

OPTIMIZATION OF QUINOLINE SYNTHESIS BY QUALITY BY DESIGN

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ABSTRACT

Quinoline is one of the most important N-based heterocyclic aromatic compounds in the fields of medicinal and industrial chemistry, forming the scaffold for compounds of great significance. Quinoline recently is one of the priorities in lead selection by researchers because of its broad range of activities and also for their wide applications. These include anti-inflammatory and antitumor agents, the antimalarial drugs quinine and chloroquine, and organic light-emitting diodes. 6-Methoxy-8-aminoquinoline is a metabolite of primaquine belongs to 8-Amino Quinoline derivative which is used to treat malaria. The present article having focus on the optimization study of the synthesis of 6-Methoxy-8-nitroquinoline which is used in the synthesis of 6-Methoxy-8-aminoquinoline by QbD. The sulphuric acid and arsenic trioxide showed best results at 120°C for 4 hrs. The net percentage yield was found to be 27%. The novel method can be emitable for industrial applications.

1. INTRODUCTION

Quinoline is one of the most important N-based heterocyclic aromatic compounds in the fields of medicinal and industrial chemistry, forming the scaffold for compounds of great significance. Quinoline recently is one of the priorities in lead selection by researchers because of its broad range of activities and also for their wide applications. These include anti-inflammatory and antitumor agents, the antimalarial drugs quinine and chloroquine, and organic light-emitting diodes. Quinolines were first synthesized in 1879, and since then a synthetic routes have been developed.^[1] Many of these methods, such as the Skraup, Doebner-Von Miller, and Friedlander quinoline syntheses, are well-known but suffer from inefficiency, harsh reaction conditions, and toxic reagents.

The present article having focus on the synthesis of 6-Methoxy-8-nitroquinoline which is used in the synthesis of 6-Methoxy-8-aminoquinoline. 6-Methoxy-8-aminoquinoline is a metabolite of primaquine belongs to 8-Amino Quinoline derivative which is used to treat malaria.

It presents the optimization study of synthesis of 6-Methoxy-8-nitroquinoline.

Malaria is the complex mosquito born infectious disease which affect the humans and other animals and caused by parasitic protozoans (a group of single-celled microorganisms) belonging to the Plasmodium type. According to WHO, there was 212 million cases of malaria in 2015 and 429 000 malaria deaths. Most of the

deaths occurred in the African region 92%.^[2] The disease is most commonly transmitted by an infected female Anopheles mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites travel to the liver where they mature and reproduce.^[3] There are five species of Plasmodium that are P. falciparum, P. malariae, P. ovale, P. vivax and P. knowlesi. Which can infect and spread by humans? Most deaths are caused by P. falciparum because P. vivax, P. ovale, and P. malariae generally cause a milder form of malaria. The species P. knowlesi rarely causes the disease in the humans.^[4]

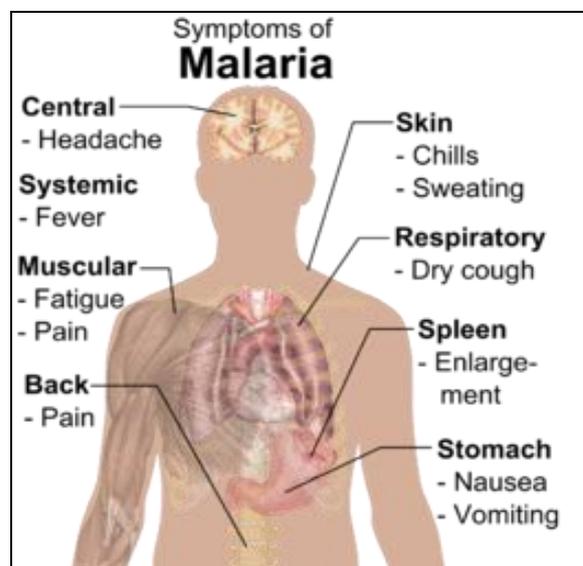


Fig.1: Sign and symptoms.

