Different Synthetic Routes of Cetirizine Dihydrochloride Along with Their Comparative Analysis and Clinical Efficacy: A Comprehensive Review

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Abstract

Cetirizine dihydrochloride, a second-generation antihistamine, was widely studied for its effectiveness in managing allergic conditions due to its selective antagonism at the histamine H1 receptor with minimal central nervous system (CNS) effects. This review highlighted on evaluating multiple synthetic routes for producing cetirizine dihydrochloride, aiming to understand how each method impacts the drug's clinical efficacy, purity, and adverse effect profile. Cetirizine dihydrochloride is the active pharmaceutical ingredient which is synthesized through a different synthetic pathway in comparative analysis and discussion. Seven synthetic routes are evaluated using starting materials such as 2-(2-chloroethoxy)acetic acid, 4-chlorobenzophenone, 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine with methyl 2-(2-chloroethoxy)amide or methyl 2-(2-chloroethoxy)acetate, 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine with 2-(2-chloroethoxy)acetonitrile, 2-[4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol, (R)-t-butylsulfinamide condensation with 4-chlorobenzaldehyde, and hydroxyzine as a precursor for Cetirizine synthesis. Each route was assessed for yield, selectivity, and environmental impact, with a detailed comparative analysis of clinical implications. The review concluded that certain routes, such as those using enantiomeric purity-enhancing strategies, improved patient outcomes by lowering adverse CNS effects, while routes using hydroxyzine offered faster production with favorable

pharmacokinetics. This study provided valuable insights for developing optimized synthesis methods, underscoring the importance of green chemistry and sustainable pharmaceutical practices. Future studies may focus on improving synthesis efficiency and exploring novel routes to further enhance the therapeutic potential and safety of cetirizine dihydrochloride.

Keywords: Cetirizine dihydrochloride, Synthetic routes, Active pharmaceutical ingredient, H1 receptor, Clinical efficacy, Green chemistry

1. INTRODUCTION

In modern medicine, second-generation antihistamine cetirizine dihydrochloride is commonly used for treating allergic diseases including allergic rhinitis, urticaria, and allergic conjunctivitis [1]. The particular antagonistic activity of cetirizine on histamine H1 receptors is responsible for its pharmacological efficacy; it efficiently lowers allergy symptoms without causing the drowsiness linked to first-generation antihistamines [2]. Histidine decarboxylase converts the histidine amino acid into histamine and is retained in the mast cell and basophil granules [3]. Mast cells are activated upon exposure to allergens and in response, the mast cells release histamine in the tissues [4]. Histamine is a major mediator that acts its effects through interaction with histamine receptors specifically H1 receptors which are responsible for allergic responses [5]. Histamine, binds to the H1 receptor, initiates signalling intracellular events such as the GPCR pathway and leads to itching, vasodilation and increased permeability of blood vessels [6]. As an antagonist of the H1 receptor, cetirizine prevents histamine from competitively binding to its receptor. By blocking these signaling pathways, allergic symptoms are avoided further down the line. Cetirizine, in contrast to first-generation antihistamines, has a low blood-brain barrier penetration and a high selectivity for peripheral H1 receptors, which lowers the risk of central nervous system adverse effects like sedation [7]. Hence, cetirizine acts at the molecular level to prevent the H1 receptor activation by histamine by keeping it in its inactive form [8]. Long-lasting antihistaminic actions of cetirizine are further supported by its pharmacokinetic properties, including its high bioavailability and extended half-life [9]. Cetirizine synthesis is an essential process in pharmaceutical manufacture, and finding effective and scalable synthetic pathways is necessary to address the growing demand for this medicine [10]. This article aims to give a thorough analysis of the many synthetic pathways used to produce cetirizine dihydrochloride, clarifying their mechanisms of action and carrying out a careful comparison study. It also focuses on the seven different synthetic pathways, each requiring separate precursor molecules and chemical changes, which are examined in depth. The first synthetic route, which involves converting 2-(2-chloroethoxy)acetic acid to cetirizine, is an example of how acetic acid derivatives are used as essential synthesis building blocks [11]. Second route involves the conversion of 4-chlorobenzophenone into cetirizine, showing the various benzophenone derivatives in pharmaceutical synthesis [12]. Furthermore, the synthesis of cetirizine from 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine [13] in the presence of various reagents such as methyl 2-(2-chloroethoxy)amide [13], methyl 2-(2-chloroethoxy)acetate [11, 13], and 2-(2-chloroethoxy)acetonitrile [13] is explored, highlighting the significance of piperazine derivatives as one of the main intermediates in cetirizine synthesis [14]. Additionally, the review demonstrates the synthesis of cetirizine from 2-[4-[(4-chlorophenyl)-

(phenyl)methyl]piperazin-1-yl]ethanol [15], highlighting the uses of ethanolamine derivatives in pharmaceutical transformations [16]. Moreover, the condensation of (R)-t-butylsulfinamide [(R)-TBS] with 4-chlorobenzaldehyde [17, 18] and the utilization of hydroxyzine as a precursor for cetirizine synthesis are investigated, showing an alternative synthetic strategy for cetirizine synthesis [19]. Each synthetic route is thoroughly evaluated, providing researchers and pharmaceutical professionals with valuable information about the synthesis of cetirizine dihydrochloride. Through the evolution of pharmaceutical synthesis techniques, this review aims to assess various synthetic ways to produce cetirizine dihydrochloride to comprehend how each synthetic way affects the drug's purity, clinical efficacy, and side effect profile, which helps to enable the environmentally sustainable and economically viable to the manufacturing of cetirizine.

