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Derivatization of racemic propranolol by naproxen based chiral reagent and separation on RP-HPLC, and structural study using DFT

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Abstract: In this study, pentafluorophenol was coupled to create (S)-naproxen-based active chiral derivatizing reagents (CDR), which were then synthesized and characterized using UV, IR, HRMS, NMR, and CHNS. In this work racemic propranolol (β-blocker) was chosen for the chiral recognition study. Highly reactive CDR was used to create the diastereomers of the selected β-blocker under microwave heating conditions. Highly reactive CDR was used to create the diastereomers of the selected -blocker under microwave heating conditions. , RP-HPLC was employed to separate the produced diastereomers. The diastereomers and chromatographic conditions were studied by altering the mobile phase and sample concentrations. The synthesized diastereomer's elution order was predicted using the optimized structures. The optimized structures were used to predict the elution order of diastereomers synthesized. LOD (0.192 ng mL^{-1}), LOQ (0.576 ng mL^{-1}), calibration range (0.01-1.0 mg mL^{-1}), correlation coefficient, and recovery were the validation parameters for our method (99.54 percent for intra-day assay and 99.89 percent for inter-day assay).

Keywords: Propranolol, (*S*)-naproxen, pentafluorophenol, chiral derivatizing reagents, RP-HPLC.

I. INTRODUCTION

Cardiovascular and respiratory illnesses are commonly treated with amino alcohol [β-agonists and β-blockers; Figure 1] drugs. The majority of amino alcohol medicines are offered for sale as racemic mixtures. The (*S*)-enantiomer generally has the desired pharmacological effects, but the (*R*)-enantiomer has adverse effects such as gastrointestinal discomfort, fatigue, vertigo, depression, paresthesia, muscular aches, and asthmatic wheeze [1–5]. They have been used to develop derivatizing reagents [6] and impregnating reagents/mobile phase additives as chiral selectors. They also provide a starting point for researching and creating new enantioseparation methods and processes [5]. However, it is critical in many scientific domains in industry and academia to distinguish amino alcohol enantiomers. A few review studies in the literature only focus on the direct and indirect separation of amino acids [1-6].

(*S*)-naproxen (Nap; Figure 1), due to the presence of a carboxylic acid group and a methoxy-substituted naphthyl residue, possesses a high molar absorptivity (ε). It is available for the market in pure enantiomer form. Up to now, lots of chiral derivatizing reagents (CDRs) have been synthesized by the reaction of (*S*)-Nap with N-hydroxysuccinimide, 1H-benzotriazole and hydrazine hydrate [7-12] due to its characteristic features. These were used for high-performance liquid chromatographic enantioseparation of DL-Penicillamine, Cysteine and Homocysteine, and certain carbonyl compounds, respectively. Other derivatives

of (*S*)-naproxen that have been produced and utilized as CDRs include amine derivatives for the enantioseparation of 2-aryl propionic acids [13] and chloroformate and isothiocyanate derivatives for the enantioseparation of β-adrenoceptor antagonists [12].

According to previously published studies, the various CDRs utilized for the enantioseparation of amino acids require a derivatization period ranging from 30 to 180 min and a temperature range of 30-80 °C. The resolution values of the several diastereomers produced ranged from 2.20 to 13.34. Because of the above and the search for certain new CDRs for enantioseparation of amino acids, it was considered worthwhile to prepare diastereomers of some necessary racemic pharmaceuticals (in the current study, racemic propranolol that is a β-blocker; Figure 1) under microwave irradiation (MWI), using (*S*)-naproxen-pentafluorophenol ester as the CDR, and to investigate their separation by RP-HPLC. As far as the authors are aware, no studies have used (*S*)-naproxen-pentafluorophenol ester to enantioseparate (*RS*)-propranolol.

Figure 1. Chemical structures of (*S*)-naproxen and racemic propranolol.

