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Synthesis and Characterization of Compounds Related to Terbinafine Hydrochloride

Sridevi Somepally[1], **Bala Murali Krishna Khandapu**[1], **Hari Babu Bollikolla**[1,2]*

[1]Department of Chemistry, Acharya Nagarjuna University, N Nagar-522 510, Andhra Pradesh, India.

[2]Department of Chemistry, Andhra Kesari University-523001, Ongole, Andhra Pradesh, India.

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KEYWORDS

Terbinafine Hydrochloride; Related substances; Origin; Characterization; Impurities

ABSTRACT: Terbinafine hhydrochloride is a drug of the allylamine derivative having a broad spectrum of antifungal activity, this is primarily used in treating skin and nails infections caused by dermatophytes. During the scale-up of the terbinafine hydrochloride process, two unknown impurities were observed and is identified. The emergence, synthesis, construal, and control of these contaminants are all covered in the current work. The production and characterization of four more impurities are also covered in this study listed in the European Pharmacopoeia 11.0 (Impurity D, E and F, and naphthalene intermediate dimer).

1. Introduction

N-[(2*E*)-6,6-dimethyl-2-hepten-4-ynyl]-n-methyl-1-naphthalenemethanamine hydrochloride is the chemical name of an allylamine derivative [1]. Terbinafine hydrochloride (**Figure 1**) is invented by SANDOZ (Novartis Pharmaceutical Corporation) and in sales by brand name LAMISIL® and have a broad spectrum of antifungal activity. It is given by mouth in treating infections like dermatophyte in nails and skin [2,3]. It is also applied to dermatophytosis on the skin, in pityriasis versicolor and in cutaneous candidiasis [4]. In terbinafine molecule a *tert*-butyl acetylene group is in conjugation with the allylamine double bond presented.

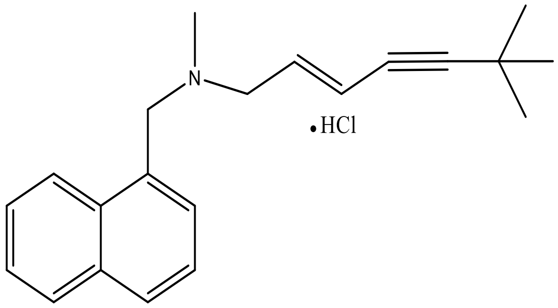


Figure 1: Chemical structure of Terbinafine hydrochloride.

It is essential to recognize and characterize any impurities in the process of making drug [5]. Any drug material must undergo an impurity profile examination because any active pharmaceutical ingredient contamination could affect the efficacy and safety of the drug [6,7].

To assess the analytical performance parameters comprising linearity, precision, specificity, accuracy, range, limit of detection- the LOD, robustness, limit of quantification-the LOQ, system appropriateness testing, relative retention factor, and contaminants are also needed in pure form.

In the process of scaling up tterbinafine-hydrochloride (**1**), two unknown impurities were observed at a level of 0.1-0.2% long with other impurities listed in the European Pharmacopoeia [8]. The unknown impurity detected was monitored and based on its disintegration trends in the LC-MS study, a tentative assignment of the structure was made. Further, this impurity was synthesized, characterized, and co-injected with tterbinafine-hhydrochloride in HPLC analysis to confirm its structure. Four more pharmacopoeia-listed impurities are synthesized and characterized in the current work using a variety of spectroscopic techniques.

2. Materials and Methods

2.1. Chemicals

Commercially available solvents and reagents were utilized sans being purified.

2.2. Instrumentation and conditions

^{1}H-NMR and ^{13}C-NMR spectral data were executed with spectrometer, Bruker-Avance 300-MHz in DMSO-d_6 and D_2O wherever related. Tetramethyl silane (TMS) was used as an internal reference and the chemical shift values were given in ppm-parts per million. Employing Perkin-Elmer FT-IR Spectrophotometer, the IR spectra were captured when the KBr pellets were in the solid state. Perkin-Elmer PE SCIEX-API 2000 arrayed with an ESI source and an online HPLC system preceding ultraviolet (UV) detector was used to record the mass spectrum.

2.3. Preparation of (E) -2-Terbinafine (EP impurity-F) (14):

Step-1: Added 40% (*w/w*) aaqueous mono methyl amine solution (35 gm, 10 m.eq.) into sodium hydroxide (45 gm 10 m.eq.) at 20-30 °C and agitated in same temperature for 30 mins to take anhydrous monomethyl amine (40.7). Then cooled to -20 to -40 °C, and added a lot wise 2-bromomethyl naphthalene (25 gm) to above reaction mass at same temperature. Added tetrahydrofuran (25 mL) to reaction mass at -20 to -40 °C agitated in same temperature for about 2 to 3 hrs and the reaction was monitored by TLC [methanol/methylene chloride (0.5 mL /9.5 mL)]. At 20-30 °C, reacting mass remained concentrated beneath lowered pressure. Added DW water (75 mL) into concentred mass and pH was adjusted to 2.30 with concentrated hydrochloride solution (50 mL). The reaction substance was dribbled using methylene chloride (2 × 50 mL) at 20-30 °C. Isolating aqueous layer and adjusting pH to 9.2 thru 50% aqueous solution of sodium hydroxide (15 mL) at 20-30 °C. Product was extracted into toluene (2×100 mL) in 20-30 °C and toluene layer had been segregated around 20-30 °C. In 45 °C, the toluene layer was concentrated with reduced pressure. Added acetone (75 mL) in to concentrated residue and bringing the pH to 1.0 with IPA.HCl at 20-30 °C. Product was formed and ruffled for about 30 min in 20-30 °C. The product was filtered, washed in acetone, and then dried in a vacuum oven around 50 °C to yield 15.6 grams.

