MICROWAVE ASSISTED SYNTHESIS OF NOVEL 2-PHENYL SUBSTITUTED -1, 3, 4-THIADIAZOLE-2-YL)-2,3-DIHYDROQUINAZOLINE-4(1H)-ONE DERIVATIVES AND ITS ANTIMICROBIAL, ANTIFUNGAL STUDY

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A simple, eco-friendly, experimental and rapid synthesis of a new series of 2, 3-dihydroquinazoline-4(1H)-one derivatives were synthesized by the one-pot three-component reaction of isatoic anhydride, aromatic aldehyde and 4-chlorophenyl-1,3,4-thiadiazol-2-amine under microwave irradiation catalyzed by l-proline. Furthermore, The newly synthesized 2-phenyl substituted -1, 3, 4-thiadiazole-2-yl)-2,3-dihydroquinazoline-4(1H)-one derivatives were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and HRMS methods. All the synthesized compounds were tested for their in vitro antimicrobial, antifungal activity against bacterial and fungal strains. The remarkable features of this technique are easy procedure, high conversion and excellent yield with a short reaction time.

Key words: Monowave-50, isatoic anhydride, l-proline, aldehyde, 2, 3-dihydroquinazoline-4(1H)-one, antimicrobial study.

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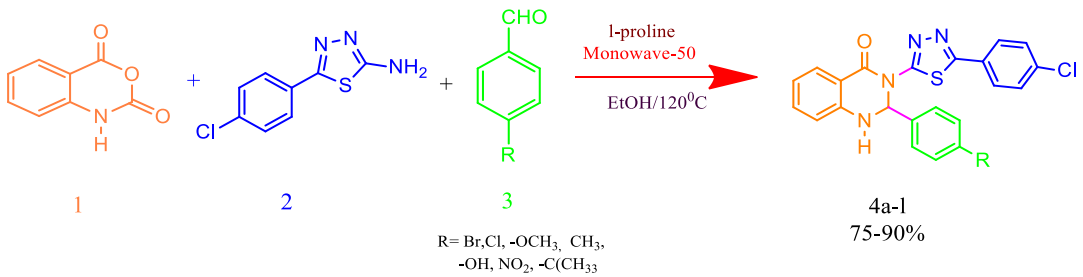
INTRODUCTION

Microwave-assisted organic reactions comprise the use of microwave irradiation to speed up chemical reactions in organic synthesis. This practice has grown reputation in recent years due to its ability to provide faster reaction times, higher yields, and sometimes different selectivity's compared to traditional heating methods. [1,2]

Quinazolinone derivatives belong to the N-containing heterocyclic compounds, which have gained universal attraction owing to their widely and distinct biopharmaceutical activities. 2,3-dihydroquinazolin-4(1H)-ones is an important nitrogen-containing motif consisting of a phenyl ring condensed with a six-membered ring with two nitrogen atoms on positions 1 and 3, and a keto group on carbon 4 are considered as the privileged fused heterocyclic skeletons for drug design with various biological activities; such as antifungal [3], antimalarial [4], CDK5 inhibitors [5], anti-leishmanial agents [6] anti-inflammatory [7] analgesic [8,9], cytotoxic [10], antiviral [11, 12], antitumor [13, 14], antibacterial [15,16], anticancer [17], diabetic management [18], angiotension II receptor antagonists [19]. In addition, these compounds can be easily oxidized to their quinazolin-4(3H)-one analogues [20], which also include important pharmacologically active compounds [21]. Also the quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids [22], such as glycosminine [23], luotonin [24], and drugs like methaqualone [25] and piriqualone [26]. Owing to the diverse range of pharmacological activities [27], various synthetic routes for the synthesis of quinazolinone derivatives have been fabricated by employing 2-aminobenzoic acid [28], anthranilamide [29], isatoic anhydride [30, 31], as starting materials among them, a more attractive and atom efficient strategy for preparation of these compounds is one-pot three-component condensation of isatoic anhydride, amines and aldehydes, several catalyst such as SSA [32], povidone-phosphotungstic acid hybrid [33], heteropoly acid ionic liquid [34], triethanol amine/NaCl [35], EDDA [36], p-TSA [37], $Zn(PFO_2)$ [38], Cu-CNTs [39], montmorillonite K-10 [40], β-CD-SO_3H [41], ionic liquid [42] were used. These reported methodologies produce good results in many cases, whereas most of those procedures are associated with different negative aspects, such as long reaction times, low yields, harsh acidic conditions, tedious work-up, use of expensive reagents and toxic catalysts.

