CHAPTER-III

The development of convenient asymmetric synthesis of duloxetine
Introduction

Depression is the common mental disorders that can affect a person's thoughts, behavior, feelings and physical well-being. Depression is characterized by a number of common symptoms. These include a persistent sad, anxious, or “empty” mood, and feelings of hopelessness. They no longer take interest or pleasure in hobbies and activities that were once enjoyed. Insomnia, early-morning awakening, and oversleeping are all common. In the United States, around 3.4% of people with major depression commit suicide, and up to 60% of people who committed suicide had depression or another mood disorder.¹

An antidepressant is a psychiatric medication used to treat depression disorders. Most antidepressant medications increase the levels of one or more of the monoamines; the neurotransmitters serotonin, norepinephrine and dopamine in the synaptic cleft between neurons in the brain. Some medications affect the monoamine receptors directly.

![Chemical structures of serotonin, norepinephrine, and dopamine](image)

**Figure-1**

Depression arises when low serotonin levels promote low levels of norepinephrine, another monoamine neurotransmitter.¹ Some antidepressants enhance the levels of norepinephrine directly, whereas others raise the levels of dopamine, a third monoamine neurotransmitter. Norepinephrine related to alertness and energy as well as anxiety, attention, and interest in life; lack of serotonin to anxiety, obsessions, and compulsions; and dopamine to attention, motivation, pleasure, and reward, as well as interest in life.¹ Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs) are the two major types of antidepressant drugs.
SSRIs are believed to increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. Drugs in SSRI class are escitalopram, dapoxetine, fluoxetine, indalpine, paroxetine, sertraline, vilazodone and zimelidine.\textsuperscript{2}

SNRIs act upon and increase the levels of two neurotransmitters in the brain that are known to play an important part in mood, these being serotonin and norepinephrine. This can be contrasted with the more widely-used selective serotonin reuptake inhibitors (SSRIs) which only act on serotonin. Drugs in SNRI class are venlafaxine, desvenlafaxine, duloxetine, milnacipran, sibutramine, bicifadine, SEP-227162, and LY 2216684. In comparative to SSRIs, SNRIs are among the most widely used antidepressants today. In 2009 Cymbalta and Effexor were the 11th and 12th most prescribed branded drugs in the United States.\textsuperscript{3}

**Duloxetine** (sold under the brand names Cymbalta, Ariclaim, Xeristar, Yentreve) is a serotonin-norepinephrine reuptake inhibitor manufactured and marketed by Eli Lilly.

![Duloxetine](image)

Duloxetine was created by Lilly researchers. David Robertson, David Wong and Joseph Krushinski are listed as inventors on the patent application filed in 1986 and granted in 1990.\textsuperscript{4} Duloxetine was first synthesized as racemic mixture and later on (+)-enantiomer was chosen for further studies, because it inhibited serotonin reuptake in rat two times more potently than (–)-enantiomer.\textsuperscript{5}

The main uses of duloxetine are in major depressive disorder, general anxiety disorder, stress 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.
Literature Review

Several synthetic routes for the preparation of duloxetine as a racemate or an enantiomerically pure form have been disclosed in literature. Though many routes available for asymmetric synthesis of duloxetine, but few routes are industrially scalable.

1. Eli Lilly group, USA (1990)  

![Scheme-1]

Weigel et al. given reduction of prochiral ketone 3 with 2:1 complex of L (Mosher’s reagent or Chirald) and lithium aluminum hydride provided the corresponding enantiopure aminol intermediate 4 with 80-88% ee (scheme-1). Intermediate 4 arylated by 1-naphthalene using sodium hydride as a base and duloxetine 1 was prepared after demethylation of 5.

2. Eli Lilly group, USA (1993)  

Berglund et al. prepared racemic intermediate 4a and then resolved to obtain enantiopure intermediate 4 and developed efficient arylation reaction of 4 using 1-fluronaphthalene in the presence of sodium hydride and potassium benzoate as a catalyst (scheme-2). The advantage of potassium benzoate was yield improvement up to 95% with very little racemization.
Scheme-2

3. Eli Lilly group, USA (1995)

Wheeler et al. synthesized enantiopure intermediate 8 by asymmetric reduction of 6 using oxazaborolidine catalyst 7 and borane·THF complex (scheme-3). Intermediate 8 was converted into iodo compound 9 which was reacted with excess of methyl amine to obtain advance intermediate 10 and finally duloxetine was prepared by arylation of 10 using 1-fluronaphthalene in the presence of sodium hydride.


