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Match Maker/ Pharmaceutical Process Innovations/ 20 March 2025

A PROCESS FOR THE SYNTHESIS OF IVACAFTOR IN A CONTINUOUS FLOW

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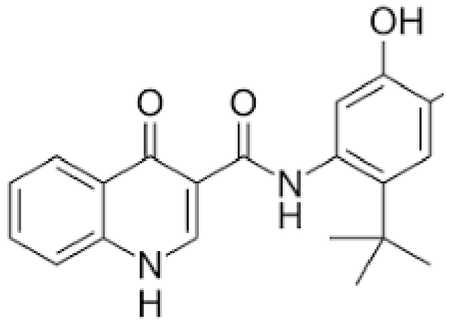
Organization: CSIR-NCL
TechEx.in Case Manager: Pradnya Aradhye (pradnya@ventercenter.co.in)

What is Ivacaftor ?



Ivacaftor is a medication used to treat cystic fibrosis in people with certain mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (primarily the G551D mutation), who account for 4–5% cases of cystic fibrosis

Approved by the U.S. Food and Drug Administration (FDA) in January 2012

Cost : ~ $300,000 per patient per year (2 tablets per day) of treatment

Market Opportunities

The global Ivacaftor API market size was valued at USD 1.5 billion in 2023.

Industry

Innovator: US based VERTEX PHARMACEUTICALS INC which is expected to expire in 2027 in USA and 2025 India.

Licensed manufacturers in India:

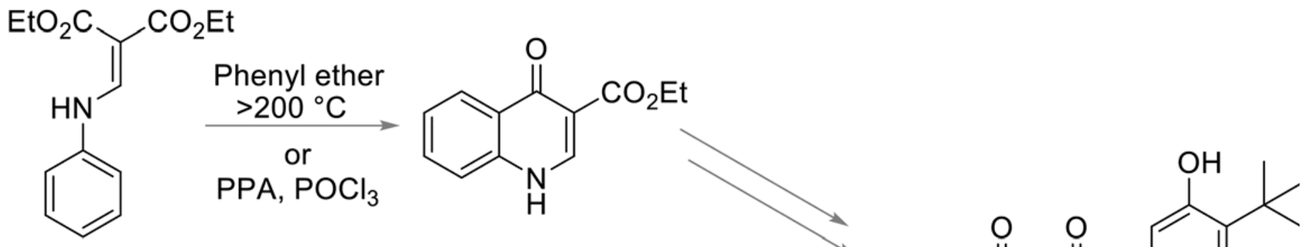
Lupin's Approval in Jan 2025:

- Lupin has received tentative approval from the U.S. FDA for its Abbreviated New Drug Application for Ivacaftor Oral Granules.
- Lupin is the exclusive first-to-file for this product. Source: Lupin.

Generic version: No therapeutically equivalent version of Kalydeco available.

Existing Process Used

Vertex pharma



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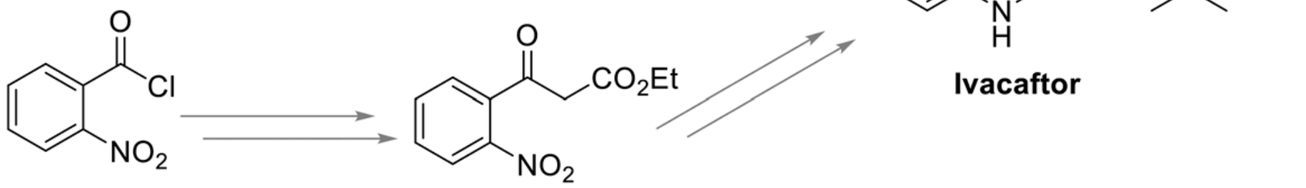
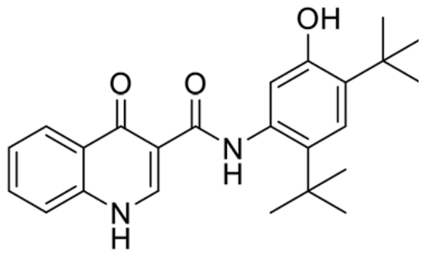


