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A COMPARATIVE REVIEW OF SYNTHETIC STRATEGIES FOR CIPROFLOXACIN ACTIVE PHARMACEUTICAL INGREDIENT

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ABSTRACT

Ciprofloxacin is a second-generation fluoroquinolone antibiotic widely used in the treatment of Gram-negative and selected Gram-positive bacterial infections. It has global clinical importance and inclusion in the World Health Organisation Model List of Essential Medicines. Ciprofloxacin continues to be manufactured extensively as a generic active pharmaceutical ingredient (API). The development of efficient, scalable, and impurity-controlled synthetic routes remains a major focus in pharmaceutical process chemistry. This review provides a comprehensive comparative analysis of reported synthetic methodologies for ciprofloxacin, encompassing classical batch processes, modified Gould–Jacobs strategies, nucleophilic aromatic substitution pathways, boron-chelate-mediated synthesis, solid-phase approaches, and modern continuous-flow techniques. Each route is critically evaluated with respect to key reaction steps, operational conditions, yield, purity, scalability, and environmental impact. Comparative assessment highlights the advantages and limitations of traditional multistep syntheses versus emerging streamlined and flow-based processes. Recent continuous manufacturing strategies demonstrate improved efficiency, reduced reaction times, and enhanced sustainability compared with conventional batch methods. Overall, this review aims to provide an integrated perspective to guide rational route selection, process

optimisation, and future development of greener and economically viable ciprofloxacin API manufacturing.

KEYWORDS: Ciprofloxacin; Fluoroquinolones; API synthesis; Process chemistry; Continuous flow synthesis.

1. INTRODUCTION

Ciprofloxacin is a second generation member of the fluoroquinolone class of antibiotics, distinguished by a 4-oxo-3-carboxylic quinolone scaffold substituted with a fluorine atom at the C-6 position and a piperazinyl group at C-7. These structural modifications play a crucial role in enhancing cellular uptake, inhibition of bacterial DNA gyrase, and broad spectrum antibacterial activity against Gram-negative bacteria and selected Gram-positive organisms.[1,2] In addition, the presence of a cyclopropyl substituent at the N-1 position contributes to improved binding affinity toward DNA gyrase and expanded antimicrobial potency, while the C-7 piperazinyl moiety further refines Gram-negative coverage, pharmacokinetic behaviour, and target interactions without markedly increasing lipophilicity or toxicity.[3,4]

Following its patenting by Bayer in 1983 and subsequent approval by the U.S. Food and Drug Administration in 1987, ciprofloxacin rapidly achieved global clinical acceptance and emerged as one of the most extensively prescribed fluoroquinolones for both community acquired and nosocomial infections.[5] The drug exhibits strong, concentration dependent bactericidal activity against a broad array of pathogens, including members of the Enterobacteriaceae family such as *Escherichia coli* and non-fermenting organisms like *Pseudomonas aeruginosa*, often at low minimum inhibitory concentrations. Importantly, ciprofloxacin also maintains clinically meaningful efficacy against methicillin susceptible *Staphylococcus aureus* and other Gram-positive bacteria.[6,7]

From a therapeutic perspective, ciprofloxacin is a versatile systemic antibacterial agent administered orally or intravenously for the management of complicated and uncomplicated urinary tract infections, lower respiratory tract infections including inhalational anthrax related disease gastrointestinal infections such as typhoid fever, and deep-seated skin, bone, and joint infections that require effective tissue penetration.[8,9,10] Its mechanism of action involves interaction with bacterial DNA gyrase and topoisomerase IV at the enzyme DNA cleavage complex, resulting in stabilization of the cleaved DNA state and inhibition of strand

relegation. This disruption halts DNA replication, induces double-strand breaks, interferes with SOS repair mechanisms, and ultimately leads to rapid bacterial cell death.[11]

Ciprofloxacin is listed in the World Health Organization (WHO) Model List of Essential Medicines and is produced worldwide as a generic active pharmaceutical ingredient (API), resulting in sustained global demand and large scale manufacturing. As a result, the development of efficient, economical, and quality controlled synthetic processes is essential to maintain affordability, ensure bioequivalence among generic formulations, and guarantee consistent access, particularly in low and middle income regions.[6,12] The production of high quality ciprofloxacin API requires rigorous control of impurities, as process related byproducts and degradation impurities can adversely affect drug potency, increase toxicity, and cause non-compliance with pharmacopeial standards, thereby impacting clinical safety and effectiveness.[13,14]

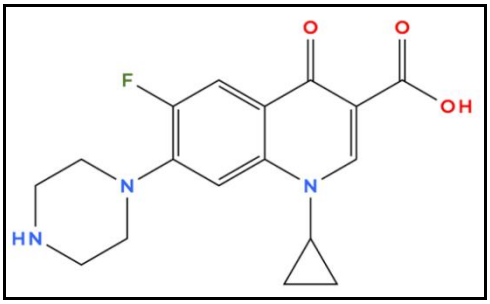


Figure No. 1: Structure of ciprofloxacin.

The synthesis of ciprofloxacin is inherently complex, involving multiple reaction steps and photolabile intermediates that necessitate stringent process control. Even minor changes in synthetic pathways or reaction conditions can substantially alter impurity profiles, product yield, purity, and environmental impact. Over the years, ciprofloxacin manufacturing approaches have progressed from traditional batch processes to modern continuous flow technologies, enabling higher yields (approximately 60-91%), improved scalability, and shorter reaction times through telescoped reaction sequences. Optimization strategies have included the selection of alternative starting materials such as 2,4,5-trifluorobenzoyl chloride, modification of reaction order (acylation followed by amination), variation of cyclization bases including DBU and TBAOH, and replacement of conventional solvents like acetonitrile with greener options such as 2-methyltetrahydrofuran or DMSO.