l-proline has been gracefully used as an adaptable organo-catalyst in different synthetic routes for the synthesis of C-N and C-C bond formation [43], due to its easy availability, simple handling, nontoxic nature make this molecule a prominent organo catalyst for preparing molecules of biological advantage.

In continuation of our efforts to develop more versatile methodologies for the synthesis of heterocyclic compounds [44], herein we report Microwave (Anton Paar Monowave-50) assisted, rapid, easy and efficient method for the synthesis of novel 2-phenyl substituted -1, 3, 4-thiadiazole-2-yl)-2,3-dihydroquinazoline-4(1H)-one derivatives using l-proline as catalyst.



Scheme-1: Synthesis of 2-phenyl substituted -1, 3, 4-thiadiazole-2-yl)-2,3-dihydroqunazoline-4(1H)-one derivatives

EXPERIMENTAL

Chemicals and Materials

All solvents and chemicals were purchased commercially and used as received. Melting points were recorded on the Contech digital melting point apparatus and are uncorrected. NMR spectra were taken on Bruker Avance Neo 500 MHz using DMSO –d_6 as the solvent and mass spectra recorded on Waters, Q-Tof micro mass (ESI-MS).

General procedure: General procedure for the preparation of 5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-amine (2).

5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-amine was prepared as per the previous reported method [45]

using 4-chloro benzoic acid (50 mmol), thiosemicarbazide (50 mmol) and 15 mL of $POCl_3$ heated at 80^0C for 1 hour in water bath, then 50 mL of ice cold water was added, till the fumes of HCl ends. Then the reaction mixture was kept at reflux for 3-4 hours. After completion of the reaction, it was neutralized by using 40% KOH solution to form crystals of the compound and further purification was carried out to re-crystallize in ethanol.

General procedure for the preparation of 2-(3-chlorophenyl)-1, 3, 4-thiadiazole-2-yl-2, 3-dihydroquinazoline-4(1H)-one: (4a)

To a 10 mL reaction vial, isatoic anhydride **1** (2 mmol), 5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-amine **2** (2 mmol), 3-chlorobenzaldehyde **3** (2 mmol) were mixed in 5 mL ethanol and l-proline (10 mol%) catalyst was added. Then the reaction vial was kept in Anton paar monowave-50 for irradiation at 120ºC. The progress of the reaction was monitored by TLC (TLC Silica gel 60 F254 Aluminium sheets) by using pet-ether and ethyl acetate solvents (7:3). After completion of the reaction, the crude product was separated out by filtration and further it was purified by re-crystallization from ethanol to give the pure product. (Scheme-1).

Characterization Methods

Biology:

Disks diffusion assay

The antibacterial and antifungal potential of the synthesized compounds were evaluated as per the previously reported methodology [46, 47]. In brief, each dried paper disk (whatman filter paper No.1) contained the synthesized compounds 50 µL (Conc.1 mg/ mL). Each disk was then placed on the surface of the sterile solidified Mueller-Hintonagar/ Potato Dextrose agar medium, which was spread with 24 hrs old inoculums of bacterial and fungal cultures respectively. Penicillin (for S. aureus, B. subtilis, B. megaterium, E. coli), Fluconazole (for R. oryzae, M. mucido, A. niger, C. albicans) were used as standards (at concentrations 1 mg/mL). The plates were kept in a refrigerator for diffusion for 3 hrs and then transferred to the incubator at 37ºC, 30ºC respectively, for 24 hrs. After incubation, the zones around the disks were measured by the zone scale (Himedia Pvt. Ltd. Mumbai).