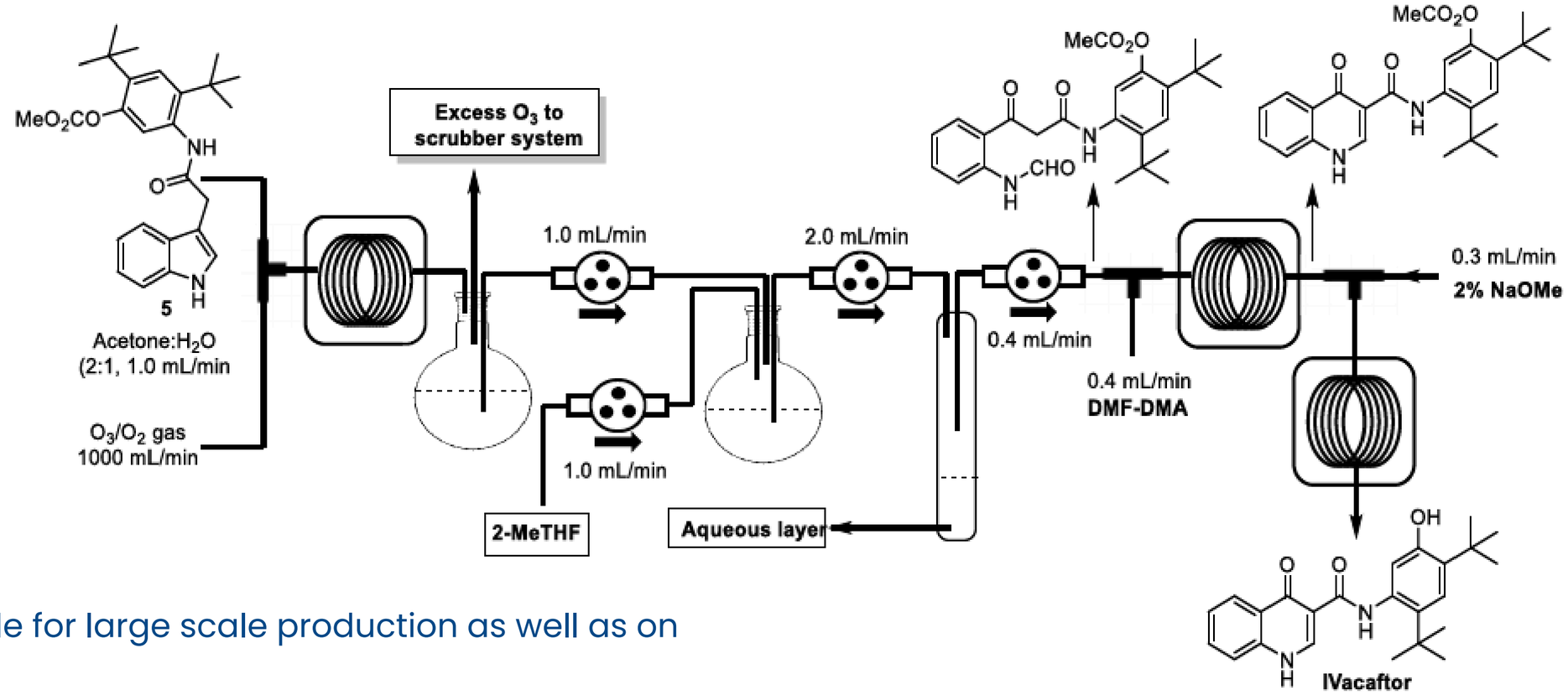


Ivacaftor

The Drawbacks
of current known synthesis are:

- Harsh conditions
- High temperature reactions, carried out in batch mode
- Use of large excess of polyphosphoric acid and corrosive phosphoryl chloride.