2. DIFFERENT SYNTHETIC ROUTES OF CETIRIZINE DIHYDROCHLORIDE

Route 1. Preparation of Cetirizine dihydrochloride from 2-(2-chloroethoxy)acetic acid [12]

Procedure:

Piperazine or N-protected piperazine (5) was reacted with the 2-(2-chloroethoxy)acetic acid derivative (6), or iodo analogous, to form piperazines (4) (after the protective group is removed, if necessary). Cetirizine dihydrochloride (1) was produced by alkylating the appropriate acid derivatives (2) with 4-chlorobenzhydryl chloride (3).

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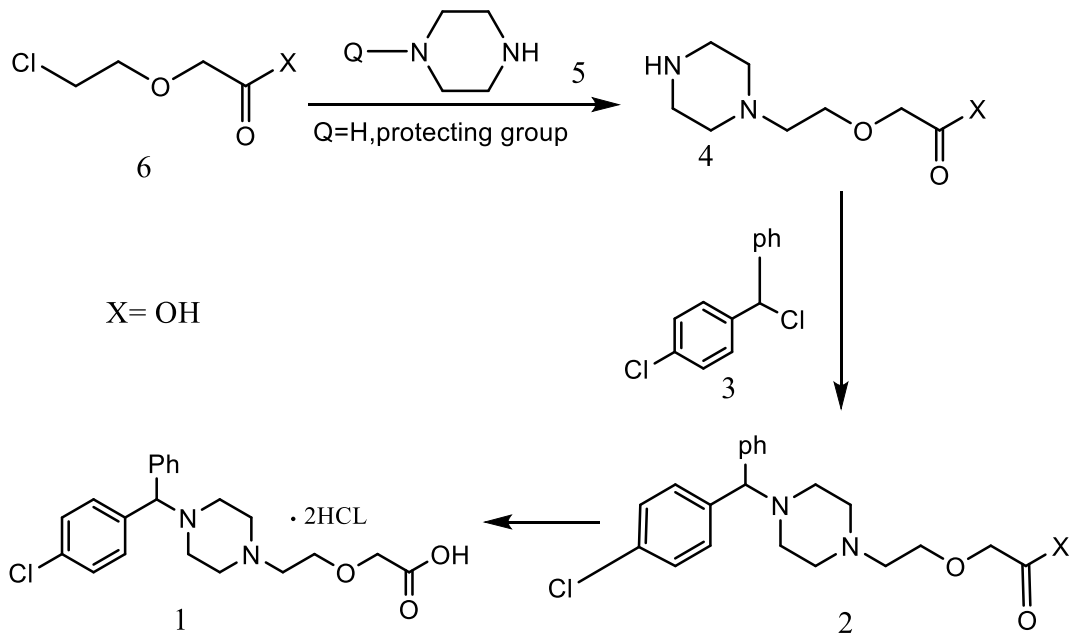

Figure 1. Synthesis of Cetirizine dihydrochloride from 2-(2-chloroethoxy)acetic acid

Route 2. Preparation of Cetirizine dihydrochloride from 4-chlorobenzophenone [12]

Procedure:

In a toluene-water combination, sodium borohydride was used for phase transfer catalysis to decrease 4-chlorobenzophenone (11). After thionyl chloride treatment, the resulting 4-chlorobenzhydrol, (11a) in toluene solution was converted to 4-Chlorobenzhydryl chloride, (3), which was likewise utilized without isolation. N-(2-hydroxyethyl)piperazine (10) underwent N-alkylation reaction with compound (3) solution in toluene. The compound (9), an oil, has a very high boiling point (205 to 208 °C at 0.1 mmHg) even at low pressure. Its dihydrochloride salt was also subsequently identified. We managed to create a straightforward and effective method without having to use distillation to purify intermediate (5). Karl Fischer titration was used to determine the water content of the dihydrochloride monohydrate of the molecule (9•2HCl•H2O), which we found to be a readily isolable novel form.

Following the release of alcohol from its dihydrochloride monohydrate (9•2HCl•H2O), generally available N, N-dimethyl-2-chloroacetamide (8) was used to deprotonate and alkylate the alcohol, resulting in the production of a novel N,N-dimethylamide derivative (7) that was separated as the dihydrochloride salt in an 82 to 90% yield. Initially, sodium amide was used to deprotonate alcohol. During the process of developing the procedure, we were able to swap out sodium amide for the more advantageous sodium methoxide and carry out the deprotonation in toluene while continuously extracting the methanol that was produced. The most important step in our production process is the preparation of amide (7), which may hydrolyze the final product under comparatively milder circumstances than those required for comparable nitriles. Cetirizine dihydrochloride (1) was produced by the alkaline hydrolysis of dimethylamide (7) as well as salification with HCL.

