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Original Article

Design Synthesis and Characterization of Some Impurities of Miconazole

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ABSTRACT

Background: The quality, safety, and regulatory compliance of miconazole, a broad-spectrum imidazole antifungal agent, depend on the identification and control of process and degradation-related impurities. According to International Council for Harmonization (ICH) guidelines, well-characterized impurity reference standards are essential for impurity profiling, analytical method development, and quality assurance. **Objectives:** In order to develop reliable impurity reference standards for pharmaceutical quality control and regulatory compliance, the present study aimed to synthesize, purify, and characterize four miconazole-related impurities. **Materials and Methods:** A series of organic synthesis reactions, including α-bromination, reduction, epoxidation, epoxide ring-opening, and Williamson ether synthesis, were employed to prepare four miconazole-related impurities: Miconazole European Pharmacopoeia (EP) Impurity A, Miconazole EP Impurity H, Miconazole Impurity B, and Miconazole Impurity D. The synthesized compounds were purified using appropriate purification techniques and characterized by Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR), and Mass Spectrometry (MS). Their physicochemical properties, including molecular formula, molecular weight, melting point, and percentage yield, were also evaluated. **Results:** All four specified miconazole-related impurities were successfully synthesized, purified, and obtained in acceptable yields. The proposed chemical structures of each impurity were confirmed by spectroscopic characterization using FTIR, ^{1}H NMR, ^{13}C NMR, and MS. The analytical data confirmed the successful synthesis and structural characterization of the miconazole impurity reference standards. **Conclusion:** The developed synthetic pathways provide efficient and reproducible methods for the preparation of significant miconazole-related impurities. The impurity reference standards support impurity identification, analytical development, quality control, and regulatory compliance.

Keywords: Antifungal agents, Chemical synthesis, Impurity profiling, Miconazole, Spectrum analysis.

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INTRODUCTION

Purity of a drug product means the percentage of drug active substances determined by an analytical technique. if the drug substance contains impurities that have pharmacological or toxicological properties more potent than those of the drug substance, then the Active Pharmaceutical Ingredient (API) may occur declared crude even when the impurities have no effect on quality of the drug. The identification of contaminants in active pharmaceutical ingredients and the requirement to guarantee their purity are becoming important to regulatory organizations including Health Canada, The United States Food and Drug Administration (USFDA) and International Council for Harmonization (ICH).[1-4] A key part of impurity profiling involves the synthesis process, which ensures the material achieves the intended structure. Comparing the retention and spectral properties of the material together with those of the impurity being several studied can be useful in developing and validating analytical methods. studies have described a method for identifying and isolating impurities and breakdown products related to the manufacturing process in pharmaceutical compounds. these studies make use of analytical systems, including MS, NMR, and Fourier Transform Ion Cyclotron Resonance (FTICR).[5-7] Both Pharmacopoeial and non-pharmacopeial organizations provide available materials for impurity analysis in pharmaceutical products. However, their synthesis and purifying process is rarely described in depth. Although they are not commonly utilized,

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straightforward and successful purification approaches for these reference standards can offer an affordable substitute for the chromatographic methods previously discussed.[8] Miconazole is an imidazole-type antifungal agent that is used to treat fungal infections due to *dermatophytes, Candida* species and other pathogenic fungi.[9] The chemical structure of Miconazole is shown in (Figure 1). Miconazole is an imidazole antifungal agent that works by inhibiting the biosynthesis of ergosterol in fungi by inhibiting 14α-demethylase, which disrupts the integrity of the fungal cell membrane and inhibits fungal growth.[10] Miconazole is widely used as an antifungal agent for the treatment of fungal infections. It is essential to ensure that Miconazole retains its quality, stability, and purity throughout its entire shelf life to provide patients with safe and effective treatment.[11] The synthesis of Miconazole impurities involves multiple important chemical reactions, including α-bromination,[12,13] reduction,[14] epoxide formation, and epoxide ring opening, as shown in (Figure 2). The Williamson ether synthesis pathway[15,16] for the preparation of Miconazole EP Impurity H, Miconazole Impurity B, and Miconazole Impurity D is shown in (Figure 3). All impurities synthesis method related research paper was not found and it's marketed by some companies and available commercially. These impurities are process related impurities and their safety thresholds and acceptable limit has specified by ICH And other guideline The aim of this study was to synthesize selected Miconazole impurities and characterize them using analytical techniques.

