CHAPTER V

Synthesis of Optically Pure Duloxetine Hydrochloride from Undesired (R)-3-Dimethylamino-1-thiophen-2-yl-propan-1-ol
5.1 Introduction
Duloxetine [Cymbalta®] is a serotonin-norepinephrine reuptake inhibitor (SNRI) manufactured and marketed by Eli Lilly. It is prescribed for major depressive disorders and generalized anxiety disorders (GAD). Duloxetine has approval for the use in osteoarthritis and musculoskeletal pain also. It can even relieve the symptoms of painful peripheral neuropathy, particularly diabetic neuropathy,¹,² and it is used to control the symptoms of fibromyalgia. Duloxetine failed the U.S. approval for stress urinary incontinence amidst concerns over liver toxicity and suicidal events; however, it was approved for this indication in Europe, where it is recommended as an add-on medication in stress urinary incontinence instead of surgery.³

5.1.1 History
Duloxetine was created by Lilly researchers. David Robertson, David Wong, a co-discoverer of fluoxetine, and Joseph Krushinski are listed as inventors on the patent application filed in 1986 and granted in 1990.⁴ The first publication on the discovery of the racemic form of duloxetine known as LY227942, was made in 1988.⁵ The (+)-enantiomer of LY227942, assigned LY248686, was chosen for further studies, because it inhibited serotonin reuptake in rat synaptosomes to twice the degree as the (–)-enantiomer. This molecule was subsequently named duloxetine.⁶ Initial trials conducted in patients using regimens of 20 mg/day or less did not convincingly demonstrate its efficacy⁷ and the dose was increased to as high as 120 mg in subsequent clinical trials.⁸

In 2001 Lilly filed a New Drug Application (NDA) for duloxetine with the U.S. Food and Drug Administration (FDA). However, in 2003 the FDA "recommended the application as not approvable from the manufacturing and control standpoint" because of "significant cGMP (current Good Manufacturing Practice) violations at the finished product manufacturing facility" of Eli Lilly in Indianapolis. Additionally, "potential liver toxicity" and QTc interval prolongation appeared as a concern. The FDA experts concluded that
"duloxetine can cause hepatotoxicity in the form of transaminase elevations. It may also be a factor in causing more severe liver injury, but there are no cases in the NDA database that clearly demonstrate this. Use of duloxetine in the presence of ethanol may potentiate the deleterious effect of ethanol on the liver." The FDA also recommended "routine blood pressure monitoring" at the new highest recommended dose of 120 mg, "where 24% patients had one or more blood pressure readings of 140/90 vs. 9% of placebo patients."

After the manufacturing issues were resolved, the liver toxicity warning included in the prescribing information, and the follow-up studies showed that duloxetine does not cause QTc interval prolongation, duloxetine was approved by the FDA for depression and diabetic neuropathy in 2004. In 2007 Health Canada approved duloxetine for the treatment of depression and diabetic peripheral neuropathic pain.

Duloxetine was approved for the treatment of stress urinary incontinence (SUI) in the EU in 2004. In 2005, Lilly withdrew the duloxetine application for stress urinary incontinence (SUI) in the U.S., stating that discussions with the FDA indicated "the agency is not prepared at this time to grant approval based on the data package submitted." A year later Lilly abandoned the pursuit of this indication in the U.S. market.9,10 The FDA approved duloxetine for the treatment of generalized anxiety disorder in February 2007.

Cymbalta is Eli Lilly's top selling drug. It brought in just shy of $5 billion in 2012 with $4 billion of that in the U.S., but its patent protection terminated in January 1, 2014. Lilly received a six month extension beyond June 30, 2013 after testing for the treatment of depression in adolescents, which may produce $1.5 billion in added sales.11,12
5.1.2 Medical uses
The main uses of duloxetine are in major depressive disorder, general anxiety disorder, urinary incontinence, painful peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain associated with osteoarthritis and chronic lower back pain. It is being studied for various other indications.

5.1.2.1 Major depressive disorder
Duloxetine was approved for the treatment of major depression in 2004. While duloxetine has demonstrated improvement in depression-related symptoms compared to placebo, trials comparing duloxetine to other antidepressant medications have been less successful. A 2012 Cochrane review failed to demonstrate improved efficacy of duloxetine compared to SSRIs and newer antidepressants. Additionally, the review found evidence that duloxetine has increased side effects and reduced tolerability compared to other antidepressants. Thus it did not recommend duloxetine as a first line treatment for major depressive disorder, given the high cost of duloxetine compared to off-patent antidepressants and lack of increased efficacy.\textsuperscript{13}

5.1.2.2 Generalized anxiety disorder
Duloxetine is more effective than placebo in the treatment of generalized anxiety disorder (GAD)\textsuperscript{14}. Major guidelines such as Maudsley Prescribing Guidelines\textsuperscript{15} and Canadian Psychiatric Association Guidelines\textsuperscript{16} do not list duloxetine among the recommended treatment options. However, a review from the Annals. Internal Med. lists duloxetine among the first line drug treatments, along with citalopram, escitalopram, sertraline, paroxetine, and venlafaxine. Cognitive behavioral therapy remains the first line nonpharmacologic treatment for generalized anxiety disorder.\textsuperscript{17}

5.1.2.3 Diabetic peripheral neuropathy
Duloxetine was approved for the treatment of pain associated with diabetic peripheral neuropathy (DPN), based on the positive results of two clinical trials. The average daily
pain was measured using an 11-point scale, and duloxetine treatment resulted in an additional 1.0-1.7 points decrease of pain as compared with placebo.\textsuperscript{18-20} At least 50\% pain relief was achieved in 40-45\% of the duloxetine patients vs. 20-22\% of placebo patients. Pain decreased by more than 90\%, in 9-14\% of duloxetine patients vs. 2-4\% of placebo patients. Most of the response was achieved in the first two weeks on the medication. Duloxetine slightly increased the fasting serum glucose; however this effect was deemed to be of "minimal clinical significance".

Duloxetine was not effective for the numbness or tingling associated with diabetic neuropathy, nor for the other complications of diabetes. It reduced the pain without treating the underlying nerve damage.\textsuperscript{18} Only tight glycemic control was unequivocally demonstrated to slow the progression of neuropathy.\textsuperscript{19,21} Benfotiamine, alpha-lipoic acid, and ranirestat have also shown some promise.\textsuperscript{21}

The comparative efficacy of duloxetine and established pain-relief medications for DPN is unclear. An independent systematic review in \textit{BMJ} noted that tricyclic antidepressants (imipramine and amitriptyline), traditional anticonvulsants and opioids have better efficacy than duloxetine. Duloxetine, tricyclic antidepressants and anticonvulsants have similar tolerability while the opioids caused more side effects.\textsuperscript{20} A review in Drug and Therapeutic Bulletin saw no place for duloxetine in the treatment of DPN, based on its high cost and insufficient evidence of the comparative efficacy with tricyclic antidepressants. Another independent review in Prescrire International, considered the moderate pain relief achieved with duloxetine to be clinically insignificant and the results of the clinical trials-unconvincing. The reviewer saw no reason to prescribe duloxetine in practice.\textsuperscript{22} The comparative data collected by reviewers in \textit{BMC Neurology} indicated that amitriptyline, other tricyclic antidepressants and venlafaxine may be more effective. However, the authors noted that the evidence in favor of duloxetine is much more solid.\textsuperscript{23}
5.1.2.4 Fibromyalgia and chronic pain
A review of duloxetine found that it reduced pain and fatigue, and improved physical and mental performance compared to placebo.\textsuperscript{24} The Food and Drug Administration regulators approved the drug for the treatment of fibromyalgia in June 2008. Evidence also supports its use in chronic pain from osteoarthritis.\textsuperscript{25} On November 4, 2010, the U.S. Food and Drug Administration approved duloxetine to treat chronic musculoskeletal pain, including discomfort from osteoarthritis and chronic lower back pain.

