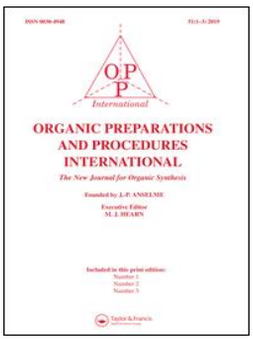

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EXPERIMENTAL PAPER

An Improved Process for Synthesis of (*S*)-Duloxetine Hydrochloride Involving Enzymatic Asymmetric Carbonyl Reduction on a Novel Ketoamine

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(*S*)-Duloxetine hydrochloride **1** is a medication used to treat major depressive disorder, generalized anxiety disorder, fibromyalgia and neuropathic pain (Figure 1).[1,2] Due to its versatility in different treatments, many researchers have been attracted towards the development of different cost-effective synthetic routes. The drug contains a 3-aryloxy-3-aryl propylamine sub-unit in its basic structure. It acts as a dual inhibitor of serotonin and norepinephrine reuptake.[3–5]

A literature search reveals that most of the reported methods involve synthesis of enantiomerically pure alcohols as key chiral synthons, as presented in Scheme 1.[6–20]

In our research work, we have focused on the development of an efficient route for the synthesis of *(S)*-duloxetine hydrochloride **1** by modification of ketoamine intermediate **a** (Scheme 1), followed by enzymatic asymmetric reduction to obtain enantiomerically pure alcohol intermediate **b** (Scheme 1). To help with our planning, we did the retrosynthetic analysis shown in Scheme 2.

In our previous experience in the synthesis of **1**, we observed that demethylation of **7** (Scheme 2, when $R = CH_3$) to produce duloxetine free base **8** gives a low yield. This was because of impurity formation during demethylation. Indeed, for the ease of demethylation, many researchers had tried different substituents on the nitrogen of ketoamine **5** in their synthetic routes.[17,21–24] We anticipated that the presence of a chiral auxiliary on the nitrogen of ketoamine intermediate **5** could provide a suitable chiral environment during enzymatic carbonyl reduction and could be more easily dealkylated. Accordingly, we designed the synthetic route depicted in Scheme 3.

A Mannich reaction was carried out using 2-acetylthiophene, paraformaldehyde and *(S)*-N-methyl-1-phenylethan-1-amine hydrochloride in aqueous ethanol using conc. hydrochloric acid to obtain ketoamine intermediate **9** (Scheme 3) in good yield. As we know that enzymes are substrate specific and behave differently on different substrates, even for the same reaction, it was necessary to carry out a screening study. Screening experiments were done using 21 different commercially available ketoreductase enzymes

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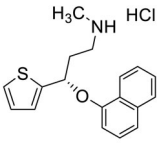

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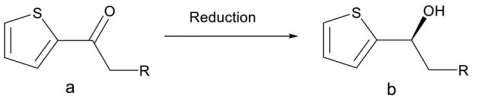
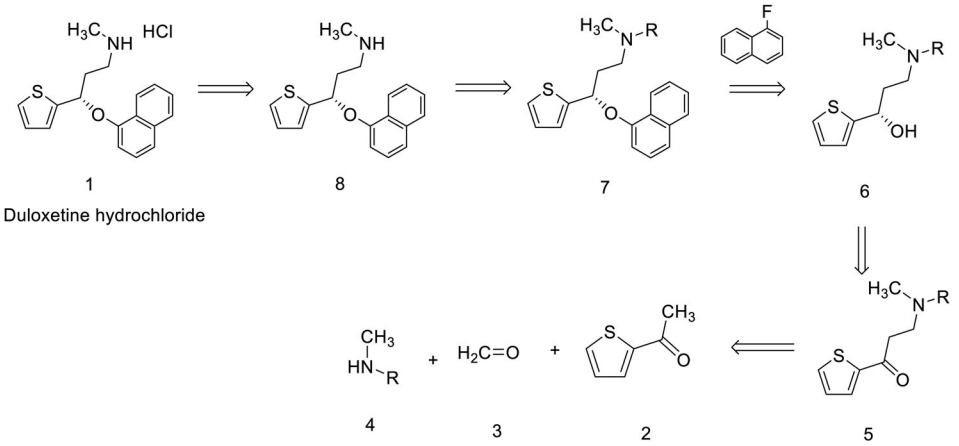
Figure 1. (*S*)-Duloxetine hydrochloride.



	a	b
	Ketone intermediate	Hydroxyl intermediate
R = -CH_2NHCH_3 [6,14,19]	Ia	Ib
R = -$CH_2N(CH3)_2$ [6,10-12,19]	IIa	IIb
R = -CH_2Cl [16]	IIIa	IIIb
R = -CH_2CN [20]	IVa	IVb

Scheme 1. Literature routes for carbonyl reduction.



