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Green and efficient one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and their anthelmintic studies

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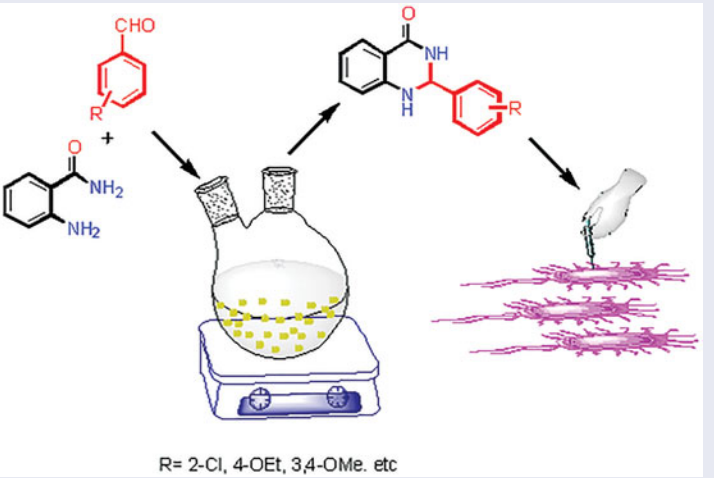
ABSTRACT

A facile and highly efficient one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives has been developed by the condensation of anthranilamide with aldehydes using sulfonic acid functionalized L-Proline@Fe_3O_4 nanoparticles as a catalyst. The advantages of this protocol are easy recovery and reusability of the catalyst besides simple work-up procedure and short reaction time. In addition, the anthelmintic activities of some selective compounds were investigated and it was found that 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one exhibited profound anthelmintic activity against two helminth models.

GRAPHICAL ABSTRACT



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KEYWORDS
2,3-Dihydroquinazolin-4(1H)-ones; anthranilamide; chlorosulfonic acid; functionalized organo-nanocatalyst; magnetic nanocatalyst

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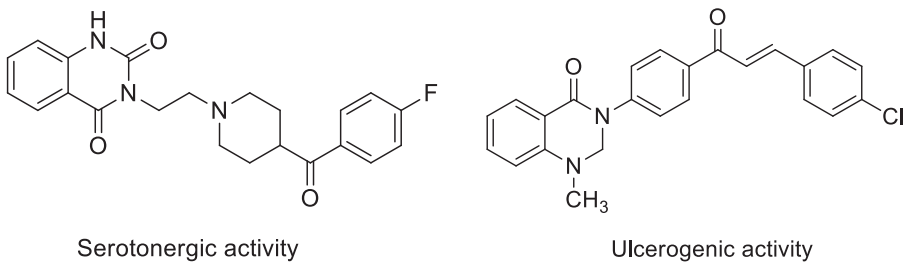
Introduction

The development of a simple, efficient, and environmentally benign process in organic synthesis is in great demand, in recent years. Multicomponent reactions (MCRs) have emerged as an attractive strategy for synthetic chemists, due to the fact that products can be easily obtained in a single step, thereby, reducing the consumption of solvents, catalysts, and energy besides minimizing the generation of waste. In addition, the utilization of a catalyst having high recyclability feature promotes a more economical and environmental friendly benign protocol.

Quinazolinones constitute a very important heterocyclic core in various organic molecules having diverse biological activities. 2,3-dihydroquinazolin-4(1*H*)-ones, in particular, have received notable attention because of their wide range of biological and pharmaceutical activities, such as antifungal,[1] anti-inflamatory,[2] antimicrobial,[3] anticonvulsant,[4] analgesic,[5] antibacterial,[6] anticancer,[7] and diuretic.[8] Some biologically active compounds are shown below, in which (*E*)-3-(4-(3-(4-chlorophenyl)acryloyl)phenyl)-1-methyl-2,3-dihydroquinazolin-4(1*H*)-one exhibited ulcerogenic activity[9] and 3-(2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl)quinazoline-2,4(1*H*,3*H*)-dione (ketanserin) showed a positive serotonergic activity.[10]

