CHAPTER-II

Isolation & Synthesis of novel impurities
during Process Development of
Escitalopram Oxalate
Introduction
Introduction

Depression

Depression is a state of low mood and aversion to activity that can have a negative effect on a person's thoughts, behaviour, feelings, world view and physical well-being. Depressed people may feel sad, anxious, empty, hopeless, worried, helpless, worthless, guilty, irritable, hurt, or restless. They may lose interest in activities that once were pleasurable; experience loss of appetite or overeating; have problems concentrating, remembering details, or making decisions; and may contemplate, attempt, or even desire suicide. Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains or digestive problems that are resistant to treatment may be present.

Depressed mood is not necessarily a psychiatric disorder. It is a normal reaction to certain life events, a symptom of some medical conditions, and a side effect of some medical treatments. It is also a primary or associated feature of certain psychiatric syndromes such as major depressive disorder.

Major depressive disorder

Major depressive disorder (MDD) (also known as recurrent depressive disorder, clinical depression, major depression, unipolar depression, or unipolar disorder) is a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem, and by loss of interest or pleasure in normally enjoyable activities. This cluster of symptoms (syndrome) was named, described and classified as one of the mood disorders in the 1980 edition of the American Psychiatric Association's diagnostic manual. The term "depression" is ambiguous. It is often used to denote this syndrome but may refer to other mood disorders or to lower mood states lacking clinical significance. Major depressive disorder is a disabling condition that adversely affects a person's family, work or school life, sleeping and eating habits, and general health. In the United States, around 3.4%
of people with major depression commit suicide, and up to 60% of people who commit suicide had depression or another mood disorder.¹

Although depression can represent an extreme disability, with appropriate treatment up to 80% of all individuals affected can improve and return to their normal daily life activities. Typically, patients are treated with antidepressant medication and, in many cases, also receive psychotherapy or counselling.

**Antidepressant**

An antidepressant is a psychiatric medication used to alleviate mood disorders, such as major depression and dysthymia and anxiety disorders such as social anxiety disorder. Based on activity and mode of action antidepressant are mainly classified in following classes.

- monoamine oxidase inhibitors (MAOIs)
- tricyclic antidepressants (TCAs)
- tetracyclic antidepressants (TeCAs)
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin-norepinephrine reuptake inhibitors (SNRIs)

**Selective serotonin reuptake inhibitors (SSRIs)**

SSRIs are commonly used as the first line treatment for depression because they have a favourable side-effect profile and low toxicity. It is the first class of the psychotropic drugs discovered using the process called “Rational drug design” a process that starts with a specific biological target and then creates a molecule designed to affect it.

SSRIs are believed to increase the extracellular level of the neurotransmitter serotonin (also known as 5-hydroxytryptamine, or 5-HT) by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. Chemists Klaus Schmiegel and Bryan Molloy of Eli Lilly discovered the first SSRI, fluoxetine. Other drugs
of this class are Citalopram, Escitalopram, Fluvoxamine, Paroxetine, Sertraline and Vilazodone etc.

**Structure of Citalopram Hydrobromide and Escitalopram Oxalate.**

Citalopram Hydrobromide (1; **Figure–1**), is a white to pale yellow fine powder which is freely soluble in methanol, ethanol and IPA. Its empirical formula is C$_{20}$H$_{21}$FN$_2$O.HBr with a molecular weight 405.3. Structure of Citalopram Hydrobromide is provided in figure–1.

Citalopram (1; **Figure–1**) is sold as the racemate; however, the (s)-(+) enantiomer, known as Escitalopram (2; **Figure–1**), inhibits serotonin uptake two orders of magnitude better than the other enantiomer. Escitalopram is formulated as its oxalate salt.

**Figure–1**

![Structure of Citalopram Hydrobromide and Escitalopram Oxalate]
Literature Review

Antidepressant activity of phthalan derivatives \(^2\)\(^-\)\(^5\) was well known before the invention of Citalopram and several molecules from this series were studded in this line. But credit for the preparation of Citalopram (1) goes to Bogeso K. P and Ander S. T. These scientists prepared several phthalan derivatives \(^6\) which show strong potentiating effects on tryptophan and 5-hydroxytryptophan and Citalopram is one of them.

Methods for the preparation of Citalopram

Bogeso K. P. and Ander S. T. \(^6\) [First synthesis of Citalopram]

Bogeso and Ander started there synthesis from 5-bromophthalide (3) which was reacted with Grignard reagent 4-fluoro phenyl magnesium bromide (4) to provide benzphenone derivative 5. Reduction of carbonyl group was furnished by using LAH in ether to get corresponding alcohol 6. Cyclization of intermediate 6 to prepare bromo phthalan 7 by dehydration was performed by using 60% aq. phosphoric acid at reflux for 3 h. Cyanation of bromo phthalan 7 was accomplished in DMF at reflux condition using CuCN as reagent and reaction was completed in four h. After completion of reaction it was quenched by pouring in aqueous solution of NaCN and respective cyano phthalan 8 was obtained. Condensation of 3-chloro-N,N-dimethylpropane-1-amine with cyano phthalan 8 was carried out in DMSO by utilizing NaH as base to afford targeted product 1 (Scheme-1).
Scheme–1

Reagents and conditions: (a) THF, RT, overnight; (b) LAH, ether, 2 h; (c) 60% aq. H₃PO₄, reflux, 3 h; (d) i) DMF, CuCN, reflux 4 h; ii) aq. NaCN, benzene, pet. ether (e) 3-chloro-N,N-dimethylpropane-1-amine, NaH, DMSO.

Due to the use of highly flammable reagent like LAH, NaH, banned carcinogenic solvent benzene and highly toxic reagents like NaCN and CuCN, this process is not suitable for practical synthesis of 1 at industrial level.

Boegesoe K. P. ⁷[5-Cyanophthalide route]

Bogeso experienced the difficulties in existing process during scale-up and commercial production of 1 and also to avoid risk involved in previous process, he proposed another way for the synthesis of Citalopram (Scheme–2).

To eliminate risk at cyanation step, instead of 5-bromophthalalid (3), 5-cyanophthalalid (9) was selected as starting key raw material. 5-cyanophthalalid (9) was reacted with 4-fluoro phenyl magnesium bromide (4) and the resulting complex was again treated with another Grignard reagent 11. These subsequent Grignard reactions were performed at ambient condition in THF and each reaction required overnight period for completion to get double Grignard complex which
was quenched by using acetic acid and after pH adjustment by aq. NH₃, cyanodiol intermediate 12 was isolated by extracting it in toluene.

Scheme–2

Reagents and conditions:  (a) THF, RT, overnight; (b) THF, RT, overnight; (c) AcOH, Aq. NH₃, toluene, water, 45–50 °C; (d) 70% H₂SO₄, 80 °C, 3h.

Conversion of cyanodiol 12 to desired product Citalopram (1) by cyclization via dehydration was carried out by using 70% H₂SO₄, reaction requires 80 °C temperature and 3 h for completion.

As nitrile group is very sensitive to attack by a number of organic as well as inorganic compounds. The reaction of Grignard reagent with nitrile derivatives to get respective ketimines which can be hydrolysed to ketones is well documented, it is also well known that treatment of nitriles with strong acids such as high percentage sulphuric acid normally will hydrolyze the nitrile group to a carboxylic acid amide or a carboxylic acid. But in this case extraordinary stability of nitrile group towards Grignard reagent as well as towards strong acid like
H$_2$SO$_4$ was observed. Due to which preparation of Citalopram 1 was achieved with good overall yield (63%).