Step-2: Added 2-isomer (5 gm) in to DM water (13 mL) and 25 % aqueous NaOH soln., (6 mL) in 20-30 °C. Then heated to 95-100 °C, added 1-chloro-6,6-dimethyl-2-hepten-4-yle (4.4 gm) in to above reaction mass at same temperature. Stirred for 3 hr at 95-100 °C. Reaction monitored by TLC [methanol/methylene chloride (0.5 mL/9.5 mL)]. Methylene chloride-20 mL was added to the reaction mass and agitated for 20 minutes at the same temperature before the reaction mass was segregated into an MDC and an aqueous layer that was extracted using MDC (10 mL) about 20–30 °C. Combined MDC layer and dribbled with 10 mL DM water, 15% aqueous hydrochloride solution (28 mL) and followed by DM water (1 × 10 mL) at 20-30 °C. Isolated the MDC layer also concentrated under reduced pressures at 45 °C. Added ethyl acetate (30 mL) in to concentrated mass and 2 h of reflux temperature. Then chilled to 30-40 °C and being ruffled about 30 mins. The result was filtered, and 10 mL of preheated ethyl acetate was used for rinsing. Finally, the product formed was vacuum-dried at 60 °C to yield 4.7 gm.

2.4. Preparation of 4-Methyl Terbinafine (EP impurity-D) (15):

Step-1: Added 40% (*w/w*) aqueous mono methyl amine solution (35 gm, 10 m.eq.) into sodium hydroxide (45 gm 10 m.eq.) at 20-30 °C then whisked at the steady temperature for 30 minutes. To take anhydrous monomethyl amine (40.7), then cooled to -20 to -30°C, added a lot wise 1-chloromethyl-4-methyl naphthalene (25 gm) to above reaction mass at same temperature. Added tetrahydrofuran (25 mL) to reaction mass at -20 to -40 °C and whisked to 2-3 hr at unchanged temperature. Reaction monitored by TLC [hexane/ethyl acetate (9 mL /1 mL)]. The reaction mass was amassed at 20–30 °C under decreased pressure. 200 mL of DW water and 200 mL of MDC were added to the concentrated substance at 20–30 °C. The aqueous layer was isolated and MDC layer at 20-30 °C. Aqueous Layer was extracted with MDC. Combined the MDC layer and washed with DM water at 20-30 °C. Separated the MDC layer and MDC layer was focalized in reduced pressure in 30 °C. Added acetone (75 mL) in to concentrated residue and pH was adjusted to 1.0 with IPA.HCl at 20-30 °C. Product was formed and whisked around 30 min at 20-30 °C. The substance was filtered, dribbled with acetone, then dried in a vacuum oven around 50 °C to produce 15.4 grams.

Step-2: Added 4-Methyl naphthyl intermediate (10 gm) in to DM water (25 mL) and 25 % aqueous sodium hydroxide solution (12 mL) at 20-30 °C. Then heated to 95-100 °C, added 1-chloro-6,6-dimethyl-2-hepten-4-yle (7.7 gm) in to above reaction mass at same temperature. Stirred for 3 hr at 95-100 °C. Reaction monitored by TLC [hexane /ethylacetate (9 mL 1 mL)]. Reaction mass was chilled to 20-30 °C, added methylene chloride (20 mL) and whisked around 20 min in the same temperature, isolated MDC layer and extraction of aqueous layer was performed using 10 mL MDC around 20-30 °C. Combined the MDC layer and washed with DM water (10 mL), 15% aqueous hydrochloride solution (28 mL) and followed by DM water (1 × 10 mL) at 20-30 °C. Separated MDC layer then concentrated under reduced pressures at 45 °C. Added ethyl acetate (30 mL) in to concentrated mass and reflux temperature for 2 hr. Then cooled to 30-40 °C and ruffled till 30 min. The product was filtered and rinsed using 10 mL pre heated ethyl acetate. Product vacuum dried in oven at 60 °C to obtained yield 8.7 gm.

2.5. Preparation of Naphthalene Intermediate Dimer (16):

Added chloromethyl naphthalene (50 gm) in to MDC (250 mL) about 20-30 °C then chilled to 0-5°C. Methyl amine (~ 20 gm) gas was passed to above reaction mass slowly for 2 hr at 0-5 °C. After that, the reaction product was quelled in 20 mL of DM water at the same temperature. Separate the MDC layer and washed with 5% aqueous hydrochloride solution and followed by 50 mL DM water around 20-30 °C. Separated the MDC layer and concentrated under reduced pressure at 45 °C. Added acetone (240 mL) and heated to refluxed temperature, whisked in mentioned temp., to 30mins. Chilled to 0 to 5 °C and swirled at that temperature for an hour. Strained the product and used previously cooled acetone to rinse it. Collected the acetone ML`s and concentrated under reduced pressure at 45 °C. Added n-hexane (160 mL) to above concentrated mass at 20-30 °C. Chilled up to 0-5 °C and ruffled about 30 min, strained the product and dribbled using 30 mL *n*-hexane. Product had been dried out in vacuum oven at 50 °C to obtained yield 16 gm.