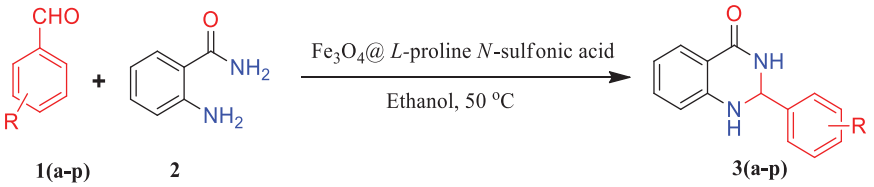


Serotonergic activity Ulcerogenic activity

Biologically active 2,3-dihydroquinazolin-4(1*H*)-ones

Taking into account their biological significance, several strategies have been reported for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. Generally, the simplest and efficient methods for their synthesis involves the cyclo-condensation of 2-aminobenzamide with aromatic aldehydes in presence of various salts such as $CuCl_2$,[11] $InCl_3$,[12] $ZrCl_4$,[13] $TiCl_4$/Zn,[14] NH_4Cl,[15] and acids such as trichloroacetic acid,[16] succinimide-*N*-sulfonic acid,[17] 2-morpholinoethanesulfonic acid,[18] and *p*-toluenesulfonic acid[19] as catalysts.

For green and sustainable approaches, ionic liquids,[20–22] nanocrystalline sulfated zirconia[23] and PEG-400[24] have been employed for the preparation of these derivatives. Organo-catalysts such as L-proline,[25] chiral organo-catalyst,[26] etc. have also been reported for the synthesis of a wide range of 2,3-dihydroquinazolin-4(1*H*)-ones. Lately, organic compound encapsulated on magnetic nanoparticles have received paramount attention, due to the various advantages it offers. Earlier, we have reported the synthesis of magnetic nanoparticles Fe_2O_3@SiO_2 encapsulated with thiamine hydrochloride[27–29] and employed it as an efficient catalyst for the synthesis of benzo[*b*]pyran and spiro compounds. Similarly, a novel basic catalyst 3-methylaminopropyl-functionalized Fe_3O_4 nanoparticles (Fe_3O_4@MAP nanoparticles) was also prepared and utilized for the



Scheme 1. Synthetic pathway for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

synthesis of [1,3]oxazines compounds,[30] In continuation, with our on-going work, we report herein the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using L-Proline *N*-Sulfonic acid functionalized magnetic nanoparticles as a green and efficient organo-nanocatalyst.

Results and discussion

A two-component condensation reaction, consisting of anthranilamide and aromatic aldehydes, was carried out in the presence of a catalytic amount of sulfonic acid functionalized L-Proline@Fe_3O_4 in ethanol to effectively yield 2,3-dihydroquinazolin-4(1*H*)-ones (Scheme 1).

First, the L-proline coated Fe_3O_4 nanoparticles (Fe_3O_4@L-proline) was synthesized by chemical co-precipitation of ferric and ferrous salt solution in the presence of L-proline using ammonium hydroxide as a precipitating agent. The Fe_3O_4@L-proline thus obtained was further functionalized by condensing it with chlorosulfonic acid. The resultant product, i.e., L-proline sulfonic acid functionalized nanoparticles (Fe_3O_4@L-proline-SO_3H) was then characterized using Fourier transform infrared (FT-IR) spectroscopy, powder X-ray diffraction (XRD), transmission electron microscope (TEM), field emission scanning electron microscope (FE-SEM), energy-dispersive X-ray spectroscopy (EDS), thermogravimetric analysis (TGA), and vibrating sample magnetometry (VSM). The FT-IR spectrum of L-proline, Fe_3O_4@L-proline, and Fe_3O_4@L-proline-SO_3H is given in Figure 1. The peaks observed at 1124 cm^{-1} and 655 cm^{-1} in L-proline (a) corresponds to the twisting and rocking mode of N–H and CH_2 of the pyrrolidine ring, respectively. A peak at 1155 cm^{-1} in Fe_3O_4@L-proline (b) indicates the presence of the organic moiety (L-proline) embedded on Fe_3O_4 nanoparticles. The L-proline *N*-sulfonic acid functionalized magnetic nanoparticles (c) showed a peak at 1628 cm^{-1}, 1108 cm^{-1} and 602 cm^{-1} corresponding to the C=O, S=O, and Fe–O stretching frequencies, respectively, indicating the immobilization of the organic moiety on the magnetic nanoparticles. The powder XRD data of Fe_3O_4@L-Proline (a) and Fe_3O_4@L-Proline-SO_3H (b) is given in Figure 2. The peaks obtained at $2\theta = 30.1°$, 35.6°, 43.3°, 53.6°, 57.4°, 63.1° corresponding to (220), (311), (400), (422), (511), (440) planes, respectively, reveals that the crystalline structure of the Fe_3O_4 nanoparticles are retained in both a and b.

The size of the sulfonic acid functionalized Fe_3O_4@L-proline nanoparticles were calculated using Debye Scherrer equation and the average size was found to be 17.44 nm.