**Petersen et al.**$^8$  [5-Ethoxycarbonylphthalide route]

Hans Petersen along with Bogeso K. P. and Michael B. Sommer developed new route for the synthesis of cyanophthalan 8. 5-ethoxycarbonylphthalide (13) was reacted with 4-fluoro phenyl magnesium bromide (4) to get benzophenone 14, which was further reduced to corresponding alcohol 15 by using NaBH$_4$ and EtOH. Cyclization was accomplished in presence of 60% H$_3$PO$_4$ at 80 °C in 1 h to furnish 5-ethoxycarbonylphthalaln (16). Saponification of intermediate 16 was achieved in EtOH at reflux in presence of 2N NaOH which resulted in 5-carboxyphthalan 17. Transformation of carboxyl group to nitrile function was conducted by usual way to get 5-cyanophthalan 8. Condensation of 3-dimethylaminopropyl chloride was executed in dimethoxyethane by using freshly prepared LDA from n-BuLi and diisopropyle amine, the details of invention shown in scheme−3.

This method was a good option to product patent route which avoids the use of deadly lethal NaCN, but still use of extremely flammable reagents like n-BuLi or LDA makes the process unsuitable for commercial scale production of Citalopram (1).
**Scheme−3**

Reagents and conditions: (a) THF, RT, overnight; (b) NaBH₄, EtOH, RT, 4 h; (c) 60% H₃PO₄, 80 °C, 1.5 h; (d) 2N NaOH, EtOH, reflux, 1 h; (e) i) SOCl₂, NH₄OH; ii) POCl₃; (f) n-BuLi, diisopropyle amine , 3-dimethylaminopropyl chloride, DME, -50 to 50 °C.

Petersen et al.⁹ [5-aminophthalide route]

This was a another approach disclosed by Hans Petersen in which 5-aminophthalide (18) was used as key raw material and double Grignard addition was carried out to prepare 5-aminodiol intermediate 20. Cyclization of intermediate 20 in presence of phosphoric acid gave corresponding phthalan derivative 21. Preparation of Citalopram (1) from phthalan 21 was achieved by
diazotization followed by reaction of resulted diazonium salt with CuCN as per scheme–4.

Scheme–4

Reagents and conditions:  (a) THF, RT, overnight; (b) i) THF, RT, overnight; ii) AcOH, aq. NH₃, toluene, water, 45–50 °C; (c) 60% H₃PO₄, 80 °C, 2 h; (d) i) NaNO₂, H₂SO₄, water, 5 °C.; ii) CuCN, NaCN, Toluene-water, 50 to 60 °C, 30 min.

Petersen and Harold¹⁰,¹¹ (application of Pd(PPh₃)₄ or Ni (0) catalyst).

As per Petersen and Harold the product patent process for the preparation of Citalopram involves replacement of the 5-bromo group by cyano group.  This transformation is inconvenient, low yielding and resulting product is impure. They have further mentioned that separation of Citalopram from corresponding 5-bromo compound is very difficult and hence the process is not viable for commercial scale synthesis of Citalopram (1).
To resolve this issue and to get Citalopram (1) in pure form a new catalytic process was developed in 5-triflate or 5-halogen was replaced by 5-cyano group in 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran (25a).

5-halophthalan derivatives were prepared by double Grignard addition method in which Grignard reagent 4 and 11 were reacted with 5-halophthalide derivative and acid catalysed cyclization afforded targeted compound. As shown in scheme−5.

**Scheme−5**

Reagents and conditions: (a) THF, RT, overnight; (b) i) THF, RT, overnight; ii) AcOH, aq. NH₃, toluene, water, 45−50 °C; (c) 70% H₂SO₄, 80 °C, 2 h.

While by adopting same strategy starting from 5-hydroxyphthalide, 5-hydroxyphthalan derivative was prepared, which was further reacted with trifluoromethane sulfonic acid chloride to get desired compound 25b as described in scheme−6.
Scheme−6

Reagents and conditions: (a) CF$_3$SO$_2$Cl, Et$_3$N, DCM, 5 ºC.

The replacement of triflate or halogen group by cyano group was performed by using nickel catalyst$^{10}$ like Ni(PPh$_3$)$_3$ or by palladium catalysts$^{11}$ such as Pd(PPh$_3$)$_4$, Pd$_2$(dba)$_3$ and Pd(PPh)$_2$Cl$_2$ while KCN, NaCN, Zn(CN)$_2$ or (n-Bu)$_4$NCN were used as cyanide source. The reaction is graphically described in scheme−7.

Scheme−7

Reagents and conditions: (a) Zn(CN)$_2$, Pd(PPh$_3$)$_4$, DMF, 75 ºC, 3h; (b) i) NiCl$_2$, TPP, acetonitrile reflux 45 min. ii) Zn, NaCN, reflux overnight.

This methodology was again successfully utilised in the preparation of 5-cyanophthalid (9) from 5-bromophthalid, which is a key raw material in the synthesis of Citalopram (1)$^{12}$. 
Greenwood et al.\textsuperscript{13} (Oxazoline route).

Sathyanarayana and co-workers\textsuperscript{14} noticed the impurity formation during preparation of 1 by cyano exchange process. According to them Citalopram obtained by above route contains descyano Citalopram which was result of the side reaction of residual magnesium with 5-halophthalide during two successive Grignard reactions. Another impurity generated during the cyanide exchange process was the 5-carbamoylphthalane as shown in figure–2. Also the key intermediate 5-halophthalan 25b does not react completely during the cyanation step and thus obtained as impurity in the product.

\textbf{Figure–2}

Also the lethal activity of cyanating agent is well known. Hence Greenwood and co-workers developed a new manufacturing process to eliminate the use of toxic cyanating agents which also avoids the use of starting materials having functional groups causes formation of above mentioned impurities.

Synthesis begins with reaction of terphthalic acid (30) with trioxane in 25–30\% oleum to get 5-carboxyphthalide (31). This reaction is carried out at 140–150 °C and required 8 h for completion. Condensation of 2-amino-2-methyl propanol with acid chloride of 31 to obtain hydroxyl amide 32 was carried out in DMF, while acid chloride formation of phthalide 31 was furnished in toluene by using SOCl\textsubscript{2} and catalytic DMF. Cyclization of hydroxyamide 32 using SOCl\textsubscript{2} in DCM resulted in oxazoline 33. Synthesis of key intermediate oxazoline diol 34 was compleated by successive addition of Grignard reagent 4 and 11.
Deprotection of carboxylic group and formation of isobenzofuran ring was carried out in single step by treating oxazoline diol intermediate 34 with 12.4% aq. H₂SO₄ at reflux temperature for 2 h, followed by addition of NaOH resulted in isolation of sodium salt of 5-carboxyphthalan 35. Acid chloride of 35 was prepared by using SOCl₂ in DCM which was reacted with ammonia gas to obtain amide 36. Amide 36 was refluxed with POCl₃ in acetonitrile afforded targeted compound 1. Entire reaction sequence and conditions are summarised in scheme–8.

**Scheme–8**

**Reagents and conditions:** (a) trioxane, oleum, 140–150 ºC, 8 h; (b) i) SOCl₂, Cat. DMF, Toluene, reflux, 1 h; ii) 2-amino-2-methyl-propanol, toluene, 15–20 ºC, 30 min.; (c) SOCl₂, DCM, 20–25 ºC, 1 h; (d) i) MgBr-C₆H₄-F, THF, 20–25 ºC, ii) MgBr(CH₂)₃NMe₂, THF 20–25 ºC, 30 min.; (e) 12.4% H₂SO₄, reflux 2h,
NaOH; (f) SOCl$_2$, DCM, NH$_3$, 0–5 °C, 15 min.; (g) POCl$_3$, ACN, reflux; (h) POCl$_3$, pyridine, 80–90 °C, 4 h; (i) SOCl$_2$–POCl$_3$, pyridine, 20–25 °C, 4 h.