MATERIALS AND METHODS

Chemicals and Solvents

All chemicals and solvents used in this study were of analytical grade. Methanol (MeOH), ethyl acetate, hexane, Dichloromethane (DCM), N,N-dimethylformamide (DMF), and Tetrahydrofuran (THF) were purchased from Advent Chembio Pvt. Ltd., Mumbai, India. 2,4-Dichloroacetophenone, bromine, Sodium Borohydride ($NaBH_4$), Sodium Hydride (NaH), imidazole, benzyl bromide, 4-chlorobenzyl bromide, 2,6-dichlorobenzyl bromide, and acetone were purchased from BLD PharmTech Private Limited, Hyderabad, India. Sodium sulfate and sodium thiosulfate were obtained from Merck Specialities Pvt. Ltd., Mumbai, India. Glacial acetic acid was used for the synthesis reactions.

Miconazole Impurity A was synthesized in four steps

Step 1. Synthesis of 2-bromo-1-(2,4-dichlorophenyl) ethan-1-one

A solution of 2,4-dichloroacetophenone (10 g, 0.528 mol) in acetic acid (50 mL) was prepared under cooling and stirred for 10-15 min. Bromine (2.7 mL) was introduced dropwise with stirring, after which the reaction was allowed to proceed overnight at Room Temperature (RT). the progress of the reaction was monitored by Thin-Layer Chromatography (TLC) using hexane as the mobile phase. After the reaction was finished, the mixture was diluted with water and quenched with sodium thiosulfate. Extraction with ethyl acetate followed by concentration under reduced pressure afforded the desired compound in 70.35% yield.

Step 2. Synthesis of 2-bromo-1-(2,4-dichlorophenyl) ethan-1-ol

The crude intermediate, 2-bromo-1-(2,4-dichlorophenyl) ethan-1-one (5 g,0.186 mol), obtained in the previous step, was stirred in methanol (40 mL). Sodium borohydride (0.750 mg,0.01982 mol) was added dropwise to the stirred reaction mixture, and the mixture was stirred for 10 min. The mixture was allowed to react at RT for 2 hr. The progress of the reaction was monitored using (TLC) with MeOH/DCM (5:95, v/v) as the mobile phase. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, extracted with ethyl acetate, and the final compound was obtained in 69% yield.

Step 3. Synthesis of 2-(2,4-dichlorophenyl)oxirane

The raw material from Step 2, 2-bromo-1-(2,4-dichlorophenyl) ethan-1-ol (4.476g 0.0167 mol), was dissolved in THF (40 mL) and stirred for 5-10 min. Sodium hydride (0.801mg,0.0333 mol) was then added in small portions under controlled conditions. Subsequently, the reaction was carried out at RT for 2 hr with stirring. The reaction was followed by TLC with the mobile phase being MeOH/DCM (5:95, v/v). After completion of the reaction, the mixture was quenched with water, extracted with ethyl acetate, and concentrated under reduced pressure to afford the final compound in 45% yield.

Step 4. Synthesis of Impurity A

The crude product from Step 3, 2-(2,4-dichlorophenyl)oxirane (3.156 g,0.0117mol) was dissolved in THF (40 mL) under cooling. Imidazole (0.880 mg,0.0129mol), was added gradually, and the reaction mixture was stirred for 5 min. Sodium hydride (0.880 mg, 0.0366 mol), was added portion-wise under cooling with stirring. the reaction mixture was stirred at RT for 2 hr 30 min. the reaction progress was monitored by TLC using MeOH/DCM (5:95, v/v) as the mobile phase. After completion the reaction was quenched with water, followed by extraction with ethyl acetate. The organic phase was concentrated under reduced pressure to obtain the desired product Column chromatography was performed on silica gel g (100-200 mesh) using methanol/DCM (2:98, v/v) as the mobile phase. The desired fractions were identified by TLC and concentrated to obtain the purified compound in 55.57% yield.

