)**	**Solution**	**Crude harvests**	
			ee (%)	**Mass (g)**	**ee (%)**
Test 1	53	0	-11.88		
	35	36	-3.47		
	30	46	9.75	**0.5012 g**	**-94.04%**
60 min at 53°C			**Compensation 0.5120 g of rac. Bahma and 1.2 mL of solvent**		
Test 2	53	0	5.70		
	35	36	-9.90		
	30	46	-17.87	**0.4679 g**	**+84.61%**
30 min at 53°C			**Compensation 0.4621 g of rac. Bahma and 1 mL of solvent**		
Test 3	53	0	-8.86		
	35	36	6.62		
	30	46	15.26	**0.5496 g**	**-95.07%**
30 min at 53°C			**Compensation 0.5469 g of rac. Bahma and 1.5 mL of solvent**		
Test 4	53	0	8.16		
	35	36	-8.64		
	30	46	-17.34	**0.6465 g**	**+92.52%**
30 min at 53°C			**Compensation 0.5122 g of rac. Bahma and 1.5 mL of solvent**		
Test 5	53	0	-8.02		
	35	36	9.69		
	30	46	19.47	**0.6463 g**	**-88.51%**
30 min at 53°C			**Compensation 0.5136 g of rac. Bahma and 1.75 mL of solvent**		
Test 6	53	0	11.09		
	35	36	-5.15		
	30	46	-17.59	**0.6124 g**	**+91.71%**
30 min at 53°C			**Compensation 0.4975 g of rac. Bahma and 1. 5 mL of solvent**		

Test 7	53	0	-12.35		
	35	36	-2.47		
	30	46	12.65	**0.5378 g**	**-91.71%**
30 min at 53°C			**Compensation 0.5306 g of rac. Bahma and 2 mL of solvent**		
Test 8	53	0	7.46		
	35	36	-4.89		
	30	46	-14.73	**0.5254 g**	**+88.90%**
30 min at 53°C			**Compensation 0.5238 g of rac. Bahma and 0.5 mL of solvent**		
Test 9	53	0	-6.25		
	35	36	10.26		
	30	46	19.42	**0.6444 g**	**-89.51%**
30 min at 53°C			**Compensation 0.5183 g of rac. Bahma and 1 mL of solvent**		
Test 10	53	0	8.00		
	35	36	-7.59		
	30	46	-16.49	**0.7194 g**	**+87.05%**

Example 3: Resolution in acidified water by auto-seeded preferential crystallization

The solubility of the racemic Bahma salt at various temperatures was determined in pure water (ρ = 1 g.mL^{-1}), in aqueous 1M HCl solution (ρ = 1.017 g.mL^{-1}) and in aqueous 2M HCl solution (ρ = 1.030 g.mL^{-1}). The calculated values are presented in the table below.

Temperature	Solubility Water	Solubility 1M HCl	Solubility 2M HCl
20°C	0.75%	4.51%	6.48%
35°C	1.00%	6.86%	11.44%
50°C	1.78%	12.54%	22.24%

Thus, the use of an acidified aqueous solution advantageously makes it possible to increase the solubility of the racemic Bahma salt, which makes it possible to improve the productivity of the preferential crystallization. For HCl concentrations of 1M and 2M at these temperatures, the solid phases do not contain any hydrochloride.

Entrainment was performed in 1M HCl using a saturated racemic solution at 50°C and following the experimental device described previously.

Initial system:	40 mL saturated at 50°C (5.8326 g of rac. Bahma and 40.68 g of 1M HCl) and 0.1735 g of Bahma-100%ee				
	Temperature (°C)	Time	Solution	Crude harvests	
		(min)	ee (%)	Mass (g)	ee (%)
Test 1	50.25	0	-2.89		
	47.5	6	-2.81		
	45	11	-2.03		
	42.5	16	-0.90		
	40	21	3.76		
	37.5	26	11.55	**0.8885**	**-90.56%**

Entrainment was performed in 2M HCl using a saturated racemic solution at 50°C and following the experimental device described previously.

Initial system:	40 mL saturated at 50°C (11.7835 g of rac. Bahma in 41.2 g of 2M HCl) and 0.2501 g of Bahma-100%ee				
	Temperature (°C)	Time (min)	Solution	Crude harvests	
			ee (%)	Mass (g)	ee(%)
Test 1	50.5	0	-3.53		
	47.5	6	-2.66		
	45.0	11	-2.09		
	42.5	16	-5.98		
	40.0	21	3.74		
	37.5	26	10.52	**1.7437 g**	**-89.94%**
60 min at 50.5°C			**Compensation: 1.7457 g of rac. Bahma and 2 mL of 2M HCl**		
Test 2	50.5	0	/		
	40.0	21	-2.77		
	37.5	26	-11.80	**2.1713 g**	**+98.37%**

Example 4: Enantiomeric purification process according to the invention

The enantiomeric purification process according to the invention was performed using 0.4239 g of Bahma salt at -50.43 %ee, i.e. a mixture of 0.2138 g of (R)-Bahma and 0.2101 g of racemic Bahma mixture, to which a mass of 27.0787 g of water (m_{H0} = 26.7258 g of water, i.e. an

excess Δm = 1.32% of water) was added.

The system was then left under magnetic stirring at 20°C overnight and the suspension was filtered.

The solid was then washed twice with water and the harvest was thus able to be analyzed. 0.1905 g of solid (R)-Bahma salt at -98.59%ee is obtained and the filtrate has a measured purity of -11.56 %ee.

Example 5: Process for obtaining pure baclofen from baclofen hydrogen maleate salt

1 g of enantiomerically pure baclofen hydrogen maleate salt (corresponding to a mass of 0.6480 g of baclofen and 0.3520 g of maleic acid) is dissolved in 10 ml of 1M NaOH solution at 25°C with stirring.

The pH of the solution is then adjusted by adding a known volume of 37 mass% hydrochloric acid solution. The temperature is controlled in parallel. The addition of hydrochloric acid entrains the precipitation of the B form of baclofen, which is then filtered off, dried, weighed and analyzed by x-ray diffraction and by NMR (nuclear magnetic resonance) analysis.

Three tests were then performed in order to check that the process is viable at various final pH values and various temperatures.

Test 1:

Test	Volume of HCl added	Final temperature	Final pH	Mass harvested
Test 1	230 µL	25°C	9.02	0.5485 g

Test 2:

Test	Volume of HCl added	Final temperature	Final pH	Mass harvested
Test 2	320 µL	25°C	7.90	0.5546 g

Test 3:

Test	Volume of HCl added	Final temperature	Final pH	Mass harvested
Test 3	240 µL	10°C	9.29	0.5786 g

For each of the tests, x-ray diffraction analyses of the solids obtained and NMR analyses are performed (see figures 8 to 16).