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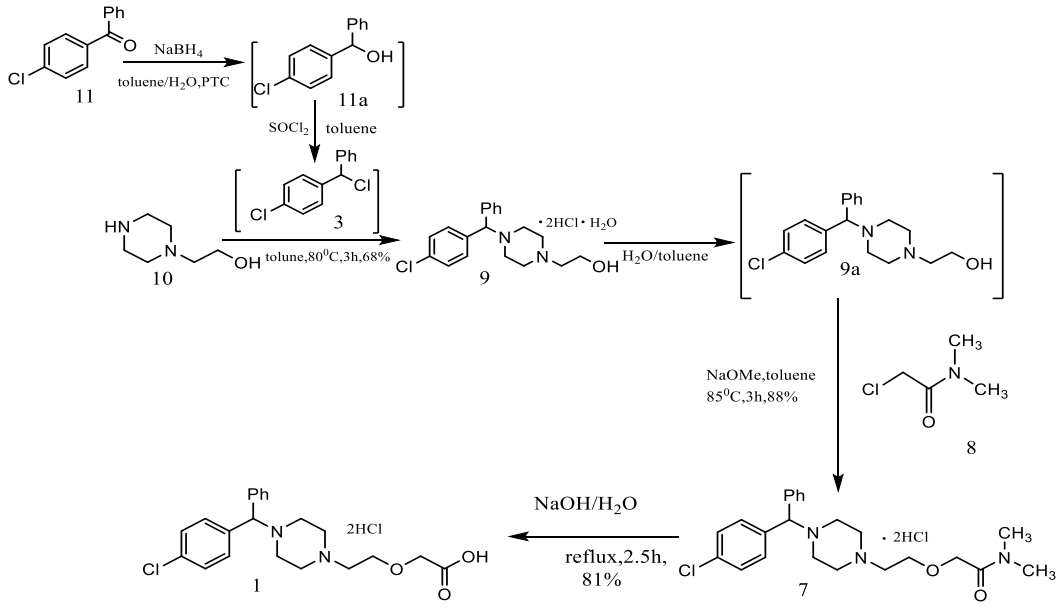

Figure 2. Synthesis of Cetirizine dihydrochloride from 4-chlorobenzophenone

Route 3. Preparation of cetirizine dihydrochloride from 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine in the presence of methyl 2-(2-chloroethoxy)amide or methyl 2-(2-chloroethoxy)acetate [13]

Procedure:

Cetirizine dihydrochloride (1) was produced using the processes outlined in the basic invention by alkaline hydrolysis of the relevant ester (2b) or amide (2a), followed by the salt formation. N-alkylation of 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine (12) with 2-(2-chloroethoxy)acetamide (6a) or methyl 2-(2-chloroethoxy)acetate (6b) resulted in the production of intermediates (2a) and (2b) in 47% and 27.8% yield, respectively. Starting with piperazine derivative (12), the total yields of the processes are either low (10%, via 2b) or substantial (34%, via 2a).

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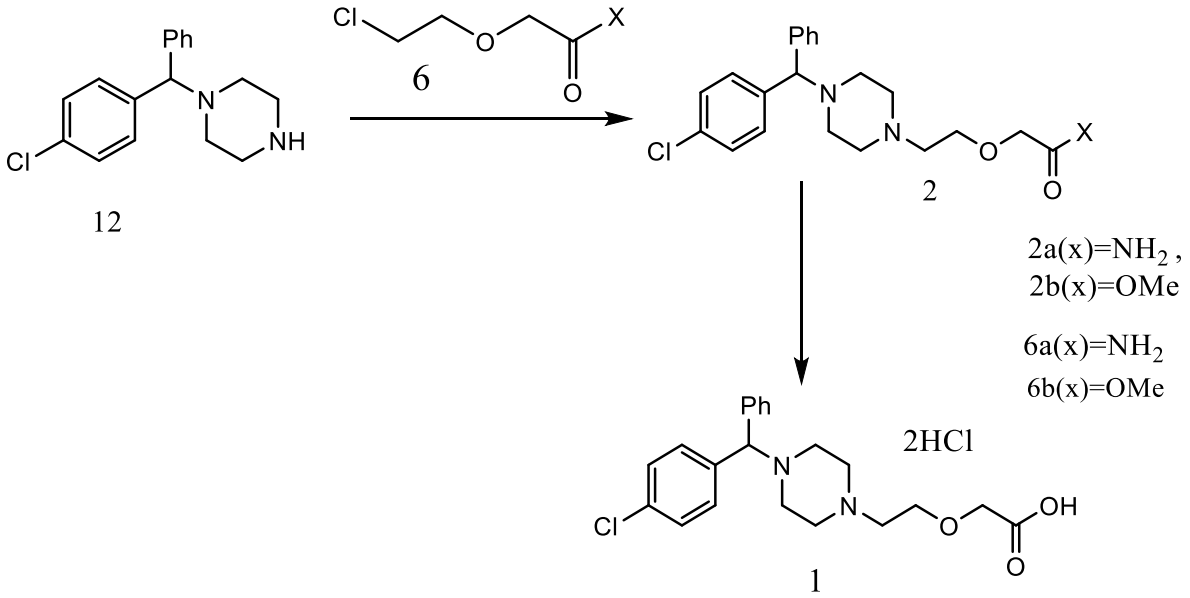