2.6. Terbinafine Diene (EP impurity-E) (13):

Part-A: Added naphthalene hydrochloride intermediate (60 gm) in to DM water (150 mL) at 20-30 °C. Added 20% aqueous sodium hydroxide solution (72 mL) and methylene chloride (300 mL) at same temperature. Stirred for 30 min and separated the MDC layer at 20-30 °C. Separated the MDC layer and concentrated under reduced pressure at 35 °C. Added acrolein (16.4 gm) in to above concentrated mass at 20-30 °C and ruffled till 1 hr in same temp. Added MDC (200 mL) in to above reaction mass and stirred for 12 at 20-30 °C. Added 10% aqueous hydrochloric acid (204 mL) in to reaction mass and whisked till 30 min in 20-30 °C. Separated the aqueous layer and pH was adjusted to 9.0 with aqueous sodium hydroxide solution at 20-30 °C. Product was exerted with MDC (500 mL) at 20-30 °C. Stirred for 30 min and separated the MDC layer, concentrated under reduced pressure at 35 °C to obtained yield 56 gm.

Part-B: Added THF (95 mL) and *t*-butyl acetylene (7.6 mL) at 20-30°C within nitrogen atmosphere. Cool to -30 to -35 °C. Added *n*-butyl lithium (50 mL) in to above reaction substance between -30 to -35 °C and stirred for 1 hr same temperature. Further cooled to -40 °C and added above part-A solution [part-A (56 gm) dissolved in THF (95 mL) at 20-30 °C] in to above reaction substance for 1 hr at -35 to -40 °C. Stirred for 1 hr at same temperature. Reaction substance temperature was raised to 20-30 °C and stirred for 15 hr at 20-30 °C. Reaction substance was quenched in DM water (500 mL) at 20-30 °C and pH was attuned to 1.5 with 15% aqueous hydrochloric acid solution (50 mL) at 20-30 °C. Stirred for 30 min and separated the aqueous layer at 20-30 °C. Aqueous layer was pH was adjusted to 8.5 with 15% aqueous sodium hydroxide solution (70 mL) and MDC (400 mL) in to Reaction substance whisked for about 20 min at 20-30 °C. Segregated MDC layer and concentrated in reduced pressure at 45 °C yielding 45 gm.

To remove the water, toluene (400 mL) was added to the aforementioned remnant (42 gm) as well as PTSA (35 gm), which was then heated to reflux temperature. Afterward, it was brought down to between 20 and 30 °C and quenched in 210 mL DM water at that temperature. With 50 mL of 15% aq. NaOH solution, reaction mass pH was brought down to 8.5 at 20–30°C. At 20–30 °C, the toluene and aqueous layers were separated. MDC (300 mL) was used to remove the aqueous layer, and the MDC layer was separated at 20 to 30 °C. Blended the organic layer by carbon (5.25 gm), treated it, and whirled it for around 30 minutes at 20 to 30 °C. Hyflux bed

filtering and 50 mL of MDC cleansing at 20 to 30 °C. Total filtrate was concentrated under reduced pressure at 45 °C, obtained residue was purified by column chromatography with ethyl acetate andhexane, yields Terbinafine Diene to 25 gm.

2.7. Preparation of Terbinafine-1, 5-Dimer (12):

Step-1: Preparation of 1,5-bis (*N*-methyl amino methyl) naphthalene: Added mono methylamine (14.4 gm) in cold finger at -20 C to -15 ºC and add slowly 1-chloro methyl-4-chloro naphthalene (6.5 gm) at same temperature. Added THF (10 mL) at -20 to -15 ºC and stirred for 2 hr in same temp., to 4 hr. Substance of reaction was supervised by TLC [ethyl acetate / n-hexane, 1 mL/9 mL)]. Distilled out THF and added DM water (50 mL) under reduced pressure at 20-30 °C. Whisked for about 30 min then appended with 50 mL MDC at 20-30 °C, ruffled for about 30 min same temperature. Segregated aqueous layer and was extracted with 25 mL MDC in 20-30 °C. Separated the MDC layer and combined the MDC layer, dribbled with DM water (10 mL) at 20-30 °C. Separate the MDC layer and concentrated under reduced pressure at 30°C. Added acetone (20 mL) to above residue and stirred for 20 min at 20-30 °C. Reacting substance pH was made up to 2.09 with IPA. HCl at 20-30 ºC. Ruffled for 30 min and filtered the product and dribbled using acetone (7 mL) and product was parched in vacuum oven about 4 h in 20-30 °C to obtained yield 3.78 gm.

Step-2: Added 1,5-bis-*N*-methyl amino methyl naphthalene dihydrochloride (1 gm) in to DM water (2.5 mL) at 20-30 °C. Add 0.4% aqueous sodium hydroxide (2.1 mL) at 20-30 °C. Reaction mass temperature raised to 95-100 °C. Added slowly (2*E* and 2*Z*) 1-chloro-6,6-dimethyl-2-hepten-4-yne at 95-100 ºC for 5 min and stirred for 3 hr at 98-105 ºC. Reacting substance was monitored by TLC [Hexane: ethyl acetate; 9.5 mL: 0.5 mL)]. Cooled the reaction mass to 20-30 ºC and added ACN (4 mL) and methanol (4 mL), stirred for 1 hr at 20-30 °C. Decanted solvent from reacting substance and stirred for 15 hr at 20-30 °C. Filtered the product and washed with methanol (5 mL) at 20-30 ºC. Product was dried in vacuum at 20-30 ºC for 1 hr to obtained yield 0.4 gm. ML`s was concentrated under reduced pressure at 40-45 °C. Added methanol to the concentrated mass at 20-30 °C and ruffled to 15 hr identical temperature. Distilled out methanol to obtained yield 0.35 gm.