II. EXPERIMENTAL

1. Apparatus

Knauer (Berlin, Germany) provided the HPLC, which included a 10 mL pump head 1000, management 5000 degassers, a photodiode array detector 2600, a Knauer manual injection valve, and Eurochrom operating software. Perkin-Elmer (Shelton, Connecticut, USA) provided the Microwave-Multiwave 3000 (800 W). The pH meter utilized was a Cyberscan 510 (Singapore) model. Knauer supplied the C_{18} column (Eurospher, 250 x 4.6 mm i.d., 5 mm). Using a Perkin-Elmer 1600 FT-IR spectrometer (Boardman, OH, USA), IR spectra of KBr pellets were captured. Double-distilled water (18.2 MΩcm^3) was purified using the Milli-Q system from Millipore (Bedford, MA, USA). A UV-1601 spectrophotometer from Shimadzu was used to capture UV-visible spectra in MeCN. A vario EL III elemental analyzer was used to do the elemental analysis. ^{1}H NMR spectra were recorded on a Bruker 500 MHz instrument using deuterated chloroform.

2. Chemicals and reagents

(S)-Naproxen, pentafluorophenol, dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), and racemic propranolol were obtained from Sigma-Aldrich (St. Louis, MO, USA). Glacial acetic acid, triethylamine (Et3N), sodium hydrogen carbonate (NaHCO3) and phosphoric acid of analytical grade, and acetonitrile (MeCN) and methanol (MeOH), of HPLC grade, were obtained from E. Merck (Mumbai, India).

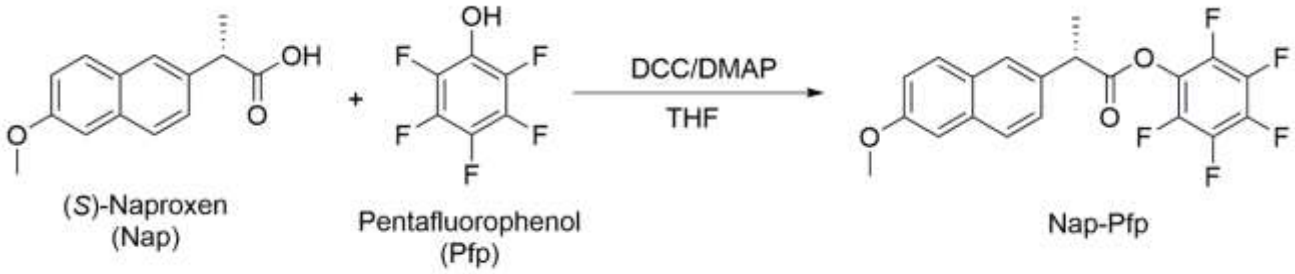

Figure 2. Synthesis of CDR.

3. Synthesis of chiral derivatizing reagent

A mixture of (*S*)-naproxen (5 mL, 0.2 M) and pentafluorophenol (5 mL, 0.2 M) in 5 mL DCM was added to a solution of (3 mL, 0.36 M) DCC under nitrogen atmosphere at room temperature. The reaction mixture was sonicated for 30 minutes, and after the reaction, the precipitated urea (side product) was filtered out. The filtrate was vacuum-concentrated, and 10 mL of ethyl acetate was used to completely eliminate the residue [14, 15]. The extract was washed five times (5 mL) with water, five times (5 mL) with brine, and twice (5 mL) with ice-cold saturated $NaHCO_3$. Recrystallizing the dried extract from hot EtOH produced a solid white reagent (The chemical structure of Nap-Pfp is given in Figure 2).

Yield: 388 mg (98%); $[\alpha]_D^{25}$ = + 62° (c =0.3, MeOH); m.p. 108–112 °C; UV (λ_{max} in MeOH, 232 nm); IR (KBr): 3424, 2878, 2416, 1742, 1642, 1587, 1465, 1364 and 1235 cm^{-1}; ^1H NMR (400MH_Z, $CDCl_3$-d_1): δ 7.74 – 7.67 (m, 3H), 7.67 (dd, J = 2.3, 1.3 Hz, 3H), 7.40 (dd, J = 8.2, 1.9 Hz, 2H), 7.15 (t, J = 2.4 Hz, 2H), 7.10 (dd, J = 8.8, 2.4 Hz, 2H), 3.89 – 3.81 (m, 2H), 3.83 (s, 5H), 1.53 (s, 3H); HRMS: Calcd for $C_{20}H_{13}F_5O_3$: 397.08 (M^++H), found 397.12; anal. Calcd for $C_{20}H_{13}F_5O_3$: C, 60.61%; H, 3.31%; Found: C, 59.89%; H, 3.41%.

