Asian Journal of Chemistry; Vol. 35, No. 5 (2023), 1153-1160

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.27593

Response Surface Methodology (RSM) Approach for Optimization of Parameters for Synthesis of Organic Compounds and Evaluation of Biological Activity with Molecular Docking

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Received: 22 January 2023; *Accepted*: 7 April 2023; *Published online*: 28 April 2023; AJC-21223

The triazolidine derivatives were synthesized by green and sustainable chemistry approach. The response surface methodology (RSM) was applied to optimize the reaction parameters during the synthesis. Reaction parameter which affect the yield of product were studied, which includes the temperature and time of the reaction. Various statistical RSM with different central composite designs (CCD) such as circumscribed (CCC), face-centered (CCF) and inscribed (CCI) were used to find the maximum yield of the product (%) of reaction at the given parameters and selected, which gave the maximum possible yield. The relationship between reaction parameters (temperature and time) and the yield of product modeled using second-order response surface model. The optimum reaction parameters given by CCI were 80.8 ºC reaction temperature and 15.03 min reaction time with yield of product is up to 94.57%. The adequacy and reliability of the predicted model was checked by ANOVA, R-square and adjusted R-square and revealed the good agreement between predicted model and actual experimental data. The study described here can be efficiently applied for the optimization of parameters in the synthesis of any organic compound. The molecular docking was carried out by using AutoDock vina 1.2.0 on (CYP51) [PDBID: 1EA1] and (DprE1) [PDBID: 4FDO] for target anti-tuberculosis activity while (FabH) [PDBID: 1HNJ] for target antimicrobial activity. There was better interaction within receptor amino acids compound **3d** and **3b** with FabH and CYP51 enzyme, respectively for anti-tuberculosis activity and compound **3d** with DprE1 enzyme for antimicrobial activity observed very good docking score among all compounds.

Keywords: Triazolidine derivatives, Response surface methodology, Green chemistry approach, Green solvents, Molecular docking.

INTRODUCTION

In order to ensure the long-term viability of the chemical industry, "green chemistry," which employs a set of principles to minimize or eliminate the release of hazardous substances during the design, synthesis and use of chemicals, is becoming increasingly popular [1,2]. 1,2,4-Triazoles derivatives [3,4] are one of the important class of compounds in synthetic, medicinal and pharmaceutical fields due to their various biological activities such as antibacterial [5-8], antifungal [5-9], analgesic [10], anticancer [11-13], antiviral [14,15], antitubercular [16-22], anti-inflammatory [23,24], anticonvulsant [25,26] and antidepressant [27] and antioxidant [28], *etc.*

In the field of organic synthesis, the design-of-experiments (DoE) strategy which is utilized the most is the response surface method (RSM). An experimental design, an optimization technique and a statistical model are the three components that make up the RSM. Each of these components is a mathematical and statistical instrument that is based on multivariate statistics. This method can offer some highly desirable advantages, such as absence of solvents, an inexpensive catalyst and the reaction designed in a single pot step, in addition to the reduction of synthetic waste, saving of time and the simplification of practical aspects through efficiency and environmental sustainability [29-33]. In addition, as an alternative to trying to broaden and optimize, the development of fast automated process research

approaches for the green synthesis of triazolidine derivatives reaction optimization, in combination with the statistical design of experimental (DoE), has been investigated. The DoE method has been utilized and evaluated in a great number of studies in order to discover the ideal reaction conditions [34-36]. In this work, the comparative study of RSM-CCD models for the optimization of reaction parameters in organic synthesis was also done.

In *in silico* technique, docking is frequently used to predict binding orientation of small drug entity to their target proteins in order to in turn predict the affinity. Ramesh & Lalitha [1] synthesized triazolidine 3-thione derivatives and reported their antimicrobial activity. In continuation of this work, herein two component synthesis of triazolidine-3-one derivatives were synthesized in the presence of heterogeneous catalyst nanocellulose/hydroxyapatite for one pot cyclocondensation reaction between semicarbazide and aromatic aldehyde in the ethanolic medium by applying the statistical response surface methodology (RSM) technique. Moreover, the molecular docking studies were also carried out with three receptor binding proteins *viz*. cytochrome P450 14α-sterol demethylases (CYP51), decapreny lphosphoryl-β-d-ribose 2′-epimerase (DprE1) and β-ketoacyl-acyl carrier protein synthase III (FabH), which are majorly inhibited by triazoline/thiazolidines and its derivatives [37].

EXPERIMENTAL

Synthesis: The experimentation commenced with the reaction of 4-nitrobenzaldehyde (**1**) and semicarbazide (**2**) in water as solvent system in the presence of nanocellulose/hydroxyapatite as catalyst under reflux conditions for about 1 h, the obtained product proven to be 5-(4-nitrophenyl)-1,2,4-triazolidine-3-ones (**3**) with a yield of 76%. The work up of this technique involves only the easy filtration leading to the formation of the highly pure compounds. When the same reaction was performed using mixture of aldehyde (1 mmol) and semicarbazide (1 mmol) in the acetic acid-water (25%) solvent system (10 mL) under the same reflux conditions, the corresponding product **3** was obtained in high yield (**Scheme-I**). In this reaction scheme, temperature was found to be highly effective for the time specified (Table-1). The products were characterized by usual techniques (*i.e.* IR, ^{1}H, ^{13}C NMR and MS).

