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# DEVELOPMENT OF NOVEL PROCESS FOR SYNTHESIS OF 2-PHENYL-4H-3,1-BENZOXAZIN-4-ONE THROUGH MICROWAVE SYNTHESIZER

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## ABSTRACT
The microwave assisted synthesis approaches comply to all 12 principles of green chemistry. The enhanced penetration power of microwaves are supposed to be the main troubleshooter in field of synthetic chemistry. The Quality by Design (QbD) approach has been used by several formulation chemist but we implemented this approach in synthetic chemistry. The novel proposed method was firstly developed using Quality by Design approach and then the method was improvised for wet lab synthesis. The statistical validation of the method was and finally spectral analysis confirmed the structure of the synthetic compound. The validation of the proposed method was carried out and these validated batches were simultaneously compared with the conventional procedure for synthesis of 2-phenyl-4H-3,1-benzoxazin-4-one. The results of the spectral data, validation and comparison showed that the proposed method was more economical than that of conventional method and also followed green approaches.

**KEYWORDS:** Microwave assisted synthesis, Quality by Design (QbD), benzoxazinones.

## INTRODUCTION
The microwave region of electromagnetic spectrum has been developed and improvised in several technologies since 1970's but these have been used in the field of organic synthesis since 1980's. Several reports have been published in past decades that claims the efficacious role of Microwave technology[1] in chemistry. The slow uptake of the technology has been attributed to its initial lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. However, in the past few years, heating chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. Since the first published reports on the use of microwave irradiation to carry out organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986.[2] The microwave assisted synthesis uses all the 12 principles of green chemistry and transforms the chemistry approaches towards E-Chemistry where "E" stands for Easy, Effective, Eco-friendly and Economic.[3]

## MATERIAL AND METHODS
The chemicals used for the synthesis were of LOBA and identified for its purity before use. The microwave synthesizer[4] was used for synthesis of compounds. Design Expert® was used for designing the experiment

### Development and optimization of process by Quality by Design (QbD)
The novel method was first developed using the QbD[5] approach so that the optimization is possible. The 3 level factorial design model was used which consisted of 2 factors. Power and Time were the two factors that were selected for QbD. Lower, Higher and Average were the 3 levels based on which the model were developed. The model was operated at power of (100 watt, 200 watt, 300 watt) and for time of (5 min, 10 min, 15 min). The complete work of optimization was done at the pharmaceutical chemistry lab of Priyadarshini J. L. College of Pharmacy, Nagpur on Design Expert®.[6] The statistically approved batches were further approved for wet lab synthesis.

### Statistical Validation of Process
Any process developed needs approval through the statistical parameters as ANOVA. Design expert provide in-built protocol for calculation of ANOVA, correlation values, P values etc. These statistical parameter were calculated and scrutinized for each models developed and comparison were reported.

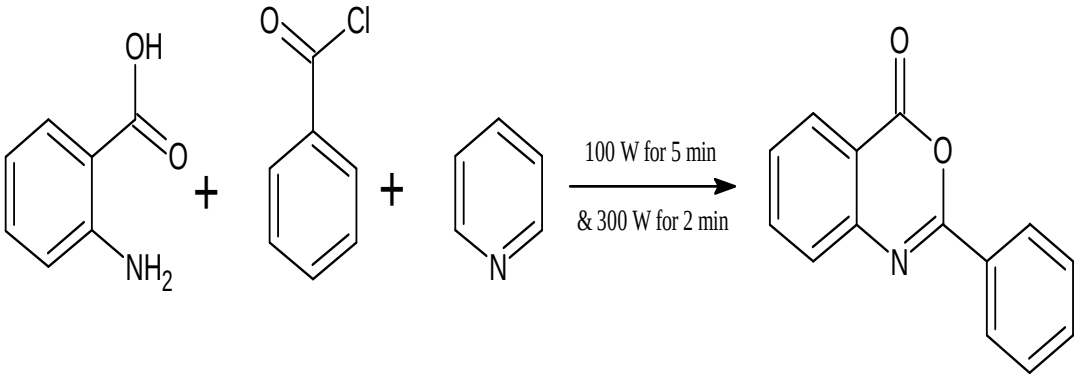
### Synthesis of 2-phenyl-4H-3, 1-benzoxazin-4-one
The 2-phenyl-4H-3,1-benzoxazin-4-one are widely used parent structures for the synthesis of several biologically active compounds.