Rao et al. reported the arylation reaction of 4a by 1-fluronaphthalene in presence of potassium hydroxide and tetra butyl ammonium bromide as a catalyst (scheme-4). Enantiopure duloxetine was prepared by resolution of racemic duloxetine using (-) di-\(p\)-toluyl tartaric acid.
5. Yamakawa Chemical Co., Japan (2003)\textsuperscript{10}

Sakurai et al. reported an efficient industrial resolution process of 3-(methylamino)-1-(2-thienyl)propan-1-ol 10a, key intermediate for the synthesis of duloxetine, with (S)-mandelic acid 11 has been developed by using 2-butanol as a solvent with a small amount of water (scheme-5). From an X-ray crystal structure analysis, the existence of a unique hydrogen-bonding network mediated by water molecules was confirmed.

6. Eli Lilly & Co., USA (2003)\textsuperscript{11}

Borghese reported resolution of intermediate 10a with S-2-pyrrolidone-5-carboxylic acid or 2,3,4,5-di-O-isopropylidene-2-keto-L-gulonic acid. Undesired enantiomer obtained after resolution was racemized using hydrochloric acid.

7. BASF, Germany (2003)\textsuperscript{12}

Stürmer reported a process for preparation of duloxetine, wherein intermediate 10 prepared by reacting thiophene 12 with 3-chloropropionic acid chloride 13 using aluminum chloride and subsequent reaction with methylamine to produced aminoketone intermediate 14 (scheme-6). Finally enantiopure intermediate 10 was obtained by asymmetric reduction using Mosher’s reagent as shown in scheme-1.
Kuniyoshi et al. reported novel route for synthesis of duloxetine comprises acylation of thiophene 2 using Friedel-Crafts catalyst to provide chloroketone intermediate 6. Noyori asymmetric hydrogenation of intermediate 6 and reacting chlorohydrine intermediate 8 with methylamine (scheme-3).


Kuniyoshi et al. reported novel route for synthesis of duloxetine comprises acylation of thiophene 2 using Friedel-Crafts catalyst to provide chloroketone intermediate 6. Noyori asymmetric hydrogenation of intermediate 6 and reacting chlorohydrine intermediate 8 with methylamine (scheme-3).


Kuniyoshi et al. reported novel route comprises formation of N-benzyl Mannich base 16 and its Noyori asymmetric hydrogenation to obtain aminol intermediate 18. Duloxetine was obtained after arylation of aminol 10 and subsequent debenzylation (scheme-7).
10. Degussa, Germany (2003)\textsuperscript{15}

Reichert et al. developed novel route for asymmetric synthesis of duloxetine (scheme-8). Carbamate intermediate 19 was prepared from 16 using methyl chloroformate which was enantioselectively reduced using Corey-Itsuno condition using borane-THF complex and after hydrolysis of 20, key intermediate 10 was obtained.

\[
\begin{align*}
\begin{array}{c}
\text{Cl} \quad \text{NaHCO}_3 \\
\text{OH} \quad \text{NaOH}
\end{array}
\end{align*}
\]

Scheme-8

11. Boehringer, Germany (2004)\textsuperscript{16}

Robert et al. reported an improved process for preparation of chiral N-benzyl N-methyl-3-hydroxy-3-(2-thienyl)-propylamines 18. An asymmetric hydrogenation of 16 using a catalyst system consisting of bis-(1,5-cyclooctadiene)dirhodium(I)dichloride 21 and (2R,4R)-4-(dicyclohexylphosphino)-2-(diphenyl-phosphino-methyl)-N-methyl-aminocarbonyl-pyrrolidine 22 which provided 18 in 98\% ee (scheme-7).