5.1.2.5 Stress urinary incontinence
Duloxetine was first reported to improve outcomes in stress urinary incontinence (SUI) in 1998.\textsuperscript{26} The safety and utility of duloxetine in the treatment of incontinence has been evaluated in a series of meta analyses and practice guidelines.

- A 2013 meta-analysis covering ten trials with 5738 subjects concluded that duloxetine decreased incontinence episodes significantly more than placebo. Duloxetine-treated patients were about 56\% more likely than placebo-treated patients to experience a 50\% decrease in episodes. Adverse effects were experienced by 83\% of duloxetine-treated subjects and by 45\% of placebo-treated subjects.\textsuperscript{27}

- A 2012 review and practice guideline published by the European Association of Urology concluded that the clinical trial data provides Grade 1a evidence that duloxetine improves but does not cure urinary incontinence. In addition it causes a high rate of gastrointestinal side effects (mainly nausea and vomiting) leading to a high rate of treatment discontinuation.

- The National Institute for Clinical and Health Excellence recommends (as of September 2013) that duloxetine not to be routinely offered as first line treatment, and that it only to be offered as second line therapy in women wishing to avoid therapy. The guideline further states that women should be counseled regarding the drug's side effects.
5.1.3 Pharmacology

5.1.3.1 Mechanism of action
Duloxetine inhibits the reuptake of serotonin and norepinephrine in the central nervous system. Duloxetine is also considered a less potent inhibitor of dopamine reuptake. However, duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors and therefore can be considered to be a selective reuptake inhibitor at the 5-HT and NA transporters. Duloxetine undergoes extensive metabolism, but the major circulating metabolites do not contribute significantly to the pharmacologic activity.\textsuperscript{28,29}

Major depressive disorder is believed to be due to increase in pro-inflammatory cytokines within the central nervous system. Antidepressants including ones with a similar mechanism of action as duloxetine, i.e. serotonin metabolism inhibition, cause a decrease in proinflammatory cytokine activity and increase in anti-inflammatory cytokines; this mechanism may apply to duloxetine in its effect on depression but research on cytokines specific to duloxetine therapy is lacking.\textsuperscript{30}

The analgesic properties of duloxetine in the treatment of diabetic neuropathy and central pain syndromes such as fibromyalgia are believed as the results of sodium ion channel blockade.\textsuperscript{31}

5.1.3.2 Pharmacokinetics

5.1.3.2.1 Absorption
Duloxetine is acid labile, and is formulated with enteric coating to prevent degradation in the stomach. Duloxetine has good oral bioavailability, averaging 50\% after one 60 mg dose. There is an average 2 hour lag until absorption begins with maximum plasma concentrations occurring about 6 hours post dose. Food does not affect the $C_{\text{max}}$ of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours.\textsuperscript{29}
5.1.3.2.2 Distribution
Duloxetine is highly bound (> 90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. Volume of distribution is 1640 L.

5.1.3.2.3 Metabolism
Duloxetine undergoes predominately hepatic metabolism via two cytochrome P450 isozymes viz. CYP2D6 and CYP1A2. Circulating metabolites are pharmacologically inactive.

5.1.3.2.4 Elimination
Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and their pharmacokinetics is dose proportional over the therapeutic range. Steady-state is usually achieved after 3 days. Only trace amounts (< 1%) of unchanged duloxetine are present in the urine and most of the dose (approx. 70%) appears in the urine as metabolites of duloxetine with about 20% excreted in the feces.

5.2 Previously reported synthetic approaches
Synthesis of duloxetine 1 reported (Scheme 4.1) by Robertson et al. and asymmetric synthesis of duloxetine hydrochloride 1 through kinetic resolution method has been reported (Scheme 4.3) by Berglund. In continuation to Berglund et al. work (Scheme 4.3), Satyanarayana Reddy et al. reported (Scheme 5.1) an improved process for the preparation of pure duloxetine hydrochloride 1 through kinetic resolution method. 2-Acetyl thiophene 2 on reaction with N,N-dimethylamine hydrochloride 3 and para formaldehyde 4 in presence of conc. hydrochloric acid to yield 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride 5, which upon reduction with sodium borohydride in presence of sodium hydroxide solution afforded 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-ol 6. Resolution of (±) 6 with (S)-(+) mandelic acid to afford diastereomeric salt 8, which up on hydrolysis with 10% sodium carbonate afforded (S)-alcohol 6. Condensation of (S)-6 with 1-fluoro naphthalene 8 in presence of sodium
hydroxide and dimethylsulfoxide followed by demethylation with phenyl chloroformate in the presence of diisopropylethylamine afforded duloxetine. Salt formation of duloxetine with oxalic acid to yield duloxetine oxalate 9. Free base of duloxetine oxalate 9 with aqueous ammonia followed by salt formation with ethyl acetate hydrochloric acid afforded duloxetine hydrochloride 1. Purification of duloxetine hydrochloride in ethyl acetate and methanol gave pure duloxetine hydrochloride 1.

Scheme 5.1 Reagents and Conditions: (a) Conc. HCl, isopropyl alcohol, reflux, 6 h, 87%; (b) 20% NaOH, MeOH, H₂O, NaBH₄, rt, 6 h, 89%; (c) (i) (S)-(+)−mandelic acid, EtOAc, 75 °C to 35 °C, 10 h; (ii) 10% Na₂CO₃, CH₂Cl₂, 0 °C, 47%; (d) (i) NaOH, DMSO, TBAB, 65 °C, 50 h; (ii) DIPEA, phenyl chloroformate, 45 °C, 4 h; (iii) DMSO, NaOH, 45 °C, 3 h; (iv) oxalic acid, rt, 4 h, 69%; (e) (i) aq. NH₃, H₂O, CH₂Cl₂, EtOAc. HCl, 0 °C, 2 h, 52%; (ii) EtOAc, MeOH, 60 °C to 25 °C, 4 h, 70%.
5.3 Objective of the research work

Prior art synthetic approaches were appreciable in terms of the strategies adopted to address the chemistry. The common deficiency in these resolutions is that 50% of the material is lost as unwanted isomer, which will greatly diminish their synthetic utility for scale-up.