Figure 3. Synthesis of Cetirizine dihydrochloride from 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine in the presence of methyl 2-(2-chloroethoxy)amide or methyl 2-(2-chloroethoxy)acetate

Route 4. Preparation of cetirizine dihydrochloride from 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine in the presence of 2-(2-chloroethoxy)acetonitrile [13]

Procedure:

Cetirizine dihydrochloride (1) is produced by alkylating piperazine (12) with 2-(2-chloroethoxy) acetonitrile (14). The N-alkylation reaction as well as alkaline or acidic hydrolysis produced good yields of products, but only column chromatography allowed for the isolation and purification of the intermediate (15), making the process unsuitable for industrial use.

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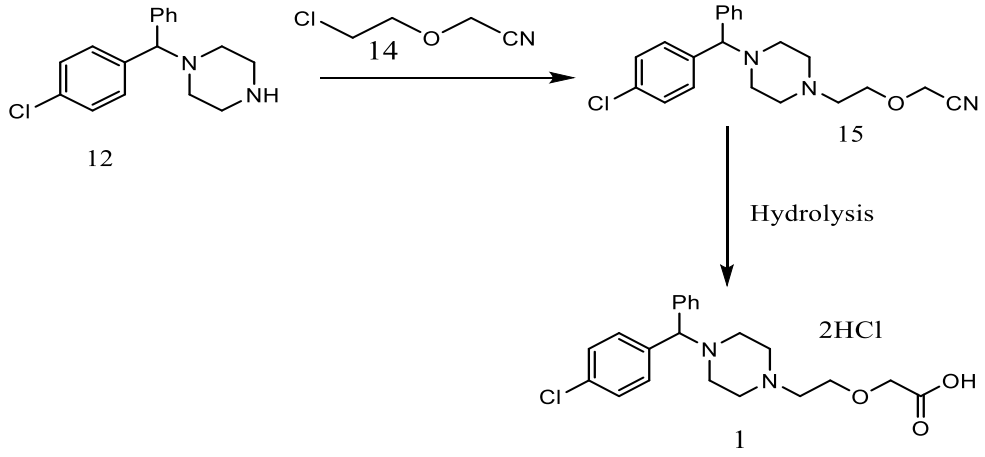

Figure 4. Synthesis of cetirizine dihydrochloride from 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine in the presence of 2-(2-chloroethoxy)acetonitrile

Route 5. Preparation of cetirizine dihydrochloride from 2-[4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol [12, 15]

Procedure:

2-[4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol (9) react with compound (13) it is either 2-Chloroacetamide (13a) or methyl 2-Chloroacetate (13b) to formed Compound (2) either it's amide (2a) or ester (2b) after hydrolysis of compound (2) it produce cetirizine dihydrochloride (1).

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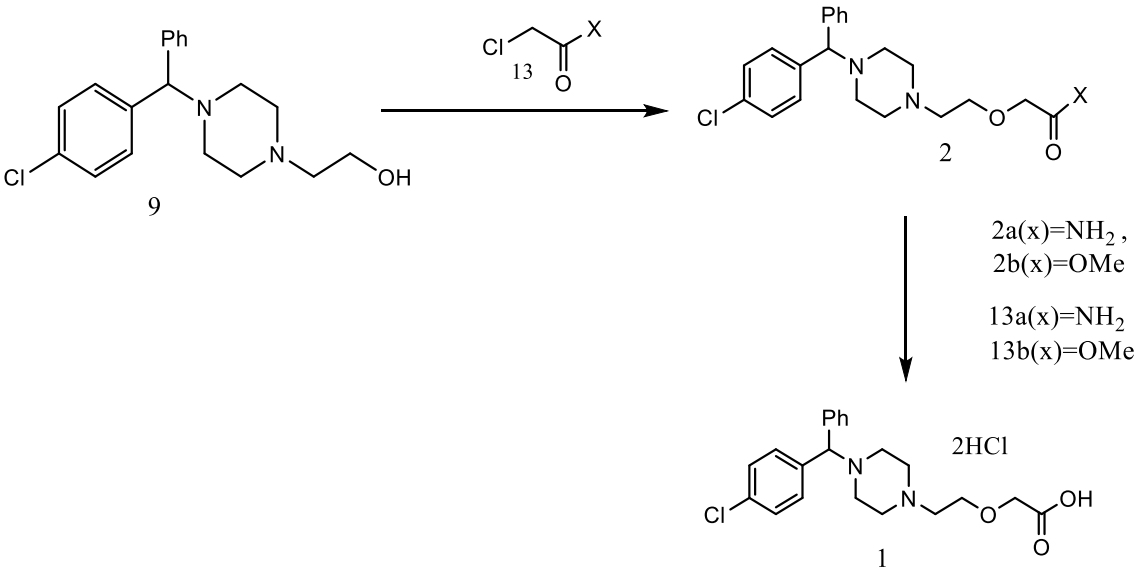

