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APPLICATION OF TARTARIC ACID DERIVATIVES IN ENANTIOSEPARATION OF RS-IBUPROFEN

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ABSTRACT

A novel Tartaric acid derivative-based chiral resolving agent has been discovered for the enantiosepration of racemic Ibuprofen [(RS)-2-(4-(2-methyl propyl) phenyl) propanoic acid]. The processinvolves optimization of diastereomeric salt formed between (±) Ibuprofen and optically pure tartaric acid derivatives, followed by separating the individual enantiomer by acid salt preparation. Characterization of the synthesized compound has been carried out by elemental analysis, melting point, FT-IR, UV, HPLC, and ^{1}H NMR spectra. The developed separation method is simple, cost-effective, and industrially viable.

Keywords: Enantiomeric Resolution, Diastereomeric Salt, RS-Ibuprofen, O, O'-Disubstituted Tartaric Acid Derivatives.

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INTRODUCTION

Ibuprofen having a chemical name[(RS)-2-(4-(2-methyl propyl) phenyl) propanoic acid] belong to NSAIDs and is generally used to treat arthritis, degenerative joint deceases, rheumatoid, and inflammatory rheumatic related diseases.[1] The NSAIDs class drugs consist of propanoic acid, and aromatic groups at the alpha position; Naproxen and Ibuprofen are the most recognized and used compounds of this family used for the cure of arthritis and body pains.[2]

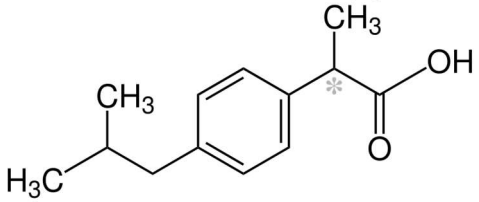


Fig.-1: Molecular Structure of Ibuprofen

In this molecule, the chiral carbon is the α-carbon of the carboxyl group. The S-Ibuprofen is pharmaceutically more active than the R-Ibuprofen.[3] The harmful effect such as gastrointestinal problemswere caused by the R-Ibuprofen. Study shows that the S-Ibuprofen is 160 times more effective than R-Ibuprofen.[4]Hence it is essential to develop a simple and efficient enantioseparation scheme to obtain pure (S)-ibuprofen.[5-7]Currently, there are three ways to produce enantiopure drugs. Chiral pool synthesis is a low-cost way to produce enantiopure drugs using natural or biological approaches like fermentation processes.[8-9] However, this process is restricted by precursors of natural sources. Asymmetric synthesis is a substitute way to produce single enantiomers.[10-11] Developing an appropriate route or efficient catalyst for every molecule is hard. Recently racemic resolution approaches to get single-enantiopure drugs have gotten more interest. These approaches include diastereomeric crystallization, preferential crystallization, enantioselective liquid-liquid extraction, chromatography, capillary electrophoresis, etc.[12-21]Preferential crystallization is the widely used approach for the enantioseparation of the racemic mixture on large scale. Capillary electrophoresis and chromatography methods have high-resolution potential and can be normally used and scaled up productively. These two