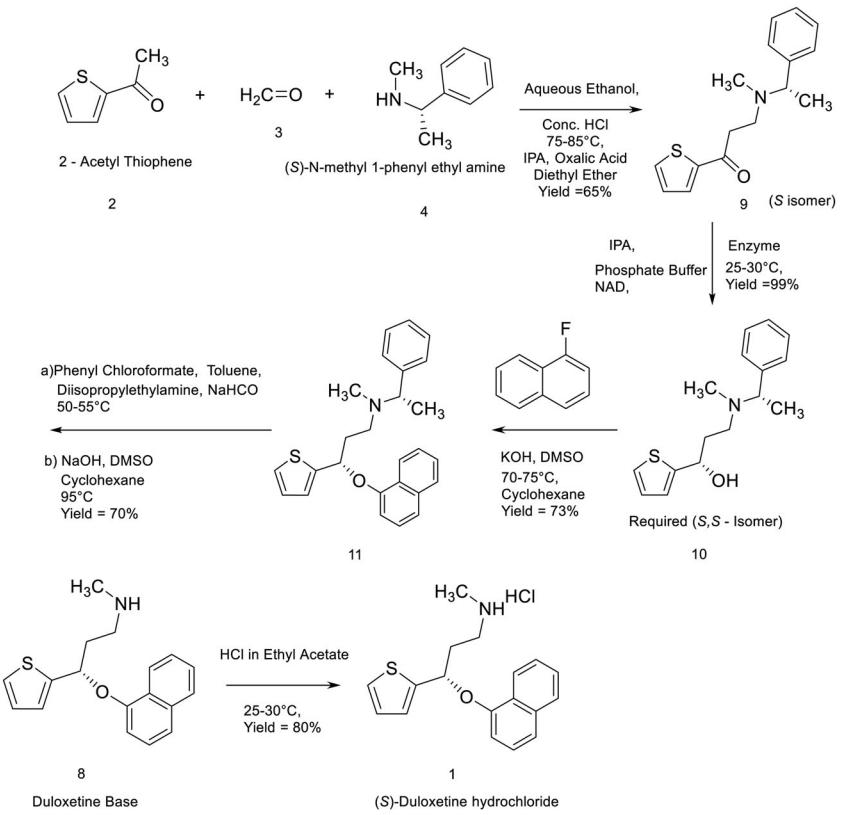
1 Duloxetine hydrochloride; 8; 7; 6; 4; 3; 2; 5

Scheme 2. Retrosynthetic analysis of *(S)*-dloxetine hydrochloride.

(10 mg), substrate **9** (5 mg in 100 µl isopropanol) and 900 µl phosphate buffer having pH 7.0 at a temperature 25-30 °C. (Table 1)

Chiral HPLC analysis was carried out for the performed experiments, which showed that enzyme CDX-008 (Table 1, Entry 13), does not have reactivity towards the substrate. Enzyme KRED-P2-C02 (Entry 19) showed 98.8% conversion with 100% selectivity. Enzymes at Entries 5, 10, and 15 gave the unwanted *R* isomer in 11.1%, 11.4% and 19.0%, respectively. The rest of the enzymes showed 100% conversion with 100% selectivity. Based on the screening study experiments, we decided to work with CDX-021 (Entry 14) enzyme, as this is commercially available and has a low cost.

Bioreduction optimization conditions are important in the enantiomerically pure production of chiral secondary alcohols since optimization of key conditions has been



Scheme 3. Proposed reaction scheme for synthesis of *(S)*-Duloxetine hydrochloride.

shown to affect the enantiomeric excess (ee) of the product and conversion of the substrate.[25] To study the impact of pH on the reaction, phosphate buffers of different pH were prepared and experiments were conducted (Table 2) which showed that reaction at pH 6.0 had 15% conversion, but unidentified impurities formation was less. At pH 7.0, complete conversion was observed with formation of 5-10% unidentified impurities. At pH 8.0, unidentified impurities formation was 50-60% and at pH 9.0 unidentified impurities were observed at the level of 70-80%.