**Conventional Procedure**

To a stirred solution of anthranilic acid (0.05 mole) in pyridine (60 ml), benzoyl chloride (0.05 mole) was added dropwise, maintaining the temperature near 0-5°C for 1 hour. The reaction mixture was stirred for another 2 hours at room temperature until a solid product was formed. The reaction mixture was neutralized with saturated sodium bicarbonate solution and the pale yellow solid of benzoxazinone[7] were separated, filtered, washed with water and recrystallized from ethanol.

**Proposed Procedure[8]**

The anthranilic acid 0.1 mole was dissolved dry pyridine and benzoyl chloride 0.1 mole was added slowly through glass rod in round bottom flask. The flask was attached to the microwave synthesizer and reaction was carried out for 5 min at 100 watt. The reaction mixture was mixed and again started for 2 min at 300 watt. The reaction mixture was added to ice cold water with sodium carbonate. The foam like consistency occurs which is allowed to stand and then was filtered and recrystallized with ethanol. The yield of 2-phenyl-4H-3,1-benzoxazin-4-one was reported.




**Spectral Identification[9]**

The synthetic reactions of the conventional and new proposed method was optimized for the completion through simultaneous thin layer chromatography (TLC). The structure of the recrystallized compounds were confirmed by using advance spectral techniques like Infrared spectroscopy (IR). Other properties of the optimized and structurally validated compounds were performed like melting point determination, solubility determination. The melting point determination of the synthesized compounds were carried out in open capillary using LABHOSP meting point apparatus in degree celsius ($^{o}$C). The TLC was carried out on the silica plates using the mixture of hexane:ethyl acetate in ratio of (7:3). The IR was recorded using SHIMADZU-FTIR IRA-Affinity-1® spectrophotometer at Priyadarshini J. L. College of Pharmacy, Nagpur.

**Validation of proposed method[10]**

The proposed method was repeated several times to compare the yield and quality of the product. This also confirmed the reproducibility of the method. The final comparison was made with the products of conventional method and that synthesized by new proposed method in microwave synthesizer. The proposed method was compared on the basis of several platforms like net power utilization, waste production and the net time of synthetic reaction.

## RESULTS AND DISCUSSION

**Results of QbD**

The results factorial designing using 3 level approach and two factors are listed in tabular for in the fig 1 and fig 2. It includes data corresponding to optimization of both the factors simultaneously.

| Std | Run | Block | Factor 1 A:Power Watt | Factor 2 B:Time Min | Response 1 Yield % |
|---|---|---|---|---|---|
| 2 | 1 | Block 1 | 200.00 | 5.00 | 68 |
| 10 | 2 | Block 1 | 200.00 | 10.00 | 87 |
| 5 | 3 | Block 1 | 200.00 | 10.00 | 73 |
| 3 | 4 | Block 1 | 300.00 | 5.00 | 92 |
| 8 | 5 | Block 1 | 200.00 | 15.00 | 90 |
| 6 | 6 | Block 1 | 300.00 | 10.00 | 93 |
| 9 | 7 | Block 1 | 300.00 | 15.00 | 91 |
| 12 | 8 | Block 1 | 200.00 | 10.00 | 75 |
| 4 | 9 | Block 1 | 100.00 | 10.00 | 69 |
| 7 | 10 | Block 1 | 100.00 | 15.00 | 89 |
| 13 | 11 | Block 1 | 200.00 | 10.00 | 84 |
| 11 | 12 | Block 1 | 200.00 | 10.00 | 86 |
| 1 | 13 | Block 1 | 100.00 | 5.00 | 56 |