methods are limited by the drawbacks of high cost and low yield. The large-scale manufacture of chiral drugs was carried out by the Diastereomeric crystallization technique. Bhushan and Vineet discovered the method for the resolution of (R, S)-Ibuprofen by Thin layer chromatography using silica gel plates.[22] Optically pure L-arginine was used for the impregnation of the silica gel plates which separate the ibuprofen enantiomer by acting as a chiral selector. The enantiomers were identified on the TLC plate by exposure to iodine vapors. The ninhydrin experiment shows the presence of (-)-arginine in both spots, confirming the formation of diastereomers and the separation of enantiomers of (R, S)-ibuprofen. For enantioseparation of Ibuprofen isomers, Melahatsadat and Masoud tried chiral carbon nanotube in their study. They found a considerable adsorption energy difference between the two enantiomers of Ibuprofen inside the chiral carbon nanotube. Hence this carbon nanotube can be used effectively for enantioseparation.[23]Trung and co-workers develop an effective process for the synthesis of R-(-)-Ibuprofen by diastereomer crystallization.[24] The diastereomer obtained in the above process had yields of 56% and 11% respectively which were further purified by liquid-liquid extraction to get 99.97% pure enantiomer with an overall yield of (R)-Ibuprofen2.4%. Rodriguez-Rojo also studied the prospective of the crystallization process to separate the racemic ibuprofen into separate enantiomers.[25] The resolution was performed *via* diastereomeric salt formation and followed by subsequent salt precipitation in a supercritical CO_2 atmosphere. Tartaric acids have been used to resolve several racemic compounds. These can be used in their native and/or derivatized form.[26-27]The uses of L (+) tartaric acid and its derivatives such as disubstituted tartaric acids as resolving agents have been widely studied and are well recognized.[28-30] Report on tartaric acid being used in chromatography as mobile phase additives is also available.[31]However most of the available methods had limitations for their use on an industrial scale with greater efficacy. Hence there is a requirement to develop a new simple and cost-efficient method. In this invention, we describe a new simple economical, and efficient process for the preparation of both enantiomers of Ibuprofen and their salts, in unexpectedly good yield and enantiomeric purity by using O,O'-di-*p*-toluoyl-D-tartrate as a resolving agent which is not used by any researcher in the available literature. The separation method comprises the reaction of the mixture of isomers with either O,O'-di-*p*-toluoyl-D-tartaric acid or O,O'-di-*p*-toluoyl-L-tartaric acid in an organic solvent containing sufficient isopropanol for the precipitation of (S)- (-)-ibuprofen- O,O'-di-*p*-toluoyl-D-tartrate (I-D-DTTAS) or (R)-(-)-ibuprofen- O, O'-di-*p*-toluoyl-L-tartrate(I-L-DTTAR) respectively. The separation of the precipitate was carried out by filtration. The precipitate and the filtrate obtained were enriched in the desired isomer.

EXPERIMENTAL

Material and Methods

The chemicals and reagents used in this study are listed in Table-1 and used without further purification.

Table-1: Reagent and Chemicals Used

Sr. No.	Reagent Name	Purchased from
1	RS-Ibuprofen	Zeta Scientific, Malaysia
2	O, O'-Di- p -toluoyl- L-tartaric acid (L-DTTA)	Loba Chemie Pvt Ltd
3	Isopropanol	Rankem
4	Acetonitrile	Rankem
5	O, O'-Di- p -toluoyl- D-tartaric acid (D-DTTA)	Loba Chemie Pvt Ltd
6	Dimethylformamide	Rankem
7	Gentisic acid (2,5-Dihydrobenzoic acid)	Tokyo Chemical industry Co., Ltd., Japan
8	Sodium hydroxide	Thomas Baker

Analytical Method

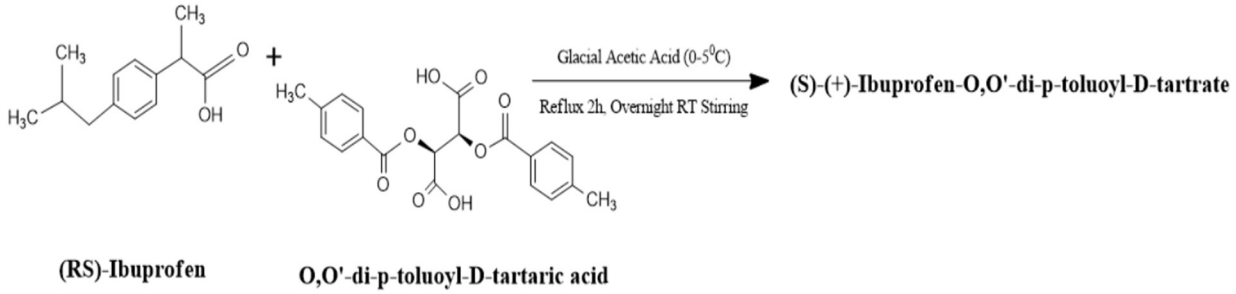
The estimation of ibuprofen enantiomers was done by a chiral high-performance liquid chromatographic technique using a UV detector (Shimadzu Prominence I series) at 220 nm wavelength. The HPLC Column from DAICEL, Chiralpak – AGP (*α 1-acid glycoprotein*) of (100 x 4.6) mm, 5.0µm, and guard column of (10 x 4.0) mm, 5.0µm were used. The mobile phase was prepared by mixing 98 volumes of sodium dihydrogen orthophosphate buffer solution (0.1 mol L^{-1}) and 2 volumes of organic solvent i.e., methanol. The flow rate of the HPLC system was maintained at 0.5 mL/min. The column compartment of HPLC was operated at 25ºC temperature. 20 µL of sample solution was injected into the system. The

retention time of R-ibuprofen and S-ibuprofen was observed at about 8.0 min and 11.0 min respectively.[31] Jasco Polarimeter (Model No. P-2000) was used for observation of the optical rotation. JASCO V-650 spectrophotometer was used for the measurement of absorption spectra of compounds. Perkin-Elmer spectrum-100 spectrophotometer was used for the recording of the infrared absorption spectrum. The ^{1}H NMR spectra of obtained compounds were obtained by using Brucker AV 400 NMR spectrometer in Dimethyl Sulfoxide solvent. Flash 2000 CHNS/O analyzer was used for elemental analysis of the compounds.

