

Synthesis and characterisation of s - luliconazole active pharmaceutical ingredient

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Abstract

Heterocyclic compounds play a crucial role in medicinal chemistry due to their wide range of biological activities, with imidazole being a prominent scaffold in many therapeutic agents. The present study focuses on the synthesis, characterization, and enantiomeric resolution of S-luliconazole, a potent imidazole-based antifungal drug widely used for the treatment of dermatophytic and candidal infections. Luliconazole, a chiral molecule with multiple stereoisomers, exhibits significant differences in pharmacological activity depending on its stereochemistry, with the active enantiomer showing superior efficacy. Two synthetic approaches were evaluated for the preparation of luliconazole, emphasizing scalability, yield, and environmental compatibility. The synthesized compound was characterized using advanced analytical techniques including Nuclear Magnetic Resonance (NMR), High Performance Liquid Chromatography (HPLC), and Gas Chromatography–Mass Spectrometry (GC-MS), confirming its structural integrity and high purity. The HPLC analysis indicated a purity of 96.76%, while mass spectral data confirmed the presence of dichloro-substituted molecular features. NMR studies further validated the aromatic and heterocyclic framework of the compound. Additionally, efficient enantiomeric separation was achieved using modern chromatographic techniques, highlighting the importance of chirality in drug development. The study also emphasizes the application of green and scalable synthetic strategies for industrial production. Overall, the results demonstrate that S-luliconazole possesses significant potential as an effective antifungal agent, and the developed methodology provides a reliable and sustainable approach for its synthesis and analysis.

Keywords:

Imidazole, Luliconazole, Chiral resolution, Antifungal activity, HPLC, NMR spectroscopy, GC-MS, Heterocyclic compounds, Enantiomers, Green synthesis, Pharmaceutical analysis.

Introduction

Heterocycles are among the most extensively used scaffolds in drug and agrochemical development, representing a major research area in medicinal chemistry. Many marketed drugs are heterocyclic, including Indomethacin (indole), Nitrofurantoin (furan), Tolmetin (pyrrole), Ethosuximide (pyrrolidine), and Pyrantel (thiophene) [1,2,3]. Imidazole, a five-membered aromatic heterocycle with nitrogen atoms at positions 1 and 3, can form hydrogen bonds due to its electron-rich environment, improving aqueous solubility in many drug molecules [4,5].

Imidazole moieties are found in several bio-relevant compounds like purines, histidine, vitamin B12, and co-factors [6,7]. Their amphoteric nature and ability to participate in hydrogen bonding, π - π interactions, and metal coordination make them highly interactive with biological targets [8]. This privileged structure is widely used in pharmaceuticals, agrochemicals, biomimetics, and supramolecular chemistry [9,10].

Imidazole is also considered a bioisostere of other heterocycles such as pyrazole, oxazole, triazole, and thiazole, modulating both pharmacological and physicochemical profiles [11,12]. Several imidazole-based molecules have demonstrated diverse biological activities such as antibacterial, antifungal, antitubercular, antimalarial, anti-HIV, anti-Alzheimer, antioxidant, and anticancer properties [13,14,].

Luliconazole (LLZ) is a topical imidazole antifungal agent active against *Trichophyton* spp. and other pathogenic fungi. It functions by inhibiting the 14 α -demethylase enzyme in ergosterol biosynthesis [15]. However, LLZ is poorly water-soluble and highly lipophilic, leading to efforts for enhanced delivery using nanocarriers to improve solubility, permeability, and skin retention [16].

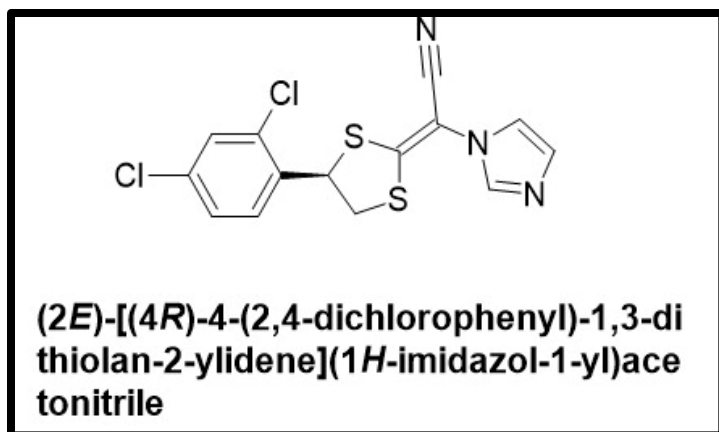


Fig.1: Structure of S-Luliconazole

Most analytical studies use RP-HPLC for luliconazole determination, though UV methods are also reported. Quantification is mostly in raw materials and formulations, with limited data in biological matrices [17]. LLZ demonstrates superior pharmacokinetics compared to older imidazoles [18].