Further experiments were carried out to optimize the temperature using CDX-021 enzyme in phosphate buffer at pH 7.0, substrate 5 mg/100 µl isopropanol and 900 µl buffer, nicotinamide adenine dinucleotide (NAD) 0.2%, enzyme 1% (Table 3).

An experiment conducted at 20 °C showed around 75% conversion along with 5-10% impurity formation, whereas at 40 °C due to impurity formation only 40% of product **10** was obtained. At 30 °C, reaction progress was satisfactory with 90% yield. Further, to optimize enzyme load, two reactions were carried out using 10% and 1% CDX-021 enzyme with respect to substrate **9**. Both the reactions showed the same conversion using 30% isopropyl alcohol (IPA) and 70% phosphate buffer having pH 7.0 at temperature 28-30 °C.

The reduction reaction was studied using different ratios of the phosphate buffer and isopropanol with CDX-021 enzymes in phosphate buffer at pH 7.0, NAD 0.2%, enzyme 1% (10 mg/ml), at temperature 28-30 °C (Table 4).

Table 1. Screening of enzymes.

Entry	Enzyme code	Enzyme supplier	% Conversion[a]	*R*-Isomer[a]	*S*-Isomer[a]
1	KRED-P1-B10	Codexis	100%	–	100%
2	KRED-P1-B12	Codexis	100%	–	100%
3	KRED-P1-C01	Codexis	100%	–	100%
4	KRED-P1-H08	Codexis	100%	–	100%
5	KRED-P2-B02	Codexis	100%	11.1%	88.9%
6	KRED-P2-D03	Codexis	100%	–	100%
7	KRED-P2-D11	Codexis	100%	–	100%
8	KRED-P2-D12	Codexis	100%	–	100%
9	KRED-P2-H07	Codexis	100%	–	100%
10	CDX-022	Codexis	100%	11.4%	88.6%
11	IEP_Ox58	Cambrex	100%	–	100%
12	IEP_Ox56	Cambrex	100%	–	100%
13	CDX-008	Codexis	–	–	–
14	**CDX-021**	**Codexis**	**100%**	**-**	**100%**
15	KRED-101	Codexis	100%	19.0%	81%
16	KRED-NADH-110	Codexis	100%	–	100%
17	KRED-P1-B02	Codexis	100%	–	100%
18	KRED-P1-B05	Codexis	100%	–	100%
19	KRED-P2-C02	Codexis	98.8%	–	100%
20	KRED-P2-G03	Codexis	100%	–	100%
21	KRED-P2-C11	Codexis	100%	–	100%

[a]Determined by HPLC.

Table 2. Study for impact of pH.

Entry	Enzyme	pH	Substrate loading	Buffer	% conversion	Observation
1	KRED-P1-B10	6.0	5 mg/ 100 µl	900 µl	10-15	5 % Impurity formation
2	**KRED-P1-B10**	**7.0**	**5 mg/ 100 µl**	**900 µl**	**100**	**5 - 10%** Impurity formation
3	KRED-P1-B10	8.0	5 mg/ 100 µl	900 µl	100	50-60% Impurity formation
4	KRED-P1-B10	9.0	5 mg/ 100 µl	900 µl	100	70-80% Impurity formation

Note: All observations are based on TLC estimates.

Table 3. Study of effect of temperature.

Entry	Enzyme	Temp	Time	% unreacted	% conversion	% impurity	Yield
1	CDX-021	20 °C	21 Hr.	10 - 15%	75-80 %	5-10%	70%
2	**CDX-021**	**30 °C**	**21 Hr.**	**0**	**100** %	**5 - 10%**	**90%**
3	CDX-021	40 °C	21 Hr.	0	100 %	50-60%	40%

Note: All observations are based on TLC estimates.

Experiments conducted using 10 to 30% IPA had given 100% conversion with less impurity. With the increasing percentage of IPA, conversion went down with increasing levels of impurities.

Based on our optimization experiment data, asymmetric reduction on ketoamine **9** was carried out on 10 g scale. Alcohol intermediate **10** was obtained with yield 98.5% having enantiomeric excess 100%. Isolated alcohol intermediate **10** was condensed with 1-fluoronaphthalene using potassium hydroxide in dimethyl sulfoxide at 75 °C. Intermediate **11** was obtained by solvent distillation followed by column chromatography. Debenzylation of **11** was carried out using palladium on carbon under hydrogen gas but was not successful. Hence, duloxetine base **8** was obtained by reaction of **11** with phenyl chloroformate and subsequent hydrolysis of the carbamate intermediate

Table 4. Study of buffer and solvent ratio.