12. Shanghai Institute of Organic Chemistry, China (2005)\textsuperscript{17}

Zhao et al. reported enantioselective reduction of β-ketonitrile intermediate 24 to enantiopure 1, 3 aminol 26 in one step using an excess of borane-DMS complex as a
reductant and polymer supported enantiopure sulfonamide 25 as a catalyst (scheme-9). Monomethylated compound 10b was obtained by reducing carbamate group of 27 using lithium aluminum hydride followed by arylation using 1-fluronaphthalene to obtain R-duloxetine 1b.

13. Zentiva, Czech Republic (2005)\textsuperscript{18}

Ludek et al. was resolved dimethyl duloxetine 5a first using chirally pure acid and duloxetine was obtained after demethylation.

14. Pennsylvania State University, USA (2005)\textsuperscript{19}

Zhang et al. reported hydrogenation of series of β-secondary-amino ketone hydrochlorides with remarkably high enantioselectivities (93-99% ee) by using a Rh complex containing chiral bisphospholane ligand L.

15. Solmag, Italy (2005)\textsuperscript{20}
Frigoli et al. reported a process for the preparation of duloxetine via Mitsunobu reaction of 1-fluoronaphthalene with 10 using 1,3-dimethyl-2-oxo-hexahydropyrimidine 28 as the solvent followed by fractional crystn. and N-demethylation.

16. University of Bologna, Italy (2006) 21

Panunzio et al. reported synthesis of 5-phenylthio-1,3-oxazinan-4-ones 34a, through a hetero Diels–Alder strategy. The cycloadducts 34a showed useful intermediates for the synthesis of intermediates 1,3-aminoalcohols of duloxetine (scheme-11). In the course of this elaboration a novel microwave assisted desulfurization reaction was developed for conversion of 34a to 35.
17. Nagase & Co., Japan (2006)\(^{22}\)

Ikunaka et al. reported novel procedure for synthesis of intermediate of duloxetine (scheme-12). Intermediate 4 first converted to O-ethyl carbonate 38 at mild condition (90°C) and then demethylated (120 °C). Conversion of 4 in to 10 in successive steps minimized the formation of byproducts.

18. Eli Lilly & Co., USA (2006)\(^{23}\)

Butchko et al. developed arylation reaction using potassium hydroxide base in mixture of dimethyl sulfoxide and toluene solvents to minimize racemization (scheme-13).
According to procedure described by Patel et al. the racemization occurring during naphthylolation of 18a can be avoided by carrying out the resolution step (39 to 40) after introducing the naphthyl group in to the molecule 18a (scheme-14). Undesired antipode of 40 was racemized using strong base potassium-t-butoxide and duloxetine was prepared based on RRR synthesis.

Ini et al. developed process for asymmetric reduction of aminoketone 3 using oxazaborolidine catalyst 7 and two equivalents of borane. THF complex to obtained borane complex of enantiopure 4c (scheme-15). Novel intermediate 4c was converted to 41 as oxalate salt after arylation using 1-fluronaphthalene.
21. Dipharma Francis, Italy (2007)\(^{26}\)

Simone et al. reported alkylation of ether intermediate 42 with (2-chloroethyl)-dimethylamine in presence of lithiumdiisopropropamide to obtained racemic intermediate 5 of duloxetine (scheme-16).

22. Medicem, Spain (2005)\(^ {27}\)

Stephen reported a process comprises reaction of intermediate 4 and 1-fluoronaphthalene in the presence of alkali metal hydroxides or alkoxides in DMSO in the absence of phase transfer catalysts to obtain advance intermediate 5 with 88% ee (scheme-2). After chloroformates treatment of 5, duloxetine was obtained.

23. Richter Gedeon, Hungary (2007)\(^ {28}\)
Bódi et al. developed process for duloxetine based on RRR synthesis. Intermediate 18\textsuperscript{a} was resolved by N-benzoyl-D-phenylglycine 43 and undesired antipode 18\textsuperscript{b} was racemized to 18\textsuperscript{a} in presence of sulfuric acid. Arylation of 18 and then debenzylation of 40 was carried to obtain duloxetine 1 (scheme-17).

24. Laboratorios del Dr. Esteve, Spain (2008)\textsuperscript{29}
Torrens et al. claimed ligand 46 to be used as catalyst for enantioselective addition of thiophene given by 45 to aldehyde 44 in preparation of duloxetine precursors 8 with 67% ee (scheme-18).

