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Original Article

Solvent-free Synthesis and Antimicrobial Activity of Dihydroquinazolinone Derivatives

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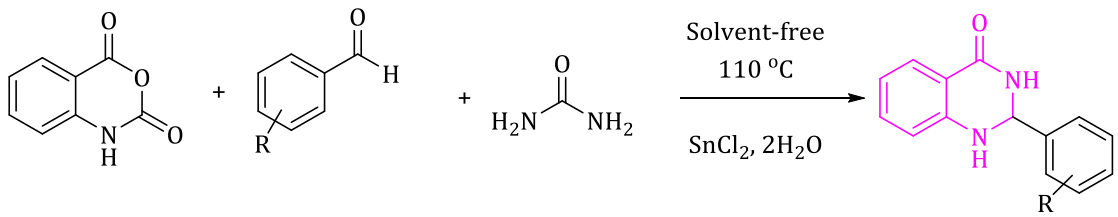
ABSTRACT

In this research, a new series of dihydroquinazolinone analogs (**4a-f**) was synthesized using a one-pot reaction supporting solvent-free conditions at the presence of $SnCl_2.2H_2O$ as catalyst. All final products were proved by FT-IR, ^{1}H-NMR, and ^{13}C-NMR analysis. The preliminary antimicrobial activity was assessed against Gram-negative *(Escherichia coli*, *Pseudomonas aeruginosa*), Gram-positive *(Staphylococcus aureus, Bacillus subtilis, Lactobacillus rhamnosus)*, and antifungal activities against *Candida albicans.* Most of the synthesized derivatives revealed considerable activity, significantly compounds **4d** and **4e** at 0.25 mg/mL concentration had the highest activity against *P. aeruginosa.* Also, the MIC of compound **4d** was 0.25 mg/mL against *B. subtilis,* and *L. rhamnosus.* Furthermore, the tested molecules demonstrated moderate antifungal activities against the *C. albicans*.

GRAPHICAL ABSTRACT



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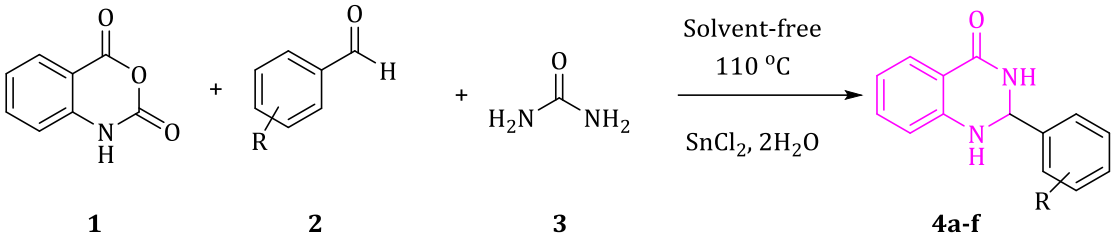
Introduction

The emergence of antimicrobial resistance is a broadly identified public health threat [1]. The search for novel antibacterial drugs is an attractive purpose for medicinal chemists [2]. Quinazolinone derivatives have shown biological activities including, anticancer [3], Antiepileptic [4], antiplasmodial [5], and antihistaminic activities [6]. Rezaee Nasab *et al*. [7], reported quinazolinone derivatives as potential antibacterial agent. Hamidi and co-worker, synthesized thio- and oxazepino[7,6-b]quinolones and evaluated their anti-bacterial activity[27]. Vibhute *et al*. synthesized [1,2,4] triazoloquinazolinone derivatives using anthranilic acid as green catalyst[28]. Also El-Hashash and co-worker, prepared novel quinazoline derivatives using 2-Ethoxyquinazolin- 4-yl hydrazine and evaluated their antimicrobial activity [29].

Among various chemical approaches, one-pot, multicomponent reactions have gained significant importance due to their high yielding, clean, and eco-friendly approach, which became the current area of interest in medicinal chemistry research [8–13].

In this work, we report a three-component, one-pot approach for the preparation of novel dihydroquinazolinone derivatives using $SnCl_2.2H_2O$ as catalysis via a multicomponent reaction (Scheme 1). The synthesized molecules have been investigated for their antibacterial activity against both Gram-negative and Gram-positive bacteria together with fungal strains.



