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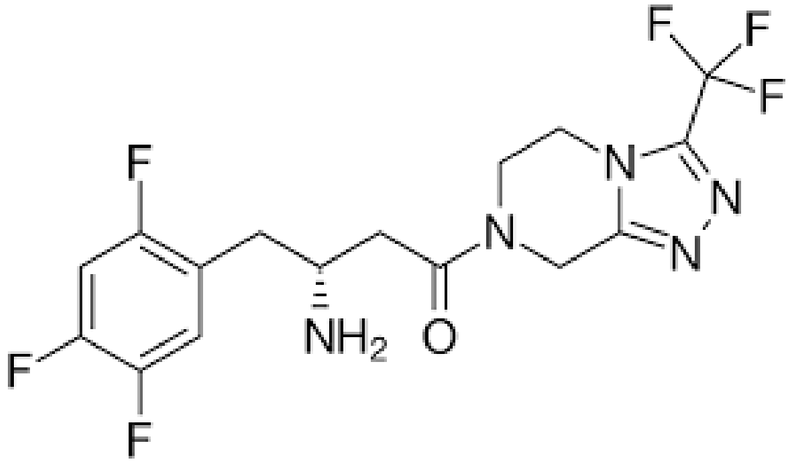
Match Maker/ Pharmaceutical Process Innovations/ 20 March 2025

Highly efficient process for the preparation of sitagliptin via rhodium catalyzed asymmetric hydrogenation

Lead Inventor: Dr. Samir Chikkali
Organization: CSIR-NCL
TechEx.in Case Manager: Vedang Pawar (vedang.pawar@ventercenter.co.in)

What is Sitagliptin ?



- Sitagliptin is a Small Molecule ($C_{16}H_{15}F_6N_5O$) used in **Oral formulations** for treating **Type 2 Diabetes Mellitus.**
- Molecule Class: DPP-IV (Dipeptidyl Peptidase IV) Inhibitors or **Gliptins**
- **Gliptins** helps improve glycemic control and reduces hemoglobin A1c (HbA1c) levels.
- **Therapeutic Use** as monotherapy (Phosphate salt) or add-on therapy with metformin and thiazolidinediones.
- National Pharmaceutical Pricing Authority (NPPA) has fixed current price at ₹8/50mg Sitagliptin Phosphate

Market Opportunities

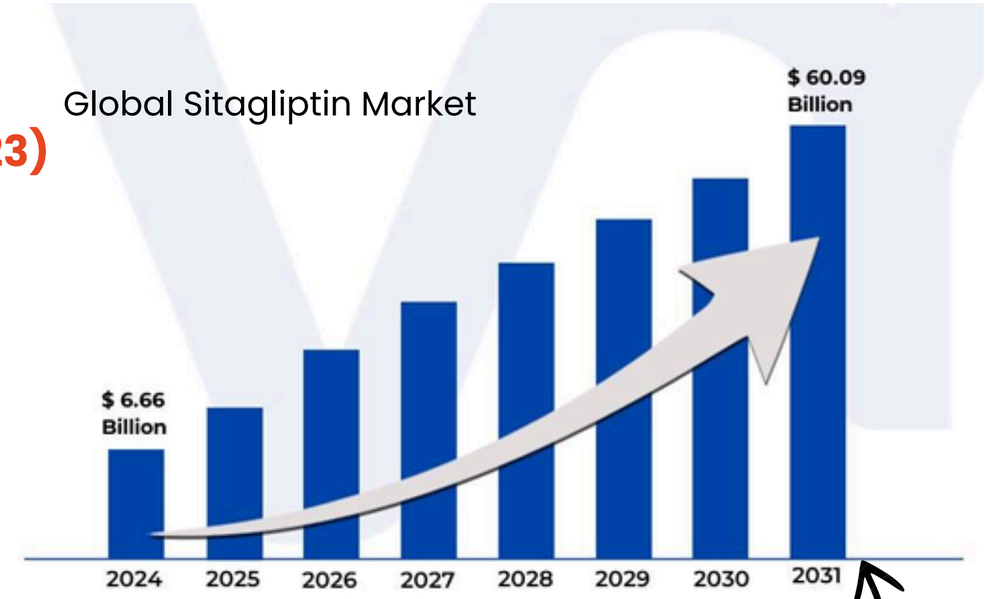
Global Sitagliptin market was valued at USD 6.6 Billion (2023)
(Source : Cognitive Market Research)