Resazurinmicrotiter assay (REMA)

The REMA plate assay was carried out as described previously [48]. Briefly, one hundred µL of Mueller-Hinton/ Potato Dextrose broth medium was dispensed in each well of a sterile flat-bottom 96-well plate, and serial twofold dilutions of each synthesized compound were prepared directly in the plate. One hundred micro liters of inoculums was added to each well. Sterile cold water was added to all perimeter wells to avoid evaporation during the incubation. The plate was covered, sealed in a plastic bag, and incubated at 37°C. After 24 hrs of incubation, 30 µL of resazurin solution (0.01% in sterile D/W) was added to each well, and the plate was re-incubated overnight. A change in color from blue to pink indicated the growth of bacteria, and the MIC was defined as the lowest concentration of the drug that prevented this change in colour. The drug concentration ranges used were as follows: for the synthesized compounds and standards 0.97- 500 µg/mL.

RESULTS AND DISCUSSION

In continuation of our efforts on synthesis of heterocyclic compounds [45], herein we present microwave assisted rapid and efficient synthesis of novel 2-(3-chlorophenyl)-3-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one derivatives by the three component reaction of isatoic anhydride, with 3-chloro benzaldehyde and 5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-amine using l-proline as catalyst under monowave-50 irradiation (Scheme 1). This reaction is considered as a model reaction.

To optimize the reactions, the reaction was conducted in different solvents at different temperatures using l-proline as catalyst. Initially, the model reaction was stirred at room temperature, using ethanol and water as solvents; unluckily, the reaction did not proceed even after 12 hrs. We tried a model reaction at reflux condition for optimizing the reaction conditions and temperature. At reflux in water there is 48% of desired product was observed in 6 hrs while in ethanol 60% formation of product in 4.5 hrs was observed (by Tlc). Then the reaction was subjected to Monowave-50 irradiation using ethanol as a solvent at higher temperature and pressure (**Figure- 1**). The best result in terms of time and yield for the model reaction has been observed at120ºC (**Table 1**).From 78 to 120ºC, not only the appearance of product yield increased, but the time it took to complete the reaction also decreased. However, a further rise in the temperature resulted in the reduction of the yield. This suggested the optimum temperature condition to be 120ºC.