Step 5. Synthesis of Miconazole Impurity H

1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-ol (Miconazole Impurity A)

(2 g, 0.0072 mol) was added to 10 mL of DMF and stirred until dissolved. At RT, sodium hydride (0.373 mg, 0.155 mol), was added portion-wise with stirring, followed by addition of benzyl bromide (1.208 g, 0.0076 mol), and stirring for 5-10 min. The reaction mixture was stirred overnight at RT until completion. Reaction progress was monitored by TLC using MeOH/DCM (5:95, v/v) as the mobile phase. After completion, the reaction was quenched with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the final compound. Column chromatography was performed on silica gel (100-200 mesh) using methanol/DCM (1:99, v/v) as the mobile phase. The desired fractions were identified by TLC and concentrated to obtain the purified compound in 55.55% yield.

Step 6. Synthesis of Miconazole Impurity B

1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol (Miconazole Impurity A) (2.5g), (0.0097 mol) and N,N-dimethylformamide (20 mL) were taken in a Round-Bottom Flask (RBF) and stirred until dissolved. After cooling, sodium hydride (0.466 mg) was added portion-wise with stirring. After 10 min, 4-chlorobenzyl bromide (1.99 g, 0.0096 mol) was added under cooling. After brief stirring of the reaction mixture under cooling, the cooling was stopped, and the reaction was allowed to proceed at RT for 2 hr. The reaction progress was monitored by TLC using MeOH/DCM (5:95, v/v) as the mobile phase. After completion of the reaction, the reaction mixture was extracted with ethyl acetate and water. The organic layer was separated and dried to remove residual moisture, and the final product was obtained by concentration under reduced pressure. Column chromatography was performed on silica gel (100-200 mesh) using methanol/DCM (1:99, v/v) as the mobile phase. The desired fractions were identified by TLC and concentrated to obtain the purified compound in 37.63% yield.

Step 7. Synthesis of Miconazole Impurity D

Miconazole Impurity A (2.5 g, 0.0097 mol) was dissolved in DMF (20 mL) in a Round-Bottom Flask (RBF). After cooling, sodium hydride (0.466 mg,0.0194 mol) was added portion-wise with stirring. After 10 min, 2,6-dichlorobenzyl bromide (2.32 g, 0.009 mol) was added under cooling. The reaction mixture was stirred at RT for 2 hr. The reaction progress was monitored by TLC using MeOH/DCM (5:95, v/v) as the mobile phase. After completion of the reaction, the reaction mixture was extracted with ethyl acetate and water. The organic layer was separated and dried to remove residual moisture, and the final product was obtained by concentration under reduced pressure. Column chromatography was performed on silica gel (100-200 mesh) using methanol/DCM (1:99, v/v) as the mobile phase. The desired fractions were identified by TLC and concentrated to obtain the purified compound in 19.75% yield.

Analytical Method

Chromatography using thin layers

A silica gel-coated metal sheet was employed for the TLC investigation. By using ultraviolet light to examine the TLC plates, the spots were made apparent.

Infrared spectroscopy

Using Potassium Bromide (KBr) pellets and a JASCO FTIR-4100 spectrophotometer as the sample preparation technique, the infrared spectra of the produced compounds were acquired. The results were given in wavenumbers (cm^{-1}).

Mass Spectrometry

A Bruker Impact HD mass spectrometer was used to gather the mass spectra.

Nuclear Magnetic Resonance Spectroscopy

The ^1H NMR spectra were obtained using a 400 MHz NMR spectrometer, with the solvent chosen based on the solubility of the synthesized compounds, either deuterated Chloroform ($CDCl_3$) or deuterated Dimethyl Sulfoxide (DMSO-d_6). Chemical shifts are measured in parts per million (ppm) and use Tetramethyl Silane (TMS) as the reference standard.

