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Optimization and study of variables in microwave assisted organic synthesis of some biologically active chalcones

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Abstract

Chalcones are α,β-unsaturated ketone compounds, constituting an important class of natural products belonging to the flavonoid family. They have been reported to possess a wide spectrum of biological activities, including anti-bacterial, anti-inflammatory, anti- tumor, anti-malarial, anti-fungal and anti-viral etc. Thus, synthesis of Chalcones has generated great interest among organic as well as medicinal chemists. This synthesis can be achieved by conventional methods or by Greener methods, like Microwave assisted organic synthesis (MAOS). Advantages of microwave synthesis over conventional synthesis include energy efficient reactions, less consumption of time to complete the reaction and improved yields. The conventional technique for any organic synthesis suffers from several pitfalls such as utilization of more time, energy and efforts, wastage of solvents and reactants and compromised yields. These inconsistencies can be overcome by the use of optimization techniques. Optimization techniques require lesser experiments to achieve an optimum result, yields "best" solution in presence of competing objectives, makes problem tracing and rectification quite easy. Optimization techniques encompass experimental design, mathematical models and graphical outcomes. With this background, in present work, eight Chalcones were synthesized using Microwaves. The synthetic procedure was optimized using 3^2 Factorial design as the statistical technique. Yield and time required to complete reaction were considered as response factors. The validation of optimized solutions was also performed.

Keywords: Chalcones, Factorial design, MAOS, Optimization, Green Chemistry

Introduction

Quality assurance is a technique of ensuring that product meets the desired quality. It is a wider concept and a way of preventing defects, which allows to deliver a better services to consumers. It covers all matters that individually or collectively influence the quality of a product. While considering pharmaceuticals, quality assurance is divided into development, quality control, production, distribution, and inspections. Design and development of a novel drug product, drug intermediate or pharmaceutical process involves multiple steps. For a very long time this task has been fulfilled through trial and error method and which leads to wastage of chemicals, time and money. This problems can be reduced by optimization techniques. Optimization technique is an act of making something fully functional and requires less experimentation to achieve an optimum result.

Microwave assisted organic synthesis has emerged as an alternative method for synthesis of organic compounds, inorganic compounds, nanomaterials, polymers. This approach offers fast, simple, economic synthetic method. The main advantage of this synthesis is lesser or no solvent consumption. MAOS is considered as a green technology approach for its toxic free synthesis. It is based upon principle of interaction of charged particles with microwave frequency which generates heat in the reaction mixture. Every solvents will absorb different microwave frequency based upon its degree of polarity. A more polar solvent will absorb more and gets heated quickly while comparing with less polar solvents. The heat generated in the reaction mixture makes the synthesis faster.

Chalcones are α-β unsaturated ketones obtained by condensation of two carbonyl containing aromatic rings. They are coloured compound due to presence of an auxochrome (C=C-CO) and belongs to flavonoid family. Chalcones shows various biological activities like anti-bacterial, anti-inflammatory, anti-fungal, anti-tumour, anti-malarial, anti-viral and anti-diabetic. Some Chalcones have also been found to inhibit enzymes like xanthine oxidase and protein kinase. They are precursor to various heterocyclic compounds and are used for their synthesis.

Experimental section

Materials and Method: All the chemicals like acetophenones, benzaldehydes, sodium hydroxide and solvents were purchased from Loba Chem, Mumbai. Solvents were used after distillation throughout this work. Melting points were determined by open capillary method. TLC was done using silica gel G plates of size 3 × 8 cm (Sigma-Aldrich) and visualised by UV or in iodine chamber. The IR spectra was recorded in the 4000-400 cm^{-1} ranges using Shimadzu spectrometer. ^1H NMR Spectra were recorded on Varian mercury (300 MHz) spectrometer in DMSO- d_6 as solvent using Trimethyl silane (TMS) as an internal reference standard and values are expressed in δ ppm. Microwave synthesis was carried out using catalyst microwave type oven, at power level ranging from 1-9 at 140-700 watts. Mass spectra and ^1H NMR were

recorded at IIT, Mumbai. Optimization was done using software *Statease* 8.0.2.