A comparative assessment of representative synthetic methodologies, including Lin's ultra-fast 9-minute continuous flow process yielding approximately 60% and Armstrong's scalable continuous manufacturing strategy achieving 94% product purity, highlights key differences in efficiency, cost, scalability, and environmental sustainability relative to conventional batch production. Such comparative analyses are essential for informed route selection, process optimization, and guiding future research and development efforts toward sustainable and economically viable ciprofloxacin manufacturing.[15,16]

2. METHODOLOGY

This work was conducted as a comparative analytical review aimed at assessing and contrasting different synthetic routes reported for the synthesis of ciprofloxacin. A structured and systematic strategy was applied to identify, evaluate, and compare protocols documented across both traditional and recent literature in synthetic chemistry. The key methodological steps followed in this review are summarized below.

2.1. Literature review

A comprehensive survey of the published literature was performed using major scientific databases, including PubMed, ScienceDirect, Scopus, SpringerLink, and Google Scholar. Search terms such as *ciprofloxacin synthesis*, *ciprofloxacin preparation* and *reaction optimization* were applied to retrieve relevant studies. Only publications providing explicit experimental information such as the reagents employed, reaction conditions, duration, yield, and purity were considered for inclusion. To enable a thorough comparison, both conventional synthetic methods and more recent advanced approaches were analysed.

2.2 Data Extraction and Protocol Categorization

The selected ciprofloxacin synthesis methods were organized into distinct categories according to the nature of the starting materials, the strategy used for quinolone ring cyclization, and the sequence of amination steps involved in core formation. A total of ten representative synthetic routes were examined, covering traditional batch based procedures, acylation followed by amination pathways, base-mediated intramolecular cyclization employing reagents such as DBU or TBAOH, C-7 piperazine substitution reactions, solid phase synthesis, and advanced continuous flow manufacturing processes. Additional variations arising from the use of different fluorinated benzoyl intermediates, solvent choices, and processing technologies were incorporated to facilitate a comprehensive comparison. For each synthetic approach, key experimental parameters including reaction conditions,

mechanistic features, intermediate profiles, product yield, purity, and scalability were systematically collected and assessed.

2.3 Comparative Analysis Framework

To enable a standardized and objective comparison, an evaluation matrix was developed to assess each ciprofloxacin synthetic route based on relevant process parameters. These included the nature of key starting materials and reagents, cyclization and amination strategies involved in quinolone core formation, reaction mechanisms and critical steps, operating temperature and reaction time, overall yield and product purity, impurity profile, and potential for green chemistry implementation with respect to solvent selection, waste generation, and reagent toxicity. In addition, industrial feasibility, scalability, and process robustness were considered to assess the suitability of each route for large scale manufacture.

2.4 Data Validation and Synthesis

Wherever possible, reported values were cross verified from multiple sources. If discrepancies existed, averages or ranges were considered. Graphical illustrations and reaction schemes were drawn using MolView and ChemDraw, while comparative data were made in table format for better understanding.

2.5 Scope and Limitations

This methodological analysis does not include pilot scale or commercial production data. Instead, it focuses on laboratory-scale procedures and published protocols. Economic analyses (cost per gram, energy use) were beyond the current review's scope and are suggested for future exploration.

3. Different synthetic routes of ciprofloxacin

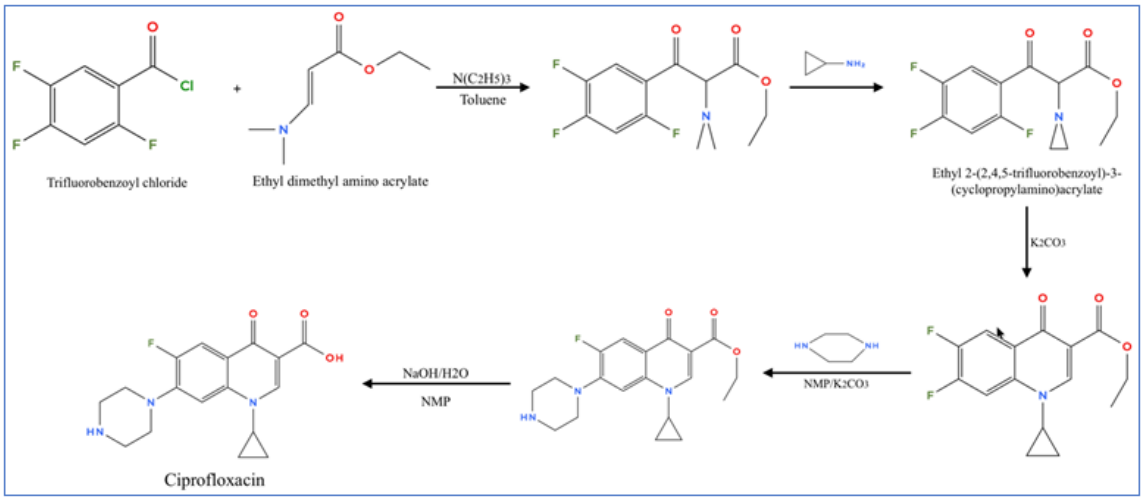
Synthetic route-: Preparation of ciprofloxacin from 2,4,5-trifluoro benzoyl chloride and amino acrylate by original method formulated by Bayer[17,18,19]

Procedure

The synthesis of ciprofloxacin is initiated by charging dimethylaminoacrylate (35.8 g) and triethylamine (27.3 g) into toluene (50 mL), followed by the controlled dropwise addition of 2,4,5-trifluorobenzoyl chloride (24.3 g) at 50°C over a period of 30 minutes. The reaction mixture is then maintained at 50-55°C with continuous stirring for 1 hour to ensure completion of the acylation step. Subsequently, glacial acetic acid (17.3 g) and cyclopropylamine (15.5 g) are introduced slowly while the temperature is regulated between