Transmission electron microscopy (TEM) images of the prepared catalyst reveals that the size of the particles ranges between 5 and 20 nm (Figure 3), which further substantiates the calculated size. The surface morphology of the catalyst was characterized using

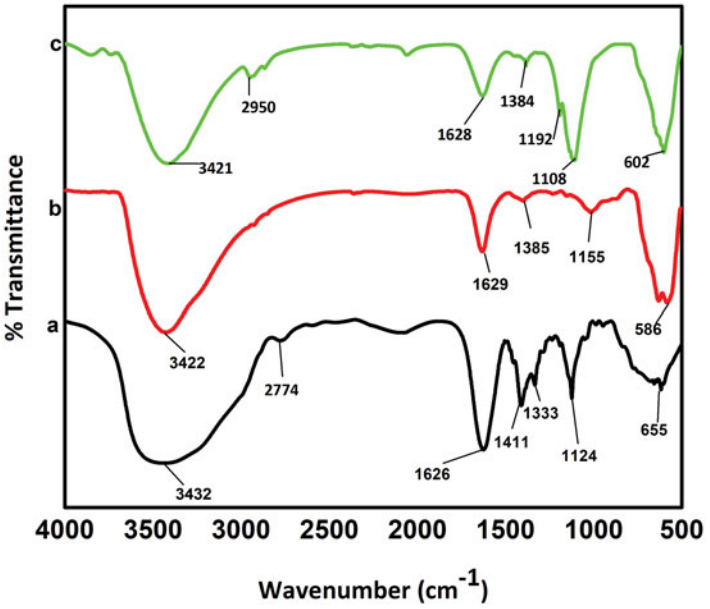


Figure 1. FT-IR spectra of (a) *L*-proline, (b) Fe_3O_4@*L*-proline, and (c) Fe_3O_4@*L*-proline-SO_3H.

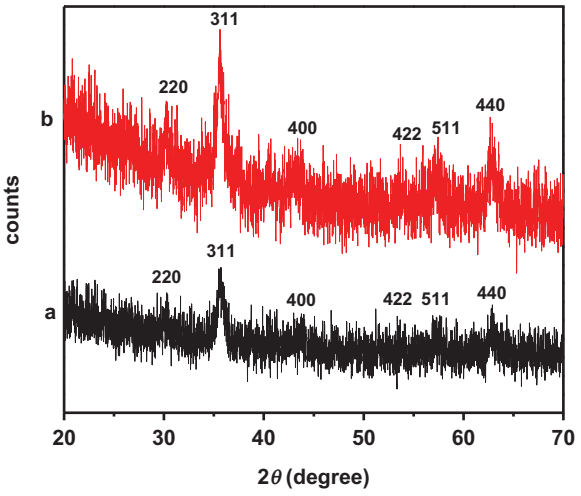


Figure 2. Powder-XRD of (a) Fe_3O_4@*L*-proline and (b) Fe_3O_4@*L*-proline-SO_3H.

field emission scanning electron microscopy (FE-SEM) technique, and it was observed that the nanoparticles are non-uniform in nature (Figure 4). The energy-dispersive X-ray spectroscopy (EDS) of the nanoparticles displayed the presence of Fe, S besides C and O which confirmed the formation of the target catalyst (supplementary).

To ascertain the stability of the catalyst, a thermal gravimetric analysis (TGA) of the catalyst was performed and it was found that the catalyst was stable up to 240 °C, beyond which, the proline moiety starts to decompose (Figure 5). The weight loss occurring up to 240 °C may be attributed to the elimination of the adsorbed water and other solvents from the surface of the catalyst. Similarly, the weight loss observed within

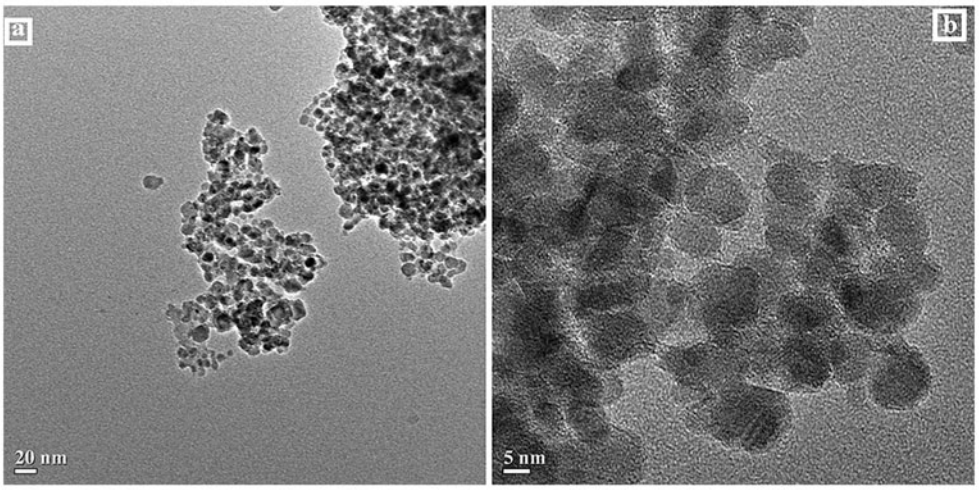


Figure 3. TEM images of Fe_3O_4@*L*-proline-SO_3H at (a) lower and (b) higher magnification.