Factors driving the market growth:

- Increasing Production Volumes for premium and generic brands
- Reach Increasing as Prices Reduce
- Current Market Price - Rs. 40K -100K /kg
- Oral Administration Advantage
- Global Market Accessibility

Industry :

Innovator : Merck & Co.(JANUVIA ®) -
Basic Compound Patent Expired in July 2022



Sitagliptin market is predicted to grow at 34% CAGR from 2024-2031
Source : Cognitive Market Research

34% Global CAGR 2024-2031

Licensed to Sun Pharma to manufacture and sell under the brand names *Istavel* and *Istamet*.

Generic Manufacturers : Dr Reddy's, Glenmark, Sun Pharma, JB Chemicals, Cipla, Torrent, Zydus Cadila, Lupin +15 (>1% market share)

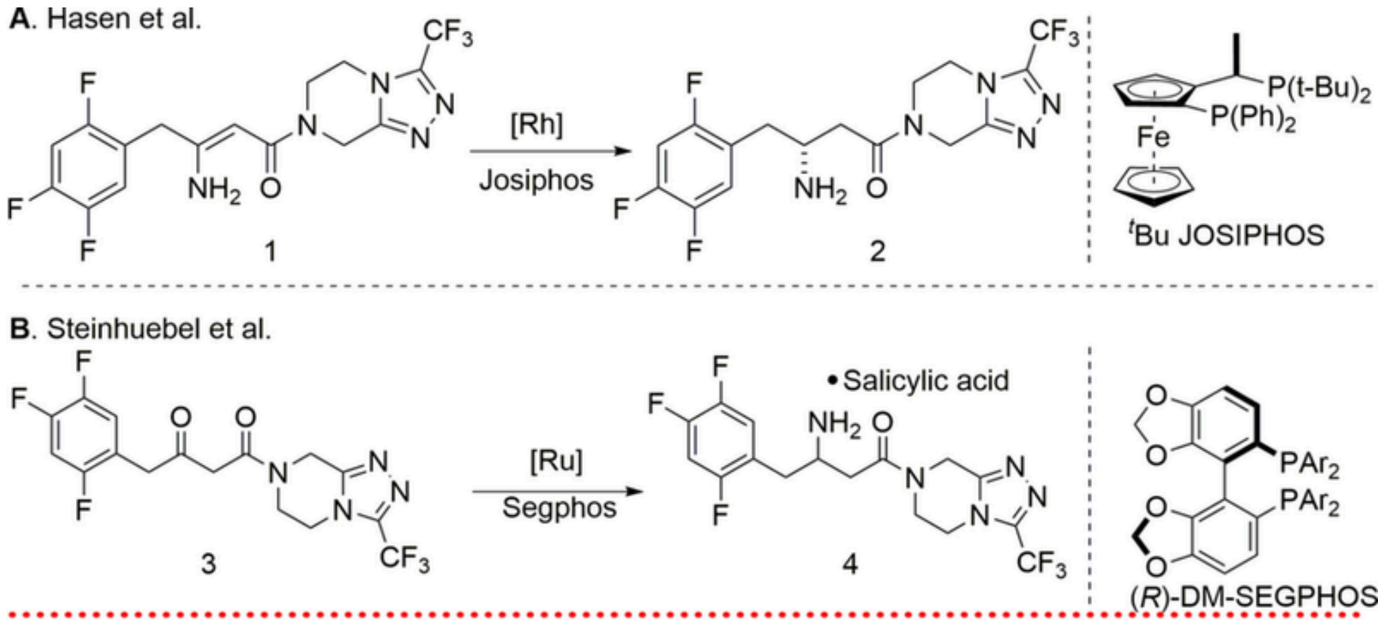
Match Maker/ Pharmaceutical Process Innovations/ 20 March 2025/ Highly Efficient Sitagliptin Production

