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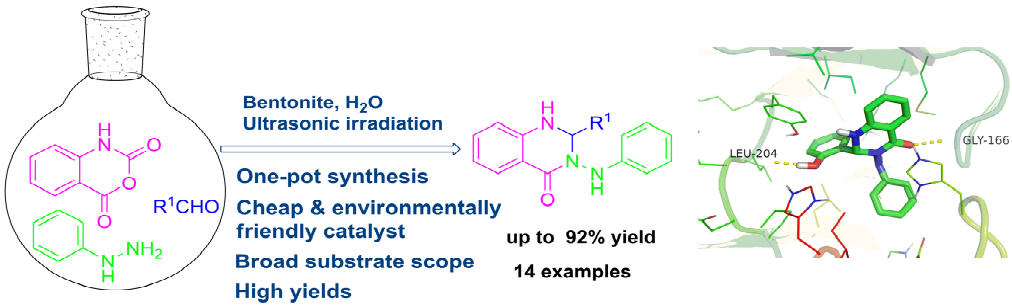

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ABSTRACT

An eco-friendly procedure for synthesis of 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones by three-component reactions, with bentonite as a low cost and reusable catalyst under ultra sonic irradiation, is described. The novel method offers several advantages, such as high yields, short reaction time, environmentally friendly reaction media and recyclable catalyst. All the synthesized 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones were screened for anti-bacterial activity against *Escherichia coli.* Some of these compounds exhibited interesting anti-bacterial activity against the Gram-negative bacteria *Escherichia coli.* The molecular docking of some compounds explained that some moieties played an important role in increasing the bind interaction.

Multi-component reactions (MCRs) have emerged as powerful tool in synthetic organic and medicinal chemistry. These reactions proceed via one-pot procedures to form complex structure target products in a single operation. The major advantages of MCRs include shorter reaction times, lower costs, high atom-economy, convergent character and operational simplicity. MCRs have provided versatile method for formation of new C-C and C-N bonds to synthesize numerous heterocyclic scaffold products.[1]

Quinazolinones are an important class of heterocyclic compounds that are widespread in nature[2] and exhibit interesting pharmacological properties. Quinazolinone is considered to be a privileged structure in the discovery of protein kinase inhibitors, one of the current key areas in the development of chemotherapeutic agents, [3] and therefore it is not surprising that its derivatives exhibit antitumor, antitubercular, antiviral, antifungal and antibacterial activities. [4] Due to their wide range of applications, considerable attention has been paid toward these heterocyclic compounds. Many synthetic methods have been reported for the preparation of quinazolinone derivatives and their analogues. [5]

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis. Compared with those traditional methods, ultrasound-assisted organic synthesis is known to be faster and more convenient. [6]

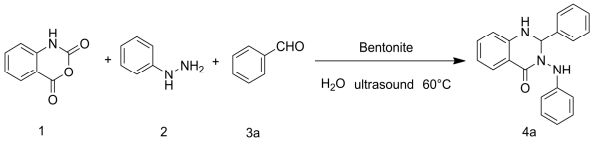
Bentonite, a cheap and abundant natural material, is a layered clay mineral in the aluminosilicate smectite family.[7] The chemical composition and structure, exchangeable ion type and small particle size of aluminosilicate smectites are responsible for several properties, including high cation exchange capacity, large specific surface area and physico-chemical properties such as swelling, adsorptive properties, colloidal properties, compressibility, strength, particle size, pore structure, specific surface area, and catalytic activity.[8] Nowadays, bentonites as acid catalysts are used to support transition metals. Such catalysts have been widely studied in organic catalytic conversion process.[9]

In continuation of our previous work aiming at the synthesis of biologically important heterocyclic systems and green chemistry protocols, [10] we report herein a simple and efficient method for the synthesis of novel 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones via a domino, one-pot, three-component condensation reaction between isatoic anhydride, aldehydes or ketones, and aromatic amine in the presence of bentonite as a cheap, efficient, recyclable heterogeneous catalyst under ultrasonic irradiation condition. All the synthesized quinazolin-4(1*H*)-ones were screened for anti-bacterial activity against *Escherichia coli.* The molecular docking of some compounds explained that some moieties played an important role in increasing the bind interaction.

