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Hydroxypatite nanoparticles (HAP NPs): As a green and efficient heterogeneous catalyst for three-component one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in aqueous media

Nasrin Razavi, Batool Akhlaghinia*

Abstract

Hydroxypatite nanoparticles (HAP NPs) is found to be an efficient catalyst for synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in aqueous media via a three-component one-pot condensation of isatoic anhydride and aromatic aldehydes with primary amines or ammonium salts. The nano catalyst (which characterized by FT-IR, XRD, SEM-EDS and TEM techniques) is easily recyclable six times without the significant loss of catalytic activity. Other remarkable features include the wide range of functional group tolerance and providing good to excellent yields of the products under mild reaction conditions.

Keywords:

Hydroxypatite nanoparticles (HAP NPs), 2,3-dihydroquinazolin-4(1*H*)-ones, one-pot reaction, three-component reaction, heterogeneous catalyst.

Introduction

Quinazolinones derivatives as an important class of fused heterocyclic compounds and valuable intermediates in synthetic organic chemistry are present in a large family of products with potential biological and pharmaceutical activities.[1] These exhibit various medicinal properties such as anti-tumor,[2] anti-cancer,[3] antibacterial,[4] anticonvulsant,[5] anti-inflammatory,[6] antifungal,[7] antihypertension,[8] anti-diabetes,[9] analgesic,[10] herbicidal, diuretic, as well as plant growth

regulation[11] and some of them have been shown to act as potent HIV-1 reverse transcriptase inhibitors.[12] In view of their widely increased application value, a number of classical methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported in the literature.[13-15] These methods include: (i) condensation of *o*-aminobenzamide with aldehydes or ketones using Lewis or Brønsted acids[16] (ii) reductive cyclization of *o*-nitrobenzamide /or *o*-azido-benzamide with aldehydes or ketones using $SnCl_2$/or metallic samarium in the presence of iodine or SmI_2 [16 a, 17] (iii) condensation of isatoic anhydride, primary amine or ammonium salts with aldehydes or ketones in the presence of *p*-toluenesulfonic acid (PTSA),[16 b] citric acid,[18] silica sulfuric acid (SSA),[19] silica-bonded *N*-propylsulfamic acid,[20] silica-bonded S-sulfonic acid,[21] MCM-41-SO_3H,[22] ethylenediamine diacetate,[16 g] $Ga(OTf)_3$,[23] $KAl(SO_4)_2.12H_2O$,[24] $Al(H_2PO_4)_3$,[25] montmorillonite K-10,[26] heteropolyacids (HPAs),[27] powdered diethylaminoethyl cellulose as biomass-derived support for phosphotungstic acid,[28] $SrCl_3.6H_2O$,[29] molecular iodine,[30] magnetic Fe_3O_4, nano-indium oxide, Al/Al_2O_3 nanoparticles,[31-33] or with the aid of ultrasound irradiation catalyzed by dodecylbenzenesulfonic acid[34] and microwave in the presence of Amberlyst-15[35] or Cu-CNTs.[36]

2,3-Dihydroquinazolin-4(1*H*)-one derivatives were previously prepared by multi-step reactions.[37] In comparison multi-component reactions (MCRs), not only produced 2,3-dihydroquinazolin-4(1*H*)-one derivatives in a single step but also the diversity could be achieved simply by varying the reacting components. Moreover, today development of an efficient, rapid, simple, low cost, easy work-up and environmentally benign protocol with energy conservation using a recyclable catalyst and a green solvent under mild reaction conditions for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives is desirable and in demand.[38]

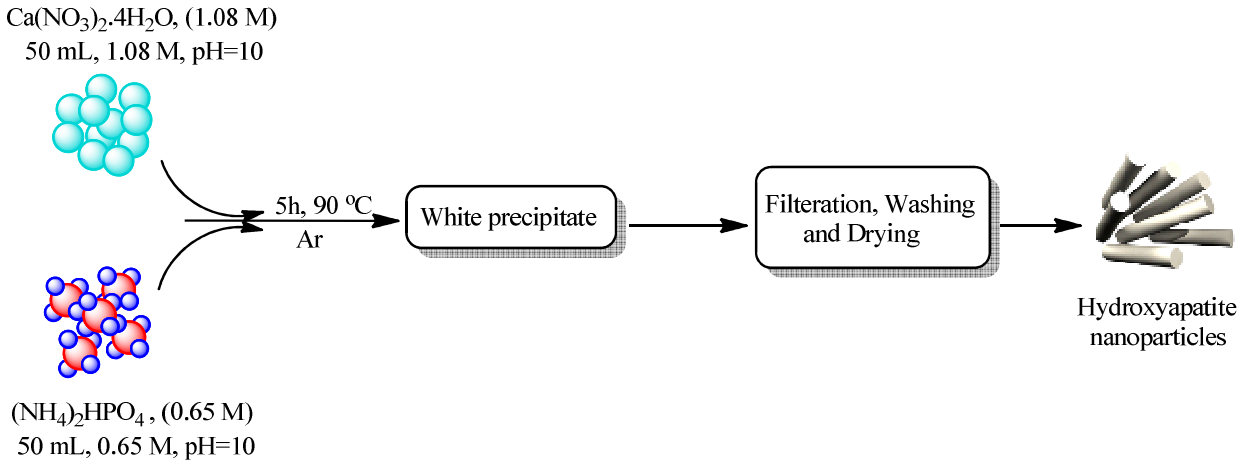
In recent years, HAP has attracted considerable interest in many areas. HAP as the main component of hard tissues of vertebrates such as bones and teeth has properties such as ion-exchange ability, adsorption capacity, acid-base properties and efficient catalytic activity in organic reactions. The small size of HAP NPs as one of the important biocompatible and bioactive material with higher surface area and lower particle size can provide greater catalytic activity in organic synthesis. However, few common applications as catalyst or catalyst support have emerged so far.[39]

In the present study, we would like to report a new application of HAP NPs, as an inexpensive, non-toxic, non-inflammatory, green heterogeneous catalyst for three-component one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in aqueous media.

Results and Discussion

Synthesis and characterization of HAP NPs

Following our interest in development of efficient and environmentally benign heterogeneous catalysts in organic transformation,[40] in this research, initially, HAP NPs was simply synthesized according to the method reported previously (Scheme 1).[41]



Scheme 1 Preparation of HAP NPs.

The nano catalyst was characterized by the following techniques: FT-IR spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM-EDS) and transmission electron microscopy (TEM).

The FT-IR spectrum of HAP NPs is shown in Figure 1. Broad bands centered at 3421 and 1649 cm^{-1} are due to stretching and bending vibrations of molecularly adsorbed water. Also, the stretching vibration around 3570 cm^{-1} confirms the presence of hydroxyl groups. The absorption bands at 1093 ($\nu_{s,\ as}$), 1036 ($\nu_{s,\ as}$), 604 (δ) and 567 (δ) cm^{-1} are attributed to asymmetric stretching and bending vibration frequencies of PO_4^{3-} ion respectively. The symmetric stretching vibrations of the PO_4^{3-} ion were also found at around 962 and 470 cm^{-1}. The above results of FT-IR spectrum suggest that the HAP NPs were synthesized successfully.

