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2-Aminoethanesulfonic acid: An efficient organocatalyst for green synthesis of spirooxindole dihydroquinazolinones and novel 1,2-(dihydroquinazolin-3(4*H*)isonicotinamides in water

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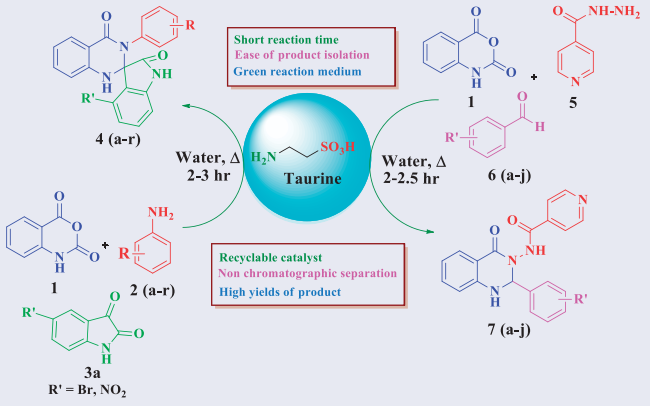
ABSTRACT

A facile and efficient one-pot procedure for the preparation of spirooxindole dihydroquinazolinone derivatives and new *N*-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4*H*)-yl)isonicotinamides from reaction between isatoic anhydride, isoniazid and substituted aldehydes catalyzed by 2-aminoethanesulfonic acid (taurine) is describe. This new protocol has the advantages of environmental friendliness, good yields, and convenient operation. The reaction proceeds efficiently using water as green solvent and nontoxic catalysts that could be efficiently reused. Together with this simple workup procedure, use of the organocatalyst, and water as solvent without the need of column chromatographic purification, are the notable features of this methodology, which make this protocol a very efficient and green alternative to the traditional methods.

GRAPHICAL ABSTRACT



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KEYWORDS
2-Aminoethanesulfonic acid (taurine); 2,3-dihydroquinazolin-4(1H)-ones; multicomponent reaction; spirooxindole

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Introduction

On the ground of environmental concerns, chemists and researchers are switching their interest towards synthetic processes which incorporate the environmentally benign reagents for the synthesis of highly privileged scaffolds and this has emerged as a phenomenally recommended platform.[1] Within this context, Chemical reactions in the presence of organocatalysis[2] have gained widespread attention as a result of the efficiency and selectivity for many reactions. Novel methods employing organic molecules are advantageous from both a practical and an environmental standpoint.

Recently, the commercially available and inexpensive amino acid such as taurine (2-aminoethanesulfonic acid) has been elegantly used to catalyze some organic reaction. 2-Aminoethanesulfonic acid is ubiquitous sulfur-containing amino acids in nature, which can be extracted from many biological organisms.[3] For the existence of the $-SO_3H$ group, taurine has the potential to function as proton-acid catalysts in the oxidation of sulfides to sulfoxides employing aqueous hydrogen peroxide as oxidant. Some different applications of taurine derivatives comprise nanosensors,[4] organogelators,[5] or water-soluble dyes.[6] In addition to this, they improve water solubility and are capable to form H-bonds while their strong inductive effect can be utilized to tune pKa values of adjacent or remote amino groups.[7] On the other hand the structural and electronic properties might mimic transition states to tetrahedral intermediates.[8] Besides being 2-aminoethanesulfonic acid is a readily available and environmentally benign catalyst. These features make 2-aminoethanesulfonic acid not only an alternative catalyst for a transition-metal free approach but also a good choice in strategies of catalytic chemistry for some organic transformation. Several groups have studied the organic transformation using taurine of sul-fonic acids.[9]

Over the past few decades, multicomponent reactions (MCRs) have gained considerable interest in both academia and industry owing to exceptional synthetic efficiency, intrinsic atom-economy, high reactivity, and procedural simplicity.[10] These strategies were subsequently replaced by the cascade/domino or multicomponent reaction, which allow the formation of complex molecular architectures under ambient conditions and without the need of protecting groups and purification of intermediates.[11,12] In addition, they are recognized as processes with minimal waste generation. In this way, multicomponent or cascade reactions fall under the category of green chemical transformations. The development of new organocatalyst for the construction of structurally and stereochemically diverse compounds by MCRs approach would be significant and extremely useful.[13]

Nitrogen-containing heterocycles are among the most common structural motifs in bioactive compounds.[14] In particular, 2,3-Dihydroquinazolinone is increasingly attractive scaffolds, which play a key role in various cellular processes. Furthermore, quinazolinone skeleton is frequently found in various natural products.[15,16] They also possess a wide range of pharmacological activities such as antitumor, analgesic, antiviral, and antimicrobial activities.[17–20] In addition, these compounds can be easily oxidized to the corresponding 4(3*H*)-quinazolinones,[21,22] which are important biologically active heterocyclic compounds. Spiro compounds contain two rings fused at a central spiro atom, and they possess a unique 3 D conformation. Chemists are fascinated with spirocycles for more than a hundred years, since there is an impressive number of spirocyclic