Scheme of Synthesis

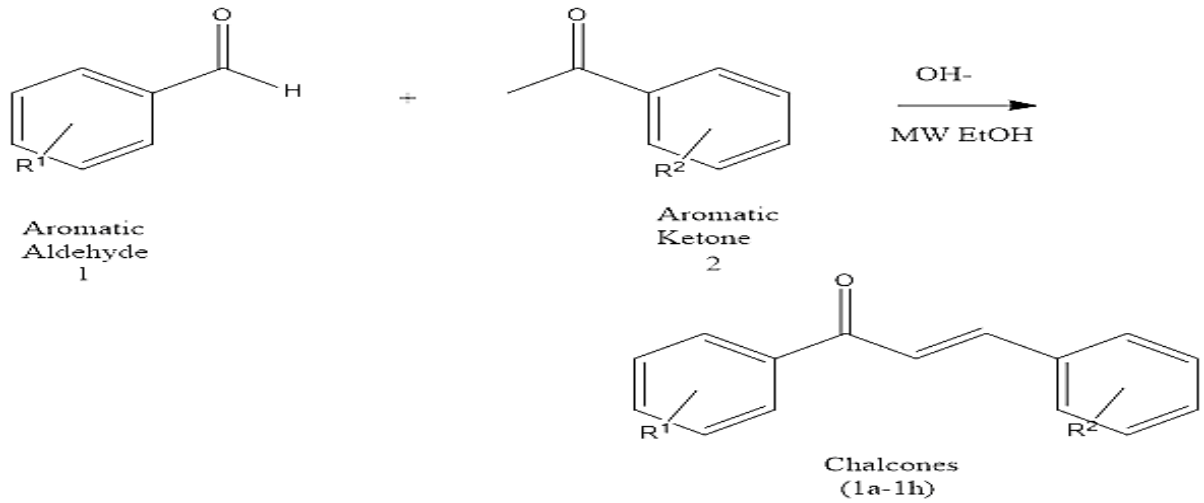


Fig. 1a: Scheme for Chalcones synthesis

General procedure for synthesis of Chalcones*:* An equimolar mixture of aromatic aldehyde (0.01 mole) and aromatic ketone (0.01 mole) were dissolved in dissolved in distilled ethanol. The mixture was stirred with a magnetic stirrer and 10 ml of NaOH (50%) was added drop wise into it. The mixture was heated to reflux in a microwave oven for about 1-1.5 hours. After the completion of the reaction, the crude mixture was neutralized with 10%HCl solution in cold condition, if required. The solid compound obtained was collected on a Buckner funnel under suction pump. The solid was dried and recrystallized from absolute ethanol to give the corresponding substituted Chalcones. (**3a-3h**)

Spectral properties of synthesized compounds

1-(4-Hydroxyphenyl)-3-phenyl-2-propen-1-one (3a): Yellowish white solid; Yield: 55%; m.p. 174 °C; IR (cm^{-1}): 3259 (OH, *str*), 3087, 2891 (Ar-CH, *str*), 1651 (C=O, *str*), 758, 750 (Ar-CH, *bend*) ; ^{1}H NMR (DMSO-d_6): δ 10.4 (s, 1H, OH), 7.88-7.80 (d.d, 4H, phenyl), 6.86-6.80 (m, 5H, phenyl), 2.6 (d, 2H, CH).

3-(4-Chlorophenyl)-1-phenyl-2-propen-1-one (3b): yellowish white solid; Yield: 57%; m.p. 120^{0}C; IR (cm^{-1}): 3081, 2885 (Ar-CH, *str*), 1648 (C=O, *str*), 768, 740 (Ar-CH, *bend*), 676, 566 (C-Cl *bend*), ^{1}H NMR (DMSO-d_6): 7.92-7.80 (d.d, 4H, phenyl), 6.98-6.80 (m, 5H, phenyl), 2.1 (d, 2H, CH).

1-(4-Aminophenyl)-3-phenyl-2-propen-1-one (3c): Orange coloured solid; Yield: 60%; m.p.: 130^{0}C; IR (cm^{-1}): 3458 (NH, *str*), 3015 (Ar-CH, *str*), 1649 (C=O, *str*), 770, 750 (Ar-CH, *bend*), Mass Spectra: 224 (M^+), 223 (M^+-1), 132 (M^+-92).