Ethics statement

This study did not involve human participants, animals, or human/animal biological samples. Therefore, ethical approval and informed consent were not required.

Statistical analysis

Statistical analysis was not applicable to this study because the work focused on chemical synthesis and structural characterization rather than experimental comparison.

CHARACTERIZATION OF COMPOUNDS

Spectral Data of Miconazole EP Impurity A

The solid-state IR spectrum (cm^{-1}) reveals an O-H and aromatic C-H stretching band at 3107.72-2850.27 cm^{-1}, aromatic C=C and imidazole ring stretching at 1600.44-1550.49 cm^{-1}, CH_2 bending at 1508.06 cm^{-1}, C-N stretching at 1233.25-1082.83 cm^{-1}, C-O stretching at 1148.08-1046.12 cm^{-1}, and aromatic C-H bending and C-Cl stretching at 912.52-789.27 and 644.64 cm^{-1}, respectively. The ^1H NMR spectrum (400 MHz, DMSO-d_6) exhibits the following peaks: δ 7.59-7.60 ppm (singlet, 1H, imidazole H-2), 7.43-7.46 ppm (multiplet, 3H, 2,4-dichlorophenyl), 6.83-7.04 ppm (multiplet, 2H, imidazole), 6.02-6.03 ppm (singlet, 1H, OH), 5.05-5.09 ppm (multiplet, 1H, CH-OH), and 4.14-4.19 ppm

(multiplet, 2H, CH_2-N. The observed chemical shifts and splitting pattern confirmed the proposed structure of Miconazole EP Impurity A. The ESI-MS spectrum showed a major peak at m/z 257.6**,** consistent with the calculated molecular weight of 257.1 g/mol, supporting the proposed molecular formula and structure.

Spectral Data of Miconazole EP Impurity H

The FTIR spectrum of Miconazole Impurity H confirmed the structure of Miconazole Impurity H with characteristic absorption bands at 3058.55-2807.85 cm-^{1} (aromatic C-H stretching), 1685.48-1587.84 cm^{-1} (aromatic C=C and imidazole ring stretching), 1495.40-1431.89 cm-1 (CH_2 bending), 1290.36 cm-^{1} (C-N stretching), 1184.08-1043.00 cm^{-1} (C-O-C and C-O stretching), 912.52-789.27 and 644.64 cm^{-1} (aromatic C-H bending and C-Cl stretching). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) exhibited characteristic peaks at δ 7.42-7.46 (m, 1H), 7.28-7.35 (m, 5H), 7.14-7.17 (d, 2H), 7.02 (s, 1H, imidazole), 6.90 (s, 2H, imidazole), 4.96-4.99 (m, 1H, CH-O), 4.44-4.47 (s, 2H, OCH_2), and 4.16-4.25 (m, 2H, CH_2-N), confirming the proposed structure of Miconazole EP Impurity H. The ESI-MS spectrum showed a major peak at m/z 347.6, consistent with the molecular weight of 347.2 g/mol, supporting the proposed structure.

Spectral Data of Miconazole Impurity B

FTIR Spectrum: 3119.39, 3059.51 cm^{-1} (stretching of aromatic C-H), 2944.77, 2878.24 cm^{-1} (stretching of aliphatic C-H), 1671.98, 1591.95 cm^{-1} (stretching of aromatic C=C and imidazole ring), 1460.41 cm^{-1} (bending of CH_2), 1353.78, 1263.12 cm^{-1} (stretching of C-N), 1184.4, 1095.52, 1032.65 cm^{-1} (stretching of C-O-C), 1008.29 cm^{-1} (vibration of imidazole ring), 906.29, 789.85 cm^{-1} (bending of aromatic C-H), 628.68, 574.83, 529.58, 494.66 cm^{-1} (stretching of C-Cl).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H, imidazole H-2), 7.66-7.67 (s, 1H, 2,4-dichlorophenyl), 7.40-7.49 (d, 2H, 2,4-dichlorophenyl), 7.33-7.37 (m, 3H, benzyl ring), 7.18-7.20 (d, 2H, aromatic protons), 6.86-7.04 (d, 2H, imidazole), 4.98-5.01 (m, 1H, CH-O), 4.39-4.43 (s, 2H, OCH_2), and 4.21-4.32 (m, 2H, CH_2-N). confirming the proposed structure of Miconazole EP Impurity B. The ESI-MS spectrum showed a major peak at m/z 383.4, consistent with the expected molecular mass (381.07 g/mol) of the synthesized compound, supporting its proposed structure.