Being a chiral drug with one chiral center and a double bond, LLZ exists as four stereoisomers: RZ(+), SZ(-), RE(+), and SE(-), with only RE(+) being pharmacologically active [19,20]. The drug was first launched in Japan (2005) and approved by the FDA in 2013 [21].

Chiral resolution is vital as stereoisomers differ in pharmacokinetics, pharmacodynamics, and toxicity [22,23]. Although chiral HPLC and CE methods exist, very few are reported for all four stereoisomers of LLZ [24,25].

Supercritical Fluid Chromatography (SFC) is an emerging green technique that offers rapid separation using CO₂ with polar organic modifiers, reducing solvent use and improving efficiency [26,27]. Chiralpak IH columns have been employed for LLZ isomer separation. Studies were also carried out to examine the role of temperature, pressure, and mobile phase in enantioselective resolution and thermodynamic behavior [28].

Applications of S-Luliconazole

1. Treatment of Dermatophytosis

S-Luliconazole is highly effective against dermatophytes such as *Trichophyton rubrum* and *Trichophyton mentagrophytes*, which are responsible for infections like:

- **Tinea pedis** (athlete's foot)
- **Tinea cruris** (jock itch)
- **Tinea corporis** (ringworm of the body)

2. **Treatment of Candidiasis**

It shows strong activity against various *Candida* species, especially **Candida albicans**, making it useful for: Cutaneous candidiasis and Intertrigo (in skin folds)

3. **Onychomycosis (Nail Fungal Infections)**

Though primarily topical, its potent antifungal action and skin penetration suggest its potential in early or adjunctive therapy for nail infections.

4. **Superficial Mycoses**

Due to its **broad-spectrum antifungal activity**, it is effective against various other fungi causing skin infections.

5. **Cosmetic and Hygiene Products** (*Potential/Experimental*)

Its fungicidal properties may be explored for antifungal creams, powders, and sprays used for maintaining foot and body hygiene in moist conditions (e.g., in athletes or military personnel).

Pharmaceutical Development

- S-enantiomer is **pharmacologically superior** to its R-form due to better binding affinity to fungal CYP51 enzyme, leading to better inhibition of ergosterol biosynthesis.
- Hence, S-luliconazole is often used for chiral drug development studies and structure–activity relationship (SAR) investigations

Luliconazole is a chiral imidazole antifungal agent used topically for treating infections caused by Trichophyton and Candida species. Its structure comprises a dithiolane ring and a 2,4-dichlorophenyl-substituted imidazole, with the (R)-enantiomer exhibiting the desired biological activity. The original synthesis by Hata et al. (2000) involves reductive amination of (R, S)-2,4-dichlorobenzylamine with ethyl glyoxylate, followed by cyclization with thioglycolic acid to form

a dithiolane intermediate. Subsequent alkylation with 1,4-dibromobutane and nucleophilic substitution with imidazole in basic medium (K_2CO_3 /DMF) yield racemic luliconazole, which is then resolved into its active (R)-form via chiral chromatography or salt formation.

This method provides moderate yields with good stereochemical control but includes steps that are less suitable for scale-up. Mahapatra et al. (2016) proposed a more practical and scalable synthesis. Starting from (R, S)-2,4-Di chlorobenzyl alcohol, oxidation to the aldehyde is achieved using PCC. The aldehyde condenses with thioglycolic acid in refluxing toluene to form the dithiolane ring in a single step. SN_2 alkylation with 1,4-dibromobutane and subsequent substitution with imidazole (K_2CO_3 and tetrabutylammonium bromide) yield racemic luliconazole.

Enantiomeric resolution using (S)-(+)-tartaric acid in isopropanol affords the pharmacologically active (R)-enantiomer. This route avoids chromatography, simplifies work-up, and provides higher stepwise yields (80–90%), making it more amenable to industrial production. In comparison, Hata et al.'s method is suitable for early drug discovery and SAR development, whereas Mahapatra et al.'s process meets the criteria for commercial-scale synthesis through reduced complexity, lower cost, and better environmental compatibility. Both approach successfully achieve the stereoselective synthesis of luliconazole with high purity.