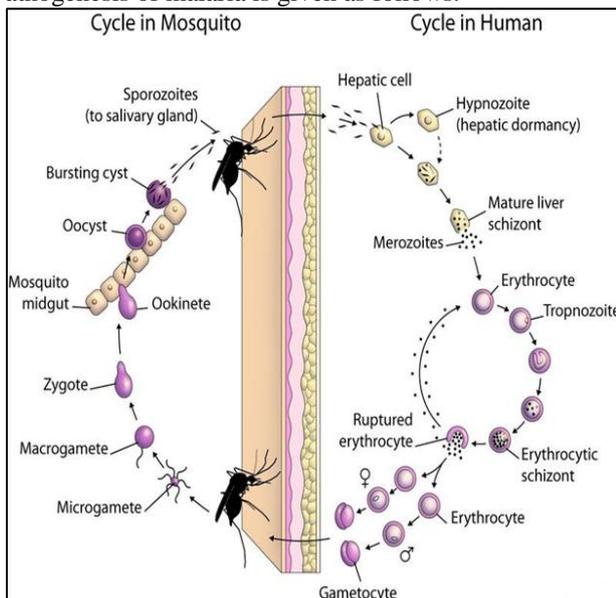
The signs and symptoms of malaria begin 8–25 days after infection; however, the symptoms may occur later in those patients who have taken antimalarial medications as a prevention.^[5]

A. Life Cycle of Malaria

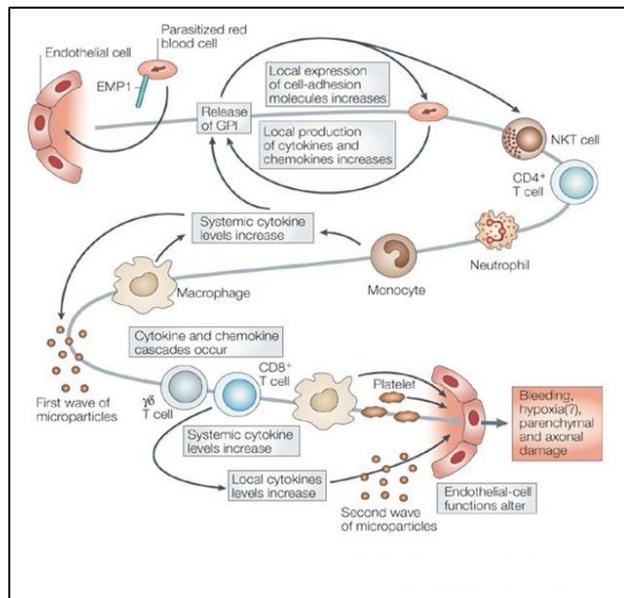
In the life cycle of the *Plasmodium*, a female anopheles mosquito (the definitive host) which transmits a motile infective form (called the sporozoite) to a vertebrate host such as a human (the secondary host), and hence acting as a transmission vector.^[6]

Life cycle of malaria is described in following figure.

Pathogenesis of malaria is given as follows.



Life Cycle of Malaria



Pathogenesis

Fig.2: Life Cycle and Pathogenesis of Malaria

C. Chemotherapy of Malaria

Majority of malaria cases is based on *artemisinin* combination therapy. The World Health Organization's Guidelines for the treatment of malaria provides recommendations on topics such as:

- Treatment of uncomplicated *p. falciparum* malaria
- Treatment of uncomplicated malaria caused by *p. vivax*
- Treatment of severe malaria.^[9]

D. Classification of Antimalarial Drugs

- **Cinchona alkaloid** - Quinine, Quinidine
- **4-Aminoquinolines**- Chloroquine, Amodiaquine, Piperaquine
- **Diaminopyrimidines**–Pyrimethamine
- **8- Aminoquinolines** - Primaquine, Bulaquine
- **Sulfonamides and sulfone** - Sulfadoxine, Sulfamethopyrazine, Dapsone
- **Sesquiterpine Lactones** - Artesunate, Artemeter, Arteether

- **Quinoline-Methanol** - Mefloquine
- **Tetracyclines** - Tetracycline, Doxycycline
- **Amino Alcohols** - Halofantrine, Lumefantrine
- **Mannich base** – Pyronaridine
- **Naphthoquinone**–Atovaquone
- **Biguanides**– Proguanil, Chlorproguanil