Spectral Data of Miconazole Impurity D

FTIR Spectrum: 3157.86, 3073.98 cm^{-1} (aromatic C-H stretching), 2940.91, 2895.95 cm^{-1} (aliphatic C-H stretching), 1679.31, 1501.89 cm^{-1} (aromatic C=C and imidazole ring stretching), 1437.67, 1350.89cm^{-1} (CH_2 bending), 1322.66, 1221.98 cm^{-1} (C-N stretching), 1095.21, 1045.72, 999.53 cm^{-1} (C-O/C-O-C stretching), 899.63, 738.60, 699.76 cm^{-1} (aromatic C-H bending), and 617.03 cm^{-1} (C-Cl stretching).

The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) exhibited characteristic peaks at δ 7.67 (s, 1H, imidazole), 7.44-7.46 (m, 3H), 7.47-7.49 (m, 2H), 7.35-7.39 (s, 1H), 6.83-7.01 (d, 2H, imidazole), 5.04-5.07 (m, 1H, CH-O), 4.53-04.63 (m, 2H, O-CH_2), and 4.19-4.21 (m, 2H, CH_2-N), confirming the proposed structure of Miconazole EP Impurity D. The ESI-MS spectrum showed a major peak at m/z 417.4, consistent with the expected molecular mass of 416.1 g/mol, supporting the proposed structure.

RESULTS

The proposed synthetic pathways were used to create Miconazole EP Impurity A, H, B, and D. these impurities act as a process related synthesis intermediate or impurities tract during quality control and regulatory filing of azole antifungal drugs across global market like the European Medicine Agency EMA, USP, Japanese pharmacopoeia JP and BP asper ICH Q3A/Q3B guidelines its regulatory relevance canter on strict pharmacopeial specification limit (Not more than 0.25%) All synthesized impurities were purified by column chromatography and their ^{1}H NMR and

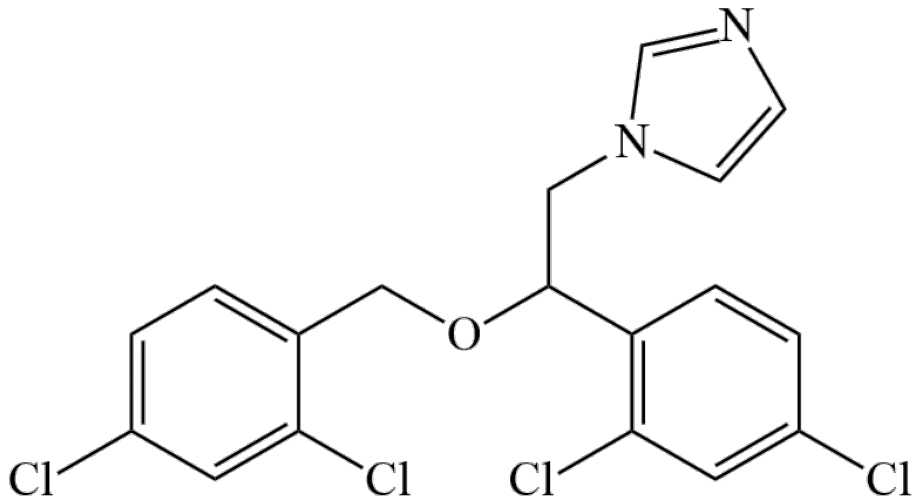
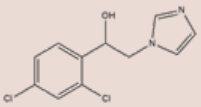
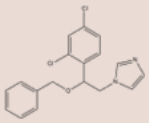
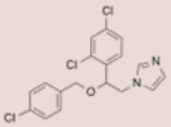
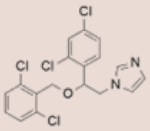


Figure 1: Chemical structure of Miconazole.

