Nature of Invention: Chemical molecule and synthesis route

Applicant: SynergyX

Inventors: Aryan Singh, Satyam Kumar

Chemical Formula: ($C_{18}H_{20}FN_3O$)

Chemical Name: Levofloxacin

Chemical synthesis routes:

a. Synthesis of Levofloxacin from Piperazine:

RAW MATERIALS REQUIRED:

1. Piperazine ($C_4H_{10}N_2$)
2. N-Fluorinating reagent (e.g., N-fluorobenzenesulfonimide (NFSI), N-fluoropyridinium salts)
3. Cyclopropylating reagent (e.g., cyclopropyl isocyanate, cyclopropyl carbamate)
4. Chiral resolving agent (e.g., tartaric acid)
5. Hydrochloric acid (HCl)
6. Ethanol
7. Methanol
8. Dichloromethane (DCM)
9. Acetonitrile
10. Water (for aqueous reactions and crystallization)

UTILITIES REQUIRED:

1. Reactor vessel
2. Jacketed reactors or external heat exchangers
3. Mechanical stirrers or agitators
4. UV-visible spectrophotometer, HPLC (High-Performance Liquid Chromatography), or GC (Gas Chromatography) systems
5. Vacuum filtration apparatus or centrifuges
6. Rotary evaporators or distillation units
7. Filtration units, drying ovens, or vacuum dryers
8. Acid addition tanks or automated pH control units PROCESS ANALYSIS:

1. **Fluorination of Piperazine**:
   - Temperature: Room temperature (around 20-25°C)
   - Pressure: Atmospheric pressure
   - Solvent: Typically an inert solvent like dichloromethane (DCM) or acetonitrile is used, but sometimes the reaction can be performed without a solvent.
   - Reaction Time: Several hours to overnight, depending on the specific conditions and reagents used.
   - Stirring: Mild to moderate agitation to ensure good mixing of reactants.
   - Chemical Equation:

$$Piperazine + N - Fluorinating\ Reagent \rightarrow Fluorinated\ Intermediate$$

The specific N-fluorinating reagent commonly used in this process is Nfluorobenzenesulfonimide (NFSI).

$$C_4H_{10}N_2 + NFSI \rightarrow 1 - Cyclopropyl - 6 - fluoro - 1{,}4 - dihydro - 7 - (4 - ethyl - 1 - piperazinyl) - 4 - oxoquinoline - 3 - carboxylic\ acid + Byproducts$$

2. **Cyclopropyl Group Addition**:
   - Reactor Type: Stainless steel or glass-lined
   - Temperature: Maintain the reaction temperature in the range of 50-100°C, depending on the specific reagents and reaction kinetics.
   - Solvent: Depending on the reagents used, you may need an appropriate solvent (e.g., dichloromethane, acetonitrile) for dissolving the reactants and promoting the reaction.
   - Reaction Time: Allow the reaction to proceed for several hours, typically around 4-12 hours, to ensure sufficient conversion of the intermediate to levofloxacin.
   - Agitation: Use mechanical stirrers or agitators to ensure thorough mixing of the reactants and promote uniform reaction conditions.
   - Inert Atmosphere: In certain cases, maintaining an inert atmosphere (e.g., nitrogen or argon) can help prevent unwanted side reactions or degradation of sensitive compounds.
   - Monitoring: Continuously monitor the reaction progress using analytical techniques such as TLC (Thin-Layer Chromatography) or HPLC (HighPerformance Liquid Chromatography) to assess the conversion and purity of the product.
   - Chemical Equation: The fluorinated intermediate reacts with a cyclopropylating reagent (e.g., cyclopropyl isocyanate) to introduce the cyclopropyl group at the 1-position of the quinolone ring, yielding levofloxacin.

$$Fluorinated\ intermediate + Cyclopropylating\ reagent \rightarrow Levofloxacin$$

3. **Chiral Resolution**:
   - Solvent: Suitable solvent such as ethanol or methanol.
   - Temperature: Controlled temperature around room temperature (20-25°C).