4. Preparation of stock solutions

Stock solutions of (*RS*)-propranolol (1 mmol/L) were prepared in 1 M $NaHCO_3$. Solution of Nap-Pfp reagent (1 mmol/L) was prepared in acetonitrile. Triethylammonium phosphate buffer solution was prepared by dissolving triethylamine (10 mM) in ultra-pure water; pH was adjusted to 3.5 by adding phosphoric acid.

5. Microwave-assisted synthesis of diastereomers

The reaction mixture was prepared by adding a Solution of (*RS*)-propranolol (50 µL, 50 nmol), chiral derivatizing reagent in MeCN (56 µL, 56 nmol) and and 5 µL of TEA in a 2 mL vial [16]. The propranolol and Nap-Pfp were in the mole ratio of 1:1.2. The reaction mixture was irradiated with microwave (MWI) for 45s at 75% (800W) and then cooled to room temperature. The reaction was quenched by the addition of NH_4OH (1 M, 50 µL). The diastereomers of all the analytes were also synthesized by sonicating the reaction mixture (in the same mole ratio as used for MW based synthesis) for 10 min at room temperature. Aliquots (10 µL) of resulting solution of diastereomers were diluted 10 times with MeCN and injected (20 µL) on to the column. The chemical structures of the prepared diastereomers are given in Figure 3.

The effects of pH, reagent excess, reaction duration, and microwave power were considered while optimising the experimental conditions for synthesising diastereomeric pairs of (*RS*)- propranolol with Nap-Pfp.