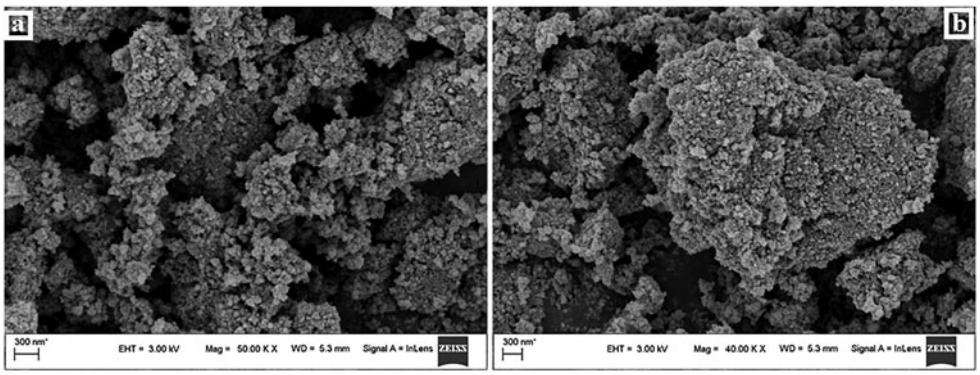


Figure 4. FE-SEM images of Fe_3O_4@*L*-proline-SO_3H at (a) lower and (b) higher magnification.

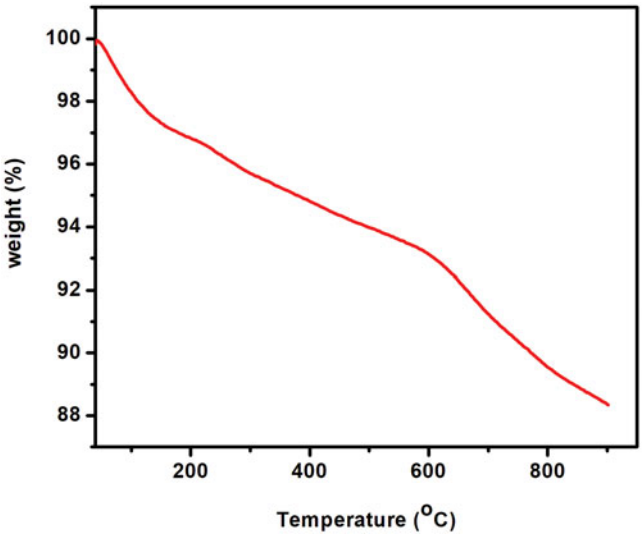


Figure 5. TGA graph of Fe_3O_4@*L*-proline-SO_3H.

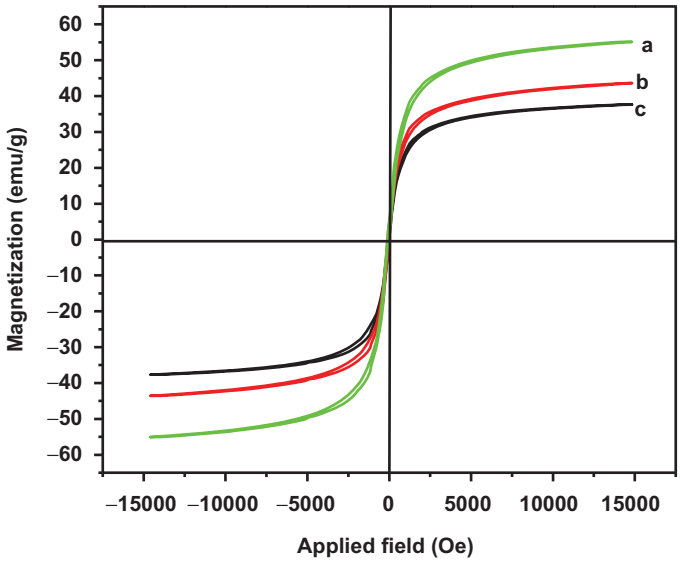


Figure 6. VSM curve of (a) Fe_3O_4, (b) Fe_3O_4@*L*-proline, and (c) Fe_3O_4@*L*-proline-SO_3H.

