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Separation of Amlodipine Enantiomers by Diastereomeric Salt Formation

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Abstract: Despite the dramatic development of enantioselective synthesis and chromatographic separation methods, optical resolution still remains the most cost effective and operationally simplest method for producing pure enantiomers on an outsized scale. No extreme conditions or expensive reagents are required, and resolving agents are often recovered. The present invention relates to method of resolving racemic amlodipine into enantiomerically enriched composition with good yield and high optical purity by precipitation with tartaric acid derivative in the presence of non-aqueous solvent. Optically active O, O'-Di-p-toluoyl-D-tartaric acid and O, O'-Di-p-toluoyl-L-tartaric acid is used as chiral reagent. The process can be performed by first reacting racemic amlodipine and O, O'-Di-p-toluoyl-tartaric acid in the presence of solvent mixture including acetonitrile/isopropanol in the ratio of 1/9v/v to produce (R) or (S) amlodipine di-p-toluoyl tartrate diastereomer. Further treating the prepared (R) or (S) amlodipine diastereomeric salt with a base and gentisic acid obtaining enantiomerically pure (R) or (S) amlodipine gentisate.

Keywords: (RS)-Amlodipine, Enantiomeric Resolution, O, O'-Di-p-toluoyl-tartaric acid, Diastereomeric salt, Isopropanol.

I. INTRODUCTION

Amlodipine with a chemical name 3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate, is a potent third generation dihydropyridine derivatives calcium channel blocker useful as an anti-ischemic and anti-hypertensive agent when administrated alone and in grouping with other antihypertensive agents. Amlodipine has one chiral center, due to the presence of an asymmetric carbon atom in position 4, which automatically generate two optical isomers. Amlodipine is available in pharmaceutical dosage form as racemic mixture. Amlodipine is a racemic mixture of two enantiomers S-(-) isomer and R-(-) isomer. Two enantiomers of racemic drug often act differently with each other in bio-environment and the enantiomers can exhibit different pharmacokinetic and pharmacodynamic properties (Huisman & Collier, 2013). The difference in pharmacodynamic and pharmacokinetic properties of enantiomers is related to the differences in affinity or intrinsic activity at receptor sites.

The pharmacological activity may reside only in one enantiomer, while the other may be inactive or have desirable or undesirable activity (Nguyen et al., 2006). Production of the chiral molecule is one of the rapidly progressing fields of modern science. Importance of this field is growing continuously due to various therapeutic benefits of single enantiomers over racemic (Tishkov & Zaitseva, 2008).

It is known that two enantiomers of amlodipine have different pharmacological profiles. (S)-amlodipine shows a potent calcium channel blocking activity (Abernethy, 1989) whereas (R)-amlodipine has been shown to release nitric oxide into the peripheral blood vessel which can cause peripheral edema (Lee et al., 2009). Hence so as to scale back the incidence of peripheral edema and other side effects, it's beneficial to separate (R)-amlodipine from racemic amlodipine (Park et al., 2006). The (R)-amlodipine is additionally shown to be effective within the treatment or prevention of atherosclerosis. In sight of the pharmacological studies of such drug the separation of enantiomers constitutes a serious challenge from the stand point of efficacy and safety of drug (Reddy & Mehvar, 2004).

From the literature serve it's found that there are many methods tried for the enantioseparation of amlodipine from the racemic mixture. Arrowsmith and John Edmund in European patent separated the racemic mixture of Amlodipine by formation of its salts with cinchonidine and separating said salt into its diastereomeric form by fractional crystallisation

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(Arrowsmith & Edmud, 1989). Spargo et al (1997) and Gharpure (2008) in international publication uses L- or D-tartaric acid in an organic solvent containing sufficient Dimethyl sulfoxide (DMSO) and Dimethyl formamide (DMF) respectively. Enantioselective extraction of racemic amlodipine using tartaric acid and cyclodextrin derivatives as chiral selectors reported by Abdul Halim et al, (2011).

In the present work we carried out a method for optical resolution of amlodipine enantiomer from (R, S)-amlodipine by using acetonitrile/isopropanol solvent mixed in the ratio of (1/9) and optically active O, O'-Di-p-toluoyl-tartaric acid as a resolving agent. Further on reacting with gentisic acid form amlodipine gentisate.