Duloxetine hydrochloride 1 was successfully prepared as per Scheme 5.1. In this, the mother liquor, after resolution step, was decomposed with base and analyzed for both isomers percentages, and found that ~ 92% undesired (R)-isomer 6 and 8% (S)-isomer 6 in crude stage. To make this process economically feasible, there is a need to racemize (R)-6 from the mother liquor.

These factors driven us to develop a simple and economically workable process for the preparation of duloxetine hydrochloride 1 through racemization of undesired isomer, produced during the resolution step. This chapter is dedicated to the synthesis of optically pure duloxetine hydrochloride from undesired (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol.

The basic objective is to transform (R)-isomer into keto compound and subsequent reduction with sodium borohydride. Conversion of (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol into 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride has been achieved with potassium permanganate in the presence of sulfuric acid.

5.4 Results and discussion

As outlined in Scheme 5.2, synthesis of duloxetine hydrochloride 1 starts with conversion of (R)-isomer 6 to 3-dimethylamino-1-thiophen-2-yl-propan-1-ol (±) 6 through 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride 5. Reduction of 5 with NaBH₄ in the presence of aqueous sodium hydroxide gave racemic compound (±) 6 in one pot.
Scheme 5.2 Reagents and Conditions: (a) (i) KMNO₄, H₂SO₄, acetone, H₂O, 10% HCl, 20 °C, 10 min; (ii) NaBH₄, 20 °C, 2 h, 70%; (b) (S)-(+) mandelic acid, EtOAc, 75 °C to 30 °C, 10 h, 90%; (c) 10% Na₂CO₃, CH₂Cl₂, 0 °C, 93%; (d) (i) NaOH, DMSO, 50-55 °C, 45 min; (ii) TBAB, DMSO, 65 °C, 55 h, oxalic acid, 60%; (e) (i) 10% Na₂CO₃, toluene, H₂O, Et₃N, phenyl chloroformate, 55 °C, 4 h; (ii) DMSO, 25% NaOH, 55 °C, 35 h; (iii) EtOAc. HCl, 0 °C; (iv) MeOH, EtOAc, 60 °C to 30 °C, 4 h, 52%.

Typically, the mother liquor evaporated and the residue was decomposed with 10% sodium carbonate solution at about 9.8 pH in the presence of dichloromethane and water. Separated organic layer was concentrated and isolated in cyclohexane which was contained approximately 8-10% of the (S)-isomer 6 and 90-92% of the (R)-isomer 6.
Oxidation of (R)-isomer 6 with potassium permanganate and sulfuric acid in acetone followed by salt formation with hydrochloric acid gave 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride 5, followed by reduction with NaBH$_4$ in the presence of aqueous sodium hydroxide afforded (±) 6.

In order to confirm that the reaction goes through 5, the reaction of (R)-6 with potassium permanganate and sulfuric acid in acetone at 15-20 °C was terminated after 30 min and adjusted the pH to 2 with 10% hydrochloric acid, and washed with ethyl acetate. Separated aqueous layer was concentrated and isolated in isopropyl alcohol.

Isolated product was confirmed as 5 by spectral data. In the mass spectrum (Figure 5.1) peak at 184.1 corresponds to (free base, M+H$^+$). The IR spectrum (Figure 5.2) displayed a peak at 3445 cm$^{-1}$ corresponds to tertiary amine stretching, peak at 3078 cm$^{-1}$ belongs to aromatic –CH stretching, peak at 2917 cm$^{-1}$ corresponds to aliphatic –CH stretching, peak at 1651 cm$^{-1}$ belongs to ketone and peak at 1522 cm$^{-1}$ and 1474 cm$^{-1}$ corresponds to aromatic C=C stretching. The $^1$H NMR spectrum (Figure 5.3, DMSO-$d_6$) displayed broad peak at δ 10.9 (br s, 1H) corresponds to HCl proton, a signal at δ 8.1 (d, 2H) belongs to aromatic protons of thiophene, a signal at δ 7.3 (t, 1H) corresponds to aromatic proton of thiophene, a signal at δ 3.6 (t, 2H) belongs to methylene (CH$_2$) protons adjacent to ketone, a signal at δ 3.35 (t, 2H) corresponds to methylene (CH$_2$) protons adjacent to nitrogen atom and signal at δ 2.8 (s, 6H) belongs to CH$_3$ protons attached to nitrogen atom.

The compound (±) 6 was characterized on the basis of its spectral data. In the mass spectrum (Figure 5.4) peak at 186.1 corresponds to molecular ion (M+H$^+$). The IR spectrum (Figure 5.5) displayed a peak at 3422 cm$^{-1}$ corresponds to alcohol (-OH) stretching, peak at 3073 cm$^{-1}$ belongs to aromatic –CH stretching, peak at 2932 cm$^{-1}$ corresponds to aliphatic –CH stretching, peaks at 1611 cm$^{-1}$ and 1460 cm$^{-1}$ belongs to aromatic C=C stretching. The $^1$H NMR spectrum (Figure 5.6, DMSO-$d_6$) displayed a
doublet at δ 7.37 (d, 1H) corresponds to aromatic proton of thiophene, a signal at δ 6.90-6.97 (dd, 2H) belongs to aromatic protons of thiophene, a broad peak at δ 5.79 (brs, 1H) corresponds to alcoholic (OH) proton, a signal at δ 4.85 (t, 1H) belongs to –CH proton adjacent to oxygen atom, a signal at δ 2.30 (t, 2H) corresponds to methylene (CH₂) protons adjacent to nitrogen atom, a signal at δ 2.17 (s, 6H) belongs to CH₃ protons attached to nitrogen atom and a signal at 1.80 (q, 2H) corresponds to methylene (CH₂) protons adjacent to alcohol.

Resolution³³ of (±) 6 with (S)-(+) mandelic acid afforded diastereomeric salt 7, which upon hydrolysis with 10% sodium carbonate solution afforded (S)-(−)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6. The compound (S)-6 was characterized on the basis of its spectral data.

TBAB-catalyzed³⁴ condensation of (S)-6 with 1-fluornaphthalene 8 in the presence of NaOH and DMSO selectively furnished (S)-(+)N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine as an oxalate 10. The compound 10 was characterized on the basis of its spectral data.

Mass spectrum – Ref. Figure 4.6 in Chapter IV
IR spectrum – Ref. Figure 4.7 in Chapter IV
¹H NMR spectrum – Ref. Figure 4.8 in Chapter IV

Hydrolysis³³ of 10 in the presence of 10% sodium carbonate solution, followed by demethylation with phenyl chloroformate in the presence of 25% NaOH solution afforded (S)-(+)N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine as a sodium salt 11. Salt formation of 11 with conc. HCl³³ afforded duloxetine hydrochloride 1.