Table 1. Optimization of catalyst loading in the reaction.

Sl. No	Amount of catalyst (mg)	Time (min)	Yield[a] (%)
1	–	40	Trace
2	2	30	50
3	4	30	80
4	6	20	93
5	8	15	95
6	**10**	**10**	**96**
7	12	10	96
8	14	10	96

[a]Isolated yield.
Bold represents the optimized parameter with maximum yield of the products.

300–600 °C corresponds to the decomposition of the organic moiety (*L*-proline-*N*-sulfonic acid) of the prepared catalyst.

Vibrating-sample magnetometer (VSM) analysis (Figure 6) of the Fe_3O_4 nanoparticles (a), Fe_3O_4@*L*-proline (b), and Fe_3O_4@*L*-proline-SO_3H (c) showed a saturation magnetization value of 55.12, 43.63, and 37.66 emu/g, respectively. The decrease in the magnetic properties of the sulfonic acid functionalized Fe_3O_4@*L*-proline may be associated with the presence of organo-coated layer on the Fe_3O_4 nanoparticles.

The catalytic activity of nano-Fe_3O_4@*L*-proline-SO_3H was explored for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. Initially, a model reaction comprising of benzaldehyde (1.0 mmol) and 2-aminobenzamide (1.0 mmol) was studied for the optimization of the amount of catalyst and solvent. The results are represented in Table 1. It was found that only trace of the product was obtained in the absence of the catalyst. However, on addition of the catalyst, the yield of the product increased considerably, and it was found out that 10 mg of the catalyst gave the best yield in minimum reaction time. Further, increase in the amount of the catalyst did not show any significant change in the yield of the products.

Table 2. Optimization of reaction condition using different catalysts and solvents.

Sl. No	Catalyst	Solvent	Yield[a] (%)	Time (min)
1	–	EtOH	Trace	40
2	L-proline	EtOH	45	30
3	Fe_3O_4	EtOH	60	25
4	Fe_3O_4@SiO_2	EtOH	56	25
5	Fe_3O_4@L-proline-SO_3H	H_2O	90	15
6	**Fe_3O_4@L-proline-SO_3H**	**EtOH**	**96**	**10**
7	Fe_3O_4@L-proline-SO_3H	EtOH/H_2O	90	20
8	Fe_3O_4@L-proline-SO_3H	MeOH	90	22
9	Fe_3O_4@L-proline-SO_3H	CH_3CN	68	40
10	Fe_3O_4@L-proline-SO_3H	Toluene	20	30

[a]Isolated yield.
Bold represents the optimized parameter with maximum yield of the products.

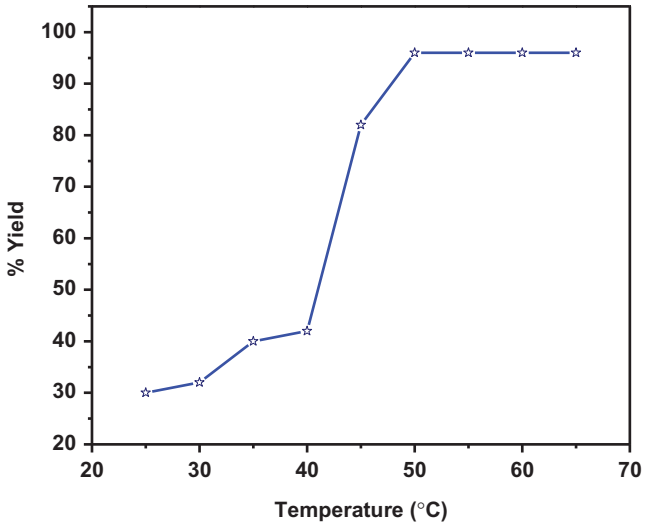


Figure 7. Effect of temperature on the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

Using the optimized amount of the catalyst, the model reaction was investigated in different solvents such as water, ethanol, methanol, water–ethanol (1:1) mixture, acetonitrile, and toluene to select a suitable reaction media (Table 2). The results indicated that optimum yield of the product was obtained with ethanol, at a shorter reaction time. It was also observed that with the increase of temperature, the yield of the product also increases and the optimum yield was obtained at 50 °C (Figure 7).