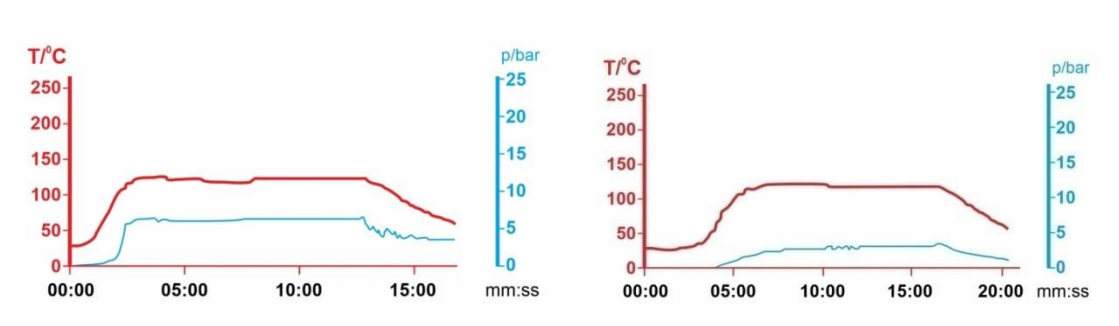


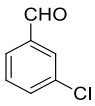
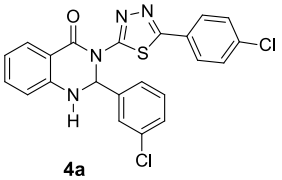
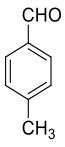
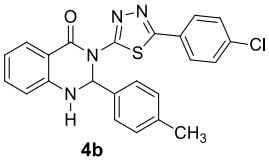
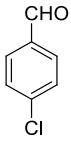
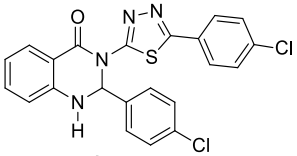
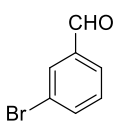
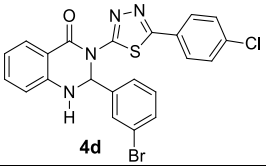
Figure 1: Reaction temperature and pressure for model reaction.

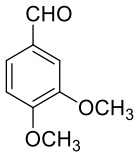
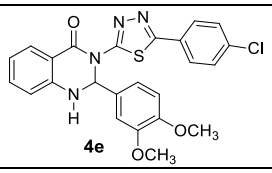
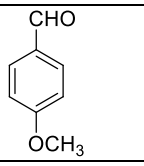
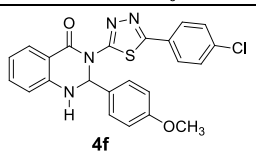
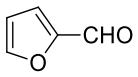
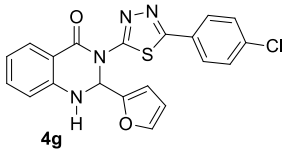
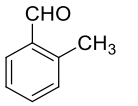
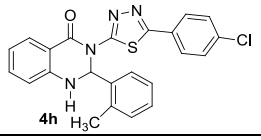
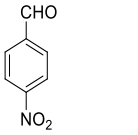
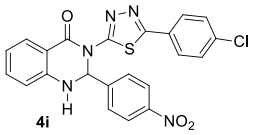
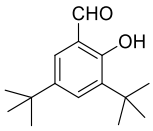
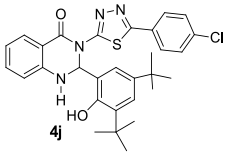
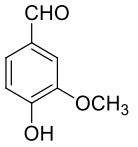
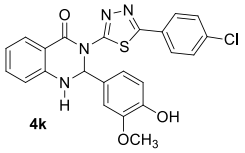
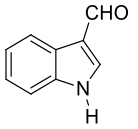
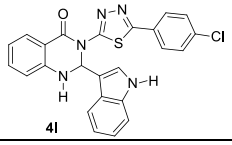
Table 1: Optimization of reaction condition

Entry	Solvent	Temperature (°C)	Time (h)	Yields (in %)
1	Water	Room temp.	12	--
2	Ethanol	Room temp.	12	--
3	Water	Reflux	6	48
4	Ethanol	78	4.5	60
5	Ethanol	100	2.5	72
6	Ethanol	110	1	82
7	Ethanol	**120**	**0.5**	**90**
8	Ethanol	130	0.5	85

To extend the strength and scope of this protocol, we investigated a reaction with a variety of substituted aromatic aldehydes. The results are summarized in **Table 2,** These synthesized compounds were further studied for their biological activity.

Table 2: Synthesis of novel 2-(phenyl substituted)-1,3,4-thiadiazole-2-yl-2,3- dihydroquinazoline-4(1H)-one under Microwave irradiations. [a]

Entry	Aldehyde	Product	Time (min)	Yields [b] (%)	Mp (°C)
a		 **4a**	30	90	261.3
b		 **4b**	40	83	275.7
c		 **4c**	30	90	264.3
d		 **4d**	40	85	270.1

e			35	82	263.5
f			40	85	231.5
g			35	78	268.5
h			30	82	264.0
i			30	85	265.6
j			40	75	280.2
k			25	88	233.1
l			40	80	260

[a] Reaction condition: Isatoic anhydride **1** (2 mmol), 5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-amine **2** (2 mmol), aromatic aldehyde **3** (2 mmol), in 5 mL ethanol and l-proline (10 mol %) catalyst; [b] Isolated yields.