General Procedure

Preparation of Diastereomeric Compound of (S)- (+)-Ibuprofen and D-tartaric Acid Derivative (I-D-DTTAS)

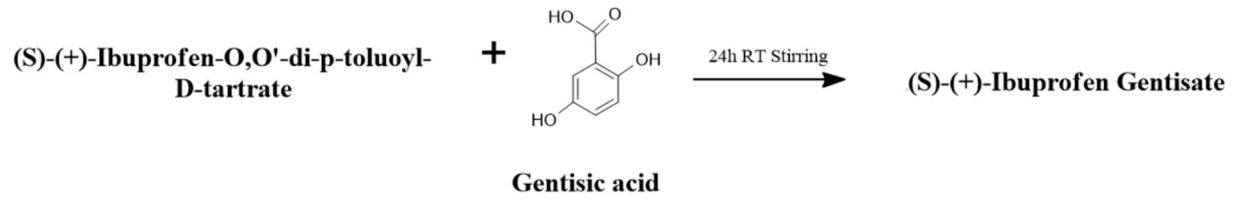
16.36 g (0.079 mol) of (R, S)-Ibuprofen was dissolved in isopropanol and this mixture was cooled to 0 - 5ºC. Maintaining the temperature glacial acetic acid (1mL) was added dropwise. To this reaction mixture, D-DTTA solution dissolved in 50mL of isopropanol was gradually added. The mixture was then heated in a water bath up to 90ºC for 2hours and permitted to stand overnight at 25ºC temperature. The solid precipitate obtained was filtered, washed with 50% isopropanol, and recrystallized in isopropanol (Scheme-1).



Scheme-1: Reaction Scheme of (S)- (+)-Ibuprofen-O,O'-di-*p*-toluoyl-D-tartrate Preparation

Preparation of (S)- (+)-Ibuprofen Gentisate

5.88 g of the I-D-DTTAS was stirred for 30 minutes in a mixture of an equal volume of 2 N NaOH and methylene dichloride. Later, the organic layer from this mixture was filtered and further washed with water.1.54 g of gentisic acid dissolved in 5 mL of acetone was added to this organic layer and further this solution was continuously stirred at room temperature for 24 hours. The obtained solid precipitate was filtered and dried at 50° C under vacuum (Scheme-2).



Scheme-2: Reaction Scheme of (S)- (+)-Ibuprofen Gentisate Preparation

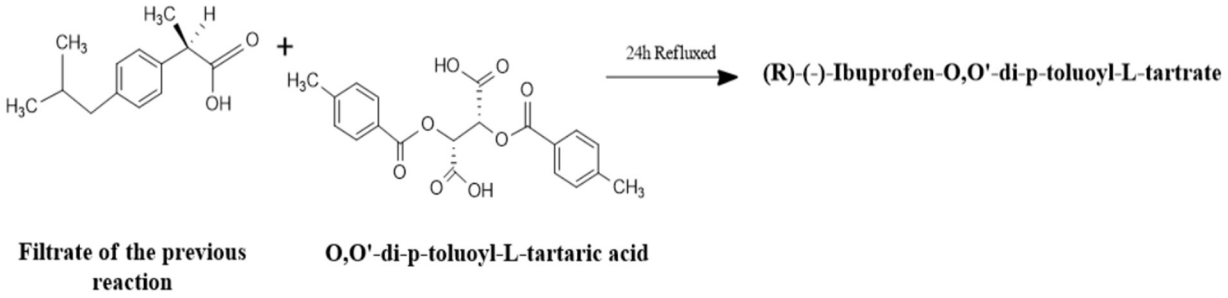
Preparation of Diastereomeric Compound of (R)- (-)-Ibuprofen and L-tartaric Acid Derivative (I-L-DTTAR)

A filtrate of reaction (scheme-1) of preparation of I-D-DTTAS and 0.25 molar equivalent of L-DTTA (3.58g) was mixed and heated in a water bath at 100ºC under a nitrogen atmosphere with stirring for 48 hours. The obtained solid precipitate was filtered and recrystallized by using isopropanol and dried at 50° C under a vacuum (Scheme-3).