To increase the scope of the reaction, various substituted aromatic aldehydes were used (Table 3). It was observed that, with electron withdrawing substituents, the reaction was completed within a shorter reaction time as compared to those with electron donating substituents. On completion of the reaction (monitored by TLC), the catalyst was separated from the reaction mixture with the help of an external magnet. It was then washed with ethanol followed by acetone and dried in the oven at 60 °C before reusing for the next reaction. The recycled catalyst did not show much alteration in its activity even after five runs (Table 4). Studies were also carried out by replacing the aromatic aldehyde with aliphatic aldehydes under similar reaction condition. However, it was observed that only traces of the corresponding products were formed even at higher temperature.

Table 3. Fe_3O_4@*L*-proline-SO_3H catalyzed one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

Entry	(R)	Product	Time (min)	Yield (%)[a]
1	H	**3a**	10	96
2	4-OH	**3b**	15	92
3	4-Br	**3c**	20	96
4	4-F	**3d**	10	96
5	4-Cl	**3e**	10	96
6	4-OEt	**3f**	12	95
7	4-CH_3	**3g**	15	90
8	4-OCH_3	**3h**	10	92
9	4-NO_2	**3i**	10	94
10	3-Cl	**3j**	8	95
11	3-Br	**3k**	10	96
12	4-OH,3-OMe	**3l**	15	92
13	2-Cl	**3m**	10	96
14	1-Napthaldehyde	**3n**	15	96
15	3,4-OCH_3	**3o**	15	96
16	4-NMe_2	**3p**	12	95

[a]Isolated yield.

Table 4. Reusability of the catalyst.

No. of runs	Product	Amount of catalyst after recycled (mg)	Time (min)	Yield[a] (%)
1st	3a	10	10	96
2nd	3a	9	10	93
3rd	3a	8	10	93
4th	3a	8	10	92
5th	3a	6	10	87

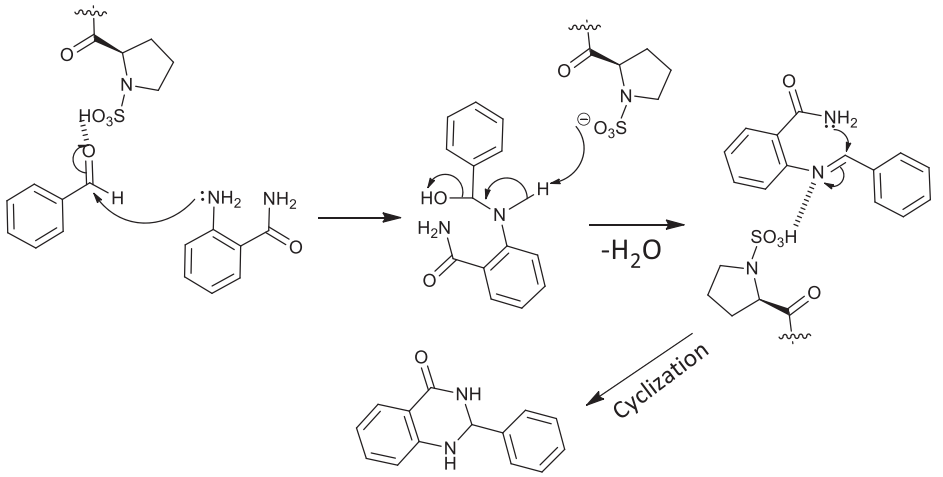
[a]Isolated yield.

The plausible reaction pathway for the formation of 2,3-dihydroquinazolin-4(1*H*)-ones can be rationalized *via* the activation of the carbonyl carbon of benzaldehyde by protonation from the sulfonic acid proton of the catalyst, thereby enhancing the nucleophilic attack by nitrogen lone pair. The conjugate base then abstracts the nitrogen proton which eventually leads to the removal of water *via* the E1cB mechanism. Further, cyclization leads to the formation of C–N bond, thereby leading to a fused six-membered ring product (Scheme 2).

Anthelmintic studies

The prevalence of intestinal helminth infection remains staggeringly high in tropical and sub-tropical condition. Helminth infections are not normally fatal, but heavy worm burden may result in severe adverse effects, like malnutrition, anorexia, anemia, and retarded growth.[31] Children are most affected with worm burden, over 267 million preschool age and over 568 million school-age children are in need of treatment and preventive interventions.[32] Rise in report of anthelmintic resistance from all over the world has alarmed new drug development programs. More importantly, reduced efficacy of broad spectrum anthelmintic albendazole against intestinal helminth, *Ascaris lumbricoides* in school children has raised deep concern.[33]

Anthelmintic screening of six dihydroquinazolinones derivatives was carried out and it was found that one of the derivative namely 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one exhibited activity at all test concentrations against both *Raillietina* and *Syphacia*



