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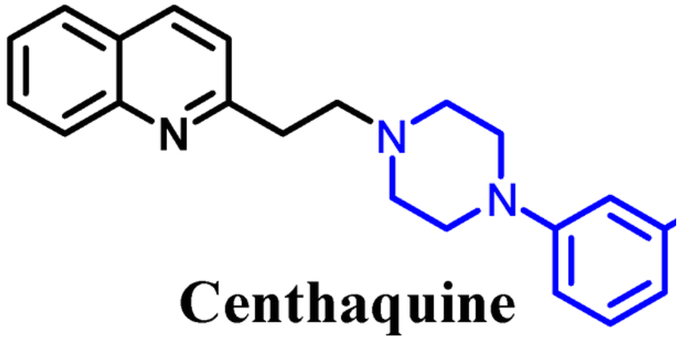
Match Maker/ Pharmaceutical Process Innovations/ 20 March 2025

IMPROVED PROCESS FOR CENTHAQUINE

Lead Inventor: Dr. Ajay Kumar Srivastava
Organization: CSIR-CDRI
TechEx.in Case Manager: Kavita Parekh (kavita.parekh@ventercenter.co.in)

About Centhaquine

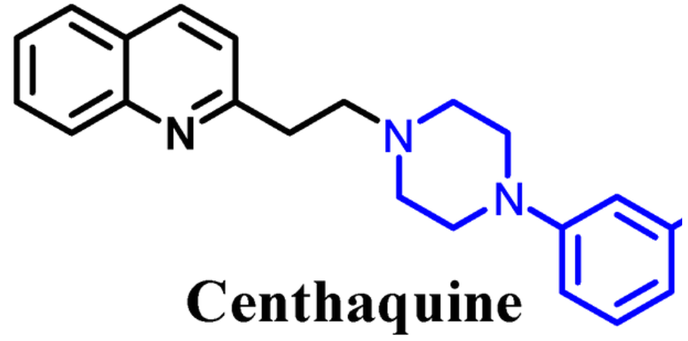
- Centhaquine was invented at CSIR-CDRI in 1989 as an hypotensive agent.
- It was further developed by US-based Pharmazz, Inc.
- It got approval in 2020, was introduced in the Indian market (brand name Lyfaquin) in 2022 for the management of hypovolemic shock.
- Dr Reddy's Laboratories has currently entered a licensing agreement with Pharmazz to commercialise in India.



Centhaquine

Market Opportunities

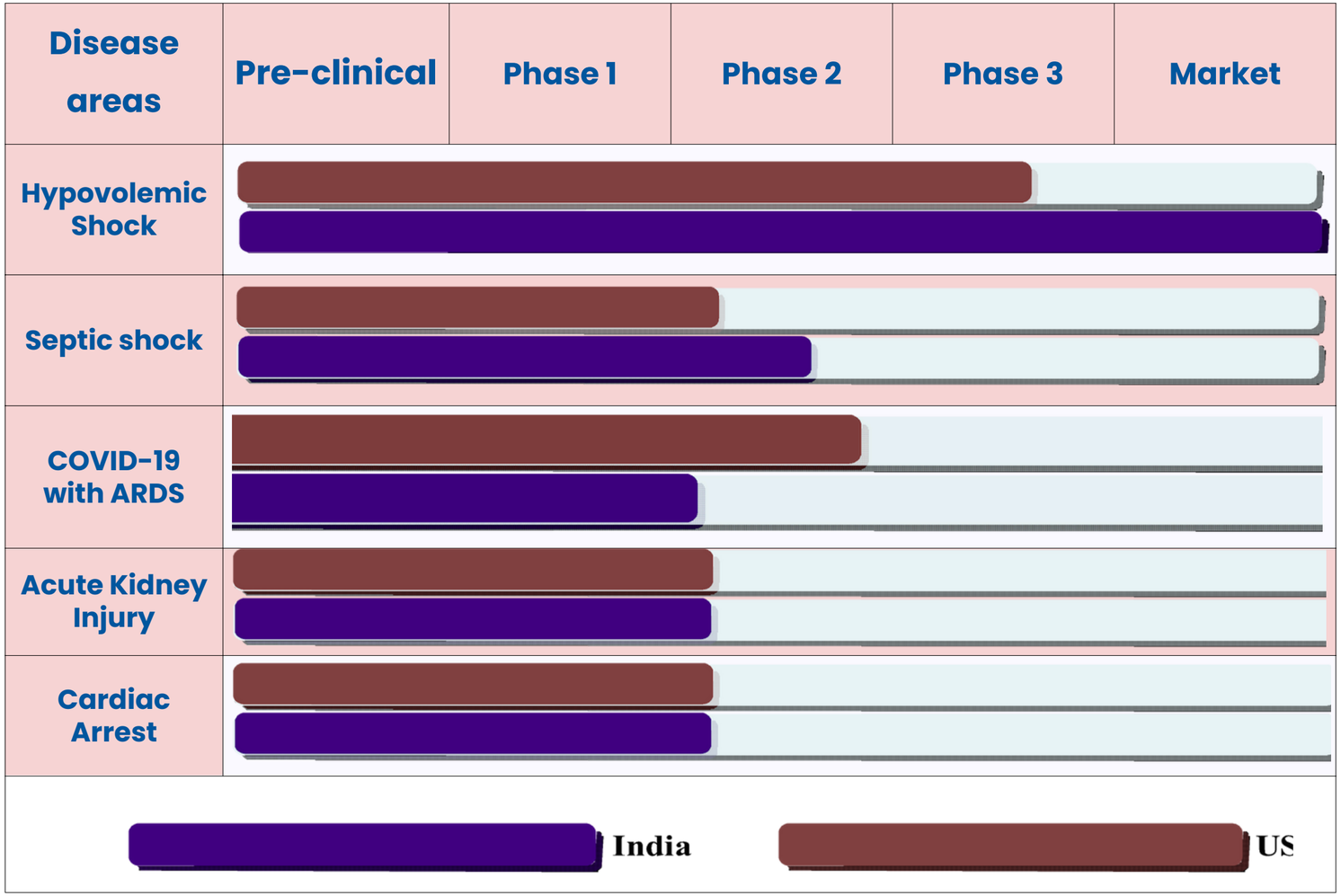
- Every year ~1.7 Million Americans suffer hypovolemic shock, of which 348,000 suffer severe symptoms and are therefore eligible for Centhaquine. Market size estimate is approximately 40m$ per year in USA.
- In India there are estimated 2 million patient with market cost of approximately 200M$ (~ Rs 2000Cr)