The compound 1 was characterized on the basis of its spectral data. In the mass spectrum (Figure 5.7) peak at 298.1 corresponds to free base molecular ion (M+H)⁺. The IR spectrum (Figure 5.8) displayed a peak at 3197 cm⁻¹ corresponds to secondary –NH
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stretching, a peak at 3062 cm\(^{-1}\) belongs to aromatic –CH stretching, peak at at 2778 cm\(^{-1}\) corresponds to aliphatic –CH stretching, peak at 1579 cm\(^{-1}\) & 1463 cm\(^{-1}\) belongs to aromatic C=\(\text{C}\) stretching, peak at 1395 cm\(^{-1}\) corresponds to aralkyl ether stretching. The \(^1\)H NMR spectrum (Figure 5.9, CDCl\(_3\)) displayed a singlet at \(\delta 9.77\) (s, 2H) corresponds to –NH proton and HCl proton, a signal at \(\delta 8.29\)-8.27 (m, 1H) belongs to aromatic proton of naphthalene adjacent ro oxygen atom, a signal at \(\delta 7.77\)-7.75 (m, 1H) corresponds to aromatic proton of thiophene adjacent to sulphur atom, a signal at \(\delta 7.49\)-7.11 (m, 6H) belongs to aromatic protons of naphthalene, and a signal at \(\delta 6.88\)-6.85 (m, 2H) corresponds to chiral proton adjacent to oxygen atom, a signal at \(\delta 3.19\)-3.15 (m, 2H), corresponds to methylene (CH\(_2\)) protons adjacent to nitrogen atom, a signal at \(\delta 2.82\)-2.76 (m, 2H) belongs to methylene (CH\(_2\)) protons and a signal at \(\delta 2.62\) (s, 3H) corresponds to methyl protons (CH\(_3\)) respectively.

5.5 Conclusions

In conclusion, an efficient and economically feasible process for the preparation of duloxetine hydrochloride 1 was accomplished through racemization of \((R)\)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6 using potassium permanganate as an oxidizing agent and robust resolution process for the synthesis of \((S)\)-6 by means of inexpensive \((S)\)-(+) mandelic acid. Upon practicing the disclosed process, a significant cost reduction in the synthesis of duloxetine hydrochloride 1 was realized.
5.6 Experimental section

General: The $^1$H NMR spectra were recorded in DMSO and CDCl$_3$ at 200, 300 and 400 MHz with a Varian Gemini FT NMR spectrometer. Chemical shifts are relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersions by using a Perkin-Elmer 1650 FT-IR spectrophotometer. Mass spectra (70 ev) were recorded on an Agilent 6310 Ion Trap LC-MS spectrometer. Optical rotations were measured using Rudolph Autopol-V polarimeter and $[\alpha]_D^{25}$ values are given in units of $10^{-1}$ deg. cm$^2$ g$^{-1}$. The solvents and reagents were used without any purification.

5.6.1 3-Dimethylamino-1-thiophen-2-yl-propan-1-ol (±) 6. (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (R)-6 (5 Kg, 27.02 mmol) and acetone (60 L) mixture was stirred for 10 min at 25-30 °C, cooled, and added H$_2$SO$_4$ (0.66 Kg, 6.75 mmol) at 15-20 °C. KMNO$_4$ solution (4.27 Kg KMNO$_4$, 27.02 mmol + 8 L H$_2$O) was added to the reaction mixture in 45 min and stirred for 10 min at 15-20 °C. On completion of reaction (TLC), the mixture was filtered through celite and the filtrate was acidified (pH ~2) with 10% HCl (45 L), and washed with ethyl acetate (2x25 L). Separated aqueous layer was distilled under reduced pressure up to 60 L at < 70 °C and cooled to 5-10 °C. Sodium borohydride (0.8 Kg, 21.62 mmol) was slowly added to the above aqueous layer in three equal lots over a period of 3 h at 5-10 °C, and stirred for 2 h at 15-20 °C. On completion reaction (TLC), 48% NaOH solution (7 L) was added and stirred for 2 h at 25-30 °C. The precipitated solid was filtered, and recrystallized in hexanes (50 L) to afford pure compound (±) 6 (3.5 Kg, 70%) as an off-white solid; $[\alpha]_D^{25}$ +0.1 (c 1, MeOH); IR (KBr, cm$^{-1}$): 3080, 2968, 2778, 1595, 1467, 1427, 1356, 690; $^1$H NMR (200 MHz, DMSO-d$_6$): $\delta$ 7.37 (d, 1H), 6.90-6.97 (dd, 2H), 5.79 (br s, 1H), 4.85 (t, 1H), 2.30 (t, 2H), 2.17 (s, 6H), 1.80 (q, 2H); MS: m/z = 186.1 [M+H]$^+$. 

5.6.2 (S)-(+-)3-dimethylamino-1-thiophen-2-yl-propan-1-ol mandelate 7. A mixture of 3-Dimethylamino-1-thiophen-2-yl-propan-1-ol 6 (3.5 Kg, 18.92 mmol), ethyl acetate (35 L), and (S)-(+-)-mandelic acid (1.75 Kg, 11.51 mmol) was stirred for 1.5 h at 25-30
°C. The mixture was then stirred for 3 h at 70-75 °C and further cooled and maintained for 10 h at 25-30 °C. The precipitated solid was filtered, and washed with ethyl acetate (1.75 L). Wet solid and ethyl acetate (17.5 L) were stirred for 1 h at 60-65 °C, cooled and stirred for 1.5 h at 25-30 °C. The separated solid was filtered, washed with ethyl acetate (3.5 L) and dried at 60-65 °C under vacuum for 5 h to afford compound 7 (2.87 Kg, 90%, 99.3% de) as a white solid.

5.6.3 (S)-(+)3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6. A mixture of (S)-(+)3-dimethylamino-1-thiophen-2-yl-propan-1-ol mandelate 7 (2.5 Kg), water (5 L) and chloroform (15 L) was cooled to 0-5 °C, and adjusted the pH to 9.5-10.0 with 10% Na₂CO₃ solution (18.15 L), and the solution was stirred for 20 min at 0-5 °C. Both layers were separated and the aqueous layer was extracted with chloroform (12.5 L). The combined organic extracts were washed with sat. NaCl (12.5 L) solution, dried (Na₂SO₄), and concentrated completely under reduced pressure at < 35 °C. Cyclohexane (0.75 L) was added to the above residue and concentrated under reduced pressure at < 35 °C to give residue. The residue was mixed with cyclohexane (5 L), and the mixture was stirred for 1 h at 40-45 °C, and cooled to 0-5 °C. The precipitated solid was filtered, washed with cyclohexane (1.25 L) and dried at 40-45 °C under vacuum for 6 h to afford compound (S)-6 (1.27 Kg, 92.5%, 99.94% ee) as a white solid; [α]D²⁵ = -7.0 (c 1, MeOH); IR (KBr, cm⁻¹): 3422, 3073, 2932, 2801, 1611, 1460, 1385; ¹H NMR (300 MHz, DMSO-d₆): δ 7.37 (d, 1H), 6.91-6.96 (dd, 2H), 5.79 (s, 1H), 4.85 (t, 1H), 2.30 (t, 2H), 2.17 (s, 6H), 1.80 (q, 2H); MS: m/z = 185.9 [M]+.

