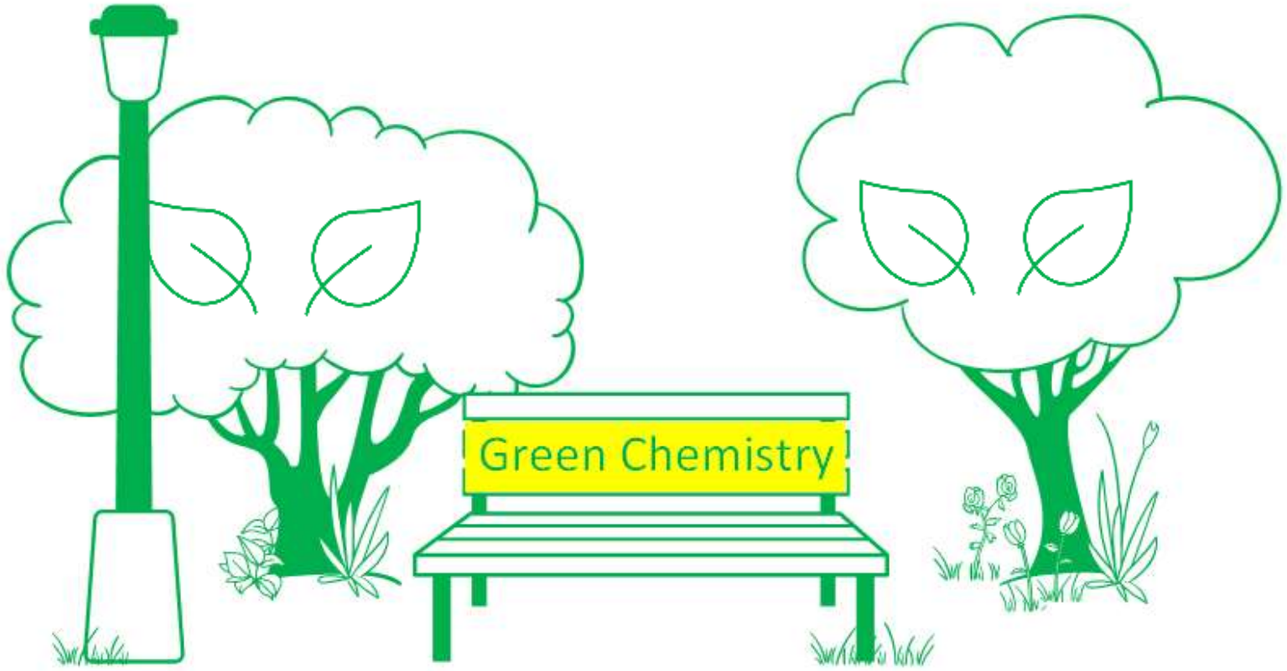

# API Case Studies Developed Through Application of Green Principles/Technologies

Dr. Harishchandra S Jadhav
Assistant Director, Lupin Limited

# Talk Covers….

- Introduction and Significance of Green Chemistry
- Green Principles and Green Metrics
- API-Case Studies at Lupin Limited
- Challenges and Limitations
- Future Trends in Green Chemistry
- Conclusion
- Q & A
- Acknowledgements

# Introduction




## Green Chemistry

**The <u>design</u> of chemical products or processes to reduce or eliminate the use and generation of hazardous* substances.**

***Hazardous includes global, physical and toxicological hazards**

# The Significance of Green Chemistry

**UN World Commission on Environment and Development :**

**Report of the World Commission on Environment and Development:**

**Our Common Future**

- **The report defined the principle of sustainable development as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs."**
- **The publication of the report is considered a milestone in triggering international awareness and discourse on the importance of global sustainable development.**

**Industry: Producing More With Less**

**I. Industrial Growth and its Impact**

**II. Sustainable Industrial Development in a Global Context**

**III. Strategies for Sustainable Industrial Development**


Reference : *UN World Commission on Environment and Development, ed., Report of the World Commission on Environment and Development: Our Common Future | Environment & Society Portal (environmentandsociety.org)*

# Principles of Green Chemistry

Silver Jubilee Year
2023

Prof. Paul Anastas

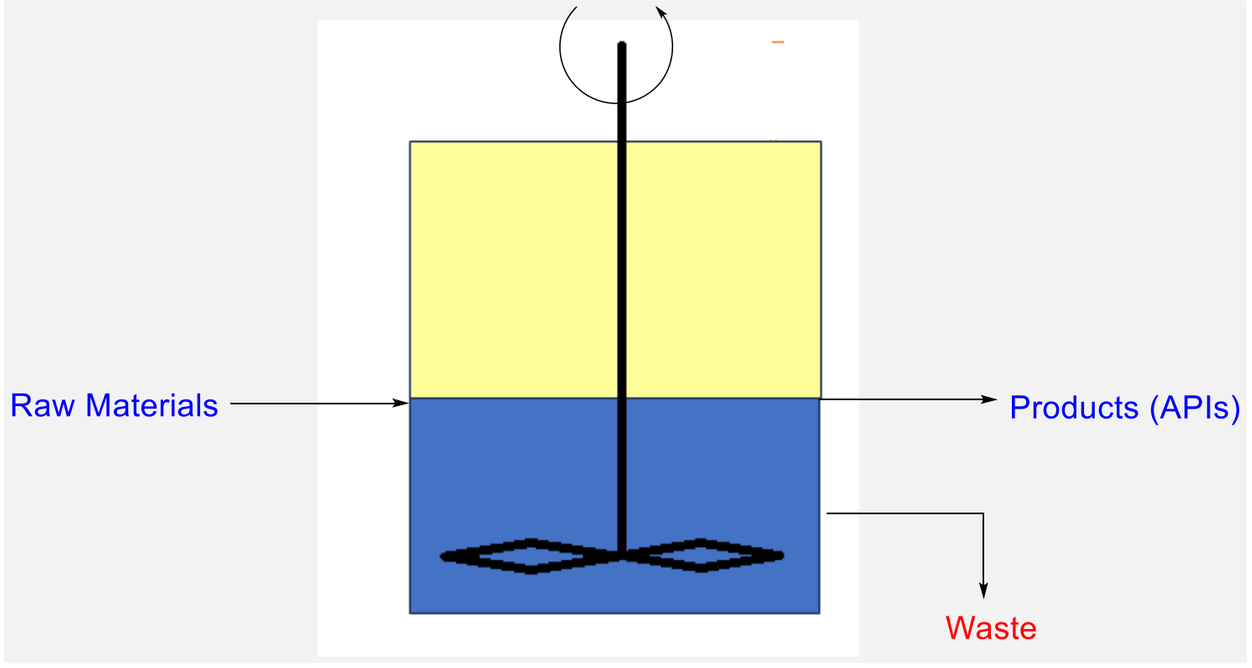
Prof. John Warner

1. Prevent pollution and waste
2. Design safer chemicals and products: Atom Economy
3. Design less hazardous chemical syntheses
4. Design safer chemicals
5. Use safer solvents and auxiliaries
6. Increase energy efficiency
7. Use renewable feedstocks
8. Reduce derivatives
9. Use catalysts, not stoichiometric reagents
10. Design for degradation
11. Analyze in real-time to prevent pollution
12. Minimize the potential for accidents

***Reference : P. T. Anastas, J. C. Warner, "Green Chemistry: Theory and Practice," Oxford University Press, New York, 1998, pp. 30***

## API in Pharmaceuticals

- Biologically active components of a drug
- Chemical-based compounds that have produced globally
- Used to create drugs and pharmaceutical products to diagnose, cure, mitigate, and treat the disease



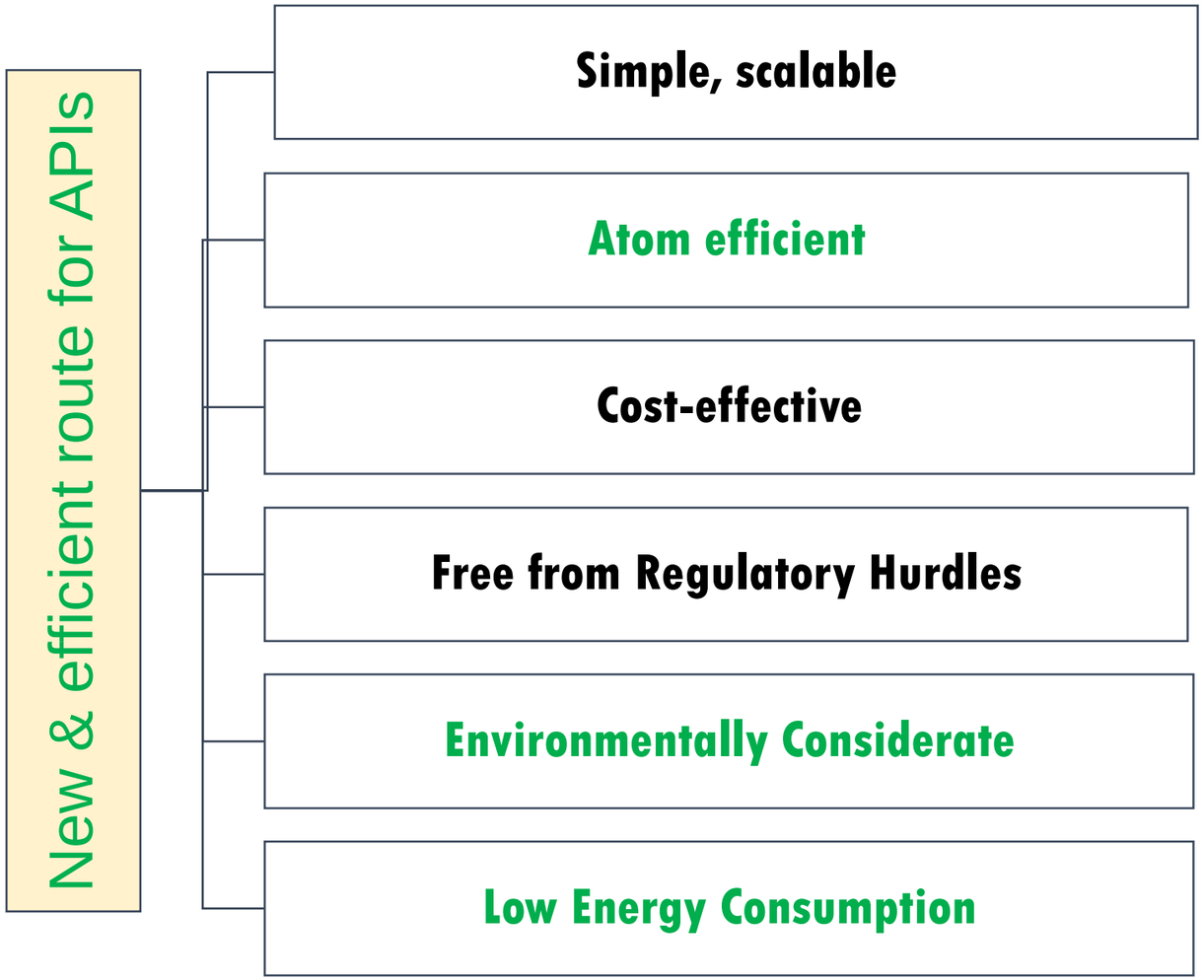

$$E = \frac{\text{Kg waste}}{\text{Kg product}}$$

### E - Factors in the chemical industry

| Sector | Product tonnage (p/a) | E-Factor |
|---|---|---|
| Bulk Chemicals | $10^4$–$10^6$ | <1–5 |
| Fine Chemicals | $10^2$–$10^4$ | 5–50 |
| Pharmaceuticals | 10–$10^3$ | 25 –<100 |