Biological Study:

Disks diffusion assay

The antibacterial and antifungal assay was performed by disks diffusion method and the results are summarized in Table 3. The results showed that among the synthesized compounds **4a, 4b, 4d & 4l** showed the highest inhibition towards all tested microorganisms. The assay was performed in triplicate.

Table 3: Zone of inhibition of synthesized compounds against some pathogenic microorganisms.

Zone of Inhibition of synthesized compounds against some pathogenic microorganisms							
Compound code	**Bacterial strains**			**Fungal strains**			
	B. subtilis	***B. megaterium***	***S. aureus***	***A. niger***	***R. oryzae***	***M. mucido***	***C. albicans***
4a	++	++	**NZ**	++	++	+	**NZ**
4b	++	++	++	**NZ**	++	++	+
4c	**NZ**	**NZ**	**NZ**	++	**NZ**	++	**NZ**
4d	+++	+	++	++	+++	++	++

4e	++	**NZ**	**NZ**	**NZ**	**NZ**	++	**NZ**
4f	+	++	++	++	**NZ**	**NZ**	**NZ**
4g	**NZ**	+	**NZ**	**NZ**	**NZ**	++	**NZ**
4h	+	+	++	**NZ**	**NZ**	++	+
4i	**NZ**	**NZ**	**NZ**	**NZ**	**NZ**	**NZ**	**NZ**
4j	**NZ**	+	**NZ**	**NZ**	**NZ**	++	**NZ**
4k	+	+	++	**NZ**	**NZ**	++	+
4l	+++	+++	+++	**NZ**	**NZ**	**NZ**	++
Penicillin	+++	+++	+++	**NA**	**NA**	**NA**	**NA**
Fluconazole	**NA**	**NA**	**NA**	+++	+++	+++	+++

+= < 5 mm, ++= >5 &<10 mm, +++= >10 &< 18 mm, NZ=No zone, NA= Not applicable
Results are the average mean of three parallel experiments. N=3

Resazurinmicrotiter plate assay (REMA)

For checking the MIC, one of the proficient and sensitive method REMA assay was used. The basic mechanism involves the reduction of blue colour to pink by the metabolically active live cells. No change in blue colour indicates total the absence of metabolically live cells. The MIC values of the synthesized compounds were assessed in that compounds **4a, 4b, 4d and 4l** showed minimum inhibitory concentration towards the tested microorganisms as compared to the standards used. The results are expressed as the mean values of three independent experiments (N=3) as shown in Table 4.

Table 4: Minimum inhibitory concentration of compounds against some pathogenic microorganisms.

Minimum Inhibitory Concentration of synthesized compounds against some pathogenic microorganisms							
Compound code	**Bacterial strains**			**Fungal strains**			
	B. subtilis	***B. megaterium***	***S. aureus***	***A. niger***	***R. oryzae***	***M. mucido***	***C. albicans***
4a	62.5	125	31.2	62.5	31.2	>250	500
4b	62.5	31.2	31.2	62.5	250	250	125
4c	62.5	31.2	31.2	62.5	250	250	125
4d	15.6	62.5	62.5	125	250	250	250
4e	>500	500	500	500	>500	>500	>500
4f	500	500	>500	>500	>250	>250	500
4g	250	250	500	500	>500	>500	>250
4h	15.6	62.5	62.5	125	250	250	250
4i	500	500	>500	125	>250	>250	500
4j	250	250	250	500	125	>500	125
4k	250	250	125	125	500	500	>500
4l	31.2	31.2	15.6	250	125	>250	125
Penicillin	1.95	3.9	1.95	NA	NA	NA	NA
Fluconazole	NA	NA	NA	1.95	1.95	1.95	3.9