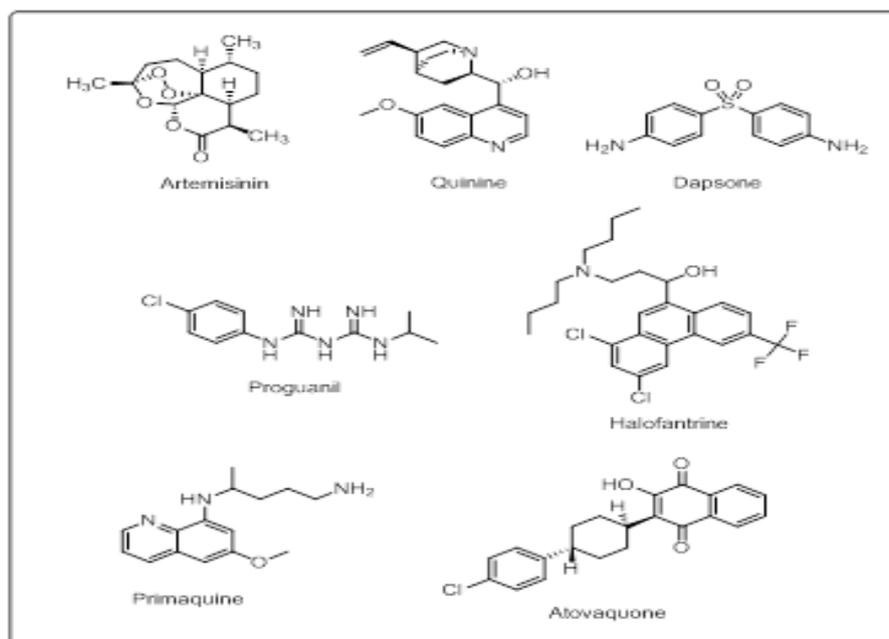


Fig.3: Antimalarial Drugs.

E. SAR

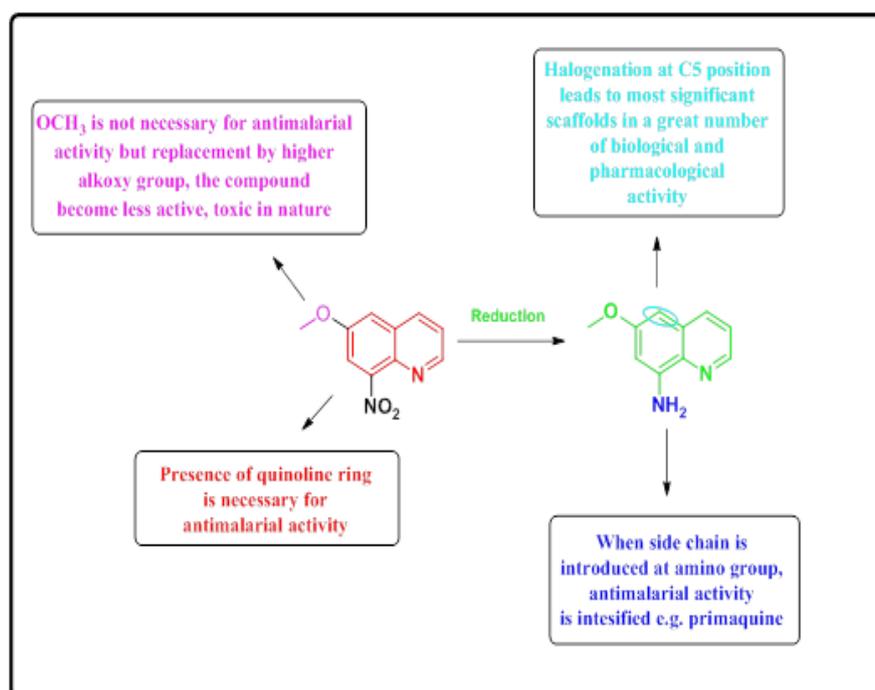


Fig.4: SAR of Quinoline moiety.

2. Quality By Design

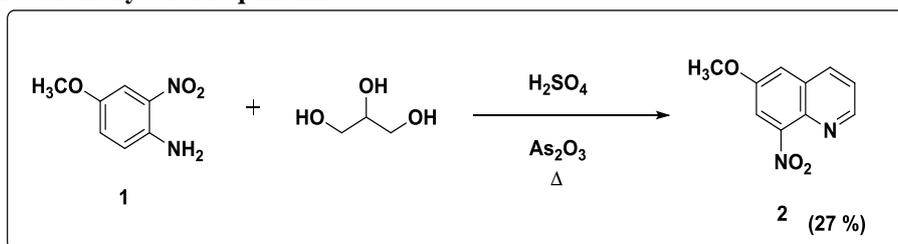
The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance. Software like Design expert® can be used to apply QbD approach.