1 **2** **3** **4a-f**

4a: R_1=H
4b: R_2=4-CH_3
4c: R_3=4-isopropyl
4d: R_4=4-OCH_3
4e: R_5= 2,3-di-OCH_3
4f: R_6=3,4,5-tri-OCH_3

Scheme1: The condensation of isatoic anhydride, aryl aldehydes, and urea using $SnCl_2.2H_2O$

Materials and Methods

Chemistry

All chemicals and solvents were purchased from Merck chemical company and were exerted. Melting points of the compounds were recorded using an Electrothermal 9300 device and were uncorrected. Infrared spectra were reported at a Nicolet 4700 FT-IR spectrophotometer in wave number range 400-4000 cm^{-1}. Respectively, ^{13}C and ^{1}H NMR spectra were measured by Bruker-Instrument DPX-400 Avance 2 in dimethyl sulfoxide (DMSO)-*d6* at 100 and 400 MHz. The reactions were checked by thin-layer chromatography (TLC).

The general method for the synthesis of novel dihydroquinazolinone derivatives

A mixture containing an appropriate aryl aldehyde (2 mmol), corresponding urea (2.2 mmol), isatoic anhydride (2 mmol), and $SnCl_2.2H_2O$ (18 mol%) were heated in an oil bath at 110 °C for the required time before the reaction was complete. After finishing the reaction, whichever was determined by TLC, the reaction mixture was cooled, methanol (15 mL) was combined. The combination was stirred for 35 min. Then the catalyst was extracted through a sinter funnel; after that the solvent was evaporated and precipitate filtered. Finally, crystallization of the precipitated solid from ethanol afforded product.

*2-phenyl-2,3-dihydroquinazolin-4(1H)-one (**4a**)*

White solid, mp 218-220 °C. IR (KBr, cm^{-1}) νmax: 3310 (N-H), 2921(C-H arom, str.), 1687 (C = O), 1611 (C = C). 1599 (C=N, str.), ^{1}H NMR (400 MHz, DMSO-*d*6) δ= 8.20 (s, 1H), 7.67 (t, *J* =8.0Hz, 1H), 7.52 (d, *J* = 7.2Hz, 2H), 7.30-7.45 (m,3H), 7.25-7.27 (m, 1H), 7.15 (s, 1H), 6.72 (d, *J*=8.0Hz, 1H), 6.64 (t, *J*=7.2Hz, 1H), 5.55 (s,1H) ppm; ^{13}C NMR (DMSO-d6, 100MHz) δ: 165.0, 147.3, 141.1, 132.7, 123.9, 124.7, 125.8, 126.3, 116.5, 114.4, 113.8, 106.5, 66.0 ppm.

*2-(4-Methylphenyl)-2,3-dihyroquinazolin-4(1H)-one (**4b**)*

White solid, mp 226-227 °C. IR (KBr, cm^{-1}) νmax: 3100 (N-H), 2821 (C-H arom, str.), 1657 (C = O), 1601 (C = C). 1433 (C=N, str.), ^{1}H NMR (400 MHz, DMSO-*d*6) δ= 8.25 (s, 1H,), 7.64 (d, *J* =7.2Hz, 1H), 7.42 (d, *J* = 8.0Hz, 2H), 7.21-7.35 (m, 3H), 7.05 (s, 1H), 6.15 (d, *J* = 8.0 Hz, 1H), 6.52 (t, *J*=7.6Hz, 1H), 5.63 (s, 1H), 2.45 (s,3H) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ: 167.0, 144.3, 142.1, 131.7, 124.9, 125.7, 126.8, 127.3, 115.5, 113.4, 112.8, 108.5, 64.0ppm.

*2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**4d**)*

1661 (C = C). 1453 (C = N, str.), ^{1}H NMR (400 MHz, DMSO-*d*6) δ= 8.15 (s, 1H,), 7.62 (d, *J* = 7.2Hz, 1H), 7.32 (d, *J* = 8.0Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 6.85 (d, *J* = 7.4 Hz, 2H), 6.62 (d, *J* = 8.0Hz, 1H), 6.64(t, *J* = 7.2 Hz, 1 H), 5.61 (s, 1 H), 3.51 (s, 3H)) ppm; ^{13}C NMR (100MHz, DMSO-d6) δ: 164.1, 146.3, 145.1, 135.7, 125.9, 126.7, 127.8, 128.3, 116.5, 112.4, 111.8, 105.5, 66.0 ppm.