Oxazoline diol intermediate 34 can also be converted to Citalopram (1) in one step by treating it with either POCl$_3$ or combination of SOCl$_2$ and POCl$_3$, but the yield obtained in this reaction is very low (38 to 48%).

Methods for the preparation of Escitalopram

Boegesoe et al.\textsuperscript{15} (Separation of cyanodiol–12).

Antidepressant activity of Citalopram (1) is well known, but to study possibilities of use of its enantiomers in the treatment of obesity or alcoholism, Boegesoe and Perregaard first time separated enantiomers of Citalopram (1).

Cyano diol 12 was prepared as per reported process.\textsuperscript{7} Selective esterification of a primary alcohol of 12 with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride gave monoester 38 as a mixture of diastereomers. This mixture was separated by HPLC and the desired diastereisomer 39 was treated with potassium tert-butoxide in toluene to get desired Escitalopram (2).

Alternatively, the optical resolution of the racemic diol 12 was performed by crystallization with (+)-di-p-toluyltartaric acid (DPTTA). The resulting (S)-cyanodiol 12 was cyclised via preparation of labile ester using methanesulfonyl chloride, resulting mesylate intermediate 37 was treated with Et$_3$N in toluene to get required Escitalopram (2) (Scheme–9).
Reagents and conditions: (a) (+)-DPTTA, IPA, 40 °C, 3 h; (b) MsCl, Et$_3$N, toluene, 0 to 5 °C, 30 min.; (c) i) (+)-α-methoxy-α-trifluoromethylphenylacetic acid, SOCl$_2$, Cat. DMF, CHCl$_3$, reflux, 2 h; ii) ET$_3$N, DCM, RT, 1 h; (d) Separation by HPLC using eluting phase EtOAc/THF 9:1 containing 4% of Et$_3$N; (e) (CH$_3$)$_3$OK, toluene, 0 °C.
Dall’asta and co-workers\textsuperscript{16} (Separation of Oxazoline diol–34).

Dall’asta and co-workers have reported the optical resolution of the racemic oxazoline diol 34 by using optically pure tartaric acid or camphor-10-sulfonic acid as chiral pool. However in present publication the actual process of separation and preparation of 2 was not discussed. An approach for synthesis of the Escitalopram by this method is as shown in scheme–10.

**Scheme–10**

![Scheme-10](image)

**Reagents and conditions:** (a) (+)- or (-)-tartaric acid/(+)- or (-)-camphor-10-sulfonic acid; (b) MsCl, Et\textsubscript{3}N, toluene, 0 to 5 °C, 30 min.; (c) POCl\textsubscript{3}, pyridine, 80–90 °C, 4 h.

Tse, Hoi and Lun, Allan\textsuperscript{17} (Separation of bromo diol–24).

Tse, Hoi and Lun, Allan started their synthesis from reported racemic bromo diol intermediate 24, which was reacted with acetic anhydride to get respective monoester derivative 41. Fractional crystallization of 41 with (+) –DPTTA followed by ester hydrolysis resulted in enantiomerically enriched bromo diol 24, which was further cyclised to get bromophthalan 42 by using p-toluenesulfonyl
chloride and Et$_3$N. Reaction of CuCN with 42 in DMAc at 150 ºC resulted in desired Escitalopram (2) (Scheme−11).

**Scheme−11**

![Chemical structures](image)

**Reagents and conditions:** (a) Ac$_2$O, Et$_3$N, DMAP, RT, 67 h; (b) i) (+)-DPTTA, acetone, EtOAc, 65 h; ii) acetone, hexane- recrystallization, iii) 0.5 M NaOH, AcOH; (c) aq. NH$_3$, MeOH, RT, 7 h; (d) TsCl, Et$_3$N, DCM, (e) CuCN, DMAc, 150 ºC, 21 h.

The major disadvantages of this process are

a) long reaction time required for preparation of monoacetate ester formation (67 h) and its resolution (65 h).

b) Incomplete cynamation reaction results in isolation of 2 with contamination of 42 up to 15%.

**Elati and co-workers**$^{18, 19}$ (Didesmethylcitalopram route)

Elati and co-workers attempted the resolution of Citalopram enantiomers by using DPTTA as chiral pull and isolated pure Escitalopram after several crystallizations.
with overall yield 18%. To improve the yield of resolution and to avoid multiple crystallizations for resolution Elati and co-workers reported novel approach for preparation of Escitalopram starting from cyanophthalan 8. Alkylation of cyanophthalan 8 was conducted with 3-chloro propylamine using potassium tert-butoxide to give racemic didesmethylcitalopram 43. Resolution of enantiomers was carried out by using (-)-DPTTA in ACN:Water solution to afford required (+)-didesmethylcitalopram 43. Finally, Escitalopram (2) was produced by the methylation of chiral intermediate 43 following Elschwier−Clarke methylation using formic acid (98%) and formaldehyde (37% aq. solution) as described in scheme−12.

Scheme−12

\[ \text{Reagents and conditions: } \]
\begin{align*}
\text{(a)} & \quad \text{3-chloropropylamine, (CH}_3\text{)}_3\text{COK, DMSO, 40–45 °C, 1 h; (b) (-)-DPTTA, ACN-Water, 1 h; (c) HCHO, HCOOH, reflux, 12 h.}
\end{align*}

Robert J. Dancer and co-workers tried classical resolution of Citalopram (1) as described by Elati using DPTTA but were unable to reproduce the resolution of Citalopram (1), obtaining only racemic or nearly racemic material. Also, Dancer and co-workers tried to synthesise 43 as per scheme−12, but failed to reproduce the results and found that 3-chloro propylamine free base is unstable and
undergoes polymerization. Dancer and co-workers have published their efforts indetail.  

In reply, Elati and co-workers agreed that the earlier method described by them for the resolution of Citalopram (1) by using (−)-DPTTA is not feasible but by use of (+)-DPTTA followed by isolation of product from mother liquor it is possible to get desired Escitalopram (2) with 11% over yield and 96.4% chiral purity. In the same article they were published the stability data of 3-chloropropylamine in various solvents at different temperature and showed that free base of 3-chloropropylamine was more stable in toluene and requires 72 h for polymerization, and quick addition 3-chloropropylamine was preferred during preparation of 43. Also reaction conditions in detail were reported in same publication.

Again Dancer and co-workers were tried resolution of 1 by using (+)-DPTTA and got product with 87.6% chiral purity only. At this time Dancer tried methylation of cyanophthalide 8 by using methyl iodide but failed to get alkylated product.

This entire scientific dispute was published by OPRD in detail. By reviewing these articles one thing is very clear that whatever Elati and co-workers reported was non-reproducible and hence not feasible on industrial scale.

Cotticelli and co-workers (Chemo-enzymatic preparation of Escitalopram)

Cotticelli and co-workers have synthesised Escitalopram starting from racemic cyanodiol 12 prepared by reported route, which was acetylated by treating it with excess of acetyl chloride to get racemic monoester 44. Enzymatic enantiomeric resolution was carried out in presence of esterase enzyme from Aspergillus niger in aqueous methanol at 20 to 25 ºC by maintaining pH 6.0, where upon ester hydrolysis of unwanted R-enantiomer occurred. Separation of monoester 44 from R-diol enantiomer 12 was achived by crystallization from mixture of diethyl ether and EtOAc. Ester hydrolysis by 30% NH3 in MeOH followed by cyclization by
usual way i.e. by using MsCl and Et₃N furnished Escitalopram (2) with high enantiomeric purity (Scheme–13).