5.6.4 (S)-(+)N,N-dimethyl-3-(1-naphthalenyl)oxy)-3-(2-thienyl)propylamine oxalate 10. Ref. Experimental section 4.8.1 in Chapter IV.

5.6.5 Duloxetine hydrochloride 1. (S)-(+)N,N-dimethyl-3-(1-naphthalenyl)oxy)-3-(2-thienyl)propylamine oxalate 10 (3.2 Kg, 7.98 mmol), toluene (3.2 L), and water (1.6 L) were stirred for 10 min and pH was adjusted to 8.2 for 3-4 h with 10% Na₂CO₃ solution
(1.4 L), and stirred for 30 min at 25-30 °C. The aqueous layer was discarded, and the organic layer was washed with water (0.64 L), and dried with Na₂SO₄. A mixture of organic layer and triethylamine (0.8 Kg, 7.98 mmol) was heated to 55 °C, and phenyl chloroformate (4.9 Kg, 31.92 mmol) was added for 30 min and stirred for 4 h at 55 °C. On completion of reaction (TLC), the solution was cooled to 30 °C and added water (0.64 L). The resulting mixture pH was adjusted to 9.1 with 10% Na₂CO₃ solution (1.9 L) and stirred for 30 min at 25-30 °C. Separated organic layer was washed with water (0.64 L), 10% Na₂CO₃ (1.6 L), 10% NaHCO₃ (1.6 L), and 10% oxalic acid (1.6 L) successively. Separated organic layer was evaporated completely under reduced pressure at < 45 °C to give residue. The residue was mixed with dimethylsulphoxide (6.4 L) and heated to 45 °C. 25% NaOH (1.28 L) solution was added to the mixture for 3-4 h and stirred for 35 h at 55 °C. On completion of reaction (TLC), mixture was cooled and diluted with water (3.2 L), ethyl acetate (2.56 L) and the mixture was stirred about 15 min at 15-20 °C. Separated aqueous layer was extracted with ethyl acetate (0.64 L). The organic layer was washed with water (2x0.64 L), dried, and concentrated under reduced pressure at < 40 °C up to volume reaches 1.5 L to afford 11.

11 (1.5 L) was cooled to 0-5 °C, pH was adjusted to 1.5-2.0 with ethyl acetate hydrochloride (0.32 L) and stirred for 1-2 h. The precipitated solid was filtered, washed with ethyl acetate (0.32 L), and dried at 50 °C under vacuum for 4 h to give crude product. A mixture of crude product, methanol (0.15 L), and ethyl acetate (0.6 L) was stirred for 1.5 h at 60 °C, cooled, and stirred for 4 h at 25-30 °C. The solid was filtered, washed with ethyl acetate (0.08 L) and dried at 50 °C under vacuum for 4 h to afford pure duloxetine hydrochloride 1 (1.4 Kg, 52%, 99.9% ee) as a white solid; Purity by HPLC: 99.9%; IR (KBr, \text{cm}^{-1}): 3197, 3062, 2960, 2778, 1596, 1579, 1463, 1395, 1264, 1095; \textsuperscript{1}H NMR (400 MHz, CDCl₃): \(\delta\) 9.77 (s, 2H), 8.29-8.27 (m, 1H), 7.77-7.75 (m, 1H), 7.49-7.11 (m, 6H), 6.88-6.85 (m, 2H), 5.93 (dd, \(J = 5.1\) Hz, 1H), 3.19-3.15 (m, 2H), 2.76-2.82 (m, 2H), 2.62 (s, 3H); MS: \(m/z = 298.1\) [M+H]+ (free base).
Figure 5.1 Mass spectrum of 5

Figure 5.2 IR spectrum of 5
Figure 5.3 200 MHz $^1$H NMR spectrum of 5 in DMSO-$d_6$

Figure 5.4 Mass spectrum of (±) 6
Figure 5.5 IR spectrum of (±) 6

Figure 5.6 200 MHz $^1$H NMR spectrum of (±) 6 in DMSO-$d_6$
Figure 5.7 Mass spectrum of 1

Figure 5.8 IR spectrum of 1
Figure 5.9 400 MHz $^1$H NMR spectrum of 1 in CDCl$_3$
5.7 References


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LIST OF PUBLICATIONS

I Referred International Journals


**II Conferences**

ABSTRACT

Title of the thesis: Synthesis and characterization of antithrombotic and antipsychotic active pharmaceutical ingredients

Name of the student: Suthrapu Sashikanth
Name of the supervisor: Dr. K. Venugopal Reddy

This thesis entitled “Synthesis and Characterization of Antithrombotic and Antipsychotic Active Pharmaceutical Ingredients” has been divided in to five chapters.

Chapter I: Introduction to Antithrombotic and Antipsychotics.
This chapter deals with introduction of antithrombotics and anitipsychotics.

Chapter II: An Asymmetric Synthesis of Clopidogrel Hydrogen Sulfate.
This chapter deals with an asymmetric synthesis of clopidogrel hydrogen sulfate through application of a Strecker reaction.

This chapter deals with an alternate synthesis for the preparation of Prasugrel through a Grignard reaction.

Chapter IV: An Investigation on Key Parameters that Influences the Synthesis of (S)-(+-)N,N-dimethyl-3-(1-naphthalenyl)-3-(2-thienyl)propylamine: A key intermediate for Duloxetine.
This chapter deals with an investigation on key parameters that influences the synthesis of (S)-(+-)N,N-dimethyl-3-(1-naphthalenyl)-3-(2-thienyl)propylamine.

Chapter V: Synthesis of Optically Pure Duloxetine Hydrochloride from Undesired (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol.
This chapter deals with synthesis of optically pure Duloxetine hydrochloride from undesired \((R)-3\text{-dimethylamino-1-thiophen-2-yl-propan-1-ol.}\)

**Chapter I: Introduction to Antithrombotics and Antipsychotics.**

**Active pharmaceutical ingredients**

An active pharmaceutical ingredient (API)\(^1,2\) is the substance in a pharmaceutical drug or a pesticide that is biologically active. Terms in similar use include bulk active in medicine, and active substance in pesticide formulations. Some of the medications and pesticide products may contain more than one active ingredient. The traditional word for the API is pharmacon or pharmakon (from Greek, adapted from pharmacos) which originally denotes a magical substance or drug. A dosage form of a drug is traditionally composed of two things: The API, which is the drug itself; and an excipient also called as bulk pharmaceutical chemical (BPC),\(^3\) which is the substance of the tablet, or the liquid the API is suspended in or other material that is pharmaceutically inert. Drugs are chosen primarily for their active ingredients. Because homoeopathic products no longer have any biologically active ingredients, their list of ingredients refers to the original ingredients used in their preparation and the finished product no longer contains any active ingredients.