2.8. Preparation of Terbinafine-1,4-Dimer (11):

Step-1: Preparation of 1-bromo methyl-4-chloro methyl naphthalene: Added 1-chloromethyl-4-methylnaphthalene (12.5 gm) into carbon tetra chloride (70 mL) at 20-30 °C. Added *N*-bromo succinimide (12.8 gm, 1.195 m.eq.) and benzyl peroxide (0.4 gm, 0.025 m.eq.). Reacting substance was heated to 68-70 °C and stirred for 2 hr at identical temperature and monitored by TLC [*n*-hexane\ ethylacetate (9.5 mL\0.5 mL)]. Later the same was brought down to 10-15 °C and stirred for 1 hr at same temperature. Filtered the product and washed with carbon tetra chloride (10 mL). Wet weight: 20 gm. above product was slurry in DM water (500 mL) for 1 hr at 20-30 °C and filtered and washed with DM water (20 mL). Product was dried in vacuum oven at 16 hr at 20-30 °C to obtained yield 6.69 gm.

Step-2: Preparation of 1, 4-Bis (*N*-methyl amino methyl) naphthalene: (16): Added mono methylamine (14.4 gm) in cold finger at -20 °C to -15 °C and added slowly 1-bromo methyl-4-methyl naphthalene (6.5 gm) at identical temperature. Augmented THF (10 mL) at -20 °C to -15 °C and stirred for 2 hr at identical temperature about 4 hr. Reaction mass was monitored by TLC [ethyl acetate/*n*-hexane, 1 mL/9 mL)]. Distilled out THF and add DM water (50 mL) under reduced pressure at 20-30 ºC. Whipped around 30 min and added MDC (50 mL) to reaction mass at 20-30 °C, stirred for 30 min same temperature. Separated the aqueous layer and was extracted with MDC (25 mL) around 20-30 °C. Isolated and combined the MDC layer, rinsed with 10 mL DM water around 20-30 °C. Isolated the MDC layer and concentrated in the reduced pressure at 30 °C. Added acetone (20 mL) to above residue and ruffled for 20 min around 20-30 °C. The reaction mass pH was brought up to 2.09 with IPA. HCl at 20-30 °C. Ruffled till 30 min and strained and rinsed the product with 7 mL acetone patted to dry in vacuum oven about 4 h in 20-30°C to obtained yield 3.78 gm.

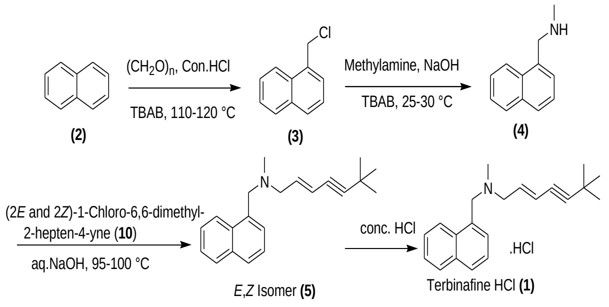
Step-3: Added 1,4-Bis-*N*-methyl amino methyl naphthalene dihydrochloride (1 gm) in to DM water (2.5 mL) at 20-30 °C. Added 0.4% aqueous sodium hydroxide (2.1 mL) at 20-30 °C. Reaction mass temperature raised to 95-100 °C. Added slowly 1-chloro-6,6-dimethyl-2-hepten-4-yne at 95-100 °C for 5 min and whisked till 2 hr around 98-105 °C. The reacting compound monitored by TLC [Hexane: ethyl acetate; 9.5

mL: 0.5 mL)]. Cooled the reacting compound to 20-30 °C and add MDC (20 mL), stirred for 20 min. Isolated MDC and aqueous layer at 20-30 °C. Aqueous layer was extracted with MDC (10 mL) and combined the MDC layer at 20-30 °C. MDC layer was dribbled with 15% aq. HCl (20 mL) trailed by 20 mL DM water around 20-30 °C. The MDC layer was segregated and concentrated under reduced pressure in 35 °C. Appended 10 mL ethyl acetate heating to reflex temperature, ruffling till 1 hr at same temperature. The reacting compound was chilled till 20-30 °C whisked around 30 min, strained product was rinsed with 4 mL ethyl acetate) , dried in vacuum in the oven at 20-30 °C to 6 hr to obtained yield 1 gm.

3. Results and Discussion

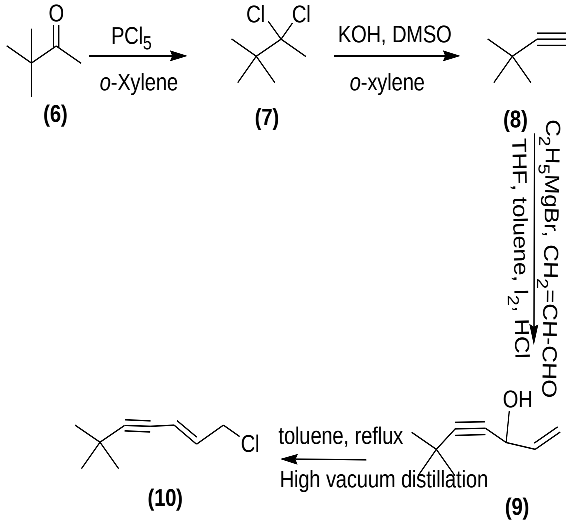
3.1 Synthesis of Terbinafine

Terbinafine hydrochloride (**1**) is produced from olefin metathesis of 1,3-dichloro propene and neohexene followed by reaction with *N*-methyl-1-naphthalene methanamin. Terbinafine hydrochloride (**1)** was synthesized according to the known literature methods,[9-10] and route of synthesis for terbinafine hydrochloride from naphthalene (**2**) is shown in **Scheme 1**. The *N*-Methyl-1-naphthylmethylamine hydrochloride (**4**) obtained from (**2**) through (**3**) by formylation and amination respectively is condensed with the 1-chloro-6,6-dimethyl-2-hepten-4-yne (2*E*/2*Z*) (**10; Scheme 2**), in presence of aqueous sodium hydroxide to produce (*E*)- and (*Z*)- isomers of *N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethyl-amine (**5**) blends. This isomeric mixture is treated with hydrochloric acid to obtain the corresponding hydrochlorides mixture. Subsequent heating with ethyl acetate results in purification to yield (*E*)-isomer of *N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine hydrochloride (Terbinafine hydrochloride, **1**).