II. EXPERIMENTAL PROCEDURE

A. Reagent and Chemicals

All reagents and chemicals used in this work are; racemic amlodipine was purchased from Zeta Scientific, Malaysia. O, O'-Di-p-toluoyl-D-tartaric acid, O, O'-Di-p-toluoyl-L-tartaric acid was purchased from Loba Chemie Pvt Ltd. Gentisic acid (2,5-Dihydrobenzoic acid) was purchased from Tokyo Chemical industry, Japan). The other solvents and chemicals such as acetonitrile, isopropanol, Dimethyl formamide, Sodium hydroxide etc. used in this work were of AR grade, commercially available and used without further purification.

B. Preparation of (S)-(-)-amlodipine-O,O'-di-p-toluoyl-D-tartrate (ADTAS_D) by using O,O'-di-p-toluoyl-D-tartaric acid as resolving agent.

16.36 g of (R, S)-amlodipine was dissolved in a 200 mL of solvent mixture prepared by mixing an acetonitrile /isopropanol in the ratio of 1/9 v/v and heated at 55° C while stirring. To this solution 3.58 g (0.25 molar equivalent) of O, O'-di-p-toluoyl-D-tartaric acid dissolved in 50 ml of solvent prepared by mixing an acetonitrile/isopropanol in the ratio of 1/9 v/v was added and stirring was performed for 24h. The resulting solid substance was filtered and collected, washed with 50 mL of solvent prepared my mixing an acetonitrile/isopropanol in the ratio of 1/9 v/v and dried under vacuum at 50° C. (Scheme 1)

C. Preparation of (S)-(-)-amlodipine gentisate (ADGAS_D) by using O,O'-di-p-toluoyl-D-tartaric acid as resolving agent.

5.88 g of the (S)-(-)-amlodipine-O,O'-di-p-toluoyl-D-tartrate was stirred in a mixture of 56 mL of methylene dichloride and 56 mL of 2N NaOH (aqueous solution) for 30 minutes. Subsequently, the organic layer was separated and washed once with water. The organic layer was filtered with a filter paper, 1.54 g of gentisic acid dissolved in 5 mL of acetone was added and stirring was performed for 2 hours at room temperature. The resulting solid substance was filtered, collected and dried under vacuum at 50° C. (Scheme 2)

D. Preparation of (R)-(+)-amlodipine-O,O'-di-p-toluoyl-L-tartrate: (ALTAR_D) by using O,O'-di-p-toluoyl-D-tartaric acid as resolving agent.

3.58 g (0.25 molar equivalent) of O, O'-di-p-toluoyl-L-tartaric acid dissolved in 50 mL of solvent mixture prepared by mixing an acetonitrile/ isopropanol in the ratio of 1/9 v/v was added into the filtrate of (S)-(-)-amlodipine-O, O'-di-p-toluoyl-D-tartrate and heated at 55°C for 12 h while stirring. The resulting solid substance was filtered, collected and washed with 50 mL of solvent prepared by mixing an acetonitrile/isopropanol in the ratio of 1/9 v/v and dried under vacuum at 50° C. (Scheme 3)

E. Preparation of (R)-(+)-amlodipine gentisate (ALGAR_D) by using O,O'-di-p-toluoyl-D-tartaric acid as resolving agent.

3 g of the (R)-(+)-amlodipine-O, O'-di-p-toluoyl-L-tartrate was stirred in a mixture of 56 mL of methylene dichloride and 56 mL of 2N NaOH (aqueous solution) for 30 minutes. Subsequently, the organic layer was separated and washed once with water. The organic layer was filtered with a filter paper, 1 g of gentisic acid dissolved in 5 mL of acetone was added and stirring was performed for 2 h at room temperature. The resulting solid substance was filtered, collected and dried under vacuum at 50° C. (Scheme 4)

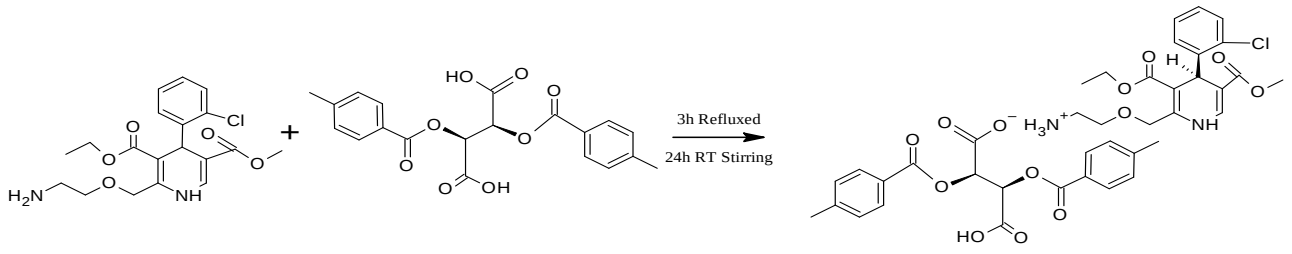
F. Preparation of (R)-(+)-amlodipine-O,O'-di-p-toluoyl-L-tartrate (ALTAR_L) by using O,O'-di-p-toluoyl-L-tartaric acid as resolving agent.