Conclusion:

The x-ray diffraction analyses of the solids obtained demonstrate that all the solids obtained are constituted of enantiomerically pure baclofen in its B polymorphic form (see figures 8, 10 and 12).

The NMR analyses confirm that the samples recovered are mainly constituted of baclofen with a few possible remaining traces of maleic acid (peak at 6 ppm) (see figures 9, 11, 13, 14, 15 and 16).

The masses harvested and the purity indicate a good yield of the process (compared with the initial mass of baclofen dissolved). Tests 2 and 3 indicate that this yield can be optimized without affecting the purity.

Patentkrav

1. Racemisk salt av baklofenhydrogenmaleat (Bahma), **karakterisert ved at** den har et smelte-/spaltingspunkt på 164±1°C.

2. Anvendelse av et baklofenhydrogenmaleatsalt som definert i krav 1 for å skille (S)- og (R)-enantiomerene av baklofen.

3. Fremgangsmåte for å skille (S)- og (R)-enantiomerene av baklofen, **karakterisert ved at** racemisk baklofen blir omdannet til racemisk baklofenhydrogenmaleatsalt i nærvær av maleinsyre, og **ved at det** nevnte salt blir deretter skilt ved foretrukket krystallisering for å separere de to (S)- og (R)-enantiomerene.

4. Fremgangsmåte ifølge krav 3, **karakterisert ved at** skillingen av det racemiske saltet utføres ved foretrukket selvpodet krystallisering eller ved foretrukket podet krystallisering, fortrinnsvis ved foretrukket selvpodet krystallisering.

5. Fremgangsmåte ifølge krav 3 eller 4, **karakterisert ved at** den foretrukne krystalliseringen utføres med et løsningsmiddel valgt fra et alkoholisk løsningsmiddel, en vandig løsning, en sur, vandig løsning og blandinger derav.

6. Fremgangsmåte ifølge krav 3 eller 4, **karakterisert ved at** den foretrukne krystalliseringen utføres med en sur, vandig løsning, syren er valgt fra saltsyre, eddiksyre, salpetersyre, fortrinnsvis en vandig saltsyreløsning, mer fortrinnsvis en vandig 2 mol/L saltsyreløsning.

7. Fremgangsmåte ifølge hvilket som helst av kravene 3 til 6, **karakterisert ved at** den foretrukne krystalliseringen er selvpodet og **ved at** den omfatter følgende trinn:

a) å forberede et volum V av en mettet løsning av racemisk Bahmasalt ved en temperatur T_L;

b) å tilsette minst 5 vekt% av den første Bahmaenantiomeren som utvinnes i forhold til vekten av det racemiske Bahmasaltet;

c) å varme opp blandingen til en temperatur $T_B = T_L + 3°C$;

d) å anvende en avkjølingsprogrammeringslov på blandingen fra T_B til T_F, T_F er lavere enn T_B, slik at blandingen opprettholder en lav overmettelse som fremmer veksten av den første Bahmaenantiomeren som er til stede i form av

krystaller, mens den forhindrer spontan kjernedannelse av den andre Bahmaenantiomeren løst i løsningen;

e) å høste krystallene av den første Bahmaenantiomeren ved temperaturen TF;

f) å tilsette vesentlig den samme massen av racemisk Bahmasalt som massen til innhøstingen utført i det foregående trinnet til blandingen, å komplettere med løsningsmiddel for å nå volumet V og å bringe den nye enheten til temperaturen T_B;

g) å opprettholde temperaturen T_B i en tid t slik at systemet kan gå tilbake til termodynamisk likevekt;

h) å anvende den samme avkjølingsprogrammeringsloven som i trinn (d) på blandingen fremstilt i trinn (g) som inneholder den andre Bahmaenantiomeren, slik at blandingen opprettholder en lav overmettelse under krystalliseringen for å fremme veksten av den andre Bahmaenantiomer som er til stede i form av krystaller, mens den forhindrer spontan kjernedannelse av den første Bahmenantiomeren som er til stede i løsningen;

i) å høste krystallene av den andre Bahmaenantiomeren ved temperaturen T_F;

j) å tilsette vesentlig den samme massen av racemisk Bahmasalt som massen til innhøstingen utført i det foregående trinnet til blandingen, å komplettere med løsningsmiddel for å nå volumet V og å bringe den nye enheten til temperaturen T_B;

k) å opprettholde temperaturen T_B i en tid t slik at systemet kan gå tilbake til termodynamisk likevekt;

l) å gjenta trinn (d) til (k) for suksessivt å tilveiebringe den ene og deretter den andre av de to enantiomerene.

8. Fremgangsmåte ifølge krav 7, **karakterisert ved at** temperaturen T_L varierer fra 30 til 70°C; fortrinnsvis varierer T_L fra 40 til 60°C og mer fortrinnsvis er T_L 50°C.

