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Match Maker/ Pharmaceutical Process Innovations/ 20 March 2025

A PROCESS FOR PREPARATION OF NINTEDANIB

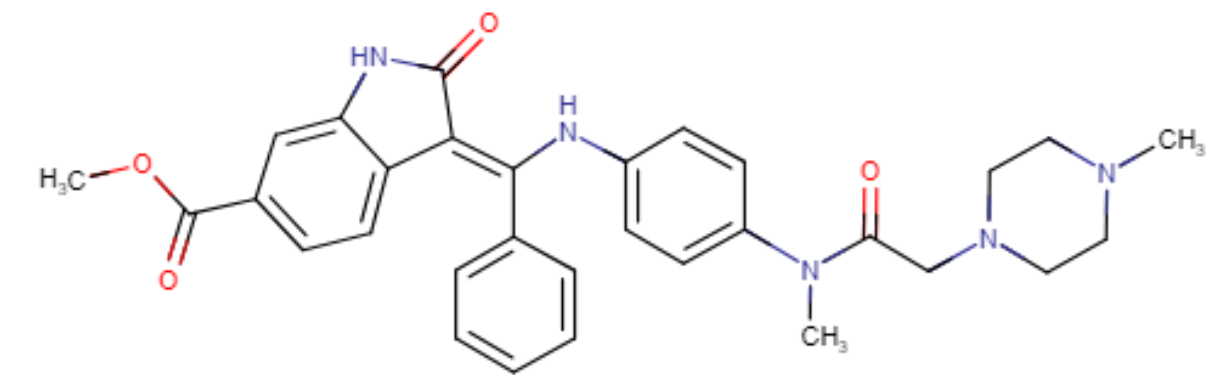
Lead Inventor: Dr. Gautam Panda

Organization: CSIR-CDRI

TechEx.in Case Manager: Kavita Parekh (kavita.parekh@ventercenter.co.in)

About Nintedanib

- Nintedanib is a small-molecule tyrosine kinase inhibitor which is orally administered as capsules
- Approved by the US FDA for the treatment of idiopathic pulmonary fibrosis.
- The EMA and the PMDA have also approved Nintedanib for the treatment of non small cell lung cancer (NSCLC).
- Currently In India, Nintedanib may cost Rs. 5000–6000/day which is unaffordable to most..
- Price of generic version is Rs 85–90 per 150 mg tablet.



Market Opportunities

The Nintedanib Market Size was valued at USD 1.5 Billion in 2023
(Source : Dataintel)

Industry :

Innovator : **Boehringer Ingelheim under the brand names of *Ofev* and *Vargatef***