Table 1: Physicochemical properties of synthesized miconazole impurities

Sl. No.	Designation of Impurity	Structural and IUPAC Name	M.F	M.W (g/mol)	Appearance	Yield (%)	MP
1.	Miconazole Impurity A	 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl) ethan-1-ol	$C_{11}H_{10}Cl_2N_2O$	257.1	Orange solid Crystalline Powder	57.63%	134-137°C
2.	Miconazole Impurity H	 1-[2-(benzyloxy)-2-(2,4-Dichlorophenyl) ethyl]-1H-imidazole	$C_{18}H_{16}Cl_2N_2O$	347.2	Pale Yellow Oil	55.55%	205-207 °C
3.	Miconazole Impurity B	 1-{2-[(4-chlorophenyl) methoxy]-2-(2,4-dichlorophenyl) ethyl}-1H-imidazole	$C_{18}H_{15}Cl_3N_2O$	381.7	Pale Yellow Thick Oil	37.63%	115-120 °C
4.	Miconazole Impurity D	 1-{2-(2,4-dichlorophenyl)-2-[(2,6-dichlorophenyl) oxy] ethyl}-1H-imidazole	$C_{18}H_{14}Cl_4N_2O$	416.1	White Crystalline Powder	19.75%	170-185 °C

Note. M.F. = Molecular Formula; M.W. = Molecular Weight; MP = Melting Point. Molecular weight values are reported in g/mol.

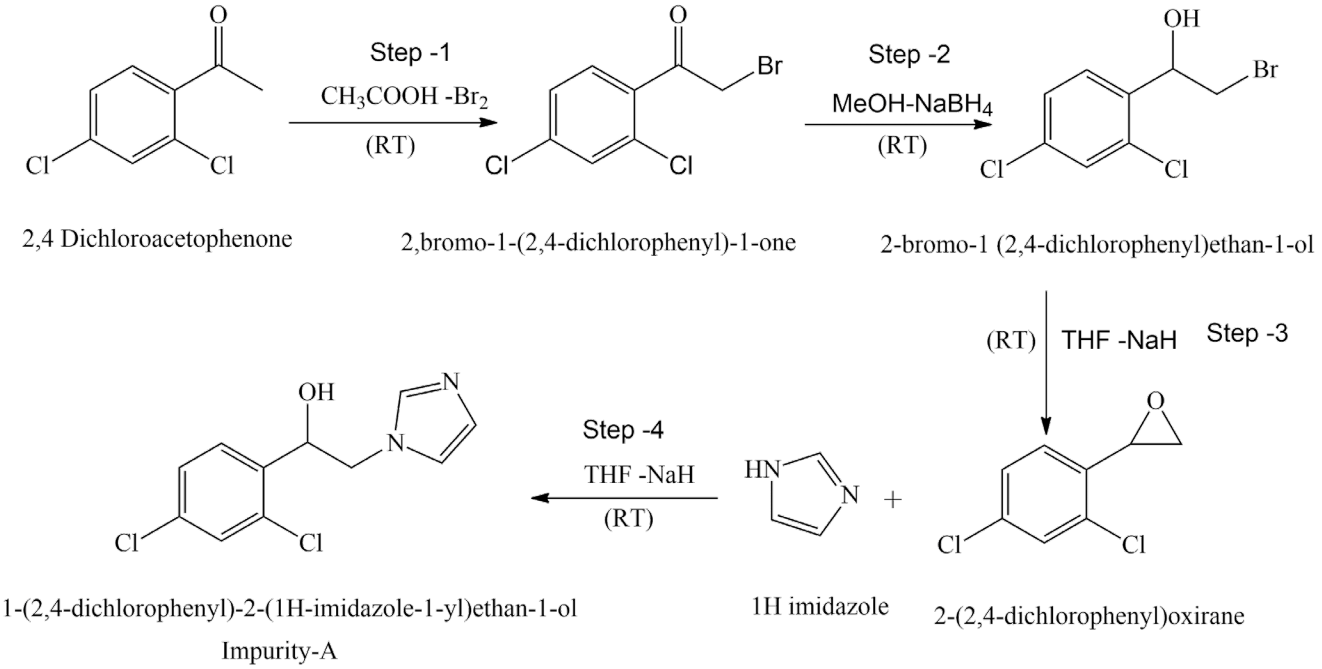


Figure 2: Synthetic scheme for Miconazole EP Impurity A.