30 and 36 °C. After stirring for an additional hour, the inorganic salts formed during the reaction are removed by extraction with water (100 mL). The organic layer is then concentrated under reduced pressure using a water-pump vacuum at 40 °C, affording 81.5 g of ethyl 2-(2,4,5-trifluorobenzoyl)-3-(cyclopropylamino)acrylate as an oily intermediate. This intermediate is subsequently dissolved in N-methylpyrrolidone (250 mL) and heated in the presence of potassium carbonate (48.4 g), with the temperature gradually raised from 90 to 120 °C. After 2 hours, piperazine (86 g) is added, and the reaction mixture is stirred at 80-90 °C for 1 hour. The reaction mass is then diluted with water (150 mL), followed by the addition of sodium hydroxide (20 g), and maintained at 70 °C for a further 1 hour. Subsequent dilution with additional water (500 mL) facilitates the removal of trace insoluble impurities by filtration. The pH of the clear solution is adjusted to 7.5 using half-concentrated hydrochloric acid, after which the mixture is cooled to 0-5 °C. Upon standing for 2 hours, ciprofloxacin precipitates as a solid, which is collected by suction filtration, washed twice with water (200 mL each), and dried overnight under vacuum to yield the final product.

Reaction



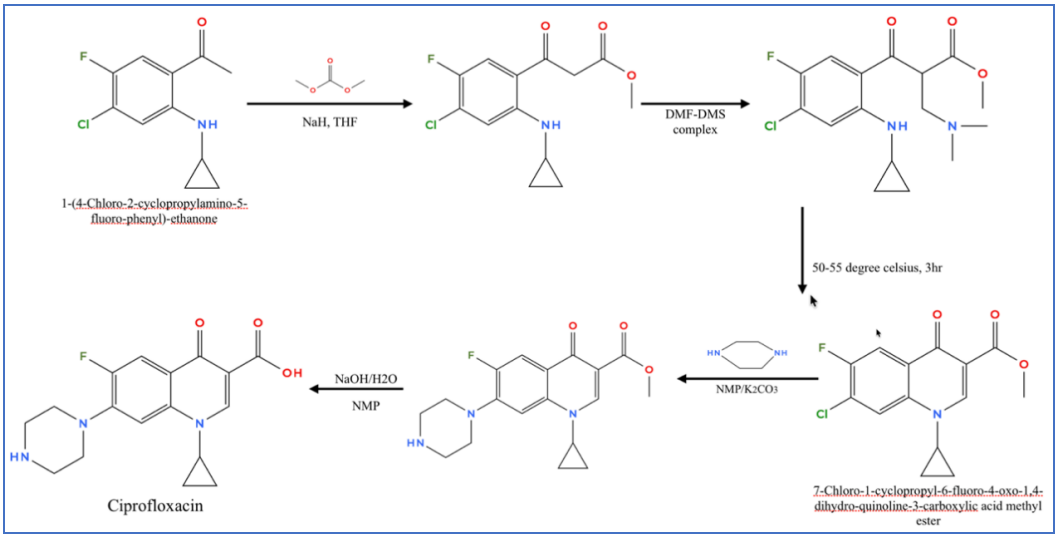
Synthetic route-2: Preparation of ciprofloxacin from 1-(4-Chloro-2-cyclopropylamino-5-fluoro-phenyl)-ethanone and dimethyl carbonate.[17,19,20]

Procedure

The synthetic sequence commences with the generation of a reactive carbonate species by treating sodium hydride (0.70 g) in tetrahydrofuran (30 mL) with dimethyl carbonate (1.58 g), which is introduced at 20-25°C over a period of 5-6 minutes. The reaction temperature is subsequently elevated to 60-65°C, and the mixture is stirred for 20 minutes to ensure complete activation. To this system, a solution of 1-(4-chloro-2-cyclopropylamino-5-

fluorophenyl)ethanone (1.0 g) dissolved in tetrahydrofuran (200 mL) is added at 60-65°C over 10 minutes. The reaction mixture is then maintained at 60–65 °C under stirring for 3 hours to facilitate cyclization. Upon completion, the reaction mass is cooled to 0-5°C, followed by the controlled addition of a DMF–DMS complex (3.5 g) at the same temperature over 5 minutes. The mixture is stirred at 0-5 °C for 1 hour and subsequently heated to 50-55 °C, where it is maintained for 4 hours to drive the reaction to completion. After cooling the mixture to 25-30 °C, the reaction is quenched into ice water (50 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers are washed with water (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1.0 g of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methyl ester. In the subsequent transformation, piperazine (86 g) is introduced to the reaction mass, and the mixture is stirred at 80-90 °C for 1 hour. The reaction is then diluted with water (150 mL), followed by the addition of sodium hydroxide (20 g), and the temperature is maintained at 70 °C for an additional hour. Further dilution with water (500 mL) allows for the removal of trace insoluble impurities by filtration. The pH of the resulting solution is carefully adjusted to 7.5 using half-concentrated hydrochloric acid. Upon cooling the mixture to 0-5 °C and allowing it to stand for 2 hours, ciprofloxacin precipitates as a solid. The product is isolated by suction filtration, washed twice with water (200 mL each), and dried overnight under vacuum to yield the final compound.