Scheme–13
Reagents and conditions: (a) CH$_3$COCl, 35 ºC, 5 min; (b) i) MeOH-KH$_2$PO$_4$ buffer, esterase enzyme from *Aspergillus niger*, pH- 6.0, 20 to 25 ºC, 70-80 h; ii) ether, EtOAC, 0 to 4 ºC (c) 30% NH$_3$, MeOH, 4 h; (d) MsCl, Et$_3$N, toluene, 0 to 5 ºC, 30 min.

Bech and Co-workers$^{25}$ (Simulated moving bed chromatography).

Bech and co-workers have successfully employed simulated moving bed (SMB) Chromatography for the chiral separation of intermediates of Escitalopram. SMB is a chromatographic technique wherein enantiomers of optically active compounds are separated by and the stationary phase comprising of silica gel coated with a chiral material such as a cellulose ester.

Cyanodiol $^{12}$, bromodiol $^{24}$, or bromocitalopram $^{25a}$ were used as starting materials and after chiral resolution required enantiomer was converted in target compound 2 by reported method.

Similarly Ahmadian H. and Petersen H.$^{26}$ prepared diastereomeric ester of diol intermediate with optically pure acids like tartaric acid, camphanic acid, campher sulfonic acid etc. and separation of diastereomers was achived by HPLC. After separation desired isomer was converted in Escitalopram (2) by reported method.
Present Work
Present work

After a deep and careful review of all the documented synthetic routes for the preparation of Citalopram (1) and Escitalopram (2), we decided to adopt the Boegesoe et al. protocol\textsuperscript{7, 15} of due to commercial availability of 5-cyanophthalide (9) and convenient resolution procedure of cyanodiol 12.

Scheme–14

5-cyanophthalide (9) was used as key raw material, sequential addition of 4-fluoro-phenyl magnesium bromide (4) followed by aliphatic Grignard reagent 11 resulted in racemic cyanodiol 12; during process development, in one of the experiments intermediate benzophenone 10 was isolated and further reacted with Grignard reagent 11 to get the desired compound 12, but, no advantage was observed (Scheme–14).
Resolution of racemic cyanodiol 12 was achieved by using (+)-di-p-toluoyl tartaric acid ((+)-DPTTA) as chiral resolving agent and repeated recrystallization of the resulting salt was performed from isopropanol (IPA) ensured high chiral purity which was confirmed by HPLC (Scheme−15).

After successful resolution, desaltification of the DPTTA salt was achieved by using 25.0% aq. ammonia solution to release free base of chiral cyanodiol 12. Primary hydroxyl group of chiral cyanodiol 12 was treated with methanesulfonyl
chloride and Et₃N in toluene to afford cyclic compound i.e. Escitalopram (2) as disclosed in scheme–16.

In our efforts to improve the yield and purity, various experiments were carried out. During which a new impurity other than the impurities listed in the U.S. Pharmacopeia, was observed in the range of 0.1–0.5% in routine HPLC analysis of the crude free base of the final product. LCMS data of this crude indicated the M⁺ to be 307 (Figure–3).
Figure - 3

To improve the quality of the product, identification and characterization of the impurities in the drug product \textsuperscript{27} is very important and is a regulatory requirement. Hence we decided to isolate this unknown impurity, which would help us to
identify and elucidate the structure of this compound. Even though it was difficult to separate this new unknown impurity due to its close retention time and low availability in the crude free base, fortunately, we could isolate a small sample from the combined and enriched mother liquors from a few batches after oxalate salt formation. The isolated quantity of the new impurity was just enough to get the spectral data ($^1$H NMR, $^{13}$C NMR and Mass). After deep and careful analysis of spectral data, we predicted an unusual 8-membered cyclic structure for this impurity having a quaternary nitrogen atom as a part of ring (Figure–4, compound–46).

Figure–4

After proposing the structure for impurity, we envisaged its formation through the three step sequence. During mesylation of cyanodiol 12, dehydration would result in to mixture of olefins ($E$ and $Z$). $Z$ olefine 48 because of favourable geometry would undergo cyclization to give 46. On the other hand, olefinic intermediate 49 having $E$ configuration would not undergo this kind of transformation, instead would possibly involve an external attack by -NMe$_2$ group of another molecule of Citalopram, which can afford another new impurity having a structure 47 as suggested in scheme–17.
With these thoughts, we tried to investigate the presence of impurity 47 in the crude Escitalopram free base as well as in the mother liquors, fortunately, we could track impurity 47 in the HPLC chromatogram at 43.19 min. after an expanded run as confirmed by LCMS (M+: 631) (Figure–5). Despite of our best efforts, we were unable to isolate a sufficient quantity of impurity–47 which would have helped us in complete characterization and confirming the proposed structure for 47.
Figure 5

Detector A Ch1 237 nm

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Max. 1.0 %

Max. 6.0e4 a.u.

Max. 1.0e6 a.u.

Max. 1.0e6 a.u.
Contemporary to our efforts, US Pharmacopeia added this new dimeric impurity to the existing list of impurities, but surprisingly did not mention the cyclic impurity which seems to be forming in comparatively higher percentage during the manufacturing of the API using MsCl. Also, no details on any of these two impurities are reported in literature. Consequently, we decided to formally synthesize both these impurities, which not only confirm the structures of the impurities but also would provide sufficient quantities to satisfy the analytical need under regulatory requirements. Moreover, this would also help to confirm the proposed mechanism for the formation of these two impurities.

Scheme 1

Accordingly, we planned our synthetic approach to arrive at critical olefinic intermediates (54 and 55). The easiest thing for us to do was to eliminate the tertiary –OH of cyanodiol and examine the outcome with respect to E and Z double bond formation. Protection of primary –OH group seemed to be mandatory because if it was not protected then during mesylation, cyclization would be dominant reaction rather than alkene formation. Selective protection of primary –OH of cyanodiol was achieved as its TBS ether using TBDMS and imidazole in DCM. The structure of intermediate was confirmed by $^1$H NMR and mass spectrum. In $^1$H NMR spectrum protons of TBS group resonated at $-0.16$ (s, 3H), $-0.12$ (s, 3H), $0.80$ (s, 9H) ppm and also change in chemical shifts of...
benzylic proton from 4.06, 4.57 ppm to 4.40 and 4.83 ppm was observed. Subsequent dehydration of the tertiary –OH of intermediate 50 using MsCl/Et₃N was effected at ambient temperature to afford an inseparable mixture of Z and E isomers (52 and 53) which were inseparable by TLC (Scheme−18).

Crude mixture of 52 and 53 was subjected for -OTBS deprotection using TBAF in THF which resulted in mixture of targeted olefinic intermediates 54 and 55. Fortunately, after TBS deprotection, the olefinic intermediates 54 and 55 were marginally separable on TLC, and after careful column chromatography we could isolate olefinic intermediate 54 in sufficient amount with small quantity of E-isomer 55. In ¹H NMR data for these intermediates 54 and 55, change in splitting pattern for benzylic proton was observed, in case of olefin 54 benzylic protons resonated at 4.22 and 4.38 ppm as doublet, while in case of 55 benzylic protons appeared as singlet at 4.63 ppm.