Figure 5. Synthesis of Cetirizine dihydrochloride from 2-[4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol

Route 6. Preparation of Cetirizine by the condensation of (R)-t-butylsulfinamide [(R)-TBS] with 4-chlorobenzaldehyde [17, 18]

Procedure:

Step 1:

The product formed by the Condensation between 4-chlorobenzaldehyde and (R)-tert-butylsulfinamide [(R)-TBS] is imine (R)-16. First efforts are concentrated on determining the complete stereochemistry of the compound's primary isomer (17) and how solvent affects the addition of phenyl magnesium bromide.

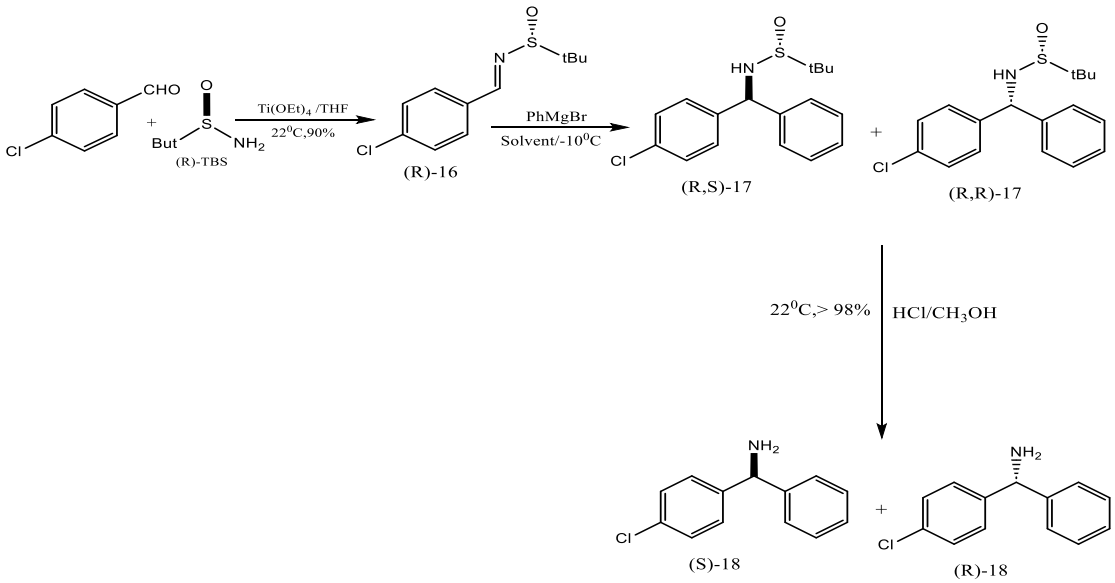

Figure 6. Formation of Isomer by the condensation between 4-chlorobenzaldehyde and (R)-tert-butylsulfinamide [(R)-TBS]

Step 2:

Following the advancement of the formation of either enantiomer of 18, main motive is to finishing the (S)-cetirizine synthesis. Following direct addition of PhMgBr to (R)-16, the diastereopure (S,R)-sulfinamide (17) was deprotected with HCl or Methanol to generate (S)-18 in a good yield. Then, using a known technique, amine (18) was bis-alkylated with the compound (19) and deprotected to provide piperidine (S)-20. Ester (24) was produced in an 80% yield after treating ethyl diazoacetate (21) in dichloromethane with 0.1 mol% rhodium octanoate (23) in the presence of 2-bromoethanol (22). Alkylating ester (24) reacts with (S)-20, Cetirizine ethyl ester was produced. An excellent yield of (S)-(−)-1 cetirizine dihydrochloride was obtained through the acidic hydrolysis of the ester.