We commenced our study by taking isatoic anhydride (**1**), phenylhydrazine (**2**) and benzaldehyde (**3a**) as the model substrates in aqueous ethanol under ultrasonic irradiation conditions for 60 min in the presence of different catalysts, such as silica gel, acidic alumina, basic alumina and bentonite (5 mol %) (**Table 1**, entries 1-5). It was found that bentonite was most efficient catalyst for the reaction in aqueous ethanol, and the yield of product **4a** was 75% (**Table 1**, entry 5). To examine the effect of different solvents on the reaction, ethanol and water were investigated (**Table 1**, entries 6-7). It was clear that the yield of product 4a was 83% when reaction was performed in

water (**Table 1**, entry 7). At the same time, the reaction time shortened to 30 min when the solvent is pure water (**Table 1**, entry 7). Therefore, water was the best solvent for this organic reaction because of the hydrophobic effect, which enhanced hydrogen bonding in the transition state.[11] Furthermore, the influence of the amount of bentonite catalyst was examined to increase the efficiency of the reaction. On the one hand, when the amount of bentonite catalyst was decreased from 5 to 1 mol %, the yield of compound **4a** was no significant change for the same reaction (**Table 1**, entries 7-9). With further decreasing the amount of bentonite catalyst to 0.5 mol %, the yield of compound **4a** decreased to 75% (**Table 1**, entry 10). On the other hand, it should be noted that the yield of compound **4a** was not significantly improved when the amount of bentonite catalyst was increased from 5 to 7 mol % (**Table 1**, entries 7, 11) and 1 mol % amount of bentonite catalyst was efficient enough to catalyze the reaction.

Table 1 Optimization of the reaction conditions for the formation of **4a**[a]

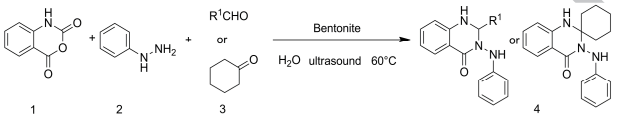


Entry	Solvent	Catalyst (mol %)	Time (min)	Yield (%)[b]
1	EtOH:H_2O=1:1(*V/V*)	-	60	trace
2	EtOH:H_2O=1:1(*V/V*)	Silica gel (5)	60	22
3	EtOH:H_2O=1:1(*V/V*)	Acidic alumina (5)	60	40
4	EtOH:H_2O=1:1(*V/V*)	Basic alumina (5)	60	45
5	EtOH:H_2O=1:1(*V/V*)	Bentonite (5)	60	75
6	EtOH	Bentonite (5)	60	68
7	H_2O	Bentonite (5)	30	83
8	H_2O	Bentonite (3)	30	82
9	H_2O	Bentonite (1)	30	83
10	H_2O	Bentonite (0.5)	30	75
11	H_2O	Bentonite (7)	30	82

[a] Conditions: isatoic anhydride **1** (1.0 mmol), phenylhydrazine **2** (1.1 mmol), benzaldehyde **3a** (1.1 mmol) in 5 mL of aqueous media under ultrasonic irradiation conditions. Ultrasonic irradiation was performed in an ultrasound cleaning bath (KQ-250DE, China) with a frequency of 40 kHz and power of 250 W.
[b] Isolated yields.