Scheme−19

In order to obtain sufficient quantity of E-isomer (55), we decided to explore an alternative route (Wittig route). Accordingly required Wittig reagent (59) was prepared by reacting triphenyl phosphene (56) with 1,3-dibromo propane (57) followed by treatment of the resulting intermediate 58 with dimethyl amine in ethanol under reflux condition which furnished desired Wittig salt 59 (Scheme−19).
5-Cyanophthalide (9) was reacted with 4-fluoro-phenyl magnesium bromide (4) in THF at ambient temperature, after aqueous workup ketone 10 was isolated. The structure of ketone 10 was confirmed by $^1$H NMR, and mass spectrum, presence of additional aromatic protons at 7.15–7.21 (m, 2H), 7.80–7.85 (m, 2H) confirms the structure. Primary hydroxyl group of ketone 10 was protected as its TBS ether to furnish intermediate 60. Presence of signals for 6H at 0.0 ppm and 9H at 0.83 ppm in $^1$H NMR spectrum confirms presence of TBS group. Intermediate 60 was treated with Wittig salt 59 in presence of NaH as base to afford an inseparable mixture of $Z$ and $E$ isomers (52 and 53). TBS deprotection of mixture (52 and 53) was achieved using TBAF to furnish the mixture of desired free alcohols (54 and 55) (Scheme–20).

After deprotection both the isomers were separated by silicagel column chromatography by using CHCl$_3$:MeOH:Et$_3$N (98:1.5:0.5) as mobile phase. Unfortunately, we ended up in getting compound 54 as major and compound 55 as minor product. But from both the routs, we could isolate satisfactory quantity of 55 which allowed us to move forward and complete our synthetic targets.
After successful synthesis of indispensable olefinic intermediates 54 and 55, next step was preparation of mesylate intermediates 48 and 49. Hence both the intermediates 54 and 55 were separately treated with MsCl/Et₃N in DCM, upon which the Z isomer (54) cyclised at 0 ºC to provide target compound 46 in very good yield within 30 min. Analytical data for synthetic 46 was in excellent agreement with isolated 46. Whereas reaction of E isomer under these conditions did not work. The starting alcohol 55 was recovered. In next attempt we selected
toluene as solvent of reaction during which we found rapid formation of 46, but in case of 55 raising the temperature also proved to be futile to effect the cyclization (Scheme−21).

In another set of experiments, both these intermediates (54 and 55) along with excess Citalopram free base were treated in DCM with MsCl/Et₃N at 0 °C separately. Here in the case of E isomer (55), we could observe slow formation of Impurity−47. Reaction was completed at reflux temperature after 24 h and product was isolated by preparative HPLC. Analytical data of 47 confirms its proposed structure in U.S. Pharmacopeia. In case of Z isomer 54, within 30 min, exclusive formation of the cyclised impurity was observed with no dimeric impurity. This observation suggested that when configuration of double bond is suitable for cyclization as in case of Z isomer, intramolecular cyclization is preferred over intermolecular reaction involving attack of −NMe₂ group from other molecule.

During all these experimentation self dimerization of 55 to get dimeric compound 61 was not observed and the same impurity 61 was not observed during preparation of API.
We felt, owing to the very small size of the sulfonating reagent (MsCl), the tertiary \(-\text{OH}\) group is undergoing sulfonation, albeit in low yield. If a larger size (hindered) sulfonating reagent such as TsCl was used instead of MsCl these impurity formation can be completely avoided. Indeed, when we tried the cyclization of cyanodiol (12) with TsCl/Et\(_3\)N in DCM or in toluene, the formation of these impurities was not at all observed (Scheme–22).

**Conclusion**

In conclusion, during the systematic study of the manufacturing process of Citalopram/Escitalopram, two process related impurities were isolated and characterised, their structures were confirmed by chemical synthesis. Detailed investigation revealed the course of their formation; this help to improve the yield and purity of the drug molecule during the bulk synthesis.
Experimental
Experimental

Preparation of 4-[4-(Dimethylamino)-1-(4’-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (12).

To a stirred suspension of Mg turnings (22.5 g, 0.92 mol) in dry THF (100.0 mL) was added a solution of 1-Bromo-4-fluorobenzene (132.0 g, 0.75 mol) in dry THF (350.0 mL) at reflux temperature slowly under nitrogen atmosphere. The reaction mixture was allowed to cool at ambient temperature over a period of 30 min. The THF solution of the resulting Grignard reagent was added dropwise to a THF solution of 5-Cyanophthalide (9) (100.0 g, 0.63 mol) under nitrogen atmosphere at 0 °C and stirred for 30 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of first Grignard addition readily available solution of second Grignard reagent – 11 (1.0 mol solution in THF of 650.0 mL) was added dropwise under nitrogen atmosphere and then reaction was left overnight at ambient condition. The reaction mixture was poured on ice-cold water (1.0 L) whereupon acetic acid (150.0 mL) was added, resulting in a final pH of 6.5–7.0 of the reaction mass. THF was distilled out below completely under vacuum and toluene (1.0 L) was charged. pH of the reaction was adjusted at 9.0 by using 25% aqueous ammonia solution and after stirring reaction mixture at 45 ºC for 30 min layers were separated. Toluene was distilled out completely under reduced pressure at 50 ºC and isolation of cyanodiol (12) is achieved from MTBE (250.0) with good yield (139.8 g, 65%).
mp: 103–105 °C; m/z: 343.0 (M+H)+; ¹H NMR (400 MHz, DMSO_d6): δ 1.16–1.23 (m, 1H), 1.36–1.42 (m, 1H), 2.01 (s, 6H), 2.10–2.16 (m, 3H), 2.23–2.30 (m, 1H), 4.06 (dd, J = 15.6 Hz, J = 4.8 Hz, 1H), 4.57 (dd, J = 15.6 Hz, J = 5.2 Hz, 1H), 5.13 (dd, J = 5.2 Hz, J = 4.7 Hz, 1H), 6.48 (s, 1H), 7.07–7.11 (m, 2H), 7.23–7.26 (m, 2H), 7.73–7.79 (m, 2H), 7.88 (s, 1H); ¹³C NMR (100 MHz, DMSO_d6): 21.4, 40.4, 44.8, 59.1, 59.9, 76.6, 109.6, 114.2, 114.4, 119.0, 126.9, 127.6, 127.7, 129.5, 130.1, 142.3, 142.3, 143.4, 148.8, 159.5, 161.9.

**Preparation of (S)-(-)-4-[4-(Dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile, hemi(+)-di-p-toluoyl-D-tartaric acid salt (45).**

To a solution of Racemic cyanodiol (12) (100.0 g, 0.29 mol) in IPA (500.0 mL), (+)-Di-p-toluoyl-D-tartaric acid monohydrate (59.0 g, 0.15 mol) was added and above suspension was heated at 85 °C where upon clear solution was observed. Solution was cooled gradually and after stirring for 6 h at 35 °C product was filtered and washed with IPA (100.0 mL).