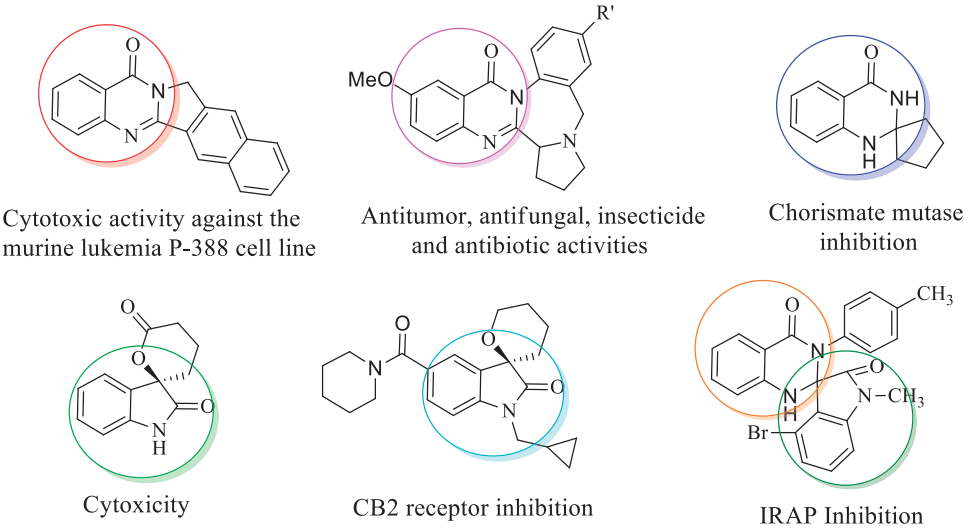


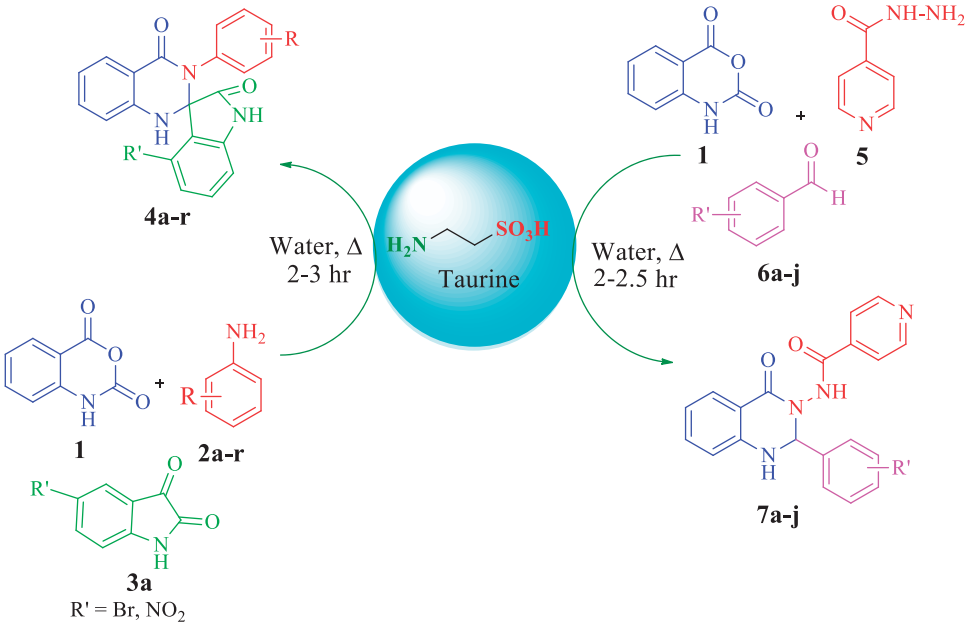
Figure 1. Some natural and synthesized bioactive molecules contained quinazolinone or spirooxindole scaffolds.

representatives, in natural product synthesis,[23] such as Marcfortine B, Spirotryprostatin B, and Cyclopiamine B.[24] Considering the intriguing molecular architecture and potent biological activities, various protocols have been developed to synthesize this class of molecules.[25,26] It is notable that spirooxindole dihydroquinazolinone derivatives combine two pharmacophoric subunit into one molecule, leads to the design of new hybrid architectures. Furthermore, quinazolinone skeleton with spirocyclic compound (Fig. 1). is frequently found in various natural products and significant role in medicinal chemistry for their biological activity as antibacterial, antiinflammatory, anticancer and laxatives.[27,28]