3-(4-Chlorophenyl)-1-(4-Hydroxyphenyl)-2-propen-1-one (3d): yellowish colored solid; Yield: 60%; m.p: 190^{0}C; IR (cm^{-1}): 3270 (OH, *str*), 3081, 2885 (Ar-CH, *str*), 1650 (C=O, *str*), 758, 750 (Ar-CH, *bend*), 674, 565 (C-Cl *bend*), Mass Spectra: 259 (M^+), 258 (M^+-1), 165 (M^+-94).

3-(2-Chlorophenyl)-1-(4-Hydroxyphenyl)-2-propen-1-one (3e): yellowish colored solid; Yield: 63%; m.p.: 180^{0}C; IR (cm^{-1}): 3224 (OH, *str*), 3065 (Ar-CH, *str*), 1651 (C=O, *str*), 748, 740 (Ar-CH, *bend*), 665, 572 (C-Cl *bend*), ^{1}H NMR (DMSO-d_6): δ 8.3 (s, 1H, OH), 7.8-7.60 (d.d, 4H, phenyl), 7.6-7.5 (m, 5H, phenyl), 2.45 (d, 2H, CH).

3-(3-Nitrophenyl)-1-(4-Hydroxyphenyl)-2-propen-1-one (3f): white colored solid; Yield: 60%; m.p.: 182^{0}C; IR (cm^{-1}): 3255 (OH, *str*), 1521, 1340 (NO, *str*), 3055 (Ar-CH, *str*), 1649 (C=O, *str*), 725, 740 (Ar-CH, *bend*), ^{1}H NMR (DMSO-d_6): δ 10.4 (s, 1H, OH), 8.1-7.8 (d.d, 4H, phenyl), 7.6-7.48 (m, 4H, phenyl), 2.5 (d, 2H, CH).

3-(2-Chlorophenyl)-1-(4-Aminophenyl)-2-propen-1-one (3g): pale yellow colored solid; Yield: 64%; m.p.: 108^{0}C; IR (cm^{-1}): 3430 (NH, *str*), 3056 (Ar-CH, *str*), 1648 (C=O, *str*), 760, 755 (Ar-CH, *bend*), 668, 547 (C-Cl *bend*), ^{1}H NMR (DMSO-d_6): δ 2.4 (s, 2H, NH_2), 7.8-7.5 (d.d, 4H, phenyl), 6.9-6.4 (m, 4H, phenyl).

3-(4-Chlorophenyl)-1-(4-Aminophenyl)-2-propen-1-one (3h): pale yellow colored solid; Yield: 58%; m.p.:158^{0}C; IR (cm^{-1}): 3438 (NH, *str*), 3066 (Ar-CH, *str*), 1649 (C=O, *str*), 750, 755 (Ar-CH, *bend*), 678, 557 (C-Cl *bend*), ^{1}H NMR (DMSO-d_6): δ 2.5 (s, 2H, NH_2), 7.8-7.5 (d.d, 4H, phenyl), 6.8-6.2 (m,4H, phenyl).

Optimization

For optimization of reactions, it is important to consider the various factors that dictate the overall reaction. For any chemical reaction to be carried out in the microwave, the microwave power and the concentration of the base (catalyst) are the two significant independent factor considered. The response would be the two dependent factors namely the

percentage yield and the time required to attain the optimum yield. The 2 independent factors were considered at 3 level i.e. High, intermediate and low level. Thus 3^2 factorial designs were used to optimize the reactions.

Optimization of 1-(4-Hydroxyphenyl)-3-phenyl-2-propen-1-one (3a): The parameters considered in the optimization of **3a** were **microwave power** (watts) and the **concentration of the base** (%). They are outlined in **Table 2 and 3** below. The 3^2 factorial designs thus include 3 X 3 = 9 experiments to be performed. Thus according to the mentioned design patterns in **Table 2 and 3,** the experiments were performed and the time required for the completion of the reaction was noted by confirming the TLC of the reaction. The percentage yield was then calculated for each reaction and the time required to complete the reaction were noted. Based on the responses and the factors the **Table No 4** was constructed using the software *Stat-ease 8.0.2*. Based on the constructed data, time and yield analysis was done, wherein first a model is selected i.e. either linear, 2F1, quadratic or cubic and checked for the significance in terms of the experimental data input. In yield analysis, the Quadratic model was found to be significant, thus the ANOVA was generated as shown in **Table 5 and 6** below. This created a regression **Equation 1** as follows:

Equation 1: % Yield = 52.89 - 0.33 x A +19.17 x B + 0.50 x AB + 0.67 x A^2 - 25.83 x B^2

Once the model was found to be significant, the graphical plots were generated. The counter plot and the 3-D surface response plot (**Fig. 1**) were plotted. The plots give an overview of the yield range and the corresponding relation with the microwave power and concentration of base. The curve gives a three dimensional view of the effect of each independent parameter (i.e. concentration of base and microwave power level) on the dependant factor (i.e. percentage yield of the product formed). The overview denotes regions in graph where the percentage yield of the compound ranges from 10.4 % to 59.5 %. Similarly, the 2-D surface response plot (**Fig. 2**) was plotted.