Centhaquine

Clinical Studies

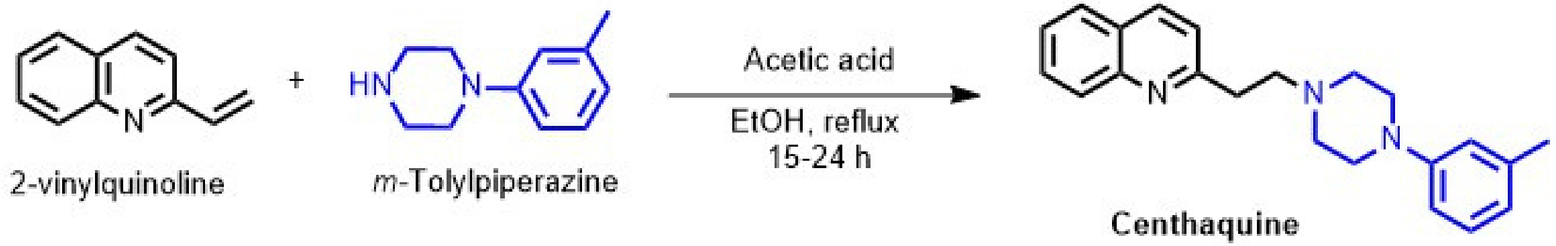
- Clinical Investigations going for septic shock, acute kidney injury, cardiac arrest and COVID-19 with acute respiratory distress syndrome (ARDS) making it an interesting drug for process development.



Currently used methods

i) 1989, US3983121; Patent Expired -
First method by Nitya Anand et. al. Yield = 47%
ii) 2015, US20150250782A1, Patent Active - Improved procedure by Gulati et. al. Yield = 73%

(a) Acid-catalyzed addition of *m*-tolylpiperazine to 2-vinylquinoline

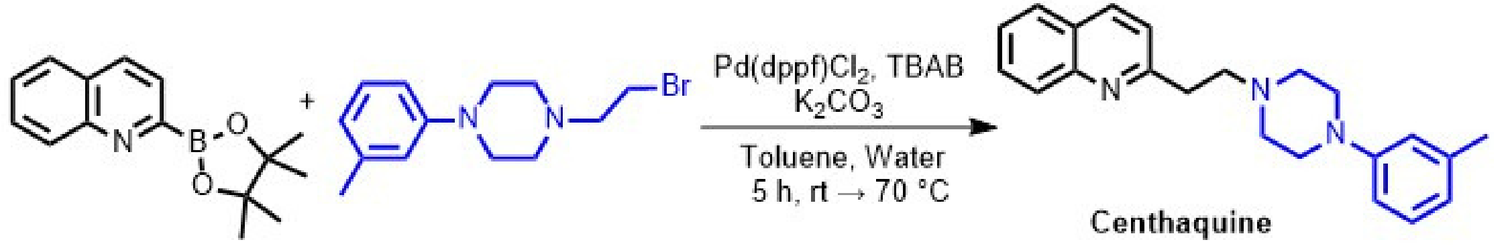


Key Limitations:

- *Use of acid*
- *High temperature*
- *Moderate yield*
- *Impurity formation*

2020, CN114685366A, Patent Pending
by Hanpu et. al. Yield = 81%

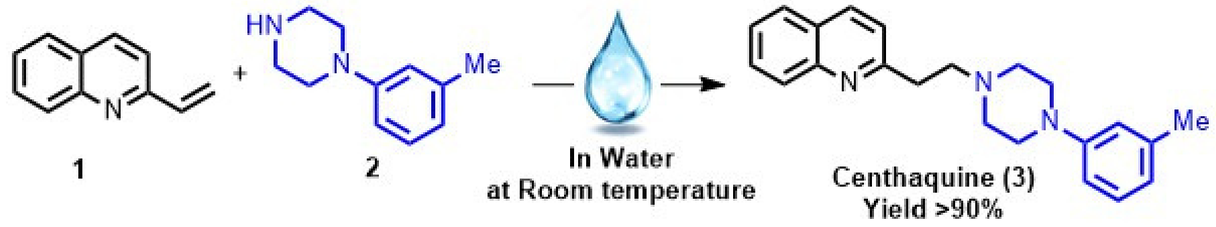
(b) Pd-catalyzed coupling of boronic acid with alkyl halide

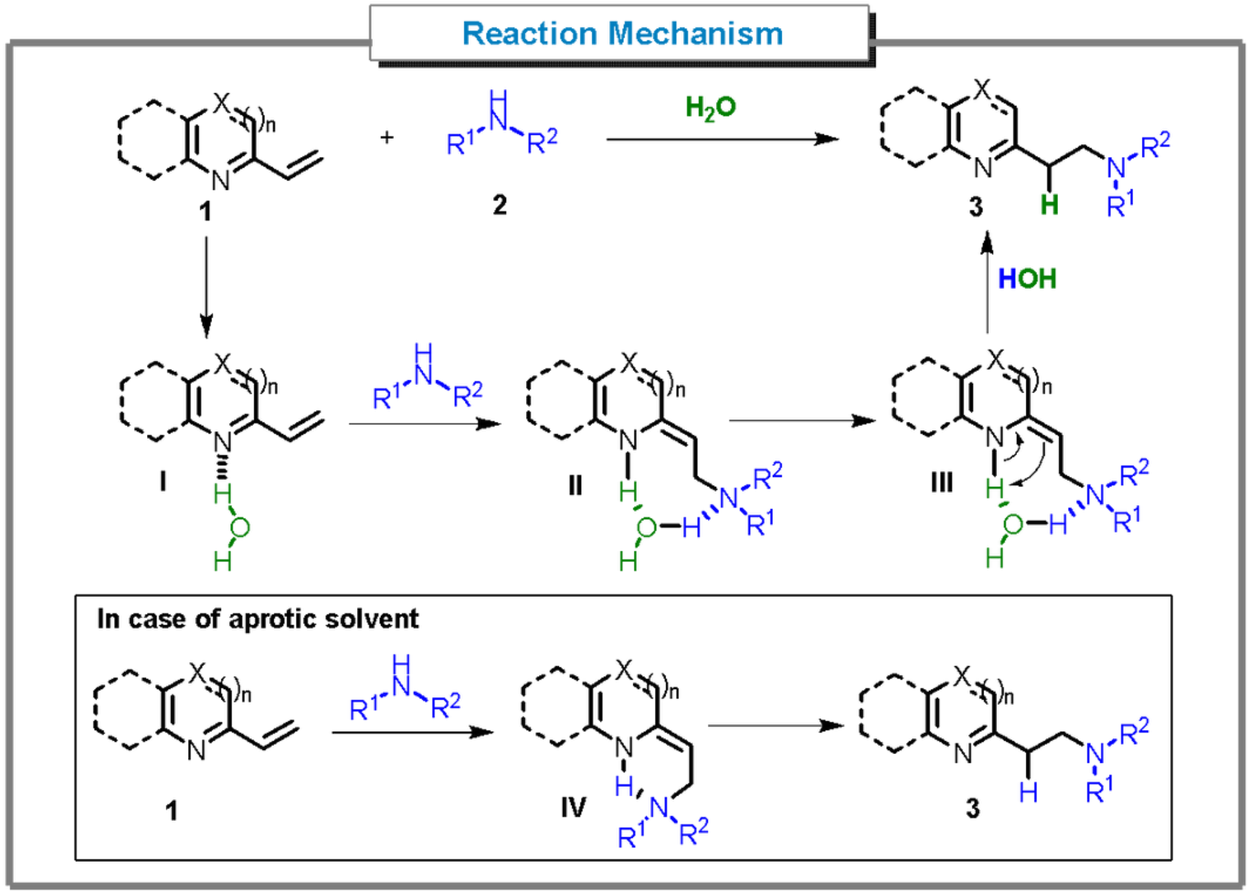


Key Limitations:

- *Use of Pd catalyst*
- *High temperature*
- *Expensive starting materials*

Improved Method by CDRI





Key advantages:

- Aqueous Process
- No acid catalyst
- Room temperature process
- No Column Purification required
- Reduces impurity formation
- Greener synthesis process.
- High-yielding

Estimated Cost of Raw Materials :
USD ~224 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. 202111044824
- Priority Date: 01/10/2021
- Publication Date(U/S 11A): 07/04/2023

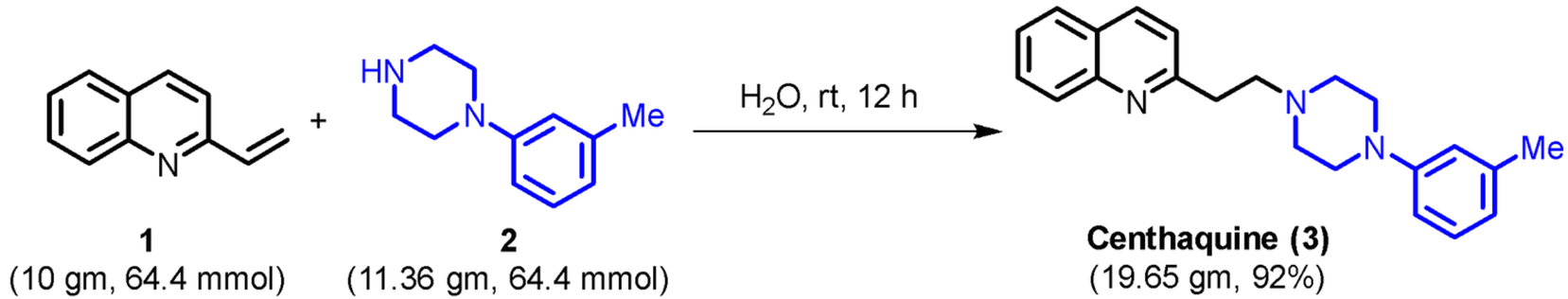
Publications :

- Yadav, A.; Ambule, M. D.; Srivastava, A. K. Catalyst-Free Anti-Markovnikov Hydroamination and Hydrothiolation of Vinyl Heteroarenes in Aqueous Medium: An Improved Process Towards Centhaquine. Org. Biomol. Chem. **2024**, 22, 1721–1726.

Value Proposition of the CDRI Process

- High yield: >90% (current method) vs 47% or 71% (previous methods)
- Lower estimated Raw Material Cost $ 224/kg.
- Higher purity ==> Lower cost of purification
- Green credentials
    a. Aqueous synthesis
    b. Room temperature operation
    c. Lower E-Factor
- Optimised at >50g scale in three batches
- Complete characterisation of impurities and API
- Prepared Citrate Salt

A Comparison in Green-Metrics Parameters



1
(10 gm, 64.4 mmol)

2
(11.36 gm, 64.4 mmol)

Centhaquine (3)
(19.65 gm, 92%)

Green metrics	Existing approach 1	Existing approach 2	Our approach
Yield	46.82%	72.56%	**92%**
Carbon Efficiency	46.54%	72.81%	**92.05%**
E-Factor*	25.06	16.12	**0.08**
Atom Efficiency Factor	46.82%	72.5%	**92%**
Mass Intensity*	26.06	17.12	**1.08**

*lower is better

Who should be interested and why?

Who

Pharmaceutical API Manufacturers :

- Interested in making and selling Centhaquine approved indications

Why

Advantages offered by this method :

- Cost Effective & High Yielding
- Greener Method

Lead Inventor

Dr Ajay Kumar Srivastava

Principal Scientist,
CSIR-CDRI, Lucknow

- Holds a MSc in Chemistry from Delhi University and a doctoral degree in Chemistry from Jadavpur University.
- Has two years Postdoctoral research experience in the field of Chemistry and Chemical-Biology with Prof. S. B. Park at Department of Chemistry, Seoul National University, South Korea.
- Aug 2011-March 2017 he worked as Scientist at CSIR-IICT, Hyderabad
- Since March 2017, he is working as Principal Scientist at CSIR-CDRI, Lucknow.
- His expertise include total synthesis, process development, medicinal chemistry and green chemistry.
- He has published 54 research articles and has supervised 10 PhD students
- His group has transferred the process for the Umifenovir to Medizest Pvt Ltd. for the repurposing during Covid-19
- His groups is also working with Dr Reddys' Lab and with ARKN Pvt. Ltd. on various sponsored projects.

Organisation – CSIR–CDRI's Sucess 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

Next Steps

Possible to scale up with support from industry partners from >50 g batch 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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