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Eco-Friendly Preparation of Quinazolinone and Spiroquinazolinone Derivatives in Water Using Surfactant Assisted Method

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Abstract

An environmentally safer and efficient method has been developed for the synthesis of quinazolinone and spiroquinazolinone derivatives in aqueous medium using a surfactant-assisted catalytic system. The present work mainly focuses on the use of water as green solvent along with Triton X-100 surfactant and L-proline as organocatalyst for carrying out multicomponent reactions under mild reaction conditions. Quinazolinone derivatives are known for a wide range of biological activities and therefore continue to attract attention in medicinal and synthetic chemistry. In the developed method, isatoic anhydride, substituted benzaldehydes or isatins, and different primary amines were reacted smoothly at room temperature to afford the desired products in good to excellent yields. The use of surfactant played an important role in improving the solubility of reactants in water by formation of micelles, which enhanced the reaction efficiency significantly. A series of quinazolinone and spiroquinazolinone analogues were synthesized and characterized using IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. The effect of substituents on reaction progress was also studied and it was observed that electron withdrawing groups reduced the reaction rate while halogen substituted substrates reacted more efficiently. The present protocol offers several advantages such as easy workup, reduced reaction time, avoidance of toxic organic solvents, simple purification process and ecofriendly reaction conditions. Due to operational simplicity and greener nature, the developed synthetic procedure may become useful for future preparation of biologically active quinazolinone based heterocyclic compounds.

Keywords: Quinazolinone, Spiroquinazolinone, Green synthesis, Water medium, Surfactant catalysis, Heterocyclic compounds

Introduction

Nitrogen-containing heterocyclic compounds are very important in medicinal and synthetic chemistry because many of them show useful biological activities.[1-3] Among these compounds, quinazolinones have attracted considerable interest due to their broad pharmacological properties such as antibacterial, anticancer, antifungal, anti-inflammatory and anticonvulsant activities. Because of these applications, researchers are continuously trying to develop easier and cleaner methods for their synthesis.[4-8] Figure **1** represents the structure of some compounds having heterocyclic pharmacophore with nitrogen atoms and showing diverse range of biological activity.