5-(4-Chlorophenyl)-1,2,4-triazolidin-3-one (3a): White solid; m.p.: 232-234 ºC; FT-IR (λ_{max}, ν_{max}, cm^{-1}): 3456.44 (NH), 1674.21 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.55 (s, 2H, NH), 7.57 (d, *J* = 8.53 Hz, 2H, ArH), 7.70 (d, *J* = 8.53 Hz, 2H, ArH), 7.80 (s, H, CH), 10.33(s, 1H, NH).

TABLE-1
AN OVERVIEW OF THE EFFECTS OF DIFFERENT SOLVENTS

Entry	Solvent	Time (min)	Yield (%)
1	THF	60	38
2	DMF	60	49
3	CH_3CH_2OH	60	70
4	CH_3OH	60	65
5	$(CH_3)CHOH$	75	63
6	CH_3CN	90	55
7	H2O	45	76
8	25%CH_3COOH	15	93
9	DCM	32	45
10	$CHCl_3$	40	65

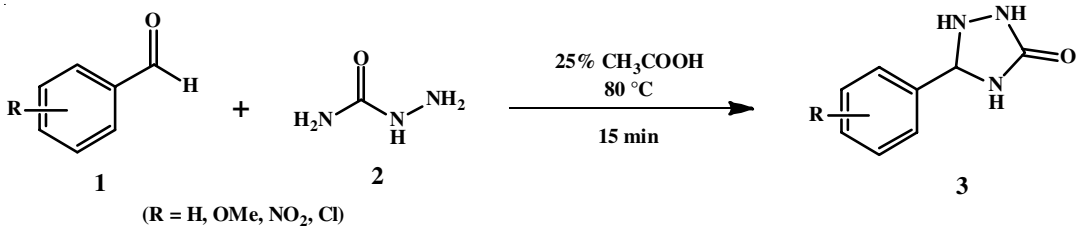
5-(4-Hydroxy-3-methoxy)-1,2,4-triazolidine-3-one (3b): Light yellow solid; m.p.: 218-220 ºC; FT-IR (λ_{max}, ν_{max}, cm^{-1}): 3448 (NH), 1666 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.77 (s, 3H, OCH_3), 6.30 (s, 2H, NH), 6.95 (dd, *J* = 8, 2 Hz, 1H, ArH), 6.80 (d, *J* = 2 Hz, 1H, ArH), 6.82 (d, *J* = 8 Hz, 1H, ArH), 6.21 (s, 1H, CH), 10.82 (s, 1H, NH); 9.96 (s, 1H, ArOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 56.1, 71.7, 112.4, 115.4, 120.6, 138.0, 146.7, 147.3, 159.8; MS [$C_9H_{11}N_3O_3$] (*m/z*): found: 209.21 M$^+$; calcd.: 209.08.

5-(4-Methoxyphenyl)-1,2,4-triazolidin-3-one (3c): Light yellow solid; m.p.: 221-223 ºC; FT-IR (λ_{max}, ν_{max}, cm^{-1}): 3448 (NH), 1666 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.78 (s, 3H, OCH_3), 6.44 (s, 2H, NH), 6.95 (d, *J* = 8 Hz, 2H, ArH), 7.66 (d, *J* = 9.5 Hz, 2H, ArH), 7.79 (s, 1H, CH), 10.123 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 55.67, 114.52, 127.91, 128.50, 139.63, 157.34, 160.48; MS [$C_9H_{11}N_3O_2$] (*m/z*): found: 194.2 M$^+$; calcd.: 193. 81.

5-(4-Nitrophenyl)-1,2,4-triazolidin-3-one (3d): Light yellow solid; m.p.: 234-236 ºC; FT-IR (λ_{max}, ν_{max}, cm^{-1}): 3441 (NH), 1666 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.70 (s, 2H, NH), 7.93 (s, 1H, CH), 8.025 (d, *J* = 8 Hz, 2H, ArH), 8.20 (d, *J* = 8 Hz, 2H, ArH), 10.63 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 124.25, 127.83, 137.16, 141.85, 147.54, 156.94; MS [$C_8H_8N_4O_3$] (*m/z*): found:207.1; calcd.: 208.0596.

5-(4-Phenyl)-1,2,4-triazolidin-3-one (3e): White solid; m.p.: 221-223 ºC; FT-IR (λ_{max}, ν_{max}, cm^{-1}): 3448 (NH), 1666 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.50 (s, 2H, NH), 7.35 (d, *J* = 8.73 Hz, 2H, ArH), 7.72 (d, *J* = 9.18 Hz, 2H, ArH), 7.84 (s, 1H, CH), 10.273 (s, 1H, NH).