9. Fremgangsmåte for enantiomerrensing av Bahmasalter, omfattende å rekrystallisere Bahmasalter i et løsningsmiddel.

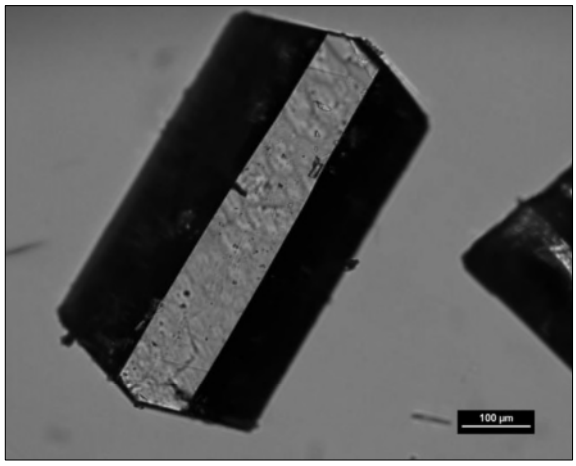
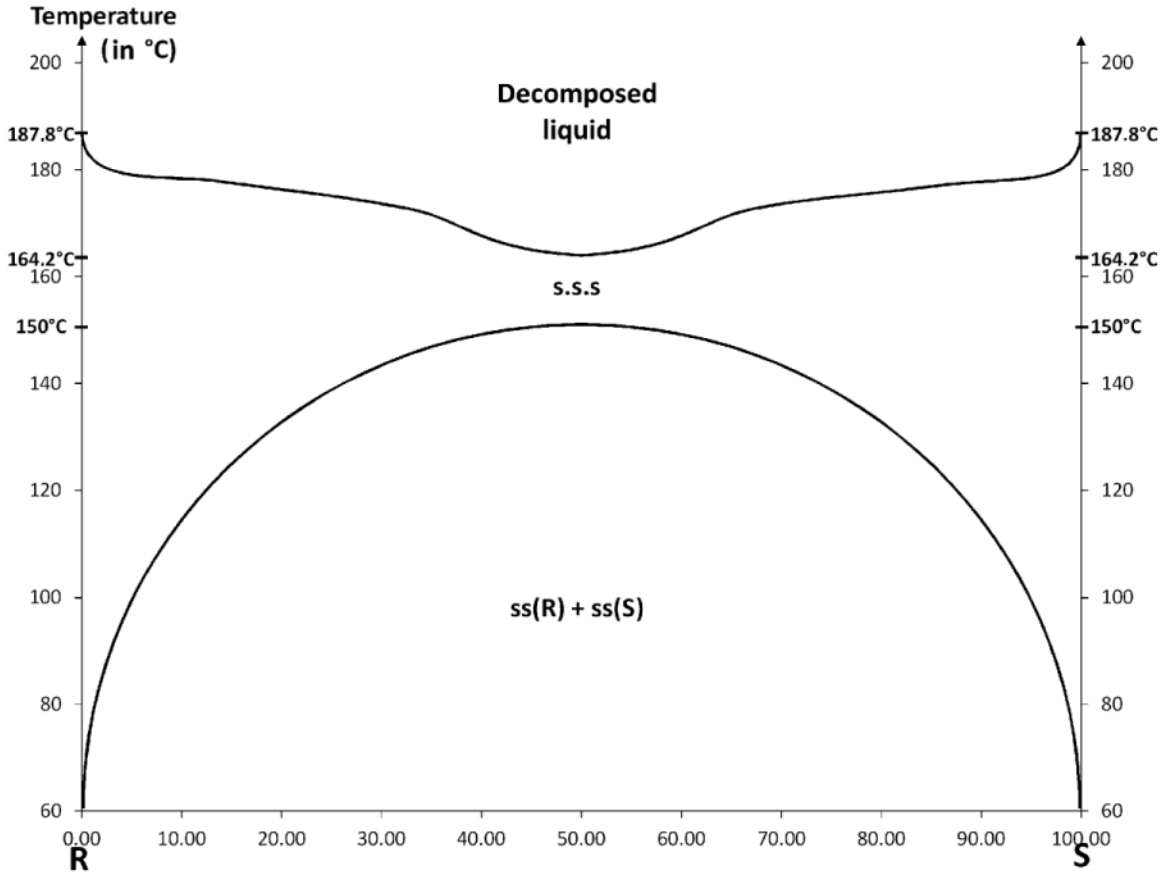