- pH Control: Adjust the pH of the solution to promote salt formation and crystallization.
- Crystallization: Allow the diastereomeric salts to crystallize under controlled conditions.
- Separation: Use filtration or centrifugation to separate the crystals of the resolved levofloxacin salt.
- Chemical Equation (assuming tartaric acid as the resolving agent):
  The racemic mixture of levofloxacin (Rac-Levofloxacin) reacts with tartaric acid to form diastereomeric salts, with only one enantiomer of levofloxacin forming a crystalline salt and precipitating out:

$$Rac - Levofloxacin + Tartaric\ Acid \rightarrow Diastereomeric\ Salts$$

- Procedure:
  1. Dissolve the racemic mixture of levofloxacin in ethanol or methanol.
  2. Add a stoichiometric amount of tartaric acid to the solution and stir until complete dissolution.
  3. Adjust the pH of the solution to promote salt formation (typically pH 2-4 for tartaric acid).
  4. Allow the diastereomeric salts to crystallize by controlled cooling or evaporation of the solvent.
  5. Separate the crystals of (S)-Levofloxacin tartrate by filtration or centrifugation.
  6. Wash the crystals with cold solvent to remove impurities.
  7. Dry the purified (S)-Levofloxacin tartrate crystals under vacuum to obtain pure levofloxacin.

4. **Salt Formation**:
   - Chemical Equation:
     $$Levofloxacin + Hydrochloric\ acid\ (HCl) \rightarrow Levofloxacin\ hydrochloride$$
   - Operating Conditions:
     1. Reactor vessel: Suitable for handling the acid-base reaction and mixing the reactants uniformly.
     2. Temperature: Typically carried out at room temperature (20-25°C) to avoid excessive heat generation.
     3. pH control: Maintain the pH around 2-3 to ensure the formation of levofloxacin hydrochloride.
     4. Reaction time: Allow sufficient time for the reaction to complete, usually a few hours.
     5. Solvent: Water or a water-miscible solvent may be used as the reaction medium.
     6. Safety precautions: Handle hydrochloric acid with care due to its corrosive nature. Provide adequate ventilation and use appropriate personal protective equipment (PPE).
   - Detailed Description:

The reaction proceeds as follows:

$$Levofloxacin + HCl \rightarrow Levofloxacin\ hydrochlorideLevofloxacin + HCl \rightarrow Levofloxacin\ hydrochloride$$

Levofloxacin, which is a weak base, reacts with hydrochloric acid (HCl), a strong acid, to form levofloxacin hydrochloride. This salt formation occurs due to the protonation of the amino group in levofloxacin by the hydrogen ion (H+) from hydrochloric acid. The resulting salt, levofloxacin hydrochloride, is often preferred for pharmaceutical use due to its improved solubility and stability compared to the free base form of levofloxacin.

b. <u>Synthesis of Levofloxacin from Piperazine:</u>

MATERIALS REQUIRED:

1. Asymmetric Synthesis of the Quinolone Core:
   Chiral ketone or aldehyde precursor (e.g., chiral α-amino acid-derived ketone)
   Nucleophile or reagent (e.g., amine, alkoxide)
   Chiral catalyst (e.g., chiral organometallic complex or ligand)
   Solvents (e.g., dichloromethane, ethanol)
   Reaction vessels and equipment
   Enantioselective Fluorination:

2. Quinolone core with desired stereochemistry
   Fluorine source (e.g., hydrogen fluoride, boron trifluoride etherate)
   Chiral fluorinating agent or catalyst
   Solvents
   Reaction vessels and equipment

3. Completion of Levofloxacin Structure:
   Fluoroquinolone intermediate
   Additional reagents or functional groups for final modifications (specific compounds depend on the synthetic route)
   Solvents
   Reaction vessels and equipment

UTILITIES REQUIREMENTS:

1. Reaction Vessels:
   Round-bottom flasks: Commonly used for carrying out reactions, especially those involving reflux.
   Reaction tubes or vials: Used for smaller scale reactions or reactions requiring sealed conditions.
   Pressure vessels: In case reactions require elevated pressure conditions.
   Stirred reactors: Used for reactions requiring continuous stirring.

2. Heating and Cooling Equipment:
   Heating mantles or oil baths: Provide controlled heating for reactions conducted at elevated temperatures.
   Heating blocks: Used for heating reaction tubes or vials.
   Refrigerated circulators: Provide precise temperature control for reactions conducted at low temperatures.
   Cryogenic baths: Maintain temperatures below ambient for reactions requiring very low temperatures.

3. Stirring and Mixing Equipment:
   Magnetic stirrers: Used for stirring reaction mixtures to ensure uniform mixing.
   Stir bars: Placed inside reaction vessels to facilitate stirring.
   Overhead stirrers: Employed for more vigorous stirring in larger reaction vessels.

4. Reaction Monitoring Equipment:
   Spectroscopic instruments: Such as NMR, IR, or UV-Vis spectrometers for monitoring reaction progress and product identification.
   Chromatography equipment: Including HPLC or GC systems for analyzing reaction mixtures and purifying products.