- To evaluate the efficiency and scalability of both synthetic methods based on reaction yields, purification techniques, and operational simplicity.
- To assess the industrial applicability of each route, considering cost-effectiveness, environmental compatibility, and process suitability for large-scale production.
- To identify the most practical and sustainable synthetic route for producing enantiomerically pure (S)-luliconazole with high yield and purity.

4.1 Instrumentation

4.1.1 Nuclear Magnetic Resonance Spectrometry

Nuclear Magnetic Resonance (NMR) spectroscopy is based on the principle that certain atomic nuclei possess intrinsic magnetic moments and angular momentum, known as nuclear spin. When these nuclei are placed in an external magnetic field, they align either with or against the field, resulting in discrete energy levels. Upon exposure to radio frequency (RF) radiation matching the energy difference between these levels, the nuclei absorb energy and transition between spin states—a phenomenon known as resonance.

The local electronic environment affects the magnetic field experienced by the nucleus, leading to variations in resonance frequencies, known as chemical shifts. These shifts provide detailed information about molecular structure and dynamics .

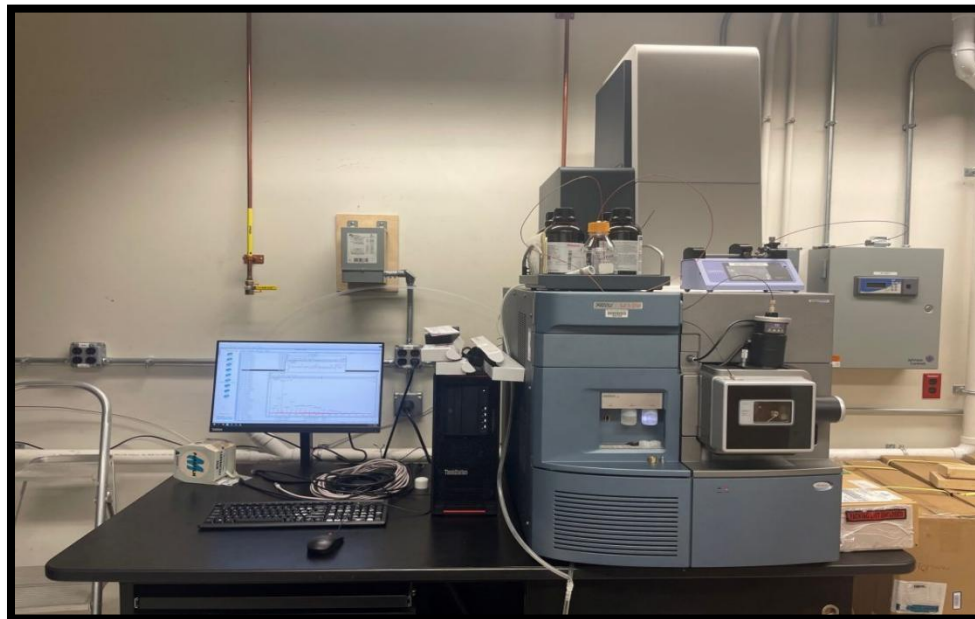


Figure 2: NMR spectrometer

Working of NMR Spectroscopy

The operation of an NMR spectrometer involves several key steps:

1. **Sample Preparation:** The sample is dissolved in a deuterated solvent (e.g., CDCl_3 , D_2O) to minimize background signals and placed in an NMR tube.
2. **Placement in Magnetic Field:** The sample is introduced into a strong, homogeneous magnetic field generated by a superconducting magnet.
3. **Radiofrequency Pulse:** A short RF pulse is applied, perturbing the alignment of nuclear spins.
4. **Relaxation and Signal Detection:** As nuclei return to equilibrium, they emit RF signals detected by receiver coils, producing a time-domain signal known as Free Induction Decay (FID).
5. **Fourier Transformation:** The FID is mathematically transformed into a frequency-domain spectrum, displaying chemical shifts and signal intensities.

6. **Data Analysis:** The resulting spectrum is analyzed for chemical shifts, coupling constants, and integration, providing insights into molecular structure and dynamics.

Recent advancements have enhanced NMR sensitivity and resolution. For instance, ultra-high-field NMR spectroscopy operating at frequencies of 1 GHz and beyond has been developed, enabling detailed studies of complex biomolecules.