25. Sun Yat-sen University, China (2008)  

Yan et al. prepared duloxetine intermediate 4 via asymmetric transfer hydrogenation of aminoketone 3 (scheme-19). The Ru(II), Ru(III) and Ir(III) complexes of several chiral ligands were examined as the catalyst and Ru(II) complex with (S,S)-N-tosyl-1,2-diphenyl ethylenediamine 47 was found to provide good yield and excellent enantioselectivity.

\[
\begin{align*}
\text{RuCl}_2(p\text{-cymene})_2 & \quad \overset{\text{HCOOH/Et}_3\text{N}}{\longrightarrow} \\
\text{Ph} & \quad \text{Ph} \\
\text{NHTs} & \\
\text{H}_2\text{N} & \\
\text{NHTs} & \\
\end{align*}
\]

Scheme-19


Siyan et al. developed process for duloxetine based on RRR synthesis (RRR: Resolution-Racemization-Recycle). Racemic intermediate 5a was prepared by arylation of intermediate 4a using 1-fluronaphthalene in presence of base (scheme-20) such as sodamide, potassium amide or potassium bis(trimethylsilyl)amide in DMSO, racemic compound 5a was resolved to 5 using dibenzoyl-L-tartaric acid and undesired isomer was racemized by treating with potassium bis(trimethylsilyl)amide.

\[
\begin{align*}
\text{OH} & \quad \overset{\text{NaNH}_2}{\longrightarrow} \\
\text{DMSO} & \\
\text{1-Fluronaphthalene} & \\
\end{align*}
\]

Scheme-20
27. Srini Pharma., India (2009)\textsuperscript{32}

Karnati et al. developed arylation reaction of 4 using potassium hydroxide base in presence of phase transfer catalyst in dimethyl sulfoxide and racemization was avoided (scheme-21).

\begin{center}
\includegraphics[width=\textwidth]{scheme21}
\end{center}

Scheme-21

28. Chen, B. et al., Taiwan (2009)\textsuperscript{33}

Manich base having hydroxylamino group 48 was prepared which was reduced using Noyori asymmetric hydrogenation methodology to obtain enantiopure intermediate 49 (scheme-22). After arylation of intermediate 49 by 1-fluronaphthalene, N-O bond was cleaved easily by hydrogenation using Raney nickel catalyst.

\begin{center}
\includegraphics[width=\textwidth]{scheme22}
\end{center}

Scheme-22
Lee et al. synthesized duloxetine from 2-tosyloxy-1-(2-thiophenyl)ethanone 51 via catalytic transfer hydrogenation and further elaboration through the cyclic carbamate 54 derived from the γ-aminoalcohol 26a (scheme-23).
Present work

The retro synthetic analysis as portrayed in scheme-24 shows that duloxetine 1 could be manufactured more conveniently on commercial scale starting from thiophene 12, either through aminoketone 3 & 14 or chloroketone intermediate 6. The asymmetric reduction of prochiral ketones 3, 14 or 6 could be key step to obtain optically pure duloxetine 1.

Scheme-24

Route of synthesis of duloxetine 1 comprising asymmetric reduction of chloroketone 6 to produce chlorohydrine intermediate 8 and subsequently amination (8 to
10) and arylation (10 to 1) is seems to be more simple and short, since the demethylation step (5 to 1) not involved as shown in route through aminoketone 3 and thus is particularly valuable in commercial production of duloxetine 1. Earlier Wheeler et al. were synthesized duloxetine on preparative scale by following chloroketone route as shown in scheme-25.\(^8\)

![Scheme-25](image)

Wheeler et al. synthesized enantiopure intermediate 8 by asymmetric reduction of 6 using oxazaborolidine catalyst 7 and borane.THF complex. Intermediate 8 was converted into iodo compound 9 which was reacted with excess of methyl amine to obtain advance intermediate 10 and finally duloxetine was prepared by arylation of 10 using 1-fluronaphthalene in the presence of sodium hydride.