16.36 g of (R, S)-amlodipine was dissolved in a 200 mL of solvent mixture prepared by mixing an acetonitrile/isopropanol in the ratio of 1/9 v/v and heated at 55°C while stirring. To this solution 3.58 g (0.25 molar equivalent) of O, O'-di-p-toluoyl-L-tartaric acid dissolved in 50 mL solvent mixture prepared by mixing an acetonitrile/ isopropanol in the ratio of 1/9 v/v was added and stirring was performed for 24h. The resulting solid substance was filtered and collected, washed with 50 mL of solvent mixture prepared by mixing an acetonitrile/isopropanol in the ratio of 1/9 v/v and dried under vacuum at 50° C. (Scheme 5)

G. Preparation of (R)-(+)-amlodipine gentisate (ALGAR_L) by using O,O'-di-p-toluoyl-L-tartaric acid as resolving agent.

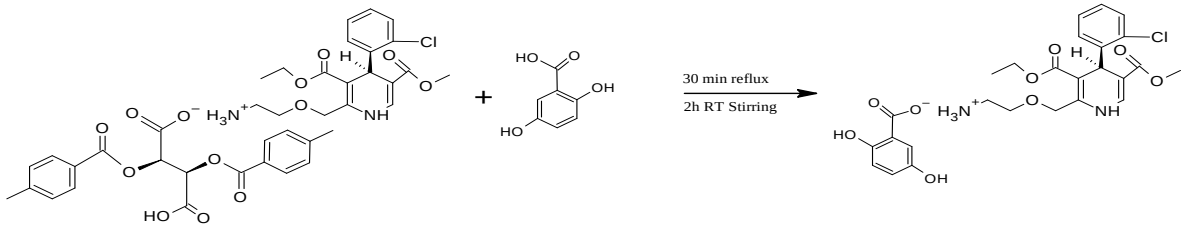
5.88 g of the (R)-(-)-amlodipine-O, O'-di-p-toluoyl-L-tartrate was stirred in a mixture of 56 mL of methylene dichloride and 56 mL of 2N NaOH (aqueous solution) for 30 minutes. Subsequently, the organic layer was separated and washed once with water. The organic layer was filtered with a filter paper, 1.54 g of gentisic acid dissolved in 5 mL of acetone was added and stirring was performed for 2hours at room temperature. The resulting solid substance was filtered, collected and dried under vacuum at 50° C. (Scheme 6)

Scheme 1



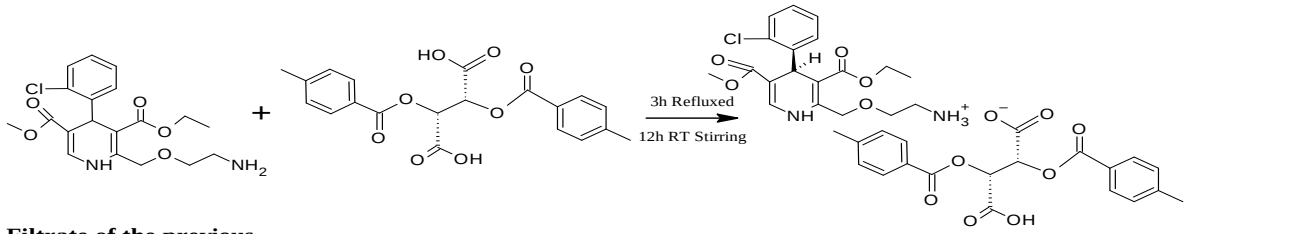
(RS)-Amlodipine **O,O'-di-p-toluoyl-D-tartaric acid** **(S)-(-)-Amlodipine-O,O'-di-p-toluoyl-D-tartrate**