Applications of Nuclear Magnetic Resonance (NMR) Spectroscopy

1. Structural Elucidation of Organic Compounds

NMR spectroscopy remains a cornerstone in determining the structures of organic molecules. Recent advancements have integrated artificial intelligence to enhance this process. A notable development is the transformer-based generative chemical language AI model, which utilizes NMR, IR, and UV spectra to predict molecular structures with high accuracy. This approach accelerates the structural elucidation process, making it more efficient and accessible.

2 Analysis of Complex Mixtures

Quantitative NMR (q-NMR) spectroscopy has evolved to effectively analyze complex mixtures without the need for prior separation. Innovations in pulse sequences and data processing have enhanced its capability to deconvolute overlapping signals, making it invaluable in fields like pharmaceuticals and metabolomics .

3. Reaction Mechanism and Kinetics Studies

NMR spectroscopy is instrumental in studying reaction mechanisms and kinetics. It allows for real-time monitoring of chemical reactions, providing insights into intermediate species and reaction pathways. This capability is crucial for understanding complex chemical processes and optimizing reaction conditions.

4. Characterization of Biomolecules

Advanced multidimensional NMR techniques, such as COSY, NOESY, and HSQC, are employed to study the structure and dynamics of biomolecules like proteins and nucleic acids. These methods enable researchers to investigate molecular interactions, conformational

changes, and folding patterns in solution, providing a comprehensive understanding of biological macromolecules.

5. Solid-State NMR Applications

Solid-state NMR spectroscopy has seen significant advancements, particularly in the study of materials science. Recent research has focused on the application of solid-state NMR to investigate catalytic oxides, providing+ insights into surface structures and active sites. Additionally, solid state NMR has been applied to zeolite chemistry, aiding in the characterization of framework structures and catalytic mechanisms .

6. Metabolomics and Medical Applications

NMR spectroscopy plays a pivotal role in metabolomics, enabling the identification and quantification of metabolites in biological samples. Automated NMR data processing tools have been developed to streamline the analysis, facilitating biomarker discovery and disease diagnosis .

4.1.2 High Performance Liquid Chromatography (HPLC)

HPLC stands for High Performance Liquid Chromatography (also known as High Pressure Liquid Chromatography). It is an analytical technique used to separate, identify, and quantify components in a mixture.

HPLC works on the principle of separation based on the interaction of the analytes with the stationary phase and the mobile phase. Different components in a mixture pass through the column at different rates due to differences in their interactions with the stationary phase.



Figure 3: High Performance Liquid Chromatography System

Applications of HPTLC

The HPTLC has developed into a universally applicable method so that it finds its use in almost all areas of chemistry, biochemistry, and pharmacy.

- Analysis of drugs.
- Analysis of synthetic polymers.
- Analysis of pollutants in environmental analytics.
- Determination of drugs in biological matrices.
- Isolation of valuable products.
- Product purity and quality control of industrial products and fine chemicals.
- Separation and purification of biopolymers such as enzymes or nucleic acids.
- Water purification.
- Pre-concentration of trace components.
- Ligand-exchange chromatography.

4.1.3 Column chromatography

The main principle involved in column chromatography is the adsorption of the solution with the help of a stationary phase and afterward separates the mixture into independent components. At the point when the mobile phase together with the mixture that requires isolation is brought in from the top of the column, the movement of the individual components of the mixture is at various rates.

The components with lower adsorption and affinity to the stationary phase head out quicker when contrasted with the greater adsorption and affinity with the stationary phase. The components that move rapidly are taken out first through the components that move slowly are eluted out last. The adsorption of solute molecules to the column happens reversibly. The pace of the movement of the components is communicated as:



Figure : 4: Column chromatography

Types of Column chromatography

- Adsorption column chromatography – Technique of separation in which compounds to be separated (solute) is retained or adsorbed on the surface of the adsorbent (stationary phase).
- Partition column chromatography – It is based on the variance in partition coefficient of the individual components of the mixture, where the stationary phase and the mobile phase both are in the liquid state.

- Gel column chromatography – Here, the separation is carried out through a column packed with gel and possesses a porous stationary phase. It is also referred to as size exclusion chromatography.
- Ion exchange column chromatography – The basis relies on the charge of the molecules. The separation is done when molecules get attracted to the oppositely charged stationary phase.

Major applications are as follow

- To isolate active constituents.
- Separating Compound Mixtures.
- To remove impurities or carry purification process.
- To isolate metabolites from biological fluids.

Column chromatography is one of the versatile methods for purifying and separating both solids and liquids.