NA = Not applicable; Results are the Mean values of three independent experiments N=3

Spectral data:

2-(3-chlorophenyl)-3-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4a):

Yield = 90%; IR (KBr)υ-: 3353, 3075, 1638, 1507, 1445, 1437 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) ∂ (ppm): 8.46 (bs, 1H), 8.01 (d, 2H), 7.81 (d, 2H), 7.62 (d, 2H), 7.32-7.43 (m, 4H), 7.17 (s, 1H), 6.96 (d, 1H), 6.82 (t, 1H); ^{13}C NMR ∂ (ppm): 162.78,160.13, 157.73, 146.51, 141.72, 135.83, 135.39 (2C), 133.31, 130.53, 129.38, 128.66, 128.63(2C), 128.40(2C), 125.80, 124.09, 118.59, 115.76, 112.41, 67.82, ppm; m/z : 453.34 (M+1).

3-(5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl)-2-(p-tolyl)-2, 3-dihydroquinazolin-4(1H)-one (4b):

Yield = 83%, IR-(KBr)υ- : 3346, 3051, 1632, 1509, 1459, 1334 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) ∂ (ppm): 8.35 (bs, 1H) 8.00 (d, 2H), 7.79 (d, 1H),7.62 (d, 2H),7.37-7.42(m, 2H) 7.17 (d,2H)), 7.10 (d 2H), 6.91 (d 1H), 6.78-6.81 (t, 1H), 2.50 (s,3H); 13C NMR ∂ (ppm):162.55, 160.35, 157.83, 146.82, 137.69, 136.22(2C), 135.63, 135.32(2C), 129.37, 129.04, 128.71, 128.62, 128.32(2C), 125.50(2C), 118.24, 115.66, 112.55, 68.29, 20.73 ppm; m/z: 433.20 (M+1)

2-(4-chlorophenyl)-3-(5-(4-Chlorophenyl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4c): Yield = 90% , IR(KBr)υ- : 3344, 3091, 1633, 1509, 1458, 1434 cm^{-1}; ^1H NMR: (500 MHz, DMSO-d_6): 8.42 (bs, 1H) , 8.00 (d 2H), 7.80 (d, 1H), 7.62 (d,2H) ,7.31- 7.44(m, 6H) 6.94 (d, 1H) ,6.81 (t,1H); 13C NMR ∂ (ppm):: 162.68, 160.11, 157.74, 146.54, 138.19, 135.75, 133.00, 129.37(2C), 128.67(2C), 128.61, 128.31(2C), 127.53(2C), 118.48 (2C), 115.73, 112.47, 112.32, 67.86 ; m/z : 453.31(M+1).

2-(3-bromophenyl)-3-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4d): Yield = 85% IR(KBr)υ- : 3352, 3087, 1638, 1509, 1445, 1437 cm^{-1}; ^1H NMR(500 MHz, DMSO-d_6): 8.0 (bs, 1H) 7.90 (d, 2H), 7.52 (d, 2H), 7.38-7.46 (m, 6H), 7.11 (t, 1H) , 6.96-7.04 (t, 1H), 6.80- 6.82 (d, 1H); m/z : 496.50.

CONCLUSION

In conclusion, we have developed an efficient, rapid, and simple synthetic protocol for the synthesis of novel 2-phenyl substituted -1, 3, 4-thiadiazole-2-yl)-2,3-dihydroquinazoline-4(1H)-one derivatives (4a-l) using l-proline as catalyst. The synthesized novel compounds were characterized by spectrochemical methods i.e. IR, ^1H NMR, ^{13}C NMR & mass. The novel compounds have been carried out for their in vitro antimicrobial, antifungal activity against bacterial and fungal strains.

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