The reaction feasibility was assessed with a number of different solvents such as acetonitrile, DMF and THF, as well as dichloromethane as reaction media and yield found to be below 55% (Table-1, entries 1, 2, 6 & 9). The model reaction was carried out with other solvents too such as methanol, ethanol, 2-propanol, water and chloroform resulted in yields ranging



Scheme-I: Synthetic route of 5-aryl-1,2,4-triazolidine-3-ones in green solvent system

from 63-76% (Table-1, entries 3, 4, 5, 7 & 10). Moreover, the solvent system H_2O:CH_3COOH (3:1) at reflux temperature is highly effective for this chemical reaction, with a 93% yield for compound **3** (Table-1 entry 8).

Response surface methodology (RSM): The objective is to find an approximation of the true functional relationship between the response and set of independent variables. The approximating function is the first order model, if the response can be well described by a linear function of the independent variable:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k + \in$$

If there is curvature in the system, then a polynomial of higher degree must be used such as the second order model:

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X_{ii} + \sum_{i=1}^{k} \sum_{j=1(i<j)}^{k} \beta_{ij} X_i X_j + \in$$

The method of least squares is used to estimate the parameters of above polynomials. The model parameters can be estimated most effectively if proper experimental designs are used to collect the data. Three types of experimental designs for fitting response surface, circumscribed (CCC), face-centered (CCF) and inscribed (CCI) central composite designs are used to compare these RSM-CCD models for the optimization of reaction parameters.

Molecular docking studies

Preparation of ligand structure: The ligand structures of the data set were prepared by Chem3D ultra-8.0, were 2D sketches of ligands drawn, Ligand 2D structure converted into 3D & PDB File format by using Pymol Visualization Tool 2.5.0., PDB file format converted into PDBQT file format by using Auto dock MGL Tools 1.5.6., These PDBQT file format is important for Docked with protein for the grid formation [38].

Selection of protein data: The selection of protein data is sensitive step in molecular docking. Three receptor binding proteins *viz*. cytochrome P450 14α-sterol demethylases (CYP51), decaprenyl-phosphoryl-β-d-ribose 2′-epimerase (DprE1) and β-ketoacyl-acyl carrier protein synthase III (FabH) were selected in this study.

The structure of the proteins were drawn by removing complex ligand using Pymol Visualization Tool 2.5.0. from downloaded Protein PDB file, PDB protein file imported into Auto dock MGL Tools 1.5.6. and optimized it by removing water molecule and add polar hydrogen, charges (Kollman charges).

Preparation of grid: Imported PDBQT file of both ligand and protein and selected individually in the Auto dock MGL Tools 1.5.6.

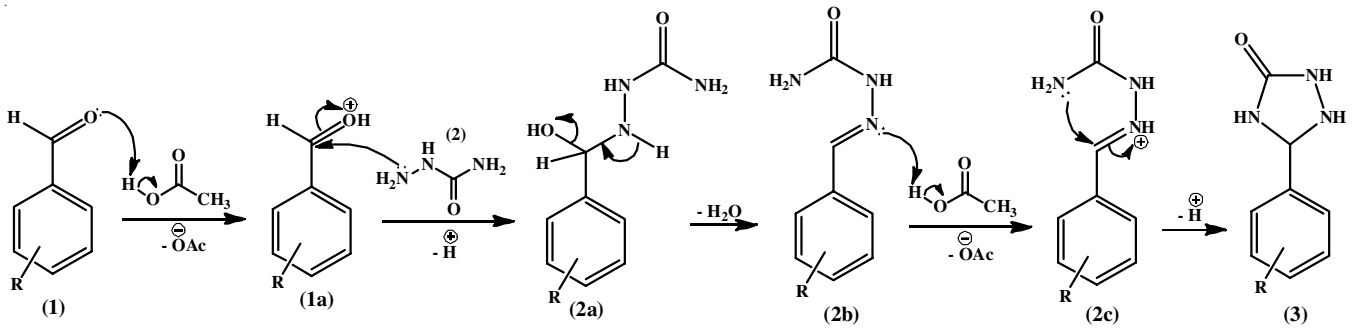
Grid generation: 3D grid generated for ligand and receptor pocket by using Grid generation suite in Auto dock MGL Tools 1.5.6, Generated result as a config. file which is save as text file [38]. Molecular docking study was done to investigate the binding mode of compound with selected PDBID for anti-TB and antimicrobial.