Scheme 2



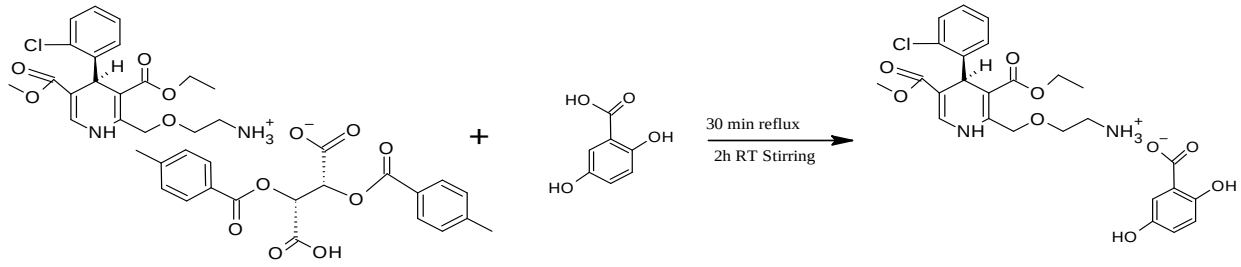
(S)-(-)-Amlodipine-O,O'-di-p-toluoyl-D-tartrate **Gentisic acid** **(S)-(-)-Amlodipine Gentisate**

Scheme 3



Filtrate of the previous reaction of (RS)-Amlodipine **O,O'-di-p-toluoyl-L-tartaric acid** **(R)-(+)-Amlodipine-O,O'-di-p-toluoyl-L-tartrate**

Scheme 4



(R)-(+)-amlodipine-O,O'-di-p-toluoyl-L-tartrate **Gentisic Acid** **(R)-(+)-Amlodipine Gentisate**

H. Preparation of (S)-(-)-amlodipine-O,O'-di-p-toluoyl-D-tartrate (ADGAS_L) by using O,O'-di-p-toluoyl-L-tartaric acid as resolving agent.

3.58 g (0.25 molar equivalent) of O, O'-di-p-toluoyl-D-tartaric acid dissolved in 50 mL of mixture of solvents mixture prepared by mixing an acetonitrile/ isopropanol in the ratio of 1/9 v/v was added into the filtrate of (R)-(+)-amlodipine-O, O'-di-p-toluoyl-L-tartrate and heated at 55° C for 12 h while stirring. The resulting solid substance was filtered and collected, washed with 50 mL of mixture of solvent mixture prepared by mixing an acetonitrile/isopropanol in the ratio of 1/9 v/v and dried under vacuum at 50°C. (Scheme 7)

I. Preparation of (S)-(-)-amlodipine gentisate (ADGAS_L) by using O,O'-di-p-toluoyl-L-tartaric acid as resolving agent.

3 g of the (S)-(-)-amlodipine-O, O'-di-p-toluoyl-D-

tartrate was stirred in a mixture of 56 mL of methylene dichloride and 56 mL of 2N NaOH (aqueous solution) for 30 minutes. Subsequently, the organic layer was separated and washed once with water. The organic layer was filtered with a filter paper, 1 g of gentisic acid dissolved in 5 mL of acetone was added and stirring was performed for 2hours at room temperature. The resulting solid substance was filtered, collected and dried under vacuum at 50° C. (Scheme 8)