Bulk pharmaceutical chemical containing an active ingredient is encapsulated with other ingredients such as flavors, cooling or heating agents, or sweeteners, within a microsphere. Upon exposure to water or pH, the microsphere releases its contents, and over an extended period of time the BPC release the encapsulated active ingredient *via* molecular diffusion and enzymatic degradation by lipase. The surface properties of the BPC can be altered to be bioadhesive or negatively or positively charged depending on the intended target site.
**Antithrombotics**

Atherothrombosis associated with pre-existing atherosclerotic plaques involves platelet activation, aggregation and thrombus formation. Long-term antiplatelet therapy is effective in the secondary prevention of vascular events in patients with acute coronary or cerebrovascular events that are at a high risk of subsequent thrombotic events. The recent development of drugs with greater selectivity, efficacy and decreased side effects resulted from a better understanding of the mechanisms of atherosclerosis, platelet aggregation, coagulation and thrombolysis.

Endothelial injury caused by shear stress, hypertension, diabetes or smoking is an important factor in the initiation and progression of arterial disease. Lipids and monocytes accumulate on the intima of damaged arteries. Adherent platelets and macrophages secrete growth factors that activate the migration and proliferation of smooth muscle cells from the media. These smooth muscle cells release collagen, proteoglycans and elastic fibres that together form the fibrous cap of the atheromatous plaques. These atheromatous plaques, usually located at vessel ostia, branches or regions where blood flow changes in velocity or direction, causing high shear stress, later become calcified. High shear stress occurring in the atherosclerotic small arteries and arterioles induces platelet activation, aggregation and enhances platelet thrombus formation.

The disruption of atherosclerotic plaques triggers platelet adhesion, activation and aggregation, causing cerebrovascular, coronary and peripheral vascular ischaemic syndromes that may progress to infarction. Platelet adhesion is mediated by the interaction of platelet glycoprotein Ib/IX with sub endothelial von Willebrand’s factor under high shear conditions, and by platelet glycoprotein Ia/IIb binding to collagen under low shear conditions. The adherent platelets recruit additional platelets into a growing thrombus. Initially, clotting factors assemble on the activated platelet surface and this process enhances thrombin generation. The resultant increase in thrombin activates more
platelets and triggers coagulation. The activated platelets also secrete ADP (from their dense granules), which activates nearby platelets. Thromboxane A\_2 released by the platelets activates additional platelets.

**Antipsychotics**

Antipsychotics (also known as neuroleptics or major tranquilizers)\(^7\) are a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, or disordered thought), in particular in schizophrenia and bipolar disorder, and are increasingly being used in the management of non-psychotic disorders (ATC code N05A). The word neuroleptic originated from the Greek word *lepsis* ("seizure" or "fit").

Antipsychotics are broadly divided into two groups, the typical or first-generation antipsychotics and the atypical or second-generation antipsychotics. The typical antipsychotics are classified according to their chemical structure while the atypical antipsychotics are classified according to their pharmacological properties. These include serotonin-dopamine antagonists, multi acting receptor targeted antipsychotics (MARTA, those targeting several systems), and dopamine partial agonists, which are often categorized as atypicals.\(^8\)

**Chapter II: An Asymmetric Synthesis of Clopidogrel Hydrogen Sulfate.**

Clopidogrel hydrogen sulfate is a potent and orally active, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. It is marketed by Sanofi-Aventis and Bristol-Myers Squibb under the trade name Plavix. The drug works by irreversibly inhibiting a receptor called P2Y\(_{12}\), an adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes. Adverse effects include hemorrhage, severe neutropenia, and thrombotic thrombocytopenic purpura (TTP). Clopidogrel works by helping to
prevent harmful blood clots. Studies shown that clopidogrel is more effective in blocking platelet aggregation than aspirin and ticlopidine even at much lower dosage. A dosage of 75 mg of clopidogrel has been shown to be more effective than a dosage of 325 mg of aspirin. Clopidogrel is widely used in combination with aspirin after placement of intravascular stents. Plavix, (Clopidogrel hydrogen sulfate) is the second best-selling drug in the world, with global sales of $6.4 billion in 2006 and $7.3 billion in 2007.

Various methods have been reported for the synthesis of this potent antithrombotic drug, most of which involve either the ortho-chloromandelate or 2-(2-chlorophenyl)glycine derivatives as starting materials. Although the synthetic approaches were appreciable in terms of the strategies adopted to address the chemistry, these methodologies suffer few drawbacks.

Recently, Perez-Fuertes and co-workers prepared enantiopure α-arylglycines using asymmetric Strecker reaction. This asymmetric synthesis encouraged us to attempt a preparation of enantiomerically pure (S)-clopidogrel 1 by a similar stereoselective route. This chapter is dedicated to an asymmetric synthesis of clopidogrel hydrogen sulfate 1.

The retro synthetic analysis for (S)-(++)-clopidogrel hydrogen sulfate 1 shown in Scheme 2.1. Methyl (S)-2-(2-chlorophenyl)glycinate 6 and 2-(2-bromomethyl)-3-(bromomethyl)thiophene 7 are precursors of (S)-(++)-clopidogrel 1. Glycinate 6 might be obtained from (2S)-(2-chlorophenyl){[(1S)-1-(4-methoxyphenyl)ethyl]amino}
acetonitrile hydrochloride 4, which in turn, could be prepared from 2-chloro benzaldehyde 2.

\[
\begin{align*}
\text{CH}_3\text{COOCH}_3 + \text{H}_2\text{NCl} & \rightleftharpoons \text{H}_2\text{NCOOCH}_3 + \text{S-Br-Br-CN-Cl-NH-CH}_3\cdot\text{HCl} \\
\text{CHO} & \underset{\text{Cl}}{\rightleftharpoons} \text{H}_2\text{CO} & \text{S}
\end{align*}
\]

Scheme 2.1 Retrosynthetic analysis for Clopidogrel hydrogen sulfate 1

Here we report a strategy involving a chiral auxiliary based Strecker reaction as the key step for the synthesis of (2S)-2-(2-chlorophenyl)glycine hydrochloride 5, followed by esterification to give the methyl ester 6, a key intermediate for clopidogrel 1.
Scheme 2.2 Reagents and Conditions: (a) NaCN, MeOH:H₂O (1:1), rt, 16 h, 75%; (b) 6M HCl, Et₂O, CHCl₃, rt, 90 °C, 4 h, 80%; (c) (i) MeOH, H₂SO₄, 0 °C to reflux, 5 h; (ii) 20% Na₂CO₃, CH₂Cl₂, rt, 85%; (d) (i) DIPEA, MeCN, EtOAc, reflux; (ii) H₂SO₄, acetone, rt to 0 °C, 6 h, 75%.

In conclusion, we achieved an asymmetric synthesis of (S)-(+)—clopidogrel hydrogen sulfate 1 by means of an asymmetric Strecker reaction.