Scheme 1: Reported synthetic rout for Terbinafine Hydrochloride (1)

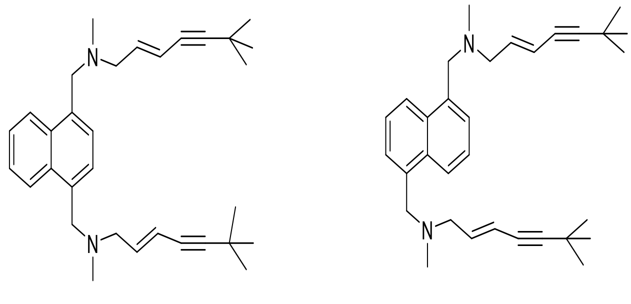
3.2. Preparation of (2E and 2Z)-1-chloro-6,6-dimethyl-2-hepten-4-yne **(10)**



Scheme 2: Reported synthetic rout for (2*E* and 2Z)-1-chloro-6,6-dimethyl-2-hepten-4-yne (10)

This paper reports the synthesis and characterization of the below unknown impurity along with four known impurities.

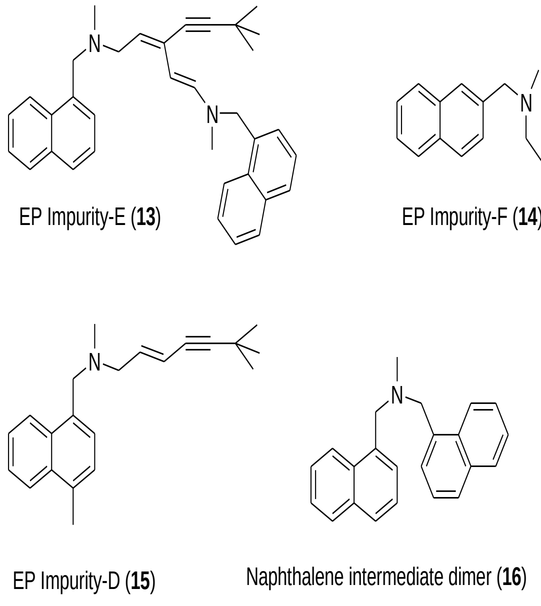
The chemical structures of the impurities listed in the European pharmacopoeia 11.0 are given below: terbinafine diene (EP impurity-E), (*E*)-2-terbinafine (EP impurity-F), EP impurity D and naphthalene intermediate dimer.



Terbinafine-1,4-dimer (11)

Terbinafine-1,5-dimer (12)

Figure 2: Structures of unknown impurities



EP Impurity-E (**13**) EP Impurity-F (**14**)

EP Impurity-D (**15**) Naphthalene intermediate dimer (**16**)

Figure 3: Structures of known impurities

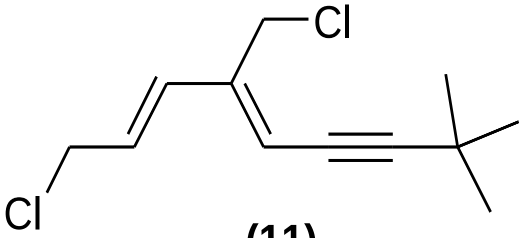
Each of these related compound's origins, synthesis, characterization, and regulation are covered in detail. Each of synthesized impurities was characterized by conventional spectroscopic studies and the presences of these impurities were confirmed by co-injection with the terbinafine hhydrochloride sample. As per the best of authors knowledge, the synthesis of these related substances was not yet reported.

3.3. Route Cause for the Formation of above-mentioned Terbinafine impurities

Terbinafine-1,4-Dimer: *N*-Methyl-1-naphthyl-methylamine hydrochloride (Terbinafine naphthalene intermediate) is used in the manufacturing of Terbinafine hydrochloride. Presence of 1,4-bis(*N*-methylaminomethyl) naphthalene hydrochloride impurity in *N*-Methyl-1-naphthylmethylamine hydrochloride results in the formation of Terbinafine-1,4-Dimer. During the preparation of *N*-Methyl-1-naphthylamine hydrochloride, formaldehyde reacted with naphthalene and there is a possibility to form 1,4-Bis (*N*-methylaminomethyl) naphthalene hydrochloride.

3.4. Terbinafine-1,5-Dimer: *N*-Methyl-1-naphthylmethylamine hydrochloride (Terbinafine naphthalene intermediate) is used in the manufacturing of Terbinafine hydrochloride. Presence of 1,5-bis(*N*-methylaminomethyl) naphthalene hydrochloride impurity in *N*-Methyl-1-naphthylmethylamine hydrochloride results in the formation of Terbinafine-1,5-dimer. During the preparation of *N*-methyl-1-naphthylamine hydrochloride, formaldehyde reacted with naphthalene and there is possibility to form 1,5-bis(*N*-methylaminomethyl) naphthalene hydrochloride.

3.5. Terbinafine Diene: The terbinafine diene impurity arises due to (2*E*, 4*E*)-1-chloro-4-(chloromethyl)-8, 8-dimethyl-2,4-nonadien-6-yne (dichloro impurity) present in tterbinafine side chain. The chemical structure of dichloro impurity is shown below. Preparation of tterbinafine side chain involves use of acrolein wherein side reactions results in formation of dichloro impurity (**Figure 4**).