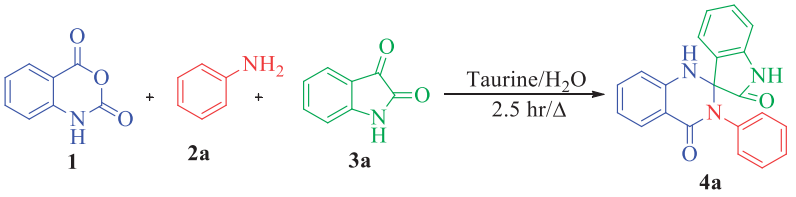
Among the different strategies reported for the preparation of 2,3-dihydroquinazolinones,[29–37] the organocatalytic synthesis *via* cascades has attracted particular interest, however, the reported methods suffered from some inconveniences such as corrosive solvent, special reactor and narrow substrate scope, etc. Therefore, keeping in mind the importance of 2,3-Dihydroquinazolinones and spirooxindole moiety, and atom economical approaches for the construction of the spirooxindole dihydroquinazolinones scaffold are still in demand, we herein wish to report a convenient, clean, facile, and organocatalytic practical method for the synthesis of spirooxindole dihydroquinazolinones molecular skeletons and a new series of functionalized *N*-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4*H*)-yl)isonicotinamides in water at heating conditions, the overall results are summarized in (Scheme 1).

Result and discussion

During the course of our initial investigation reaction of isatoic anhydride **(1)**, aniline **(2a)**, and isatin **(3a)** was used as the standard model reaction in a one-pot manner to investigate experimental conditions including catalysts and solvents (Scheme 2). Initially standard model reaction was carried out without the aids of any catalyst in the presence



Scheme 1. The pathway for synthesis of 3′-phenyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione **4a–r** and *N*-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4*H*)-yl)isonicotinamide **7a–j** derivatives.



Scheme 2. Standard model reaction.

of suitable solvent under heating conditions, thereby isolating the desired product **4a** in trace amount yield after the prolong reaction time. Then we performed the same reaction of isatoic anhydride **(1)**, aniline **(2a)**, and isatin **(3a)** in water at 80 °C in the presence of 15 mol% of catalyst 2-aminoethanesulfonic acid (taurine) gave the desired product **4a** in 90% yield (Scheme 2). We also tried different catalyst such as $KAl(SO_4)_2{\cdot}12H_2O$, *β*–CD, and Tris-buffer afforded the moderate yield as compare to taurine (Table 1, entries 1–3) under similar reaction conditions but no appreciable increment in product yield was observed. Then it was thought worthwhile to study the reaction in the presence of organocatalyst like taurine (Table 1, entries 1–3). This suggests that the presence of organocatalyst is pivotal for the catalytic efficiency. The best result was obtained with the 2-aminoethanesulfonic acid which gave 90% yield of **4a** (Table 1, entry 4), hence we decided to use 2-aminoethanesulfonic acid for further optimization studies.

Further to investigate the solvent effect on the above reaction, various solvent such as protic and aprotic solvents have been used for model reaction. Obviously, protic

Table 1. Optimization studies for the synthesis of spirooxindole dihydroquinazolinones using different catalyst.[a]

Entry	Catalyst	Time (hr)	Yield[b] (%)
1.	$KAl(SO_4)_2.12H_2O$	3–4	65
2.	β-CD	2–3	88
3.	Tris buffer	4–6	55
4.	Taurine	2–3	90

[a]All reactions were carried out using isatoic anhydride **(1)**, aniline **(2a)** and isatin **(3a)**, and solvent under reflux condition.
[b]Isolated yield.

Table 2. Optimization of solvent study for the synthesis of spirooxindole dihydroquinazolinones.[a]

Entry	Taurine (mol%)	Solvent	Condition (Reflux)	Yield[b] (%)
1.	15	CH_3CN	2–3 hr	65
2.	15	Toluene	2–3 hr	78
3.	15	Chloroform	2–3 hr	61
4.	15	methanol	2–3 hr	66
5.	15	Ethanol	2–3 hr	70
6.	15	EtOH:H_2O (9:1)	2–3 hr	76
7.	15	EtOH:H_2O (1:9)	2–3 hr	80
8.	15	Water	2–3 hr	90

[a]All reactions were carried out using isatoic anhydride **(1)**, aniline **(2a)** and isatin **(3a)** taurine and solvent under reflux condition.
[b]Isolated yield.