Scheme 2. Mechanistic pathway proposed for the synthesis of compounds **3(a–p).**

obvelata helminths species (Table 5). 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one treated against *Raillietina* sp. at 800 µg/mL showed mortality at 5.78 ± 0.36 h as compared with 1 mg/mL praziquantel (PZQ) at 6.51 ± 0.24 h and for *S. obvelata* 11.14 ± 0.23 h compared with 1 mg/mL albendazole (ALZ) at 16.56 ± 0.18 h. Bromo substituted derivatives were more efficacious than fluoro or chloro substituent and dimethoxy derivative was more effective as compared to dimethyl amino substituted. At 800 µg/mL, all derivatives have significant mortality; however, at 200 µg/mL, much reduced mortality was recorded and dose dependence predominates, though it varies with derivatives and helminth test models. Interestingly the nature of substituent (electron donating or withdrawing) and the positions of substituent were vital to achieve desired efficacy.[34,35]

Experimental

Experimental reagents and solvents were obtained from Merck, Alfa aesar and sigma Aldrich and were used without further purification. Infrared spectra of the compounds and catalyst were recorded in Perkin Elmer FT-IR 550 spectrophotometer using KBr disk. ^{1}H and ^{13}C NMR spectra were recorded in Bruker Avance II DRX 400 spectrometer. Mass spectra were recorded on WATERS (ZQ-4000) mass spectrometer. Powder XRD of the catalyst was recorded in Explorer-GNR. All the melting points were recorded in Optics Technology digital melting point apparatus and are uncorrected. A transmission electron microscopic (TEM) image of the catalyst was recorded on transmission electron microscopic make JEOL, model: JEM 2100. FE-SEM images of the nanoparticles were recorded on Field Emission Scanning Electron Microscope make Zeiss, Model: Sigma. All reactions were monitored by using a 0.2 mm thickness pre-aluminum sheet thin-layer chromatography (TLC).

General procedure for the synthesis of Fe_3O_4@L-proline

Fe_3O_4@*L*-proline was prepared as reported[36] with minor modification. Briefly, 5 mmol of $FeCl_3.6H_2O$ and 2.5 mmol of $FeSO_4$ were dissolved separately in 50 mL deionized

Table 5. Anthelmintic activity of 2,3-dihydroquinazolin-4(1*H*)-ones at different test concentration.

Compounds	Concentration	*Raillietina* sp. mean paralysis ± SEM	*Raillietina* sp. mean mortality ± SEM	*Syphacia obvelata* mean paralysis ± SEM	*Syphacia obvelata* mean mortality ± SEM
3a	200 µg	8.98 ± 0.50	10.31 ± 0.50	17.23 ± 0.22	20.03 ± 0.18
	400 µg	6.87 ± 0.34	7.81 ± 0.46	11.78 ± 0.21	13.36 ± 0.20
	800 µg	5.06 ± 0.41	5.78 ± 0.36	9.81 ± 0.18	11.14 ± 0.23
3e	200 µg	14.02 ± 0.36	15.69 ± 0.42	21.39 ± 0.27	24.04 ± 0.35
	400 µg	12.43 ± 0.29	13.89 ± 0.40	18.75 ± 0.23	20.85 ± 0.23
	800 µg	9.88 ± 0.37	11.16 ± 0.32	15.91 ± 0.20	18.06 ± 0.24
3d	200 µg	10.74 ± 0.18	12.34 ± 0.27	18.91 ± 0.16	21.73 ± 0.22
	400 µg	9.26 ± 0.36	10.43 ± 0.51	15.44 ± 0.20	17.76 ± 0.26
	800 µg	7.96 ± 0.34	8.76 ± 0.26	12.86 ± 0.19	14.76 ± 0.19
3k	200 µg	10.39 ± 0.49	11.91 ± 0.48	18.33 ± 0.22	20.98 ± 0.28
	400 µg	8.36 ± 0.19	9.54 ± 0.10	14.77 ± 0.16	16.99 ± 0.14
	800 µg	7.51 ± 0.53	8.63 ± 0.54	12.51 ± 0.16	14.64 ± 0.18
3o	200 µg	10.76 ± 0.45	12.49 ± 0.39	19.85 ± 0.17	22.53 ± 0.29
	400 µg	8.93 ± 0.44	10.49 ± 0.50	17.61 ± 0.24	20.22 ± 0.29
	800 µg	8.38 ± 0.24	9.26 ± 0.29	14.36 ± 20.22	16.12 ± 0.23
3p	200 µg	13.06 ± 0.47	15.01 ± 0.59	21.40 ± 0.20	24.20 ± 0.16
	400 µg	11.26 ± 0.44	13.46 ± 0.47	19.97 ± 0.16	22.73 ± 0.22
	800 µg	10.16 ± 0.28	11.01 ± 0.37	17.63 ± 0.14	19.66 ± 0.26
ALZ	1 mg/ mL	–	–	15.27 ± 0.20	16.56 ± 0.18
PZQ	1 mg/ mL	4.96 ± 0.23	6.51 ± 0.24	–	–
CONTROL	–	26.08 ± 0.37	31.68 ± 0.48	41.55 ± 0.67	45.88 ± 0.61