RESULTS AND DISCUSSION

The spectral data support formation of compound **3** and it is in agreement with literature data. The ^{1}H NMR spectra of compound **3** exhibited three singlets at δ 10.63,6.70 ppm confirming the presence of 3-NH proton and singlet at δ 7.93 ppm confirms the presence of benylic methane proton, while the aromatic protons on *p*-nitro substituted systems exhibited doublets at δ 8.21, 8.02 ppm. Dissimilar IR spectral absorption bands are observed at 3441, 3178 and 3070 cm^{-1} suggesting 3-NH stretching, together with at 1666 cm^{-1}, indicating –C=O stretching, an oxycarbonyl moiety can be identified in the ^{13}C NMR spectrum at δ 156 ppm. Additionally, the LCMS detected a molecular ion peak at 207.01 M^-.

Mechanism: A tentative mechanism for the synthesis of 5-(4-nitrophenyl)-1,2,4-triazolidine-3-one *via* intermolecular cyclocondensation reaction are shown in **Scheme-II**. For the dissolution of reagent (4-nitrobenzaldehyde and semicarbazide), 25% glacial acetic acid solution was used as solvent. The acid acts as a catalyst for the intermolecular cyclocondensation of 4-nitrobenzaldehyde (**1**) with semicarbazide (**2**). The electrophilicity of the carbonyl carbon increased by the protonation of carbonyl oxygen atom of 4-nitrobenzaldehyde (**1**) using glacial acetic acid. The β-amino group of semicarbazide (**2**), being more nucleophilic in nature, attack at the carbonyl carbon of protonated aldehyde (**1a**), which provide the semicarbazone (**2b**) *via* condensation reaction. Then, the imino nitrogen of intermediate (**2b**) is protonated using acetic acid to furnish imminium compound (**2c**). Finally, compound **2c** undergoes subsequent intramolecular nucleophilic addition by free NH_2 group to yield 5-(4-nitrophenyl)-1,2,4-triazolidine-3-one (**3**).

Response surface methodology (RSM) approach: In order to obtain excellent yields of 5-aryl-1,2,4-triazolidine-3-ones, the temperature effect on the reaction has been studied and the given reaction of binary mixture performed at room



Scheme-II: Mechanism for the synthesis of 5-(4-nitrophenyl)-1,2,4-triazolidine-3-one *via* intermolecular cyclocondensation reaction

temperature yielded poor results, even after 2 h of reaction. Table-1 shows that at 80 °C gives the best results, at which the reaction goes more rapidly and produced 93% yield in 15 min would be the ideal temperature. However, an increase in the temperature further did not result in an improvement in yield and reaction time. In order to obtain the maximum yield of 5-phenyl-1,2,4-triazolidine-3-ones (**3**) for reaction conditions *viz.* temperature (Z_1) and time (Z_2), a series of central composite designs (CCD) from response surface methodology (RSM) was conducted. The circumscribed (CCC), face-centered (CCF) and inscribed (CCI) designs for number of factors k = 2 is shown in Fig. 1. To fit the second order response surface model, we convert the natural variables, reaction temperature (Z_1) and reaction time (Z_2) into the coded variables as:

$$X_1 = \frac{Z_1 - 80}{5} \text{ and } X_2 = \frac{Z_2 - 15}{5}$$

Circumscribed CCD (CCC): The spherical and rotatable circumscribed central composite design (CCC) is used as experimental design having 13 runs, which contains 4 factorial points, 4 axial/star points and 5 center points. A spherical and rotatable design exists for k = 2 if and only if the distance from the center of design is $\alpha = 1.4142$. The CCC experimental design in coded and natural variables (reaction temperature and reaction time) with corresponding yield is given in Table-2.

Face centered CCD: The face centered central composite design (CCF) was used as experimental design having 13 runs which contains 4 factorial points, 4 axial/star points and 5 center points. In CCF design, the star points are at the center of each face of the factorial space, so $\alpha = \pm 1$. The CCF experimental design in coded and natural variables (reaction temperature and reaction time) with corresponding yield is given in Table-3.

TABLE-2
CCC EXPERIMENTAL DESIGN BASED ON CODED AND NATURAL VARIABLES WITH YIELD

Runs	Coded variables		Natural variables		Yield (%)
	X_1	X_2	Reaction temp. (°C) (Z_1)	Reaction time (min) (Z_2)	
1	-1	-1	75	10	91
2	1	-1	85	10	90
3	-1	1	75	20	85
4	1	1	85	20	91
5	-1.41421	0	72.9289	15	84
6	1.41421	0	87.0711	15	92
7	0	-1.41421	80	7.9289	90
8	0	1.41421	80	22.0711	91
9	0	0	80	15	94
10	0	0	80	15	94
11	0	0	80	15	92
12	0	0	80	15	93
13	0	0	80	15	94

TABLE-3
CCF EXPERIMENTAL DESIGN BASED ON CODED AND NATURAL VARIABLES WITH YIELD

Runs	Coded variables		Natural variables		Yield (%)
	X_1	X_2	Reaction temp. (°C) (Z_1)	Reaction time (min) (Z_2)	
1	-1	-1	75	10	88
2	1	-1	85	10	89
3	-1	1	75	20	88
4	1	1	85	20	90
5	-1	0	75	15	89
6	1	0	85	15	92
7	0	-1	80	10	91
8	0	1	80	20	91
9	0	0	80	15	95
10	0	0	80	15	94
11	0	0	80	15	92
12	0	0	80	15	93
13	0	0	80	15	94

Inscribed CCD: CCI design is scaled down to CCC design with each factor level of CCC design divided by α. The inscribed central composite design (CCI) was used as experimental design having 13 runs which contains 4 factorial points, 4 axial/star points and 5 center points. The CCI experimental design in coded and natural variables (reaction temperature and reaction time) with corresponding yield is given in Table-4.