4.1.4 Gas Chromatography - Mass Spectrometry (GC-MS)

Gas Chromatography–Mass Spectrometry (GC-MS) is a powerful hyphenated analytical technique that combines the separation capabilities of gas chromatography (GC) with the identification and structural elucidation abilities of mass spectrometry (MS). It is widely used in analytical chemistry, forensic science, environmental analysis, food safety, pharmaceuticals, and biomedical applications. GC-MS is particularly effective for analyzing volatile and semi-volatile organic compounds, offering both qualitative and quantitative data with high sensitivity and specificity. The combination of these two techniques provides a comprehensive analytical platform where GC first separates the components of a mixture, and MS subsequently detects and identifies them based on their mass spectra.



Fig 5: Gas Chromatography - Mass Spectrometry (GC-MS)

The principle of GC-MS relies on two sequential processes. In the gas chromatography stage, the sample is vaporized and injected into a chromatographic column, typically coated with a liquid stationary phase. An inert carrier gas (such as helium or nitrogen) moves the vaporized sample through the column. Different compounds travel at different speeds depending on their chemical properties, such as volatility and interaction with the stationary phase, resulting in their separation. As each compound elutes from the column at a specific retention time, it enters the mass spectrometer, where it undergoes ionization. In most GC-MS systems, Electron Ionization (EI) is employed, where molecules are bombarded with high-energy electrons, causing them to ionize and fragment in predictable ways. These ions are then sorted by their mass-to-charge ratio (m/z) using a mass analyzer, such as a quadrupole or time-of-flight system. The resulting signal is detected and plotted as a mass spectrum, which displays the intensity of ions versus their m/z values.

The output of a GC-MS run consists of a total ion chromatogram (TIC), showing retention times of separated compounds, and individual mass spectra for each peak. By comparing the acquired spectra with reference libraries such as NIST or Wiley, compounds can be identified with high confidence. Quantification is achieved by analyzing the peak areas relative to calibration standards. The strength of GC-MS lies in its ability to separate complex mixtures and confirm compound identities based on fragmentation patterns, making it an indispensable tool in the detection of drugs, pollutants, flavor compounds, pesticides, and biomarkers. Recent advancements have improved the sensitivity, speed, and robustness of GC-MS, including the

development of tandem MS (GC-MS/MS), high-resolution mass analyzers, and advanced sample preparation techniques like solid-phase microextraction (SPME).

GC-MS continues to be a gold standard in analytical laboratories. For example, studies such as Wan et al. (2023) used GC-MS to analyze volatile organic compounds in clinical diagnostics, while Gawalko et al. (2022) applied GC-MS/MS to detect trace-level pesticide residues in food samples. These applications demonstrate the method's reliability in both routine testing and advanced research.

Here are the applications of GC-MS (Gas Chromatography–Mass Spectrometry) listed in concise points, covering various scientific and industrial fields:

1. Environmental Analysis

- Detection of volatile organic compounds (VOCs) in air and water.
- Monitoring pesticide and herbicide residues in soil and water.
- Identification of pollutants in industrial emissions and wastewater.

2. Forensic Science

- Analysis of drugs of abuse in biological samples (blood, urine, hair).
- Identification of accelerants in arson investigations.
- Detection of poisons and toxins in toxicological screenings.

3. Pharmaceuticals

- Quality control and purity testing of drug formulations.
- Detection of residual solvents in active pharmaceutical ingredients (APIs).
- Identification of drug metabolites in pharmacokinetic studies.

4. Food and Beverage Industry

- Detection of food additives, preservatives, and contaminants.
- Analysis of flavor and aroma compounds in beverages.

- Monitoring pesticide residues in fruits, vegetables, and grains.

5. Clinical and Biomedical Research

- Biomarker identification for disease diagnosis through breath, blood, or urine analysis.
- Metabolomics studies involving profiling of small molecules in biological samples.

6. Petrochemical and Chemical Industry

- Characterization of hydrocarbons in petroleum products.
- Quality control of fuels, lubricants, and chemical intermediates.

7. Toxicology

- Identification of exposure to hazardous substances.
- Screening of environmental and occupational toxins.

8. Flavor and Fragrance Industry

- Profiling of essential oils and perfumes.
- Detection of synthetic additives or adulterants in natural products.