*Reference :* Roger Arthur Sheldon, ***The E factor at 30: a passion for pollution prevention*** *Green Chem.*, 2023,**25**, 1704-1728

# Active Pharmaceutical Ingredients (APIs) - Process Chemistry




Reference : ***ACS Sustainable Chem. Eng.*** **2022, 10, 16, 5148–5162**

# Solvent Selection Overview of the 12 principles of green chemistry

***Role of Solvents in API manufacturing :***

Solvents are extensively used in the pharmaceutical industry for a variety of processing tasks, such as

- Chemical reactions
- Separations
- Column chromatography
- Formulations

***Key impact of the solvent on API process performance***

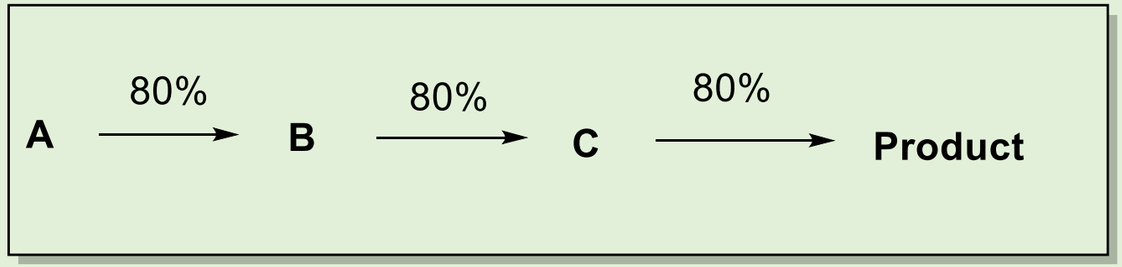
- ✓ Solvents represent a major green chemistry theme of 12 principles of green chemistry
- ✓ Solvents used in API production contribute to more than 80% of the overall mass utilization
- ✓ Most solvents are classified with respect to their environmental toxicity and biodegradability, in an Environmental Hazard Band system.

***Criteria for solvent selection***


Reference: *Proc Math Phys Eng Sci. 2015 Nov 8; 471(2183): 20150502.*

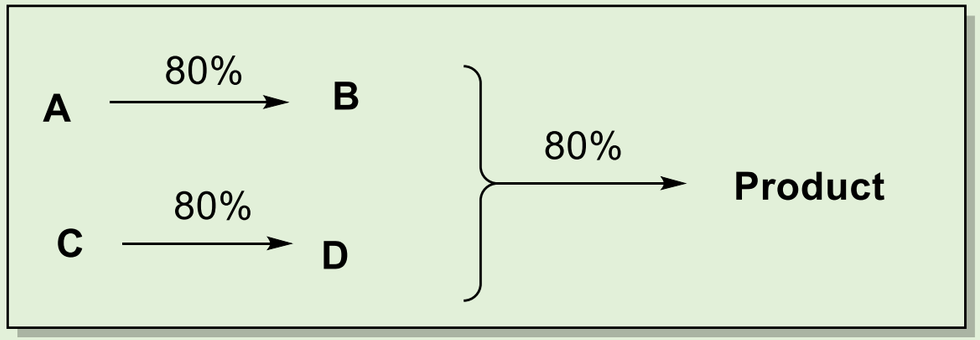
# Preferred choice for route selection: Linear Vs Convergent Synthesis

## Linear Synthesis




Overall Yield = 80% X 80% X 80% = 51%

## Convergent Synthesis




Overall Yield = 80% X 80% = 64%

*Ref : Org. Process Res. Dev.* 2012, 16, 11, 1697–1706

## Green Metrics

$$\text{Effective mass yield (\%)} = \frac{\text{Mass of Product} * 100}{\text{Mass of non benign reagents}}$$

$$\text{E-factor} = \frac{\text{Total waste (KG)}}{\text{Product (KG)}}$$

$$\text{Atom economy} = \left( \frac{\text{M.W. of Product}}{\text{M.W of reactatnt 1} + \text{M.W of reactant 2}} \right) * 100$$

$$\text{Process Mass intensity} = \frac{\text{Total mass used in the process or step (Kg)}}{\text{Mass of product (Kg)}}$$

$$\text{Reaction mass efficiency (RME)} = \left( \frac{\text{mass of product}}{\text{mass of reactatnt 1} + \text{mass of reactant 2}} \right) * 100$$

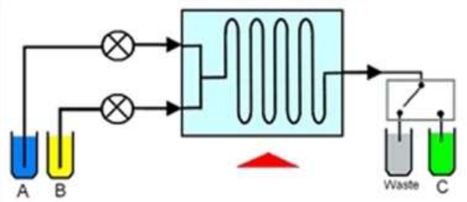
$$\text{Carbon efficiency} = \frac{\text{no. of moles of product} * \text{no. of carbons in the product} * 100}{(\text{moles of A} * \text{carbons in A}) + (\text{moles of B} * \text{carbons in B})}$$

***Reference :*** *Metrics to 'green' chemistry—which are the best? David J. C. Constable, Alan D. Curzonsb and Virginia L. Cunningham. Green Chem.*, 2002,4, 521-527

# Technology solutions to achieve Green Chemistry

- Biocatalysts
- Flow chemistry
- Process Analytical Technology
- Catalysis
- Membrane DSP
- Photo & electrochemistry
- Biomass Feedstock
- Artificial Intelligence

Biocatalysis



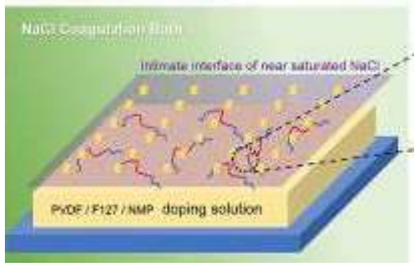

Flow Chemistry

Process Analytical Technology

Catalysis

**Biomass Feedstock**

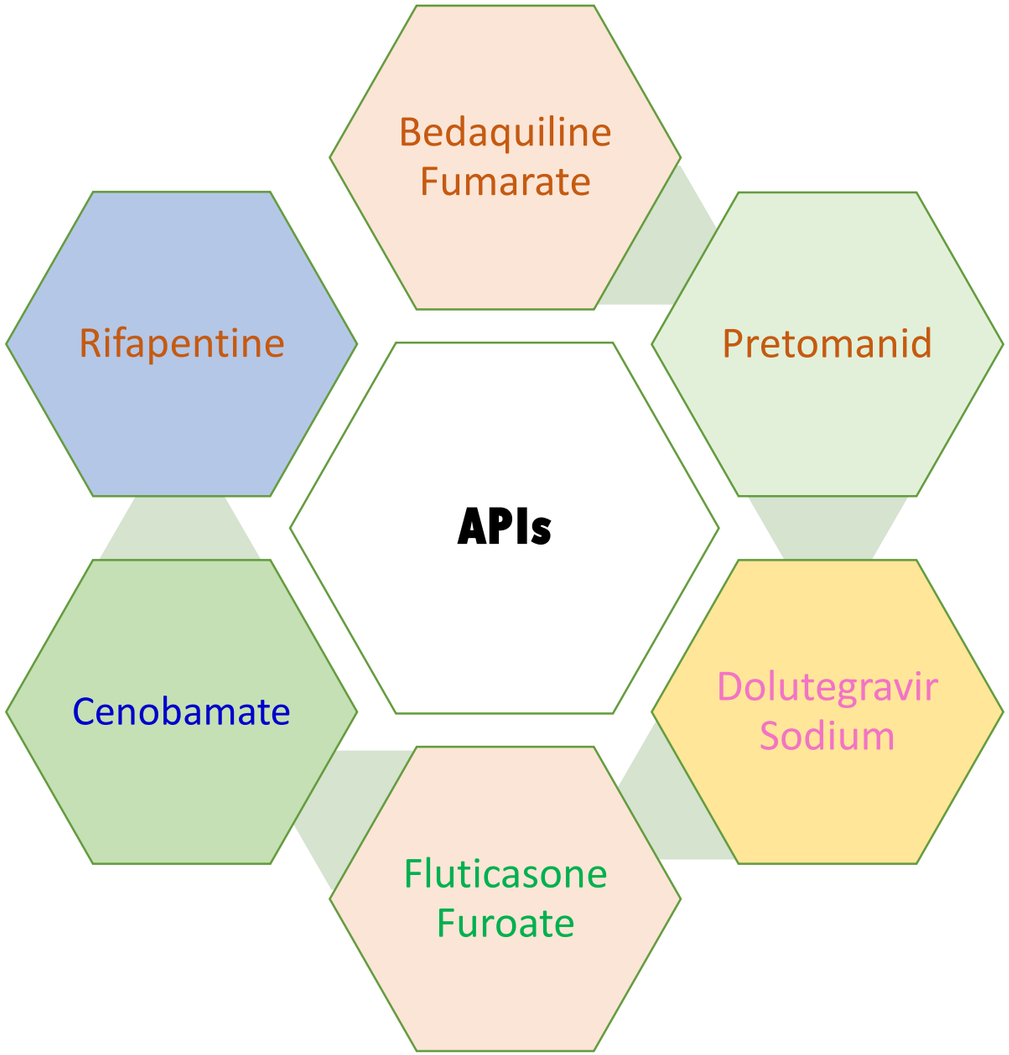
**Artificial Intelligence**




**Membrane DSP**


**Photo & electrochemistry**

# Case Studies from Lupin Limited

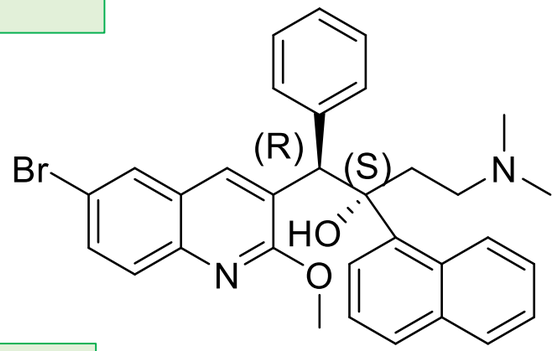



**The Green Chemistry execution in green synthesis can be performed using,**

1. ✓A holistic design of the active pharmaceutical ingredient's (API) life cycle
2. Minimizing hazards and pollution
3. ✓Capitalizing the resource efficiency in the synthesis technique