Prasugrel is a member of the thienopyridine class of ADP receptor inhibitors, like ticlopidine (TICLID®) and clopidogrel (PLAVIX®). These agents are believed to reduce the aggregation (i.e., clumping) of platelets by irreversibly binding to P2Y₁₂ receptors and it is useful as antithrombotic or antiembolic agents. They are useful as medicaments (preferably useful as therapeutic or prophylactic agents) for thrombus formation-induced or embolization-induced diseases. They can be used to prevent thrombolytic cardiovascular complications in patients with recent ischemic stroke or with acute coronary syndromes. They may also be useful for reducing secondary complications, recurrent myocardial infarction, recurrent stroke and re-hospitalization for severe angina. Prasugrel is novel platelet inhibitor that is expected to be administered as a solid dosage form. The acid addition salts of prasugrel exhibit excellent oral absorption, metabolization into the active compound, low toxicity, and excellent storage and handling stability and hence useful in preparation of the medicaments which exhibit activity in inhibition of platelet aggregation.

Figure 2 Prasugrel 1
Discovery of the synthesis of prasugrel$^{10}$ \textbf{1} is reported in Scheme 3.1, in which preparation of Grignard reagent from 2-fluorobenzylbromide \textbf{2} followed by reaction with cyclopropyl cyanide in the presence of ether affords 1-cyclopropyl-2-(2-fluorophenyl)ethanone \textbf{3}. Bromination of 1-cyclopropyl-2-(2-fluorophenyl)ethanone \textbf{3} with liquid bromine in the presence of carbon tetrachloride affords 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone \textbf{4}. Condensation of 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone \textbf{4} with 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridine-2-one$^{11}$ \textbf{5} in the presence of potassium carbonate in dimethylformamide affords 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine \textbf{6} which upon acetylation with acetic anhydride in the presence of sodium hydride affords prasugrel \textbf{1}.

\begin{center}
\textbf{Scheme 3.1 Reagents and Conditions:} (a) Cyclopropyl cyanide, Mg powder, Et$_2$O, rt, 70%; (b) Br$_2$, CCl$_4$, rt, 69%; (c) K$_2$CO$_3$, DMF, rt, 32%; (d) Ac$_2$O, NaH, DMF, 0 °C to rt, 65%.
\end{center}
Reported synthetic approaches were appreciable in terms of the strategies adopted to address the chemistry. But the disclosed processes have certain drawbacks. These processes either involve time consuming processes, such as, for example, column purifications, lengthy process or tedious separations to reduce the impurities level. These processes involve the use of high solvent quantities. Hence, there remains a need for viable processes to prepare prasugrel or its salts.

Besides all approaches, Scheme 3.1 encouraged us to attempt to develop an alternate synthesis for the preparation of prasugrel through a Grignard reaction.

The retro synthetic analysis for prasugrel 1 is shown in Scheme 3.2. 5-(α-Cyclopropyl-carbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno [3,2-c]pyridine 6 is precursor of prasugrel 1. Pyridine 6 might be obtained from 6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl-(2-fluorophenyl)acetonitrile 10, which, in turn, could be prepared from 2-fluorobenzylcyanide 7.

Scheme 3.2 Retrosynthetic analysis for Prasugrel 1
Here we report a strategy involving Grignard reaction as the key step for the synthesis of 1-cyclopropyl-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-2-(2-fluorophenyl)ethanone \( \text{11} \), followed by oxidation to give pyridine \( \text{6} \) a key intermediate for the synthesis of prasugrel \( \text{1} \).

\[ \begin{align*}
\text{7} & \xrightarrow{a} \begin{cases} \text{8} \\
\end{cases} \\
\text{11} & \xrightarrow{b} \begin{cases} \text{10} \\
\end{cases} \\
& \xrightarrow{c} \begin{cases} \text{6} \\
\end{cases} \\
& \xrightarrow{d} \begin{cases} \text{1} \\
\end{cases}
\end{align*} \]

**Scheme 3.3 Reagents and Conditions:** (a) (i) NBS, AIBN, CHCl\(_3\), reflux, 4 h; (ii) K\(_2\)CO\(_3\), MeCN, rt, 4 h, 70%; (b) cyclopropylmagnesium bromide, THF, CuBr, reflux, 1.5 h, 55%; (c) LDA, tetramethyl urea, \( n \)-BuLi, B(OBu)\(_3\), H\(_2\)O\(_2\), THF, -78 °C to 0 °C, 1 h, 67%; (d) Ac\(_2\)O, Et\(_3\)N, toluene, 0 °C to rt, 7 h, 53%.

In conclusion, we achieved an alternate approach for the synthesis of prasugrel through application of a Grignard reaction.

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Chapter IV: An Investigation on Key Parameters that Influences the Synthesis of (S)-(+-)-N,N-dimethyl-3-(1-naphthalenylxyloxy)-3-(2-thienyl)propylamine: A key intermediate for Duloxetine.

Duloxetine and related class of compounds such as fluoxetine, tomoxetine, etc. are important for treating psychiatric disorders. Fluoxetine is selective inhibitor of serotonin in serotonergic neurons; tomoxetine and nisoxetine are selective inhibitors of norepinephrine in noradrenergic neurons, while duloxetine is a dual inhibitor of serotonin (5-HT) and norepinephrine (NE) reuptake and thus has a better pharmacological profile as an antidepressant drug.

Serotonin and norepinephrine neurotransmitters are intimately involved in a number of physiological and behavioral processes, suggesting that duloxetine (with the ability to produce robust increases of extracellular serotonin and norepinephrine levels) is not only a highly efficient antidepressant agent for treating psychiatric disorders but also can be used for treating other symptoms like alcoholism, stress urinary incontinence (SUI), fatigue, stroke, intestinal cystitis, obsessive compulsive disorder, panic disorder, sleep disorder and sexual dysfunction, etc.

![Duloxetine Hydrochloride](image)

**Figure 3 Duloxetine Hydrochloride**

Synthesis of duloxetine reported in Scheme 4.1, which involves the reaction of 2-acetyl thiophene with dimethylamine hydrochloride and para formaldehyde (Mannich reaction) in the presence of conc. hydrochloric acid produced 3-(dimethyl
amino)-1-(thiophen-2-yl)propan-1-one hydrochloride 5 is reduced to the corresponding alcohol 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-ol (±) 6 by means of complex hydrides. Condensation of (±) 6 with 1-fluoro naphthalene 7 in the presence of alkali metal hydride yielded N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine (±) 8. Demethylation of (±) 8 with a chloroformic acid ester followed by alkaline hydrolysis of the carbamate to give (±) duloxetine 1 as an oxalate salt.

Scheme 4.1 Reagents and Conditions: (a) 12N HCl, EtOH, reflux 1.5 h, 73%; (b) (i) 5N NaOH, MeOH, H2O, 0 °C; (ii) NaBH4, 0 °C to rt, overnight, 78%; (c) NaH, DMA, 110 °C, 1 h, oxalic acid, 76%; (d) (i) 30% NH4OH, toluene, rt; (ii) phenyl chloroformate, reflux, 1.5 h; (iii) 5N NaOH, propylene glycol, 110 °C, 75 min, oxalic acid, 41%.