Entry	Buffer	IPA	Time	% conversion	% impurity	Yield
1	**90**	**10**	**21 Hr.**	**100**	**5-10%**	**90%**
2	**70**	**30**	**21 Hr.**	**100**	**5-10%**	**92%**
3	50	50	21 Hr.	70-80	15-20%	55%
4	10	90	21 Hr.	10-15	5-10%	Not isolated

Note: All observations are based on TLC estimates.

with yield 70.3% We were pleased to see that this is an improvement over our observed yield of 50% during the demethylation of **7**, when R = CH_3. Further conversion of duloxetine base **8** to **1** was done according to the available literature.[26]

In conclusion, we have synthesized a new ketoamine intermediate and devised experimental conditions to obtain 100% ee for the carbonyl reduction during the synthesis of *(S)*-duloxetine hydrochloride using commercially available ketoreductase enzymes. Our new method thus gives higher yield and excellent ee.

Experimental section

Reactions were conducted under an atmosphere of nitrogen wherever required. Standard enzymes received from Codexis and Cambrex were used for experiments. Reactions were monitored by TLC. TLCs were performed on silica gel using 30–50% ethyl acetate in cyclohexane, visualized under UV short wavelength or using potassium permanganate or *p*-anisaldehyde as staining reagents. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 400 and 500 MHz FT NMR spectrometers, and the chemical shifts are reported in ppm δ. Mass spectrometry was carried out using a Waters QDa system. IR analysis was carried out using a Perkin-Elmer Spectrum 400 instrument. Specific optical rotation analysis was carried out on an Autopol IV instrument. Chiral HPLC was carried out using a Shimadzu LC-2010 system with UV detector and Chiralpak IA-3 column at wavelength 207 nm.

(S)-3-(Methyl(1-phenylethyl)amino)-1-(thiophen-2-yl)propan-1-one (9)

A mixture of 2-acetylthiophene **2** (25.0 g, 0.198 mol), *(S)*-N-methyl-1-phenylethylamine HCl **4** (37.5 g, 0.218 mol), paraformaldehyde **3** (8.2 g, 0.272 mol) and conc. HCl (25 mL) in aqueous ethanol (25%, 250 mL) was heated at 75-85 °C. Reaction progress was monitored by TLC. After completion of the reaction in about 24 hr, ethanol was removed from the reaction mass under vacuum and water (100 mL) was added. The reaction mass was then extracted with diethyl ether (100 mL X 3) to wash out impurities. The pH of the aqueous reaction mass was made basic (pH > 8.0) using sodium bicarbonate solution and extracted using diethyl ether (200 mL X 2). The combined organic layer having product was concentrated under vacuum to obtain an oily mass of crude ketone intermediate **9** (35.0 g, 65%). To a clear solution of **9** (30.0 g, 0.105 mol) in isopropanol (150 mL) was added oxalic acid (14.0 g, 0.155 mol) and the mixture was heated to 50-55 °C for 10 min. The reaction mass was then cooled to room temperature. The solid was filtered and further added to a mixture of water (200 mL) and diethyl ether (200 mL) and the pH of the mixture was made basic (pH > 8.0) using sodium bicarbonate solution. The organic layer was separated, dried over anhydrous sodium sulfate,

filtered and concentrated to obtain pure ketone intermediate **9** (24.5 gm, 82%); $[\alpha]_D^{25}$ = -31.88° (c = 1, methanol); IR (KBr): ν_{max} 704, 1413, 1656 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43-1.45 (d, J = 7Hz, 3H), 2.32 (s, 3H,), 2.83-3.03 (m, 2H), 3.09-3.12 (t, J = 7.2 Hz, 2H), 3.65-3.70 (q, 1H), 7.14-7.16 (t, J = 4 Hz, 1H), 7.27-7.35 (m, 5H), 7.66-7.68 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 17.1, 34.3, 37.5, 48.8, 63.9, 128.1, 129.3, 129.5, 134.3, 134.6, 135.7, 143.6, 190.8; MS: *(m/z)* 274 (M + 1).

Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.01; N, 5.12. Found C, 70.35; H, 7.08; N, 5.25.