**(a) 100 w – 300 w_5 – 15 min**

| Std | Run | Block | Factor 1 A:Power Watt | Factor 2 B:Time Min | Response 1 Yield % |
|---|---|---|---|---|---|
| 5 | 1 | Block 1 | 150.00 | 7.50 | 75 |
| 6 | 2 | Block 1 | 200.00 | 7.50 | 80 |
| 12 | 3 | Block 1 | 150.00 | 7.50 | 73 |
| 13 | 4 | Block 1 | 150.00 | 7.50 | 68 |
| 3 | 5 | Block 1 | 200.00 | 5.00 | 53 |
| 10 | 6 | Block 1 | 150.00 | 7.50 | 71 |
| 7 | 7 | Block 1 | 100.00 | 10.00 | 63 |
| 11 | 8 | Block 1 | 150.00 | 7.50 | 73 |
| 9 | 9 | Block 1 | 200.00 | 10.00 | 84 |
| 8 | 10 | Block 1 | 150.00 | 10.00 | 79 |
| 1 | 11 | Block 1 | 100.00 | 5.00 | 65 |
| 2 | 12 | Block 1 | 150.00 | 5.00 | 69 |
| 4 | 13 | Block 1 | 100.00 | 7.50 | 56 |

**(b) 100 w – 200 w_5 – 10 min**

| Std | Run | Block | Factor 1 A:Power Watt | Factor 2 B:Time Min | Response 1 Yield % |
|---|---|---|---|---|---|
| 2 | 1 | Block 1 | 150.00 | 7.50 | 78 |
| 10 | 2 | Block 1 | 150.00 | 10.00 | 84 |
| 12 | 3 | Block 1 | 150.00 | 10.00 | 85 |
| 3 | 4 | Block 1 | 200.00 | 7.50 | 92 |
| 7 | 5 | Block 1 | 100.00 | 12.50 | 85 |
| 8 | 6 | Block 1 | 150.00 | 12.50 | 88 |
| 11 | 7 | Block 1 | 150.00 | 10.00 | 83 |
| 4 | 8 | Block 1 | 100.00 | 10.00 | 72 |
| 9 | 9 | Block 1 | 200.00 | 12.50 | 93 |
| 6 | 10 | Block 1 | 200.00 | 10.00 | 89 |
| 1 | 11 | Block 1 | 100.00 | 7.50 | 56 |
| 5 | 12 | Block 1 | 150.00 | 10.00 | 82 |
| 13 | 13 | Block 1 | 150.00 | 10.00 | 75 |

**(c) 100 w – 200 w_7.5 – 12.5 min**

| Std | Run | Block | Factor 1 A:Power Watt | Factor 2 B:Time Min | Response 1 Yield % |
|---|---|---|---|---|---|
| 4 | 1 | Block 1 | 150.00 | 10.00 | 93 |
| 6 | 2 | Block 1 | 250.00 | 10.00 | 91 |
| 3 | 3 | Block 1 | 250.00 | 5.00 | 84 |
| 7 | 4 | Block 1 | 150.00 | 15.00 | 92 |
| 2 | 5 | Block 1 | 200.00 | 5.00 | 65 |
| 8 | 6 | Block 1 | 200.00 | 15.00 | 90 |
| 9 | 7 | Block 1 | 250.00 | 15.00 | 92 |
| 13 | 8 | Block 1 | 200.00 | 10.00 | 93 |
| 10 | 9 | Block 1 | 200.00 | 10.00 | 92 |
| 1 | 10 | Block 1 | 150.00 | 5.00 | 75 |
| 11 | 11 | Block 1 | 200.00 | 10.00 | 91 |
| 5 | 12 | Block 1 | 200.00 | 10.00 | 93 |
| 12 | 13 | Block 1 | 200.00 | 10.00 | 90 |

**(d) 150 w – 250 w_5 – 15 min**

| Std | Run | Block | Factor 1 A:Power Watt | Factor 2 B:Time Min | Response 1 Yield % |
|---|---|---|---|---|---|
| 10 | 1 | Block 1 | 200.00 | 7.50 | 91 |
| 13 | 2 | Block 1 | 200.00 | 7.50 | 93 |
| 6 | 3 | Block 1 | 250.00 | 7.50 | 91 |
| 4 | 4 | Block 1 | 150.00 | 7.50 | 84 |
| 3 | 5 | Block 1 | 250.00 | 5.00 | 76 |
| 8 | 6 | Block 1 | 200.00 | 10.00 | 94 |
| 9 | 7 | Block 1 | 250.00 | 10.00 | 95 |
| 7 | 8 | Block 1 | 150.00 | 10.00 | 92 |
| 11 | 9 | Block 1 | 200.00 | 7.50 | 86 |
| 5 | 10 | Block 1 | 200.00 | 7.50 | 90 |
| 2 | 11 | Block 1 | 200.00 | 5.00 | 82 |
| 12 | 12 | Block 1 | 200.00 | 7.50 | 92 |
| 1 | 13 | Block 1 | 150.00 | 5.00 | 82 |