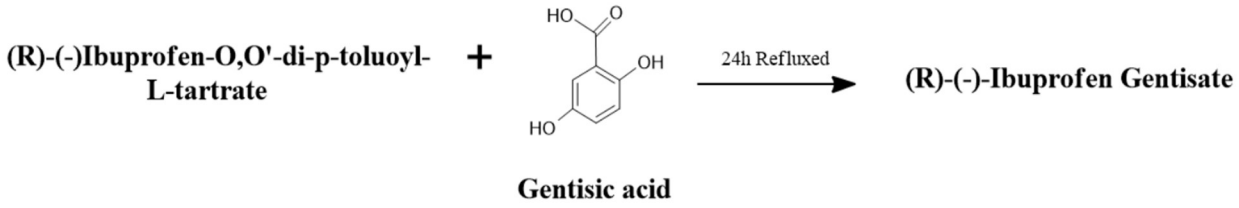
Preparation of (R)- (-)-Ibuprofen Gentisate

5.88 g of the I-L-DTTAR was stirred for 30 minutes in a mixture of an equal volume of 2 N NaOH and

methylene dichloride. Later, the organic layer from this mixture was filtered and further washed with water. 1.54 g of gentisic acid dissolved in 5 mL of acetone was added to this organic layer and further this solution was continuously stirred at room temperature for 24 hours. The obtained solid precipitate was filtered and dried at 50°C under vacuum (Scheme-4).



Scheme-3: Reaction Scheme of (R)- (-)-Ibuprofen-O,O'-di-*p*-toluoyl-L-tartrate Preparation



Scheme-4: Reaction Scheme of (R)- (-)-Ibuprofen Gentisate Preparation

RESULTS AND DISCUSSION

Synthesized compounds are characterized by using modern analytical techniques such as UV-Visible spectroscopy, Fourier transmission spectroscopy FT(IR), Proton magnetic resonance spectroscopy, chromatographic analysis, determination of elements, and specific optical rotation analysis.

Characterization of a Diastereomeric Compound of (S)- (+)-Ibuprofen and D-tartaric Acid Derivative (I-D-DTTAS)

A new compound I-D-DTTAS has been prepared. After filtration and washing with isopropanol, the bright colorless and crystalline mass was obtained. The obtained compound was soluble in dimethylformamide, dimethyl sulphoxide, alcohol, chloroform, etc. The characterization data resembles the molecular weight of 574.61g/mol and molecular formula $C_{33}H_{34}O_9$.The I-D-DTTAS has a melting point of 129°C and the chiral purity of the I-D-DTTAS was 96.38% by HPLC. Elemental analysis of $C_{33}H_{34}O_9$: C 68.76%, H 5.89%, O 24.93% theoretical: C 68.92%, H 5.92%, O 25.06%. The FT(IR) spectra of the I-D-DTTAS were measured from 4500–400cm^{-1}shows a characteristic band at 3296cm^{-1}corresponds to the (-OH) hydroxyl group. The bands due to stretching vibration of aromatic C=C and C-H are observed at 3024 and 3214cm^{-1}. The band at 1681 cm^{-1}correspond to the stretching vibration of >C=O group. The molecular structure of I-D-DTTAS is further confirmed by the proton signs obtained from the PMR spectrum as given in Table-2.

Table-2: PMR Spectrum Data of I-D-DTTAS

δ ppm	Band assignment
10.73 (s) (1H)	Hydroxyl (-OH) group
7.08-7.41 (m), (12H)	Benzene rings
3.61 (m) (1H)	Methine (-CH<) group
3.36 (q) (1H)	Methine (-CH<) group
2.42 (t) (6H)	Methyl (-CH3)2 group
2.00 (s) (2H)	Methylene (-CH2-) group
1.36 (d) (3H)	Methyl (-CH3) group
0.84 (s) (6H)	Methyl (-CH3)2 group