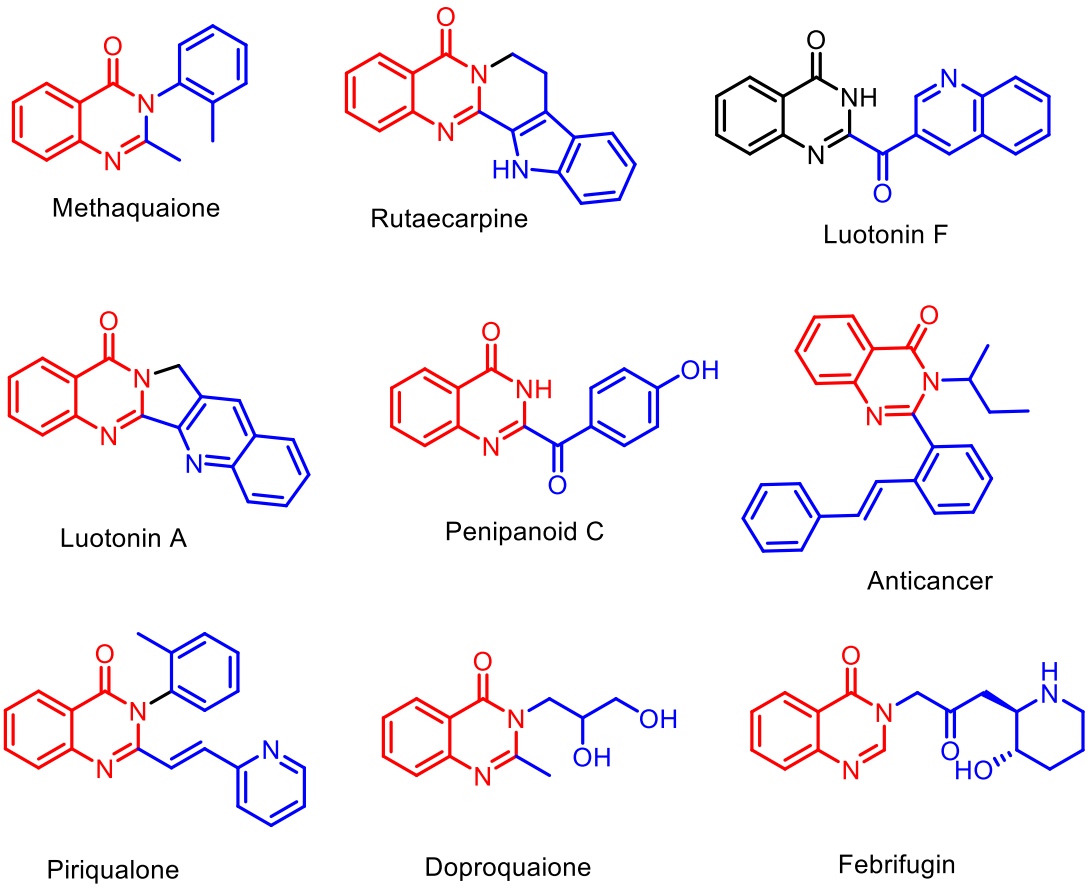


Figure 1: Structure showing new quinazolinone based drug molecules

Nowadays, green chemistry has become an important area in organic synthesis. Traditional synthetic methods often involve toxic solvents, expensive catalysts and harsh reaction conditions which generate large amounts of chemical waste.[9-12] To overcome these issues, reactions performed in water are getting more attention because water is cheap, non-toxic and easily available. Still, one common difficulty in aqueous organic reactions is the poor solubility of organic reactants. To solve this problem, surfactants can be used. Surfactants form micelles in water and these micelles create a hydrophobic cavity where organic molecules can come close together and react more efficiently. Because of this property, surfactant-mediated reactions in water are now considered useful alternatives for sustainable synthesis.[13-15]

Multicomponent reactions are also useful from green chemistry viewpoint because several reactants combine in a single step to produce complex products with minimum purification.[15] Such reactions reduce solvent consumption, save time and improve atom economy.[16-20] In the present work, an environmentally friendly method has been described for the synthesis of quinazolinone and spiroquinazolinone derivatives using aqueous surfactant medium. L-proline was used as organocatalyst while Triton X-100 acted as surfactant. The reactions proceeded smoothly at room temperature and produced the desired products in satisfactory yields.

Experimental Section

Materials and Instruments

All chemicals and solvents used in the present work were purchased from commercial suppliers and used directly without further purification. Reaction progress was monitored by thin layer chromatography (TLC) using silica gel coated plates. Melting points were recorded in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are expressed in ppm. IR spectra were recorded using KBr pellets and mass spectra were obtained through ESI-MS technique.

General Procedure for the Synthesis of Quinazolinone Derivatives

Isatoic anhydride (1 mmol), substituted benzaldehyde (1 mmol) and primary amine (1 mmol) were taken in a round bottom flask containing 15 mL water. L-proline (10 mol%) and Triton X-100 were then added to the mixture. The reaction was stirred continuously at room temperature. Completion of reaction was checked by TLC. After completion, the precipitated product was filtered, washed with distilled water and recrystallized from ethanol to afford pure quinazolinone derivatives.

General Procedure for Spiroquinazolinone Derivatives

A mixture of isatoic anhydride, isatin and substituted primary amine in equimolar ratio was stirred in aqueous medium in presence of L-proline and Triton X-100. The reaction mixture gradually produced a solid product which was isolated by filtration. Recrystallization with ethanol gave the desired spiroquinazolinone compounds.