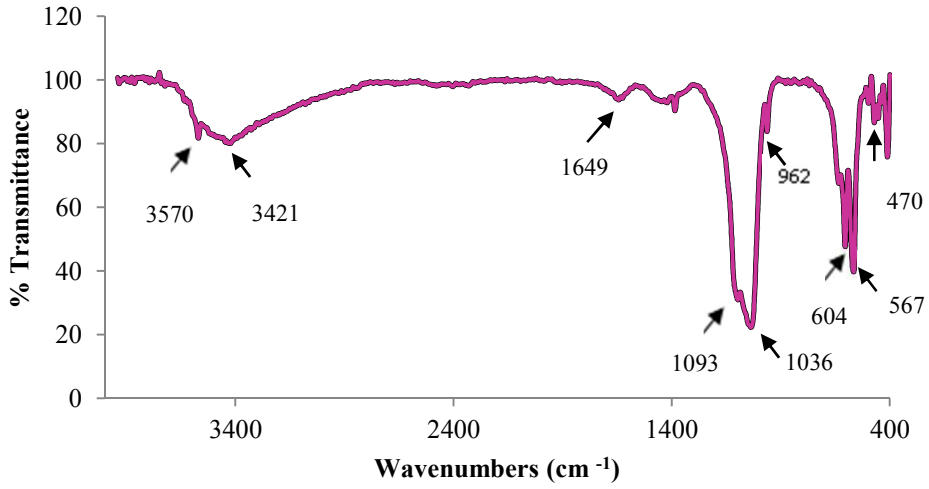


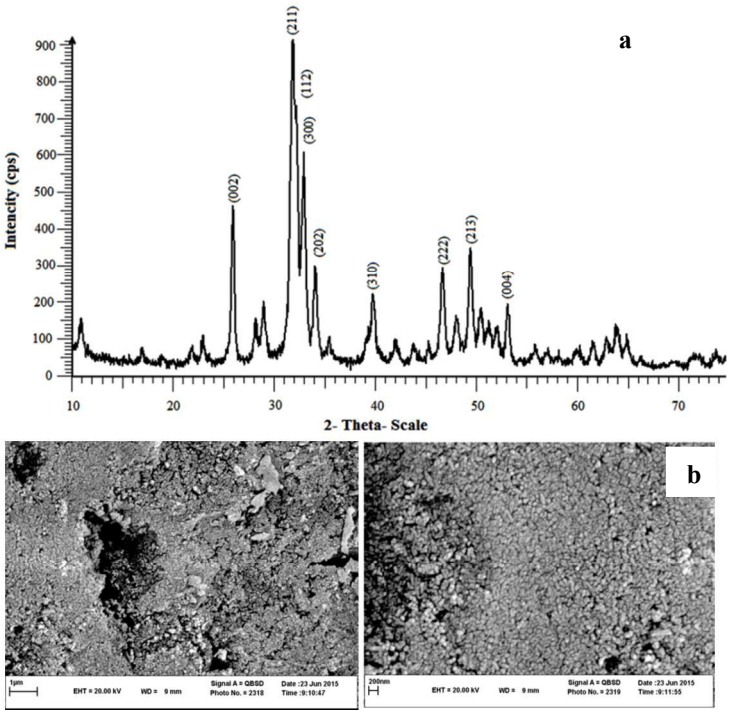
Figure 1 FT-IR spectrum of HAP NPs.

Figure 2a shows the XRD pattern of HAP NPs. In pattern, well defined Bragg peaks were obtained at specific 2θ angles indicated that nanoparticles were ordered. The diffraction peaks, particularly in the planes (002), (211), (300), (202), (310), (222), (213) and (004) are well-matched to hexagonal phase hydroxyapatite with space group of *P63/m* (JCPDS: 74-0565). The

average crystallite size of HAP NPs were calculated to be 16 nm using the Debye-Scherrer equation d=K $L/\beta\cos(\theta)$.[42]

The structure and morphology of the HAP NPs were further confirmed by scanning electron microscopy (SEM) (Figure 2b). It can be seen that the morphology of the synthesized HAP NPs are nearly nanorod particles. As the shape of the synthesized HAP NPs is not clearly defined in the SEM images (Figure 2b), the transmission electron microscopy (TEM) was recorded to determine the exact size and shape of HAP NPs (Figure 2c). The TEM analysis revealed the synthesized HAP NPs with nanorod shape and particle size of around 10 to 80 nm.

The energy dispersive spectrum (EDS) confirms the presence of Ca, P and O elements in the structure of HAP NPs (Figure 2d).



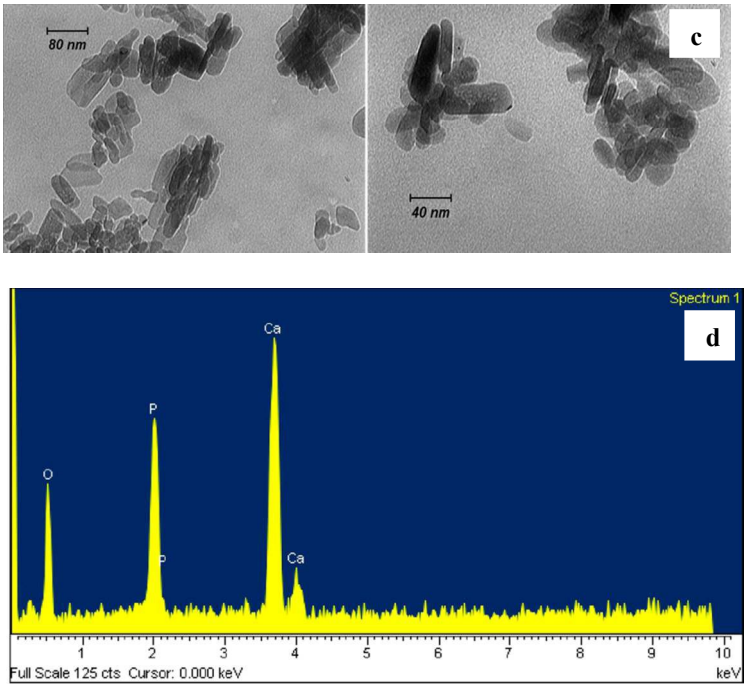
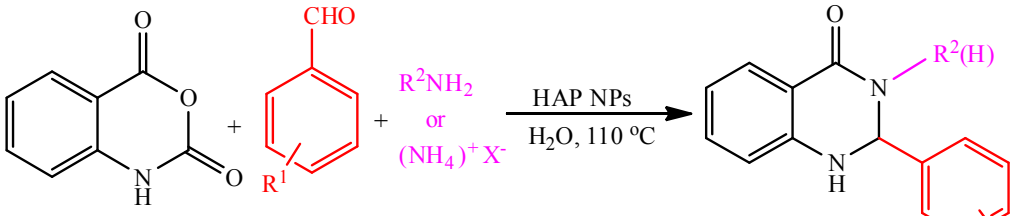


Figure 2 (a) XRD pattern of HAP NPs, (b) SEM images of HAP NPs, (c) TEM images of HAP NPs, (d) The EDS spectrum of HAP NPs.

Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in the presence of HAP NPs

As a result of our great interest in preparation of heterocyclic compounds by applying heterogeneous catalysts,[40 a, b] herein we wish to report an efficient procedure to synthesize 2,3-dihydroquinazolin-4(1*H*)-one derivatives through a three-component one-pot condensation of isatoic anhydride, aromatic aldehyde and primary amines/ or ammonium salts using HAP NPs as catalyst in aqueous media (Scheme 2).



R^1= H, 4-OH, 2-OH, 4-OMe, 3-OMe, 4-Me,4-N(Me)$_2$, 4-Cl, 2,6(Cl)$_2$, 4-Br, 4-CN
R^2= Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4
X= AcO^-, Cl^-, CO_3^{2-}

Scheme 2 Synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives in the presence of HAP NPs in H_2O.

Then, the reaction of isatoic anhydride, benzaldehyde and aniline was chosen a model reaction. Subsequently, to study the effects of solvent, temperature, molar ratios of reactants and the amount of catalyst on the reaction rate and yield, the model reaction was carried out under different conditions. The results are summarized in Table 1. By applying 1:1:1 molar ratio of isatoic anhydride: aniline: benzaldehyde in the absence of catalyst, the yield was poor even for longer time (Table 1, entry 1). Among all the solvents screened, such as EtOH, H_2O/EtOH (1:1), acetonitrile, DMF, 1,4-dioxane, EtOAc, dichloromethane and H_2O, water is the best (Table 1,entries 2-9). The reaction temperature also played an important role in this reaction. Therefore, we tried to optimize the reaction temperature on model reaction. As could be seen on Table 1, at 110ºC, the reaction proceeded quickly in highest yield (Table 1, entries 10, 11). It should be noted that 0.05 g of catalyst was efficient enough to catalyze the reaction, and increasing the amount of catalyst did not improve the yield significantly (Table 1, entry 12). The catalytic effect of HAP NPs was efficiently decreased in solvent free condition (Table 1, entry 14). Additional amounts of aniline or benzaldehyde has not any influence on the reaction rate (Table 1, entries 15-16).

Table 1 Synthesis of 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one in the presence of HAP NPs under different reaction conditions.