Figure 1

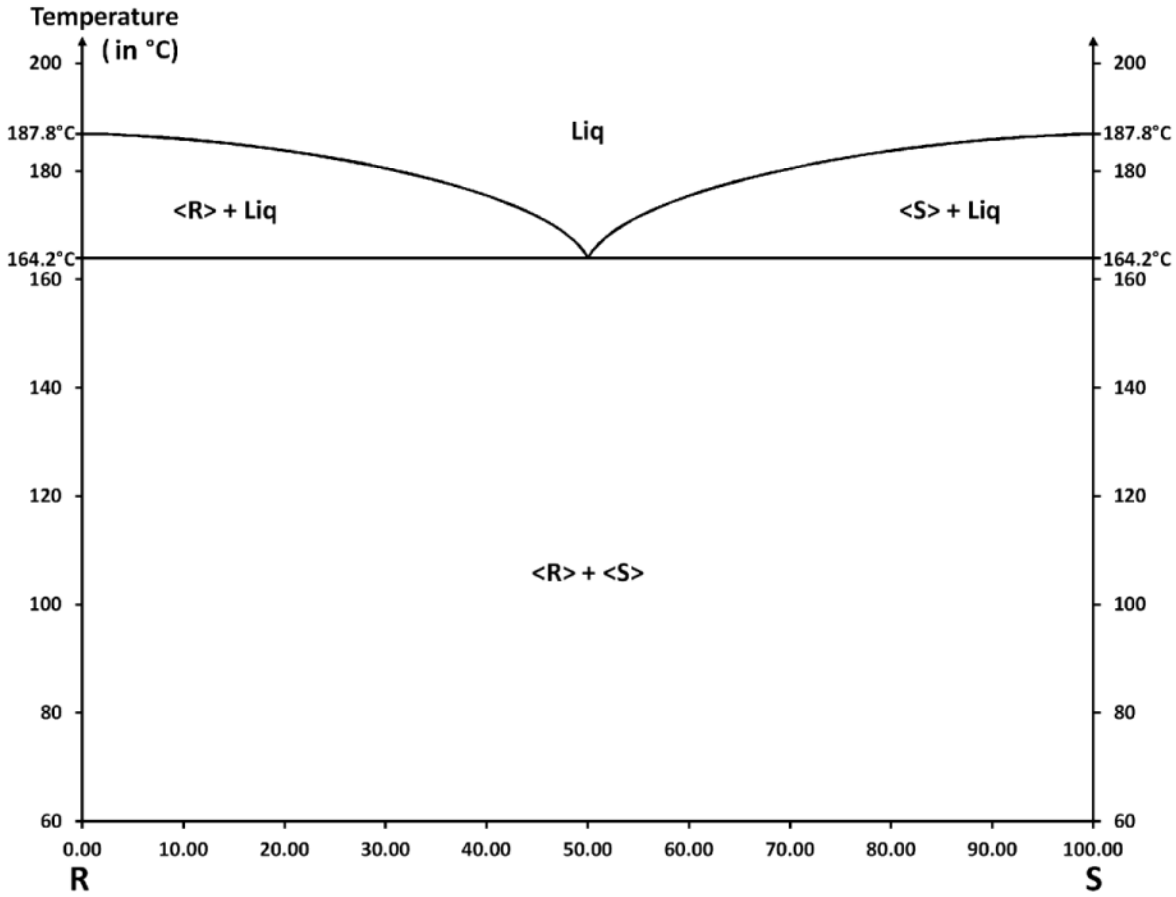


sss: total substitution solid solution

ss(S): partial solid solution enriched in Bahma (S) enantiomer

ss(R): partial solid solution enriched in Bahma (R) enantiomer

Figure 2

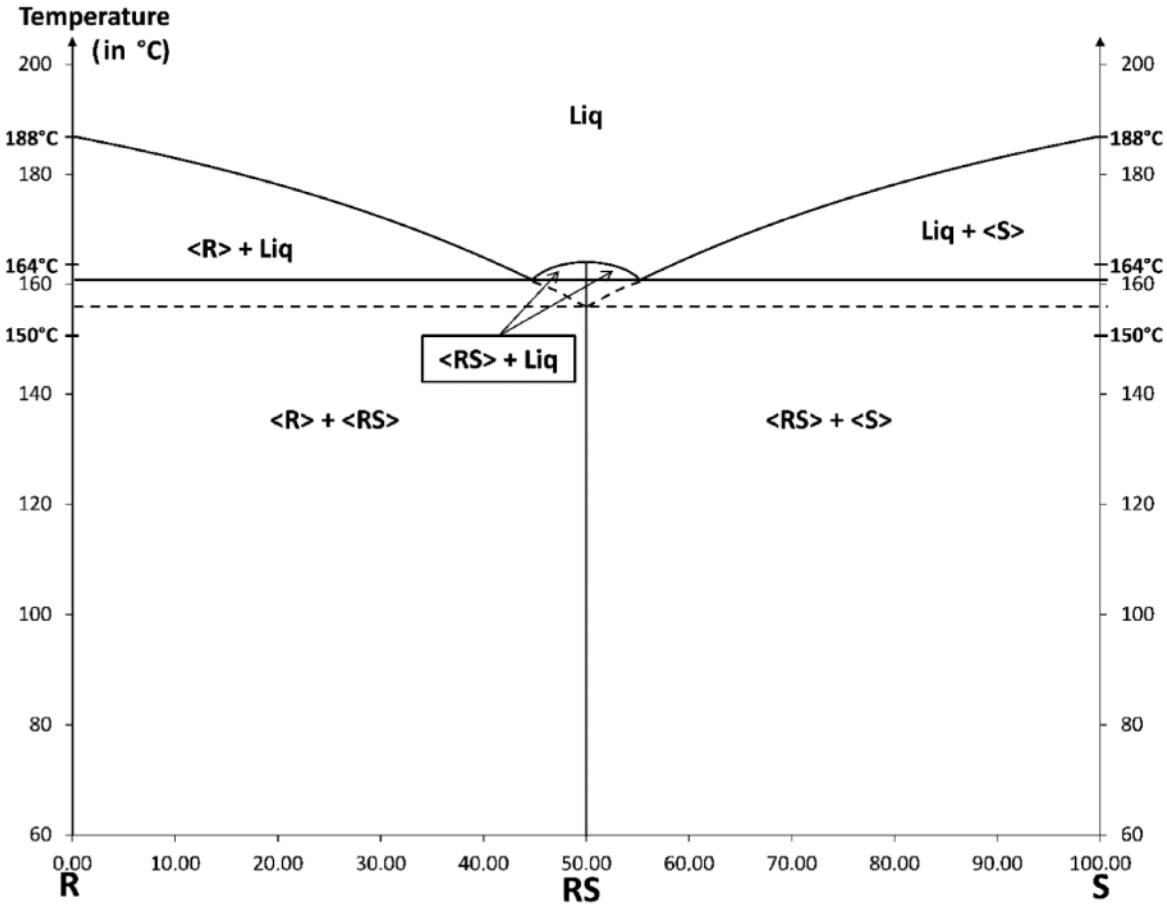


Liq: liquid

<S>: (S) enantiomer in solid form