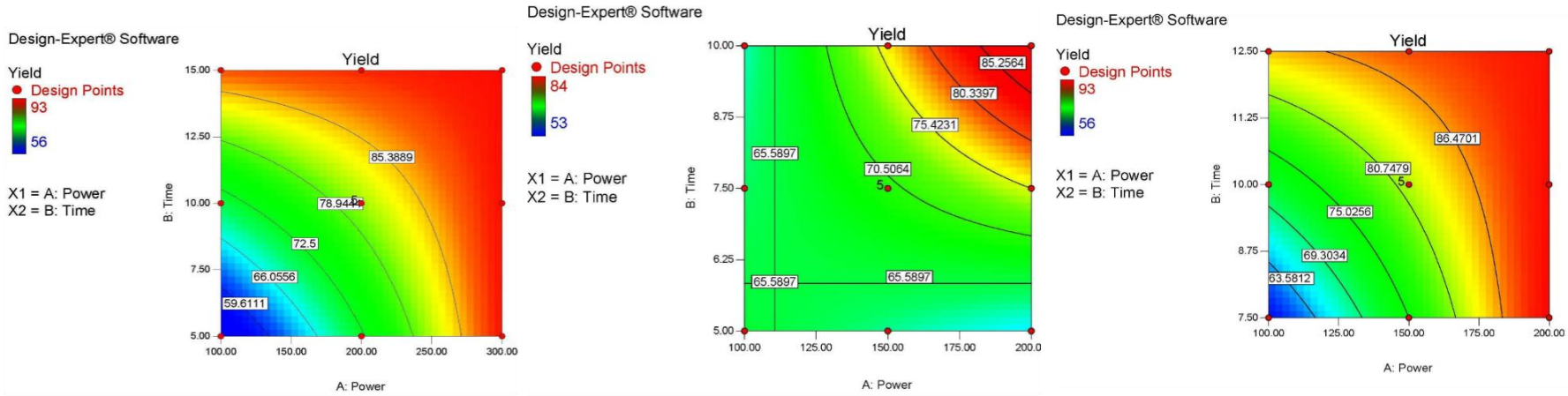
**(e) 150 w – 250 w_5 – 10 min**

| Std | Run | Block | Factor 1 A:Power Watt | Factor 2 B:Time Min | Response 1 Yield % |
|---|---|---|---|---|---|
| 8 | 1 | Block 1 | 200.00 | 12.50 | 92 |
| 12 | 2 | Block 1 | 200.00 | 10.00 | 93 |
| 6 | 3 | Block 1 | 250.00 | 10.00 | 92 |
| 7 | 4 | Block 1 | 150.00 | 12.50 | 89 |
| 13 | 5 | Block 1 | 200.00 | 10.00 | 94 |
| 1 | 6 | Block 1 | 150.00 | 7.50 | 85 |
| 10 | 7 | Block 1 | 200.00 | 10.00 | 93 |
| 3 | 8 | Block 1 | 250.00 | 7.50 | 78 |
| 4 | 9 | Block 1 | 150.00 | 10.00 | 65 |
| 11 | 10 | Block 1 | 200.00 | 10.00 | 90 |
| 9 | 11 | Block 1 | 250.00 | 12.50 | 92 |
| 2 | 12 | Block 1 | 200.00 | 7.50 | 93 |
| 5 | 13 | Block 1 | 200.00 | 10.00 | 91 |

**(f) 150 w – 250 w_7.5 – 12.5 min**

**Figure 1: Results of QbD of power and time correlation**

The above results Figure 1 represents the optimization of power and the optimized rate of power found was to be in range of 150 w – 250 w. Secondly the time which is the second factor was successfully optimized and results represent the ideal time in range of 7.5 min to 12.5 min as in Figure 1. 13 standard runs were derived by the software and those parameter was used for wet synthesis and the yields were used as response.