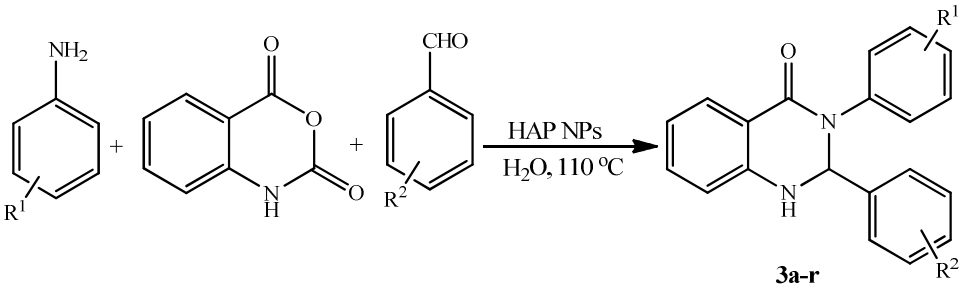
Entry	Molar ratios of isatoic anhydride: aniline: benzaldehyde	Catalyst (g)	Solvent	Temperature (ºC)	Time (h)	Isolated Yield (%)
1	1:1:1	-	H_2O	110	24	20

2	1:1:1	0.05	EtOH	80	3	85
3	1:1:1	0.05	H_2O/ EtOH (1:1)	80	3	80
4	1:1:1	0.05	CH_3CN	80	5	40
5	1:1:1	0.05	DMF	120	6	50
6	1:1:1	0.05	1,4 Dioxane	101	6	20
7	1:1:1	0.05	EtOAc	77	5	60
8	1:1:1	0.05	CH_2Cl_2	40	6	10
9	1:1:1	0.05	H_2O	100	3	85
10	1:1:1	0.05	H_2O	110	1	95
11	1:1:1	0.05	H_2O	120	1	95
12	1:1:1	0.1	H_2O	110	1	95
13	1:1:1	0.025	H_2O	110	4	80
14	1:1:1	0.05	-	110	6	60
15	1:1.2:1	0.05	H_2O	110	1	95
16	1:1:1.2	0.05	H_2O	110	1	95

Encouraged by the initial success in the production of 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one via the multicomponent reaction strategy, to investigate the general scope and versatility of this method in the preparation of substituted 2,3-dihydroquinazolin-4(1*H*)-one derivatives, isatoic anhydrides, different substituted amines and aldehydes were examined under optimized conditions. Condensation of aniline with commercially available aromatic aldehydes having electron-donating and electron withdrawing substituents produced 3a-l in high yields (Table 2, entries 1-12). According to the results, aldehydes bearing electron-donating groups

produced the desired products more quickly than the aldehydes with electron-withdrawing groups. Though *meta*- and *para* substituted aromatic aldehydes reacted quickly, *ortho*-substituted aromatic aldehydes give product in longer reaction time (Table 2, entry 9, 10). Subsequently, the substrate scope of amines was examined for this three-component reaction. From Table 2, it can be observed that in the condensation reaction of substituted anilines with aromatic aldehydes the nature of substituent on the aromatic ring of amines has no noticeable effect on the reaction rate as the corresponding products were obtained in high yields and in short reaction times (Table 2, entries 13-15). Excitingly, the results shown in Table 2 confirm that the reaction was compatible successfully with a broad range of substituents (both electron-donating and electron-withdrawing groups) in the amines or the aldehydes.

Table 2 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by HAP NPs.

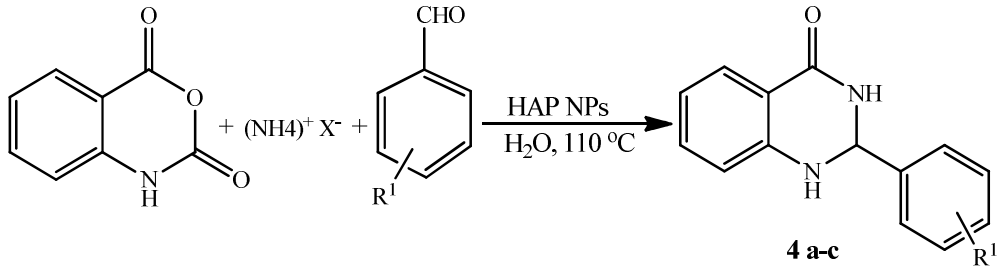


Entry	R^1	R^2	Product	Time(min)	Isolated Yield (%)
1	H	H	3a	60	95
2	H	4-OH	3b	30	90
3	H	2-OH	3c	30	90
4	H	4-OMe	3d	30	95

5	H	3-OMe	3e	30	90
6	H	4-Me	3f	30	95
7	H	$N(Me)_2$	3g	30	87
8	H	4-Cl	3h	60	85
9	H	$2,6\text{-}(Cl)_2$	3i	180	85
10	H	5-Br-2-OH	3j	60	90
11	H	4-Br	3k	60	90
12	H	4-CN	3l	60	90
13	4-Me	H	3m	30	85
14	4-Cl	H	3n	30	90
15	4-Br	H	3o	30	90
16	4-Me	4-Me	3p	40	80
17	4-Me	4-OMe	3q	45	75
18	4-Br	4-Me	3r	60	85

As some ammonium salts are the source of ammonia in the synthesis of nitrogen containing heterocyclic compounds, 2,3-dihydroquinazolin-4(1*H*)-ones derivatives were prepared under the optimal reaction conditions with different ammonium sources such as acetate, chloride and carbonate (Table 3). Accordingly, the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones (4a-c) were synthesized efficiently in the presence of HAP NPs. In comparison, under the same reaction conditions ammonium acetate was reacted more quickly with isatoic anhydride and aldehyde than ammonium chloride and ammonium carbonate.

Table 3 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives using ammonium salts in the presence of HAP NPs.



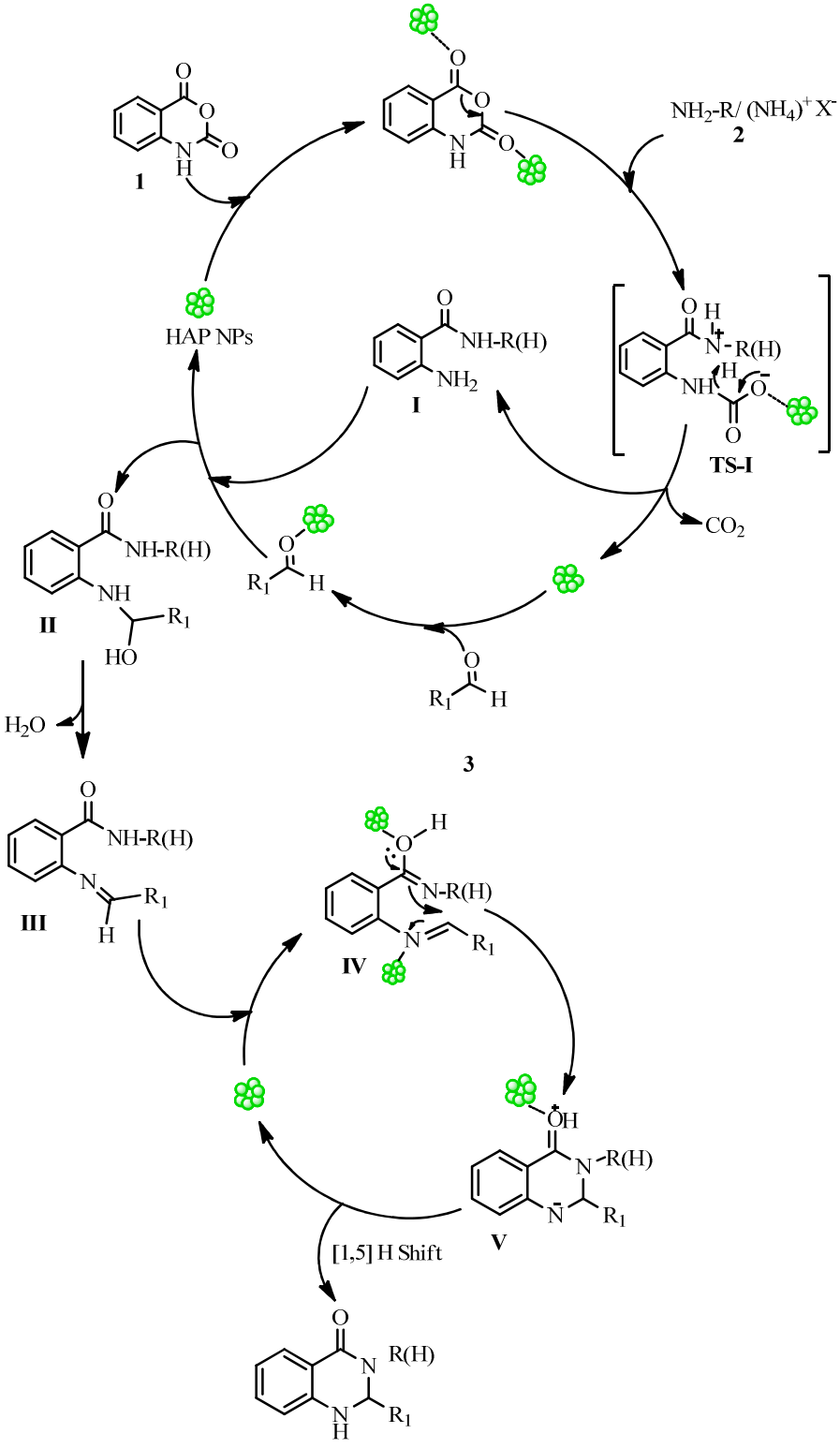
Entry	Ammonium salts	R^1	Product	Time (min)	Isolated Yield (%)
1	NH_4OAc	H	4a	60	90
2	NH_4Cl	H	4a	90	85
3	$(NH_4)_2CO_3$	H	4a	90	80
4	NH_4OAc	4-Me	4b	45	90
5	NH_4OAc	4-Cl	4c	60	85
6	NH_4Cl	4-Cl	4c	120	80