Time analysis was done in the same pattern. In time analysis, the Linear model was found to be significant, thus the ANOVA was generated as shown in **Table No 7 and 8** below. This created a regression **Equation 2** as follows:

Equation 2: Time = 116.67 -32.50 x A -32.50 xB

Once the model was found to be significant, the graphical plots were generated. The counter plot and the 3-D surface response plot (**Fig. 3**) were plotted. The plots give an overview of the time range and the corresponding relation with the microwave power and concentration of base. The curve gives a three dimensional view of the effect of each independent parameter (i.e. concentration of base and microwave power level) on the dependant factor (i.e. time required to complete the reaction). The overview denotes regions in graph where the time required for the analysis ranges from 46 minutes to 176 minutes. Similarly, the 2-D surface response plot (**Fig. 4)** was plotted.

Results and Discussions

The optimum solutions for percentage yields of the synthesis of compounds depended on the factors like microwave power, base concentration and the time required for the synthesis. The values for the independent factors are comparable. The pattern achieved by practical methodologies and the results obtained through the software are related to comparable extents.

For the synthesized substituted Chalcones (**Table 9),** experiments performed for compound **3a** showed that a maximum yield was attainable in time of nearby 65 minutes at 48% base concentration along with the microwave power of 420 watts. The results obtained through the software confirmed that the optimum condition for synthesis of the titled compounds is 55-60 minutes at 50-60% base concentration and microwave power of 420 watts. The results were more refined in case of software. Thus the validation of the obtained solution for **3a** was done by performing the synthesis of remaining seven Chalcone molecules **(3b-3h)** at the same power level and base concentration. The percentage yield obtained was in the range of 50 – 60 %. Thus it can be concluded that the optimum solutions are super-imposable and pose to be the best conditions to synthesize similar type of Chalcones as mentioned in the scheme.

Table 1: Structures of synthesized compounds

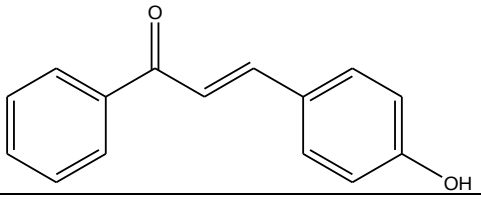
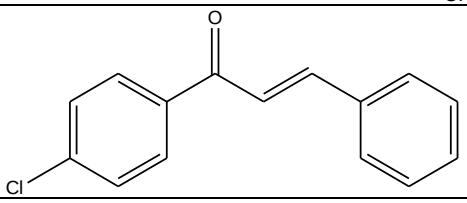
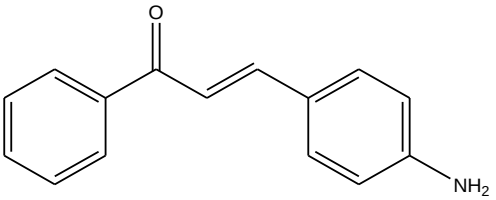
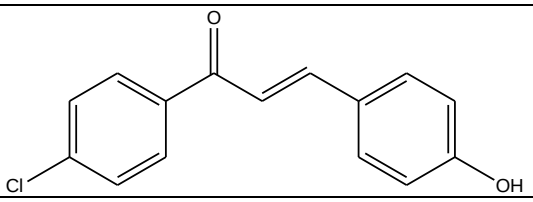
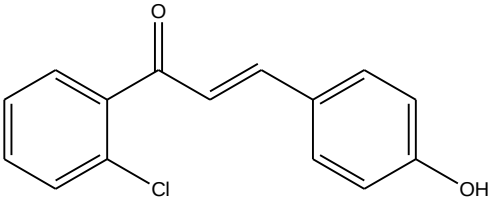
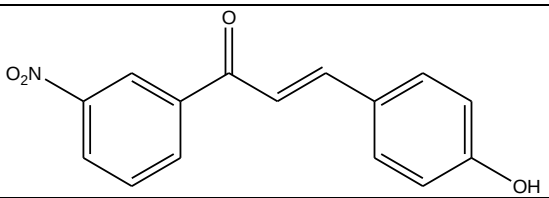
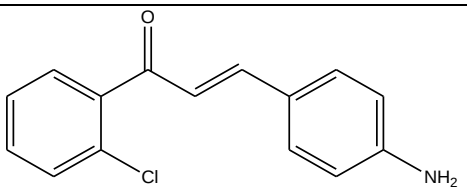
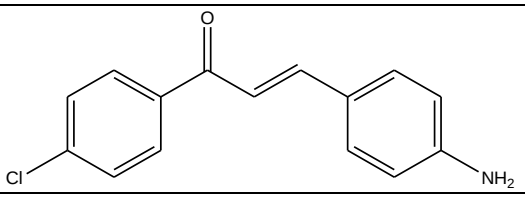
Compound no.	R^1 (Substituted benzaldehyde)	R^2 (Substituted	Compound structure
3a	-H	4-OH	
3b	4-Cl	-H	
3c	-H	4-NH_2	
3d	4-Cl	4-OH	
3e	2-Cl	4-OH	
3f	3-NO_2	4-OH	
3g	2-Cl	4-NH_2	
3h	4-Cl	4-NH_2	