Table 3. The effect of amount of taurine in the preparation of **4a** by isatoic anhydride (1), aniline (2) and isatin (3) in water.[a]

Entry	Solvent	Mol% of Taurine	Time (hr)	Yield[b] (%)
1.	Water	–	9–10	–
2.	Water	5	7–8	55
3.	Water	10	5–6	67
4.	Water	15	2–3	90
5.	Water	20	2–3	90

[a]All reactions were carried out using isatoic anhydride **(1)**, aniline and isatin, taurine and solvent under reflux condition.
[b]Isolated yield.

solvents were better for the reaction, especially when EtOH:H_2O (9:1) was applied (Table 2, entry 6), Encourage by this result, we carried on with examining the effect of solvents using different ratio EtOH:H_2O (1:9) and H_2O. It was clear that the highest yield of product **3a** was achieved when the reaction was performed in water (Table 2, entry 8). From green chemistry perspective, water is considered as a safe and uniquely redox-stable green solvent which facilitates typical solvation and molecular assembly processes, leading to the remarkable modes of reactivity and selectivity of a wide variety of organic reactions.[38–44] In order to establish the correct concentration of catalyst for the above model reaction, the model reaction was further performed by changing the concentration of taurine in 5, 10, 15 and 20 mol% respectively for 2–3 h. Increasing the catalyst loading slightly improve the yield, the highest yield of 90% when 15 mol% of 2-aminoethanesulfonic acid was used (Table 3, entry 4). On the other hand, the yield of the compound **4a** was not significantly improve when the amount of

2-aminoethanesulfonic acid catalyst increase to 20 mol% (Table 3, entry 5). Finally, 15 mol% of catalyst was concluded to be ample to catalyze the above conversion.

To explore the temperature effect, initially above model reaction performed at ambient temperature and achieved the desired product in very low yield increasing the reaction temperature to 80 °C resulted in high yield of the desired product. Further increase in temperature was detrimental for the reaction as several byproducts were observed.

With the optimized conditions in hand, to check the generality as well as effectiveness of this newly developed protocol, a number of functionalized aromatic anilines were reacted with isatin and isatoic anhydride using identical reaction conditions; all of these eighteen entries underwent the reaction smoothly, affording the corresponding 3′-phenyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-diones **4b–r** (Table 4, entries 2–18) in excellent yields ranging from 75% to 90% at heating condition within 2–4 hr. Inspired by these results, we then replace aniline with isoniazid and isatin with aldehyde and carried out a similar set of one reactions from the mixture of this isatoic anhydride, isoniazid with aldehyde in water using 15 mol% of 2-aminoethanesulfonic acid at heating condition. To our delight, the reaction produces the expected product in 90% yield respectively within 2–4 hr (Scheme 3). We then extended this methodology in synthesizing nine more new *N*-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4*H*)-yl)isonicotinamide derivatives **7b–j** from one pot reaction of isatoic anhydride, isoniazid with functionalized aromatic aldehydes using identical reaction conditions; all of them underwent the reaction in a facile manner, affording the desired products **7b–j** (Table 5, entries 2–10) with excellent yields ranging from 85% to 94% within 2.5 − 4 hr. All the synthesized compounds were well characterized by spectral ^{1}H NMR, IR, ^{13}C NMR, Mass spectra and elemental analysis data.

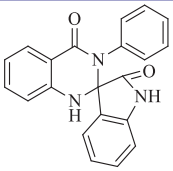
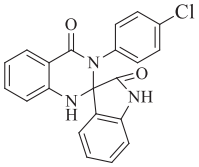
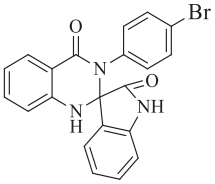
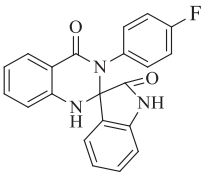
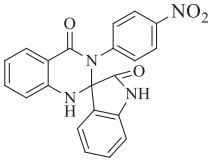
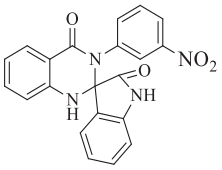
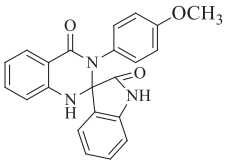
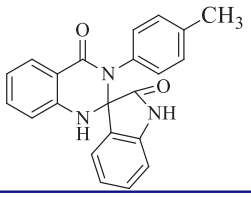
For the industrial applications through a green chemistry approach, recyclability of catalysts is highly desirable. We evaluated the reusability of 2-aminoethanesulfonic acid for both the reactions of spirooxindole dihydroquinazolinones and *N*-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4*H*)-yl)isonicotinamides. The 2-aminoethanesulfonic acid could be easily recovered and reused for at least three runs without any significant impact on the yield of the products (Fig. 2). The purification of 2-aminoethanesulfonic acid catalyst after the recycling was confirmed by IR spectra shown in (Fig. 3).