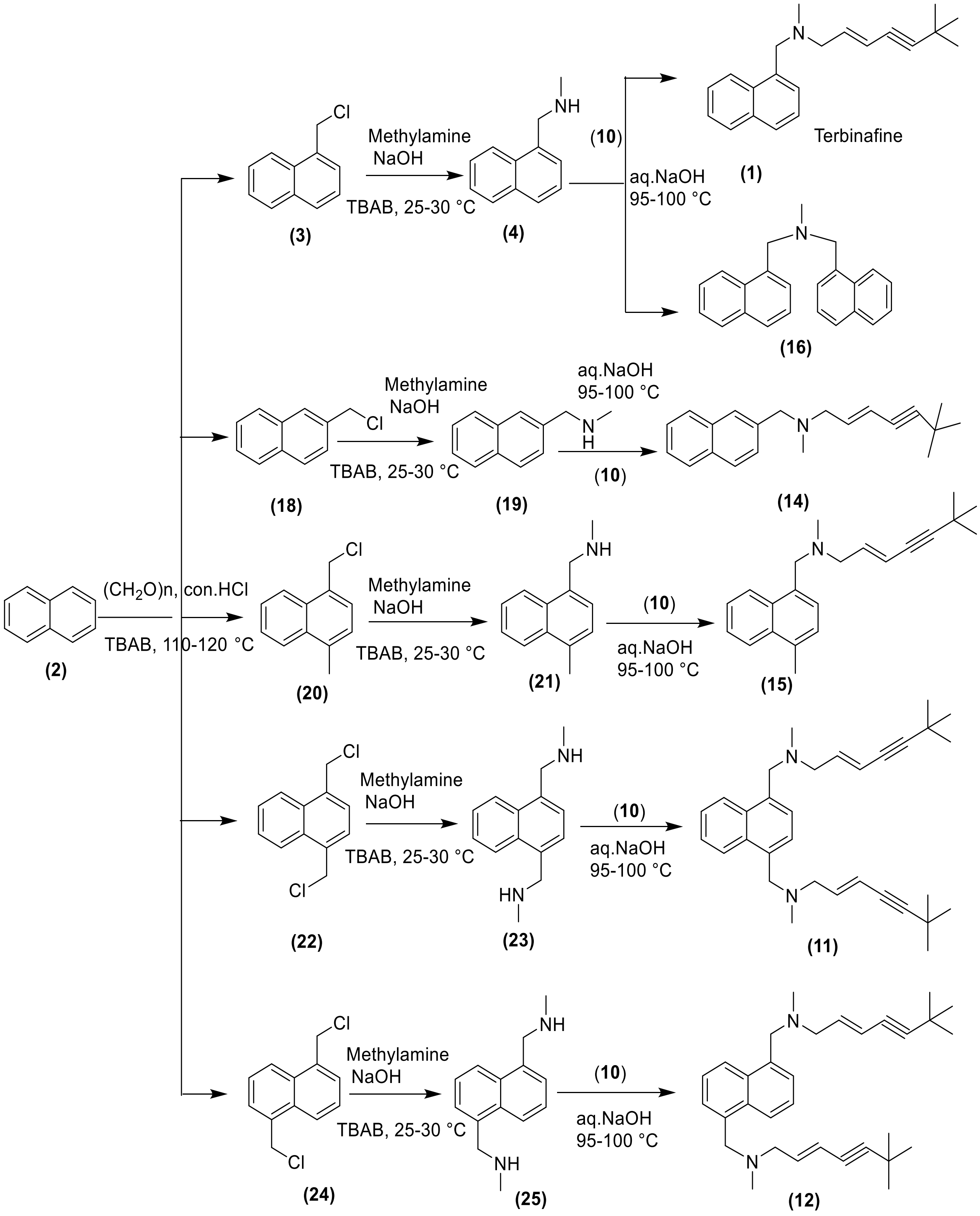
(11)

Figure 4: Dichloro impurity ((2*E*,4*E*)-1-Chloro-4-(chloromethyl)-8,8-dimethyl-2,4-nonadien-6-yne)

3.6. 4-Methylterbinafine: This arises from the condensation of 4-methylnaphthalene intermediate with (*E*)-Terbinafine side chain. The 4-methylnaphthalene intermediate is an impurity present in naphthalene intermediate raw material.

3.7. (*E*)-2-Terbinafine: This arises from the condensation of 2-isomer of naphthalene intermediate with (*E*)-terbinafine side chain. The 2-isomer is an impurity present in naphthalene intermediate raw material.