# Bedaquiline Fumarate

## Chemical Structure

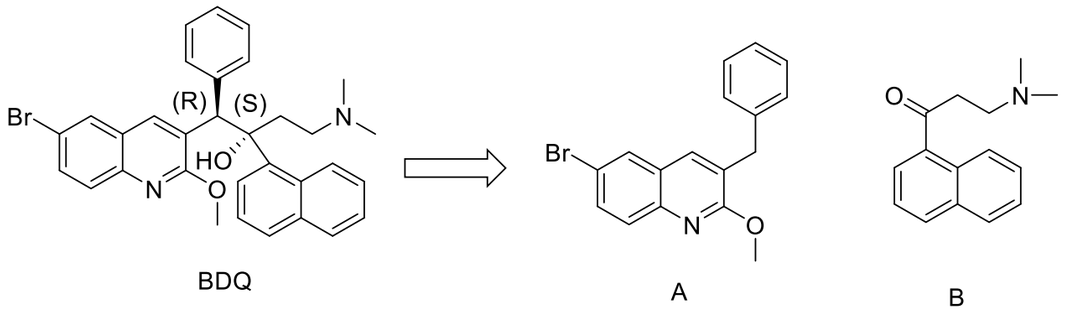


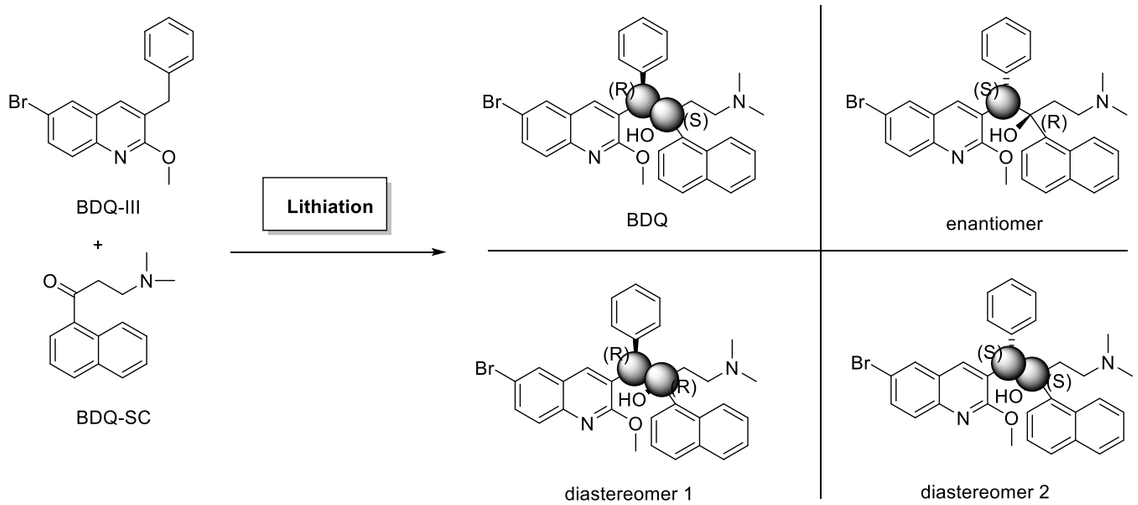

## Product Profile

**Innovator : Janssen Pharma Inc.**
**Approved indication : For treating multidrug-resistant tuberculosis for treatment of TB**
**Date of approval : Dec 28, 2012 (USA)**
**: March 5, 2014 (EU)**
**: January 14, 2015 (India)**
**Approved strengths : EQ 100MG BASE**

# Bedaquiline Fumarate

## Retrosynthesis



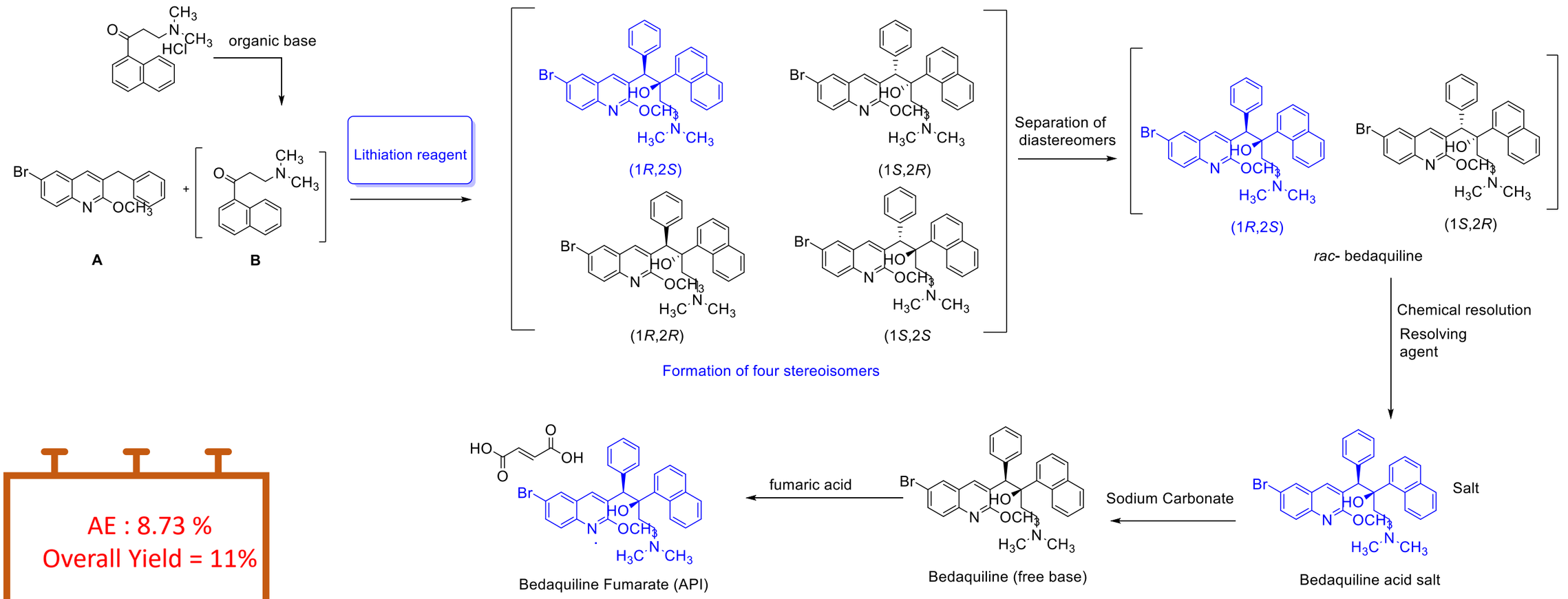

**Challenge in the synthesis :**

- Due to the stereoselective construction of the C*sp*3–C*sp*3 bond with vicinal stereocenters of BDQ and its analogues formation is being an unsolved challenge.

**Synthetic strategy adopted by the manufacturers having concerns :**

- a nucleophilic addition reaction of a quinoline fragment to a ketone
- low conversion and no stereoselectivity
- formation of undesired three isomers

# Bedaquiline : Original Route



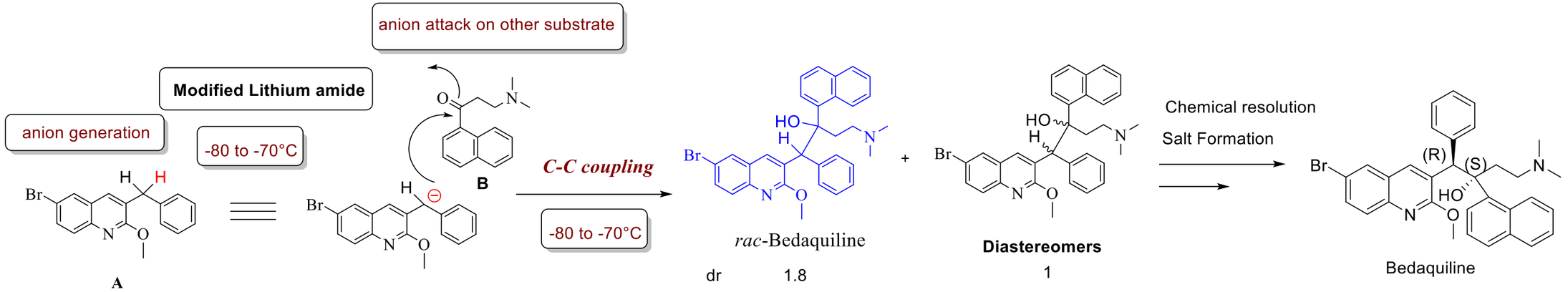

AE : 8.73 %
Overall Yield = 11%

**Safety: challenges associated with preparation and use of LDA for lithiation reaction**
**Sustainability: Complex reaction used in excess, results in less diastereoselective and significant cost/waste**

***Reference : Porstmann et al. Process for preparing (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino) ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol, Janssen Pharmaceutica, US8039628***

# Bedaquiline : Improved route

## Enabling the scale up of lithiation reaction using morpholamide base for C-C coupling for Bedaquiline




| Process | Original route | Improved route |
|---|---|---|
| Reagent | LDA | Modified lithium base |
| Reaction temp. | -78 °C | -78 °C |
| Selectivity (dr) | 1 : 1 | 1.8 : 1 |
| Yield | 11 % | 22 % |

This environmentally friendly, 'green' synthesis significantly reduces the total waste generated per KG of Bedaquiline produced in comparison with the first-generation route and reduced aqueous waste streams.

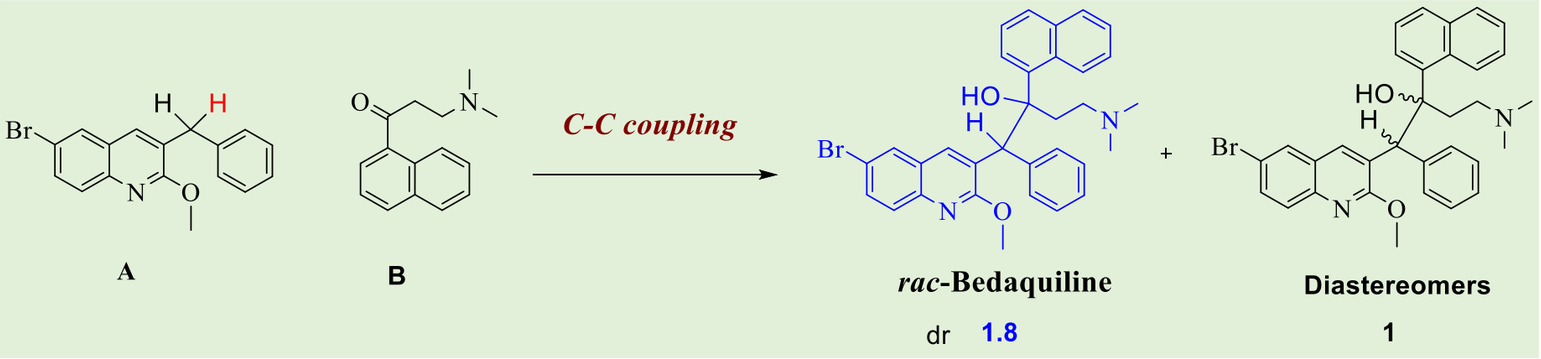
Demonstration of Green Principles

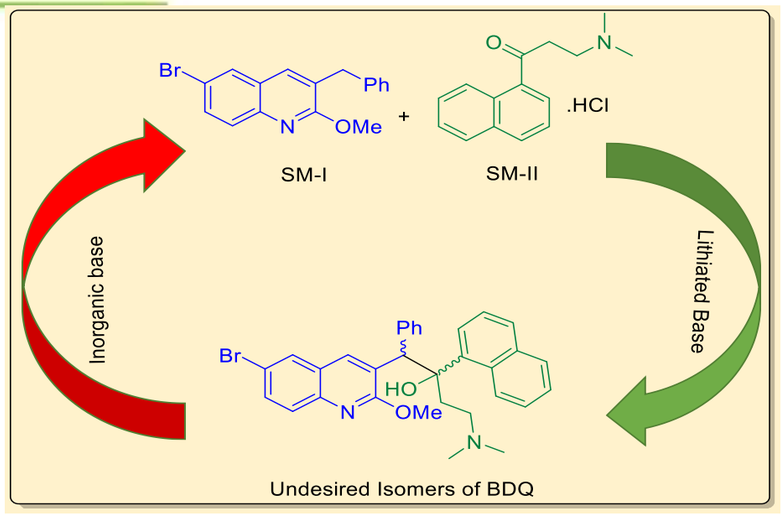
**Achievements:**

- **>50% reduction in overall *cost* and PMI to API**
- **Doubled the yield of desired product**