Although the duloxetine was prepared by this process, but it is far from commercial scale as

- Use of hazardous and unstable borane.THF complex.
- Use of expensive and sensitive oxazaborolidine catalyst 7.
- Use of stoichiometric quantity of expensive sodium iodide reagent.
- Isolation of unstable iodo intermediate 9, and
- Use of pyrophoric sodium hydride.

To ensure the commercial viability of manufacturing process of duloxetine we felt that there was need to develop above route so that use of hazardous and expensive reagent can be avoided.
Synthesis of chlorohydrine intermediate 8:

Chloroketone intermediate 6 was synthesized according to procedure reported by Stürmer et al.\textsuperscript{12} 3-Chloropropionyl chloride was reacted with thiophene 12 in presence of aluminum chloride in dichloromethane solvent. Chloroketone 6 thus obtained was reduced asymmetrically to produce 8 with 91% ee and 90% yield using our protocol as discussed in chapter-II. We also tried chiral catalyst (1\text{R}, 2\text{S})-1-amino-2-indanol 57 in place of (S)-\text{\textalpha},\text{\textalpha-}
diphenylprolinol 56 in our protocol but poor enantioselectivity (12% ee) was observed.

Synthesis of monomethyl aminol intermediate 10:

Wheeler et al. prepared monomethyl intermediate 10 from expensive iodo intermediate 9. We decided to develop new process for synthesis of monomethyl intermediate 10 from inexpensive chloro intermediate 8.
Chloro intermediate 8 was found to be poor reactive towards alkylation of monomethyl amine (table-1, entry 1). If stoichiometric quantity of sodium iodide used, good conversion was observed (table-1, entry 2). Since sodium iodide is expensive, we decided to use sodium iodide in catalytic amount in presence of potassium carbonate in closed reactor. Purpose behind the use of potassium carbonate was to generate potassium iodide in-situ from side product hydroiodoic acid. Good conversion was observed (table-1, entry 4) but dialkylated impurity 58 was observed in reaction mass (confirmed by mass spectroscopy). Reaction mass was concentrated and product monomethyl aminol 10 was obtained from residue with 70% yield after column chromatography.

### Table-1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sodium iodide</th>
<th>K$_2$CO$_3$</th>
<th>Temp/time</th>
<th>Conversion by TLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not used</td>
<td>Not used</td>
<td>50 to 55°C/10 h</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>2</td>
<td>1.1 equivalent</td>
<td>Not used</td>
<td>50 to 55°C/10 h</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>3</td>
<td>Not used</td>
<td>1.5 equivalent</td>
<td>50 to 55°C/10 h</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>4</td>
<td>0.05 equivalent</td>
<td>1.5 equivalent</td>
<td>50 to 55°C/10 h</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>5</td>
<td>0.05 equivalent</td>
<td>1.5 equivalent</td>
<td>25 to 30°C/10 h</td>
<td>~ 50%</td>
</tr>
<tr>
<td>6</td>
<td>0.05 equivalent</td>
<td>Not used</td>
<td>50 to 55°C/10 h</td>
<td>&lt; 10%</td>
</tr>
</tbody>
</table>

Production of monomethyl aminol intermediate 10 was not advisable on technical scale due to formation of dialkylated impurity 58 which needs to be separated through column chromatography.

**Synthesis of dimethyl aminol intermediate 4:**

\[
\begin{align*}
\text{S} & \text{Cl} \\
\text{S} & \text{N} \\
\text{MeOH} \\
\text{70°C}
\end{align*}
\]

Scheme-28
Chlorohydrine intermediate 8 was reacted with dimethyl amine in methanol solvent and dimethyl aminol intermediate 4 was isolated in solid form with 80% yield. Since the reaction was very clean, column chromatographic purification was not required.

**Synthesis of duloxetine 1:**

Arylation of dimethyl aminol intermediate 4 using 1-fluronaphthalene is the important step for synthesis of duloxetine 1. This is nucleophilic aromatic substitution reaction which involves treatment of aminol intermediate 4 with a strong base to form the alkoxide 59, followed by addition of 1-fluronaphthalene to obtain duloxetine intermediate 5 through anionic Meisenheimer σ-complex 60.