<R>: (R) enantiomer in solid form

Figure 3



Liq: liquid

<S>: (S) enantiomer in solid form

<R>: (R) enantiomer in solid form

<RS>: racemic compound in solid form

Figure 4

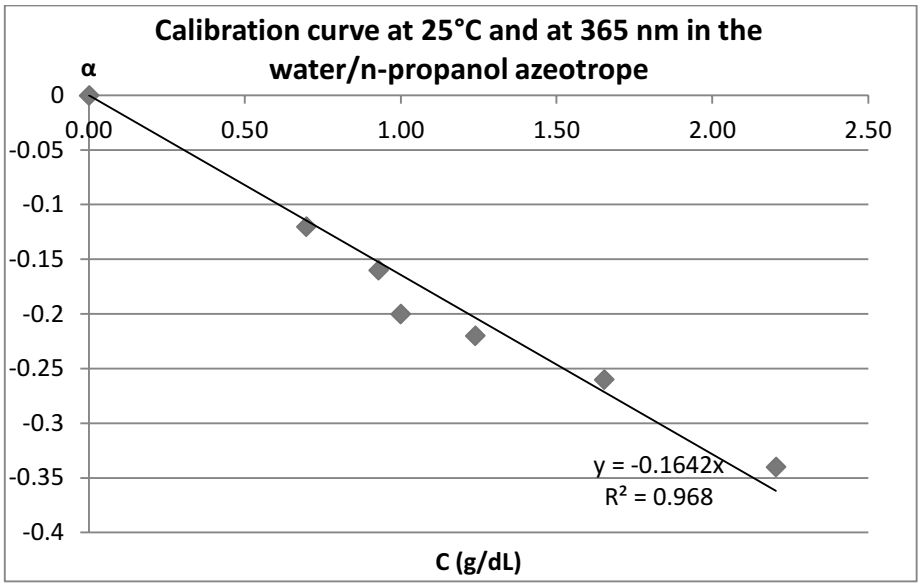


Figure 5

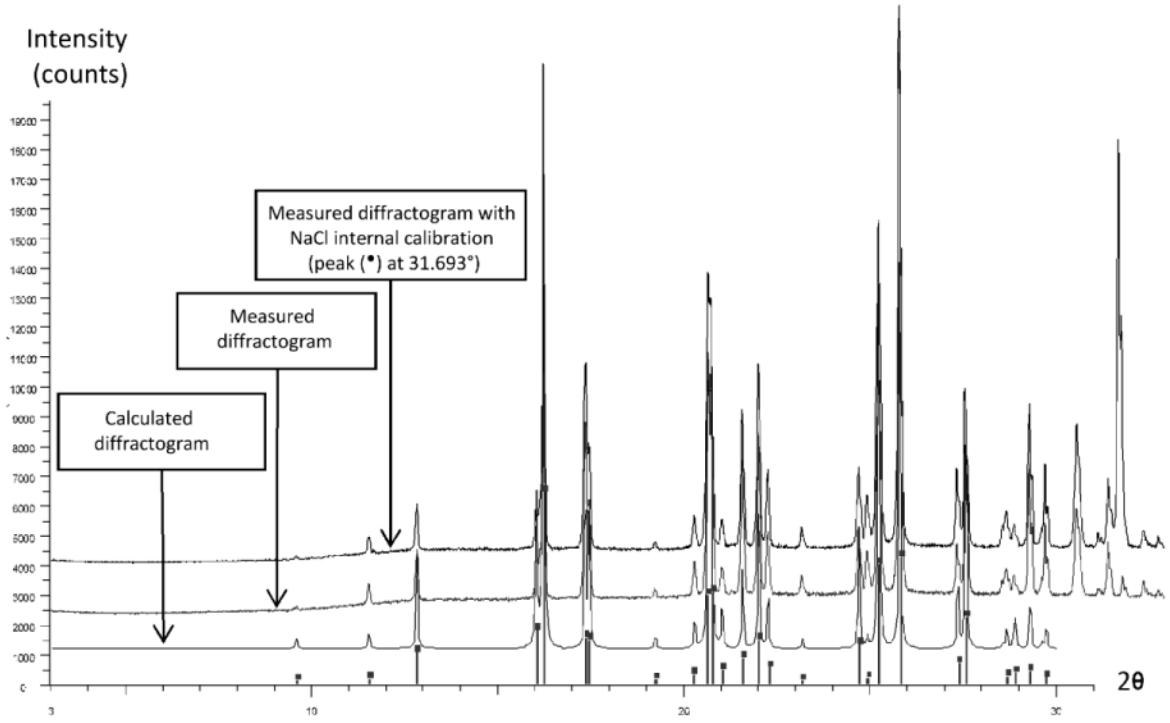
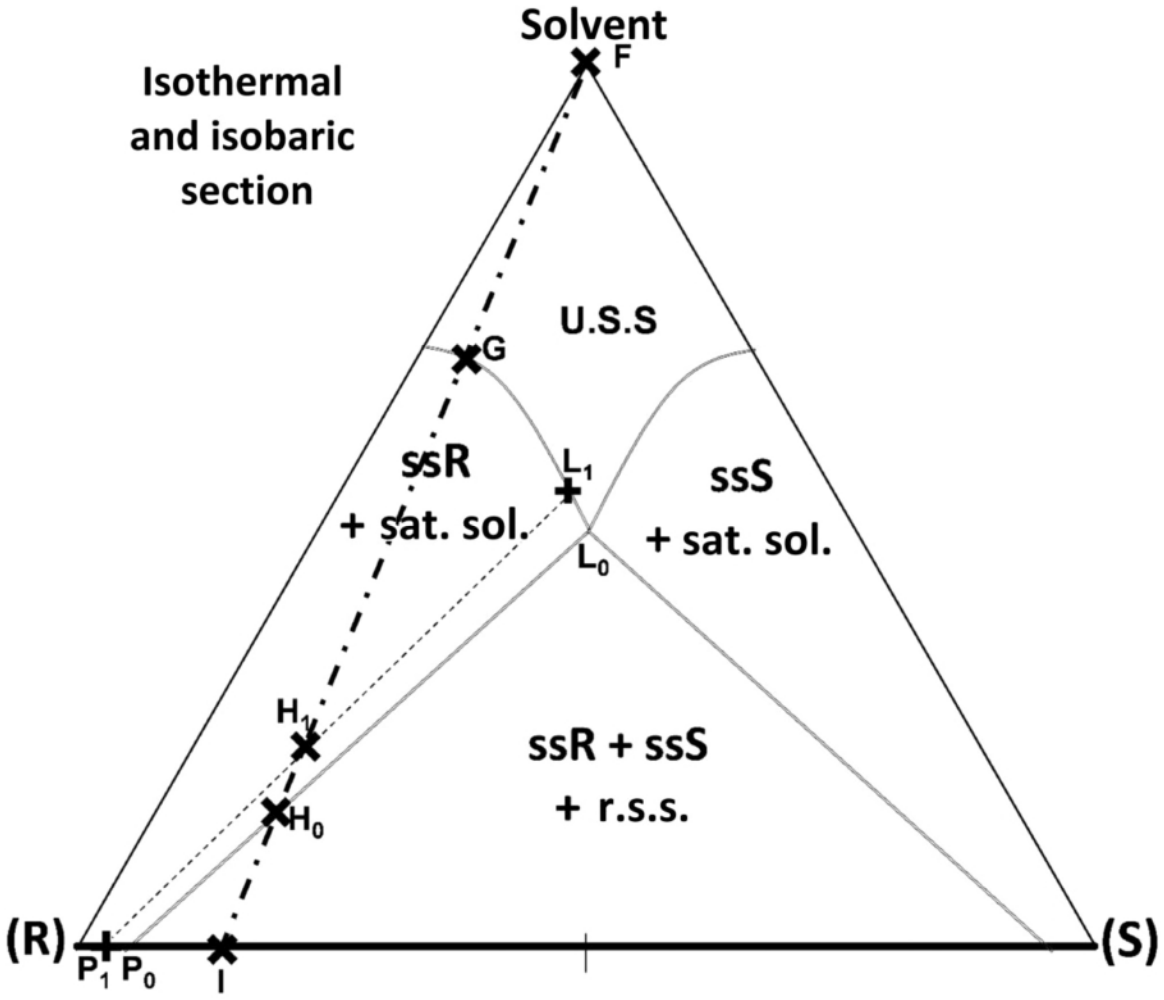