AE = 17.2%
Diastereoselective
Overall Yield = 22%

# Demonstration of Green Principles in API Bedaquiline Fumarate



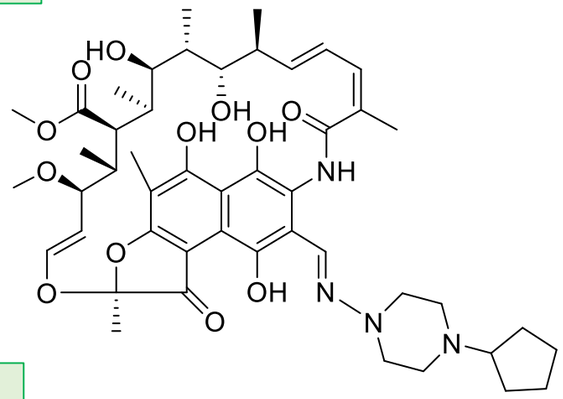




**Design safer chemicals and products: Atom Economy**

**Prevent pollution and waste**

# Rifapentine

## Chemical Structure



## Product Profile

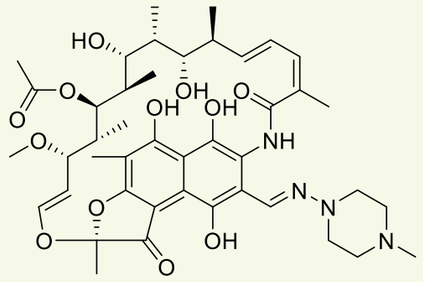
**Innovator : Sanofi**
**Marketed by : Sanofi-Avantis US Approved**
**indication : For Pulmonary tuberculosis**
**Date of approval : June 1998**
**Approved strengths : 900, 600, 300, 150 mg tablet**

## Rifamycin-derived drugs-

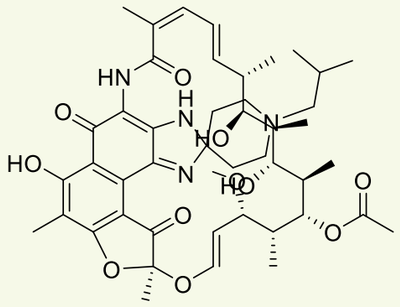
- ✓ Application for first-line therapies for the treatment of tuberculosis and other deadly infections.
- ✓ The four rifamycins approved for clinical use, rifampicin, rifabutin, rifapentine, and rifaximin), are orally formulated agents derived from rifamycin SV, the natural product of *Amycolatopsis mediterranei.*

List of drugs from Rifamycin

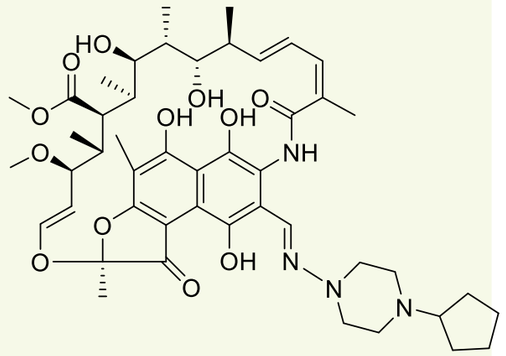
**Rifampin**



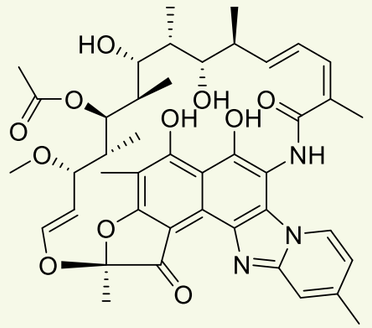
**Rifabutin**



**Rifapentine**

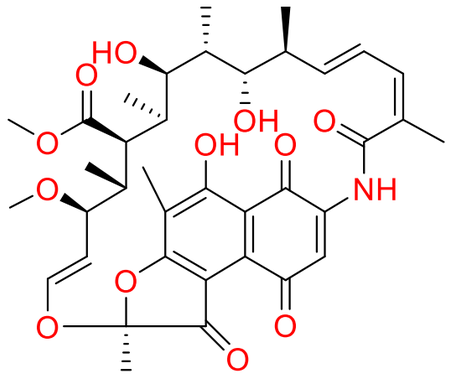


**Rifaximin**

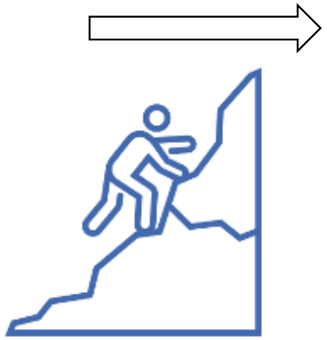


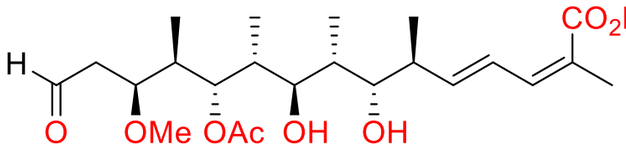
*Reference : 1. Rothstein DM. Rifamycins, Alone and in Combination. Cold Spring Harb Perspect Med. 2016 Jul 1;6(7):a027011*
*2. Tupin A, et al. Resistance to rifampicin: At the crossroads between ecological, genomic and medical concerns. Int J Antimicrob Agents 35: 519–523. 2010*

# Chemical synthesis : A total synthesis of rifamycin S



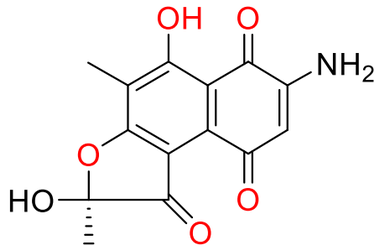
Rifamycin S





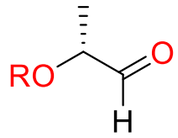
liphatic segment

+



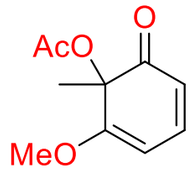
aromatic segment

multiple steps



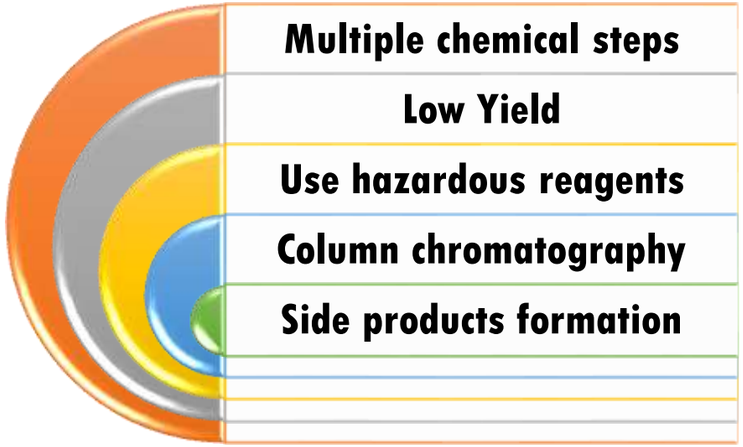
aldehyde

total 12 step
+ column chromatography



cyclohexadienone

## Limitation





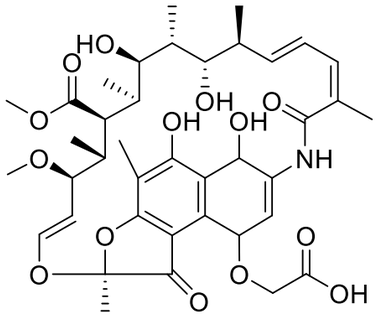
**Reference :** *J.* Am. Chem. Soc. **1980,** 102,7965-7967

# Manufacturing of Rifamycin B: Fermentation process

- Rifamycin isolated from the fermentation medium of **Norcardia mediterranei** in 1959
- Manufacturing process of Rifamycin-B prepared through **fermentation process** which is then extracted from broth using suitable process

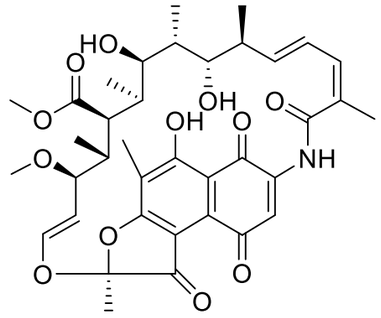
| Sr. No. | Reactant /Reagent/ Catalyst |
|---|---|
| 1 | Dextrose monohydrate |
| 2 | Soyabean flour |
| 3 | Yeast extract powder |
| 4 | Antifoam |
| 5 | $CaCO_3$ (calcium carbonate) |
| 6 | Caustic solution for pH adjustment |