We fit second order response surface model using CCC, CCF and CCI for yield using MINITAB 17 software. The coefficients of second order response surface model using CCC, CCF and CCI are given in Table-5.

From Table-5, the second order quadratic models for yield are:

$$CCC: Y = -558.129 + 16.638Z_1 - 3.95Z_2 - 0.108Z_1^2 - 0.058Z_2^2 + 0.07Z_1Z_2$$

$$CCF: Y = -619.276 + 17.264Z_1 + 1.861Z_2 - 0.108Z_1^2 - 0.088Z_2^2 + 0.01Z_1Z_2$$

$$CCI: Y = -1655.41 + 42.69Z_1 + 3.37Z_2 - 0.27Z_1^2 - 0.17Z_2^2 + 0.02Z_1Z_2$$

The adjusted R-square value for the model in CCC is 80.9% indicates the fitted second order model using CCC explains around 80.9% of variability in the yield. The adjusted R-square value for the model in CCF is 83.1% indicates the fitted second

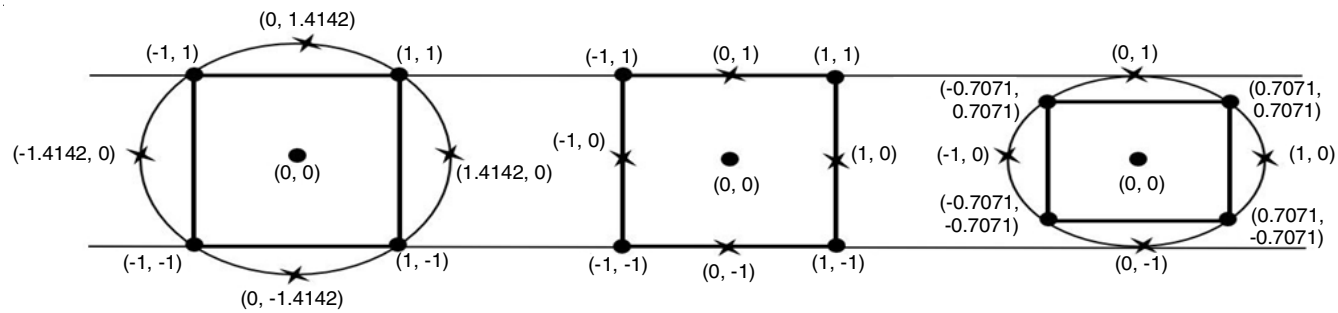


Fig. 1. Circumscribed (CCC), face-centered (CCF) and inscribed (CCI) designs for number of factors k = 2

TABLE-4
CCI EXPERIMENTAL DESIGN BASED ON CODED AND NATURAL VARIABLES WITH YIELD

Runs	Coded variables		Natural variables		Yield (%)
	X_1	X_2	Reaction temp. (°C) (Z_1)	Reaction time (min) (Z_2)	
1	-0.7071	-0.7071	76.4645	11.4645	88
2	0.7071	-0.7071	83.5355	11.4645	90
3	-0.7071	0.7071	76.4645	18.5355	86
4	0.7071	0.7071	83.5355	18.5355	89
5	-1	0	75	15	86
6	1	0	85	15	91
7	0	-1	80	10	90
8	0	1	80	20	92
9	0	0	80	15	94
10	0	0	80	15	95
11	0	0	80	15	94
12	0	0	80	15	95
13	0	0	80	15	94

TABLE-5
COEFFICIENT OF SECOND ORDER RESPONSE SURFACE MODEL USING CCC, CCF AND CCI

Term	Coefficients		
	CCC	CCF	CCI
Constant	-558.129	-619.276	-1655.41
Temp	16.638	17.264	42.69
Time	-3.95	1.861	3.37
Temp*Temp	-0.108	-0.108	-0.27
Time*Time	-0.058	-0.088	-0.17
Temp*Time	0.07	0.01	0.02
R-Square (adj)	80.9%	83.1%	85.6%

order model using CCF explains around 83.1% of variability in the yield. The adjusted R-square value for the model in CCI is 85.6% indicates the fitted second order model using CCI explains around 85.6% of variability in the yield.