Figure 6



r.s.s.: saturated solution of racemic Bahma salt

sat. sol.: saturated solution enriched in Bahma (S) or (R) enantiomer

U.S.S: under-saturated solution

ssR: partial solid solution enriched in Bahma (R) enantiomer

ssS: partial solid solution enriched in Bahma (S) enantiomer

━ · ━ · ━ · : isopleth section

L_0 = saturated racemic solution

P_0L_0 and P_1L_1: conodes

Figure 7

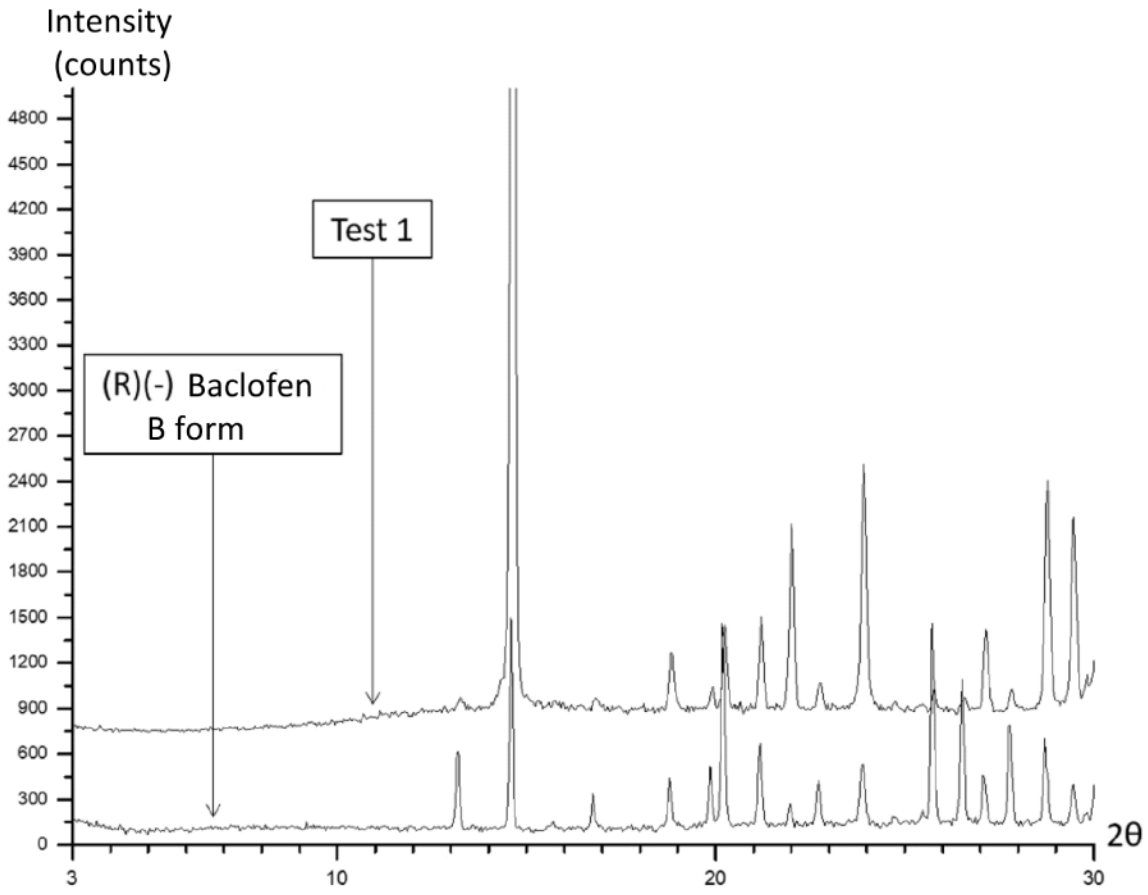


Figure 8

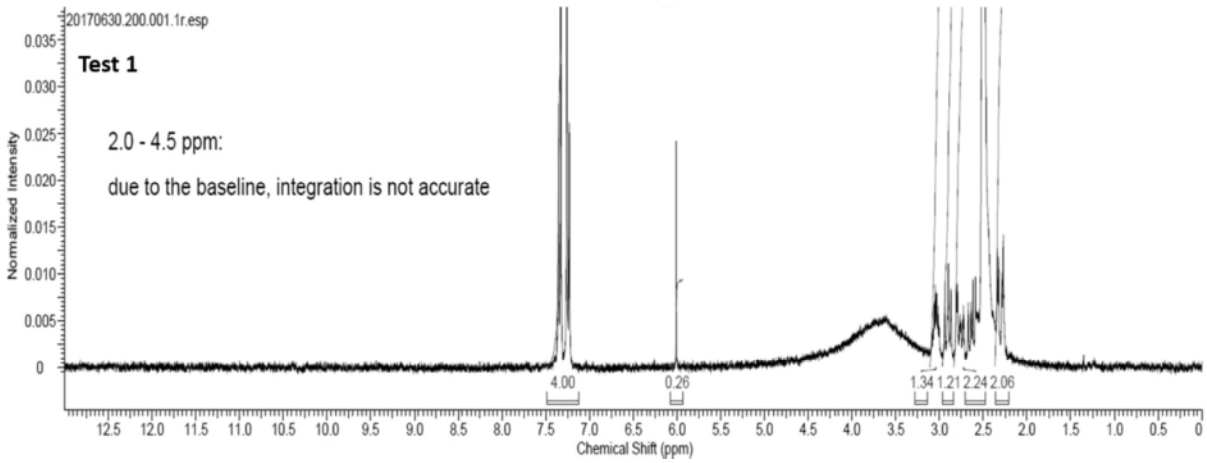


Figure 9

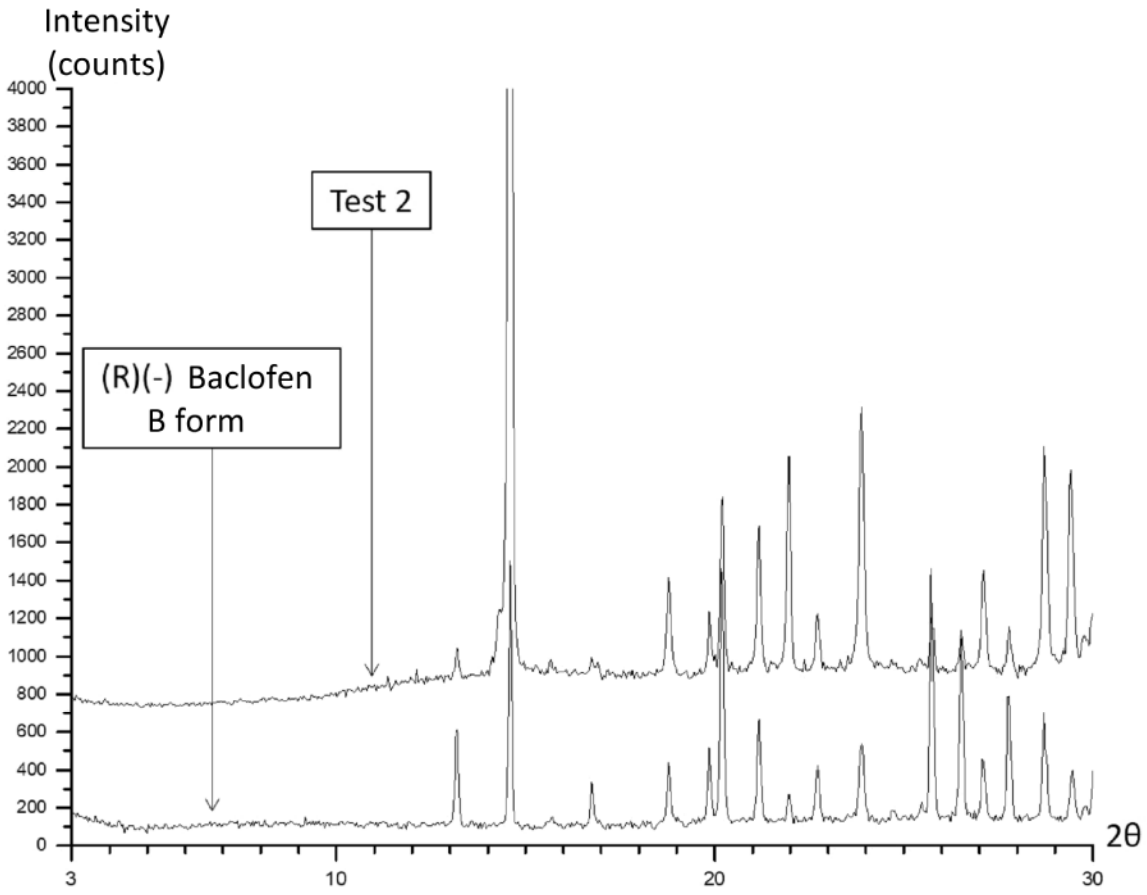


Figure 10

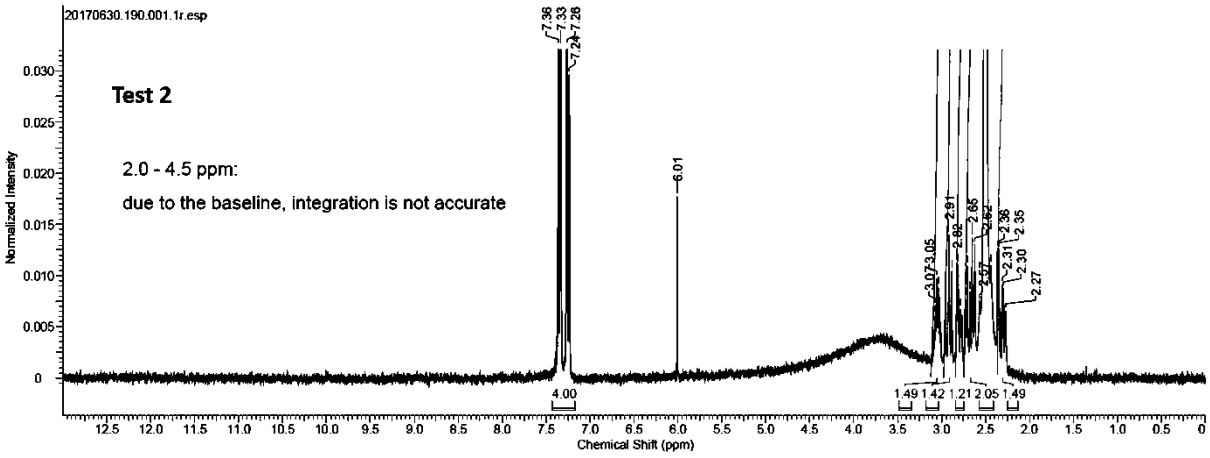