Experimental

Materials and methods

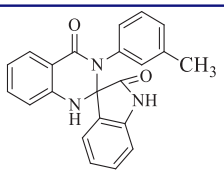
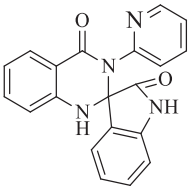
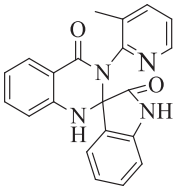
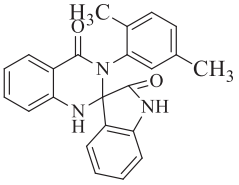
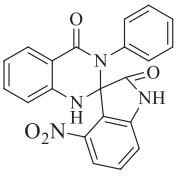
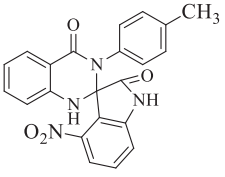
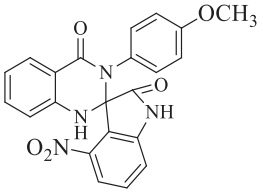
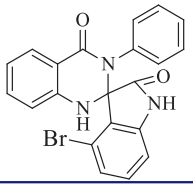
All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tube and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on Merck's silica plates and visualization was accomplished by iodine/ultraviolet light. IR spectra were obtained on a Bruker ALPHA (Eco-ATR) spectrometer. ^{1}H NMR spectra of were recorded with an NMR predict proton DMSO (BRUKER/TOPSPIN) spectrometer operating at 700 MHz using DMSO solvent and trimethylsilane (TMS) as the internal standard and chemical shift in δ ppm and ^{13}C NMR at 176 MHz, DMSO, Mass spectra were recorded on a Waters (BRUKER/TOPSPIN) (ESI-MS and APCI-MS)

Table 4. 2-Aminoethanesulfonic acid catalyzed one-pot synthesis of spirooxindole dihydroquinazolinones[a] **4a–r**.

Sr. No.	Entry	Product	Time (hr)	Yield[b] (%)
1.	**4a**		2.5	90
2.	**4b**		3	81
3.	**4c**		4	82
4.	**4d**		4	85
5.	**4e**		4	86
6.	**4f**		4.5	90
7.	**4g**		4	87
8.	**4h**		3	90

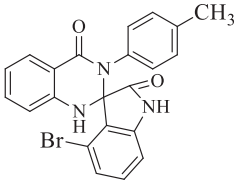
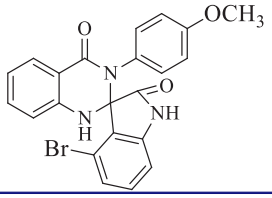
(*continued*)

Table 4. Continued.

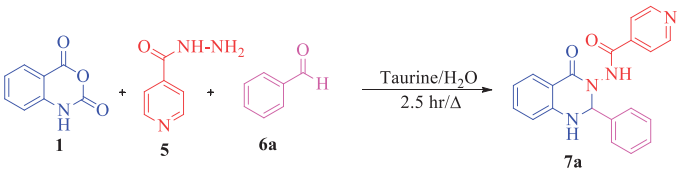
Sr. No.	Entry	Product	Time (hr)	Yield[b] (%)
9.	**4i**		3.5	86
10.	**4j**		4.5	89
11.	**4k**		5	75
12.	**4l**		6	87
13.	**4m**		6	89
14.	**4n**		6.5	90
15.	**4o**		6.5	88
16.	**4p**		5.5	90

(*continued*)

Table 4. Continued.

Sr. No.	Entry	Product	Time (hr)	Yield[b] (%)
17.	**4q**		6	89
18.	**4r**		6	88

[a]All reactions were carried out using isatoic anhydride (**1**), aniline **2 (a–r)** and isatin (**3a**), taurine and solvent under reflux condition.
[b]Isolated yield.



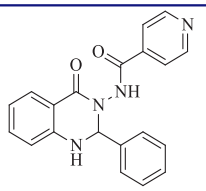
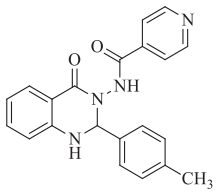
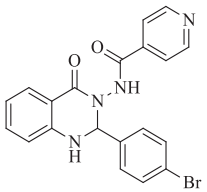
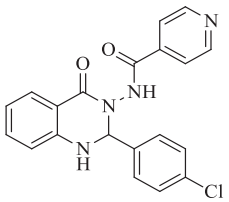
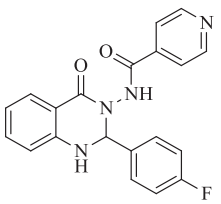
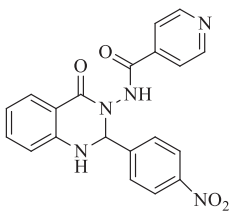
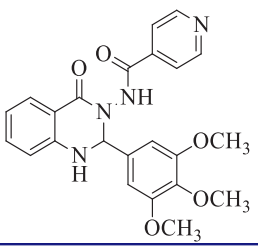
Scheme 3. Synthesis of 2,3-dihydroquinazolinones.

Instrument and elemental analysis were recorded on CHNS autoanalyser Thermofischer (FLASH EA1112 SERIES).