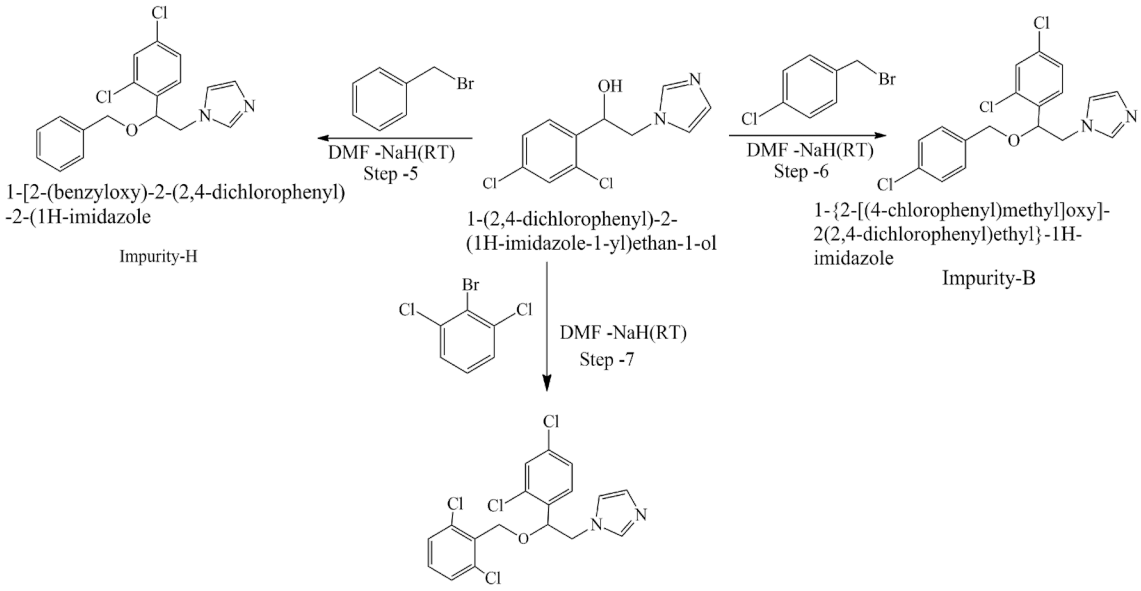


Figure 3: Synthetic scheme for Miconazole EP Impurities H, B, and D.

Mass spectrometry data met the structure elucidation criteria. The physicochemical properties of the synthesized Miconazole impurities are summarized in Table 1. The percentage yields obtained were 57.63% (Impurity A), 55.55% (EP Impurity H), 37.63% (Impurity B), and 19.75% (Impurity D). Miconazole EP Impurity A, with the molecular formula $C_{11}H_{10}Cl_2N_2O$, exhibited a mass at m/z 257.1 and the ^{1}H NMR spectrum matched all the 10 protons in the structure. The mass spectrum of Miconazole EP Impurity H, $C_{18}H_{16}Cl_2N_2O$, exhibited a peak at m/z 347.2 and the ^{1}H NMR spectrum was consistent with the observed proton integration corresponded to 16 protons in the molecule. Miconazole EP Impurity B, $C_{18}H_{15}Cl_3N_2O$ exhibited a peak at m/z 381.7 and the ^{1}H NMR spectrum was consistent with the presence of 15 protons in the structure. Miconazole EP Impurity D, $C_{18}H_{14}Cl_4N_2O$ exhibited a peak at m/z 416.1 and the ^{1}H NMR spectrum was consistent with the observed proton integration corresponded to 14 protons in the molecule. the ^{1}H NMR and mass spectrometry data showed that all synthesized Miconazole impurities have been successfully synthesized and structurally characterized.