NCL Process: Continuous flow



Process features:

- Short, mild and suitable for large scale production as well as on the spot synthesis.
- Involves only one purification step.
- Lower temperature requirement
- 1 sec ozonolysis time
- Solvent exchange happening continuously
- A continuous process for the synthesis of Ivacaftor
- Could be applied for synthesis of several quinolone based antibiotic drugs.

Estimated Raw Material Cost (using academic pricing of raw material) : XX $/Kg

Reference EXIM Data Price: 800 $/Kg

Who should be interested and why?

Who	Why
Manufacturers of Ivacaftor and similar molecules	Better, economical and high yeilding process
API manufacturers	New molecule; better process Diversification of the portfolio
Companies setting up API plans under PLI 2.0	To get financial benefits to boost manufacturing

Current status

Technology Status :

- Status of the technology - TRL 4 (Lab level results shown)
- Demonstrated at 7.2 g/ day scale

Patent Status :

- Patent coverage: India, USA, EP
- Priority date: **30 May 2016**
- Status: India: Granted, No: 374290; US: Granted, No: 11274081; EP: Granted, No: EP4043439

Publications :

- N. Vasudevan, Mrityunjay K. Sharma,. Srinivasa Reddy and Amol A. Kulkarni. A multi-step continuous flow synthesis of the cystic fibrosis medicine ivacaftor. React. Chem. Eng., 2018, 3, 520

VALUE PROPOSITION OF NCL PROCESS

- Safe ozonolysis
- Higher yield (>60% compared to ~30% for batch)
- Lower opex cost (faster, higher selectivity)
- Lower capex cost
- Patent protection for process (IN, US and EP Granted)

Team & Organization

Dr Amol Kulkarni

Principal Scientist
CEPD Division
National Chemical Laboratory, Pune.

E**xpertise**: Continuous flow synthesis (API, nanoparticles and azo colorants), Investigation of hydrodynamics of multiphase reactors and design, Experimental and computational fluid dynamics, Flow visualization and analysis in single phase and multiphase reactors

Awards and Honours:

- SS Bhatnagar Award (CSIR)
- VASVIK Award (2016)
- Scientist of the Year (NCLRF)
- Swarnajayanti Fellowship (DST)
- IUSSTF Fellow (MIT, USA)
- INSA, CSIR and INAE Medals
- Humboldt Fellow (Germany)

About the Institute

National Chemical Laboratory

CSIR-NCL is a science and knowledge based research, development and consulting organization. It is internationally known for its excellence in scientific research in chemistry and chemical engineering as well as for its outstanding track record of industrial research involving partnerships with industry from concept to commercialization.

Key assets and strengths of Dr Kulkarni's lab:

- Strength of the team: Continuous Manufacturing, Reactor Design, Scale-up for APIs, Agrochemicals, Nanomaterials, etc.
- 35 Indian patents filed, 17 granted, 95+ publications
- Well equipped labs and analytical facilities
  - Continuous flow synthesis set-ups of various capacities for L-L, G-L and L-S reactions
  - High speed imaging systems in visual and IR range
  - Pilot plants for G-L and L-L flow reactions including in-line separation/purification
  - Simulation tools: ANSYS Fluent, COMSOL, etc.
  - Eligible for CSR support for Industry Sponsored PhD
- Track record of technology transfer and working with industry
- Conducts Industry Training on Flow Synthesis (trained teams from over 40 industries so far)

Success stories and Industry collaborations

National Chemical Laboratory

Next Steps

- Scale up with support from industry partners from ~7g/hr to ~30g/hr

Seeking

Licensees for technology and IP on "as is where is" basis

Industrial partners interested in sponsoring further technology advancement and scale-up

Sponsored R&D projects for ozonolysis in continuous flow

Advisory/ consulting projects for continuous flow

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Tech Transfer Hub

National Chemical Laboratory

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