Reaction

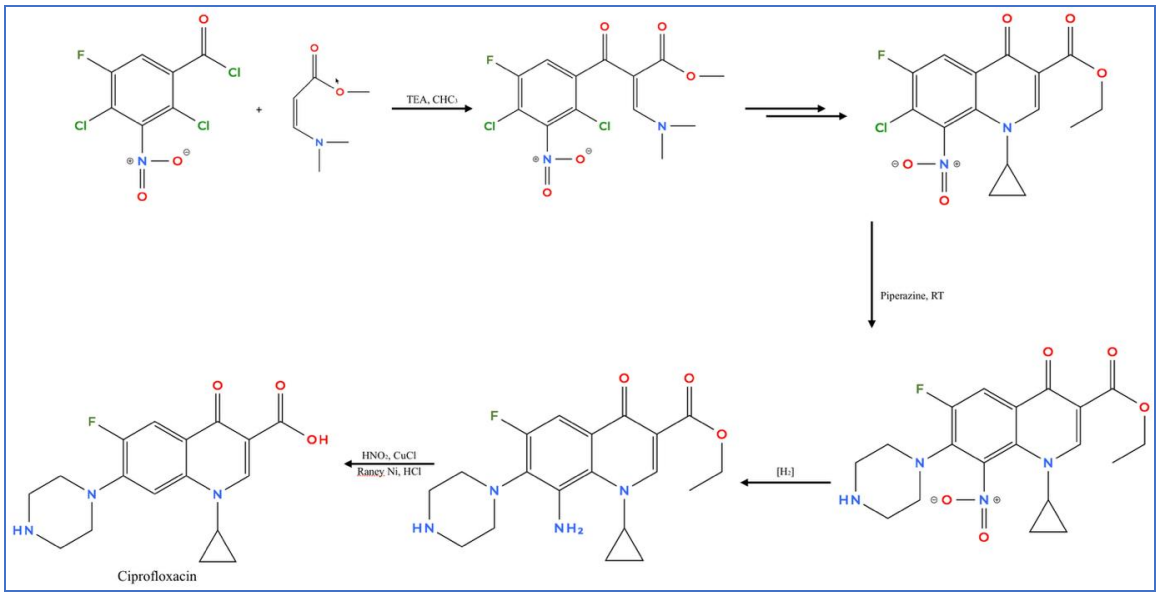


Synthetic route-3: Preparation of ciprofloxacin from 2,4-dichloro-5-fluoro-3-nitrobenzoyl chloride and methyl 3-dimethylaminoethylacrylate.[17,21]

Procedure

The synthetic route toward ciprofloxacin is initiated by combining methyl 3-dimethylaminoethylacrylate (108 g) and triethylamine (92 g) in toluene (1500 mL), with the mixture maintained at 70-80 °C. To this solution, a separate solution of 2,4-dichloro-5-fluoro-3-nitrobenzoyl chloride prepared in toluene (500 mL) is introduced, after which the reaction mixture is refluxed for 6 hours. Upon completion, the mixture is cooled to ambient temperature, diluted with water (1.5 L), and the product is extracted into the organic phase. Removal of the solvent affords 300 g of a crude residue, which is subsequently dissolved in methanol (1000 mL). Cyclopropylamine (54 g) is then added at 0-10 °C, and the mixture is stirred at room temperature for 2-3 hours. The resulting solid is collected by filtration and washed with chilled methanol (200 mL) to yield 240 g of product. A portion of this material (189 g) is next combined with potassium carbonate (57 g) in dimethylformamide (300 mL) and heated at 60-70 °C under stirring. After maintaining these conditions for 3 hours, the reaction mixture is cooled to 15-20 °C and filtered. The solid cake is thoroughly washed with water to remove inorganic residues, followed by a final wash with methanol (100 mL), furnishing approximately 170 g of product. Further functionalization is achieved by stirring 50 g of this intermediate with dimethyl sulfoxide (150 mL), piperazine (13 g), and sodium bicarbonate (13 g) at room temperature overnight. The reaction mixture is poured into water (400 mL), and the precipitated compound is isolated by filtration, affording a yield of approximately 55 g. Subsequently, 33 g of this compound is treated with acetic anhydride (70 mL) and methylene chloride (250 mL) and stirred at room temperature overnight. The reaction mixture is quenched with water, and the product is extracted into methylene chloride. Evaporation of the solvent yields a light-yellow solid weighing 35 g. Reduction of the nitro group is accomplished by charging 26 g of this compound together with Raney nickel (25 g) and methanol (500 mL) into an autoclave, followed by hydrogenation at 20-30 psi for 3-4 hours. Upon cessation of hydrogen uptake, the catalyst is removed by filtration, and concentration of the filtrate affords the reduced compound as a white solid (22 g). Diazotization is then performed by dissolving 5 g of the compound in aqueous sulfuric acid (25 mL of 10%) and cooling the solution to 0-5 °C. A solution of sodium nitrite (0.96 g) in water (3 mL) is added, and the mixture is stirred for an additional 15 minutes. The resulting diazonium solution is introduced into aqueous hypophosphorous acid (50 mL of 15%) maintained at 0-5 °C. After completion of the addition, the reaction mixture is allowed to warm to 25 °C and is maintained overnight. The mixture is then poured into ice water (100 mL), and the product is extracted into methylene chloride (50 mL). Removal of the solvent

yields the intermediate in 4.5 g yield. In the final step, this intermediate is treated with aqueous sodium hydroxide (2 g in 20 mL water) and heated at 70-80 °C for 3 hours. The resulting solution is cooled to room temperature and neutralized with acetic acid to pH 7.0. The precipitated solid is filtered and washed with water to afford ciprofloxacin with a yield of 4.5 g.

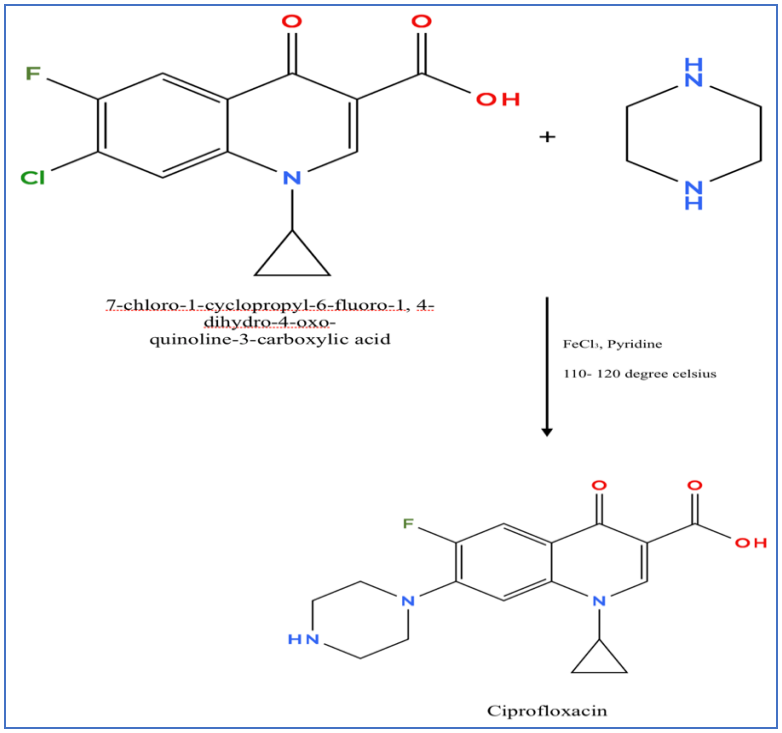


Synthetic route-4: Preparation of ciprofloxacin from 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid in the presence of $FeCl_3$ and pyridine.[17,22]