**(a) 100 w – 300 w_5 – 15 min** **(b) 100 w – 200 w_5 – 10 min** **(c) 100 w – 200 w_7.5 – 12.5 min**

**(d) 150 w – 250 w_5 – 15 min** **(e) 150 w – 250 w_5 – 10 min** **(f) 150 w – 250 w_7.5 – 12.5 min**

**Figure 2: Contour plots of QbD results.**

On carrying the analysis of the results of response achieved by wet lab synthesis by considering the relation of factors contour plots were observed as in Figure 2. The several ranges of the results were represented by colour notation as blue, green and red. The blue colour represented the lower limit, red colour represented higher limit and the green colour represented the optimum results. The results were plotted in relation to both the factors (power and time) which was represented as X1 and X2 in the plots.

**Results of statistical validation of QbD models**

The results of statistical validation of the generated models were represented by correlation value and P value. These values finally predicted a point that was known as point prediction values for each models. These results are represented in below figure. The Figure 3 represents the correlation data in form of bar graph, Figure 3 represents the bar graph of P- value which finally illustrates that the designed models were significant. The Figure 3 represents the point prediction values which was created by the Design Expert® software and Figure 3 represents the summarized representations of statistical validation.

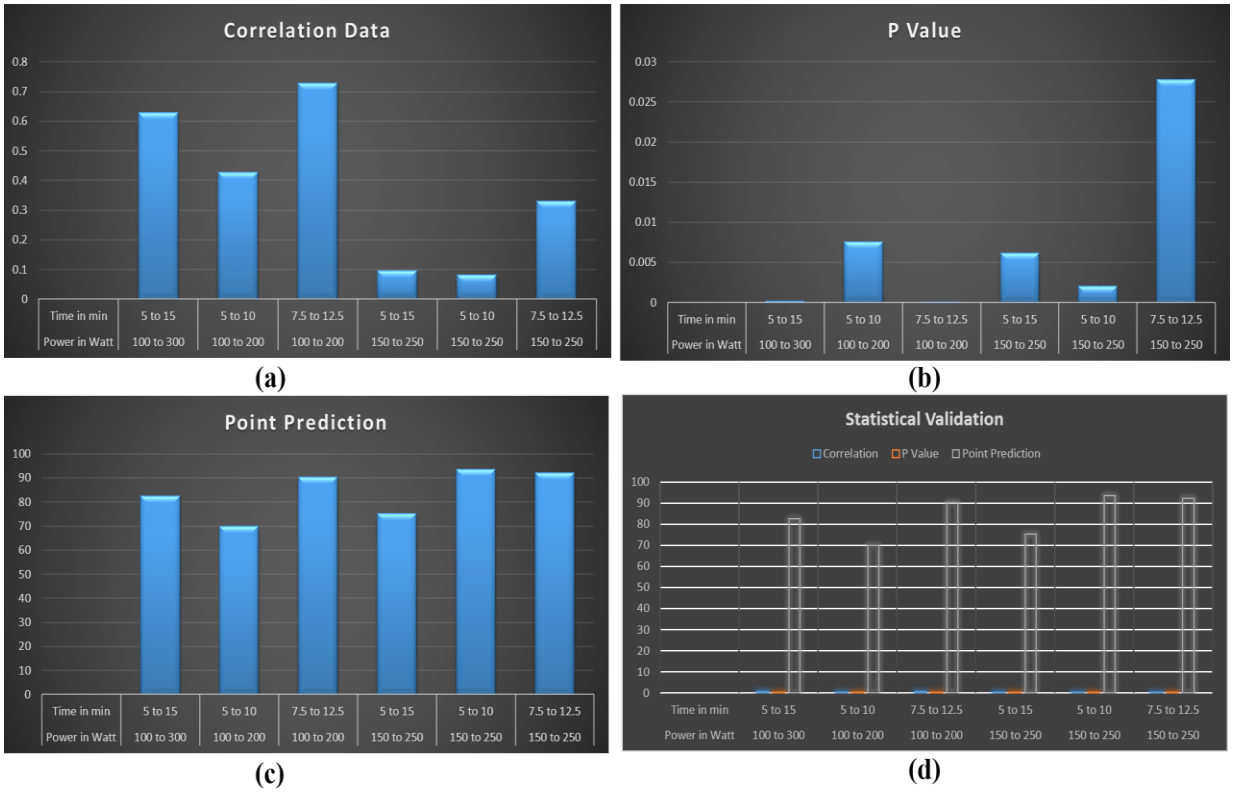
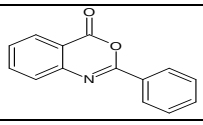


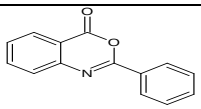

**Figure 3: Results of statistical validation**

**Results of physicochemical and spectral characterization of synthesized compounds**

All the synthetic reactions were monitored for the completion by carrying out the simultaneous TLC. The physicochemical characterization of the synthesized compounds were represented in tabular form in below Table 1. The spectral studies of the recrystallized synthetic compounds confirmed the structure and the spectral correlations helped us to optimize the newly developed process.