Characterization of (S)- (+)-Ibuprofen Gentisate

A new compound (S)-(+)-Ibuprofen Gentisate has been prepared. After filtration and washing with isopropanol, the bright yellow and crystalline mass was obtained. The obtained compound was soluble in dimethylformamide, dimethyl sulphoxide, alcohol, chloroform, etc. The characterization data resembles the molecular weight of 342.39 g/mol and molecular formula $C_{22}H_{22}O_5$.The (S)-(+)-Ibuprofen Gentisate has a melting point of 115°C and chiral purity of the (S)-(+)-Ibuprofen Gentisate is 97.39 % by HPLC. The optical rotation of the 2% solution of the compound in ethanol was [α]20 + 61.35°. Elemental analysis of $C_{22}H_{22}O_5$: C 70.12%, H 6.41%, O 23.33% theoretical: C 70.16%, H 6.48%, O 23.36%.The FT(IR)spectra of the (S)-(+)-Ibuprofen gentisate was measured in the range of 4500 – 400cm^{-1}showingthe characteristic band at 3350cm^{-1}corresponds to the phenolic hydroxyl group. The bands at 3096cm^{-1} and 3029cm^{-1} in the spectrum correspond to the stretching vibration of aromatic C=C and C-H respectively. The observed band at 1695 cm^{-1}correspond to carbonyl stretching vibration of >C=O group in (S)-(+)-Ibuprofen Gentisate. The molecular structure of the (S)-(+)-Ibuprofen Gentisate is further confirmed by the proton signs obtained from the PMR spectrum as given in Table-3.

Table-3: PMR Spectrum Data of (S)- (+)-Ibuprofen Gentisate

δ ppm	Band assignment
10.58 (s) (2H)	hydroxyl (-OH) group
6.44-7.19 (m), (7H)	Benzene rings
3.59 (m) (1H)	Methine (-CH<) group
2.75 (d) (2H)	Methylene (-CH2-) group
1.81 (q) (1H)	Methine (-CH=)
1.75 (d) (3H)	Methyl (-CH3)
0.85 (d) (6H)	Methyl (-CH3)2

Characterization of a Diastereomeric Compound of (R)- (-)-Ibuprofen and L-tartaric Acid Derivative (I-L-DTTAR)

A new compound I-L-DTTAR has been prepared. After filtration and washing with isopropanol, the bright colorless and crystalline mass was obtained. The obtained compound was soluble in dimethylformamide, dimethyl sulphoxide, alcohol, chloroform, etc.The characterization data resembles the molecular weight of 574.61g/mol and molecular formula $C_{33}H_{34}O_9$.The I-L-DTTAR has a melting point of 131°C and the chiral purity of the I-L-DTTAR is 96.08% by HPLC. Elemental analysis of $C_{33}H_{34}O_9$: C 68.76%, H 5.31%, O 25.00% theoretical: C 68.92%, H 5.92%, O 25.06%. The FT(IR)spectra of the I-L-DTTAR were measured from 4500 – 400cm^{-1}showinga characteristic band at 3295cm^{-1}corresponds to the (-OH)hydroxyl group. The bands at 3174 and 3214 cm^{-1} in the spectrum correspond to the stretching vibration of aromatic C=C and C-H respectively. The >C=O in the carbonyl group shows stretching vibration at 1638 cm^{-1}. The molecular structure of I-L-DTTAR is further confirmed by the proton signs obtained from the PMR spectrum as given in Table-4.

Table-4: PMR Spectrum Data of I-L-DTTAR

δ ppm	Band assignment
10.73 (s) (1H)	Hydroxyl (-OH)
3.59 (m) (1H)	Methine (-CH<)
3.95 (q) (1H)	Methine (-CH<)
7.08-7.41 (m), (12H)	Benzene rings
1.35 (d) (3H)	Methyl (-CH3)
0.86(s) (6H)	Methyl (-CH3)2
2.40 (d) (6H)	Methyl (-CH3)2
1.80 (t) (2H)	Methylene(-CH2-)

Characterization of (R)- (-)-Ibuprofen Gentisate

A new compound (R)-(-)-Ibuprofen Gentisate has been prepared. After filtration and washing with isopropanol, the bright yellow and crystalline mass was obtained. The obtained compound was soluble in dimethylformamide, dimethyl sulphoxide, alcohol, chloroform, etc. The characterization data resembles the molecular weight of 342.39 g/mol and molecular formula $C_{22}H_{22}O_5$.The (R)-(-)-Ibuprofen Gentisate has a melting point of 118°C and chiral purity of the (R)-(-)-Ibuprofen Gentisate is 96.66% by HPLC. The

optical rotation of the 2% solution of the compound in ethanol was [α]20 - 61.89°. Elemental analysis of $C_{22}H_{22}O_5$: C 70.12%, H 6.35%, and O 23.29% theoretical: C 70.16%, H 6.48%, O 23.36%.The FT(IR) spectra of the (R)-(-)-Ibuprofen gentisate was measured in the range of 4500 – 400cm^{-1}shows a characteristic band at 3301cm^{-1}corresponds to the phenolic hydroxyl group. The bands at 2918cm^{-1}and 3191cm^{-1} in the spectrum correspond to the stretching vibration of aromatic C=C and C-H respectively. The >C=O in the carbonyl group shows stretching vibration at 1599 cm^{-1}.The molecular structure of the (R)-(-)-Ibuprofen Gentisate is further confirmed by the proton signs obtained from the PMR spectrum as given in Table-5.