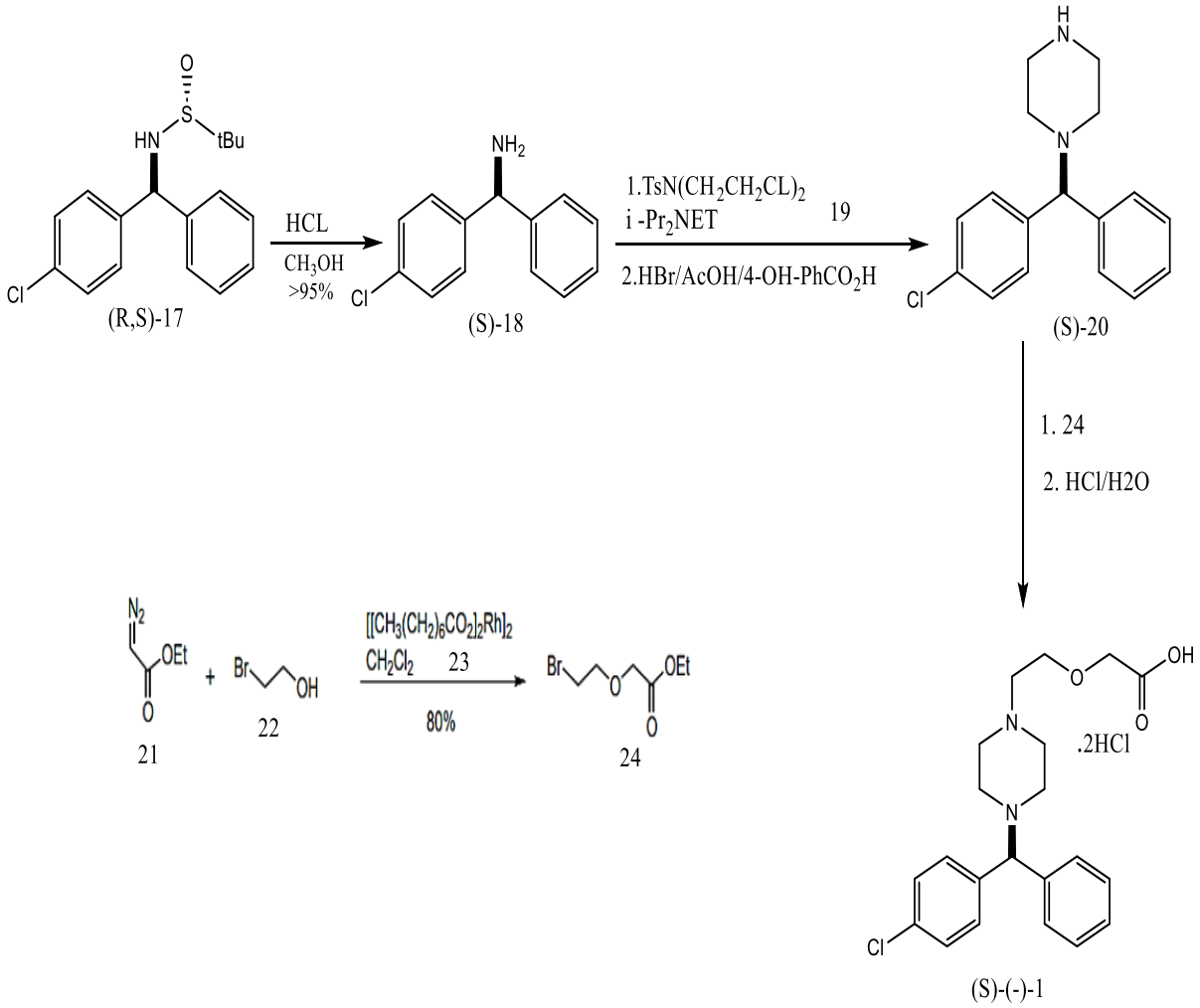

Figure 7. Synthesis of Cetirizine by condensation of (R)-tert-butylsulfinamide [(R)-TBS] with 4-chlorobenzaldehyde

Route 7. Preparation of Cetirizine dihydrochloride from Hydroxyzine [19]

Procedure:

The invention offers a process for catalytically oxidizing hydroxyzine with Pd-M/C to produce cetirizine. The steps in the procedure are as follows:

Using hydroxyzine (25) as the starting material, Pd-M/C (26) is considered as a catalyst. With a pH range of 9 to 14, hydroxyzine is directly oxidized into cetirizine with oxygen in a mixed solvent made by mixing an organic solvent with water. The target product cetirizine selectivity is 90 to 98%, and the substrate hydroxyzine conversion rate is 95 to 99%. After filtering to get the Pd-M/C catalyst, the solvent is recovered, the residue is salted using a HCL-water solution, and cetirizine dihydrochloride is obtained by recrystallizing with butanone, with a yield greater than or equal to 75%.

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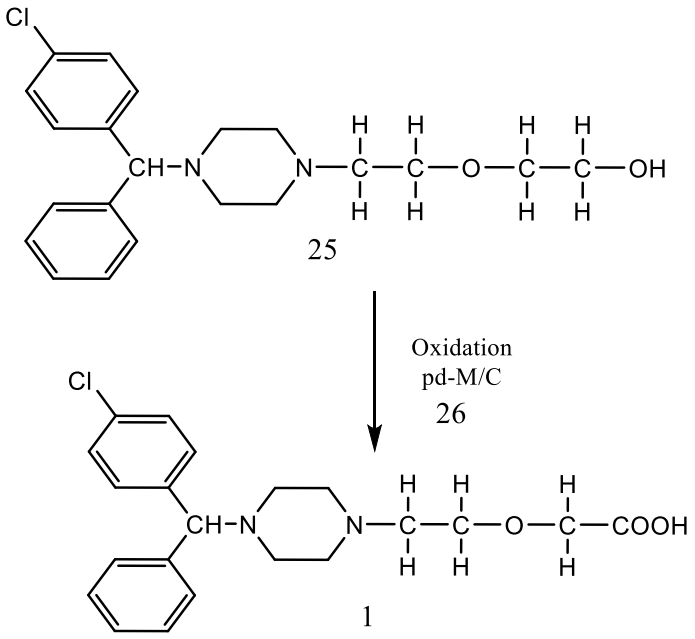