Procedure

Ciprofloxacin is carried out by heating a suspension comprising 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (100 g), piperazine (81 g), ferric chloride (5 g), and pyridine (175 mL) to reflux conditions (110-120 °C). The reaction mixture is maintained at this temperature for 8-12 hours to ensure complete substitution at the quinolone core. Upon completion, the reaction mass is allowed to cool to 70-80 °C, after which pyridine is removed completely by vacuum distillation below 80 °C and further eliminated by co-distillation with water to ensure the absence of residual solvent. Following solvent removal, water is added and the mixture is cooled to 50-55 °C. At this temperature, the pH is carefully adjusted to 11.5-12.0 using a 20% aqueous sodium hydroxide solution. Ethylenediaminetetraacetic acid (EDTA) is then introduced, and the mixture is stirred for 1-2 hours at 50-55 °C before filtration. The pH of the resulting filtrate is subsequently adjusted to 6.8-7.2 and maintained under these conditions for 2 hours at the same temperature, leading to

precipitation of the product, which is isolated by filtration and washed thoroughly with water. The wet solid is resuspended in water and heated again to 50-55 °C, after which the pH is lowered to 4.0-4.5 using acetic acid. The mixture is stirred for 1 hour under these conditions, followed by the addition of activated carbon (6.8 g) and EDTA (0.046 g). The suspension is maintained at 50-55 °C for an additional hour to facilitate decolorization and metal ion scavenging. After filtration to remove the carbon, the pH of the clear filtrate is readjusted to 6.8-7.2 using 20% aqueous sodium hydroxide solution and stirred for a further hour. The resulting solid is isolated by filtration and washed with water to afford ciprofloxacin.

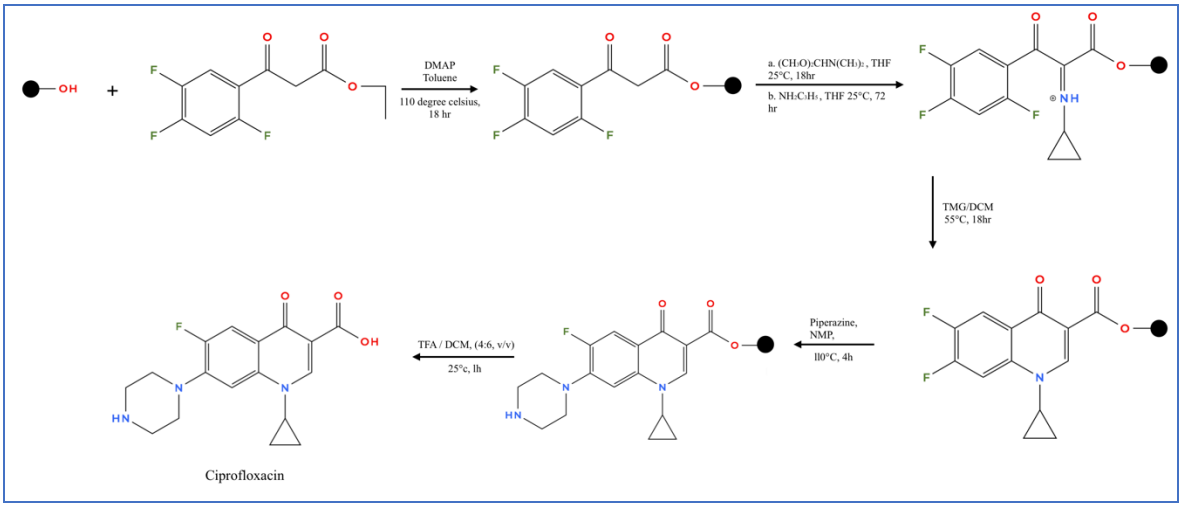


Synthetic route--5: Preparation of ciprofloxacin using solid phase synthesis.[23]

Procedure

The solid-phase synthesis of ciprofloxacin is initiated by anchoring 2,4,5-trifluorobenzoylacetic acid ethyl ester onto *p*-benzyloxybenzyl alcohol (Wang) resin. This coupling is achieved by heating the resin and the β-keto ester in toluene in the presence of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) at 110 °C for 72 hours, resulting in the formation of a resin-bound β-keto ester. Subsequent modification of the immobilized intermediate is carried out by treatment with dimethylformamide dimethyl acetal at 25 °C for 18 hours, followed by reaction with cyclopropylamine at the same temperature for 72 hours, leading to the corresponding resin-bound enamide. Intramolecular cyclization of the enamide is then induced by exposure to a solution of tetramethylguanidine (TMG) in dichloromethane,

with the reaction maintained at 55 °C for 18 hours to furnish the resin-bound quinolone framework. Functionalization at the C-7 position is subsequently achieved by reacting the immobilized quinolone with piperazine dissolved in *N*-methylpyrrolidinone (NMP) at 110 °C for 4 hours, thereby generating the resin-bound ciprofloxacin derivative. Final cleavage from the solid support is accomplished by treating the resin-bound product with a mixture of trifluoroacetic acid and dichloromethane at 25 °C for 1 hour, affording ciprofloxacin in its free form.