General procedure for synthesis of 1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-diones 4a–r

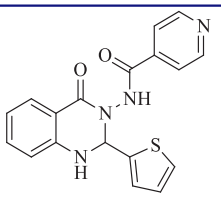
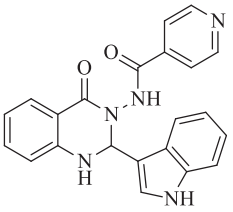
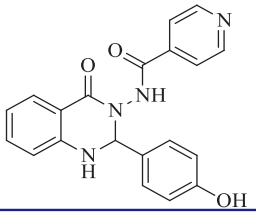
A equimolar mixture of isatoic anhydride (1.0 mole), aniline (1.0 mole), and isatins (1.0 mole) was taken in 10 mL water in 100 mL round bottom flask and 15 mol% of taurine catalyst was added to this reaction mixture. The reaction content was heated for the appropriate time given in (Table 4). After the completion of reaction, which was monitored by TLC, the reaction mixture was allowed to cool and 10 mL of water was added and stirred for 3 min. During this time, the product was precipitated and subsequently separated by filtration. The separated product was washed with water for several times. After drying, the pure product was obtained; there was no need for further purification by column chromatography or addition of any organic solvent. Furthermore, water was evaporated from the filtrate to recycle and recovered the taurine catalyst. The recovered taurine reused for same transformation 2–3 consecutive runs without any significant loss in yield and activity. The products were characterized by M. P., FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analysis and are good agreement with the reported compounds.[39]

Table 5. Synthesis of new 2,3-dihydroquinazolinones[a] derivatives**7a–j**.

Sr. No.	Entry	Product	Time (hr)	Yield[b] (%)
1.	**7a**		2.5	90
2.	**7b**		3.5	85
3.	**7c**		4	87
4.	**7d**		3.5	93
5.	**7e**		3.5	86
6.	**7f**		4.5	90
7.	**7g**		3	88

(*continued*)

Table 5. Continued.

Sr. No.	Entry	Product	Time (hr)	Yield[b] (%)
8.	**7h**		4	94
9.	**7i**		4	87
10.	**7j**		2.5	90

[a]All reactions were carried out using isatoic anhydride (**1**), isonizid (**5**) and aldehyde **6 (a–j)**, taurine and solvent under reflux condition.
[b]Isolated yield.

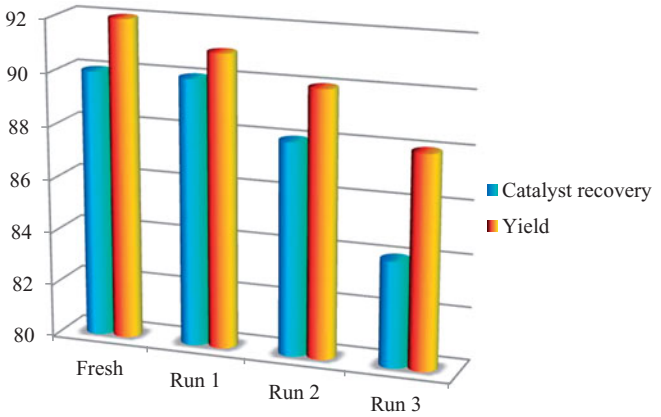


Figure 2. Reuse and recovery of 2-aminoethanesulfonic acid (taurine) and its effect on yield.

Spectral analysis of 3′-phenyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (4a)

IR (ATR) ν_{max} cm^{-1}: 3243 (NH), 3059 (NH), 1735 (C=O), 1706 (C=O), 1454, 1326 (Ar–H). ^{1}H NMR 700 MHz, DMSO): δ 10.29 (s, CONH); ^{1}H NMR (400 MHz, DMSO) δ 10.77 (s, 1 H), 7.77 (dd, $J = 7.7$, 1.5 Hz, 1 H), 7.67 (s, 1 H), 7.53 (d, $J = 7.2$ Hz, 1 H), 7.31 (ddd, $J = 8.1$, 7.4, 1.6 Hz, 1 H), 7.27 (t, $J = 7.4$ Hz, 2 H), 7.17 (ddd, $J = 9.0$, 4.9,1.2 Hz, 2 H), 7.15–6.99 (m, 2 H), 6.95 (t, $J = 7.6$, 0.9 Hz, 1 H), 6.91–6.87 (m, 1 H), 6.76 (d, $J = 8.1$ Hz, 1 H), 6.63 (d, $J = 7.7$ Hz, 1 H);^{13}C NMR (100 MHz, DMSO-d_6): δ