3.8. Naphthalene intermediate dimer: This is the impurity present in naphthalene intermediate raw material and may carry forward to tterbinafine hydrochloride finished product.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(2)
Cl
Methylamine
NaOH
TBAB, 25-30 °C
(3)
NH
(4)
(10)
aq.NaOH
95-100 °C
N
Terbinafine
(1)
N
(16)
Methylamine
NaOH
Cl
TBAB, 25-30 °C
(18)
N
H
(19)
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(14)
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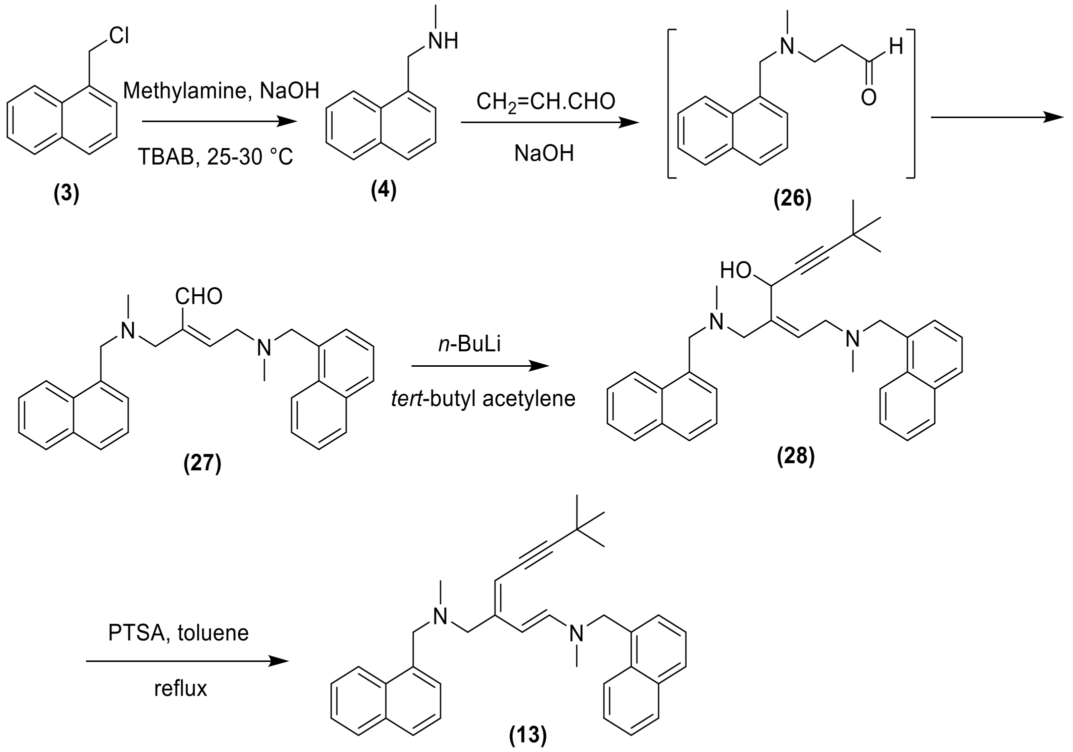
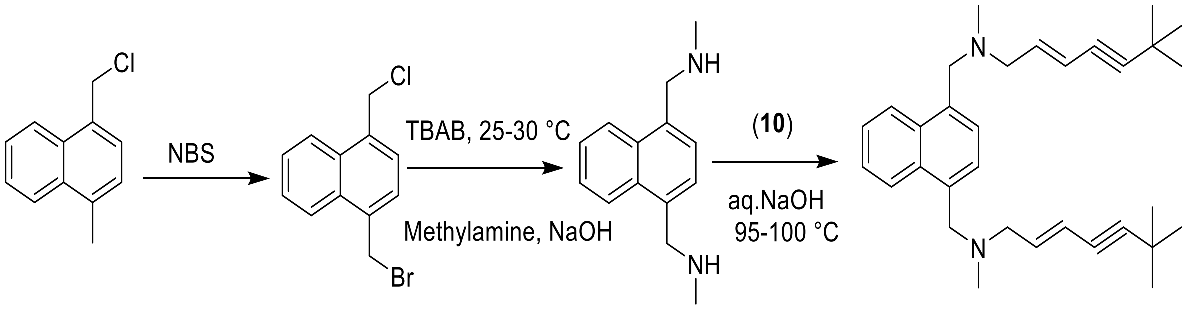
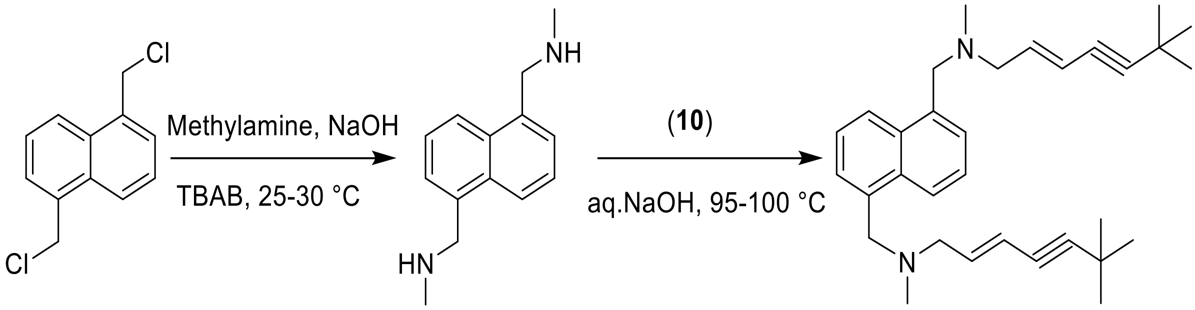


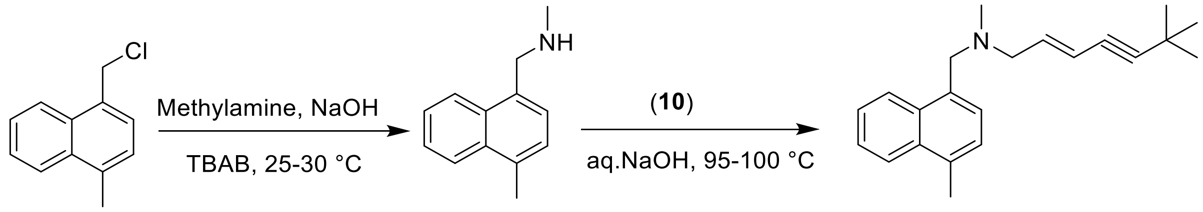
Scheme 3: Synthetic route of terbinafine diene (13) impurity.