The ANOVA tables for the second order response surface model using CCC, CCF and CCI are given in Table-6. The P-value corresponding to regression model of CCC is 0.003 (< 0.01) and the P-value corresponding to Lack-of-Fit is 0.099 (> 0.01), which indicated the fitted second order quadratic regression model using CCC is significant and it does not exhibit the lack of fit at 1% level of significance. The ANOVA results of CCF given in Table-6 reveals that the P-value corresponding to regression model is 0.002 (< 0.01) and the P-value corresponding to Lack-of-Fit is 0.798 (> 0.01) which indicated the fitted second order quadratic regression model using CCF is significant and it does not exhibit the lack of fit at 1% level of significance. The ANOVA table of CCI reveal that the P-value corresponding to regression model is 0.001 (< 0.01) and the P-value corresponding to Lack-of-Fit is 0.024 (> 0.01), which indicated the fitted second order regression model using CCI is significant and it does not exhibit the lack of fit at 1% level of significance.

Response surface plot and contour plot of yield *versus* time and temperature in CCC, CCF and CCI are given in Fig. 2. Response surface plot and contour plots correspond to CCC reveals that the yield is maximum around 82 ºC and time 15 min. The stationary point was obtained at reaction temperature of 82.04 ºC and reaction time at 15.46 min with predicted yield is 93.79%. In CCF, the response surface and contour

TABLE-6
ANALYSIS OF VARIANCE (ANOVA) FOR SECOND ORDER RESPONSE SURFACE MODEL USING CCC, CCF AND CCI

Source	DF	Seq SS	Adj SS	Adj MS	F	P
			CCC			
Regression	5	106.367	106.367	21.2733	11.17	0.003
Linear	2	34.874	58.207	29.1033	15.29	0.003
Square	2	59.242	59.242	29.6212	15.56	0.003
Interaction	1	12.25	12.25	12.25	6.43	0.039
Residual error	7	13.326	13.326	1.9037	–	–
Lack-of-fit	3	10.126	10.126	3.3752	4.22	0.099
Pure error	4	3.2	3.2	0.8	–	–
Total	12	119.692	–	–	–	–
			CCF			
Regression	5	59.776	59.7761	11.9552	12.81	0.002
Linear	2	6.167	22.0559	11.028	11.82	0.006
Square	2	53.359	53.3594	26.6797	28.59	0.000
Interaction	1	0.25	0.25	0.25	0.27	0.621
Residual error	7	6.5316	6.5316	0.9331	–	–
Lack-of-fit	3	1.332	1.3316	0.4439	0.34	0.798
Pure error	4	5.2	5.2	1.3	–	–
Total	12	66.308	–	–	–	–
			CCI			
Regression	5	114.44	114.44	22.888	15.28	0.001
Linear	2	18.218	76.2787	38.1393	25.47	0.001
Square	2	95.972	95.9725	47.9862	32.04	0.000
Interaction	1	0.25	0.25	0.25	0.17	0.695
Residual error	7	10.483	10.4831	1.4976	–	–
Lack-of-fit	3	9.283	9.2831	3.0944	10.31	0.024
Pure error	4	1.2	1.2	0.3	–	–
Total	12	124.923	–	–	–	–