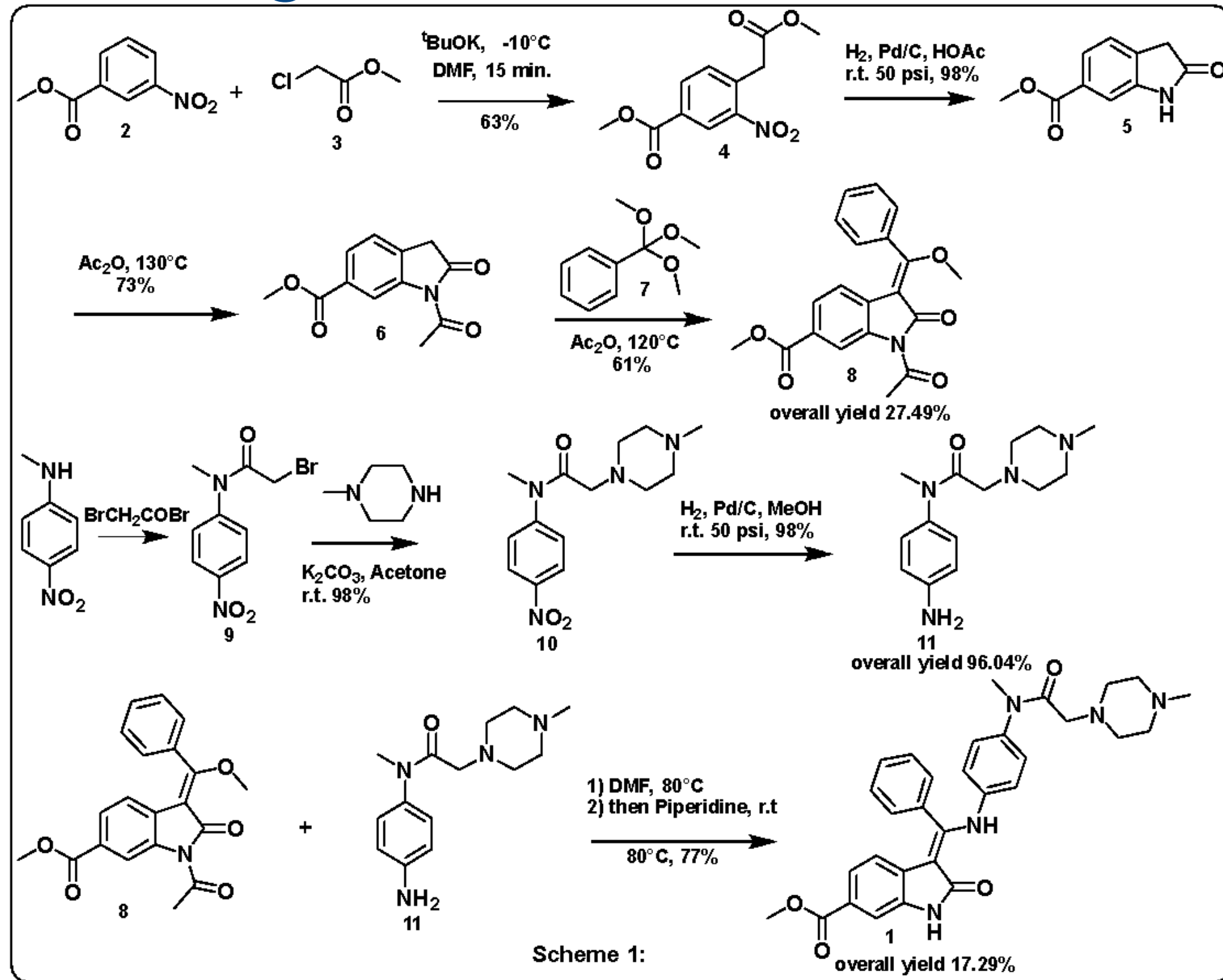
➤ Basic Product patent expired in **2023**, secondary patents possess exclusivity till **2029**

Licensed manufacturers in India:

➤ Manufactured by Cipla Ltd ,Lupin ,Zydus, Cadila,Tivan Sciences, HEMA Pharmaceuticals, MSN Labs, Sun Pharma, Glenmark Pharmaceuticals.

➤ Generics: Glenmark Pharma , Cipla Limited

Existing Process Used



THE DRAWBACKS

of current known synthesis are:

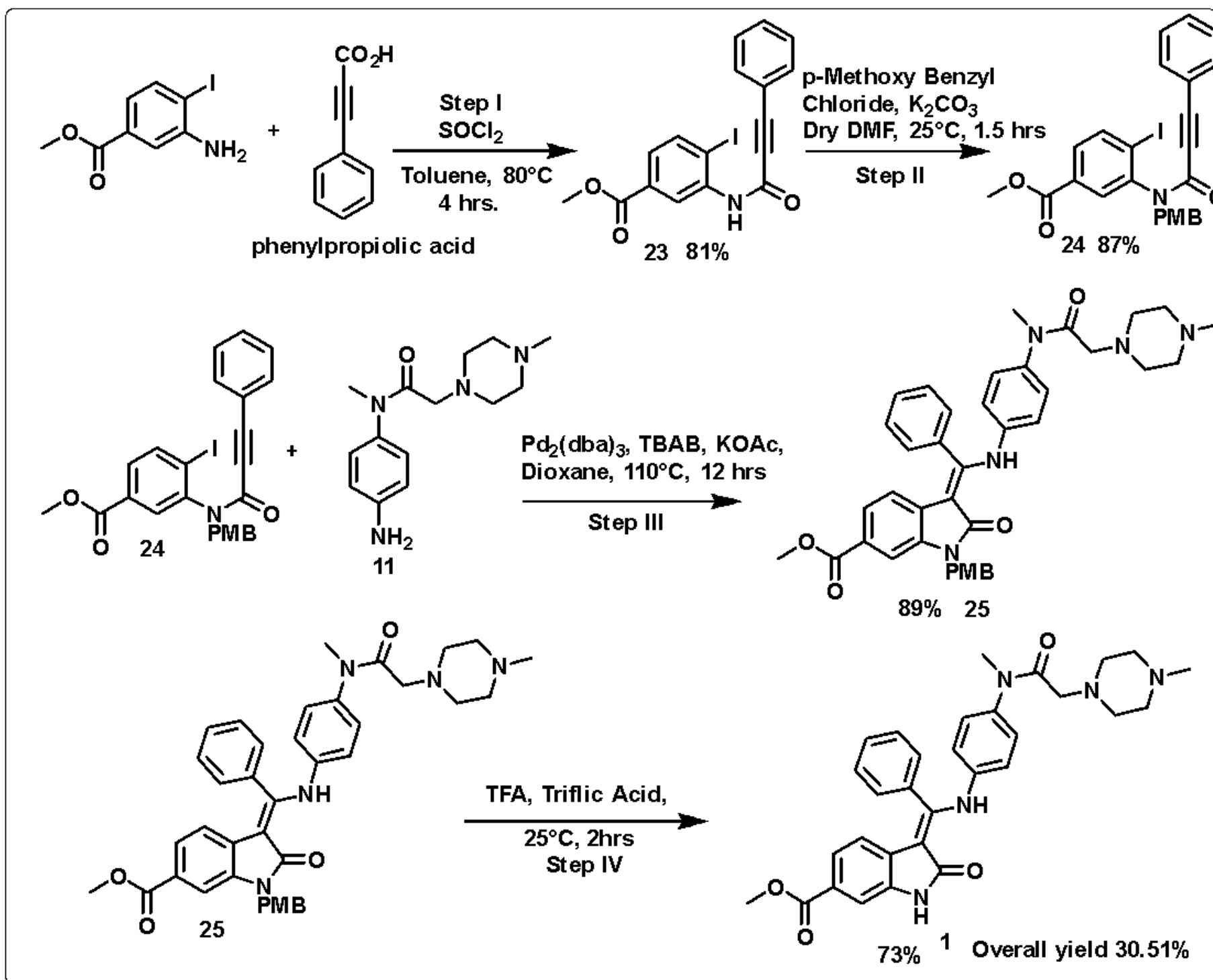
- Total Nine steps
- DMF, Acetic acid, Acetic Anhydride have been used
- Intermediate number is Eight (difficult to synthesize at large-scale)
- High temperature is used in this process
- Hydrogenation with Pd/C two times is required for two times
- Yield of the reaction is not so high (1 st step, 3 rd step, 4 th step).
- Harsh reaction condition is used in the 1st step of this process (use of strong base like potassium tert-butoxide)