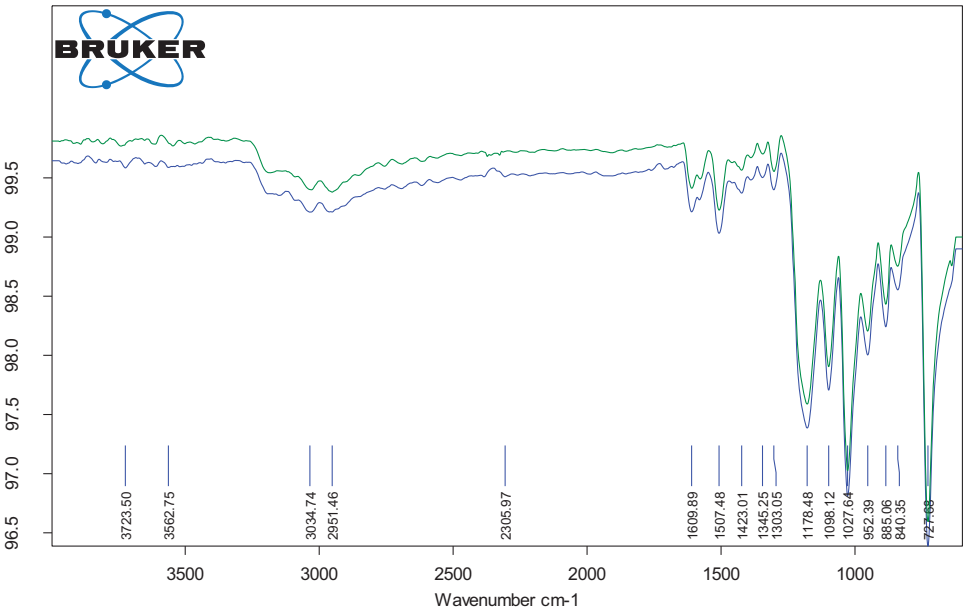


Figure 3. FT-IR spectral analysis of the fresh 2-aminoethanesulfonic acid (green) and after 3rd time reused catalyst (blue).

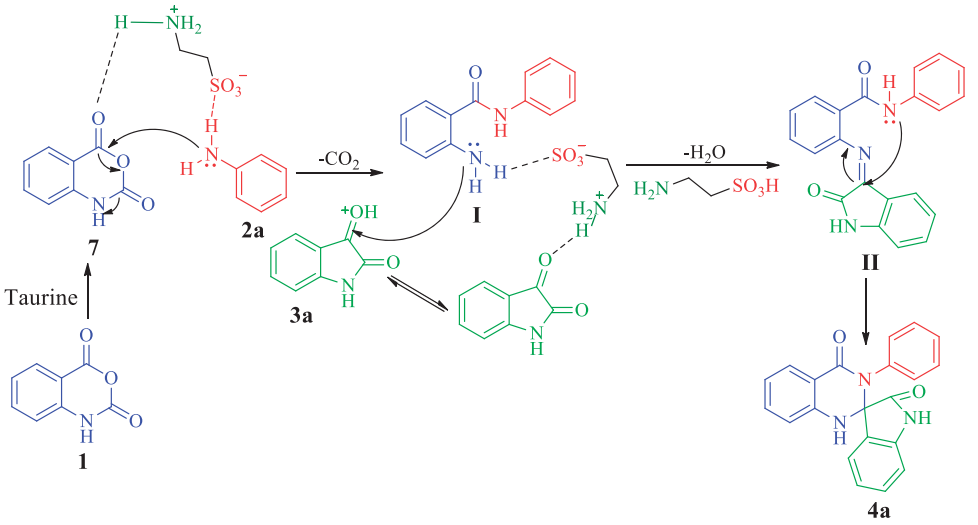
175.66, 164.56, 146.10, 131.79, 128.60, 127.69, 127.40, 127.29, 126.47, 117.75, 115.57, 114.08, 110.57, 75.33. Elemental Analysis Calcd. For $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; Found: C, 73.85; H, 4.46; N, 12.35; LC-MS (ESI, *m/z*): 342.18 (M + 1).

General procedure for synthesis of N-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4H)-yl)sonicotinamide 7a–j

A equimolar mixture of isatoic anhydride (1.0 mole), isoniazid (1.0 mole), aldehyde (1.0 mole) was taken in 10 mL water in 100 mL round bottom flask and 15 mol% of taurine catalyst was added to this reaction mixture. The reaction content was heated for the appropriate time given in (Table 5). After the completion of reaction, which was monitored by TLC, the reaction mixture was allowed to cool and 10 mL of water was added and stirred for 3 min. During this time, the product was precipitated and subsequently separated by filtration. The separated product was washed with water for several times. After drying, the pure product was obtained; there was no need for further purification by column chromatography or addition of any organic solvent. Furthermore, water was evaporated from the filtrate to recycle and recovered the taurine catalyst. The recovered taurine reused for same transformation 2–3 consecutive runs without any significant loss in yield and activity. The obtained new products were characterized by M. P., FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analysis.

N-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4H)-yl)isonicotinamide (7a)

IR (ATR) ν_{max} cm^{-1}: 3303, 3189, 3038, 1793, 1651, 1600, 1492, 1402, 1287, 1052; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65–8.80 (dd, $J = 9.2$ Hz, 2 H, Ar–H), 8.38–8.48 (dd, 2 H,



Scheme 4. A plausible mechanism for the product formation of 3′-phenyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione.