All known products were characterized by comparing their physical data and ^1H and ^{13}C NMR spectra with those of authentic samples reported in the literature. Also, most of the known products were characterized by FT-IR spectroscopy, mass spectrometry and elemental analysis. The data for novel compounds (Table 2, 3j and 3r) are reported in this paper.

In the FT-IR spectra of compounds 3a-r, the strong and sharp absorption bands due to NH and C=O groups were observed around 3379- 3282 cm^{-1} and 1655-1608 cm^{-1} respectively. Moreover, absorption bands at 3312-3303 and 3192-3187 cm^{-1} in the FT-IR spectra of compounds 4a-c can be attributed to stretching vibrations of NH and NH-CO respectively. Also, in the ^{1}HNMR spectra, the NH proton of dihydroquinazolin ring, appeared as a broad signal at

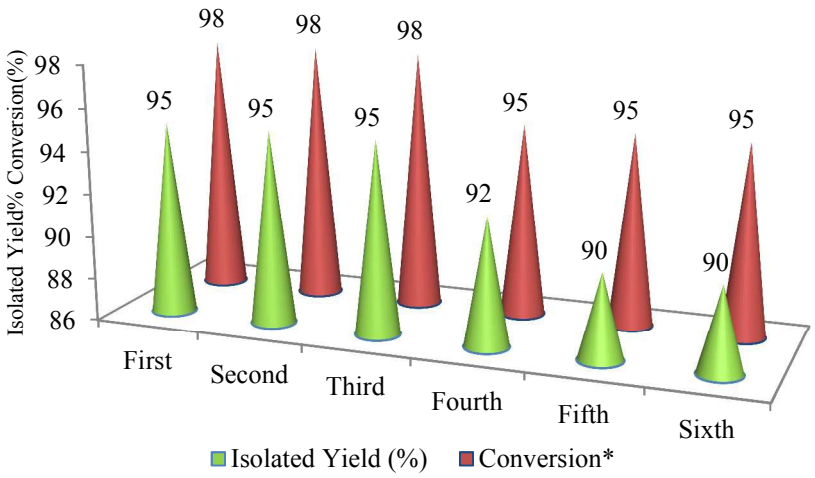
8.36-7.03 ppm. ^{13}C NMR spectra show a signal at 171-162 ppm which assigned to C=O group that confirmed the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

On the basis of our experimental results and by referring to the literature,[23, 31, 32] the plausible following mechanism was proposed to account the condensation of isatoic anhydride and aromatic aldehydes with primary amines/ or ammonium salts catalysed by HAP NPs (Scheme 3). The question is how this catalyst operates? Evidently, HAP NPs function as a good Lewis acid, which in the initial step attracts and activates the isatoic anhydride (**1**) by coordination with carbonyl groups and provides active sites on which the reaction occurs successively leading to the desired product. The nucleophilic attack of primary amine/ or ammonium salt (**2**) to carbonyl group followed by extrusion of CO_2 results the formation of intermediate **I**. HAP NPs also promote the condensation of **I** with aldehyde (**3**) which produces an imine intermediate **III**. An intramolecular nucleophilic attack of the amide nitrogen to imine, which is catalysed by HAP NPs, produces cyclized intermediate **V** which upon 1,5-proton transfer leads to formation of 2,3-dihydroquinazolin-4(1*H*)-ones. Finally, HAP NPs re-enter to the catalytic cycle. Nevertheless, at this time there is no experimental evidence for the formation of the above mentioned intermediates in this manner, and further studies to elucidate the details of the mechanism are ongoing.



Scheme 3 Plausible reaction pathway catalysed by HAP NPs.

To investigate the reusability of HAP NPs, after initial experimentation, the catalyst was recovered by centrifugation, washed with hot ethanol, dried under vacuum at 50 ºC and subjected to second run (Figure 3). The results of this experiment and five subsequent experiments were almost consistent in yields (95, 95, 95, 92, 90, 90 %). Although slightly more time was required to complete the reaction in the sixth run, the yields are comparable to those seen earlier.



* The data referred to conversion of benzaldehyde.

Figure 3 Synthesis 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one in the presence of reused HAP NPs.

Finally, the efficiency of the present protocol was compared with different heterogeneous catalysts reported previously in literature. The results are shown in Table 4. It can be seen from Table 4, that the green nano catalyst gives better yield in shorter reaction time than the other heterogeneous catalysts.

Table 4 Comparison of catalytic activity between HAP NPs and other reported catalysts.

Entry	Catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)	Reference
1	$Ga(OTf)_3$	EtOH	70	60	79	23
2	$KAl(SO_4)_2.12H_2O$	H_2O	reflux	60	65	24
3	Nano-indium oxide	EtOH/H_2O (1/2)	80	320	87	32
4*	PTA@DEAEC	EtOH	reflux	360	79	28
5	Silica sulfuric acid	EtOH	reflux	390	80	19
6	Nano Fe_3O_4	H_2O	reflux	120	80	31
7	$SrCl_3.6H_2O$	EtOH/H_2O (1/3)	reflux	90	94	29
8	Hydroxypatite nanoparticles (HAP)	H_2O	110	60	95	present study

*Powdered diethylaminoethyl cellulose as biomass-derived support for phosphotungstic acid.

Conclusion

In summary, we have described for the first time, a successful strategy for the efficient and convenient preparation of substituted 2,3-dihydroquinazolin-4(1*H*)-one derivatives using HAP NPs as a catalyst in water by the multi-component one-pot condensation of isatoic anhydride with amines/ or ammonium salts and aldehydes. The novelty and synthetic valuability of this methodology developed the mild reaction conditions, avoiding the use of organic solvents, easy experimental procedure, ease of product isolation, and recovery of the catalyst for at least six runs without any significant impact on the yield of the products. These conditions may be ideally suited for an effective synthesis on a larger scale.

Experimental

General

The purity determinations of the products were accomplished by thin layer chromatography (preparative TLC was carried out using a Merck GF 254 silica gel on a glass support). The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus. The FT-IR spectra were recorded on an Avatar 370 FT-IR Therma Nicolet spectrometer. The NMR spectra were provided on Brucker Avance 300, 400 and 500 MHz instruments in DMSO-d_6 and $CDCl_3$. Elemental analyses were performed using a Thermo Finnegan Flash EA 1112 Series instrument. Mass spectra were recorded with a CH7A Varianmat Bremem instrument at 70 eV; in m/z (rel %). Transmission electron microscopy (TEM) was performed with a Leo 912 AB (120 kV) microscope (Zeiss, Germany). Elemental compositions were determined with a Leo 1450 VP scanning electron microscope equipped with an SC7620 energy dispersive spectrometer (SEM-EDS) presenting a 133 eV resolution at 20 kV. The crystal structure of catalyst was analyzed by X-ray diffraction (XRD) with a Bruker D8 ADVANCE diffractometer using a Cu target (λ= 1.54 Å). All yields refer to isolated products after purification by recrystallization or thin layer chromatography.