Various synthetic approaches are reported in the literature for the key intermediate (±) 8, which involves the in-situ generation using different bases in combination with catalysts. However, the given selectivity could not be reproduced in our laboratory when the reaction was conducted under literature conditions. The usage of hazardous base like NaH in these processes made them commercially non-attractive. In the recent modification of this current process we have conducted the condensation reaction
in presence of catalytic amount of phase transfer catalyst (PTC) to enhance the enantioselectivity of desired S-isomer 8 to more than 99%.

This chapter describes the comprehensive study of this condensation reaction on enantioselectivity by employing different types of commercially available bases in presence of various catalysts in different solvents and different temperatures.

\[
\begin{align*}
\text{Scheme 4.2 Reagents and Conditions:} & \quad \text{(a) (i) NaOH, DMSO, 50-55 °C, 45 min;} \\
& \quad \text{(ii) TBAB, DMSO, 65 °C, 55 h, oxalic acid, 60%.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent mixture</th>
<th>Solvent (v)</th>
<th>Base</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>Ratio by HPLC</th>
<th>Ratio by chiral HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>3</td>
<td>KOBt</td>
<td>TBAB</td>
<td>8-9</td>
<td>90</td>
<td>72.0</td>
<td>98.9</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>Toluene: DMSO</td>
<td>15:1</td>
<td>KOBt</td>
<td>TBAB</td>
<td>48-50</td>
<td>60-65</td>
<td>39.8</td>
<td>45.2</td>
<td>48.2</td>
</tr>
<tr>
<td>3</td>
<td>Toluene:</td>
<td>5:5</td>
<td>NaOH</td>
<td>TBAB</td>
<td>50-55</td>
<td>60-65</td>
<td>25.0</td>
<td>68.2</td>
<td>25.8</td>
</tr>
</tbody>
</table>
Table 4.2 Screening of various amounts of TBAB

<table>
<thead>
<tr>
<th>Entry</th>
<th>TBAB (v)</th>
<th>Yield (%)</th>
<th>Ratio by HPLC</th>
<th>Ratio by chiral HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>0.10</td>
<td>53.2</td>
<td>95.3</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>0.12</td>
<td>55.8</td>
<td>99.6</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>0.14</td>
<td>56.4</td>
<td>99.4</td>
<td>ND</td>
</tr>
</tbody>
</table>

On the basis of these experimental results, we found that entry 15 was good for reaction condition and also screened different amounts of TBAB (Table 4.2) to obtain required enantioselectivity. We opted the following ideal conditions for this process (Scheme 4.2): (i) DMSO is ideal reaction medium, (ii) 5.0 equiv. of NaOH, (iii) temperature at 60-65 °C, (iv) 0.12 volumes TBAB and (v) making oxalate salt. Further, a robust purification method was developed to purge the undesired R-isomer 8.

In conclusion, we have studied the effects of temperature, base, catalyst and solvent volume on stereo selectivity of aromatic substitution in duloxetine. TBAB catalyzed condensation of (S)-(−)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6 with 1-fluoro-
naphthalene 7 in presence of sodium hydroxide and dimethylsulfoxide selectively furnished \((S)-(+)\)-\(N,\text{N}\)-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine as oxalate salt 8, a key intermediate used in duloxetine hydrochloride 1.


Prior art synthetic approaches were appreciable in terms of the strategies adopted to address the chemistry. The common deficiency in these resolutions is that 50% of the material is lost as unwanted isomer, which will greatly diminish their synthetic utility for scale-up.

Duloxetine hydrochloride 1 was successfully prepared as per Scheme 5.1\(^{14,15}\). In this, the mother liquor, after resolution step, was decomposed with base and analyzed for both isomers percentages, and found that ~ 92% undesired \((R)\)-isomer 6 and 8% \((S)\)-isomer 6 in crude stage. To make this process economically feasible, there is a need to racemize \((R)\)-6 from the mother liquor.
Scheme 5.1 *Reagents and Conditions*: (a) Conc. HCl, isopropyl alcohol, reflux, 6 h, 87%; (b) 20% NaOH, MeOH, H₂O, NaBH₄, rt, 6 h, 89%; (c) (i) (S)-(+) -mandelic acid, EtOAc, 75 °C to 35 °C, 10 h; (ii) 10% Na₂CO₃, CH₂Cl₂, 0 °C, 47%; (d) (i) NaOH, DMSO, TBAB, 65 °C, 50 h; (ii) DIPEA, phenyl chloroformate, 45 °C, 4 h; (iii) DMSO, NaOH, 45 °C, 3 h; (iv) oxalic acid, rt, 4 h, 69%; (e) (i) aq. NH₃, H₂O, CH₂Cl₂, EtOAc. HCl, 0 °C, 2 h, 52%; (ii) EtOAc, MeOH, 60 °C to 25 °C, 4 h, 70%

This driven us to develop a simple and economically workable process for the preparation of duloxetine hydrochloride 1 through racemization of undesired isomer, produced during the resolution step. This chapter is dedicated to the synthesis of optically pure duloxetine hydrochloride from undesired (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6.

The basic objective is to transform (R)-isomer 6 into keto compound and subsequent reduction with sodium borohydride. Conversion of (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6 into 3-(dimethylamino)-1-(thiophen-2-yl)propan-1-one 5 hydrochloride has been achieved with potassium permanganate in the presence of sulfuric acid.
Scheme 5.2 Reagents and Conditions: (a) (i) KMNO₄, H₂SO₄, acetone, H₂O, 20 °C, 10 min; (ii) NaBH₄, 20 °C, 2 h, 70%; (b) (S)-(+-)mandelic acid, EtOAc, 75 °C to 30 °C, 10 h, 90%; (c) 10% Na₂CO₃, CH₂Cl₂, 0 °C, 93%; (d) (i) NaOH, DMSO, 55 °C, 45 min; (ii) TBAB, DMSO, 65 °C, 55 h, oxalic acid, 60%; (e) (i) 10% Na₂CO₃, toluene, H₂O, Et₃N, phenyl chloroformate, 55 °C, 4 h; (ii) DMSO, 25% NaOH, 55 °C, 35 h; (iii) EtOAc, HCl, 0 °C; (iv) MeOH, EtOAc, 60 °C to 30 °C, 4 h, 52%.

In conclusion, an efficient and economically feasible process for the preparation of duloxetine hydrochloride 1 was accomplished through racemization of (R)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol 6 using potassium permanganate as an
oxidizing agent and robust resolution process for the synthesis of (S)-6 by means of inexpensive (S)-(+) mandelic acid. Upon practicing the disclosed process, a significant cost reduction in the synthesis of duloxetine hydrochloride 1 was realized.
References


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Remarks: Compound numbers vary in the original thesis