Existing Methods

Direct Asymmetric Reductive Amination

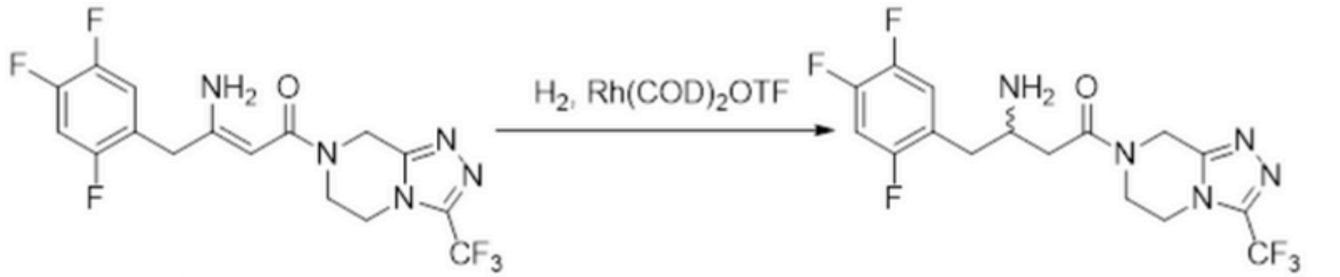
Two Methods which have been used:

- Overall yield: 96% - 99%
- Catalyst: Rhodium/Ruthenium with multiple acidic additives
- Additional costs due to separate isolation and synthesis of the active catalyst
- Merck & Co. Rhodium catalysis process patents
  (US 7.468.459 & US 7.495,123)
  are set to expire by May 2025



Source
Hansen, K. B.; Hsiao, Y.; Xu, F.; et al. Highly Efficient Asymmetric Synthesis of Sitagliptin. J. Am. Chem. Soc. 2009, 131 (25), 8798–8804. https://doi.org/10.1021/ja902462q.

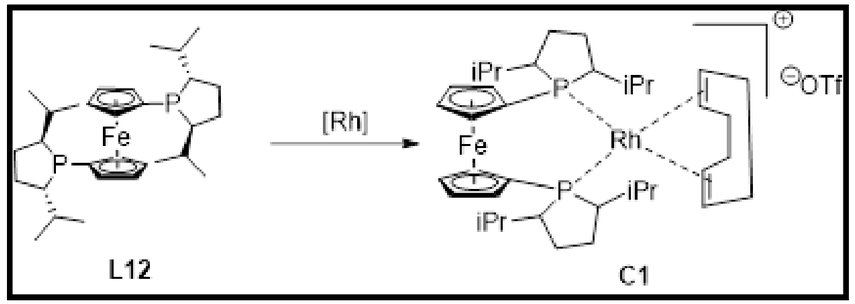
Improved Process from NCL



Dehydrositagliptin — Rhodium + Ferrolane — Sitagliptin

PROCESS FEATURES

- **Single-Step Synthesis**
- **Very High Enantiomeric Selectivity (99.8% ee)**
- **In-situ Catalyst Generation of Active form**
- **Fewer Solvent Additives**



Active Catalyst - Rhodium + Ferrolane

Estimated Cost of Raw Materials : **USD ~147 per kg** of Product Yield

Work flow

Rh Catalyst + Ferrolane

Dehydrositagliptin Formula IIa

Mixing

Argon — 25° C / 1 h

Slurry

Hydrogen 10-30 bar — 35° C - 90° C 17-24 h

Catalytic Hydrogenation

Cooling — 25° C 1 bar

Column Purification

Neutral Alumina Bed

Filtrate

Drying

Sitagliptin Formula Ia

Current status

Technology Status:

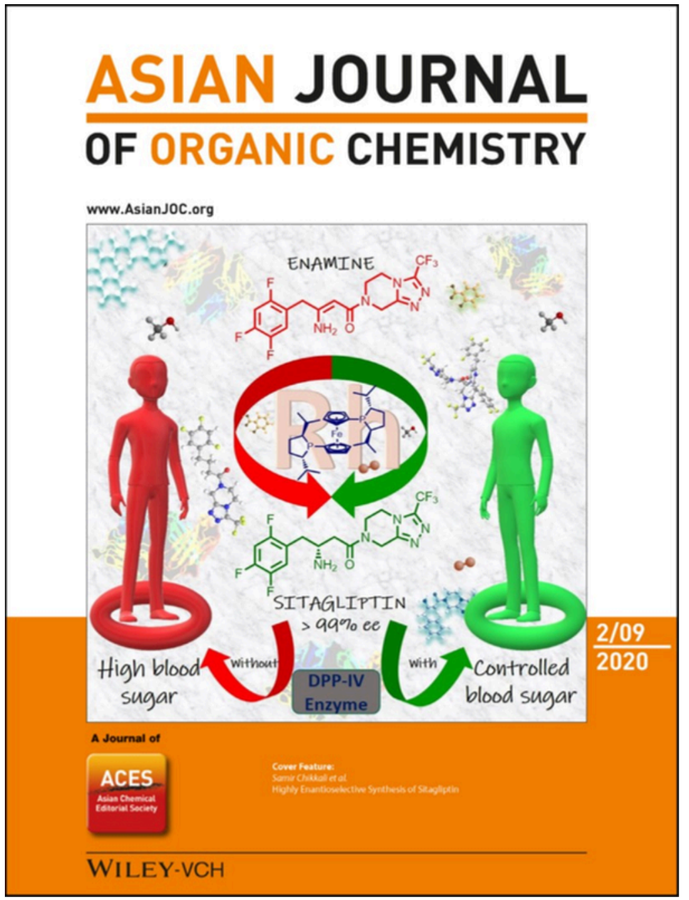
- Status of the technology - TRL 4
- Demonstrated at 5g lab scale

Patent Status:

- Patent Coverage : US, India
- Indian Patent No. 406933
- Priority Date : 11 Dec 2018
- US Patent No. US12202833B2
- PCT Filed: WO2020121321A1

Publications:

Chikkali, S.; Suryawanshi, S. R.; Samant, S. D.; Pawar, S. H. Highly Enantioselective Synthesis of Sitagliptin. Asian J. Org. Chem. 2019, 9 (2), 189–191. 10.1002/ajoc.201900709 - Asian J. Org. Chem 2019.



Selected as Cover Feature in Asian J. Org. Chem.

Value Proposition of NCL Method

- High enantiomeric excess while getting higher yield compared to Merck process (US 7733A1)
- Catalyst — Patent protected (Granted in IN, US)
- Process — Patent protected (Granted in IN, US)
- Cost effective process economics if scaled up

Who should be interested and why?

Who

Pharmaceutical companies & API Manufacturers who are vertically integrating

Why

This Single-step process for sitagliptin synthesis offers advantages such as

- Higher overall yield,
- Lower costs,
- Reduced waste,
- Simplified purification

Team & Organization

Dr Samir Chikkali

Professor & Chief Scientist (G),
National Chemical Laboratory, Pune.

- Leads Research Group : POMCAT (POlymer and OrganoMetallic CATalysis)
- Research Interests:

Catalysis, polymer chemistry, sustainable chemistry.

- Postdoctoral work at University of Amsterdam, University of Konstanz (Alexander von Humboldt Fellow).
- Ph.D. from University of Stuttgart, Germany.
- Associate Editor: Bulletin of Materials Science.
- Reviewer for several high impact journals
- Publications: High-impact journals (e.g., JACS, Angewandte Chemie, Green Chemistry).
- Numerous awards and honors.

Best Scientist Award by CSIR-NCL in the Year 2016-17 and 2022-23

About the Institute

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.

POMCAT Research Group @ CSIR-NCL

Key assets and strengths of the team:

- Well-equipped laboratories facilities with sophisticated analytical instrumentation facilities.
- Strong collaborations with academia, industries, and research organizations.
- A significant number of patents and publications in highly efficient catalysis & Polymer synthesis
- Focus on translational research to address industrial and societal challenges.
- Strong track record of developing scalable technologies for industrial applications

Industry collaborations: POMCAT Research Group

POMCAT
Dr. Chikkali's Research Group

National Chemical Laboratory

Reliance Industries Limited

IndianOil

हिन्दुस्तान पेट्रोलियम
HP

HMEL
Energising a Brighter Tomorrow

COSMO FILMS
Engineered to Enhance

गेल
GAIL

SOLVAY

Next Steps

Possible to scale up with support from industry partners from 5 g scale to pilot scale or continuous flow (as required by industry) and in partnerships with other CSIR labs

Seeking

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

Joint development and sponsored R&D partners or scaling up and advancing the technology

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