Rifamycin B

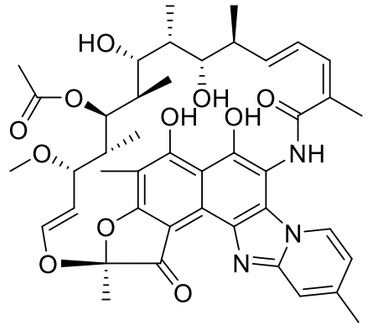


Chemical Conversion

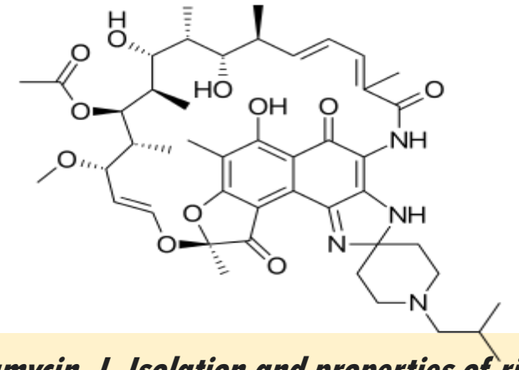
Rifamycin S



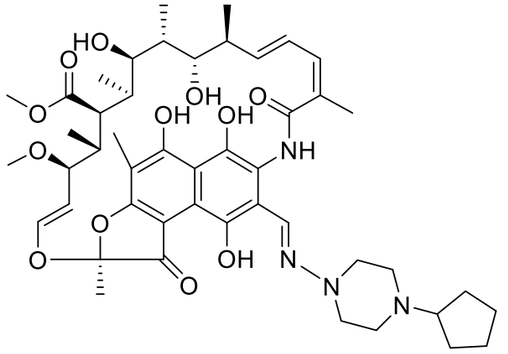
Rifaximin



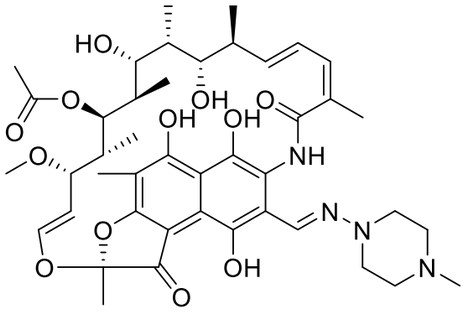
Rifabutin



Rifapentine



Rifampin



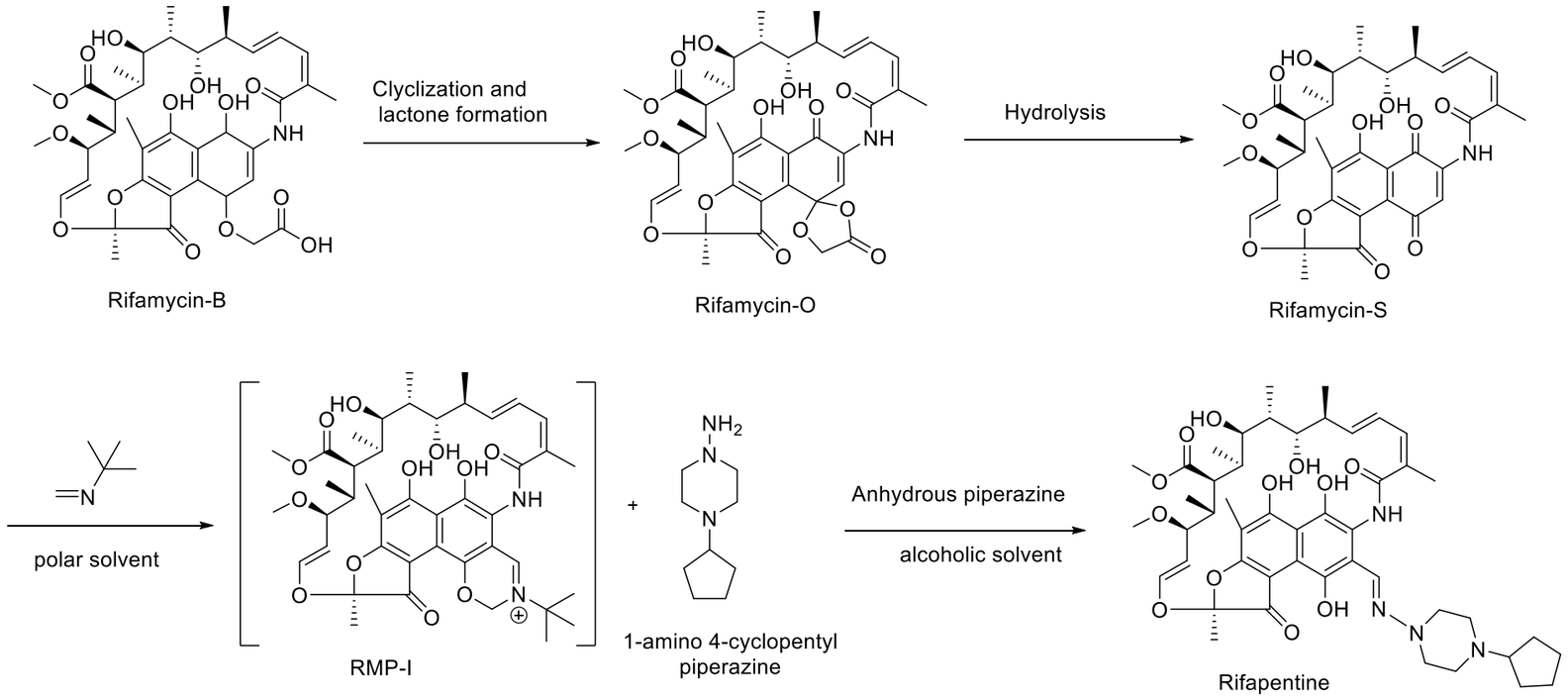
*Reference : Sensi P, Greco AM, Ballotta R. Rifamycin. I. Isolation and properties of rifamycin B and rifamycin complex. Antibiotics Annual. 1959;7:262–270.*

## Manufacturing of Rifamycin B: Fermentation process

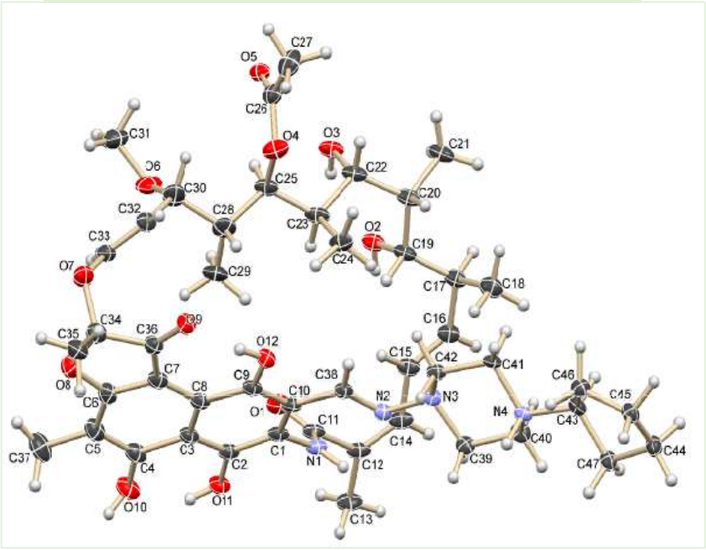
- Limits the use of organic solvents, organic reagents
- Can convert simple starting materials (e.g., Sugars, carbohydrates) into stereochemically complex natural products
- Process allows for rapid and stereospecific production
- Natural products obtained by fermentation can be efficiently converted into new structures that would be difficult to obtain synthetically
- Stereochemistry at these chiral centers get fixed during fermentation process making this process stereospecific

***Reference :*** ***Sensi P, Greco AM, Ballotta R. Rifamycin. I. Isolation and properties of rifamycin B and rifamycin complex. Antibiotics Annual. 1959;7:262–270.***

# Rifapentine -Synthesis of Rifapentine form for Rifamycin-B




## *Single Crystal X-ray Diffraction Analysis of Compound*



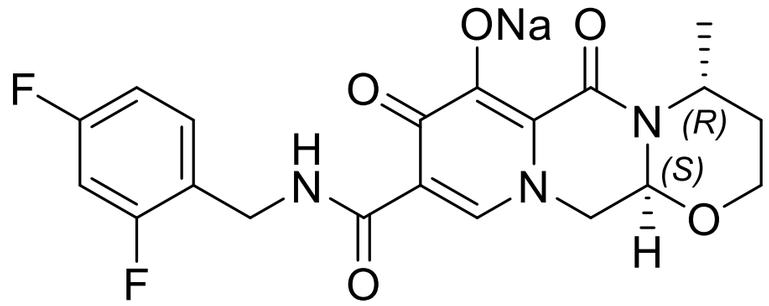
ORTEP view

## Demonstration of Green Principles in API Rifapentine

- Increase energy efficiency
- Use safer solvents and auxiliaries
- Use renewable feedstocks
- Reduce derivatives
- Minimize the potential for accidents