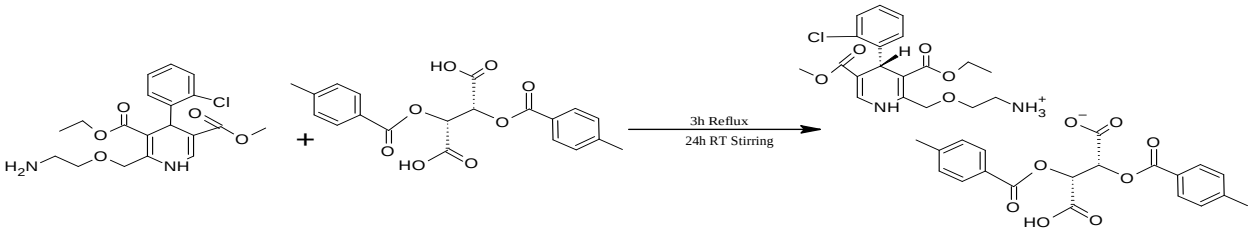
J. Analytical Method

The analytical method performed for monitoring of the process by following U.S. Patent No. 6646131 B2 (Zhang, 2003) are as follows. The chromatographic separation of the product carried out by using an Ultron ES-OVM, Ovomucoid chiral column (150 mm X 4.6 mm) 5µm, manufactured by Phenomenex. The chromatographic system consists of Shimadzu Prominence i series. The Chromatographic system was equipped with a builtin Solvent degasser, quaternary pump, column compartment photodiode assay detector with variable wavelength and autosampler. Data analysis was carried out by using Labsolution software. The pH of the aqueous phase was measured by using pH meter of Lab India (Model: Pico +), The Specific optical rotation of the resultant compound was measured by using Jasco Polarimeter (Model No. P-2000). Infrared spectrums were recorded using KBr pellets on a Perkin-Elmer spectrum-100 spectrophotometer. The absorbance spectra of the compounds obtained were recorded on JASCO V-650 spectrophotometer. Elemental analysis was recorded on Flash 2000 CHNS/O analyzer.1H NMR spectra of compounds were recorded in DMSO by using Brucker AV 300 NMR spectrometer.

K. Chromatographic Condition:

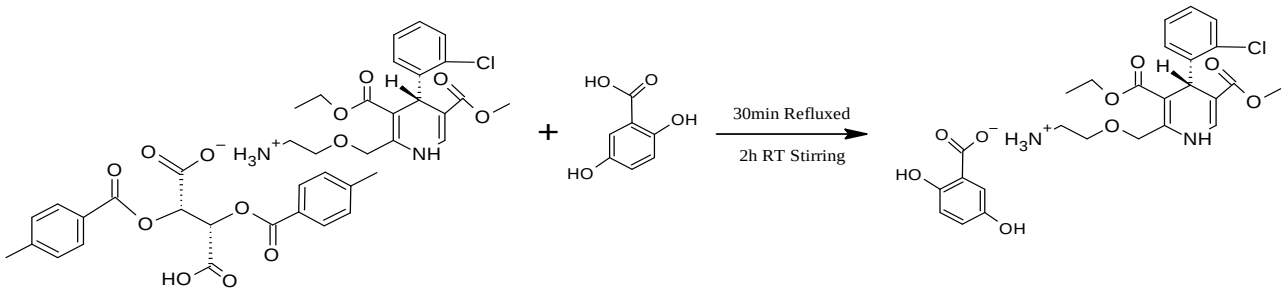
The optical purity of the compound prepared was measured by chiral HPLC method. The chromatographic separation of the amlodipine enantiomers was carried out by using Ultron ES-OVM ovomucoid chiral column (150mm x 4.6mm), 5µ. The mobile phase used for the separation was dibasic sodium phosphate buffer (20mM, pH 7.0) and Acetonitrile (80:20 v/v). The flow rate of the mobile phase was 1.0 mL/min. The HPLC column was thermostat at 25°C. The injection volume was 10µL. The detection of the compound was done by using photodiode array detector at 360 nm wavelength. The retention time of R-Amlodipine was about 8.0 minutes and for S-Amlodipine was about 11.0 minutes. Sample solution was prepared in Acetonitrile at 0.1 mg/mL concentration.

Scheme 5



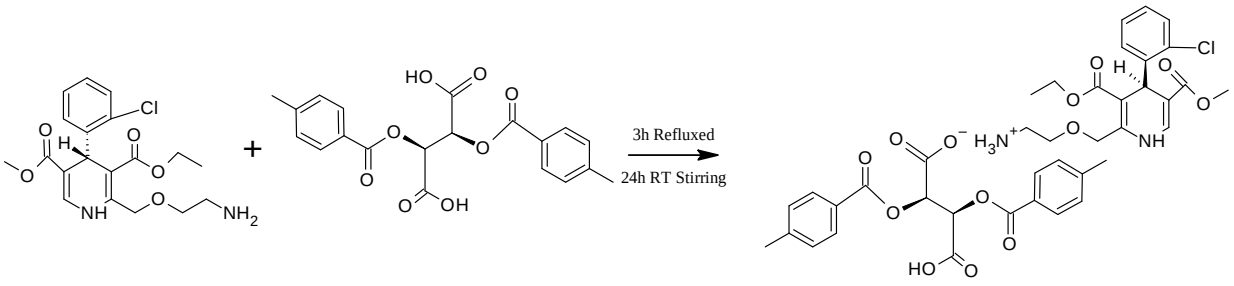
(RS)-Amlodipine **O,O'-di-p-toluoyl-L-tartaric acid** **(R)-(+)-amlodipine-O,O'-di-p-toluoyl-L-tartrate**