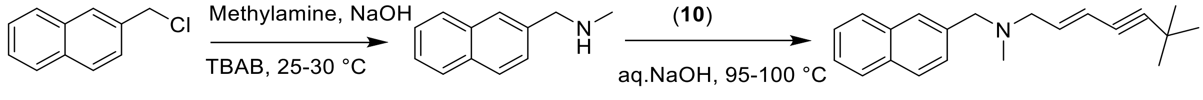
Scheme 4: Synthetic route of terbinafine-1,4-dimer (11) impurity.



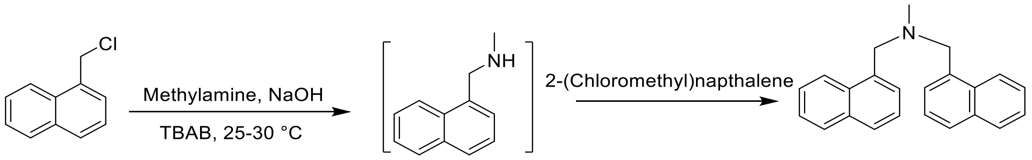
Scheme 5: Synthetic route of terbinafine-1,5-dimer (12) impurity.



Scheme 6: Synthetic route of 4-methyl terbinafine (15) impurity.



Scheme 7: Synthetic route of (*E*)-2-terbinafine (14) impurity.



Scheme 8: Synthetic route of *N*-Methyl-*N*-(2-naphthalenylmethyl)-2-naphthalene methanamine (Naphthalene intermediate dimer) (16).

3.9. Spectral characterization of impurities

2-Terbinafine (EP impurity-F) (14): M.P. 260.3 ℃; ^{1}H-NMR (DMSO-d_6, 300 MHz): 1.23 (s, 9H), 2.58 (d, 3H), 3.72-3.87 (m, 2H), 4.33-4.53 (m, 2H), 6.04 (d, *J* = 15.7 Hz, 1H), 6.17 (m, 1H), 7.58-8.13 (m, 7H ArH), 11.3 (brs, 1H, NH^{+}) **δ** (ppm); Mass: *m/z* 292.2 $[(M+H)^{+}]$. (see supplementary file: Figure 1, 2)

4-Methyl Terbinafine (EP impurity-D) (15): M.P. 284.12 ℃; ^{1}H-NMR (DMSO-d_6, 300 MHz): 1.23 (s, 9H), 2.56 (d, 3H), 2.69 (s, 3H), 3.90 (m, 2H), 4.70-4.80 (m, 2H), 6.01 (d, *J* = 15.9Hz, 1H), 6.23 (m, 1H), 7.45 and 7.82 (2d, 1H each), 7.65 (m, 2H), 8.12 and 8.36 (2m, 1H each), 11.06 (brs, 1H, NH^{+}) **δ** (ppm); Mass: *m/z* 306.5 $[(M+H)^{+}]$. (see supplementary file: Figure 3,4)

Naphthalene intermediate Dimer (16): M.P. 251.07 ℃; ^{1}H-NMR ($CDCl_{3,}$ 300 MHz): 2.25 (s, 3H), 3.97 (s, 4H), 7.23-8.06 (m, 14H) **δ** (ppm); Mass: *m/z* 312.2 [(`M+H) $^{+}$]. (see supplementary file: Figure 5, 6).

Terbinafine Diene (EP impurity-E) (13): M.P. 205 ℃; ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.34 and 137 (2s, 9H), 2.14, 2.22 and 2.29 (3s, 6H), 3.12 and 3.20 (2d, 2H), 3.26 and 3.51 (2s, 2H), 3.81, 3.89 (2s, 2H), 3.92 and 3.97 (2s, 2H), 5.70 (s, 1H), 6.05 (m, 1H), 6.21 and 6.80 (2d, *J* = 16.0 Hz, 1H), 7.36-8.31 (m, 14H, ArH) **δ**(ppm); Mass: *m/z* 501.2 $[(M+H)^{+}]$. (see supplementary file: Figure 7, 8).

Terbinafine-1,4-Dimer (11): M.P. M.P. 532.73 ℃; ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.23 (s, 18H), 2.21 (s, 6H), 3.12 (dd, 4H), 3.86 (s, 4H), 5.69 (dt, 2H) 6.14 (dt, 2H), 7.33 (s, 2H), 7.51 (dd, 2H), 8.27 (dd, 2H), **δ** (ppm), Mass: *m/z* 455 $[(M+H)^{+}]$. (see supplementary file: Figure 9, 10).

Terbinafine-1,5-Dimer (12): M.P. 532.73 ℃; ^{1}H-NMR (Acetone-d_6 + TFA, 300 MHz): 1.23 (s, 18H), 2.98 (s, 6H), 4.23 (brs, 4H), 5.14 (brs, 4H), 6.10-6.31 (m, 4H) 7.74 (t, 2H), 8.02 (d, 2H), 8.52 (d, 2H), **δ**(ppm), Mass: *m/z* 455 $[(M+H)^{+}]$. (see supplementary file: Figure 11, 12).

4. Conclusion

Two unknown impurities (terbinafine 1,4-dimer and terbinafine 1,5-dimer) was identified in terbinafine hydrochloride using HPLC with UV detection. These two impurities along with other four known impurities [terbinafine diene (EP impurity-E), (*E*)-2-terbinafine (EP impurity-F), EP impurity D and naphthalene

intermediate dimer] were synthesized and characterized using spectroscopic analyses, such as ^{1}H NMR and mass analysis. Using data obtained, the structures of the compound elucidated accurately.

Conflicts of Interest

None of conflicts of interest exist in this investigation.

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