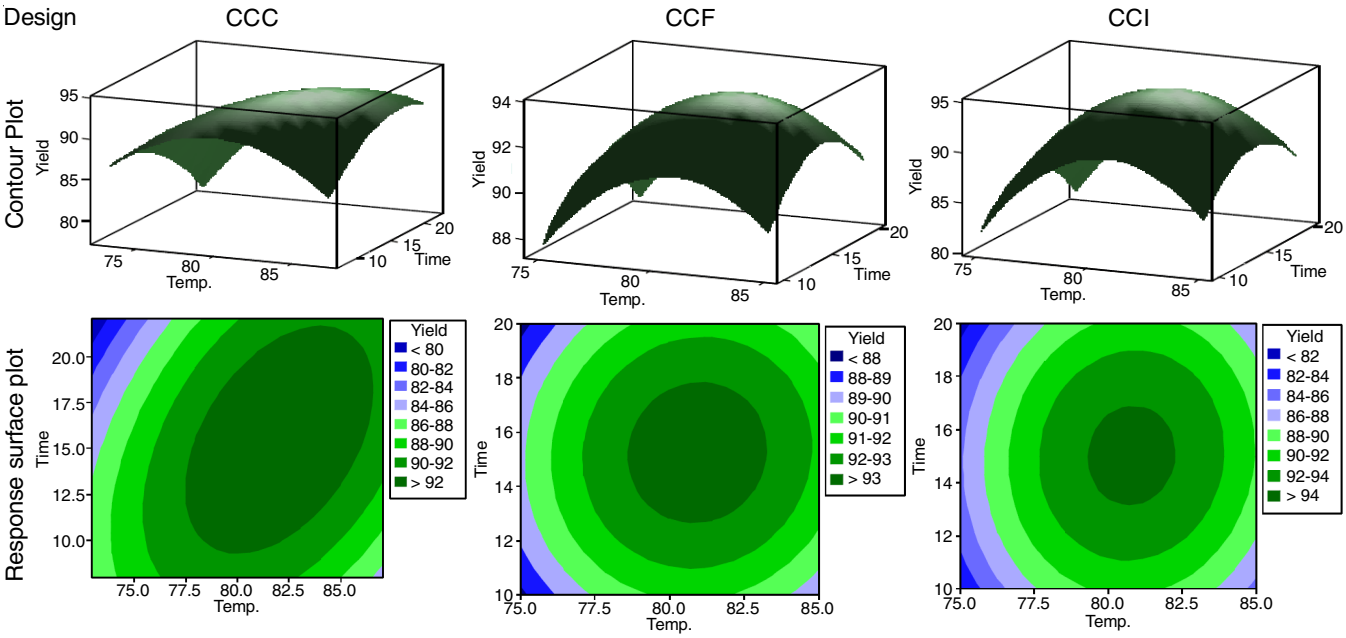


Fig. 2. Response surface plot and contour plot of yield *versus* time and temperature in CCC, CCF and CCI

plots reveals that the yield is maximum around 81 ºC and time 15 min. The stationary point was obtained at reaction temperature of 80.94 ºC and reaction time at 15.24 min with predicted yield is 93.58%. In case of CCI, the response surface plot and contour plots reveals that the yield is maximum around 81 ºC and time 15 min. The stationary point was obtained at 80.8 ºC and reaction time at 15.03 min with predicted yield is 94.57%. Thus, The CCI is best model for the synthesis of 5-aryl-1,2,4-triazolidine-3-one to get maximize yield among the three central composite designs.

Molecular docking studies: Docking study showed that compound **3d** shows best docking score whereas compounds **3a** and **3c** exhibit good docking score and compound **3b** and **3e** shows lower docking score with respect to cytochrome P450 14α-sterol demethylases (CYP51) (PDBID:1EA1) enzyme protein data, which shows anti-tubercular activity (Fig. 3). With respect to β-Ketoacyl-acyl carrier protein synthase III (FabH) (PDBID: 1HNJ) enzyme protein data compound **3b** shows very good docking score whereas compounds **3a**, **3d** and **3e** show average docking score, while compound **3c** shows the low docking score. Towards the antimicrobial activity, compound **3d** shows very good docking score whereas compound **3b** shows good docking score. But compounds **3a** and **3c** show average docking score, while compound **3e** shows low docking score respect to decaprenyl-phosphoryl-β-d-ribose2′-epimerase (DprE1) (PDBID: 4FDO) enzyme. The ligand interaction with the receptor cytochrome P450 14α-sterol demethylases (CYP51), decaprenyl-phosphoryl-β-d-ribose 2′-epimerase (DprE1) and β-ketoacyl-acyl carrier protein synthase III (FabH) is shown in Fig. 4.

Conclusion

A cyclocondensation reaction of aromatic aldehydes and semicarbazides was developed using response surface methodology (RSM) for the synthesis of 5-aryl-1,2,4-triazolidine-3-ones in one pot with low cost and sustainability. Among the three central composite designs (CCD), inscribed (CCI) central composite design was found to be better than the circumscribed