Scheme 6



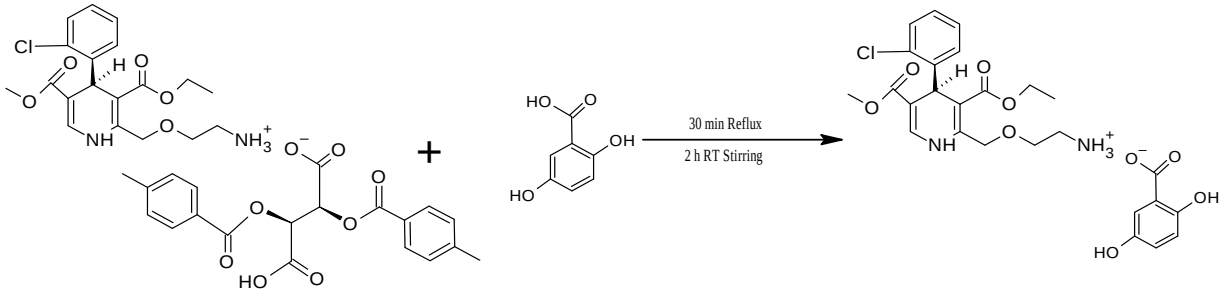
(R)-(+)-amlodipine-O,O'-di-p-toluoyl-L-tartrate **Gentisic acid** **(R)-(+)-Amlodipine Gentisate**

Scheme 7



Filtrate of the previous reaction of (RS)-Amlodipine **O,O'-di-p-toluoyl-D-tartaric acid** **(S)-(-)-amlodipine-O,O'-di-p-toluoyl-D-tartrate**

Scheme 8



(S)-(-)-Amlodipine-O,O'-di-p-toluoyl-D-tartrate **Gentisic Acid** **(S)-(-)-Amlodipine Gentisate**

III .RESULTS AND DISCUSSION

Characterization of the all-prepared compounds are accomplished by utilizing the analytical data obtained from chromatographic analysis, Specific optical rotation analysis, ultra violet-visible spectroscopy, FT(IR), PMR, and elemental analysis. Physical data of the synthesized compounds corresponds to their molecular formula and also corresponds to their molecular mass, which is in agreement with the Rast method (Vogel, 1956) of determining molecular mass by exploiting melting point depression properties. The compounds are obtained in a crystalline form, bright yellow solid, soluble in alcohol, chloroform, DMF, dimethyl sulphoxide (DMSO) etc., they are melts in the ranges118-126°C. The molecular weight and elemental analysis results are exhibited in Table I.

Table I Elemental analysis of prepared compounds

Compound Name	Molecular Formula	Formula Weight	Elemental composition expected (found) (%)				
			C	H	N	O	Cl
ADTAS_D	$C_{39}H_{38}N_2O_{13}Cl$	775.5	60.35 (60.09)	4.90 (4.54)	3.62 (3.49)	26.82 (26.80)	4.57 (4.40)
ADGAS_D	$C_{26}H_{29}N_2O_9Cl$	548.5	56.88 (56.11)	5.87 (5.22)	5.10 (5.09)	26.25 (26.19)	6.47 (6.40)
ALTAR_D	$C_{39}H_{38}N_2O_{13}Cl$	775.5	60.35 (60.40)	4.90 (4.85)	3.62 (3.57)	26.82 (26.09)	4.57 (4.39)
ALGAR_D	$C_{26}H_{29}N_2O_9Cl$	548.5	56.88 (56.08)	5.87 (5.20)	5.10 (5.00)	26.25 (25.15)	6.47 (6.42)

A. UV-visible Spectra

The ultra-violet spectrum of all compounds was taken in methanol solution at 10-4 M concentration. The ultra-violet spectrum of the methanolic solution of the synthesized compounds in the ultra-violet region shows three high intensity bands at 326-360nm, 214-238nm and 222-201nm. The analysis results are exhibited in Table II. This may be due to allowed $(\pi \rightarrow \pi^*)$ (allowed) transitions of carbonyl group environment in the molecule. In many isonitrosoketones including isonitrosopropiophenone, a band occurring at similar positions and intensity, is reported to be the $(\pi \rightarrow \pi^*)$ transitions in the compound (Deshmukh and Thakkar, 1985).