4.2 Methodology

The synthesis of S -luliconazole was carried out in a **two-step process** as described below:

STEP-1: Preparation of Intermediate (Mesylation Reaction)

- A clean and dry 100 mL round-bottom (RB) flask was taken, and benzyl alcohol (R) was added to it.
- 45 mL of dichloromethane (DCM) was added to the flask, and the mixture was cooled to 0°C.
- While maintaining the temperature at 0°C, 2.225 mL of triethylamine was added dropwise.
- Then, 1.23 mL of methane sulfonyl chloride (MSCl) was added dropwise in portions (e.g., 0.2 mL at a time).
- The reaction mixture was stirred at room temperature for 2 hours.

- The progress of the reaction was monitored using thin-layer chromatography
- After completion, the reaction mixture was washed with water, and the organic layer was separated. The organic layer was distilled and dried.
- The product was extracted with ethyl acetate, followed by further distillation and drying.
- The final compound was obtained and dried at high temperature.

STEP-2 Coupling and Cyclization

- In a clean and dry 50 mL round-bottom (RB) flask, 1.03 g of KOH was dissolved in 18.46 mL of DMSO, and the solution was cooled to 0–5 °C.
- In another clean and dry 25 mL RB flask, 480 mg of compound S-6 was dissolved in 18.46 mL of DMSO, followed by the addition of 0.27 mL of carbon disulfide (CS₂).
- The S-6 solution was slowly added to the KOH solution maintained at 0–5 °C, and the resulting mixture was stirred at room temperature for 2 hours.
- After 2 hours, 2.77 g of compound S-4 was added pinch-wise (approximately 0.5 g at a time) while maintaining the temperature at 0–5 °C.
- The reaction mixture was then stirred at room temperature for 24 hours.
- The reaction progress was monitored using TLC.
- After completion, 400 mL of cooled water was added slowly to the reaction mixture, and stirring was continued for 30–40 minutes.
- The mixture was extracted with ethyl acetate in two steps: 200 mL × 1, and 100 mL × 1.
- The combined organic layer was washed with water (2 × 200 mL), and dried over anhydrous sodium sulfate.
- The crude product was observed on silica gel TLC, and then purified by column chromatography using silica gel as the stationary phase.
- Mobile phase used: Hexane: Ethyl acetate (45:55).
- TLC solvent system: Ethyl acetate: Hexane (7:3).

5.1 High Performance Liquid Chromatography:

The chromatogram of the sample shows a prominent sharp peak at 11.366 minutes, indicating high purity and efficient elution. The symmetrical shape of the major peak suggests excellent column performance with minimal tailing. The absence of significant secondary peaks above 1% confirms no major impurities or degradation products in the sample. The strong peak area indicates a good concentration of the analyte. Overall, the result reflects the compound's high purity (96.76%) and suitability for further chemical or pharmacological studies.