DISCUSSION

In the present research work, four Miconazole impurities namely Miconazole EP Impurity A, H, B, and D were successfully synthesized. The developed synthetic procedures are simple, efficient, and can be used for laboratory-scale synthesis. These techniques can be helpful to researchers in the synthesis of impurities and pharmaceutical analysis. The synthesized impurities were purified by column chromatography and the purity was checked by single-spot TLC. The FTIR spectroscopy confirmed the presence of the expected functional groups and the MS and ^{1}H NMR spectroscopy were consistent with the proposed chemical structures, which confirmed the successful synthesis and structural characterization of all the synthesized impurities.

CONCLUSION

A multi-step synthetic route was successfully employed to synthesize Miconazole EP Impurity A from 2,4-dichloroacetophenone through α-bromination, reduction, epoxide formation and epoxide ring-opening reaction with imidazole. The synthesized impurity was successfully purified and characterized. Additionally, Miconazole EP Impurity H was synthesized by Williamson ether synthesis (O-benzylation) using benzyl bromide in the presence of sodium hydride and DMF. Furthermore, Miconazole Impurity B and Miconazole Impurity D were synthesized by alkylation reactions using substituted benzyl bromide derivatives to obtain the corresponding ether impurities. TLC was used to verify the completion of the reaction and the purity of the produced compounds, while column chromatography was employed to purify the synthesized impurities. Therefore, the synthesized impurities can be used for impurity profiling and identification, analytical method development, quality control and regulatory studies of Miconazole. Future studies on process optimization and impurity assessment in the development of antifungal drugs may benefit from this work.

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ABBREVIATIONS

ICH: International Council for Harmonisation; **USFDA:** United States Food and Drug Administration; **API:** Active Pharmaceutical Ingredient; **EP:** European Pharmacopoeia; **RBF:** Round Bottom Flask; **DMF:** Dimethylformamide; **RT:** Room Temperature; **TLC:** Thin Layer Chromatography; **THF:** Tetrahydrofuran; **DCM:** Dichloromethane; **MeOH:** Methanol; **$NaBH_4$:** Sodium Borohydride; **NaH:** Sodium Hydride; **NMR:** Nuclear Magnetic Resonance; **^1H NMR:** Proton Nuclear Magnetic Resonance; **MS:** Mass Spectrometry; **FTIR:** Fourier Transform Infrared Spectroscopy; **FTICR:** Fourier Transform Ion Cyclotron Resonance; **ESI-MS:** Electrospray Ionization Mass Spectrometry; **MF:** Molecular Formula; **MW:** Molecular Weight; **MP:** Melting Point; **BP:** Boiling Point; **eq.:** Equivalent; **$CDCl_3$:** Deuterated Chloroform; **DMSO-d_6:** Dimethyl Sulfoxide-d_6; **TMS:** Tetramethylsilane.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL AND CONSENT

Ethics approval and consent was not required.

DATA AVAILABILITY AND CONSENT

The datasets generated during the current study are available from the corresponding authors request and also the data has submitted to journal as supplementary file.

AUTHORS CONTRIBUTION

Conceptualization: Dr Amit Suryakant Tapkir, Dr Ashok Bhau Pathak, Sandip Murlidhar Bhagat. **Methodology:** Dr. A. S. Tapkir, Dr. A. B. Pathak. **Synthesis:** S.R. Pawara, S.M. Bhagat. **Characterization:** S.R. Pawara. Dr. A. S. Tapkir, Dr. A. B. Pathak. **Writing -Original Draft:** S.R. Pawara. **Formal Analysis:** Dr. A. S. Tapkir, S. N. Rashinkar, Dr. P. D. Choudhary. **Data Curation:** Dr. A. S. Tapkir. Investigation: Dr. A. S. Tapkir. **Writing -Review & Editing:** S.R. Pawara, Dr. A. S. Tapkir, Dr. P. D. Choudhary. All the authors approved the final manuscript.

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