Table 2: Independent factors and levels for compound 3a

Factors	Levels		
	High(2)	Intermediate(1)	Low(0)
Power Level (A)	420	280	210
Base Concentration (B)	60	40	20

Table 3: 3^2 factorial design for compound 3a

Factor B	Factor A		
	0	1	2
0	00	10	20
1	01	11	21
2	02	12	22

Table 4: Data Sheet for compound 3a

Run	Factor A: Power (Watts)	Factor B: Concentration of base (%)	Response 1:% Yield	Response 2: Time (min)
1	420	40	50	60
2	210	40	50	150
3	420	60	50	45
4	210	20	10	180
5	280	60	40	90
6	280	20	7	120
7	280	40	60	135
8	420	20	8	150
9	210	60	50	120

Table 5: Analysis of variance (ANOVA) table for yield analysis of compound 3a

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Remark
Model	3541.44	5	708.29	15.69	0.0232	Significant
A-Power	0.67	1	0.67	0.015	0.9110	
B-Concentration	2204.17	1	2204.17	48.82	0.0060	
AB	1.00	1	1.00	0.022	0.8911	
A^2	0.89	1	0.89	0.020	0.8973	
B^2	1334.72	1	1334.72	29.56	0.0122	
Residual	135.44	3	45.15			
Cor Total	3676.89	8				

df: Degree of freedom, Cor Total: Corrected Total

Table 6: Details of coefficient and standard error for yield analysis of compound 3a

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	52.89	1	5.01	36.95	68.83	
A-Power	-0.33	1	2.74	-9.06	8.40	1.00
B-Concentration	19.17	1	2.74	10.44	27.90	1.00
AB	0.50	1	3.36	-10.19	11.19	1.00
A^2	0.67	1	4.75	-14.45	15.79	1.00
B^2	-25.83	1	1.676361	4.49840072	15.16827	1

df: Degree of freedom, CI: Confidence Interval, VIF- Variance Inflation Factor

Table 7: Analysis of variance (ANOVA) table for time analysis for compound 3a

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Remark
Model	12675.00	2	6337.50	12.78	0.0069	significant
A-Power	6337.50	1	6337.50	12.78	0.0117	
B-Concentration	6337.50	1	6337.50	12.78	0.0117	
Residual	2975.00	6	495.83			
Cor Total	15650.00	8				

df: Degree of freedom, Cor Total: Corrected Total

Table 8: Details of coefficient and standard error for time analysis of compound 3a