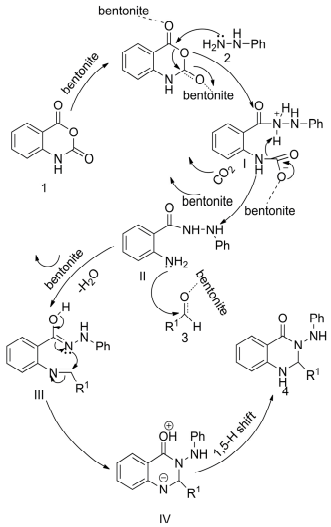
With the optimized reaction conditions in hand, multi-component reaction was then expanded to various 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones (**Table 2**). Phenylhydrazine was used as the nitrogen source to produce the 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones under mild reaction conditions. As illustrated in **Table 2**, the method showed good tolerance when phenylhydrazine was condensed with commercially available aromatic aldehydes, functional groups including nitro, hydroxyl, methoxy, styryl et al. (**Table 2**, entries 1-7) and the heteroaromatic aldehydes included picolinaldehyde, nicotinaldehyde, isonicotinaldehyde and furfural. Accordingly, the desired 2-heteroaryl-3-(phenylamino)-dihydroquinazolin-4(1*H*)-one skeleton products were obtained in good yields (**Table 2**, entries 9-12). Treatment of isatoic anhydride, phenylhydrazine and terephthalaldehyde with bentonite in pure water gave 2,2'-(1,4-phenylene)bis(3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one) (**Table 2**, entry 8). When aliphatic carbonyl compounds isobutyraldehyde and cyclohexanone were used as substrates, the reaction also gave good yields of 2-isopropyl-3-(phenylamino)-dihydroquinazolin-4(1*H*)-one and 3'-phenyl-1'*H*-*spiro*[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one (**Table 2**, entries 13-14). As shown in **Table 2**, entries 1-7, the substrates with electron-donating groups gave better yields than with electron-withdrawing groups. A total of 14 compounds were synthesized and seven compounds **4d**, **4f, 4i-4m** were reported for the first time.

Table 2 Synthesis of 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones **4** catalyzed by bentonite [a]



Entry	R^1	compound	yield (%)[b]	Mp (°C)
1	Ph	**4a**	83	179-180
2	4-MeO-Ph	**4b**	92	188-190
3	2-OH-Ph	**4c**	88	161-162
4	2-NO_2-Ph	**4d**	75	180-182
5	4-*i*Pr-Ph	**4e**	75	145-147
6	styryl	**4f**	80	168-169
7	*p*-$N(CH_3)_2$-Ph	**4g**	70	230-232
8	4-CHO-Ph	**4h**	80	265-266
9	2-pyridyl	**4i**	74	160-162
10	3-pyridyl	**4j**	76	146-148
11	4-pyridyl	**4k**	73	170-172
12	furyl	**4l**	65	170-172
13	*i*Pr	**4m**	70	169-171
14	cyclohexanone	**4n**	72	215-216

[a] Conditions: isatoic anhydride **1** (1.0 mmol), phenylhydrazine **2** (1.1 mmol), aldehydes or ketones **3** (1.1 mmol), bentonite (0.01 mmol, 1 mol %) in 5 mL of aqueous media under ultrasonic irradiation conditions.
[b] Isolated yields.



Scheme 1 Plausible reaction pathway in the synthesis of 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones.

According to the relevant literature,[12] we proposed the plausible following mechanism to account for the bentonite-catalyzed reaction (**Scheme 1**). First, the isatoic anhydride (**1**) is activated with bentonite followed by the N-nucleophilic attack of primary amine (**2**) on the carbonyl groups to form intermediate (**I**). Then decarbonylation of intermediate (**I**) occurs resulting in generation of 2-amino-*N*-substituted-benzamide (**II**). The aldehyde (**3**) promoted by bentonite with the amino group of 2-amino-*N*-substituted-amide (**II**) produces an imine intermediate (**III**). Intermediate **IV** could be prepared by intramolecular nucleophilic attack of the amide nitrogen on activated imine carbon. Finally, 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones (**4**) could be formed by 1, 5-proton transfer of **IV**.

Finally, we also checked the recyclability of the catalyst by recovering the bentonite and found that the catalyst maintained its activity after being recycled five times for synthesizing **4a** as shown in **Table 3**. This results showed that the catalyst had no significant change in activity.

Table 3 Recyclability of the catalyst for the one-pot synthesis of **4a**[a]

Run	1	2	3	4	5
Yields[b] (%)	83	80	80	78	79

[a] Conditions: isatoic anhydride **1**(1.0 mmol), Phenylhydrazine **2** (1.1 mmol), benzaldehyde **3a** (1.1 mmol) in 5 mL of aqueous media under ultrasonic irradiation condition.
[b] Isolated yields.