*2-(2,3-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**4e**)*

White solid, mp 200-201 °C. IR (KBr, cm^{-1}) νmax: 3300 (N-H), 3091(C-H arom, str.), 1720 (C = O), 1681 (C = C). 1460 (C = N, str.), ^{1}H NMR (400 MHz, DMSO-*d*6) δ= 8.01 (s, 1H,), 7.51 (d, *J* = 7.2Hz, 1H), 7.44 (d, *J* = 8.0Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.21 (s, 1H), 7.01 (d, *J* = 7.4 Hz, 2H), 6.82 (d, *J* = 8.0Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 5.44 (s, 1 H), 3.62 (s, 3H). 3.80 (s, 3H) ppm; ^{13}C NMR (100MHz, DMSO-d6) δ: 168.0, 147.3, 146.1, 131.7, 123.9, 124.7, 125.8, 126.3, 115.5, 113.4, 112.8, 103.5, 65.0ppm.

Biological assay

Antibacterial studies

The antimicrobial evaluation of the synthesized compounds were carried out using standard serial dilution technique against Gram(-)bacteria (*Pseudomonas aeruginosa* ATCC 27853, *Escherishia coli* ATCC 25922) and Gram(+)bacteria (*Bacillus subtilis* ATCC 6633, *Lactobacillus rhamnosus* ATCC 7469 and *Staphylococcus aureus* ATCC 25923) as well as one fungi (*Candida albicans* ATCC 10231). The antimicrobial evaluation was carried out according to reported methods [7,15]. Microplate Alamar Blue Assay (MABA) protocol was exerted to find out the minimum inhibitory concentrations (MICs) of the synthesized molecules [17-19]. 200 µL aliquot of the stock solution of title compounds (**4a-f**) were added to the first well of each row in a 96-well plastic plate and serially diluted in each row with 100 µL of the culture medium [20]. Then, 100 µL of bacterial suspension and 15 µL of resazurin sodium solution was transferred to each well. Following 24 h incubation at 35 °C for bacteria and 48 h at 25 °C for fungi, the wells were tested for the visible color change to pink, which was indicated bacterial growth [21]. The minimum bactericidal concentration (MBC) and the minimum fungicidal concentration (MFC) results were gathered from each well [22]. Ciprofloxacin and Nystatin were exerted as standard for antibacterial and antifungal activity, respectively [22].

Results and Discussion

To improve the reaction setting, at first, we chose the reaction of benzaldehyde (2 mmol), isatoic anhydride (2 mmol), and urea (2.2 mmol) as an ideal reaction (Scheme 1). This reaction was highly dependent on several parameters [23, 24]. By studies on ideal reaction, the reaction carried through $SnCl_2.2H_2O$ as catalyst in various solvents including EtOH, H_2O, CH_3CN, DMF, THF, and solvent-free conditions. These experiments revealed that the reaction is performed with the highest yield and shortest time under solvent-free conditions (Table1). So, the reaction completed under solvent-free conditions. As mentioned in the articles, solvent-free conditions

have some advantages for chemical reactions [25,26].

The affords to the evaluation of required catalysts in the synthesis of dihydroquinazolinone derivatives for the ideal reaction, was showed that when the reaction was loaded with 18 mol% of $SnCl_2.2H_2O$ the maximum yield of product is obtained. In contrast, the usage of large quantities of the catalysts does not increase the yield (Table2).

Furthermore, the impact of temperature on the reaction was studied. Examining of reactions development at various temperatures in the presence the optimized amount of catalysts for ideal reaction, confirmed that the maximum rate of reaction is done at 110 °C (Table 2).

When the reaction is heated above 110 ˚C do not further increase the yield and the reaction time. Based on acquired optimal conditions, we run the dihydroquinazolinone derivatives synthesis in the existence of $SnCl_2.2H_2O$ (18 mol%, at 110 °C) in solvent-free conditions. Considering optimal conditions, several arylaldehydes have been effectively condensed to give dihydroquinazolinone derivatives. In all cases, corresponding title compounds were isolated with good to excellent yields (Table 3).