Preparation of HAP NPs

To a solution of $Ca(NO_3)_2$ .4 H_2O (50 mL, 1.08 M , at pH adjusted to 10 with NH_4OH) in a three-necked 500 mL round-bottomed flask equipped with condenser, argon gas inlet tube and dropping funnel, solution of $(NH_4)_2HPO_4$ (50 mL , 0.65 M at pH adjusted to 10 with NH_4OH) was added at 90 °C with stirring. After 5h the suspension was centrifuged at 10,000 rpm for 10 min and washed repeatedly with CO_2-free distilled water (3×20 mL). HAP NPs were dried at 50°C under vacuum for 12h.[41]

Typical procedure for synthesis of 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one

HAP NPs (0.05 g) was added to a mixture of isatoic anhydride (1 mmol, 0.163 g), benzaldehyde (1 mmol, 0.106 g) and aniline (1 mmol, 0.093 g) in H_2O (5 mL). The mixture was stirred for 1h at 110 °C. The progress of reaction was monitored by TLC (EtOAc: petroleum ether, 1:2). After completion of the reaction, the nano catalyst was separated by centrifugation. The mixture was extracted by ethyl acetate (3×3 mL). The organic layer was dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure to give the crude product. Pure product was obtained by recrystallization from ethanol obtaining 0.285 g of white solid (95% yield).

2,3-Diphenylquinazolin-4(1*H*)-one (3a):[31] white solid; mp 205-206 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3294 (NH), 3064, 3031, 2917, 2827, 2761, 1634 (CO), 1613, 1510, 1488, 1454, 1390, 1358, 1311, 1248, 1159, 1025, 923, 868, 808, 751, 695, 620, 542, 506; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.27 (s, 1H, CH), 6.77-6.70 (m, 2H, Ph), 7.50-7.08 (m, 8H, Ph), 7.73-7.69 (m, 3H), 7.90 (d, *J*= 11.7 Hz, 2H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 73.7, 115.6, 115.7, 123.9, 125.9, 126.4, 126.6, 127.0, 128.5, 128.7, 129.3, 130.1, 134.1, 137.3, 141.1, 146.0, 168.4; MS, *m/z* (%): 300 [3, M^+], 195 [32, M^+-105], 119 [42, M^+-181].

2-(4-Hydroxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3b):[43] white solid; mp 228-229 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3330 (NH), 3210, 3056, 3031, 2835, 2810, 1608 (CO), 1568, 1501, 1453, 1413, 1272, 1222, 1167, 1153, 1115, 874, 835, 757, 697, 608, 531, 489; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.16 (s, 1H, CH), 6.64-6.77 (m, 4H, Ph), 7.16-7.34 (m, 8H, Ph), 7.50 (1H, br s, NH), 7.72 (dd, *J*= 7.5 Hz, *J*= 1.2 Hz, 1H, Ph), 9.49 (1H, br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 72.5, 114.6, 114.9, 115.2, 117.2, 125.9, 126.5, 127.8, 127.9, 128.4, 130.8, 133.6, 140.8, 146.7, 157.3, 162.3; MS, *m/z* (%):316 [40, M^+], 223 [84, M^+-93].

2-(2-Hydroxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3c):[43] white solid; mp 199-201 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3294 (NH), 3231, 3068, 2925, 2839, 1613 (CO), 1487, 1396,

1352, 1296, 1233, 1158, 1109, 1029, 845, 790, 751, 696, 629, 551, 527; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 6.39 (s, 1H, CH), 6.71 (t, *J*= 7.4 Hz, 2H, Ph), 6.81 (dd, *J*= 11.2 Hz, *J*= 8.8 Hz, 2H, Ph), 7.09 (t, *J*= 7.6 Hz, 1H, Ph), 7.17 (d, *J*= 13.3 Hz, 2H, Ph), 7.30-7.20 (m, 4H, Ph), 7.33 (t, *J*= 7.5 Hz, 2H, Ph), 7.76 (d, *J*= 7.6 Hz, 1H, NH), 10.01 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 68.1, 114.9, 114.9, 115.5, 117.3, 118.6, 126.0, 126.1, 126.6, 127.8, 128.5, 129.3, 133.5, 140.8, 146.6, 154.1, 162.5; MS, *m/z* (%):316 [2.5, M^+], 223 [100, M^+-93], 119 [32, M^+-197].

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3d):[43] white solid; mp 201-203 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3297 (NH), 3064, 3015, 2933, 2839, 1634 (CO), 1611, 1589, 1509, 1488, 1390, 1300, 1250, 1170, 1111, 1029, 874, 835, 750, 695, 604, 552; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 3.68 (s, 3H, OCH_3), 6.21 (s, 1H, CH), 6.86-6.77 (m, 2H, Ph), 7.35-7.09 (m, 5H, Ph), 7.49-7.44 (m, 3H, Ph), 7.90-7.69 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 55.4, 72.9, 114.1, 115.0, 115.4, 115.6, 117.8, 127.0, 127.2, 128.3, 128.8, 133.9, 134.0, 141.2, 147.2, 156.6, 163.2; MS, *m/z* (%):330 [7, M^+], 236 [100, M^+-93], 120 [33, M^+-210].

2-(3-Methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3e):[44] white solid; mp 187-189 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3290 (NH), 3011, 2933, 2843, 1637 (CO), 1610, 1503, 1489, 1395, 1319, 1263, 1172, 1155, 1033, 874, 799, 771, 760, 701, 534; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 3.68 (3H, OCH_3), 6.25 (s, 1H, CH), 6.70-6.85 (m, 3H, Ph), 6.94-6.95 (m, 2H, Ph), 7.18-7.38 (m, 7H, Ph), 7.65 (1H, br s, NH), 7.72 (dd, *J*= 7.8 Hz, *J*= 1.2 Hz, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 54.4, 73.1, 112.9, 113.7, 115.8, 118.5, 125.7, 126.0, 127.1, 127.8, 128.0, 130.7, 132.7, 139.3, 144.4, 158.9, 162.3; MS, *m/z* (%):330 [5, M^+], 236 [100, M^+-93], 119 [46, M^+-211].

2-(4-Methylphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3f):[31] white solid; mp 214-215; FT-IR (KBr): ν_{max}/cm^{-1} 3298 (NH), 3060, 2921, 2823, 1635 (CO), 1612, 1507, 1489, 1393, 1311, 1249, 1159, 1111, 1025, 874, 820, 750, 695, 604, 547, 481; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.25 (s, 3H, CH_3), 6.16 (d, *J*= 2.7 Hz, 1H, CH), 6.86-6.70 (m, 4H, Ph), 7.29-7.11 (m, 8H, Ph), 7.51 (1H, br s, NH), 7.70 (d, *J*= 11.4 Hz, 1H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 20.6, 75.8, 110.1, 115.2, 122.5, 123.4, 123.7, 125.3, 127.5, 128.0, 128.8, 129.6, 132.4, 136.8, 137.7, 141.3, 144.1, 146.9, 171.5; MS, *m/z* (%): 314 [46, M^+], 221 [100, M^+-93], 119 [65, M^+-195].

2-(4-(Dimethylamino)phenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3g):[45] white solid; mp 183-184 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3297 (NH), 3056, 2990, 2888, 2802, 1634 (CO), 1611, 1523, 1504, 1441, 1394, 1347, 1188, 1160, 1049, 947, 878, 823, 756, 694, 604, 549; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.83 (s, 6H, CH_3), 6.13 (s, 1H, CH), 6.60-6.63 (m, 2H, Ph), 6.68-6.76 (m, 2H, Ph), 7.16-7.35 (m, 8H, Ph), 7.72 (dd, *J*= 7.8 Hz, *J*= 1.2 Hz, 1 H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 72.9, 73.0, 112.2, 115.1, 115.8, 117.7, 126.3, 126.6, 127.8, 128.2, 128.3, 129.0, 134.0, 141.4, 147.1, 147.2, 150.6, 162.8; MS, *m/z* (%): 343 [3, M^+], 221 [74, M^+-122], 119 [67, M^+-224].

2-(4-Chlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3h):[34] white solid; mp 219-220 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3296 (NH), 3064, 2937, 2814, 2753, 1633 (CO), 1613, 1508, 1488, 1414, 1390, 1312, 1249, 1159, 1088, 1014, 869, 832, 754, 694, 587, 543, 516; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.33 (s, 1H, CH), 6.72-6.80 (m, 2H, Ph), 7.18-7.43 (m, 10H, Ph), 7.67 (1H, br s, NH), 7.72 (dd, *J*= 7.8 Hz, *J*= 1.2 Hz, 1H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 73.6, 114.2, 115.0, 115.5, 115.6, 117.8, 127.0, 127.2, 128.6, 128.8, 133.8, 134.0, 141.2, 147.1, 162.8; MS, *m/z* (%): 336 [3, M^++2], 334 [28, M^+], 241 [86, M^+-93], 222 [75, M^+-112].