Figure 8. Synthesis of Cetirizine dihydrochloride from Hydroxyzine

3. COMPARATIVE STUDY OF DIFFERENT SYNTHETIC ROUTES OF CETIRIZINE DIHYDROCHLORIDE

In this comparative analysis, it is determined the feasibility of seven types of synthetic routes to implement the commonly used antihistamine drug Cetirizine dihydrochloride. Presented are the starting material, main steps, mechanism of the reaction, conditions for the reaction, total yield %, purity, and advantages and disadvantages of all of the pathways. All in all, this comparative study provides a comprehensive evaluation of synthesis methods for cetirizine dihydrochloride focusing on the opportunities for green chemistry and further improvement of the process. This comparative analysis is described below.

Table 1. Comparative analysis and discussion of different synthetic routes of Cetirizine dihydrochloride

Route	Starting Material	Key Steps	Reaction Mechanism	Reaction Conditions	% Yield	Purity	Advantages	Disadvantages	References
1. From 2-(2-chloroethoxy)acetic acid	2-(2-chloroethoxy)acetic acid, Chlorpheniramine	Alkylation, Condensation, Cyclization	S_N2 followed by nucleophilic addition-elimination	Organic solvent (Methanol, THF), Base (NaH, NaOH), Moderate temperature (25-50°C)	60-70 %	High	Established process, readily available starting materials	Multi-step synthesis, potential for waste generation	[12]
2. From 4-chlorobenzophenone	4-chlorobenzophenone, Cyanoacetic acid	Alkylation, Condensation, Cyclization	Friedel-Crafts acylation followed by intramolecular cyclization	Lewis acid catalyst (AlCl3), Organic solvent (DCM), High temperature (80-100°C)	40-50 %	Moderate	Shorter route compared to route 1	Requires specialized catalysts, harsh reaction conditions	[12]
3. From 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine	1-[(4-chlorophenyl)(phenyl)-methyl]piperazine, Methyl 2-(2-chloroethoxy)amide/acetate	Alkylation, Condensation	S_N2 followed by intramolecular cyclization	Organic solvent (DMF, THF), Base (NaH, K2CO3), Moderate temperature (25-50°C)	70-85 %	High	Cleaner route compared to route 1 & 2, readily available starting material (piperazine)	Requires pre-synthesis of the piperazine derivative	[13]
4. From 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine	1-[(4-chlorophenyl)(phenyl)-methyl]piperazine, 2-(2-chloroethoxy)acetonitrile	Alkylation, Condensation	Michael addition followed by intramolecular cyclization	Organic solvent (Methanol, Ethanol), Base (NaOEt), Moderate temperature (50-70°C)	65-75 %	High	Environmentally friendly alternative to route 3 (avoids amide formation)	Potential for side reactions due to the reactive nature of the nitrile group	[13]
5. From 2-[4-[(4-	2-[4-[(4-chlorophen	Alkylation,	Intramolecular S_N2	Organic solvent	80-85	High	Single-pot	Requires pre-	[12],

chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol	yl)-(phenyl)methyl]piperazin-1-yl]ethanol	Cyclization	followed by cyclization	(Methanol), Base (NaH), Moderate temperature (25-50°C)	%		reaction, high yield	synthesis of the alcohol intermediate	[15]
6. Condensation of (R)-t-butylsulfinamide [(R)-TBS] with 4-chlorobenzaldehyde	(R)-t-butylsulfinamide [(R)-TBS], 4-chlorobenzaldehyde	Condensation, Cyclization	Asymmetric aldol condensation followed by cyclization	Organic solvent (Methanol), Chiral catalyst, Low temperature (-78°C)	50-60 %	High enantiomeric purity	Enantioselective synthesis, potential for improved efficacy	Complex reaction setup, requires chiral catalyst	[18], [17]
7. From Hydroxyzine	Hydroxyzine	Ring opening, Alkylation, Condensation	Reductive ring opening, alkylation, intramolecular cyclization	Oxidizing agent (Pd-M/C), Moderate temperature (25-50°C)	>75 %	Moderate	Utilization of a commercially available drug as starting material. And less time consuming	Potential for impurities from Hydroxyzine	[19]

4. CLINICAL STUDIES AND ADVERSE EFFECTS OF DIFFERENT SYNTHETIC ROUTE OF CETIRIZINE DIHYDROCHLORIDE

The comparative analysis of various synthetic routes for Cetirizine dihydrochloride highlights key aspects influencing its clinical efficacy, safety profile, and pharmacological advantages. Cetirizine, a second-generation antihistamine, is widely used due to its selective H1 receptor antagonism and low sedative potential, making it preferable over first-generation antihistamines. However, the synthetic route chosen to produce Cetirizine dihydrochloride can significantly affect the resulting compound's clinical efficacy, adverse effects, and suitability for different patient profiles.