Table II Ultra violet spectrum of prepared compounds

Compound	Solvent	λnm	∑	Transition
ADTAS_D	Methanol	326 234 210	5296 13592 23216	π → π* π → π* π → π*
ADGAS_D	Methanol	357 238 215	851 10305 3957	π → π* π → π* π → π*
ALTAR_D	Methanol	360 237 222	3823 11957 8353	π → π* π→ □π* π → π*
ALGAR_D	Methanol	339 214 201	13982 2278 22582	π → π* π→ π* π → π*

B. FT(IR) Spectrum

A significant features of the FT(IR) spectrum of prepared compounds are the presence of broad band at 3302-3392cm-1 due to the symmetrical and asymmetrical vibrations of the primary amines -NH2 and the spectrum shows another broad band at 3183-3198cm-1 due the presence of secondary amine group (>NH). Assignment of this band was based on comparisons with other amlodipine and their derivatives (Jae-Sun, 2010). The bands observed at 3079-3098 and 3019-3026cm-1 in the FT(IR) spectrum are ascribed to the aromatic C-H and C=C stretching vibrations respectively. The band at 1599-1679 cm-1 due to the >C=O stretching vibrations of the carbonyl group. The analysis results are exhibited in Table III.

Table III FT(IR) spectrum of synthesized compounds in cm^{-1}

Compounds	$-NH_3$	>NH	Ar C-H	Ar. C=C	>C=O	p-di-sub benzene ring	m-sub benzene ring
ADTAS_D	3363	3193	3098	3026	1649	824	702
ADGAS_D	3392	3191	3078	3028	1599	828	728
ALTAR_D	3302	3183	3084	3019	1614	816	731
ALGAR_D	3387	3198	3079	3030	1679	820	729

C. Chromatographic analysis

The optical purity of all the prepared compounds was measured by chiral HPLC as per described methodology. The data shows the enantiomeric excess of the "R" and "S" enantiomers in the prepared compounds. The enantiomeric purity also

confirms the separation of "R" and "S" enantiomers from its racemic mixture. The analysis results are exhibited in Table IV.

Table IV Chromatographic purity of the compounds

Compounds	Chiral Purity (%)		Enantiomeric Excess (% ee)
	S-enantiomer	R-enantiomer	
(RS)-Amlodipine	49.83	50.17	-
ADTAS_D	97.78	2.23	95.55
ADGAS_D	97.95	2.05	95.90
ALTAR_D	1.94	98.06	96.12
ALGAR_D	1.97	98.02	96.05

D. Specific optical rotation

Specific rotation is a property of chiral chemical compound. Racemic compound containing equal mixture of both "R" and "S" enantiomers has 0° optical rotation where as the single enantiomers rotate the plane of polarized light. The specific optical rotation of S-(-)-Amlodipine Gentisate and (R)-(+)-Amlodipine Gentisate prepared in this study was measured in methanol at 25°C and results shown in Table V.

Table V Specific optical rotation of the compounds

Compounds	SOR($[\alpha]D^{25}C=1$)
(RS)-Amlodipine	0°
ADGAS_D	-29.19°
ALGAR_D	+29.51°

E. PMR Spectrum

The NMR data were recorded on a Bruker Advance 400 spectrometer operating at 400 MHz at room temperature. All prepared compounds were freshly dissolved in 0.5 mL DMSO-d6 in 5 mm in diameter NMR tube. Chemical shifts were reported in ppm with respect to tetramethyl silane. PMR spectrum of all compounds and the molecular structure with the proton signs to further confirm the chemical structure of the all compounds. The peaks at δ 9.0-9.3 ppm (3H) and 7.9-8.0ppm (1H) are assigned to the primary amine (–NH2) and secondary amine (>NH) respectively. The peaks at around 5.2 ppm can be assigned to the methine proton. At the same time, signal appears at 4.09ppm, corresponding to the proton on the methyl (-CH2-)3 group. The peaks for -CH2-, (-CH=)2 and (-CH3) are observed at 3.43 ppm, 3.58ppm and 1.84-2.00ppm respectively. The multiplet observed at 6.4-7.1ppm, due to the aromatic protons of all compound (Deshmukh, 2003). The results are exhibited in Table VI.

Table VI PMR spectrum of synthesized compounds in ppm.