ADVANTAGES OF QBD

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change

3. EXPERIMENTAL WORK

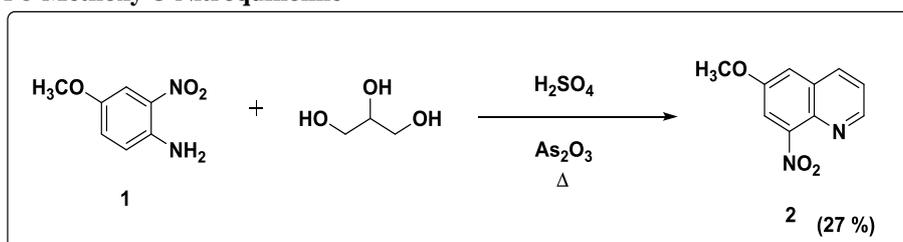
A. Synthesis Of 6-Methoxy-8-Nitroquinoline



The commercially available 3-nitro-4-aminoanisole (1) was converted to 6-methoxy-8-nitroquinoline (2) in presence of arsenic trioxide and sulphuric acid in glycerol at temperature 118 °C. After the completion of reaction, water was added and stirring was carried out

overnight. Addition of ammonia takes place in order to neutralize the acid and it was workup with water/DCM and purified by column chromatography using Hexane:EtOAc as a mobile phase.

B. Synthesis Of 6-Methoxy-8-Nitroquinoline

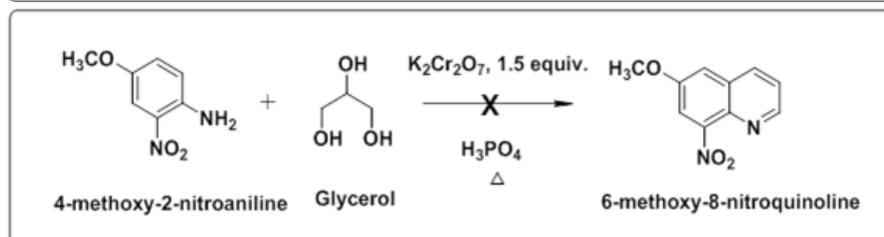
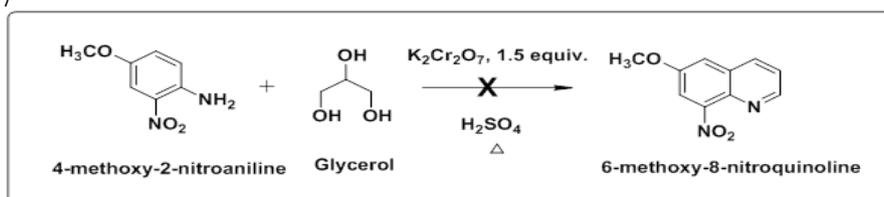