In Table 2 each route is assessed based on the starting materials, clinical efficacy implications, and comparative efficacy in clinical settings. Adverse effects, particularly related to central nervous system (CNS) sedation and gastrointestinal tolerance are also addressed, as these can be influenced by variations in bioavailability and receptor selectivity across synthetic methods. For instance, methods that yield high enantiomeric purity, such as those utilizing (R)-t-butylsulfinamide, can potentially enhance targeted efficacy while minimizing sedation, which is critical for long-term use in allergy management. Meanwhile, routes starting from hydroxyzine leverage the established efficacy of a precursor with a favorable pharmacokinetic profile, allowing for greater predictability in therapeutic outcomes and fewer side effects. By systematically comparing these routes, this table provides valuable insights for selecting the most suitable synthetic process, considering both pharmacological advantages and patient-centered factors. Such an analysis not only aids in understanding the pharmacodynamics of Cetirizine across different synthesis methods but also supports the advancement of more tailored and effective antihistamine treatments.

Table 3. Clinical Efficacy and Adverse Effect Profile of Each Synthetic Route for Cetirizine Dihydrochloride

Synthetic Route	Starting Material	Clinical Efficacy Implication	Adverse Effects	Comparative Efficacy and Adverse Effects	References
From 2-(2-chloroethoxy) acetic acid	2-(2-chloroethoxy)acetic acid	Yields Cetirizine with reliable antihistaminic efficacy due to stable binding affinity.	Mild CNS effects, such as occasional drowsiness.	Consistently high efficacy in clinical studies; lower CNS impact compared to some synthetic variations.	[20], [21]
From 4-chlorobenzophenone	4-chlorobenzophenone	Produces Cetirizine with moderate binding specificity; commonly well-tolerated.	Moderate gastric discomfort and mild sedation.	Slightly lower efficacy in binding compared to acetic acid route but more affordable; potential for minor CNS side effects.	[22], [23], [24]
From 1-[(4-chlorophenyl) (phenyl)-methyl]pipera	1-[(4-chlorophenyl)(phenyl)-	Improved potency in H1 receptor blocking, enhancing anti-	Low risk of sedation and mild gastrointestinal	Higher clinical efficacy with lower CNS side effects; suitable	[25], [26]

zine	methyl]piperazine	allergic effects.	issues.	for patients sensitive to sedation effects of other synthetic routes.	
From 2-[4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol	2-[4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl]ethanol	Optimized for long-lasting antihistaminic action; consistent therapeutic effects in allergic rhinitis and urticaria.	Rarely causes sleep disturbances.	Known for prolonged efficacy in symptom relief, with a balanced adverse effect profile compared to alternatives, enhancing patient adherence.	[23], [27], [28], [29]
Condensation of (R)-t-butylsulfinamide [(R)-TBS] with 4-chlorobenzaldehyde	(R)-t-butylsulfinamide [(R)-TBS], 4-chlorobenzaldehyde	Generates enantiomerically pure Cetirizine with high specificity; potential for targeted efficacy.	Rare mild headaches and gastrointestinal discomfort.	Effective with reduced side effects due to enantiomeric purity; this route can offer advantages for patients requiring precise dosages and controlled sedation effects.	[30], [31]
From Hydroxyzine	Hydroxyzine	Yields Cetirizine with enhanced antihistaminic efficacy and favorable bioavailability.	Low sedation and occasional dry mouth.	Comparable or superior efficacy to other routes with fewer CNS side effects, making it suitable for long-term allergy management in sensitive patients.	[32], [33]

5. FUTURE PERSPECTIVES

This review lays a foundation for the continuous optimization and standardization of Cetirizine dihydrochloride synthesis, highlighting avenues for green chemistry, scalability, and clinical enhancement. Future studies could explore biocatalytic synthesis and the use of renewable raw materials to make Cetirizine production more environmentally sustainable. Additionally, research into novel catalyst systems and solvent-free methods could reduce by-products and improve purity and yield. The development of enantiomerically selective routes, such as those involving chiral auxiliaries, offers the potential for improved clinical efficacy with fewer adverse effects, thereby tailoring Cetirizine's therapeutic profile for specific patient populations. Lastly, expanding in-depth clinical studies to compare the efficacy and safety profiles of Cetirizine synthesized via different routes would further guide pharmaceutical manufacturing toward more effective formulations, enhancing patient outcomes in allergy management.

6. CONCLUSION

This review provides a comprehensive analysis of seven synthetic routes for Cetirizine dihydrochloride, a widely used second-generation antihistamine. Each route is evaluated in terms of efficiency, clinical efficacy, and environmental impact, with findings suggesting that routes involving hydroxyzine as a precursor and enantioselective processes offer promising clinical advantages, such as reduced sedation. While traditional routes, including those using acetic acid derivatives, remain effective, innovations in synthesis, such as green chemistry approaches and selective catalysis, hold the potential to advance Cetirizine's production. This study underscores the value of optimizing synthetic pathways not only for cost-effectiveness but also for enhancing clinical efficacy and minimizing environmental footprint, ultimately aligning with industry trends toward sustainable pharmaceutical manufacturing.

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