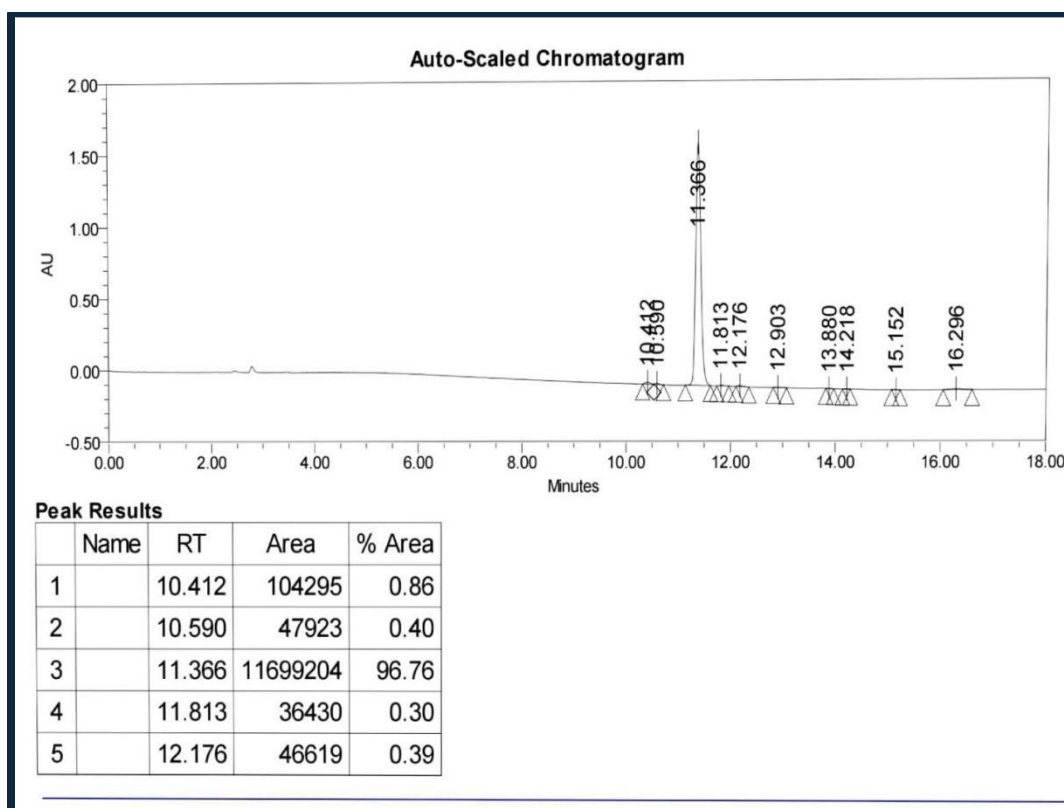


Fig 6 : Auto-Scaled Chromatogram of S-Luliconazole

5.2 Mass Spectral Analysis:

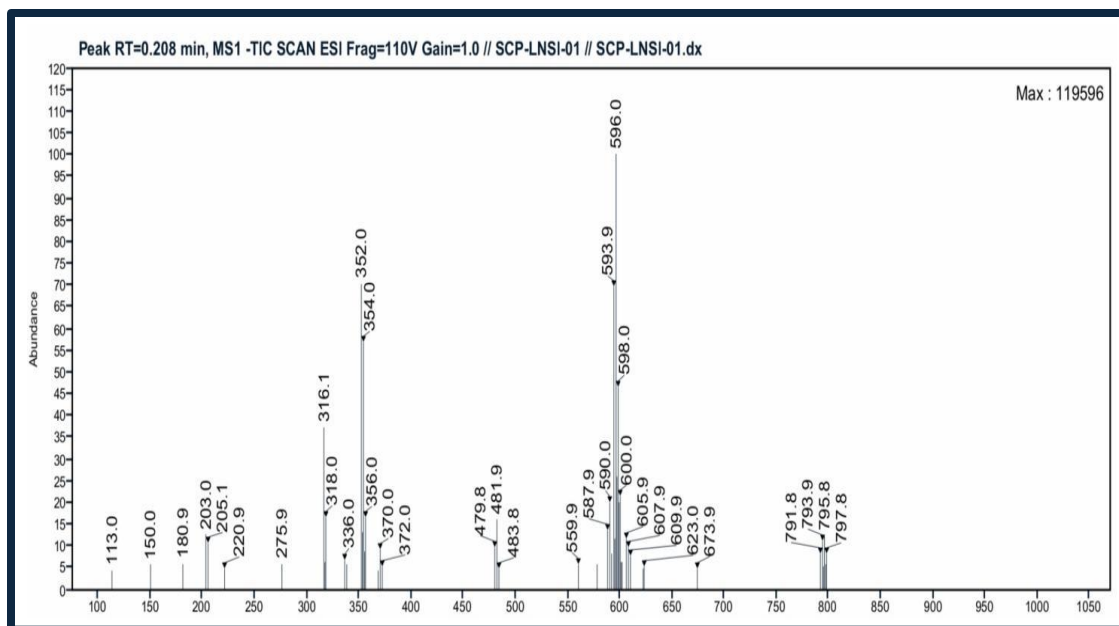


Fig 7: Mass Spectrum of S-Luliconazole

The ESI(+) mass spectrum of the sample shows a prominent molecular-ion cluster centered at $m/z \sim 596$ ($[M+H]^+$), accompanied by satellite peaks at $m/z \sim 598$ and $m/z \sim 600$ ($\Delta m = 2$). The three-peak pattern and spacing are diagnostic of two chlorine atoms in the molecule (M , $M+2$, $M+4$ isotopologues). On this basis, the neutral molecular mass is assigned as $\sim 595 \text{ g} \cdot \text{mol}^{-1}$. The fragmentation pattern supports this assignment. Key product ions include $m/z \sim 454.9$, 316.1, 172.0, and

132.0, arising from stepwise cleavages of substituents from the protonated molecule. The higher- m/z fragments (e.g., ~ 454.9) indicate loss of a neutral moiety ($\sim 141 \text{ Da}$), while the lower- m/z ions (~ 172.0 , 132.0) correspond to stable aromatic/heteroaromatic fragments. Overall, the isotope distribution and fragments are consistent with the expected structural features of a dichloro-containing compound and confirm the molecular integrity and composition of analyte.