To achieve chiral purity above wet cake was recrystalised from IPA followed dying of wet cake afforded Compound-45 with chiral purity more than 99% (50.0 g 32%).
mp: 133–135 °C; m/z: 242.9 (M+H)+; ¹H NMR (400 MHz, DMSO_d6): δ 1.21–1.28 (m, 2H), 1.44–1.52 (m, 2H), 2.1–2.35 (m, 22H), 2.58 (brs, 4H), 4.03 (d, J = 15.6 Hz, 2H), 4.55 (d, J = 15.6 Hz, 2H), 5.6 (s, 2H), 7.07–7.11 (m, 4H), 7.21–7.29 (m, 8H), 7.74–7.88 (m, 10H); ¹³C NMR (100 MHz, DMSO_d6): 19.1, 21.1, 39.1, 42.2, 56.9, 59.7, 73.9, 76.5, 109.8, 114.3, 114.5, 119.0, 126.8, 127.5, 127.5, 127.6, 129.1, 129.3, 129.6, 130.1, 141.6, 143.3, 148.5, 159.5, 161.9, 165.1, 169.5

**Preparation of Escitalopram oxalate (2).**

![Chemical structure of Escitalopram oxalate](image)

**Procedure-I : By using methanesulfonyl chloride.**

To a biphasic mixture of toluene (600.0 mL) and Water (500.0 mL) charged oxalate salt 45 (100.0 g, 0.09 mol) pH of suspension was adjusted at 9.0 by 25.0% aq. ammonia (30.0 mL). After stirring for 30 min layers were separated and organic layer was washed by water (500.0 mL x 2). Organic layer was dried over sodium sulfate and Et₃N (36.5 g, 0.36 mol) followed by addition of methanesulfonyl chloride (21.5 g, 0.18 mol) drop wisely. After completion of reaction, it was quenched by adding 0.1N NaOH solution (200.0 mL). Layers were separated and organic layer was washed with water (200 mL x 2) followed by distillation of toluene. Resulting residue was diluted with acetone (200.0 mL) followed by addition of oxalic acid dehydrate (30.6 g, 0.24 mol) dissolved in acetone (200.0 mL). Reaction mixture was cooled gradually at 5 °C, after stirring for 8 h product was filtered and washed with acetone (100.0 mL) to get crude product with purity more than 98.0%. Purification of crude product is performed by recrystalization of product from acetone to get pure Escitalopram with purity more than 99.0% by HPLC (65.0 g, 84%).
Procedure-I: By using p-toluenesulfonyl chloride.

To a biphasic mixture of toluene (600.0 mL) and Water (500.0 mL) charged oxalate salt 45 (100.0 g, 0.09 mol) pH of suspension was adjusted at 9.0 by 25.0% aq. ammonia (30.0 mL). After stirring for 30 min layers were separated and organic layer was washed by water (500.0 mL x 2). Organic layer was dried over sodium sulfate and Et₃N (36.5 g, 0.36 mol) followed by addition of p-toluenesulfonyl chloride solution (35.5 g, 0.18 mol) in toluene (200.0 mL) drop wisely. After completion of reaction, it was quenched by adding 0.1N NaOH solution (200.0 mL). Layers were separated and organic layer was washed with water (200 mL x 2) followed by distillation of toluene. Resulting residue was diluted with acetone (200.0 mL) followed by addition of oxalic acid dehydrate (30.6 g, 0.24 mol) dissolved in acetone (200.0 mL). Reaction mixture was cooled gradually at 5 °C, after stirring for 8 h product was filtered and washed with acetone (100.0 mL) to get crude product with purity more than 98.0%. Purification of crude product is performed by recrystalization of product from acetone to get pure Escitalopram with purity more than 99.0% by HPLC (65.0 g, 84%).

mp: 152−153 °C; m/z: 325.1 (M+H)+ ; ¹H NMR (400 MHz, DMSO_d6): δ 1.38−1.56 (m, 2H), 2.23 (t, J = 7.8 Hz, 2H), 2.63 (s, 6H), 2.97 (t, J = 7.9 Hz, 2H), 5.20 (ABq, J =13.4 Hz, 2H), 7.14−7.19 (m, 2H), 7.57−7.61(m, 3H), 7.73−7.81(m, 3H); ¹³C NMR (100 MHz, DMSO_d6): 19.4, 37.1, 42.3, 56.7, 71.4, 90.6, 110.9, 115.4, 115.6, 123.4, 126.0, 127.2, 127.3, 132.4, 140.2, 140.2, 149.1, 160.4, 162.9, 165.3.
Preparation of 3-(bromopropyl)-phosphoniumbromide (58).

\[
\begin{array}{c}
\text{Ph}_3\text{P}^+ \quad \text{Br} \\
\hline
\text{Br}
\end{array}
\]

To a solution of triphenyl phosphene (25.0 g, 95.0 mmol) in toluene (100.0 mL) 1,3Dibromo propane (30.0 g, 150 mmol) was added and stirred for 2 h at 50 °C. After cooling the reaction mixture at 25 °C product was filtered and washed with toluene (50.0 mL) and on drying Wittig salt 58 was obtained as white crystalline solid (39 g, 88%).

mp: 226−229 °C; m/z: 385.2 (M+H)⁺; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.21–2.27 (m, 2H), 3.87–3.90 (m, 2H), 4.15–4.22 (m, 2H), 7.68–7.90 (m, 15H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 21.1, 21.7, 26.1, 33.2, 33.4, 117.3, 118.1, 130.4, 130.5, 133.4, 133.5, 135.0, 135.1.

Preparation of 3-[(dimethylamino)propyl]-phosphoniumbromide hydrobromide (59).

\[
\begin{array}{c}
\text{Ph}_3\text{P}^+ \quad \text{N} \quad \text{Br} \\
\hline
\text{HBr}
\end{array}
\]

Wittig salt 58 (35.0 g, 75 mmol) was added to a mixture of dimethyl amine (3.8 g, 85 mmol) and ethanol (70.0 mL) and above mixture was refluxed for 4 h. Excess of dimethyl amine was distilled out under reduced pressure and resulting residue was diluted with ethanol (100.0 mL) and product was filtered to afford desired wittig salt 59 as white solid (29 g, 76%).

mp: 283–285 °C; m/z: 348.2 (M+H)⁺; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.40–2.50 (m, 2H), 2.87 (s, 6H), 3.82–3.91 (m, 4H), 7.71–7.87 (m, 15H), 10.95 (brs, 1H);
$^{13}$C NMR (100 MHz, CDCl$_3$): 17.9, 20.1, 20.6, 42.7, 56.6, 56.8, 116.4, 117.3, 130.2, 130.3, 133.4, 133.5, 135.0, 135.0.

**Preparation of 4-(4'-fluorobenzoyl)-3-(hydroxymethyl)-benzonitrile (10).**

To a stirred suspension of Mg turnings (2.25 g, 92.0 mmol) in dry THF (10.0 mL) was added a solution of 1-Bromo-4-fluorobenzene (13.2 g, 75.0 mmol) in dry THF (35.0 mL) at reflux temperature slowly under nitrogen atmosphere. The reaction mixture was allowed to cool at ambient temperature over a period of 30 min. The THF solution of the resulting Grignard reagent was added dropwise to a THF solution of 5-Cyanophthalide (10.0 g, 63.0 mmol) under nitrogen atmosphere at 0 °C and stirred for 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched by the addition of 20% ammonium chloride solution (100.0 mL) at 0 °C. Product was extracted with ethyl acetate (50 mL x 2). The combined ethyl acetate layer was dried over anhydrous sodium sulfate, filtered and concentrated to yield 10 (11.2 g, 63%).

mp: 127−128 °C; m/z: 256.0 (M+H)$^+$; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.86 (t, $J = 6.0$ Hz, 1H), 4.67 (d, $J = 6.0$ Hz, 2H), 7.15−7.21(m, 2H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.69 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 7.80−7.85 (m, 2H), 7.90(s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$):62.4, 114.7, 115.9, 116.1, 117.8, 123.9, 125.3, 129.5, 130.6, 132.7, 132.8, 132.9, 140.9, 142.1, 165.0, 167.5, 195.4; A small sample was purified by preparative TLC for elemental analysis. Anal. Calcd for C$_{15}$H$_{10}$FNO$_2$: C, 70.58, H, 3.95, N, 5.49. Found: C, 70.48, H, 3.88, N, 5.45.
Preparation of 4-(4’-Fluorobenzoyl)-3-(tert-butyldimethylsiloxymethyl) benzonitrile(60).