# Dolutegravir Sodium

## Chemical Structure




## Product Profile

**Innovator : VIIV HEALTHCARE CO**

**Approved indication : Antiviral**

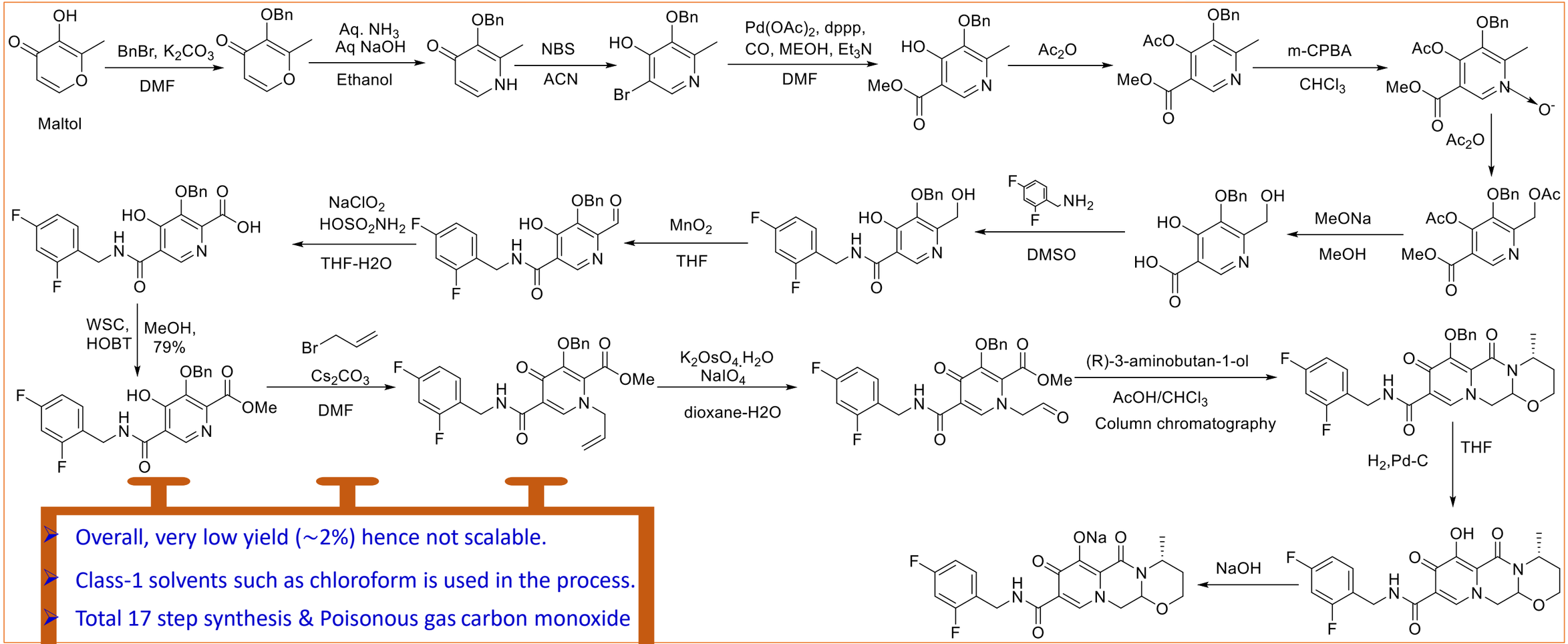
**Date of approval : Aug 12, 2013**

**Brand : TIVICAY, Triumeq, Juluca**

**Approved strengths :Oral tablet: 10 mg, 25 mg, 50 mg**

**Maximum Daily Dose : 100 mg**

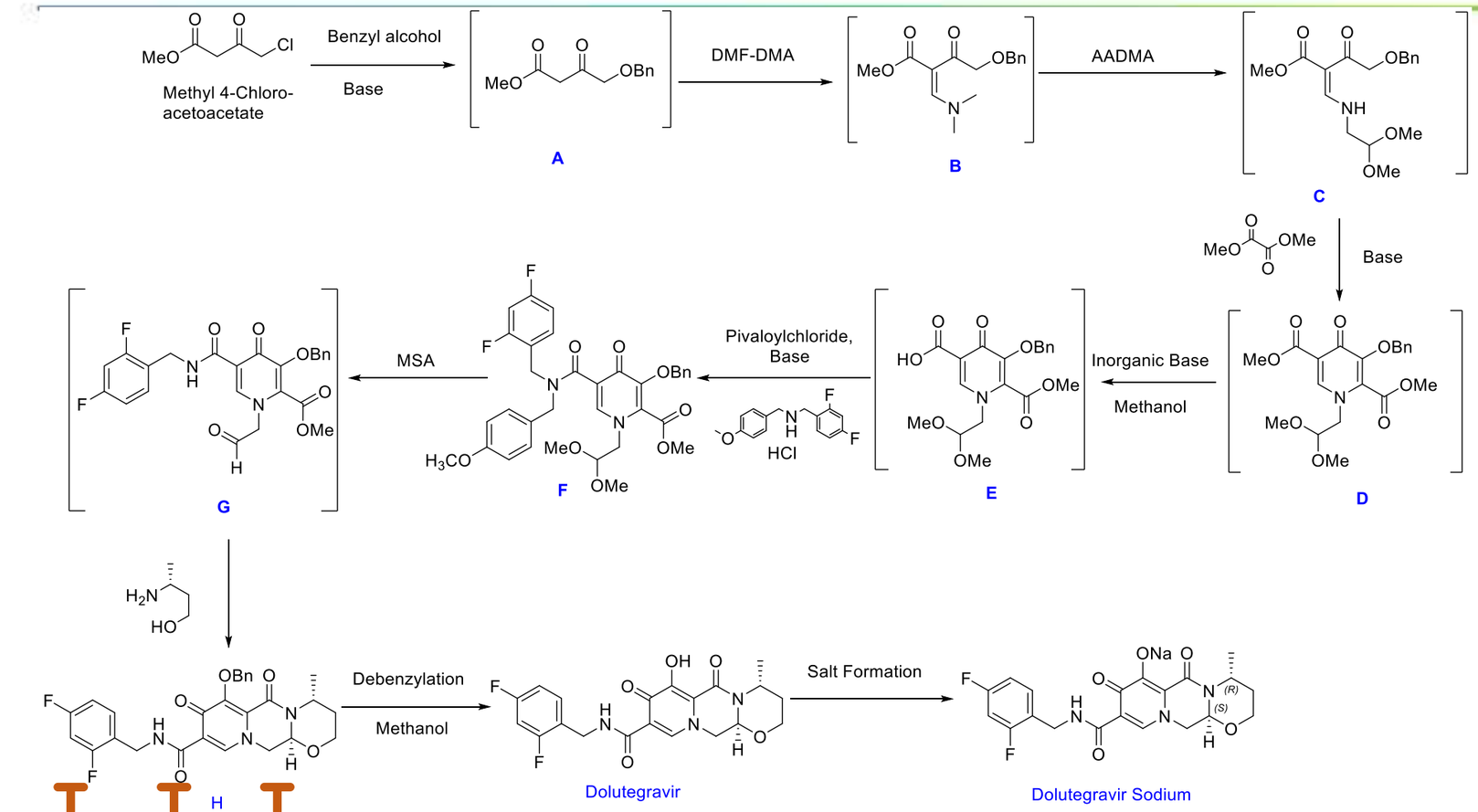
# Dolutegravir Sodium : Discovery Route




- Overall, very low yield (~2%) hence not scalable.
- Class-1 solvents such as chloroform is used in the process.
- Total 17 step synthesis & Poisonous gas carbon monoxide

***Reference : John et al. Substituted 5-hydroxy-3,4,6,9,9a, 10-hexanhydro-2h-1-oxa04a,8a-diaza-anthracene-6,10-dioness, Shionogi & Co., Ltd., GlaxoSmithKline LLC, US 8,129,385***

# Dolutegravir Sodium : Improved Route




Total 10 step synthesis

## Advantages

- **Substantial Increase in overall yield**
- **Increases the productivity (kg/day)**
- **Reduction in total waste & Mfg cost**
- **Safer handling**

## Demonstration of Green Principles

**Prevent pollution and waste**

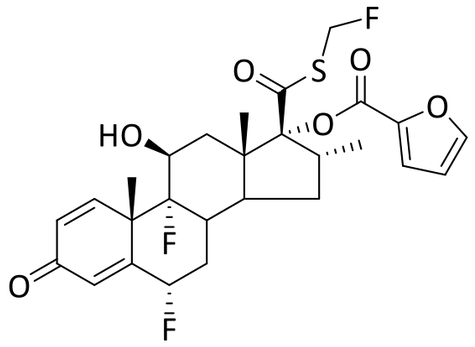
**Reduce Derivatization**

**Increase energy efficiency**

***Reference :Process for the preparation of HIV integrase inhibitors, Lupin Limited US20200172487***

# Fluticasone Furoate

## Chemical Structure




## Product Profile

**Generic Name : Fluticasone Furoate**

**Brand name : Veramyst , Breo Ellipta, Flonase Sensimist , Trelegy Ellipta**

**Therapeutic category : Anti –Allergic, Antiasthmatic, Glucocorticoid**

**Innovator : GlaxoSmithKline**

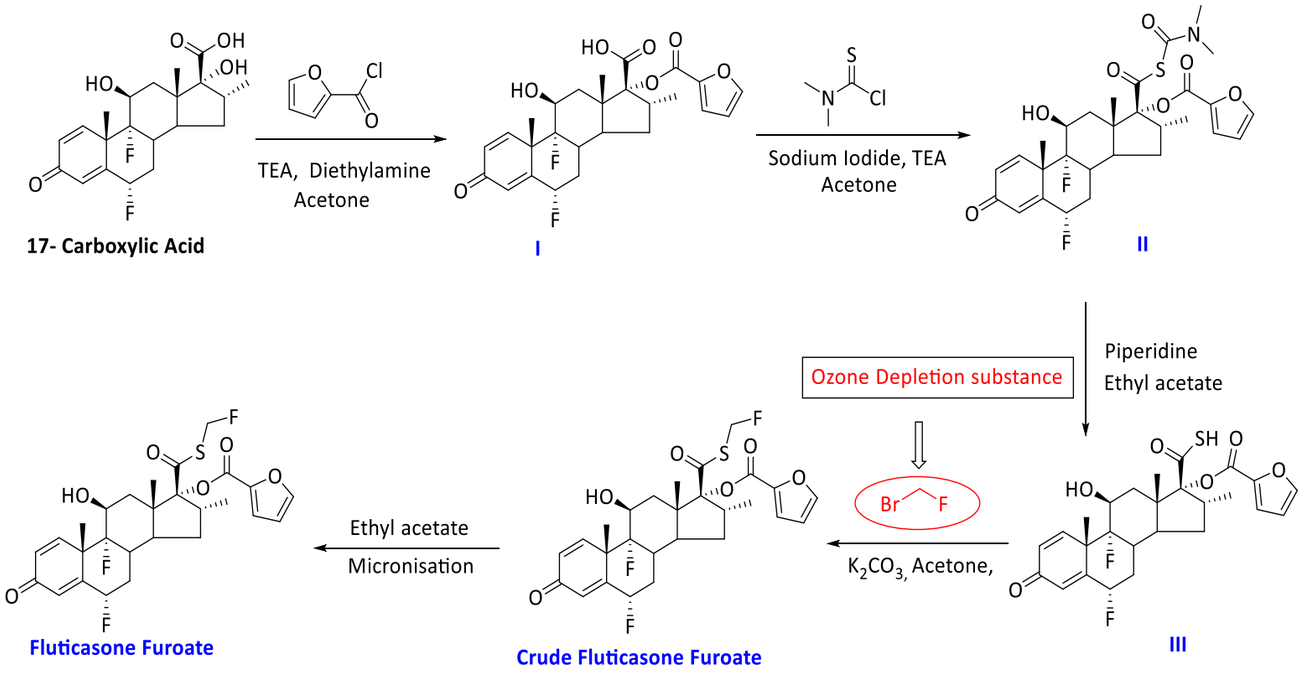
**Date of approval : April 27 , 2007 (Veramyst: Nasal Spray)**

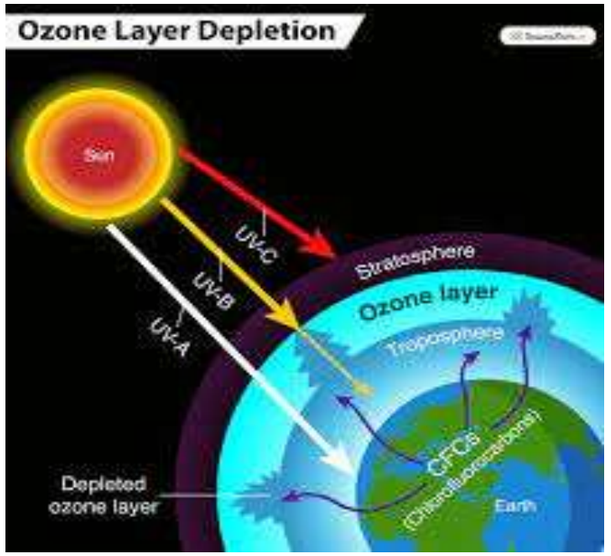
**Dosage form : Powder, Spray metered.**

**Combination Drug Product : Trelegy Ellipt(Fluticasone Furoate .**

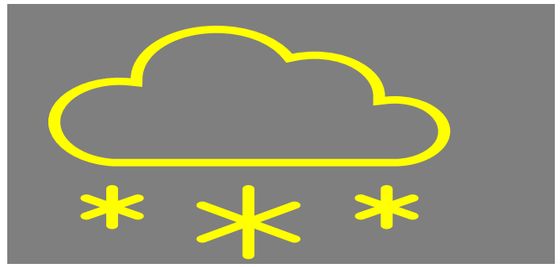
**Umeclidinium bromide and Vilanterol Trifenatate)**

# Fluticasone Furoate : Synthetic Route




Changes in Climate - Stratospheric Ozone



**Use of Ozone depletion substance- Bromofuoromethane**

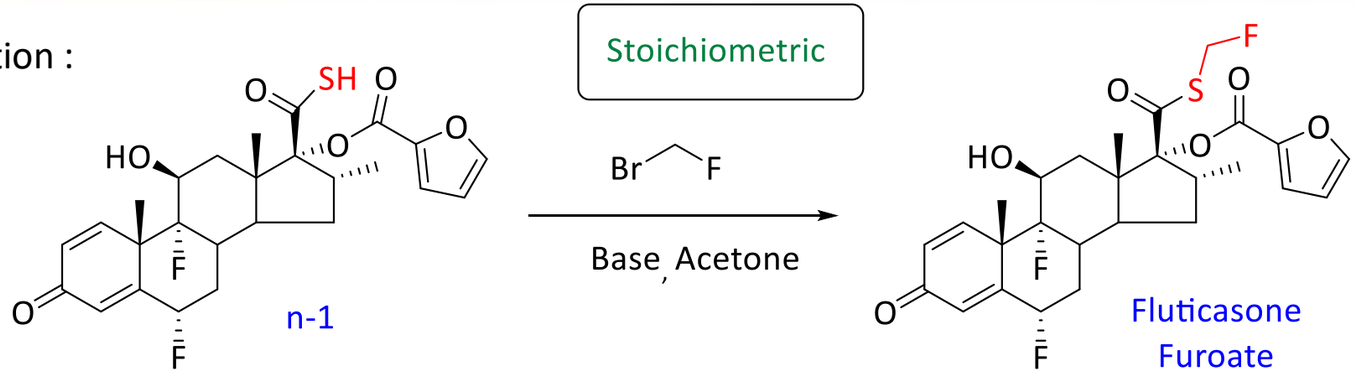
**OZONE Depletion affects-**

- **Human Health**
- **Food and Water Security**
- **Ecosystem Services**

*Reference :* *Patent US 7101866 B2, US2009/118495, GSK Ltd*

# Fluticasone Furoate : Efforts to reduce bromofluoromethane

Reaction :




| Reagent/ reagents | Literature process | Improved process |
|---|---|---|
| Bromofluoromethane | 2.1 equiv. | Equimolar |
| Solvent | Dichloromethane | tert-butyl acetate |