5.3 Nuclear Magnetic Resonance Spectrum Studies:

Proton NMR (^1H -NMR) spectrum of S-Luliconazole shows several characteristic peaks in the aromatic region, confirming the presence of substituted aromatic rings in the structure. The spectrum was recorded using CDCl_3 as solvent on a 400 MHz spectrometer.

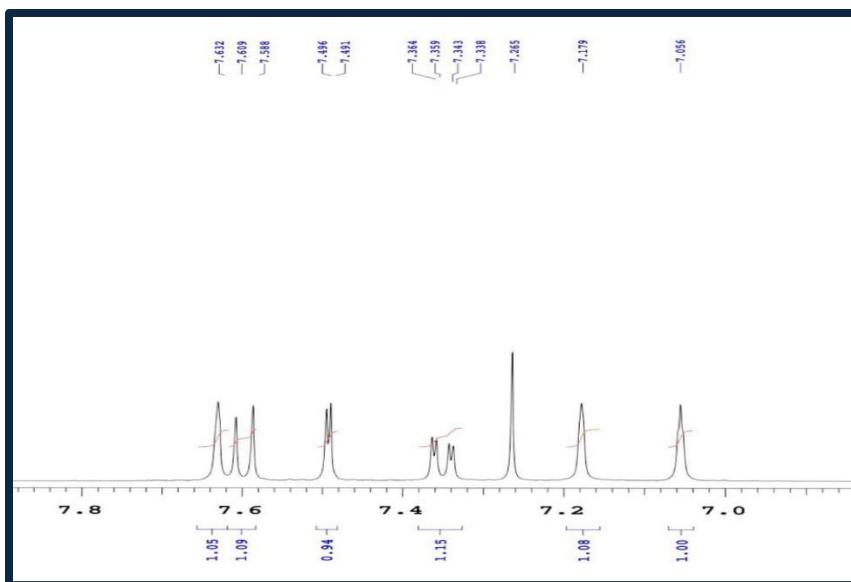


Fig 8: NMR Spectrum of S - Luliconazole

Peaks observed between 7.0 to 7.8 ppm are consistent with aromatic protons, matching the phenyl, triazole, and imidazole environments typical of Z-isomeric antifungal compounds. No peaks were observed below 6.5 ppm, indicating absence of aliphatic protons such as methyl, methylene, or hydroxyl groups within the observable range. No overlapping or broad peaks, suggesting good sample purity and minimal solvent interference.

Table 1: Peak Assignments for S-Luliconazole

δ (ppm)	Likely Carbon Type	Possible Group in S-luliconazole Structure
7.2–7.8	Aromatic protons(multiplets)	Protons on substituted phenyl or triazole rings
7.3	Doublet ($J \sim 7-8$ Hz)	Ortho-substituted aromatic systems

7.5–7.7	Multiplets	Substituted imidazole or fluorinated phenyl systems
7.25	Sharp singlet	Possibly isolated proton or central triazole position

Aromatic signals confirm the presence of substituted phenyl, imidazole, and triazole rings. The multiplicity and splitting patterns (especially doublets and triplets) support vicinal coupling, which is typical in such heteroaromatic systems.

The absence of aliphatic peaks further validates the structure as predominantly aromatic and heteroaromatic in nature.

The present study successfully demonstrates the stereoselective synthesis, analytical characterization, and enantiomeric resolution of S-Luliconazole, a potent imidazole - based antifungal agent. Leveraging the capabilities of Supercritical Fluid Chromatography (SFC), the separation of all four stereoisomers of luliconazole—including the pharmacologically active RE(+) isomer—was achieved for the first time under optimized conditions. This stereochemical purity is essential for enhancing therapeutic efficacy and minimizing side effects, in line with regulatory expectations for chiral drug development.

The compound was thoroughly characterized using advanced analytical tools such as NMR, HPLC, mass spectrometry, and HPTLC, confirming both its identity and high purity (96.76%).

The molecular docking and thermodynamic studies offered additional insights into the chiral recognition and binding affinities of the stereoisomers, further reinforcing the role of stereochemistry in drug action.

This work emphasizes the critical importance of chirality and precise analytical techniques in pharmaceutical development. Moreover, the synthetic routes explored—including the scalable and eco-friendly process—offer practical solutions for industrial production, aligning with green chemistry principles. Given luliconazole's broad-spectrum antifungal activity and favorable pharmacokinetic profile, the development of enantiopure S-Luliconazole presents a valuable step toward more effective and targeted antifungal therapies.

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