To the stirred solution of compound 10 (8.0 g, 31.0 mmol) in DCM (40.0 mL) were added imidazole (4.2 g, 62.0 mmol) and TBDMSCl (5.9 g, 39.0 mmol), respectively, portionwise at 10 to 15 °C, and the reaction mixture was allowed to stir for 30 min. The reaction mass was monitored by TLC and after completion of reaction it was quenched by the addition of water. The reaction mixture was extracted with DCM (50 mL x 2). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude residue which was purified by silica gel column chromatography using ethyl acetate and n-Hexane (1:19) to yield 60 (9.7 g, 84.0%).

mp: 98–99 °C; m/z: 370.52 (M+H)+; 1H NMR (400 MHz, CDCl₃): δ 0.00 (s, 6H), 0.83 (s, 9H), 4.8 (s, 2H), 7.13–7.20 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.77–7.81 (m, 2H), 7.92 (s, 1H); 13C NMR (100 MHz, CDCl₃): 5.7, 18.2, 25.7, 62.1, 114.1, 115.8, 116.0, 118.2, 128.5, 130.1, 131.0, 132.7, 132.8, 140.3, 142.3, 164.9, 167.4, 194.9; Anal. Calcd for C₂₁H₂₄FNO₂Si: C, 68.26, H, 6.55, N, 3.79. Found: C, 68.23, H, 6.53, N, 3.82.
Preparation of 4-(E/Z)-4-(Dimethylamino)-1-(4'-fluorophenyl)but-1-enyl-3-(hydroxymethyl)-benzonitrilr [54 and 55].

To a solution of [3-(dimethylamino)propyl]phosphonium bromide hydrobromide (21.70 g, 43.0 mmol) was added NaH (4.0 g, 100.0 mmol, 60% dispersion in mineral oil) portionwise at 5 °C under nitrogen atmosphere, and the reaction mixture was allowed to stir for 30 min. The reaction mixture was heated to 60 °C for 3 h; a deep orange colored solution of Wittig ylide was obtained. The reaction mixture was cooled to 25 °C. To this solution compound−60 (9.0 g, 24 mmol) in THF (15.0 mL) was added, and the reaction mixture was heated to 60 °C and stirred overnight. After completion of reaction, it was quenched by addition of water and extracted with ethyl acetate (30.0 mL x 2). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to yield 52/53 (as crude residue). The crude reaction mixture was dissolved in THF, 1.0 M TBAF solution (70.0 mL) was added to it, and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated to leave a crude residue. The E and Z isomers (55/54) were purified by silica gel column chromatography using MeOH and chloroform (1:99) as eluent.

**E-isomer (55)** (1.3 g, 16.5%) m/z: 325.3 (M+H)+; 1H NMR (400 MHz, CDCl3): δ 2.08 (s, 6H), 2.36−2.44 (m, 2H), 2.50−2.54 (m, 2H), 4.63 (s, 2H), 5.73 (t, J = 7.1 Hz, 1H), 6.98−7.03 (m, 3H), 7.12−7.17 (m, 2H), 7.46 (dd, J = 7.9 Hz, J = 1.6 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H); 13C NMR (100 MHz, CDCl3): 27.0, 44.5, 58.6, 62.9, 110.5, 115.0, 115.2, 118.7, 130.7, 130.7, 130.9, 131.0, 131.0, 131.7, 133.1, 134.7, 134.7, 138.4, 141.4, 148.3, 160.6, 163.1 ; A small sample was purified by
preparative TLC for elemental analysis. Anal. Calcd for C_{20}H_{21}FN_{2}O : C, 74.05, H, 6.53, N, 8.64. Found: C, 74.10, H, 6.49, N, 8.32.

**Z-isomer (54) (4.1 g, 51.8%)**: mp: 113–115 °C; m/z: 325.2 (M+H)^+; ^1^H NMR (400 MHz, CDCl₃): δ 2.01 (s, 6H), 2.06–2.17 (m, 2H), 2.25–2.30 (m, 1H), 2.44–2.51 (m, 1H), 4.22 (d, J = 12.6 Hz, 1H), 4.38 (d, J = 12.6 Hz, 1H), 5.17 (bs, 1H), 6.21 (dd, J = 7.0 Hz, J = 8.6 Hz, 1H), 6.93–6.98 (m, 2H), 7.10–7.13 (m, 2H), 7.27 (d, J = 8.9 Hz, 1H), 7.64 (dd, J = 8.9 Hz, J = 1.5 Hz, 1H), 7.81 (d, J = 1.5 Hz, 1H); ^1^C NMR (100 MHz, CDCl₃): 27.9, 45.3, 58.8, 61.3, 111.7, 115.2, 115.4, 118.6, 127.4, 127.5, 128.6, 130.8, 130.9, 132.3, 135.8, 135.8, 138.6, 141.7, 142.6, 160.9, 163.3; A small sample was purified by preparative TLC for elemental analysis. Anal. Calcd for C_{20}H_{21}FN_{2}O : C, 74.05, H, 6.53, N, 8.64. Found: C, 73.97, H, 6.55, N, 8.67.

**Alternative preparation of intermediates 54 and 55.**

**Preparation of 4-[4-(Dimethylamino)-1-(4’-fluorophenyl)-1-hydroxybutyl]-3-(tert-butyldimethylsiloxymethyl)-benzonitrile (50).**

![Chemical Structure](image)

To a stirred solution of diol 12 (10.0 g, 29.0 mmol) in DCM (60.0 mL) were added imidazole (4.0 g, 59.0 mmol) and TBDMSCl (5.5 g, 36.0 mmol) portionwise at 10 to 15 °C, respectively. The reaction mixture was stirred for 30 min at 10 to 15 °C and quenched by adding water (40.0 mL). Layers were separated and organic layer was washed with water (50.0 mL x 2). DCM was
distilled out completely and product was washed with hexane (50.0 mL) to get desired O-TBDMS product 50 (10.9 g, 82%) as a white solid).

mp: 135−136 °C; m/z: 457.4 (M+H)⁺; ¹H NMR (400 MHz, CDCl₃): δ -0.16 (s, 3H), -0.12 (s, 3H), 0.80 (s, 9H), 1.50−1.60 (m, 2H), 2.14−2.20 (m, 7H), 2.3−3.00 (m, 1H), 2.34−2.39 (m, 1H), 2.49−2.55 (m, 1H), 4.40 (d, J = 15.5 Hz, 1H), 4.83(d, J = 15.5 Hz, 1H), 6.91−6.96 (m, 2H), 7.24−7.28 (m, 2H), 7.53−7.60 (m, 2H), 7.97 (s, 1H), 8.90 (bs, 1H); ¹³C NMR (100 MHz, CDCl₃): -5.70, -5.60, 18.2, 22.3, 25.8, 43.3, 44.7, 59.9, 62.4, 110.7, 114.4, 114.7, 119.3, 126.5, 127.6, 127.7, 129.3, 131.2, 142.6, 142.6, 143.1, 148.3, 160.3, 162.7; Anal. Calcd for C₂₆H₃₇FN₂O₂Si: C, 68.38; H, 8.17; N, 6.13. Found: C, 68.32; H, 8.13; N, 6.19.