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	116.67	1	7.42	98.50	134.83	
A-Power	-32.50	1	9.09	-54.74	-10.26	1.00
B-Concentration	-32.50	1	9.09	-54.74	-10.26	1.00

df: Degree of freedom, CI: Confidence Interval, VIF- Variance Inflation Factor

Table 9: Solution for optimum conditions required for synthesis of chalcones

Optimized solution	Power (watts)	Conc. of base (%)	Time (min)	% Yield	Desirability
1	420	48	62.93	55.04	0.753
2	420	52	61.19	54.2	0.759
3	420	54	60.04	53.78	0.76
4	420	58	60.93	61.47	0.951
5	420	57	58.78	60.86	0.953
6	420	56	59.22	61.04	0.953
7	420	60	58.05	60.55	0.954

Fig 1: 3D Surface Response Curve for yield analysis of compound 3a

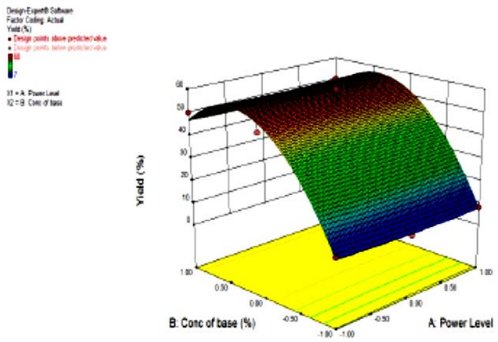


Fig 2: 2D Contour plot for yield analysis of compound 3a

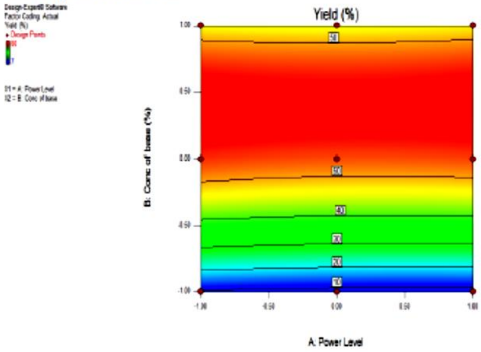


Fig 3: 3D Surface Response Curve for time analysis of compound 3a

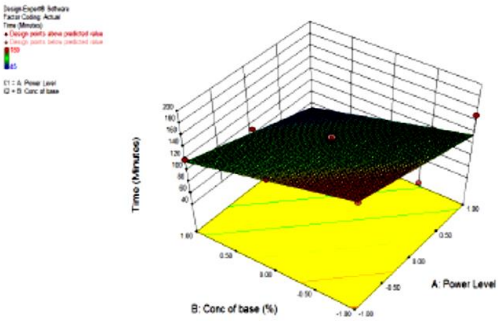
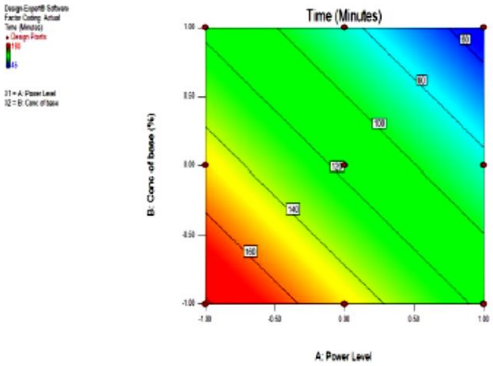


Fig 4: 2D Contour plot for time analysis of compound 3a



Conclusion

Conventional method of synthesis of organic compounds is a comparatively slow process which results in generation of final compounds with lesser yields. On the other hand, synthesizing compounds by MAOS results in final compounds with improved yields in much lesser time span. Optimization of two variables involved in the synthesis, helped achieve an economical and greener method for synthesis of Chalcones. The influence of microwave power (watts) and concentration of the base (%) on the percentage yield of the compounds was compared where microwave power (watts) and concentration of the base (%) were chosen as independent variables, while percentage yield and time required to complete the reaction was chosen as dependent variables. A 3^2 factorial approach was chosen. An appropriate statistical model was arrived at and significant optimized solutions were obtained.

One of the eight synthesized compounds was optimized by using the *Statease* software 8.0.2. The optimized solutions were obtained for gaining good percentage yield. Further, validation was performed by synthesizing the remaining seven molecules at the optimized solution i.e. at 420 power watts, at 48% base concentration for 65 minutes for the titled compounds. Thus, the optimum solutions are super-imposable and pose to be the best conditions to synthesize remaining Chalcones as mentioned in the scheme under microwave energy.

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Conflict of interest

The authors confirm that this article's content has no conflicts of interest.

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