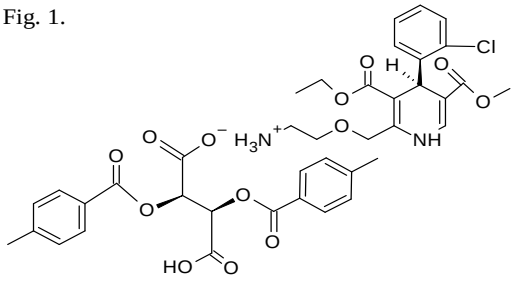
Compounds	- OH	- NH_3	>N-H	Ar. protons	(-CH<)	$(-CH_2-)_3$	$(-CH_2-)$	$(-CH=)_2$	$(-CH_3)_4$
ADTAS_D	10.3	9.3	8.0	6.4-7.1	5.2	4.09	3.43	3.58	1.84
ADGAS_D	10.54	9.0	8.0	6.4-7.1	5.2	4.09	3.43	3.58	1.84
ALTAR_D	10.5	9.3	8.0	6.4-7.1	5.2	4.09	3.43	3.58	1.84
ALGAR_D	10.5	9.01	7.92	6.59-6.62	5.2	-	3.58	-	2.00

V. CONCLUSION

The method for the preparation of an optically active amlodipine from resolution of (R, S)-amlodipine by using acetonitrile/isopropanol solvent and optically O, O'-di-p-toluoyl-tartaric acid was developed. The method comprise preparation of an optically active (S)-(-)-amlodipine-O,O'-di-p-toluoyl-D-tartrate or (R)-(+)-amlodipine-di-p-toluoyl-L-tartrate in acetonitrile/isopropanol solvent by reacting (R, S)-amlodipine and O, O'-di-p-toluoyl-D-tartaric acid or O, O'-di-p-toluoyl-L-tartaric acid. After recrystallization of tartrate salts base treatment was given. In this process optically active (S)-(-)-amlodipine gentisate or (R)-(+)-amlodipine gentisate was prepared by treating an optically active (S)-(-)-amlodipine-O, O'-di-p-toluoyl-D-tartrate or (R)-(+)-amlodipine-O, O'-di-p-toluoyl-L-tartrate with a base and gentisic acid.

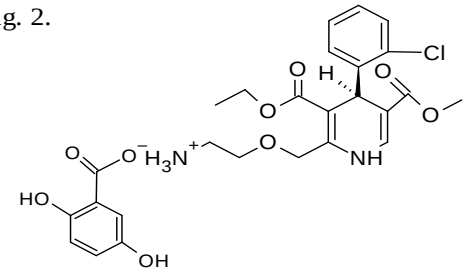
Characterization of the prepared compounds are accomplished by utilizing the analytical data obtained from chiral chromatographic analysis, specific optical rotation, ultra violet-visible spectroscopy, FT(IR), PMR, and elemental analysis. Physical data corresponds to their molecular formula and molecular mass in agreement with the Rast method of determining molecular mass by exploiting melting point depression properties. They are obtained in a crystalline form; bright yellow solid, soluble in alcohol, chloroform, DMF, dimethyl sulphoxide (DMSO) etc. On the basis of spectral analysis structure of the prepared compounds can be assigned as follows (Fig. 1 to fig. 4);

Fig. 1.



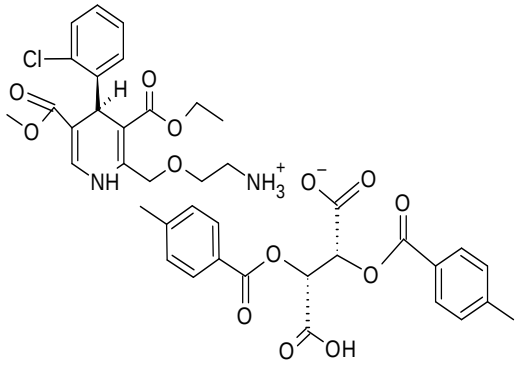
(S)-(-)-Amlodipine-O,O'-di-p-toluoyl-D-tartrate

Fig. 2.



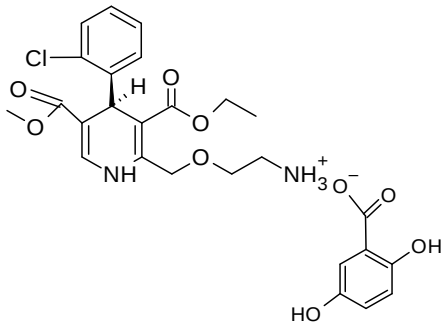
(S)-(-)-Amlodipine Gentisate

Fig. 3.



(R)-(+)-Amlodipine-O,O'-di-p-toluoyl-L-tartrate

Fig. 4.



(R)-(+)-Amlodipine Gentisate

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