2-(2,6-Dichlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3i):[46] white solid; mp 234-236 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3282 (NH), 3064, 1630 (CO), 1533, 1490, 1439, 1414, 1342, 1315, 1249, 1194, 1127, 865, 784, 749, 697, 518; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.65 (d, *J*= 8.1 Hz, 1H, Ph), 6.69 (s, 1H, CH), 7.14-7.41 (m, 10H, Ph), 7.67 (dd, *J*= 7.8 Hz, *J*= 1.2 Hz, 1H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6+$CDCl_3$, ppm) δ 69.2, 114.1, 114.4, 117.5, 125.4, 125.8, 126.4, 127.3, 127.9, 128.1, 128.6, 131.6, 132.9, 133.8, 135.0, 139.3, 144.6, 161.9; MS, *m/z* (%): 371 [30, M^++2], 369 [85, M^+], 222 [100, M^+-147], 120 [40, M^+-249].

2-(5-Bromo-2-hydroxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3j): white solid; mp 208-210 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3379 (NH), 3141, 2937, 2708, 2573, 1632 (CO), 1609, 1491, 1441, 1405, 1322, 1271, 1247, 1227, 1110, 1077, 922, 856, 816, 762, 702, 619, 525; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.38 (s, 1H, CH), 6.83-6.72 (m, 3H, Ph), 7.38-7.19 (m, 8H, Ph), 7.77 (dd, *J*= 7.8 Hz, *J*= 1.2 Hz, 1H, Ph), 10.37 (1H, br s, OH); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 68.2, 68.3, 110.3, 115.2, 115.3, 118.1, 118.2, 126.5, 126.7, 128.3, 129.0, 129.2, 129.7, 132.6, 134.3, 141.0, 146.9, 154.0, 154.2, 162.9; MS, *m/z* (%): 397 [5, M^++2], 395 [41, M^+], 222 [64, M^+-1173], 120 [44, M^+-275]; Anal. Calcd for $C_{20}H_{15}Br\ N_2O_2$. Calcd. C, 60.78; H, 3.83; N, 7.09; O, 8.10. Found, C, 60.56; H, 3.58; N, 6.85; O, 7.9 %.

2-(4-Bromophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3k):[31] white solid; mp 222-223 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3295 (NH), 3058, 3031, 2941, 2831, 2745, 1634 (CO), 1609, 1585, 1486, 1412, 1388, 1312, 1248, 1158, 1113, 1070, 1009, 910, 871, 827, 752, 694, 623, 542, 513; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.30 (d, *J*= 3.6 Hz, 1H, CH), 6.78-6.69 (m, 2H, Ph), 7.38-7.16 (m, 8H, Ph), 7.53-7.49 (m, 2H, Ph), 7.74-7.65 (m, 2H), ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 72.4, 115.3, 115.7, 118.1, 121.1, 121.9, 126.6, 128.4, 129.1, 129.2, 131.7, 134.2, 140.5,

141.0, 146.8, 162.5; MS, *m/z* (%): 381 [5, M^++2], 379 [95, M^+], 286 [96, M^+-93], 222 [95, M^+-157].

2-(4-Cyanophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3l):[31] white solid; mp 203-204 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3310 (NH), 3051, 2937, 2228 (CN), 1641 (CO), 1617, 1490, 1443, 1395, 1323, 1238, 1188, 1151, 1082, 914, 820, 761, 746, 697, 582, 530; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.045 (s, 1H, NH), 6.12 (s, 1H, CH), 6.66 (d, *J*= 8 Hz, 1H, CH), 6.93-6.85 (m, 1H, Ph), 7.34-7.06 (m, 6H, Ph), 7.47 (d, *J*= 8 Hz, 2H, Ph), 7.55 (d, *J*= 8 Hz, 2H, Ph), 7.99 (d, *J*= 7.6 Hz, 1H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 73.7, 112.8, 115.3, 117.1, 118.1, 120.2, 126.5, 127.1, 127.5, 129.1, 129.2, 132.5, 134.2, 140.2, 144.6, 145.0, 162.7; MS, *m/z* (%): 325 [2, M^+], 221 [87, M^+-104], 119 [66, M^+-206].

3-(4-Methylphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3m):[34] white solid; mp 198-199 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3298 (NH), 3060, 3035, 2921, 2835, 1635 (CO), 1611, 1511, 1486, 1455, 1395, 1334, 1313, 1241, 1157, 1111, 1029, 878, 821, 753, 699, 604, 516; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.26 (s, 3H, CH_3), 6.24 (s, 1H, CH), 6.77-6.69 (m, 2H, Ph), 7.39-7.11 (m, 10H, Ph), 7.72 (dd, *J*= 7.8 Hz, *J*= 1.5 Hz, 1H, Ph); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 20.6, 72.8, 114.8, 115.4, 117.5, 126.2, 126.6, 128.0, 128.3, 128.4, 129.2, 133.8, 135.4, 138.3, 140.8, 146.6, 162.3.

3-(4-Chlorophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3n):[31] white solid; mp 216-217 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3298 (NH), 3063, 3035, 2945, 2839, 2753, 1633 (CO), 1608, 1510, 1490, 1453, 1392, 1314, 1249, 1158, 1089, 1017, 869, 821, 754, 700, 630, 506, 438; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 6.22 (d, *J*= 3.0 Hz, 1H, CH), 6.68-6.61 (m, 2H, Ph), 7.29-7.16 (m, 10H, Ph), 7.57 (1H, br s, NH), 7.63 (d, *J*= 7.8 Hz, 1H, Ph); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ 72.9, 115.2, 115.4, 118.0, 122.1, 127.1, 128.4, 128.5, 128.7, 128.8, 128.9,

130.5, 134.3, 139.9, 140.7, 147.1, 162.8; MS, *m/z* (%): 334 [5, M^+], 254 [40, M^+-80], 206 [98, M^+-128].

3-(4-Bromophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3o):[31] white solid; mp 228-229 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3300 (NH), 3056, 3035, 2929, 2831, 1633 (CO), 1609, 1578, 1510, 1487, 1456, 1389, 1314, 1250, 1159, 1067, 1012, 872, 820, 789, 755, 701, 627, 562, 506; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.31 (d, *J*= 3.6 Hz, 1H, CH), 6.78-6.69 (m, 2H, Ph), 7.37-7.15 (m, 8H, Ph), 7.51- 7.50 (m, 2H, Ph), 7.74-7.64 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 72.7, 115.3, 115.7, 118.1, 121.1, 121.9, 126.6, 128.4, 129.1, 129.2, 131.7, 134.3, 140.5, 141.0, 146.9, 162.6; MS, *m/z* (%): 379 [30, M^+], 300 [77, M^+-79], 206 [100, M^+-173].

2,3-Di(4-methylphenyl)-2,3-dihydro-quinazolin-4(1*H*)-one (3p):[47] white solid; mp 242-243 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3297 (NH), 3060, 3039, 2962, 2933, 2835, 2757, 1637 (CO), 1609, 1510, 1484, 1439, 1391, 1300, 1245, 1157, 1107, 1028, 874, 820, 784, 753, 694, 602, 549, 515; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.26 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 6.17 (s, 1H, CH), 6.72-6.76 (m, 2H, Ph), 6.83 (d, *J*= 3 Hz, 1H, Ph), 6.87 (d, *J*= 2.7 Hz, 1H, Ph), 7.30-7.12 (m, 7H, Ph), 7.71 (dd, *J*= 7.8 Hz, *J*= 1.2 Hz, 1H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 21.0, 73.2, 115.1, 115.2, 115.8, 117.9, 126.6, 127.0, 128.6, 128.7, 128.8, 129.5, 134.1, 135.7, 138.7, 141.2, 146.9, 147.0, 162.7.

2-(4-Methoxyphenyl)-3-(*p*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (3q):[31] white solid; mp 247-249 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3297 (NH), 3060, 3032, 2964, 2836, 2761, 1637 (C=O), 1609, 1510, 1484, 1439, 1391, 1300, 1245, 1157, 1107, 1028, 882, 820, 784, 753, 695, 656, 602, 549, 515; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.25 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.16 (d, *J*= 2.7 Hz, 1H, CH), 6.86-6.70 (m, 4H, Ph), 7.29-7.11 (m, 7H, Ph), 7.50 (1H, br s, NH), 7.70 (d, *J*= 11.4 Hz, 1H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 20.6, 55.4, 72.4, 110.1, 115.3,

122.5, 123.5, 123.7, 125.3, 127.5, 128.0, 128.8, 129.6, 132.5, 136.8, 137.6, 141.3, 144.2, 146.8, 158.7, 171.3; MS, *m/z* (%): 344 [3, M^+], 236 [100, M^+-108], 91 [45, M^+-239].