Merits:

- ✓ Even though reduction in ODS reagent, achieved good yield.
- ✓ Replaced the greener solvent Dichloromethane to tert butyl acetate
- ✓ Recycle and reuse of n-1 intermediate


**Minimize the usage of BFM**

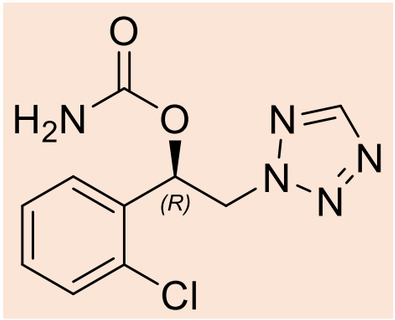
# Efforts to Demonstration of Green Principles in API Fluticasone Furoate

**Prevent pollution and waste**

**Analyze in real-time to prevent pollution**

# Cenobamate

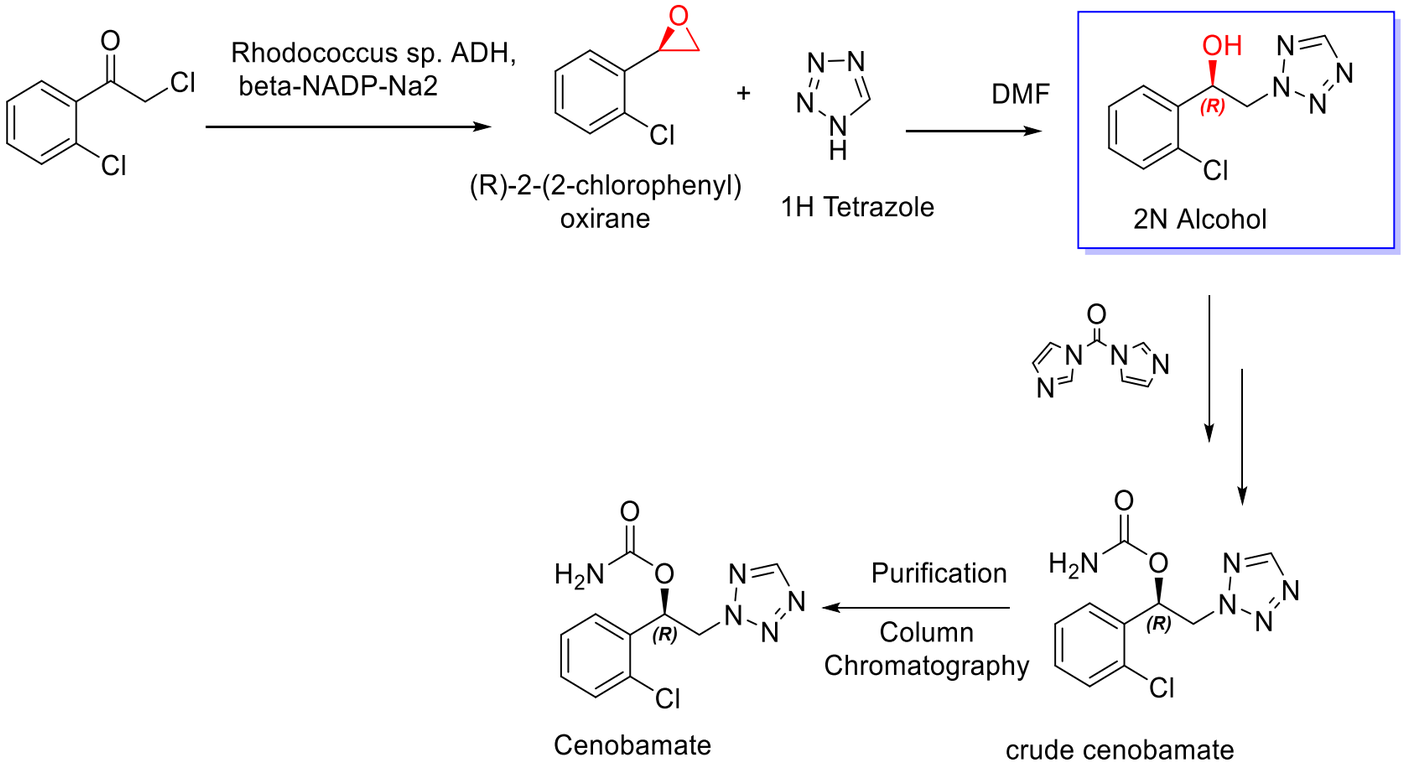
## Chemical Structure




## Product Profile

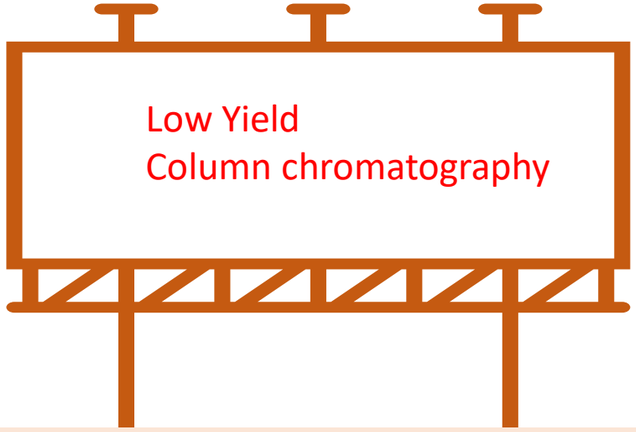
| | | |
|---|---|---|
| **Generic Name** | : | **CENOBAMATE** |
| **Innovator** | : | **SK LIFE SCIENCE INC** |
| **Brand Name** | : | **XCOPRI** |
| **Therapeutic category** | : | **treatment of partial-onset seizures** |
| **Dosage** | : | **TABLET; ORAL** |
| **Strength** | | 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg |
| **Date of Approval** | : | **Mar 10, 2020** |

# Cenobamate : Original Route




## Demerits

- KSM Oxirane is very expensive and not easily available.
- Column chromatography involved in the process.
- Concern of scalability
- This Oxirane ring leads to formation of 4 positional isomers resulting in low yield.

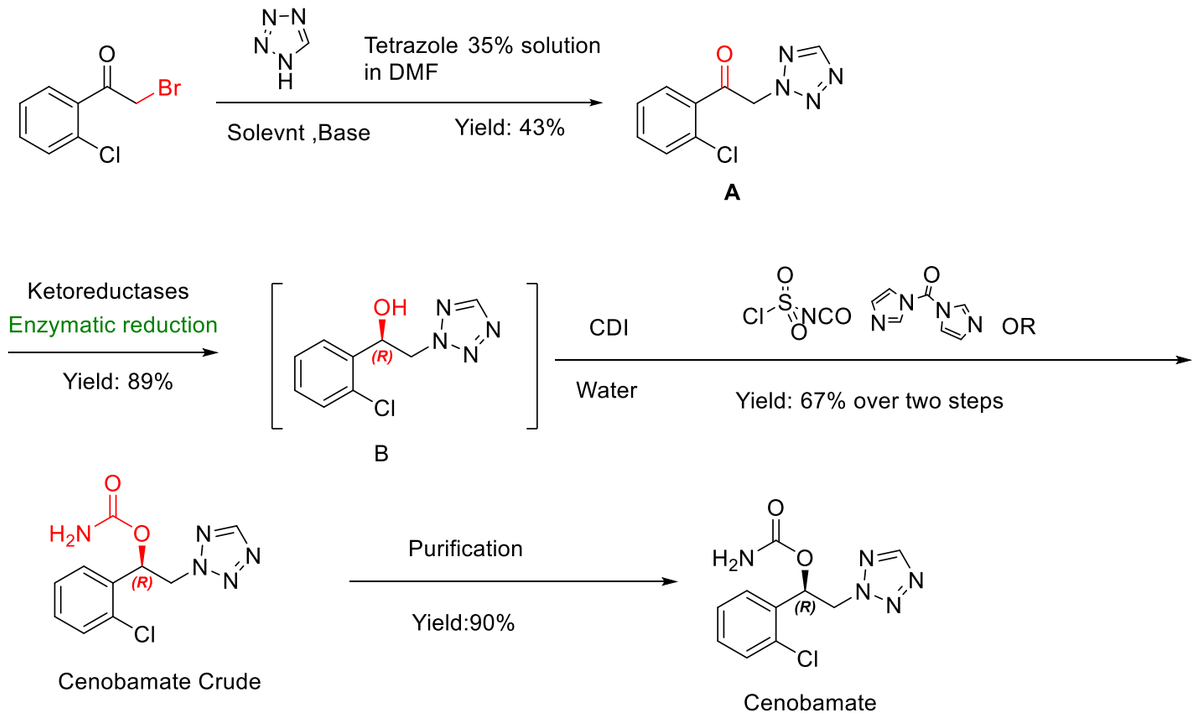



*Reference : Choi Yong-Moon et al. Neurotherapeutic azole compounds, WO2006/112685, 2006, A1, Assignee : SK HOLDINGS CO., LT*

# Cenobamate : Improved route

- **Chiral β-heteroaryl amino alcohol fragments are widely found in many bioactive compounds or drugs including Cenobamate**
- Catalytic asymmetric hydrogenation (Ruthenium catalyzed )procedure is required to achieve enantioselectivity

The preparation of (R)-1-aryl-2-tetrazolyl-ethyl alcohol by enzymatic reduction of the arylketone




**Merits KSMs are easily available.**

- **No column chromatography involved in the process.**
- **Environment friendly green chemistry is involved.**
- **Cost effective process.**
- **Plant feasible process**