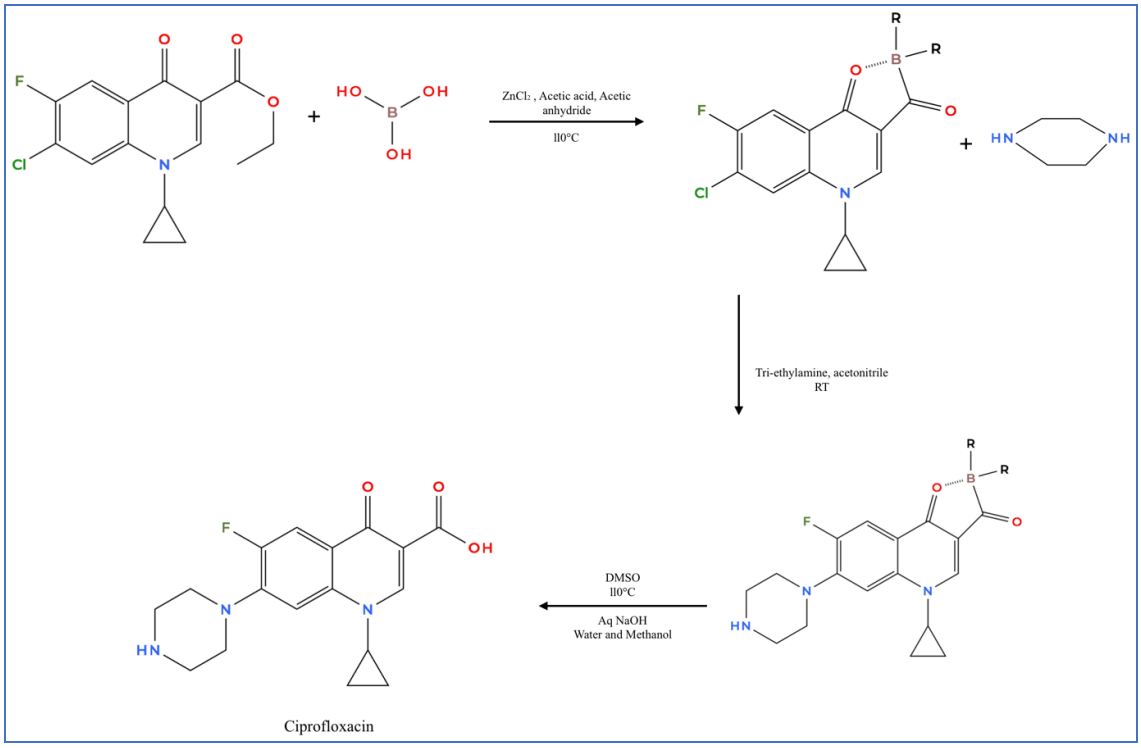


Synthetic route- 6: Preparation of ciprofloxacin from ethyl 1-cyclopropyl-6-fluoro-7-chloro-1,4- dihydro-4-oxo-quinoline-3-carboxylate with (1-cyclopropyl-6-fluoro7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylate- O^3,O^4)-bis(aceto-O)-boron as a key intermediate.[22,24]

Procedure

The synthetic sequence begins with the preparation of a boron-complexed quinolone intermediate. Boric acid (57.2 g, 0.925 mol) and zinc chloride (1.24 g) are combined and treated with acetic anhydride (300 mL), after which the mixture is stirred at 110 °C for 1.5 hours. Glacial acetic acid (400 mL) is subsequently introduced, and stirring is continued for an additional hour at the same temperature. After cooling the reaction mixture, ethyl 1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (200 g, 0.619 mol) is added at 50-60 °C, followed by the addition of glacial acetic acid (200 mL). The resulting mixture is maintained under reaction conditions for 5 hours. Upon completion, the reaction mass is concentrated under reduced pressure, and the resulting oily residue is poured into ice water (8 L). The precipitated solid is collected by filtration, resuspended in water (3 L), filtered again, and dried to afford (1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-

quinoline-3-carboxylate-O^3,O^4)-bis(aceto-O)-boron as a light orange-yellow powder (249 g). For nucleophilic substitution, a portion of this boron complex (12.3 g, 29.1 mmol) is treated with 2-methylpiperazine (4.38 g, 43.7 mmol), triethylamine (8.2 mL), and acetonitrile (30 mL). The reaction mixture is stirred at room temperature overnight. After removal of the solvent by distillation, the residue is dissolved in ethyl acetate (40 mL), washed with water, and dried over anhydrous sodium sulfate. Concentration and drying under reduced pressure furnish (1-cyclopropyl-6-fluoro-7-piperazinyl-1,4-dihydro-4-oxo-quinoline-3-carboxylate-O^3,O^4)-bis(aceto-O)-boron in 12.9 g yield (91.0%). Final conversion to ciprofloxacin is achieved by subjecting this intermediate to conventional hydrolysis using aqueous sodium hydroxide in the presence of water and methanol as solvents, affording ciprofloxacin as the final product.