water and then mixed together with vigorous stirring at room temperature. 2 mmol of *L*-proline and NH_4OH (25%, 15 mL) were added until a black suspension appears and the pH was raised to 11. The mixture was reflux at 100 °C for 6 h under stirring condition. The black suspension was removed by magnetic decantation, washed with water and methanol several times and then finally with ethanol. The solid product was dried in the oven at 60 °C.

General procedure for the synthesis of Fe_3O_4@L-proline-SO_3H

1.0 g of Fe_3O_4@*L*-proline was ultra-sonicated in 10 mL of dry hexane for 30 min and then stirred at room temperature. 0.2 mL of chlorosulfonic acid was added drop-wise and the reaction mixture was further stirred for 1 h for the complete removal of the HCl gas. The Fe_3O_4@*L*-proline-*N*-sulfonic acid nanoparticles were separated by an external magnet and then washed several times with toluene and deionized water. The coated nanoparticles was dried in the oven at 60 °C.[37]

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

To a mixture of 2-aminobenzamide (1 mmol) and aromatic aldehyde (1 mmol) in 10 mL of ethanol, 0.010 g of the catalyst was added. The reaction mixture was stirred at 50 °C for appropriate time. When the reaction has completed (monitored by TLC), the catalyst was removed by an external magnet and the product was filtered and recrystallized from hot ethanol. The recovered catalyst was washed and dried in the oven at 60 °C before reusing for the next reaction.

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

White solid, melting point: 220-222 °C [Lit.[38] 217-219 °C]. FT-IR (KBr): ν_{max} 3305, 3187, 3064, 1655, 1614, 1587, 1453 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1 H), 7.60–7.23 (m, 7 H), 7.12 (s, 1 H), 6.72–6.68 (m, 2 H), 5.74 (s, 1 H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 163.57, 147.84, 141.54, 133.30, 128.43, 128.29, 127.32, 126.82, 117.04, 114.89, 114.35, 66.50. calc. MS (ESI) *m/z*: 224. Found MS (ESI) *m/z*: 225 $[M+1]^+$.

Methods for anthelmintic studies

2,3-dihydroquinazolin-4(1*H*)-ones and its derivatives are freshly prepared and were screened for anthelmintic activity against *Raillietina echinobothridia* a fowl cestode and *S. obvelata* a pin worm nematode in mice. Derivatives were selected on the basis of side chain with electron donating (dimethoxy and dimethylamino) and electron withdrawing (Cl, F, and Br) groups.[39,40] *Raillietina echinobothridia* were collected from intestine of freshly slaughtered domestic chicken and adult *S. obvelata* obtain from cecum of necropsied mice. The collected worms were washed with warm 0.9% phosphate-buffered saline (PBS) and further maintained at 37 ± 1 °C. Test parasite was divided into five groups (5 in each) in triplicates, helminths incubated in PBS serve as control whereas praziquental and albendazole at 1 mg/mL as a standard group for cestode and nematode, respectively. 2,3-dihydroquinazolin-4(1*H*)-one derivatives at a concentration of 200, 400, and 800 µg were selected for *in vitro* studies.[41] Each group was dissolved with a minimum amount of 1% DMSO (dimethyl sulfoxide) and the volume was adjusted to 5 mL. Helminth viability was determined through physical mobility test, body movement was recorded in regular interval under a light microscope to determine paralysis and mortality time.[42]

Statistical analysis

All data are represented as mean ± standard error of mean (SEM). Data were analyzed using one-way ANOVA at significance level of $p < 0.05$.

Conclusions

We have successfully developed a green and efficient protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, starting from aldehydes and 2-aminobenzamide using Fe_3O_4@*L*-proline-SO_3H as the reusable catalyst. The notable features of the protocol include shorter reaction time, excellent yield of the products, easy separation and recyclability of the catalyst. The *in vitro* study of 2,3-dihydroquinazolin-4(1*H*)-ones revealed that 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one showed a positive result for the treatment of helminths against *Railietina* sp. and *S. obvelata* when compared with standard drugs.

Full experimental detail can be found via the "Supplementary Content" section of this article.

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