![Scheme-29](image)

Several methods are reported in the literature (table-2) for preparation of duloxetine intermediate 5. The utilization of sodium hydride as base (table-2, entry 1-3) on an industrial scale is a potentially hazardous reaction due to pyrophoric nature of hydride in presence of moisture, resulting in a requirement of stringent anhydrous condition. This compels the use of anhydrous solvents like DMSO or DMAC which is difficult to prepare on commercial scale. Potassium hydroxide when used in DMSO (table-2, entry 4), racemization was occurred therefore to avoid racemization small quantity of DMSO used
in presence of other solvent (table-2, entry 5 & 7) or use of TBAB as a phase transfer catalyst (table-2, entry 8).

**Table-2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (Reff.)</th>
<th>Solvent</th>
<th>Temp/time</th>
<th>Racemization</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (8)</td>
<td>DMAC</td>
<td>50 to 55°C/10 h</td>
<td>No</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>NaH (7)</td>
<td>DMSO (PhCOOK)</td>
<td>50 to 55°C/8 h</td>
<td>No</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>NaH (6)</td>
<td>DMSO</td>
<td>45 to 50°C/60 h</td>
<td>No</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>KOH (23)</td>
<td>DMSO</td>
<td>60-65°C/8 h</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>KOH (23)</td>
<td>DMSO/Toluene (1:15 v/v)</td>
<td>60-65°C/8 h</td>
<td>No</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>KOH (23)</td>
<td>DME</td>
<td>60-65°C/8 h</td>
<td>No</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>KOH (28)</td>
<td>DMSO/THF (1:4 v/v)</td>
<td>40-45°C/11 h</td>
<td>No</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>NaOH (32)</td>
<td>DMSO (TBAB)</td>
<td>60-65°C/55 h</td>
<td>No</td>
<td>56</td>
</tr>
</tbody>
</table>

As a part of research program, we decided to develop new protocol for such kind of nucleophilic substitution reaction for synthesis of chirally pure ethers. Sodium sulfide is strong base and used in chemical manufacturing as a sulfonation and sulfomethylation agent. Sodium sulfide has never been used before for synthesis of aryl ether rather it was used for cleavage of alkyl-aryl ether. In chapter-II part-B, desmethylomeprazole sulfide 62 was synthesized by demethylation of omeprazole sulfide 61 using sodium sulfide in NMP solvent (scheme-30).

We studied effect of sodium sulfide on coupling reaction of aminol intermediate 4 and 1-fluronaphthalene (scheme-31act) in different solvent (table-3). Surprisingly this reaction occurs only in DMSO solvent without racemization (table-3, entry-6) while in other solvent reaction was not occurring.
Monomethyl aminol intermediate 10 was also coupled successfully with 1-fluronaphthalene under similar condition and duloxetine 1 was prepared (scheme-32).
Demethylation of dimethyl aminol intermediate 5 with phenylchloroformate in the presence of diisopropyl ethylamine, followed by salt formation with conc. hydrochloric acid in the presence of ethyl acetate afforded hydrochloride of duloxetine 1 (scheme-33).

![Scheme-33](image-url)
A new procedure was developed for asymmetric synthesis of duloxetine intermediates which comprises -

- Asymmetric reduction of ketone 6 using in situ prepared \(N,N\)-diethylaniline borane (DEANB) and oxazaborolidine catalyst from sodium borohydride, \(N,N\)-diethylaniline hydrochloride and \((S)-\alpha,\alpha\)-diphenylprolinol 56 to obtained enantiopure chlorohydrine intermediate 8.
- Synthesis of dimethyl aminol intermediate 5 by reacting chlorohydrine 8 with dimethyl amine.
- New method for synthesis of duloxetine intermediate was developed by substitution reaction of dimethyl aminol intermediate 4 with 1-fluronaphthalene using novel reagent i.e. sodium sulfide in DMSO solvent.
Experimental Section