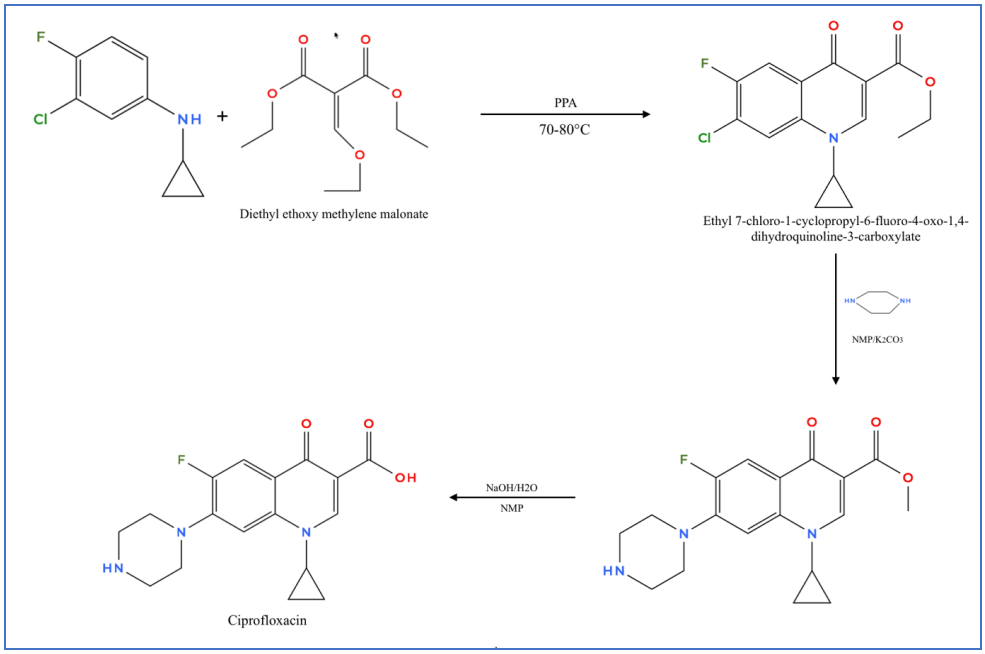


Synthetic route-7: Preparation of ciprofloxacin from 3-Chloro-N-cyclopropyl-4-fluoroaniline and diethyl ethoxy methylene malonate.[17,25]

Procedure

The synthetic sequence begins with the formation of a substituted aniline intermediate. A mixture of 3-chloro-4-fluorophenol and 2-chloro-*N*-cyclopropylacetamide is introduced into a stirred solution of potassium carbonate in toluene at 20-25 °C. The reaction mixture is gradually heated to 105-110 °C and maintained at this temperature for 6-8 hours to promote

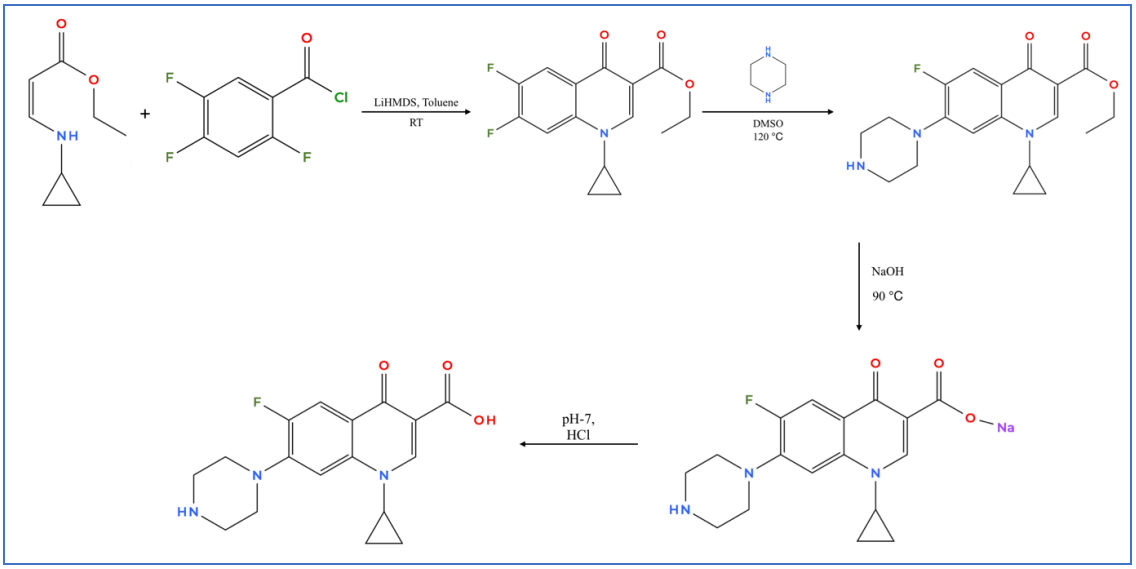
ether formation. Upon completion, the solvent is removed under reduced pressure at 50 °C. The resulting residue is transferred into 10% aqueous sodium hydroxide (200 mL) at room temperature and stirred for 2 hours to selectively remove unreacted phenol. The precipitated solid is isolated by filtration and washed thoroughly with water. This material is then added to a stirred solution of potassium hydroxide and *N*-methyl-2-pyrrolidinone (NMP) in toluene at 20-25 °C. The reaction mixture is heated to 120-130 °C and maintained for 12 hours. After cooling to 40-45 °C, water (200 mL) is added with stirring, and the organic and aqueous layers are allowed to separate. The aqueous phase is extracted with toluene (100 mL), and the combined organic layers are washed with water and concentrated by solvent evaporation to afford 3-chloro-*N*-cyclopropyl-4-fluoroaniline as a yellow liquid. This aniline intermediate is subsequently condensed with diethyl ethoxymethylenemalonate (EMME), and the resulting condensation product, diethyl {[(3-chloro-4 fluorophenyl) (cyclopropyl) amino]methylene} malonate, is subjected to cyclization using polyphosphoric acid (PPA). The reaction mixture is stirred at 70-80 °C for 2 hours, after which it is cooled and further chilled prior to the addition of water (100 mL). The aqueous suspension is stirred for 1 hour at 0-25 °C, and the precipitated solid is collected by filtration and washed with water (20 mL). The isolated solid contains the desired ethyl 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate. In the final transformation, piperazine (86 g) is introduced, and the reaction mixture is stirred at 80-90 °C for 1 hour, followed by dilution with water (150 mL). Sodium hydroxide (20 g) is then added, and the temperature is maintained at 70 °C for an additional hour. Further dilution with water (500 mL) allows for the removal of trace insoluble impurities by filtration. The pH of the clear solution is adjusted to 7.5 using half-concentrated hydrochloric acid, after which the mixture is cooled to 0-5 °C. After standing for 2 hours, ciprofloxacin precipitates and is isolated by suction filtration, washed twice with water (200 mL each), and dried overnight under vacuum to afford the final product.