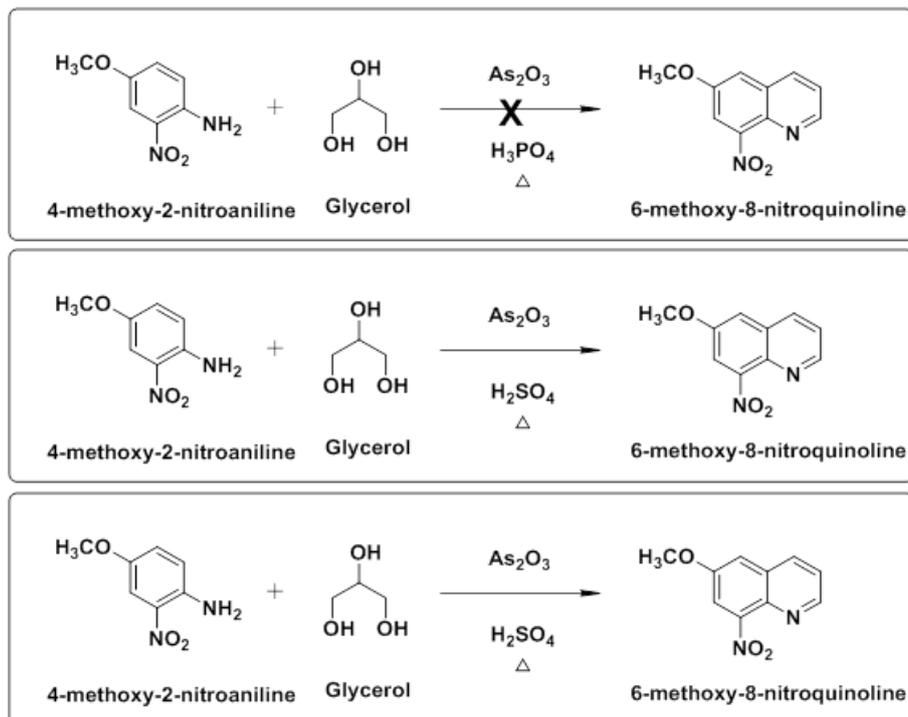
In a three-necked round-bottomed flask, homogeneous slurry of powdered arsenic oxide (2.5 equiv.), 3-nitro-4-aminoanisole (1 equiv.) and glycerol (1 equiv.) was prepared. The flask was fitted with an efficient mechanical stirrer and a dropping funnel in which concentrated sulfuric acid (3 equiv.) was placed. The sulfuric acid is dropped into the orange reaction mixture over a period of 30 minutes. The stirrer and dropping funnel were removed, and a thermometer is inserted in one neck of the flask. A 10-mm. bent glass tube was attached to the second neck by a rubber stopper and attached through a trap to a water aspirator. The heat was carefully applied at such a rate that the internal temperature slowly rises to 105°.

When the removal of the water was completed, the suction tube was removed and the stirrer and dropping funnel are replaced. The internal temperature was held 118° during the subsequent addition of concentrated sulfuric acid from the dropping funnel. The sulfuric acid was added dropwise over a period of 2 hours and the temperature was maintained at 118°. After the addition was completed the temperature was maintained at 120° for 4 hours. The reaction mixture was cooled below 100°, it was diluted with 100 ml of water and allowed to cool overnight with stirring. The diluted reaction mixture was poured with stirring into a mixture of ammonium hydroxide and sufficient ice and the resultant thick slurry was workup with water/DCM. It was purified by column chromatography using Hexane/EtOAc.^[10]

The yield obtained was very less.

Oxidant $\text{K}_2\text{Cr}_2\text{O}_7$



Oxidant As_2O_3 

4. Optimization Study

We optimised the best possible reaction conditions using QbD using 3^2 factorial designing. The factors used were temperature and time. Several trials based on permutation and combinations were examined and results were analysed. By taking the best result from above reaction conditions that is H_2SO_4 and As_2O_3 (2.5eq) constant, the time and temperature was optimised after second addition of H_2SO_4 .

The above reactions were carried out at 120°C for 4 Hrs.

5. MATERIAL AND METHOD

All chemicals were purchased from Aldrich Chemicals Ltd. Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade and were used without further purification unless otherwise stated. Reactions were monitored by TLC, which was performed with 0.2 mm Merck pre-coated silica gel 60 F254 Aluminium sheets.