Figure 11

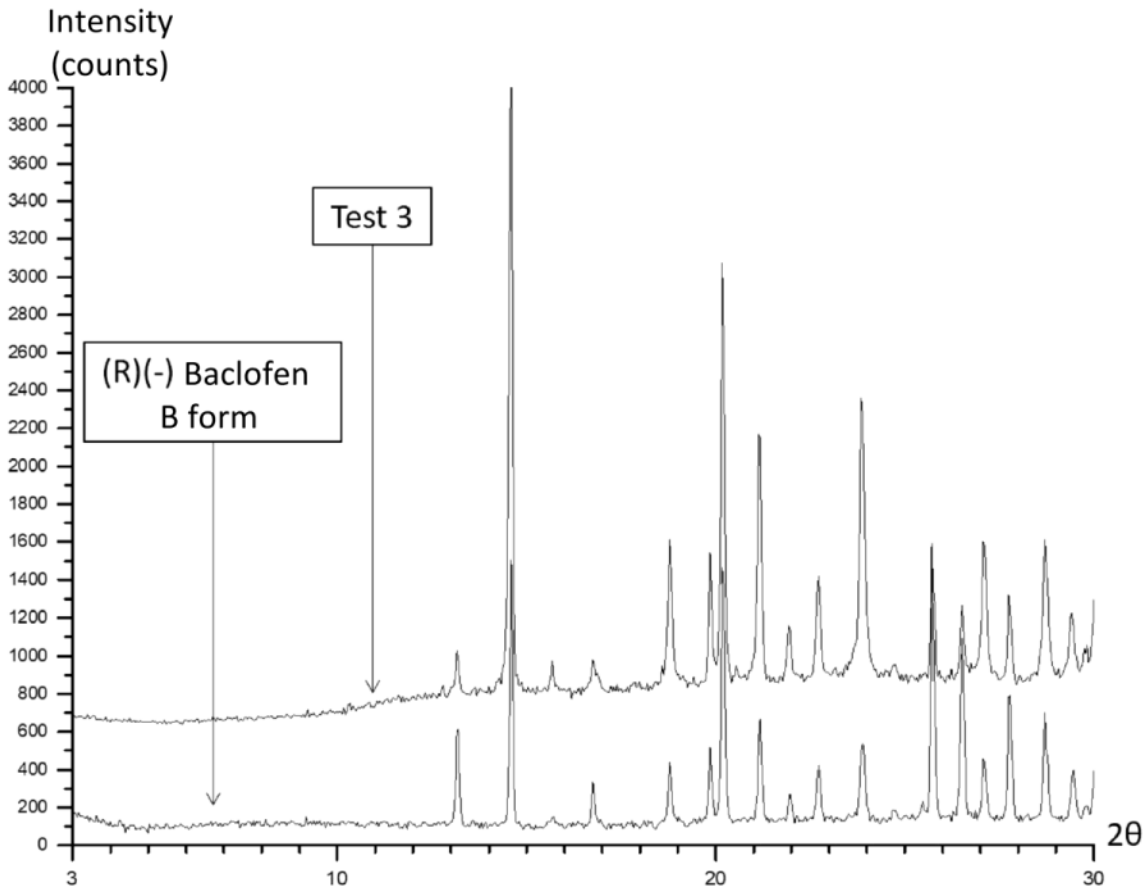


Figure 12

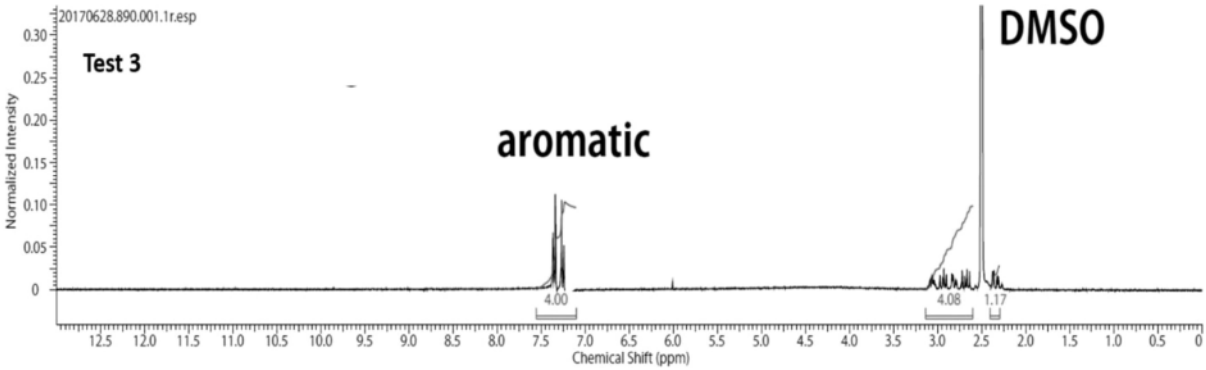


Figure 13

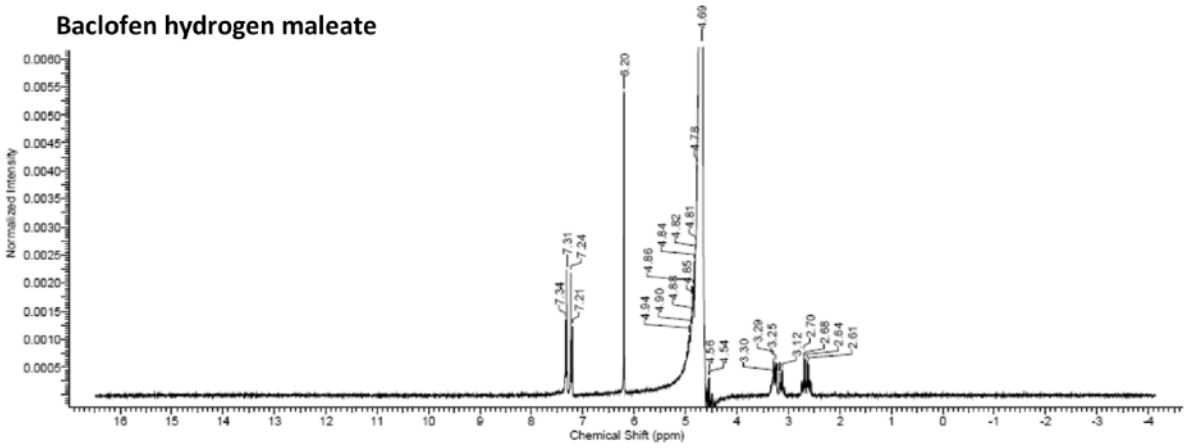


Figure 14

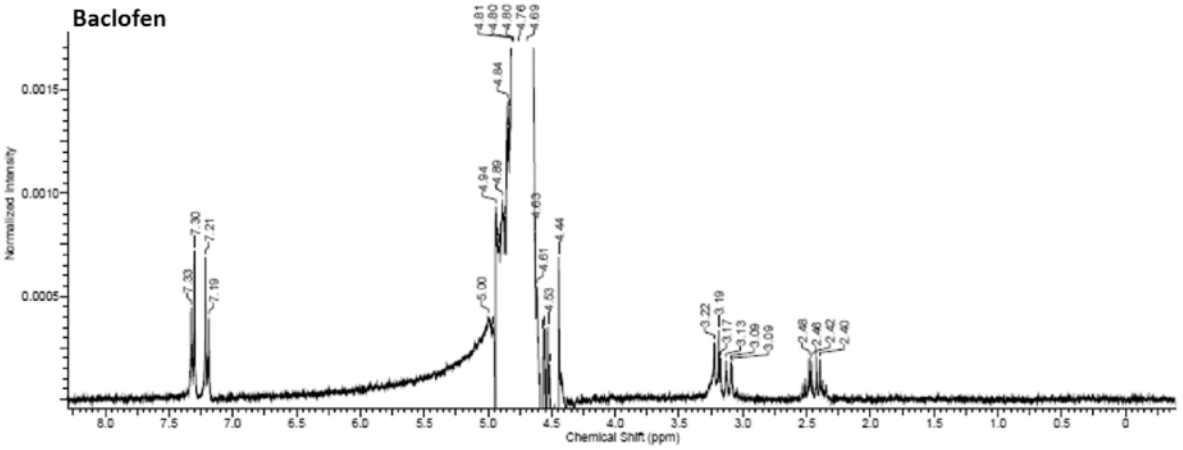


Figure 15

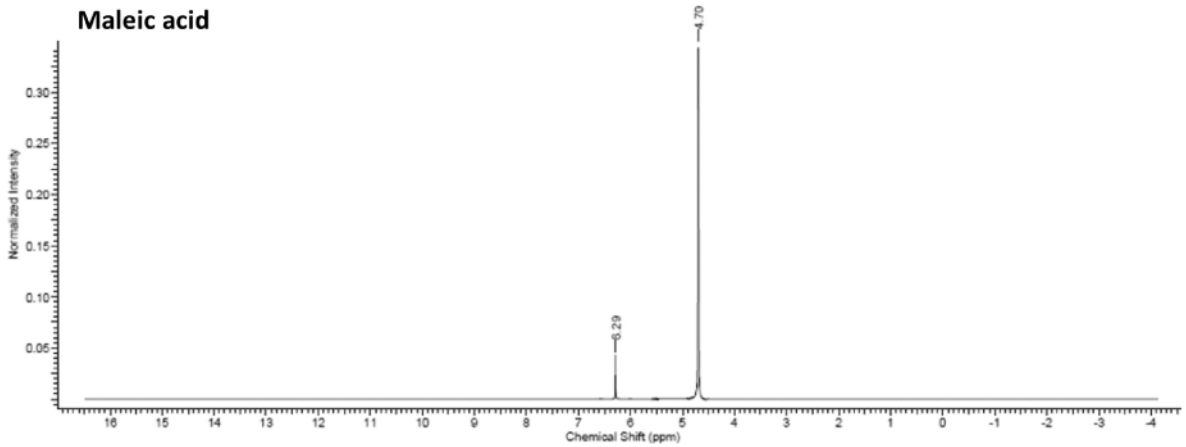


Figure 16