## Demonstration of Green Principles

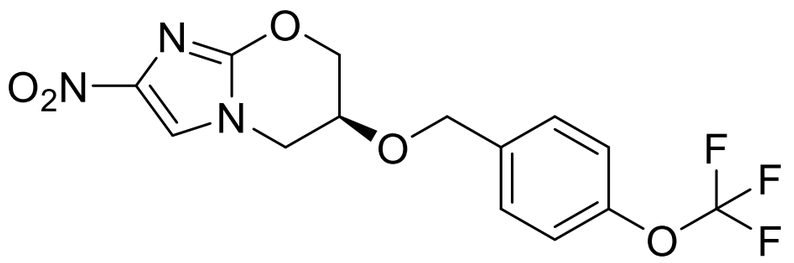
**Prevent pollution and waste**

**Safer Solvent and Auxiliaries**

**Increase energy efficiency**

# Pretomanid

## Chemical Structure

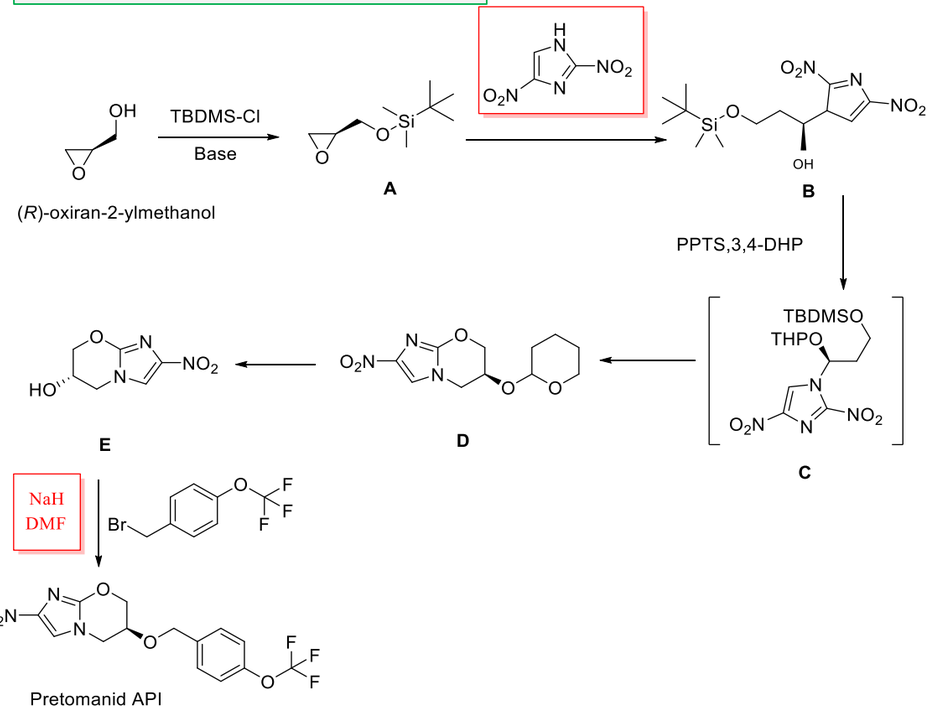



## Product Profile

| | | |
|---|---|---|
| Generic Name | : | Pretomanid |
| Innovator | : | MYLAN IRELAND LTD |
| Brand Name | : | PRETOMANID |
| Therapeutic category | : | Treatment of pulmonary extensively drug-resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) TB |
| Dosage | : | TABLET; ORAL |
| Strength | | 200 mg |
| Date of Approval | : | Aug 14, 2019 |

# Pretomanid

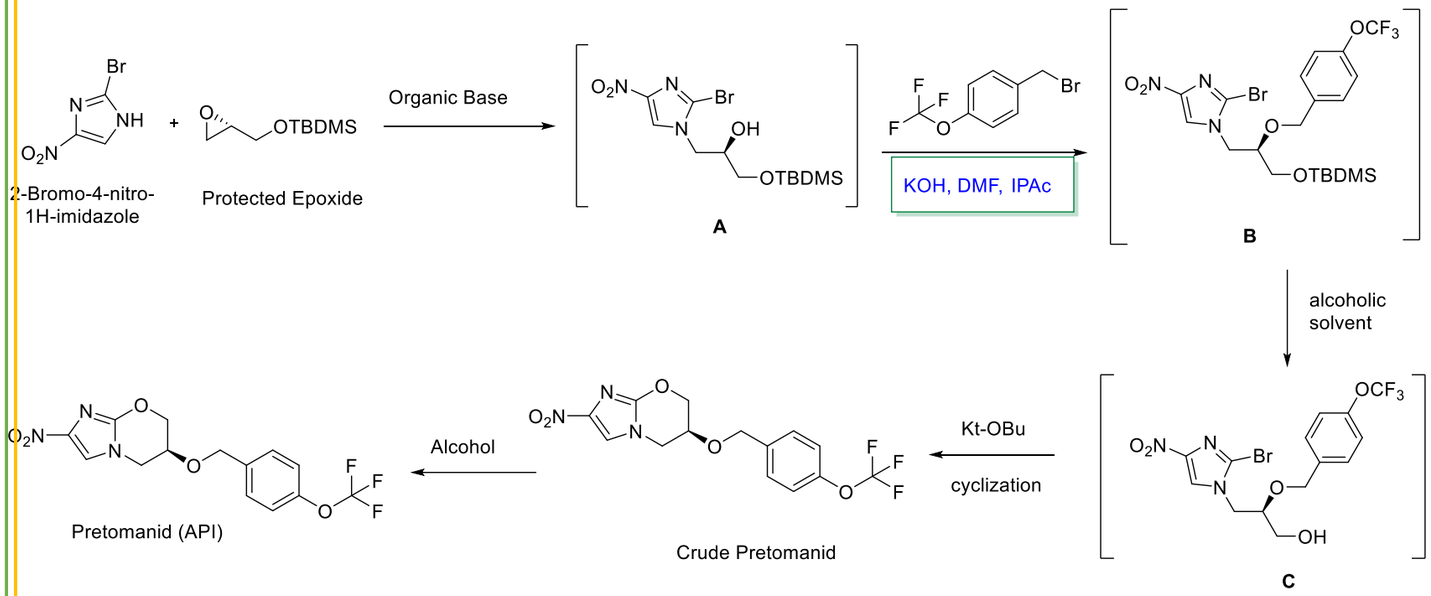
## Literature Process




- ✓ **Starting from the explosive 2,4-dinitroimidazole**
- ✓ **Five steps & 17% overall yield.**
- ✓ **Undesirable reaction conditions like the use of NaH/DMF**

***Reference : Baker et al, Pathogenesis Corp. Nitroimidazole Antibacterial Compounds and Methods of Use Thereof. US5,668,127.1997***

## Improved Process




## Demonstration of Green Principles

**Design safer chemicals**

**Minimize the potential for accidents**

*Reference : Patent IN 202121030532, lupin Limited*

# Challenges and Limitations

Just being green is not enough for a process to be a commercial success

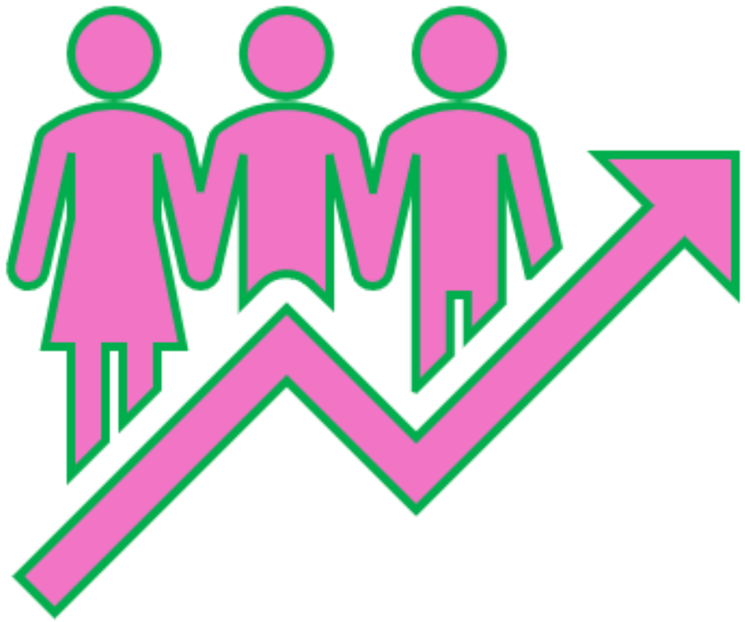
- **Industrial implementation of a green process-Hurdles**
  - ✓ **Regulatory**
  - ✓ **Economic**
  - ✓ **Political**
  - ✓ **Technical**

- **Collective and sincere efforts - make the chemistry Green**
  - ✓ **Researchers**
  - ✓ **Engineers**
  - ✓ **Corporates**
  - ✓ **Policy- makers**

# Future Trends

## Future Scope for emerging trends in green chemistry for API synthesis

- Continuous manufacturing / Flow Chemistry
- Green solvents : Ionic liquids / supercritical fluids
- Process intensification
- Green analytical tools and techniques : Near IR, PAT
- Recycling / Circular economy :
- Green Nanotechnology
- Life Cycle Assessment
- Safer Reagents
- Sustainable sourcing
- Green Catalysts : Biocatalysis
- Sustainable Process metrics
- Renewable feedstock



# Conclusion

- Presented several examples where a green chemistry mindset contributed to the development of innovative processes for the synthesis of active pharmaceutical ingredients
- Green chemistry can take many shapes and forms within the pharmaceutical industry:
  - ✓ Application of catalytic processes
  - ✓ Solvent selection
  - ✓ Route Re-Designing
  - ✓ A further increase in complexity of pharmaceuticals and encourage researchers in both academia and industry to continue the advance of synthetic methodologies to support the vision of green chemistry toward the synthesis of life-saving medicines.

# Acknowledgments


- Thanks to Dr. ERR Chandrasekhar, Head-R & D, Lupin Limited
- Bio Process Team,  Lupin Limited
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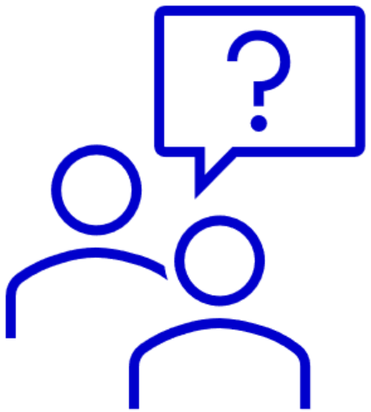
- Sincere thanks to Management of Lupin Limited
- Organizing committee, Co-Founder & Director, Green ChemisTree Foundation IGCW-2023

# References


1. P. T. Anastas, J. C. Warner, “Green Chemistry: Theory and Practice,” Oxford University Press, New York, 1998, pp. 30
2. UN World Commission on Environment and Development, ed., Report of the World Commission on Environment and Development: Our Common Future | Environment & Society Portal (environmentandsociety.org)
3. Proc Math Phys Eng Sci. 2015 Nov 8; 471(2183): 20150502.
4. Expanding GSK’s solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry, DOI: 10.1039/c0gc00918k
5. Sanofi’s Solvent Selection Guide: A Step Toward More Sustainable Processes. Org. Process Res. Dev. 2013, 17, 1517−1525
6. Roger Arthur Sheldon, The E factor at 30: a passion for pollution prevention Green Chem., 2023,25, 1704-1728
7. ***ACS Sustainable Chem. Eng.* 2022, 10, 16, 5148−5162**
8. **Rothstein DM. Rifamycins, Alone and in Combination. Cold Spring Harb Perspect Med. 2016 Jul 1;6(7):a027011**
9. **Tupin A, et al. Resistance to rifampicin: At the crossroads between ecological, genomic and medical concerns. Int J Antimicrob Agents 35: 519–523. 2010**
10. *Biggadike et al. Anti-inflammatory androstane derivative, Patent US 7101866 B2,, GSK Ltd*

## Q&A

# Open Floor For Questions & Answers



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## Registered Address

3rd Floor, Kalpataru Inspire, Off Western Express Highway, Santacruz (East),
Mumbai – 400055, India

**Phone:** +91 22664 02323 | **Fax:** +91 22664 02051 | www.lupin.com