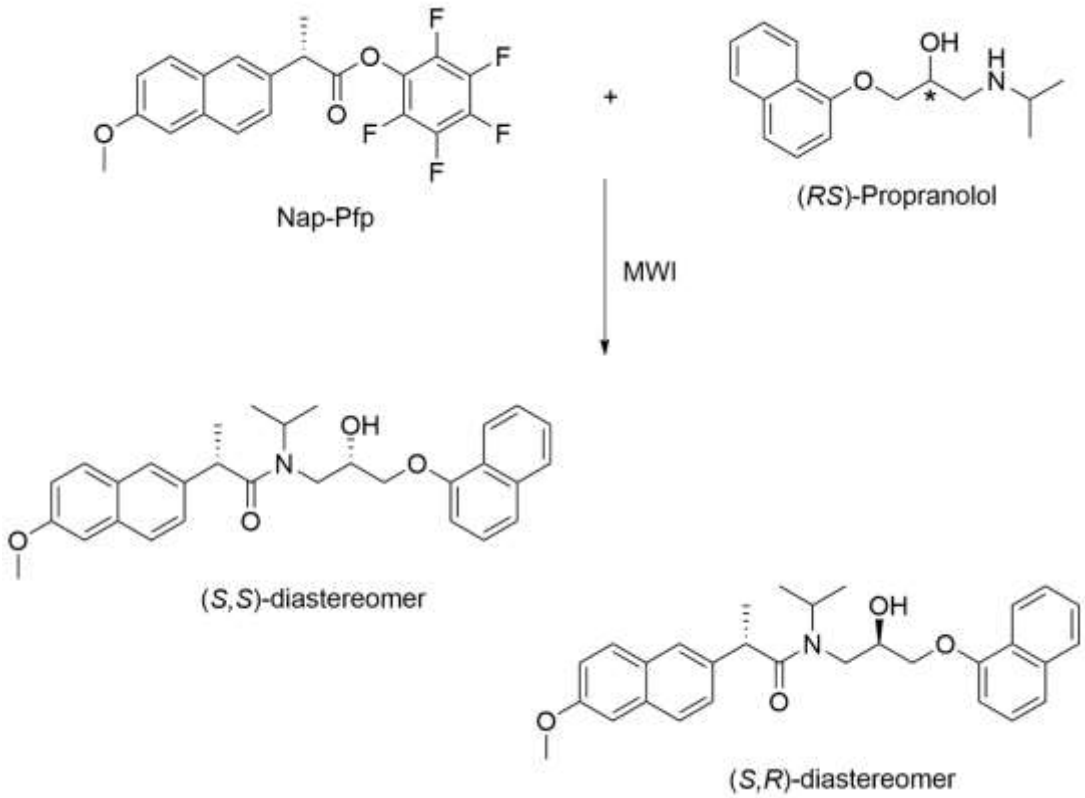

Figure 3. Synthesis of diastereomers of (*RS*)-propranolol with CDR.

6. HPLC Mobile Phase

Different binary combinations of mobile phase were used;

Mobile phase 1: MeOH (linear gradient from 35 to 70%, 30 to 65%, 25 to 70%, 25 to 80% and 10 to 90 %) with TEAP buffer (10 mM).

Mobile phase 2: MeCN (linear gradient from 35 to 70%, 30 to 65%, 25 to 70%, 25 to 80% and 10 to 90 %) with TEAP buffer (10 mM).

Before use, the mobile phase was filtered through a 0.45 µm filter, degassed using sonication, and passed through nitrogen. UV detection was done at 231 nm, and the flow rate was 1.0 mL min^{-1}.

7. Method development and validation

Studies were done to validate the (*RS*)-propranolol diastereomers made with Nap-Pfp in terms of linearity, accuracy, and precision. The slopes and correlation coefficients for the calibration graphs between the peak area (in AU; absorbance unit) responses of (*S,S*)-diastereomer and (*S,R*)-diastereomer and the corresponding concentration range of 100-1000 ng mL^{-1} were developed by the least square method using the Microsoft Excel programme.

III. Results and Discussion

1. Synthesis of CDR and diastereomers

Pentafluorophenol (Pfp) nucleophilically attacked the carbonyl carbon of Nap's carboxylic acid under mild conditions with the coupling reagent DCC/DMAP, yielding Nap-Pfp (yield > 98%) after dicyclohexylurea was removed (Figure 2). Prepared CDRs were characterised by using IR, UV, CHNS, and 1H NMR, the CDR Nap-Pfp. A chiral cellulose column was used to identify the chiral purity of Nap-Pfp was determined (chiral purity > 99%).

The DCC/DMAP coupling reagent was used in the current study to synthesise Nap-Pfp by vigorously swirling the reaction mixture for two hours at room temperature (15). The reaction required 4 hours to finish

in the absence of DMAP. The CDR (Nap-Pfp) is an ester and has more reactivity than other naproxen-based CRDs currently on the market, making it possible to synthesise (*RS*)- propranolol diastereomers quickly.

Figure 3 shows the procedure to synthesize diastereomers, with (*RS*)- propranolol used as an example. The diastereomers can be referred to as [*S,S*]- and [*S,R*]- diastereomers, where the first letter indicates the naproxen configuration and the second, the propranolol enantiomer. Using (*RS*)- propranolol, the derivatization conditions were improved by including a pH of about 11.0, a twofold molar excess of the CDR, and MW irradiation for 45 seconds at 75% power (800 W). The propranolol producing the derivative required an equivalent molar excess of the CDR to the analyte.