6. RESULT AND DISCUSSION

A. RESULTS OF SYNTHESIS

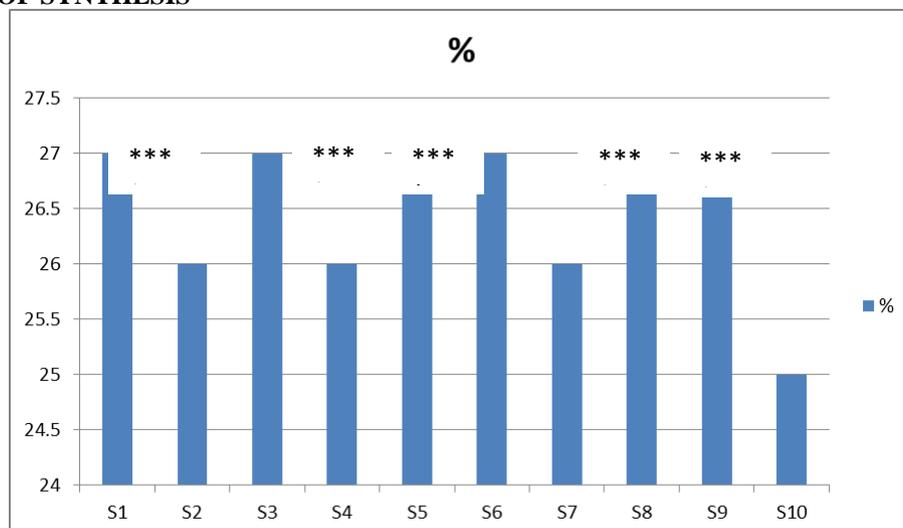
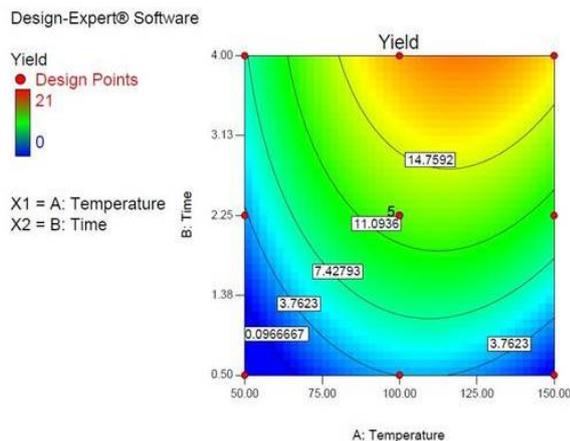


Fig.5: The graph demonstrates replication of novel method $n=10$ and the results of statistics and oneway anova resulted $*P<0.005$.

B. Results Of Qbd Approach

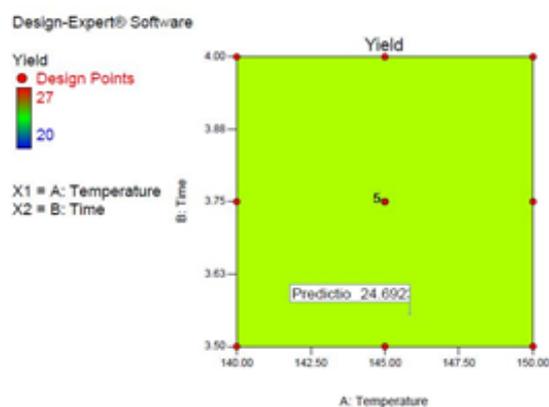
Std	Run	Block	Factor 1 A:Temperatu Degree Celsi	Factor 2 B:Time hour	Response 1 Yield %
6	1	Block 1	150.00	2.25	13
11	2	Block 1	100.00	2.25	11
8	3	Block 1	100.00	4.00	21
5	4	Block 1	100.00	2.25	12
13	5	Block 1	100.00	2.25	12
9	6	Block 1	150.00	4.00	13
1	7	Block 1	50.00	0.50	0
3	8	Block 1	150.00	0.50	0
2	9	Block 1	100.00	0.50	0
12	10	Block 1	100.00	2.25	13
4	11	Block 1	50.00	2.25	0
10	12	Block 1	100.00	2.25	14
7	13	Block 1	50.00	4.00	7



Temperature: 50-150 °C
Time: 0.5-4 Hrs.

Fig.6: Qbd approach 1.

Std	Run	Block	Factor 1 A:Temperatu Degree Celsi	Factor 2 B:Time hour	Response 1 Yield %
4	1	Block 1	140.00	3.75	26
12	2	Block 1	145.00	3.75	24
11	3	Block 1	145.00	3.75	27
5	4	Block 1	145.00	3.75	25
13	5	Block 1	145.00	3.75	26
7	6	Block 1	140.00	4.00	20
6	7	Block 1	150.00	3.75	21
2	8	Block 1	145.00	3.50	22
8	9	Block 1	145.00	4.00	26
1	10	Block 1	140.00	3.50	25
10	11	Block 1	145.00	3.75	27
9	12	Block 1	150.00	4.00	26
3	13	Block 1	150.00	3.50	26



Temperature: 140-150°C
Time: 3.5-4 Hrs.

Fig.7: Optimized Qbd approach.

7. CONCLUSION

The novel synthetic method for quinoline was developed using Qbd approach. The synthetic method was developed using several acids and oxidising reagents by considering temperature and time as major factors. The sulphuric acid and arsenic trioxide showed best results at 120°C for 4 hrs. The net percentage yield was found to be 27%. The novel method can be emitable for industrial applications.

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