Synthetic route-8: Preparation of ciprofloxacin from Ethyl-3 (cyclopropylamino) acrylate and Ethyl 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydro- quinoline-3-carboxylate.[26]

Procedure

The transformation is initiated in an oven-dried three-necked round-bottom flask fitted with a magnetic stirrer and maintained under an argon atmosphere. Lithium bis(trimethylsilyl)amide in toluene (1 M, 70.54 mL, 70.54 mmol) is introduced and the solution is cooled to -78 °C. To this cooled base, the acrylate intermediate 3a (5 g, 32.2 mmol) is added slowly, producing a bright yellow reaction mixture that is stirred for 30 minutes. Subsequently, 2,4,5-trifluorobenzoyl chloride (6.89 g, 35.48 mmol) is added dropwise over 10 minutes while maintaining the low temperature. The reaction mixture is then allowed to warm gradually to room temperature over the course of 1 hour and is stirred for an additional hour to ensure completion of the acylation step. Upon completion, the reaction mixture is diluted with dimethyl sulfoxide (30 mL), followed by the addition of piperazine (11 g, 128 mmol). The resulting mixture is heated to 120 °C and maintained at this temperature for 2 hours. After confirming complete consumption of intermediate 6a, the temperature is reduced to 90 °C and sodium hydroxide (2.6 g, 65 mmol) is added. The mixture is stirred for a further 1 hour, cooled to room temperature, and diluted with water (30 mL). The pH is then carefully adjusted to 7 using 4 N hydrochloric acid. The reaction mixture is subsequently stored at 4 °C, allowing ciprofloxacin to precipitate gradually. The resulting solid is isolated by filtration, washed three times with water, and dried to afford ciprofloxacin as a yellow solid



4. Comparative analysis of various synthetic routes of ciprofloxacin

To facilitate a clearer comparison of the different synthetic strategies reported for ciprofloxacin, a comprehensive comparative table has been compiled. This table systematically evaluates each route with respect to key factors, including the nature of the starting materials, the principal mechanistic transformations involved, reaction conditions, final yield and product purity, along with the inherent strengths and limitations of each approach. Such a structured comparison enables an informed assessment of the suitability of individual methods for laboratory-scale synthesis, industrial application, or alignment with green chemistry principles.

Sl. no	Synthetic Route	Key steps	Reaction conditions	% Yield	Purity	pros	Cons	Ref.no.
1	Classical route by Bayer (**Route-1**)	Condensation, Cyclisation, Hydrolysis	30°C-120°C, Toluene, NMP, 8.5 hrs.	84.5%	Very High	High yield	Expensive Starting Material	[17,18,19]
2	Modified Gould Jacobs route by Suven (**Route-2**)	Condensation, Cyclization, Substitution	Multi-stage heating, 50-90°C, 10 hrs.	58%	Moderate	Simple starting materials	Moderate overall yield	[17,19,20]
3	Nitro-directed quinoline synthesis (**Route-3**)	Cyclization, Reduction, Deamination	Variable temperatures, 55 hrs.	90-95%	Excellent	High selectivity, no impurities	Uneconomical, extra steps	[17,21]
4	Nucleophilic Aromatic Substitution (**Route-4**)	Condensation, Cyclization, Hydrolysis	110-120°C for 8-12 Hours	76.0%	Very High	Low Impurity Formation	Strict Solvent Removal	[17,22]

5	Solid-phase synthesis (**Route-5**)	Transesterification, enamide formation, cyclisation, nucleophilic substitution, and acid cleavage.	25-110°C, Toluene, THF, and NMP, 185 hrs.	13%	Very Low	Very High purity	Low Yield, Long Time	[23]
6	Borate Chelate Route (**Route-6**)	Chelation, Substitution, Hydrolysis	25-110°C, 13 hrs.	91%	High	High Yield and Purity	Multiple Complex Steps and expensive reagents.	[22,24]
7	Smiles rearrangement of Modified Gould-Jacobs (**Route-7**)	Rearrangement and Cyclisation	20 hrs, 70-130°C	52%	Low	Scalable and Reproducible	Unwanted Isomer Formation	[17,25]
8	One pot synthesis (**Route-8**)	Acylation, Cyclization, Coupling, Hydrolysis	6hrs, -78°C-120°C	83%	High	Streamlined and Efficient	Requires Cryogenic Cooling	26

5. CONCLUSION

An evaluation of eight distinct synthetic approaches for the preparation of ciprofloxacin reveals notable differences in cyclization and amination strategies involved in quinolone core formation, reaction pathways, and operational efficiency. Among these, the conventional Gould-Jacobs reaction followed by nucleophilic substitution with piperazine continues to dominate industrial practice owing to its operational simplicity, reproducibility, and consistently high yields. More recent methodologies, particularly microwave assisted synthesis and one pot reactions, have demonstrated considerable improvements by significantly shortening reaction times while enhancing yields and reducing environmental impact. Alternative strategies employing transition metal catalysis and solvent-free protocols introduce innovative concepts; however, their broader adoption is limited by challenges such as reduced efficiency, increased costs, or technical complexity. Collectively, the success of ciprofloxacin synthesis is governed by a balance of reaction efficiency, product purity, reagent safety, economic feasibility, and overall sustainability.

6. Future perspective

Future research should focus on designing synthetic strategies for ciprofloxacin that are both environmentally sustainable and energy efficient. In particular, microwave assisted methodologies and transition metal mediated C-H activation pathways show considerable potential and merit further refinement to enable large scale implementation. Concurrently,

exploration of photo induced cyclization processes and one pot cascade reactions may further advance compliance with green chemistry principles. Additionally, the adoption of flow chemistry and automated synthesis platforms offers significant advantages in improving process safety, reproducibility, and product yield, thereby supporting the development of more economical and sustainable ciprofloxacin manufacturing processes across industrial and academic domains.

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Data Availability Statement: All data analysed in this study are included in the article and its referenced sources.

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