3-(4-Bromophenyl)-2-(*p*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (3r): white solid; mp 247-249 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3306 (NH), 3051, 2945, 2921, 2827, 1634 (CO), 1608, 1580, 1507, 1487, 1386, 1332, 1315, 1250, 1159, 1070, 1012, 874, 820, 752, 752, 489; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.23 (s, 3H, CH_3), 6.26 (s, 1H, CH), 6.70-6.78 (m, 2H, Ph), 7.11 (d, *J*= 8.1 Hz, 2H, Ph), 7.21-7.31 (m, 5H, Ph), 7.51 (d, *J*= 8.4 Hz, 2H, Ph), 7.63 (1H, br s, NH), 7.72 (d, *J* = 7 Hz, 1H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 21.0, 72.6, 72.7, 115.2, 115.3, 115.5, 118.0, 118.9, 127.0, 128.4, 128.7, 129.4, 131.9, 134.3, 137.8, 138.2, 140.4, 147.0, 147.1, 162.8; MS, *m/z* (%): 393 [87, M^+];300 [70, M^+-93], 220 [100, M^+-173]; Anal. Calcd for $C_{22}H_{20}N_2O_2$. Calcd. C, 76.72; H, 5.85; N, 8.13; O, 9.29. Found, C, 76.42; H, 5.53; N, 7.88; O, 9.03 %.

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (4a):[30] white solid; mp 223-224 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3303 (NH), 3187 (NH), 3129, 3060, 3031, 2941, 2802, 2708, 1655 (CO), 1613, 1511, 1483, 1439, 1390, 1300, 1237, 1148, 1029, 914, 861, 810, 748, 699, 663, 641, 529, 489; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 5.76 (s, 1H, CH), 6.67 (t, *J*= 7.6 Hz, 1H, Ph), 6.75 (d, *J*= 8.0 Hz, 1H, Ph), 7.12 (s, 1H, NH), 7.24 (t, *J*= 7.6 Hz, 1H, Ph), 7.41-7.34 (m, 3H, Ph), 7.50 (d, *J*=7.6 Hz, 2H, Ph), 7.61 (d, *J*= 7.6 Hz, 1H, Ph), 8.30 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 66.5, 114.4, 114.9, 117.1, 126.9, 127.4, 128.3, 128.5, 133.3, 141.6, 147.9, 163.6; MS, *m/z* (%): 224 [5, M^+], 146 [100, M^+-78], 119 [87, M^+-105].

2-(*p*-Tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (4b):[30] white solid; mp 228-230 ºC; FT-IR (KBr): ν_{max}/cm^{-1} 3312 (NH), 3192 (NH), 3133, 3062, 2941, 2851, 1658 (CO), 1609, 1564, 1509, 1484, 1441, 1385, 1298, 1245, 1150, 1131, 1020, 943, 822, 771, 751, 685, 656, 611, 530, 503, 424; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 2.29 (s, 3H, CH_3), 5.70 (s, 1H, CH), 6.75-6.66 (m,

2H, Ph), 7.03 (1H, br s, NH), 7.38-7.16 (m, 5H, Ph), 7.60 (d, *J*= 10.2 Hz, 1H, Ph), 8.21 (1H, br s, NH);[13]C NMR (75 MHz, DMSO-d_6, ppm) δ 21.1, 66.8, 114.8, 115.4, 117.4, 127.2, 127.7, 129.2, 133.6, 138.1, 139.1, 148.3, 164.0; MS, *m/z* (%): 238 [3, M^+], 146 [96, M^+-92], 119 [100, M^+-119].

2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (4c):[30] white solid; mp 206-207 ºC; [1]H NMR (300 MHz, DMSO-d_6, ppm) δ 5.78 (s, 1H, CH), 6.67-6.77 (m, 2H, Ph), 7.17 (1H, br s, NH), 7.26 (t, *J*= 7.8 Hz, 1H, Ph), 7.41-7.61 (m, 4H, Ph), 7.64 (d, *J*= 5.5 Hz, 1H, Ph), 8.36 (1H, br s, NH); [13]C NMR (100 MHz, DMSO-d_6, ppm) δ 65.8, 114.5, 114.9, 117.3, 127.4, 128.3, 128.8, 133.0, 133.4, 140.7, 147.7, 163.5; MS, *m/z* (%): 258 [22, M^+], 146 [100, M^+-112], 120 [97, M^+-138].

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Notes and references

Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad 9177948974, Iran.
[*] *Corresponding author: Phone: +98-51-3880-5527, Fax: +98-51-3879-5457,*
E-mail: akhlaghinia@um.ac.ir

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1. D. A. Erlanson, R. S. McDowell, T. O. Brien, *J. Med. Chem*., 2004, **47**, 3463-3482.
2. H. Wu, X. Xie, G. Liu, *J. Comb. Chem.,* 2010, **12**, 346-355.
3. G. M. Chinigo, M. Paige, S. Grindrod, E. Hamel, S. Dakshanamurthy, M. Chruszcz, W. Minor, M. L. Brown, *J. Med. Chem*., 2008, **51**, 4620-4631.

4. (a) R. J. Alaimo, H. E. Russell, *J. Med. Chem*., 1972, **15**, 335-336; (b) Q. Li, L. A. Mitscher, L. L. Shen, *Med. Res. Rev*., 2000, **20**, 231-293.

5. V. K. Srivastava, A. Kumar, *Eur. J. Med. Chem*., 2002, **37**, 873-882.

6. (a) D. Rambabu, S. Kiran Kumar, B. Yogi Sreenivas, S. Sandra, A. Kandale, P. Misra, M. V. Basaveswara Rao, M. Pal, *Tetrahedron Lett.*, 2013, **54**, 495-501; (b) M. Sharma, K. Chauhan, R. Shivahare, P. Vishwakarma, M. K. Suthar, A. Sharma, S. Gupta, J. K. Saxena, J. Lai, P. Chandra, B. Kumar, P. M. S. Chauhan, *J. Med. Chem*., 2013, **56**, 4374-4392.

7. (a) R. J. Cox, D. O'Hagan, *J. Chem. Soc. Perkin Trans.*, 1991, **1**, 2537-2540.

8. V. J. Ram, B. K. Tripathi, A. K. Srivastava, *Bioorg. Med. Chem*., 2003, **11**, 2439-2444.

9. J. Rudolph, W. P. Esler, S. O'Connor, P. D. G. Coish, P. L. Wickens, M. Brands, D. E. Bierer, B. T. Bloomquist, G. Bondar, L. Chen, C. Y. Chuang, T. H. Claus, Z. Fathi, W. Fu, U. R. Khire, J. A. Kristie, X. G. Liu, D. B. Lowe, A. C. Mcclure, M. Michels, A. A. Ortiz, P. D. Ramsden, R. W. Schoenleber, T. E. Shelekhin, A. Vakalopoulos, W. F. Tang, L. Wang, L. Yi, S. J. Gardell, J. N. Livingston, L. J. Sweet, W. H. Bullock, *J. Med. Chem*., 2007, **50**, 5202-5216.

10. O. I. El-Sabbagh, S. M. Ibrahim, M. M. Baraka, H. Kothayer, *Arch. Pharm*., 2010, **343**, 274-281.

11. E. Hamel, C. M. Lin, J. Plowman, H. Wang, K. Lee, K. D. Paull, *Biochem. Pharmacol*., 1996, **51**, 53-59.

12. V. Dolle, E. Fan, C. H. Nguyen, A. M. Aubertin, A. Kirn, M. L. Andreola, G. Jamieson, L. Tarragolitvak, E. Bisagni, *J. Med. Chem*., 1995, **38**, 4679-4686.