Source – J. Med. Chem. 2009, 52, 4466–4480, WO0127081A1

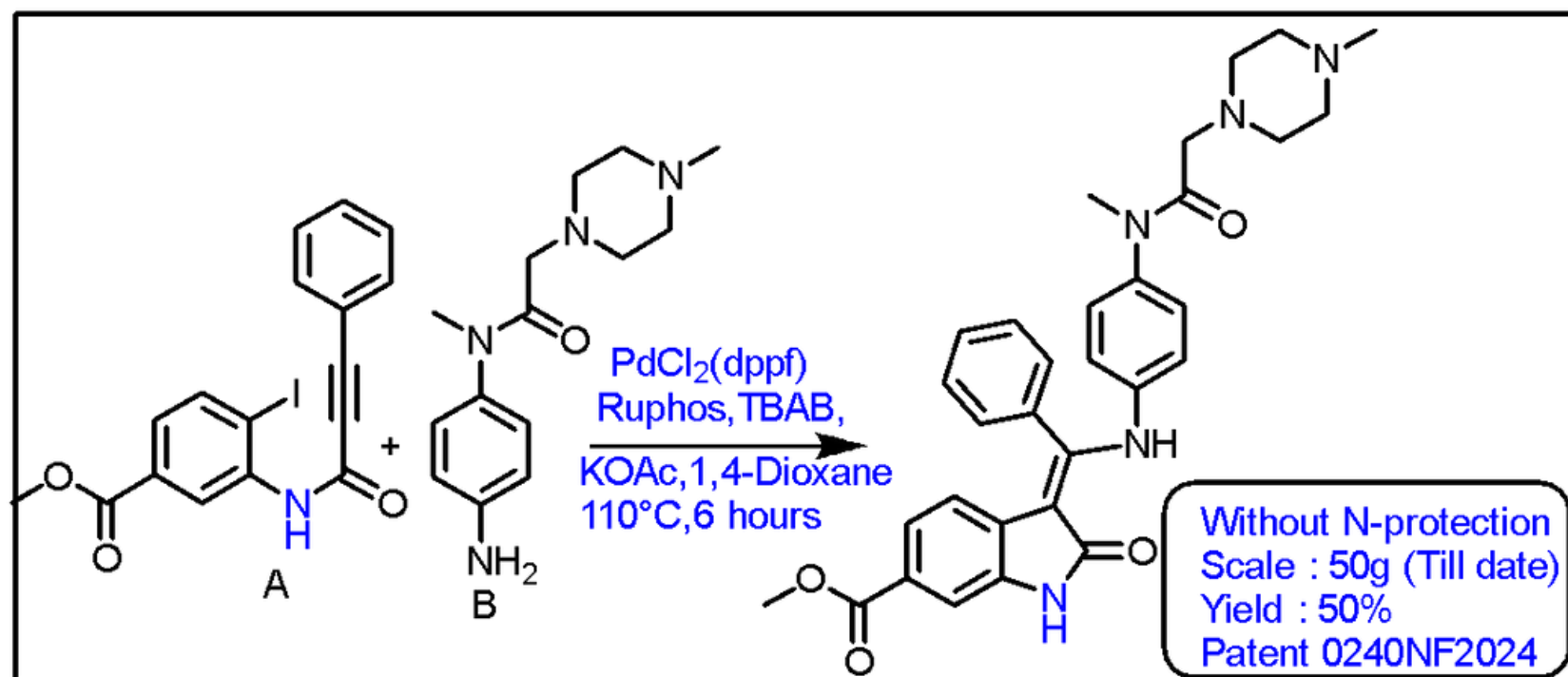
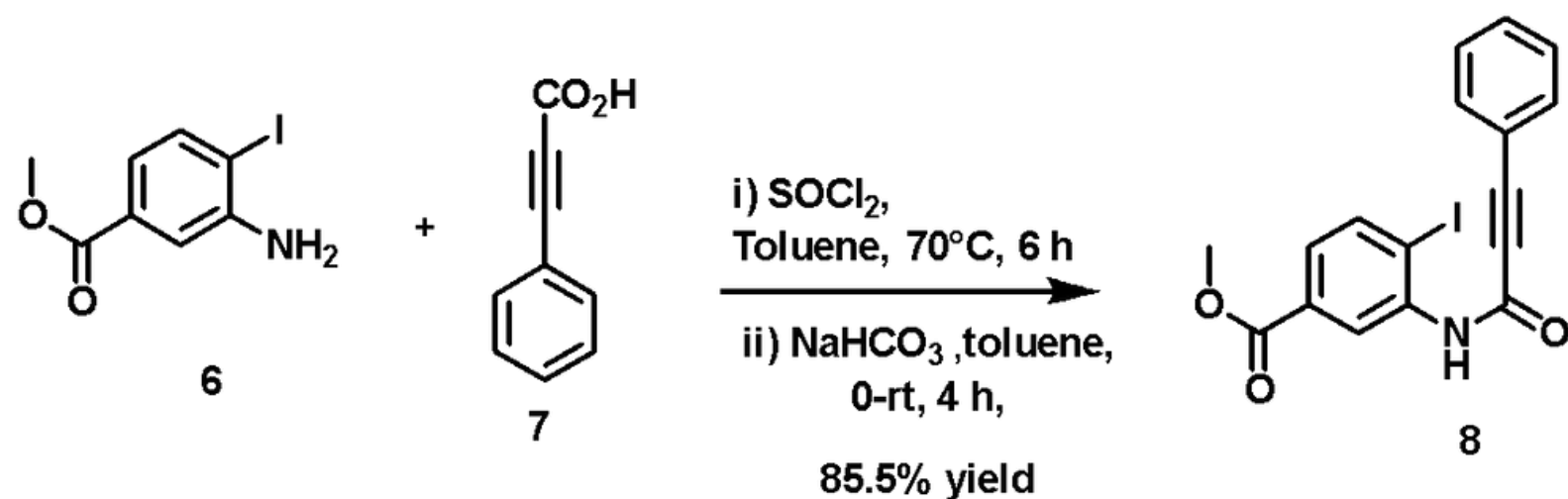
Improved Process from CDRI

ADVANCEMENTS & IMPROVEMENTS

- Lower Number of synthetic steps (4)
- Environment friendly reagents used
- Easy access to oxindole skeleton with
- Cis-selectivity via Pd(0) catalyzed domino Heck followed by Buchwald Hartwig coupling reaction