**Table 1: Physicochemical characterization of 2-phenyl-4H-3,1-benzoxazin-4-one.**

| Sr. no. | Compound name | Compound structure | Molecular Formula | Mol. Wt. | M.P.($^0$C) | % Yield | Rf value |
|---|---|---|---|---|---|---|---|
| 1 | 2-phenyl-4H-3,1-benzoxazin-4-one (Conventional) |  | $C_{14}H_9NO_2$ | 223 | 92-94 | 87.00 | 0.68 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 | 2-phenyl-4H-3,1-benzoxazin-4-one (Novel Method) |  | $C_{14}H_9NO_2$ | 223 | 91-94 | 92.00 | 0.67 |

Note:- The values included in the table above are average of six observations

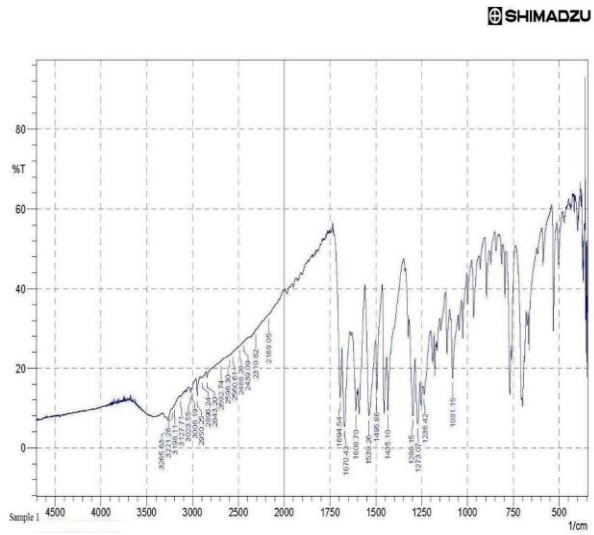



**Figure 4: IR Spectra.**

The Figure 4: IR Spectra represents the IR graph of our synthetic compound obtained from Instrumental Lab of Priyadarshini J. L. College of Pharmacy, Nagpur. The interpretation of the graph showed presence of the functional groups at the ideal positions and finally confirmed the structure.

**Results of validation of proposed method**

The proposed method was repeated several times to judge the validation. Parameters as net power utilization, waste production, net time of synthetic reaction and finally the yield was considered.

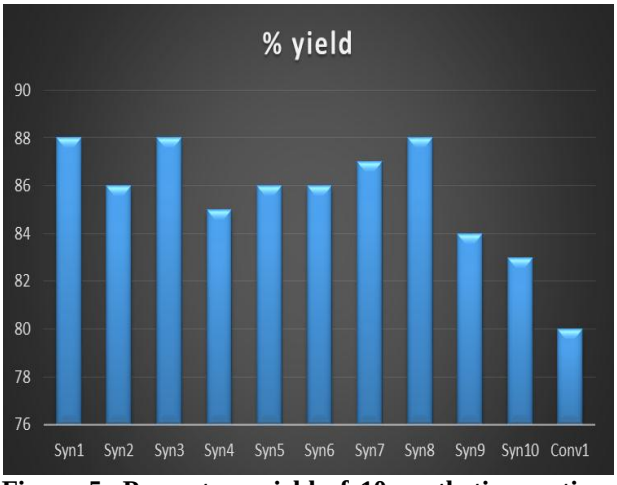



**Figure 5: Percentage yield of 10 synthetic reactions compared with conventional method.**

The Figure 5 represents the bar graph of the synthetic reactions which was repeated 10 times and finally was compared with that of conventional method of synthesis. The y-axis of the graph represents the percentage yield of the reactions. All the reactions carried out in microwave synthesizer had greater percentage yield. The enhanced penetration of the microwaves might have been one of the important parameter for higher percentage yield.