1. Preparation of (S)-3-chloro-1-thiophen-2-yl-propan-1-ol (8)

Similar procedure of (R)-(+)3-chloro-1-phenyl-propanol (example 5 of chapter II) was performed for asymmetric reduction of 6 (50 gm, 0.286 mol) using DME (200 ml) sodium borohydride (9.63 gm, 0.254 mol), solution of N, N-diethylaniline hydrochloride (48.1 gm, 0.26 mol) in dichloromethane (75 ml), and 58 (3.98 gm, 0.015 mol). After concentration of toluene layer, oily residue of 8 was obtained (45 gm) with 90% yield and 91.28% ee. [α]D25 = -10.7° (c = 2.06 in i-PrOH). 1H NMR (400 MHz, CDCl3): δ 7.27-6.97 (m, 3H, Ar-H), 5.19 (m, 1H, -CH2OH), 3.72-3.55 (dd, 2H, CH2), 2.38-2.19 (dd, 2H, CH2), 2.15 (d, 1H, -OH). 13C NMR (100 MHz, CDCl3): δ 147.3, 126.67 124.6 123.9, 67.0, 41.3.

2. Preparation of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (4)

To a solution of 8 (5 gm, 0.0283 mol) in methanol (50 ml), 40% aqueous solution of dimethyl amine (25 gm, 0.56 mol) was added at 25 to 30°C. Reaction mass was heated and stirred at 70 to 75°C for 24 hrs. Reaction mass was concentrated under vacuum up to 15 ml volume, water (100 ml) was added and extracted with toluene (125 ml) three times, toluene layer was concentrated to obtained solid residue of 10 (4.3gm) with 80% yield. 1H NMR (400 MHz, CDCl3): δ 7.21-6.91 (m, 3H, Ar-H), 5.19 (m, 1H, -CH2OH), 3.72-3.55 (dd, 2H, CH2), 2.68-2.52 (dd, 2H, CH2), 2.29 (s, 6H, -N(CH3)2), 1.95-1.90 (m, 2H, -CH2-N). 13C NMR (100 MHz, CDCl3): δ 149.6, 126.3, 123.4, 122.0, 71.7, 57.8, 45.0, 34.5. ESI-MS: 186.1 M+1 in positive mode.

3. Preparation of (S)-dimethyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine (5)

To a solution of sodium sulfide 60% (5.62 gm, 0.04 mol) in DMSO (20 ml), (S)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (4) (4 gm, 0.02 mol) was added and heated under nitrogen sweep up to 75°C to 80°C. 1-Fluronaphthalene (3.78 gm, 0.026mol) was added and stirred under nitrogen sweep for 35 hrs at same temperature. Reaction mass was cooled to ambient temperature, water (400 ml) was added and extracted by toluene (75 ml) for three times, toluene layer was washed with water and concentrated to obtained oily
residue of 5 (8.26 gm) with 88% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.33-6.88 (m, 10H, Ar-\textit{H}), 5.77 (t, 1H, -\textit{CH}-OH), 2.61-2.48 (m, 2H, CH$_2$), 2.34 (s, 6H, -N(CH$_3$)$_2$), 2.3-2.25 (m, 2H, -CH$_2$-N). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.4, 145.2, 134.5, 127.3, 126.4, 125.2, 125.1, 125.6, 125.1, 124.6, 124.5, 122.1, 120.4, 109.0, 74.6, 55.8, 45.5, 36.9. ESI-MS: 312 M+1 in positive mode.