All the synthesized compounds were screened for their in vitro antibacterial activity against Gram-negative (G^-) bacteria *Escherichia coli* (ATCC 25922) (**Table 4**). The biological activities of these compounds have been evaluated by using the minimum inhibitory concentration (MIC) method. Activities of each compound in dimethyl sulfoxide (DMSO) were compared with streptomycin sulfate against G^- bacteria and penicillin sodium against G^+ bacteria as standards. Compounds showed a wide range of antibacterial activity with MIC values 15.6–250 μg/mL. (Streptomycin sulfate showed MIC 7.8 μg/mL). The screening result of 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones, is interesting that compounds **4c**, **4i-4k** exhibit significant antibacterial activities with MIC 15.6 μg/mL against *Escherichia coli*.

Table 4 Antibacterial activity of the synthesized compounds against *Escherichia coli*, as determined by minimum inhibitory concentration (MIC) methods.

Sample	*E. coli* MIC (μg/mL)
4a	62.5
4b	31.5
4c	15.6
4d	62.5
4e	62.5
4f	250
4g	31.3
4h	62.5
4i	15.6
4j	15.6
4k	15.6
4l	62.5
4m	62.5
4n	125
Streptomycin sulfate	7.8
Penicillin sodium	-

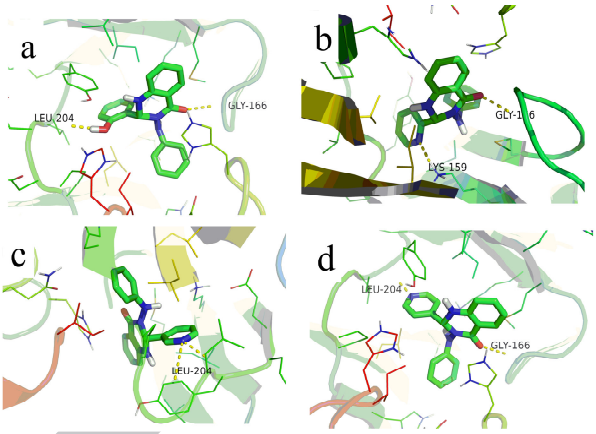


Figure 1 Docking studies on compound **4c** (a), **4i** (b), **4j** (c), **4k** (d) with biotin carboxylase.

In order to illustrate theoretically antimicrobial mechanism of these compounds, the antimicrobial potency of compound **4c**, **4i-4k** were subjected for further docking studies to explore the binding pattern against biotin carboxylase from *Escherichia coli*.[13] PDB ID 2W6O was retrieved from Brookhaven Protein Data Bank. The binding energies of the docked compound **4c**, **4i-4k** were -8.46, -7.29, -7.10, -7.45 kcal/mol, respectively. The binding modes of compound **4c**, **4i-4k** were shown in **Figure 1** a-d, respectively. As depicted in **Figure 1**, docking of compound **4c**, **4i-4k** showed hydrogen bond interactions with LEU 204 or LYS 159 which are the active site of the receptor.[13] In addition, the carbonyl group can form hydrogen bonds with residues GLY 166 (**Figure 1** a, b and d). As shown in **Figure 1** a, the hydroxyl group moiety formed two hydrogen bonds with residue LEU 204. The pyridine group can form hydrogen bond with LYS 159 or LEU 204 (**Figure 1** b-d). The results of molecular docking of compound **4c**, **4i-4k** explained that some moieties played an important role in increasing the bind interaction.

In summary, a new method was developed using bentonite as catalyst in aqueous media under ultrasonic irradiation for synthesis of 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones. This procedure showed good functional group tolerance. A total of 14 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones were synthesized and 7 of them were reported firstly. Other features of this protocol are: short reaction time, higher production rate, avoiding the use of organic solvents and little consumption of bentonite catalyst. Antibacterial activity of all compounds from above results can be concluded that all the synthesized compounds had potential antibacterial activity against *Escherichia coli.* Compounds **4c**, **4i-4k** showed an interesting activity against *Escherichia coli.*

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Supplementary Material

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