Improved Process from CDRI



ADVANCEMENTS & IMPROVEMENTS

- Robust and Scalable
- A known and linear process with 9-10 steps
- Convergence with 2-4 steps leading to the reducing the number of synthetic steps using tandem/domino reaction
- Less use of chemical reagents for acceptable overall yield :
(Known : 35-40% CDRI : 35-51%)

Estimated Cost of Raw Materials :
USD ~1919 per kg of Product Yield

Current Status

Technology Status :

- Status of the technology – TRL 4 (Lab level results shown)
- Demonstrated at 50g scale

Patent Status :

- Indian Patent Filed (Application No. **202211006560**)
- Publication Date (U/S 11A): 11 Aug 2023
- Priority date: **7 Feb 2022**

Publications :

- Maji, S.; Halder, S.; Sharma, A. K.; Madhesiya, A.; Thakur, T. S.; Panda, G. Stereoselective Construction of 3-(Aminoalkylidene)oxindoles in One Pot: Development of a Novel, Robust, and Scalable Process for the Multigram-Scale Preparation of Nintedanib. *Organic Process Research & Development* **2024**, 28, 3, 754-769.

Value Proposition of the CDRI Process

- Higher yield → 35-51% vs 35-40%
 - Number of steps lower → 2-4 vs 9-10
 - **Mild reaction conditions; c) eco-friendly solvents Toluene, dioxane are used; c) acceptable overall yield (50%)**
 - No column chromatography needed → OpEx lower
 - **98% HPLC purity**
 - **Residual palladium 10.9 ppm (ICP-MS)**
 - Estimated Raw Material Cost is comparable to landed cost
- **\$ ~1919 /kg**
- API Included in PLI 2.0 scheme

Who should be interested and why?

Who

Pharmaceutical API Manufacturers :

- New API manufacturers who wish to leverage the PLI scheme
- Companies already manufacturing Nintedanib and who want a better process

Why

An improved synthesis offers advantages such as

- Cost Effective
- Simpler Reaction Scheme
- Scalable
- Fewer Steps Required

The Lead Inventor



Dr Gautam Panda
Chief Scientist, CDRI

- **22 years of biomedical research experience** in harnessing chiral amino acids and trisubstituted methanes derived bioactive natural products, heterocycles towards drug discovery and human wellbeing.
- Worked on **cost effective synthesis of block-buster drugs**
- Author of **~132 publications (3850 citations, h-index 33)** and an inventor of **10 patents.**

Industry collaborations of the group



Organisation - CSIR-CDRI's Success Stories



Central Drug Research Institute a constituent laboratory of (CSIR) under the Department of Scientific & Industrial Research, Ministry of Science and Technology, Government of India.

Since Inception

- 13 New Drugs Discovered and Developed
- 6 Diagnostics
- > 80 Process Technologies
- > 12,000 Research Publications
- > 456 Patents Filed Abroad
- > 586 Patents filed in India
- > 2,000 Ph.D.'s
- > 2,000 Sponsored Trainings
- > 7000 Post Graduate Trainings



World's first non-steroidal once-a-week contraceptive pill for women



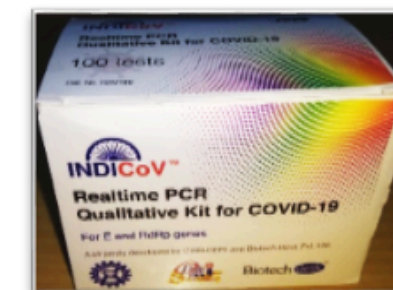
α β – Arteether for severe *P. falciparum* malaria including cerebral malaria and chloroquine-resistant cases, being marketed in > 20 countries



Clinically validated traditional medicine from Bacopa for ADHD in elderly marketed in >7 countries



Centchroman with a brand name Chhaya is part of National Family Program



Indigenised qRT-PCR Diagnostic Kits towards Atmanirbhar Bharat



Indigenized Indigenous DNA Staining Dye "GreenR" towards Atmanirbhar Bharat

Currently, 3 small molecules and 2 Phytopharmaceuticals are in clinical trial. Further, 5 small molecules and 4 Phytopharmaceuticals are in pre-clinical stage of development for various therapeutic areas of national and global importance.

Organisation - CSIR-CDRI's Industry Collaborations



Match Maker/ Pharmaceutical Process Innovations/ 20 March 2025/A Process for preparation of Nintedanib

Next Steps

Possible to scale up with support from industry partners from 50 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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