4. Preparation of duloxetine hydrochloride (1)

To a solution of 5 (5 gm, 0.016 mol) in toluene (20 ml), diisopropylethylamine (0.2 gm, 0.0016 mol) was added. Reaction mass was heated to 55°C, phenylchloroformate (3.26 gm, 0.2 mol) was added drop wise, stirred for 1.5 hrs at 55 to 60°C and aqueous solution of 1% sodium bicarbonate (50 ml) was added. After stirring the reaction mixture for 10 min at 40 to 50°C, organic layer was separated and washed with 0.5 N hydrochloric acid, then with aqueous solution of 1% sodium bicarbonate. Organic layer was evaporated under vacuum, DMSO (50 ml) and solution of sodium hydroxide (2 gm) in water (12 ml) was added. Reaction mass was heated and stirred at 45 to 50°C for 24 hrs, water (20 ml) was added and pH was adjusted to 5.2 by acetic acid. n-Hexane (50 ml) was added to the reaction mass, stirred for 15 min. and aqueous layer was separated. pH of aqueous layer was adjusted to 11.0 using dilute sodium hydroxide solution, extracted with ethyl acetate (50 ml), organic layer was washed with water and concentrated under vacuum up to 20 ml. Hydrogen chloride gas was passed in the reaction mass, cooled and stirred for 3 hrs to 0 to 5°C. Slurry was filtered, wet solid washed with chilled ethyl acetate (5 ml) and dried at 40 to 50°C to obtained duloxetine hydrochloride 1 (2.8 gm) with 52% yield. Chiral purity: 98.68% ee. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.75, 9.74 (bs, 2H, NH$_2$-), 8.28-6.6 (m, 10H, Ar-\textit{H}), 5.94-5.92 (t, 1H, -\textit{CH}-OH), 3.19 (m, 2H, CH$_2$), 2.81-2.77 (m, 2H, -CH$_2$-), 2.64 (s, 3H, -N(CH$_3$)$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.3, 147.1, 134.6, 127.3, 126.6, 126.0, 125.6, 125.5, 124.7, 124.7, 122.1, 120.4, 109.0, 73.0, 45.9, 34.6, 32.9. ESI-MS: 298.2 M+1 in positive mode.
Spectra

1) $^{13}$C NMR spectra of (S)-3-chloro-1-thiophen-2-yl-propan-1-ol (8) in CDCl$_3$

![13C NMR spectra of (S)-3-chloro-1-thiophen-2-yl-propan-1-ol (8) in CDCl$_3$]

2) $^{13}$C NMR DEPT spectra of (S)-3-chloro-1-thiophen-2-yl-propan-1-ol (8) in CDCl$_3$

![13C NMR DEPT spectra of (S)-3-chloro-1-thiophen-2-yl-propan-1-ol (8) in CDCl$_3$]
3) $^1$H NMR spectra of (S)-3-chloro-1-thiophen-2-yl-propan-1-ol (8) in CDCl$_3$

4) Mass spectra of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (10)
5) $^{13}$C NMR spectra of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (10) in CDCl$_3$

![C NMR spectrum of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (10) in CDCl$_3$]

6) $^{13}$C NMR DEPT spectra of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (10) in CDCl$_3$

![C NMR DEPT spectrum of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (10) in CDCl$_3$]
7) $^1$H NMR spectra of (S)-3-methylamino-1-thiophen-2-yl-propan-1-ol (10) in CDCl$_3$

8) Mass spectra of (S)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (4)
9) $^{13}$C NMR spectra of (S)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (4) in CDCl$_3$

\[
\begin{align*}
\text{Diagram of NMR spectrum}
\end{align*}
\]

10) $^{13}$C NMR DEPT spectra of (S)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (4) in CDCl$_3$

\[
\begin{align*}
\text{Diagram of NMR DEPT spectrum}
\end{align*}
\]
11) $^1$H NMR spectra of (S)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (4) in CDCl$_3$

12) Mass spectra of (S)-dimethyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine (5)
13) $^{13}$C NMR spectra of \((S)\)-dimethyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine in (5) CDCl$_3$

14) $^{13}$C NMR DEPT spectra of \((S)\)-dimethyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine (5) in CDCl$_3$
15) $^1$H NMR DEPT spectra of (S)-dimethyl-[3-(naphthalen-1-yl-oxy)-3-thiophen-2-yl-propyl]-amine (5) in CDCl$_3$

![NMR DEPT spectrum of (S)-dimethyl-[3-(naphthalen-1-yl-oxy)-3-thiophen-2-yl-propyl]-amine (5) in CDCl$_3$]

16) Mass spectra of duloxetine hydrochloride (1)

![Mass spectrum of duloxetine hydrochloride (1)]
17) $^{13}$C NMR spectra of duloxetine hydrochloride (1) in CDCl$_3$

18) $^{13}$C NMR DEPT spectra of duloxetine hydrochloride (1) in CDCl$_3$
19) $^1$H NMR spectra of duloxetine hydrochloride (1) in CDCl$_3$

![NMR spectrum of duloxetine hydrochloride](image1)

20) Chiral HPLC chromatogram of duloxetine hydrochloride (1)

![Chiral HPLC chromatogram of duloxetine hydrochloride](image2)

**Peak Table**

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