5. Safety Equipment:
   Fume hood: Provides ventilation to remove potentially hazardous vapors generated during reactions.
   Safety goggles and gloves: Protect against chemical exposure. Fire extinguisher: In case of emergencies.

6. Additional Equipment:
   Vacuum pumps: Used for solvent removal or creating vacuum conditions.
   Filtration equipment: Such as vacuum filtration apparatus for isolating solid products.
   pH meters and titration equipment: For controlling reaction pH or carrying out acid base reactions.
   Analytical balances: For accurately measuring reagents and reaction components.

PROCESS ANALYSIS:

Asymmetric Synthesis of the Quinolone Core:

Chemical Equation:

$$Chiral\ Ketone/Aldehyde + Nucleophile \rightarrow Quinolone\ Core$$

Description: In this step, a chiral ketone or aldehyde, often derived from chiral α-amino acids or other chiral building blocks, reacts with a nucleophile to form the quinolone core. The reaction is typically catalyzed by a chiral catalyst to induce asymmetric induction, ensuring the formation of the desired enantiomer. The choice of nucleophile and catalyst, as well as reaction conditions such as temperature, solvent, and reaction time, are critical for achieving high yields and enantiomeric excess.

Operating Conditions:

Temperature: Typically ranges from 0°C to 100°C.

Pressure: Atmospheric pressure.
Solvent: Commonly used organic solvents such as dichloromethane, ethanol, or tetrahydrofuran (THF).
Reaction Time: Several hours to days, depending on the reaction kinetics and complexity.

Process:

- Prepare a chiral ketone or aldehyde precursor from a suitable chiral starting material, such as chiral α-amino acids.
- React the chiral ketone or aldehyde with a nucleophile, such as an amine or an alkoxide, to form the quinolone core. This reaction is typically catalyzed by a chiral catalyst to induce asymmetric induction.
- Purify the quinolone core to isolate the desired enantiomer.

Enantioselective Fluorination:

Chemical Equation:

$$Quinolone\ Core + Fluorine\ Source \rightarrow Fluoroquinolone(Chiral\ Catalyst)$$

Description: In this step, the quinolone core with the desired stereochemistry obtained from the previous step reacts with a fluorine source, typically a fluorinating agent or fluoride ion, to introduce a fluorine atom at a specific position. The reaction is mediated by a chiral fluorinating agent or catalyst to ensure enantioselectivity. Selectivity of fluorination is crucial as it determines the stereochemistry of the final product, levofloxacin.

Operating Conditions:

Temperature: Ranges from -20°C to 100°C, depending on the reactivity of the fluorine source and the stability of the reaction intermediates.
Pressure: Typically atmospheric, but may vary depending on the reaction setup.
Solvent: Similar to those used in the first step.
Reaction Time: Varied, depending on the kinetics of fluorination and desired yield.

Process:

- Take the quinolone core obtained from the previous step.
- React the quinolone core with a fluorine source, such as hydrogen fluoride (HF) or boron trifluoride etherate (BF3·Et2O), under the influence of a chiral fluorinating agent or catalyst.
- Selectively introduce a fluorine atom at a specific position in the quinolone core to form the fluoroquinolone intermediate.
- Purify the fluoroquinolone intermediate to isolate the desired enantiomer.

Completion of Levofloxacin Structure:

Chemical Equation:

$$Fluoroquinolone + Additional\ Reagent \rightarrow Levofloxacin$$

Description: In this final step, the fluoroquinolone intermediate obtained from the previous step undergoes further modifications to complete the levofloxacin molecule. This may involve introducing additional side chains or functional groups necessary for levofloxacin's

pharmacological activity. The specific reactions and reagents employed depend on the synthetic route chosen.

Operating Conditions:

Temperature: Typically ranges from room temperature to over 100°C, depending on the specific reactions involved.
Pressure: Atmospheric pressure.
Solvent: Similar to those used in the previous steps.
Reaction Time: Varied, depending on the complexity of the modifications and desired yield

Process:

- Take the fluoroquinolone intermediate obtained from the previous step.
- Carry out further modifications to the fluoroquinolone core to complete the levofloxacin molecule. This may involve introducing additional side chains or functional groups necessary for levofloxacin's pharmacological activity.
- Purify the final levofloxacin product to obtain high purity and yield.

List the contributions of author : Satyam Kumar(first process), Aryan Singh(second process)

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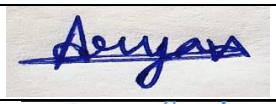
Aryan Nigam	220227	
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