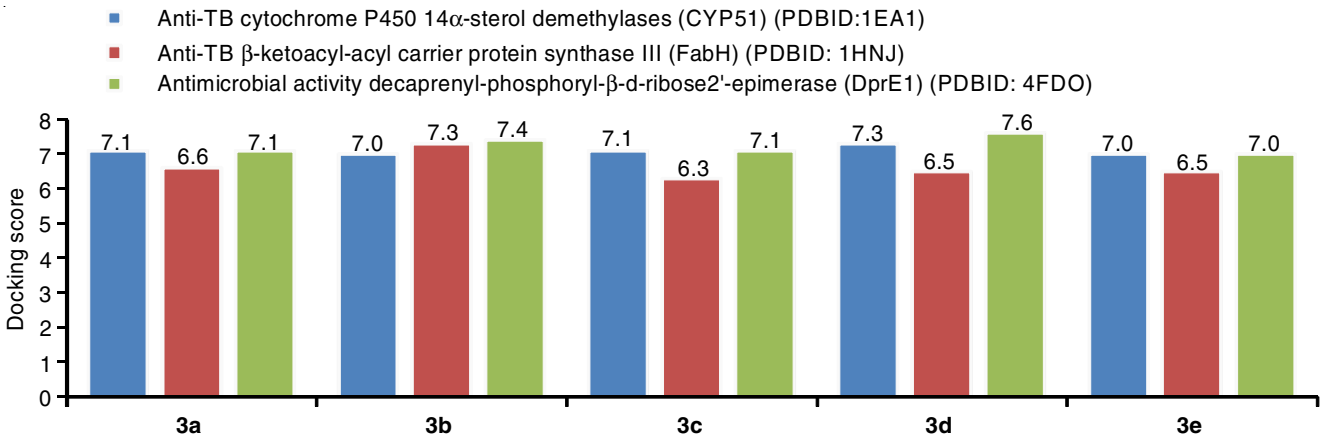


Fig. 3. Docking score with different ligands

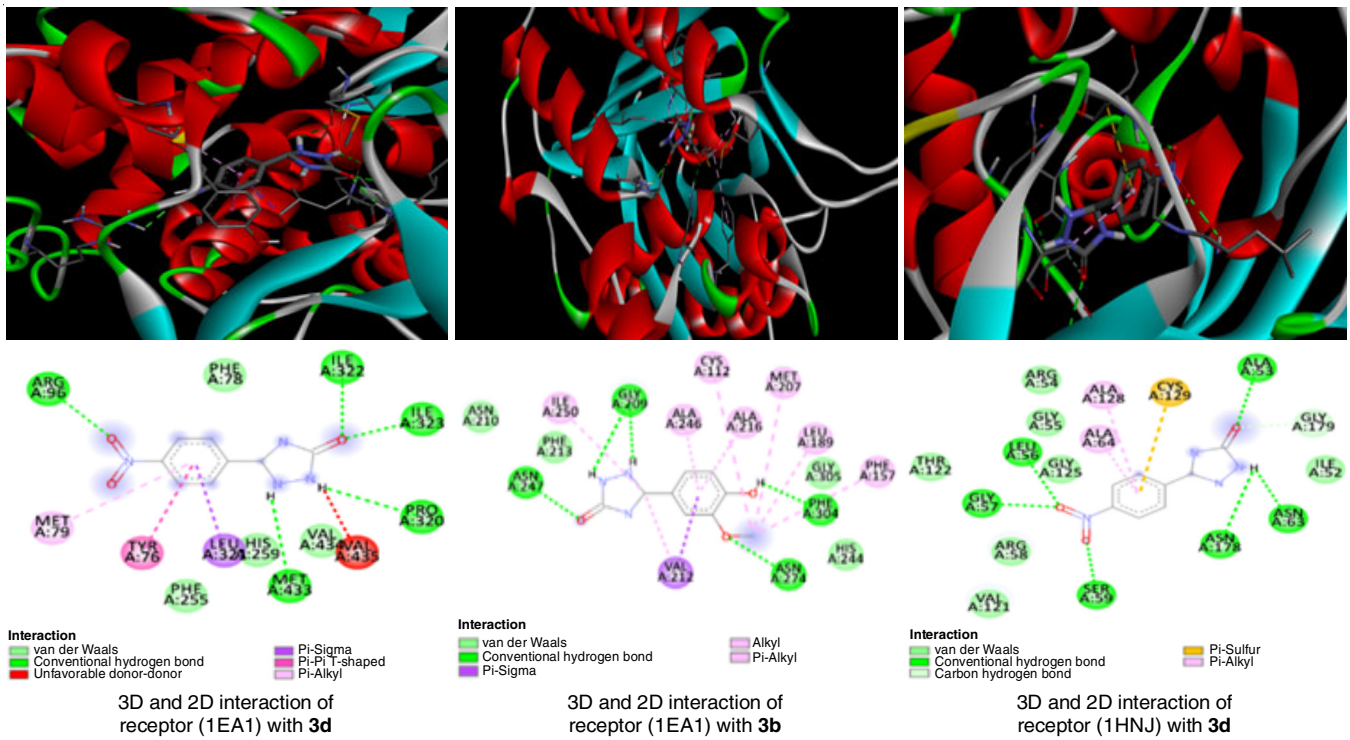


Fig. 4. Ligand interaction with receptor: anti-tubercular activity and antimicrobial activity

(CCC) and face-centered (CCF) central composite designs to get best yields of 5-aryl-1,2,4-triazolidine-3-one. The optimum operating conditions were achieved at 80.8 ºC and 15.03 min with maximum yield of 94.57%. Compound **3d** found to be most potent whereas compounds **3a** and **3c** show moderate anti-tubercular activity with respect to cytochrome P450 14α-sterol demethylases (CYP51) (PDBID:1EA1) enzyme protein data. While with respect to β-Ketoacyl-acyl carrier protein synthase III (FabH) (PDBID: 1HNJ) enzyme, compound **3b** showed maximum potency whereas compounds **3a**, **3d** and **3e** showed moderate potency. However, compounds **3d** and **3b** exhibited the maximum whereas compounds **3a** and **3c** show moderate potency towards the antimicrobial activity with respect to decaprenyl-phosphoryl-β-d-ribose-2′-epimerase (PDBID: 4FDO).

ACKNOWLEDGEMENTS

One of the authors, Vikas D. Jadhav received the financial support provided by STRIDE under UGC fund for colleges for carrying out this work. The authors express their gratitude towards Chhatrapati Shahu Maharaj Research Training and Human Development Institute (SARTHI) Pune, Maharashtra.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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