13. S. D. Sharma, V. Kaur, *Synthesis*, 1989, 677-680.

14. (a) D. Q. Shi, L. C. Rong, J. X. Wang, X. S. Wang, S. J. Tu, H. W. Hu, *Chem. J. Chin. Univ*., 2004, **25**, 2051-2054; (b) D. Q. Shi, J. X. Wang, L. C. Rong, Q. Y. Zhuang, S. J. Tu, H. W. Hu, *J. Chem. Res*., 2003, **10**, 671-673; (c) D. Q. Shi, C. L. Shi, J. X. Wang, L. C. Rong, Q. Y. Zhuang, X. S. Wang, *J. Heterocycl. Chem.*, 2005, **40**, 173-183; (d) G. P. Cai, X. L. Xu, Z. F. Li, P. Lu, W. P. Weber, *J. Heterocycl. Chem*., 2002, **39**, 1271-1272.

15. H. Asakawa, M. Matano, *Chem. Pharm. Bull*., 1979, **27**, 1287-1298.

16. (a) C. L. Yoo, J. C. Fettinger, M. Kurth, *J. Org. Chem*., 2005, **70**, 6941-6943; (b) J. Chen, W. Su, H. Wu, M. Liu, C. Jin, *Green Chem*., 2007, **9**, 972-975; (c) X. Cheng, S. Vellalath, R. Goddard, B. List, *J. Am. Chem. Soc*., 2008, **130**, 15786-15787; (d) M. Sharma, S. Pandey, K. Chauhan, D. Sharma, B. Kumar, P. M. S. Chauhan,. *J. Org. Chem*., 2012, **77**, 929-937; (e) M. Prakash, V. Kesavan, *Org. Lett*., 2012, **14**, 1896-1899; (f) M. Narasimhulu, Y. R. Lee, *Tetrahedron*, 2011, **67**, 9627-9634; (g) K. V. Sashidhara, G. R. Palnati, R. P. Dodda, S. R. Avula, P. Swami, *Synlett*, 2013, 1795-1800.

17. (a) W. K. Su, B. B. Yang, *Aust. J. Chem*., 2002, **55**, 695-697; (b) W. K. Su, B. B. Yang, *J. Chem. Res*. *Synop*., 2002, 604-605.

18. A. Ghorbani-Choghamarani, T. Taghipour, *Lett. Org. Chem*., 2011, **8**, 470-476.

19. M. Dabiri, P. Salehi, M. Baghbanzadeh, M. A. Zolfigol, M. Agheb, S. Heydari, *Catal. Commun*., 2008, **9**, 785-788.

20. K. Niknam, N. Jafarpour, E. Niknam, *Chin. Chem. Lett*., 2011, **22**, 69-72.

21. K. Niknam, M. R. Mohammadizadeh, S. Mirzaee, *Chin. J. Chem*., 2011, **29**, 1417-1422.

22. S. Rostamizadeh, A. M. Amani, G. H. Mahdavinia, H. Sepehrian, S. Ebrahimi, *Synthesis*, 2010, 1356-1360.

23. J. X. Chen, D. Z. Wu, F. He, M. C. Liu, H. Y. Wu, J. C. Ding, W. K. Su, *Tetrahedron Lett*., 2008, **49**, 3814-3818.

24. M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary, A. A. Mohammadi, *Tetrahedron Lett*., 2005, **46**, 6123-6126.

25. H. R. Shaterian, A. R. Oveisi, M. Honarmand, *Synth. Commun*., 2010, **40**, 1231-1242.

26. P. Salehi, M. Dabiri, M. Baghbanzadeh, M. Bahramnejad, *Synth. Commun*., 2006, **36**, 2287-2292.

27. S. Allameh, M. M. Heravi, M. M. Hashemi, F. F. Bamoharram, *Chin. Chem. Lett*., 2011, **22**, 131-134.

28. Sh. Li, Q. Zhang, Y. Peng, *Monatsh Chem.,* in press 2015. DOI: 10.1007/s00706-015-1475-y.

29. M. Wang, T. T. Zhang, Y. Liang, J. J. Gao, *Chin. Chem. Lett*., 2011, **22**, 1423-1426.

30. S. Rostamizadeh, A. M. Amani, R. Aryan, H. R. Ghaieni, N. Shadjou, *Synth. Commun.*, 2008, **38**, 3567-3576.

31. Z. H. Zhang, H. Y. Lü, S. H. Yang, J. W. Gao, *J. Comb. Chem*., 2010, **12**, 643-646.

32. S. Santra, M. Rahman, A. Roy, A. Majee, A. Hajra, *Catal. Commun.,* 2014, **49,** 52-57.

33. M. Z. Kassaee, S. Rostamizadeh, N. Shadjou, E. Motamedi, M. Esmaeelzadeh, *J. Heterocycl. Chem.,* 2010, **47**, 1421-1424.

34. B. H. Chen, J. T. Li, G. F. Chen, *Ultrason. Sonochem*., 2015, **23**, 59-65.

35. M. P. Surpur, P. R. Singh, S. B. Patil, S. D. Samant, *Synth. Commun*., 2007, **37**, 1965-1970.

36. J. Safari, S. Gandomi-Ravandi, *J. Mol. Catal. A: Chem*., 2013, **371**, 135-140.

37. (a) J. A. Moore, G. J. Sutherland, R. Sowerby, E. G. Kelly, S. Palermo, W. Webster, *J. Org. Chem*., 1969, **34**, 887-892; (b) J. M. Khurana, G. Kukreja, *J. Heterocycl. Chem*., 2003, **40**, 677-679; (c) Y. S. Sadanandam, R. M. Reddy, A. Bhaskar Rao, *Eur. J. Med. Chem*. 1987, **22**, 169-173.

38. J. T. Li, Y. Yin, M. X. Sun, *Ultrason. Sonochem*., 2010, **17**, 363-366.

39. (a) M. Zahouily, Y. Abrouki, B. Bahlaouan, A. Rayadh, S. Sebti, *Catal Commun*., 2003, **4**, 521-524; (b) Y. Zhang, Y. Zhao, Ch. Xia, *J. Mol. Catal. A: Chem*., 2009, **306**, 107-112.

40. (a) N. Razavi, B. Akhlaghinia, *RSC Adv*., 2015, **5**, 12372-12381; (b) S. S. E. Ghodsinia, B. Akhlaghinia, *RSC Adv*., 2015, **5**, 49849-49860; (c) Z. Zarei and B. Akhlaghinia, *Chem. Pap.*, 2015, **69**, 1421-1437; (d) M. Zarghani, B. Akhlaghinia, *Appl. Organometal. Chem*., 2015, **29**, 683-689; (e) M. Zarghani, B. Akhlaghinia, *RSC Adv*., in press 2015, DOI: 10.1039/C5RA162336J.

41. E. Boanini, M. Gazzano, K. Rubini, A. Bigi, *Adv. Mater*., 2007, **19**, 2499-24502.

42. R. Jenkins, R. L. Snyder, *Chemical Analysis: Introducti on to X-ray Powder Diffractometry*, John Wiley & Sons, Inc., New York, 1996, Vol. 138, p. 89-91.

43. J. Zhang, D. Ren, Y. Ma, W. Wang, H. Wu, *Tetrahedron*, 2014, **70**, 5274-5282.

44. R. Noel, N. Gupta, V. Pons, A. Goudet, M. Garcia-Castillo, A. Michau, J. Martinez, D. Buisson, L. Johannes, D. Gillet, J. Barbier, J. Cintrat, *J. Med. Chem*., 2013 , **56**, 3404-3413.

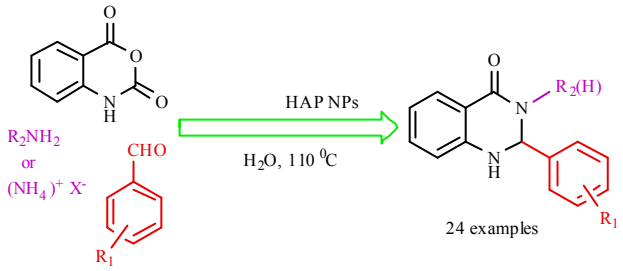
45. L. Wang, L. Hu, J. Shao, J. Yu, L. Zhang, *J. Fluorine Chem*., 2008, **129**, 1139-1145.

46. Z. Karimi-Jaberi, R. Arjmandi, *Monatsh. Chem*., 2011, **142**, 631-635.

47. K. Niknam, M. R. Mohammadizadeh, S. Mirzaee, *Chin. J. Chem*., 2011, **29**, 1417-1422.

Graphical Abstract

Hydroxypatite nanoparticles (HAP NPs): As a green and efficient heterogeneous catalyst for three-component one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in aqueous media



Nasrin Razavi, Batool Akhlaghinia*

HAP NPs were applied as a green heterogeneous catalyst for synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives.
Nanocatalyst was prepared and characterized.