According to [17-19], the diastereomeric combinations were produced by combining L-Nap-Btz with two distinct racemic amino acids at 20 ˚C in aqueous acetonitrile in the presence of triethylamine. This process took 3–12 hours. In this instance, producing the (*RS*)- propranolol diastereomers in 45 seconds using MWI or in 10 minutes by vortexing the reaction mixture at ambient temperature was simple. The Pfp moiety from the Nap-Pfp was substituted primarily because amino group served as effective nucleophiles in the basic media provided by Et3N. Under the reaction conditions used, no racemization of the CDR was seen. Under refrigeration (4 ˚C), the CDR, Nap-Pfp was stable for 90 days, while the solutions of the (*RS*)-propranolol diastereomers were fairly stable for up to 30 days. The diastereomers synthesized by two approaches (of using MWI and sonication at room temperature) were found to be identical in terms of their characterization and chromatographic data.

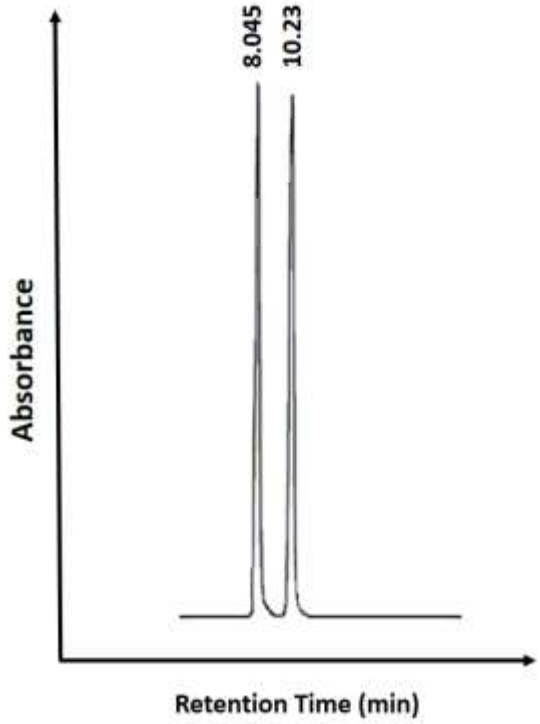

Figure 4. RP-HPLC chromatogram of the separated diastereomers.

2. HPLC analysis

The diastereomers were well separated by reversed-phase HPLC (Figure 4). The chromatographic data used to separate the (*RS*)- propranolol diastereomers are shown in Tables 1 as retention time (t_R), retention factor (k), separation factor (α), and resolution (Rs).

The (*S,S*)-diastereomers eluted before (*S,R*)-diastereomers of (*RS*)- propranolol. Figure 4 shows sections from specimen chromatograms showing the resolution of the diastereomeric pairings. MeCN and TEAP buffer (10 mM, pH 3.5) in 35 minutes (linear gradient from 30 to 65%) was the successful mobile phase. For optimisation, experiments were run in the pH range of 2.5 to 5.5 and at buffer concentrations ranging

from 5 to 30 mM. We tested MeCN and MeOH as organic modifiers. Since acetonitrile has a lower viscosity (0.38 cP) than methanol (0.59 cP), the diastereomers elute more quickly in acetonitrile-containing mobile phases than in methanol-containing ones. As a result, MeOH produced peaks with broader peaks and more extended retention periods [20, 21]. MeCN is thus used in the mobile phase as an organic modifier. To find the successful flow rate of 1.0 mL/min, flow rate was changed in increments of 0.5 mL/min within the range of 0.5 to 2.0 mL/min.