Table 1: Evaluation of solvent effect for the model reaction

		$SnCl_2.2H_2O$		
code	Solvent	Condition	Time(min)	Yield (%)
1	CH_3CN	Reflux	120	48
2	EtOH	Reflux	120	35
3	THF	Reflux	120	50
4	DMF	Reflux	120	55
5	H_2O	Reflux	24 h	58
6	-	**110** °C	**35 min**	**85%**

Table 2: Optimization of catalys and reaction temperature

code	Catalyst (mol%)	Temperature °C	Time (min)	Yield (%)
1	-	110 °C	90	Trace
3	5	110 °C	85	67
4	10	110 °C	75	75
5	15	110 °C	65	80
6	**18**	**110 °C**	**35**	**85**
7	25	110°C	35	85
8	30	120 °C	44	77
9	18	90	55	65

Table3: Synthesis of dihydroquinazolinone derivatives

code	R	Time(min)	Yield (%)	Melting point (°C)
4a	H	35	85	218-220
4b	4-CH_3	40	90	226-227
4c	4-isopropyl	30	92	230-231
4d	4-OCH_3	37	80	190-191
4e	2,3-di-OCH_3	32	83	183-184
4f	3,4,5-tri-OCH_3	30	80	220-221

Antibacterial Activity

The results of the antimicrobial evaluation (MIC values in mg/mL) of the target dihydroquinazolinone compounds (**4a-f**) listed in Table 4. The critical activity of most compounds against the chosen microorganisms compared with ciprofloxacin as a reference drug. In particular, the activity of the title compounds (**4a-f**) was more active against the Gram- positive

strains than their activity against the Gram-negative strains.

In turn, compound **4d** exhibited remarkable activity against Gram-positive strains (MIC = 0.25 mg/mL). The compounds **4d** and **4e** also discovered inhibition activity against Gram-negative strains, with enhancement in the activity against the Gram- negative strains, particularly against *p. aeruginosa* (MIC = 0.25 mg/mL). The in vitro antibacterial activity of **4a–f** against the Gram-negative and Gram-positive strains varied from moderate to weak with MIC values ranging from 0.25 to >2 mg/mL. While in the antifungal evaluation it is revealed that the title compounds (**4a-f**) have moderate to weak activity (Table5).

Table 4: MIC (mg/mL) results of the title compounds (**4a-f**) against various bacteria

Code	Gram-negative bacteria mg/ml					Gram-positive bacteria mg/ml					
	Escherichia coli		*Pseudomonas aeruginosa*			*Staphylococcus aureus*		*Bacillus subtilis*		*Lactobacillus rhamnosus*	
	MIC	MBC	MIC	MBC		MIC	MBC	MIC	MBC	MIC	MBC
4a	0.5	2	0.5	2		0.5	2	0.5	>2	0.5	1
4b	0.5	2	0.5	2		0.5	2	0.5	1	0.5	2
4c	0.5	1	0.5	2		0.5	2	0.5	2	0.5	2
4d	0.5	>2	0.25	2		0.5	2	0.25	1	0.25	1
4e	0.5	2	0.25	0.5		0.5	2	0.5	>2	0.5	2
4f	0.5	>2	0. 5	1		05	2	0.5	2	0.5	2
cipro	0.000025	0.5	0.001	0.002		0.0032	>0.0032	0.5	0.5	-	-

Table 5: MIC (mg/mL) and results of the title compounds (**4a-f**) against *C. albicans*

code	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	Nystatin
MIC	0.25	0.25	0. 25	0.25	0.25	0.25	>1
MBC	>2	>2	>2	>2	>2	>2	>1

Conclusions

In this work, a simple procedure, with short reaction times and, simple work-up was established synthesize dihydroquinazolinone derivatives applying isatoic anhydride, urea, and aryl aldehydes under the solvent-free condition in the existence of $SnCl_2.2H_2O$ as the catalyst. Clean reaction profiles, simplicity, use of readily available $SnCl_2 .2H_2O$, no use of any solvent, mild conditions, high yields of the products, and low reaction times are the main advantages of this protocol. In the biological assay, all the synthesized compounds exhibited moderate antibacterial and antifungal activities. Significantly compounds **4d** and **4e** at 0.25mg/mL concentration had the highest activity against *P. aeruginosa.*

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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