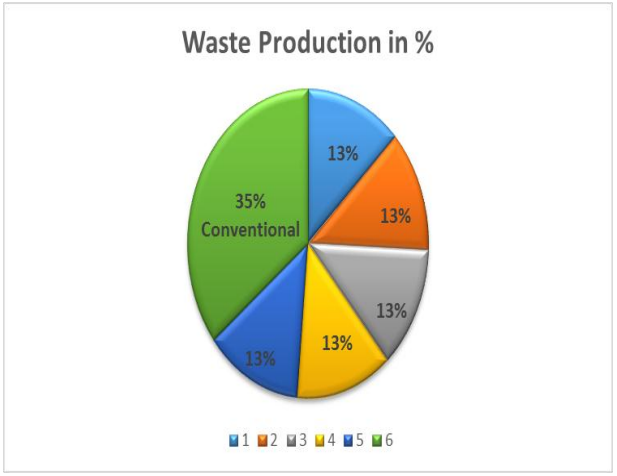



**Figure 6: Waste production by synthetic reactions compared to conventional method.**

The pie chart Figure 6 represents the waste produced during the reactions by novel proposed method and that from conventional one. The waste produced in the conventional reaction method is more than that of novel proposed method.

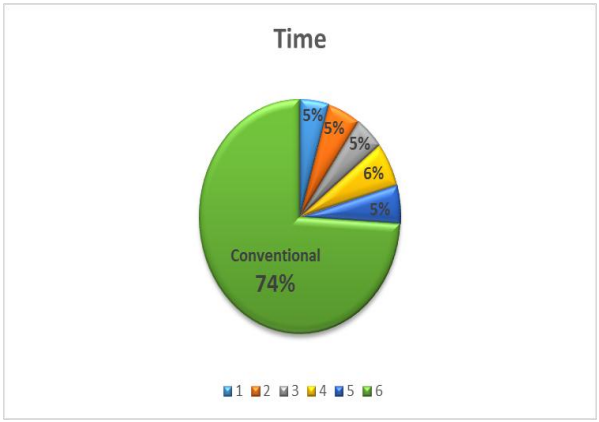



**Figure 7: Net utilized time for synthesis by novel proposed method and conventional method.**

The pie chart Figure 7 represents the net time taken for the synthetic reactions by novel proposed method and that from conventional one. The net time taken by the conventional reaction method is more than that of novel proposed method. The Figure 8 represents the relative representation of the repeated proposed reaction with conventional method.

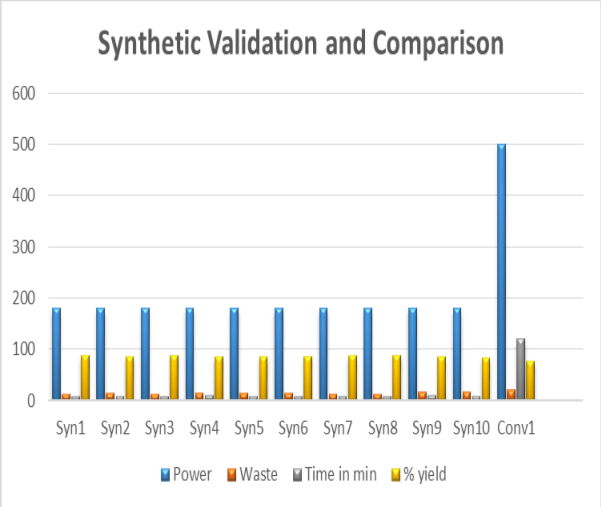



**Figure 8: Relative graph of conventional and novel proposed method.**

## CONCLUSION

The results from the QbD analysis and wet synthesis helps us to conclude that the novel proposed method for synthesis of 2-phenyl-4H-3,1-benzoxazin-4-one is ideal for synthetic chemist and can be emitted by industries. The optimized power and time through QbD were 150-200 watt for time in range of 7.5 to 12.5 min. the power and time optimized by the wet synthesis were 180 watt for 8.5 min. The results of spectral analysis successfully confirmed the chemical structure. Finally validation of the proposed method was carried out and novel proposed method proved to be better than conventional method in respect to parameters as power, waste production, yield and time.

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