Table-5: PMR Spectrum Data of (R)- (-)-Ibuprofen Gentisate

δ ppm	Band assignment
10.53 (s) (2H)	hydroxyl (-OH)
6.44-7.19 (m), (7H)	Benzene rings
3.59 (m) (1H)	Methine (-CH<)
3.39 (d) (2H)	Methylene (-CH_2-)
1.85 (m) (1H)	Methine (-CH=)
1.78 (d) (3H)	Methyl (-CH_3)
0.85 (d) (6H)	Methyl (-CH_3)$_2$

The compounds: O,O'-di-*p*-toluoyl-D-tartrate and O,O'-di-*p*-toluoyl-L-tartrate are used first time as resolving agents for the enantioseparation of RS Ibuprofen.
The best possible structures of the diastereomers and final enantiomeric salts on the basis of elemental and spectral analysis; are shown in the following Figs.- 2 to 5:

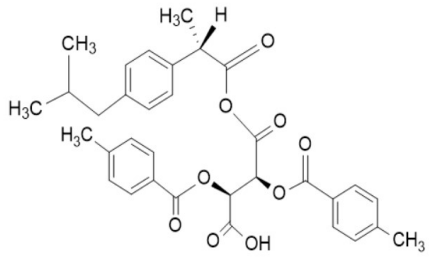


Fig.-2: (S)- (+)-Ibuprofen-O, O'-di-*p*-toluoyl-D-tartrate

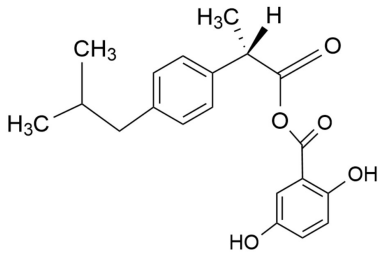


Fig.-3: Structure of (S)- (+)-Ibuprofen Gentisate

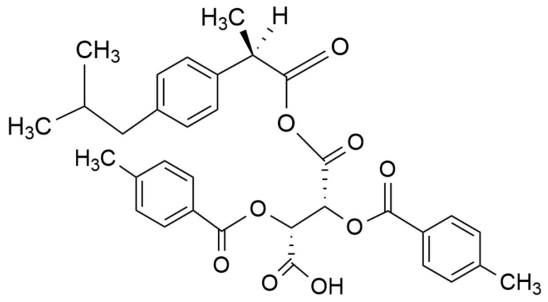


Fig.-4: (R)- (-)-Ibuprofen-O, O'-di-*p*-toluoyl-L-tartrate

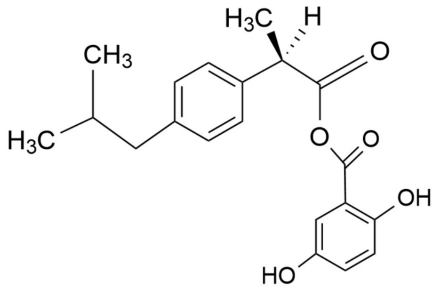


Fig.-5: Structure of (R)- (-)-Ibuprofen Gentisate

CONCLUSION

The present work has explored the enantioselective synthesis of racemic ibuprofen using O, O'-disubstituted tartaric acid derivatives in acetonitrile/isopropanol solvent. The process included the formation of the diastereomeric salt between the ibuprofen enantiomers and the optically active D-DTTA and L-DTTA derivatives. It was found that the S-Ibuprofen has the strongest recognition ability with D-DTTA derivatives and R-Ibuprofen has the strongest recognition ability with L-DTTA derivatives. The

diastereomeric salt obtained on treatment with base and gentisic acid give optically active (S)- (+)-Ibuprofen gentisate and (R)- (-)-Ibuprofen gentisate. The use of optically active D-DTTA and L-DTTA as a resolving agent for the separation of (RS)-Ibuprofen was established in this study. The process is easy and no need to use complicated and costly equipment, expensive reagents, and complicated operations, thus making it economical and industrially viable.

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