Phosphate Buffer Preparation (0.2 M, pH 7.00, 1 mM NAD, 2 mM $MgSO_4$)

Monopotassium phosphate (KH_2PO_4) (1.4 g) was dissolved in DM water (50 mL). Similarly, dipotassium phosphate (K_2HPO_4) (1.7 g) was dissolved in DM water (50 mL). Both the solutions were mixed to adjust the pH to 7.00. To 50 mL of this solution was added NAD (33.2 mg) and $MgSO_4$ (24.6 mg).

(S)-3-(Methyl((S)-1-phenylethyl)amino)-1-(thiophen-2-yl)propan-1-ol (10)

Compound **9** (10.0 g) was dissolved in a mixture of isopropyl alcohol (30 mL) and buffer solution (60 mL) (as above, i.e., 0.2 M potassium phosphate buffer, pH 7.00, 2 mM $MgSO_4$). To this mixture was added an enzyme solution (1.0 g enzyme and 0.1 mg NAD dissolved in 10 mL buffer) and the mixture was stirred at 25-30 °C for 20 hr. The reaction was monitored by TLC. After completion of the reaction in about 21 hr, the isopropanol was distilled off from the reaction mixture and the remaining mass was extracted using ethyl acetate (30 mL X 3). The combined organic layer was washed with 5% brine solution and solvent was distilled off completely to obtain **10** (9.9 g, 99%); HPLC chiral purity (ee) = 100%; $[\alpha]_D^{20}$ = -20.75° (c = 0.35, methanol); IR (Neat): ν_{max} 700, 1030, 3338 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.45-1.46 (d, J = 7Hz, 3H), 1.97-2.00 (q, 2H), 2.23 (s, 3H), 2.61-2.65 (m, 1H), 2.89-2.95 (m, 1H), 3.75-3.79 (q, 1H), 5.15-5.17 (t, J = 5Hz, 1H), 5.74 (D_2O exchangeable –OH, 1H), 6.92-6.93 (m, 1H), 6.97-6.99 (m, 1H), 7.22-7.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 16.7, 34.3, 37.5, 52.9, 63.8, 72.2, 122.2, 123.7, 126.6, 127.3, 127.9, 128.4, 141.5, 149.7; MS: *(m/z)* 276.05 (M + 1).

Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found C, 69.90; H, 7.48; N, 5.20.

(S)-N-Methyl-3-(naphthalen-1-yloxy)-N-((S)-1-phenylethyl)-3-(thiophen-2-yl)propan-1-amine (11)

A mixture of compound **10** (8.0 g, 0.029 mol), 1-fluoronaphthalene (4.6 g, 0.032 mol) and potassium hydroxide (14.4 g, 0.256 mol) in dimethyl sulfoxide (80 mL) was heated at 70-75 °C. Progress of reaction was monitored by TLC in ethyl acetate: cyclohexane (3:7) mobile phase. After completion of reaction in about 22 hr, the mass was cooled to room temperature and added to cold water (900 mL) with stirring. The reaction mixture was extracted with cyclohexane (100 mL X 2). The combined organic layer was concentrated and purified by silica gel column chromatography (60-120 mesh) using 2-7%

ethyl acetate in hexane as the mobile phase to obtain intermediate **11** as an oil (8.5 g, 73%); $[\alpha]_D^{20}$ = -29.67° (c = 0.21, methanol); IR (Neat): ν_{max} 699, 1095, 1264 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.31-1.33 (d, J = 7Hz, 3H), 2.16-2.24 (m, 1H), 2.26 (s, 3H), 2.34-2.47 (m, 1H), 2.51-2.56 (m, 1H), 2.63- 2.78 (m, 2H), 3.55-3.59 (q, 1H), 5.75-5.78 (m, 1H), 6.85-7.00 (m, 3H), 7.11-7.31 (m, 7H), 7.40-7.42 (d, J = 8Hz, 1H), 7.46-7.50 (m, 2H), 7.78-7.80 (dd, J = 1.5Hz, 8.5Hz, 1H), 8.23-8.25 (dd, J = 1.5Hz, 8.5Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm; 18.1, 36.9, 38.4, 50.3, 63.4, 74.2, 106.78, 120.4, 122.2, 124.6, 125.1, 125.7, 126.2, 126.2, 126.5, 126.7, 127.4, 127.6, 128.0, 134.6, 145.7, 153.5; MS: *(m/z)* 402.1 (M + 1).

Anal. Calcd for $C_{26}H_{27}NOS$: C, 77.77; H, 6.78; N, 3.49. Found: C, 77.70; H, 6.58; N, 3.51.

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