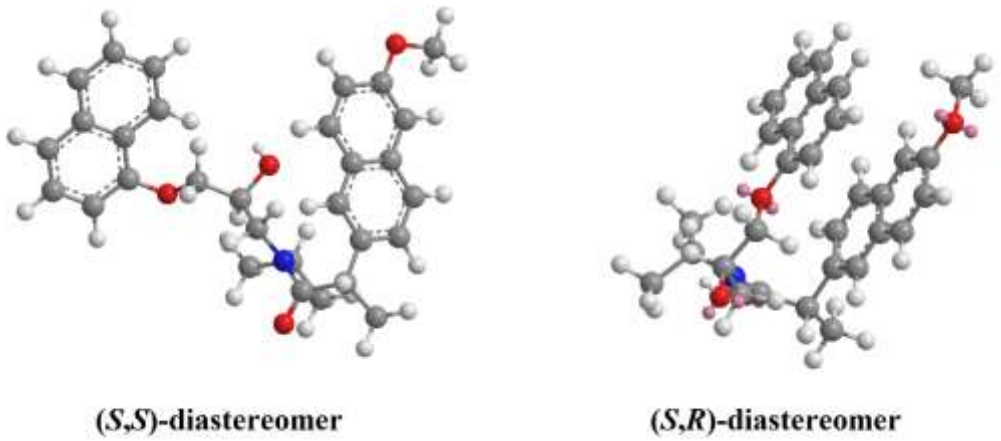

Figure 4. Optimised 3D model of the prepared diastereomers.

3. Separation mechanism

DFT (Figure 5) was used to establish the order of the diastereomers' elution. According to the reported literature [22-25], the same hypothesis was used to ascertain the diastereomers' elution order. This can be explained as follows.

(i) The amide bond between the amino nitrogen of (*RS*)-propranolol and the carbonyl carbon of naproxen, which is present in the diastereomers, may be a factor in the diastereomers' partial double bond nature and the naphthyl group's existence in the reagent platform. The two diastereomers' differing partition coefficients and retention periods can be attributed to their hydrophobic interactions with the column's reversed phase material and the effect of the mobile phase's rheological characteristics. Due to these various physical characteristics, the diastereomers elute sequentially. It may be concluded that the (*S,R*)-diastereomer interacts more strongly and is kept for a longer period of time than the *(S,S)*-diastereomer.

(ii) The diastereomers' interaction with the column's ODS material and the separation were both influenced by the hydrophobicity of the alkyl side chain of (*RS*)-propranolol. Chromatographic data analysis demonstrates that the analytes with more hydrophobic side chains are more firmly retained by the column, resulting in longer retention durations and improved resolution (*Rs*) of the diastereomers. Table 1 displays the chromatographic information for the produced diastereomers.

4. Method development and validation

Diastereomers of (*RS*)-propranolol produced using Nap-Pfp in accordance with ICH standards [ICH, 1996], as detailed in the reported literature [16, 24], were used to validate the method. The peak area was plotted against concentrations between 100 and 1000 ng/mL, and a regression equation was used to calculate the slope and correlation coefficients of the calibration curve. Studies were done to validate the (*RS*)-propranolol diastereomers made with Nap-Pfp regarding linearity, accuracy, and precision.

Validation experiments were carried out following ICH guidelines to determine linearity, accuracy, and precision [15]. For RP-HPLC separation of diastereomers in a concentration range of 100-1000 ng/mL, relative standard deviation (RSD), limit of detection (LOD), and limit of quantitation (LOQ) were established. The computed recovery values for intraday and interday tests are 99.54% and 99.89%, respectively. The results showed that the LOD and LOQ were 0.154 ng/mL and 0.462 ng/mL, respectively

Table 1. Chromatographic separation data of the prepared diastereomers

	Diastereomers of (*RS*)-propranolol **prepared with CDR**	
	(*S,S*)-Diastereomer (First eluted diastereomer)	**(*S,R*)-Diastereomer** (Second eluted diastereomer)
Retention time (min)	8.74 (t_1)	11.14 (t_2)
Retention factor (*k*)	6.29	8.28
Separation factor (α)	1.317	
Resolution (*Rs*)	8.01	

IV. Conclusion

The current experiment has demonstrated that the CDR based on (*S*)-naproxen is more successful than many other CDRs described in the literature for indirect enantioresolution of the beta-blocker propranolol when derivatization conditions and resolution are considered. The MWI (or sonication) derivatization processes took less time and were straightforward to master. Large, highly conjugated naphthyl rings with strong UV absorbance are connected to the chiral core, enabling detection at low concentrations (LOD: 0.192 ng/mL) and enantioresolution. The creation of the diastereomeric derivatives' three-dimensional structures proved their absolute configuration and validated the separation procedure.

V. Aknowledgments

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