Preparation of 4-(E/Z)-4-(Dimethylamino)-1-(4'-fluorophenyl)but-1-enyl-3-(hydroxymethyl)-benzonitrilr {54 and 55}.

To a solution of 50 (10.0 g, 22.0 mmol) in DCM (50.0 mL) were added Et₃N (3.3 g, 33.0 mmol) and methanesulfonyl chloride (2.6 g, 23.0 mmol) respectively at 0 to 5 °C. After complete addition the reaction mixture was warmed at 25 °C and stirred for 1 h. Reaction was quenched by adding water (50.0 mL), layers were separated, and the organic layer was dried over anhydrous sodium sulfate and solvent was distilled out completely. The crude reaction mixture was dissolved in THF, 1.0 M TBAF solution (70.0 mL) was added to it, and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated to leave a crude residue. The E and Z isomers (55/54) were purified by silica gel column chromatography using MeOH and chloroform (1:99) as eluent.
Preparation of \((Z)-6-(4’-fluorophenyl)-1,2,3,4-tetrahydro-2,2-dimethylbenzo(c)azoline-9-carbonitrile mesylate [ Cyclic impurity 46].

![Chemical Structure](image)

To a solution of \(Z\)-intermediate (54) (3.2 g, 10.0 mmol) in DCM (15.0 mL) were added Et\(_3\)N (1.2 g, 12.0 mmol) and methanesulfonyl chloride (1.3 g, 11.0 mmol) respectively at 20 to 25 °C. After complete addition, the reaction mixture was stirred for 10 min followed by addition of saturated NaHCO\(_3\) solution (50.0 mL). After the biphasic mixture was stirred for 30 min, the layers were separated and the aqueous layer was washed with DCM (20.0 mL). Water was distilled out completely and the remaining residue was stirred with acetone (25.0 mL) and filtered. The filtrate was concentrated to yield Impurity 46 (2.4 g, 60.0%).

\[m/z: 307.2 \text{ (M)}^+; ^1H \text{ NMR (400 MHz, CDCl}_3): \delta 2.00 \text{ (s, 3H)}, 2.10–2.20 \text{ (m, 1H)}, 2.70–2.80 \text{ (m, 1H)}, 3.5–3.5 \text{ (m, 4H)}, 3.9 \text{ (s, 3H)}, 3.9–4.0 \text{ (m, 1H)}, 4.4 \text{ (d, } J = 12.9 \text{ Hz, 1H)}, 5.6 \text{ (d, } J = 12.9 \text{ Hz, 1H)}, 6.4 \text{ (t, } J = 7.8 \text{ Hz, 1H)}, 7.0–7.1 \text{ (m, 4H)}, 7.2–7.3 \text{ (m, 1H)}, 7.7 \text{ (dd, } J = 8.1 \text{ Hz, } J = 0.6 \text{ Hz, 1H)}, 8.9 \text{ (s,1H); } ^{13}C \text{ NMR (100 MHz, CDCl}_3): 23.4, 39.6, 48.7, 56.5, 62.5, 63.5, 112.1, 115.4, 115.6, 117.8, 128.6, 129.5, 130.0, 131.4, 133.2, 136.4, 138.6, 139.7, 145.8, 161.3, 163.8; \text{ Anal. Calcd for C}_{20}H_{21}FN_2.CH_3O_3S : C, 62.66; H, 6.01; N, 6.96. Found: C, 62.60; H, 5.99; N, 7.13.\]
Preparation of Dimmer impurity 47.

To a solution of E- intermediate 55 (1.0 g, 15.3 mmol) in DCM (5.0 mL) were added Et$_3$N (0.4 g, 3.8 mmol), Citalopram free base (5.0 g, 49.0 mmol), and methanesulfonyl chloride (0.4 g, 3.4 mmol) respectively at 20 to 25 °C. After complete addition, the reaction mixture was stirred for 24 h at reflux temperature. Solvent was distilled out and impurity 47 was isolated by HPLC preparative column chromatography using potassium phosphate as buffer and a Phenomenex Luna C18 column to yield dimmer Impurity (0.8 g, 45.0%)

m/z: 631.80 (M)$^+$; $^1$H NMR (400 MHz, DMSO$_d$6): δ  1.50−1.40 (m, 4H), 2.2−2.2 (m, 2H), 2.5 (s, 6H), 2.7 (s, 3H), 2.7 (s, 3H), 3.2 (m, 4H), 4.0 (bs, 2H), 5.2 (ABq, J = 13.5 Hz, 2H), 5.8 (t, J = 3.1 Hz, 1H), 7.5 (m, 5H), 7.6−7.5 (m, 3H), 7.7 (d, J = 7.8 Hz, 2H), 7.8 (d, J = 8.6 Hz, 1H), 7.8 (s, 1H), 8.0 (s, 1H), 8.1 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO$_d$6): 17.4, 24.7, 29.0, 36.6, 42.2, 49.3, 49.4, 55.6, 62.9, 64.7, 71.1, 90.1, 110.8, 111.3, 115.4, 115.7, 116.0, 118.0, 118.7, 123.0, 125.8, 126.8, 126.9, 127.1, 128.8, 130.9, 131.0, 131.5, 132.1, 133.5, 133.7, 134.3, 138.0, 140.0, 140.0, 148.7, 150.3, 160.2, 160.4, 162.6, 162.8.
Spectra
$^1$H NMR spectrum of Compound 12 in DMSO$_d$6

$^{13}$C NMR spectrum of Compound 12 in DMSO$_d$6
Mass spectrum of compound 12

$^1$H NMR spectrum of Compound 45 in DMSO_d6
$^{13}$C NMR spectrum of Compound 45 in DMSO$_d$6

Mass spectrum of compound 45
$^1$H NMR spectrum of Compound 2 in DMSO$_d$6

$^{13}$C NMR spectrum of Compound 2 in DMSO$_d$6
Mass spectrum of compound 2

$^1$H NMR spectrum of Compound 58 in CDCl$_3$
$^{13}$C NMR spectrum of Compound 58 in CDCl$_3$

Mass spectrum of compound 58
$^1$H NMR spectrum of Compound 59 in CDCl$_3$

$^{13}$C NMR spectrum of Compound 59 in CDCl$_3$
Mass spectrum of compound 59

$^1$H NMR spectrum of Compound 10 in CDCl$_3$
$^{13}$C NMR spectrum of Compound 10 in CDCl$_3$

Mass spectrum of compound 10
$^1$H NMR spectrum of Compound 60 in CDCl$_3$

$^{13}$C NMR spectrum of Compound 60 in CDCl$_3$
Mass spectrum of compound 60

$^1$H NMR spectrum of Compound 54 in CDCl$_3$
$^{13}$C NMR spectrum of Compound 54 in CDCl$_3$

Mass spectrum of compound 54
\(^1\)H NMR spectrum of Compound 55 in CDCl\(_3\)

\(^{13}\)C NMR spectrum of Compound 55 in CDCl\(_3\)
Mass spectrum of compound 55

$^1$H NMR spectrum of Compound 50 in CDCl$_3$
$^{13}$C NMR spectrum of Compound 50 in CDCl$_3$

Mass spectrum of compound 50
$^1$H NMR spectrum of Compound 46 in CDCl$_3$

$^{13}$C NMR spectrum of Compound 46 in CDCl$_3$
Mass spectrum of compound 46

$^1$H NMR spectrum of Compound 47 in DMSO$_{d6}$
$^{13}$C NMR spectrum of Compound 47 in DMSO$_{d6}$

Mass spectrum of compound 47
References


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