Ar–H), (8.16 (s, 1 H, -NH), 7.94–7.57 (m, 4 H, Ar–H), 7.54–7.11 (m, $J = 2.8$, 5.2, 3.6 Hz, 5 H, Ar–H), 6.35 (s, 1 H, -CH), 5.35 (s, 1 H, -NH); ^{13}C NMR (125 MHz, DMSO): δ 164.42, 158.92, 150.02, 149.64, 149.13, 145.02, 143.11, 132.12, 129.71, 126.53, 124.12, 121.13, 118.19, 112.92, 85.21; Elemental Analysis Calcd. For $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27; Found: C, 69.75; H, 4.72; N, 16.23; LC-MS (ESI, *m/z*): 344.3 (M + 1).

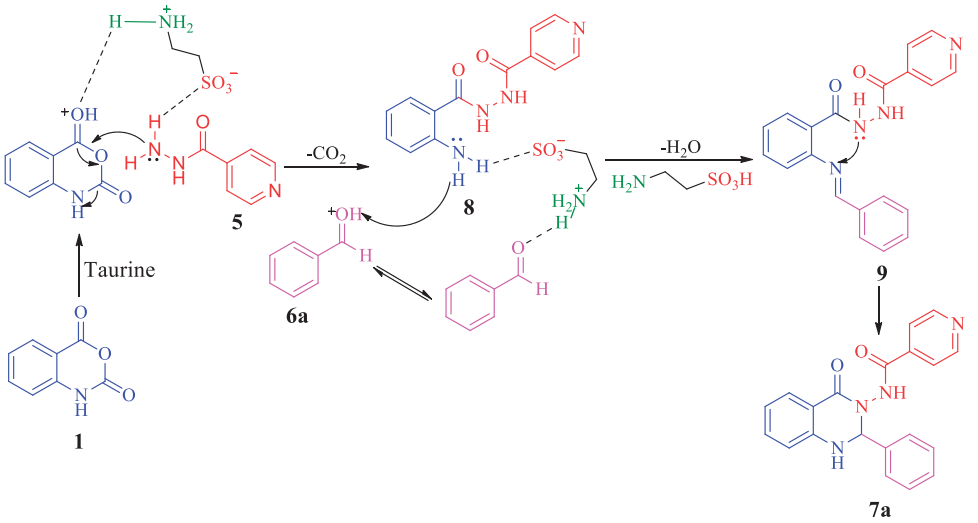
Reaction mechanism

According to the relevant literature,[36] the plausible pathway for 2-aminoethanesulfonic acid catalyzed these one-pot three component reactions was suggested in (Scheme 4). 2-Aminoethanesulfonic acid (taurine) acts as a bifunctional donor–acceptor reagent in which the isatoic anhydride **(1)** carbonyl site is activated by taurine to give intermediate **8**, which could facilitate nucleophilic attack of aniline **(2a)** on the carbonyl unit. Nucleophilic addition of aniline **(2a)** to isatoic anhydride **1**, followed by decarboxylation, produced 2-aminobenzamide **9**, condensation of **9** with protonated isatin, prepared using taurine, gave imine **10**, which underwent intramolecular cyclization to afford product **4a**.

The plausible pathway for 2-Aminoethanesulfonic acid (taurine) catalyzed these one-pot three component reactions was suggested in (Scheme 5). First, the isatoic anhydridewas activated by 2-aminoethanesulfonic acid in the protic solvent, then the N-nucleophilic attack isoniazid **(5)** to the isatoic anhydride formed intermediate **8** with the decarbonylation. Next, the imine intermediate **9** was given by nucleophilic attack of aldehyde that promoted by 2-aminoethanesulfonic acid. Finally, the product **7a** formed from **9** by intermolecular cyclization.

Conclusion

In summary, we have developed a novel, simple and efficient protocol for the synthesis of 1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-diones **4a–r** and new *N*-(4-oxo-2-



Scheme 5. A plausible mechanism for the formation of N-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4H)-yl)isonicotinamide.

phenyl-1,2-dihydroquinazolin-3(4*H*)-yl)isonicotinamide **7a–j** derivatives using 2-aminoethanesulfonic acid (taurine) as a recyclable heterogeneous organocatalyst. Additionally the use of readily available and inexpensive catalyst 2-aminoethanesulfonic acid (taurine) make this system highly atom economical which makes the overall synthesis, is applicable in the quick access to relevant pharmaceutical molecules in one pot. This reaction is expected to open a new convenient and versatile route to access the structurally important spirooxindole dihydroquinazolinones family. The catalyst could be recovered and recycled without a significant loss in the catalytic activity, which is one of the most important limitations associated with the use of homogeneous catalysts.

The supplementary information provides full experimental procedures and characterization of all compounds in this article.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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