Characterization Data of Representative Compounds

2-(4-chlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4a): Light yellow solid, IR (KBr): 3411, 1635, 1608, 1585, 1508, 1485, 1390, 1298, 1245, 1159, 1068, 1029, 956, 835, 601 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 4.81 (s, 1H), 6.02 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.25−7.31 (m, 4H), 8.01 (dd, *J* = 7.5, 1.5 Hz, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm: 74.3, 114.1, 114.5, 114.6, 116.9, 119.4, 120.6, 126.9, 128.1, 129.0, 129.5, 132.0, 133.7, 136.5, 137.9, 145.4, 159.9, 163.2; Anal. Calcd for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; N, 8.37. Found: C, 71.73; H, 4.55; N, 8.35

3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (4b): Light yellow solid, IR (KBr): 3411, 1635, 1608, 1585, 1508, 1485, 1390, 1298, 1245, 1159, 1068, 1029, 956, 835, 601 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 3.74 (s, 3H), 4.81 (s, 1H), 6.02 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.25−7.31 (m, 2H), 8.01 (dd, *J* = 7.5, 1.5 Hz, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm: 55.2, 74.4, 113.9, 114.3, 114.6, 116.9, 119.4, 120.6, 126.9, 128.1, 129.0, 129.5, 132.0, 133.7, 136.5, 137.9, 145.4, 159.9, 163.2; Anal. Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.61. Found: C, 69.19; H, 4.74; N, 7.65.

3'-(4-hydroxyphenethyl)-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione(6a): Orange powder; IR (KBr) (ν_{max}, cm^{-1}): 3361, 3254, 2946, 1712, 1650, 1503; ^{1}H NMR (300MHz, DMSO-d_6): δ ppm 2.83(t, 2H); 3.53(t, 2H); 6.68-6.75(m, 3H); 7.00-7.02(m, 3H); 7.17-7.44(m, 5H); 7.67(d, 1H); 8.29(s, 1H); 9.06(s, 1H); ^{13}C NMR (75MHz,

DMSO-d_6): δ ppm; 168.2, 141.1, 106.2, 130.7, 162.0, 155.7, 147.0, 115.2, 112.8, 116.1, 132.0, 115.8, 113.3, 127.8, 137.2, 128.2, 128.0, 130.2, 115.8, 130.1, 130.5, 116.9, 42.7, 33.7; MS (ESI) m/z = 386 $(M+H)^+$; Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90; Found: C, 71.72; H, 4.99; N, 10.88.

3'-Phenyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6b): Orange powder; IR (KBr) (ν_{max}, cm^{-1}): 3361, 3254, 2946, 1712, 1650, 1503; ^1H NMR (300MHz, DMSO-d_6): δ ppm 7.26-7.11 (m, 5H), 7.75-7.66 (m, 3H), 7.91-7.87 (m, 3H), 8.26-7.91 (m, 2H), 11.70 (s, 2H); ^{13}C NMR (75MHz, DMSO-d_6): δ ppm 86.87, 112.66, 113.06, 114.54, 114.68, 121.34, 127.94, 129.68, 129.81, 130.15, 134.03, 134.21, 135.69, 137.61, 141.44, 146.27, 163.91, 175.64; MS (ESI) m/z = 347 $(M+H)^+$; Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; Found: C, 73.80; H, 4.31; N, 15.23.

Results and Discussion

The present work was started with optimization of reaction conditions using isatoic anhydride, benzaldehyde and aniline as model substrates. Different organocatalysts such as L-proline, hydroxyproline, thiaproline and cinchonidine were examined in aqueous medium. Among all the catalysts screened, L-proline gave the best result. In absence of surfactant, the reaction proceeded very slowly and product yield remained poor even after long stirring time. However, after adding Triton X-100, the reaction became much faster and yield improved significantly. This may be due to formation of micelles which increased the interaction between hydrophobic reactants inside aqueous medium. Table **1** shows the results obtained for screening of catalysts.

Table 1. Screening of organocatalyst

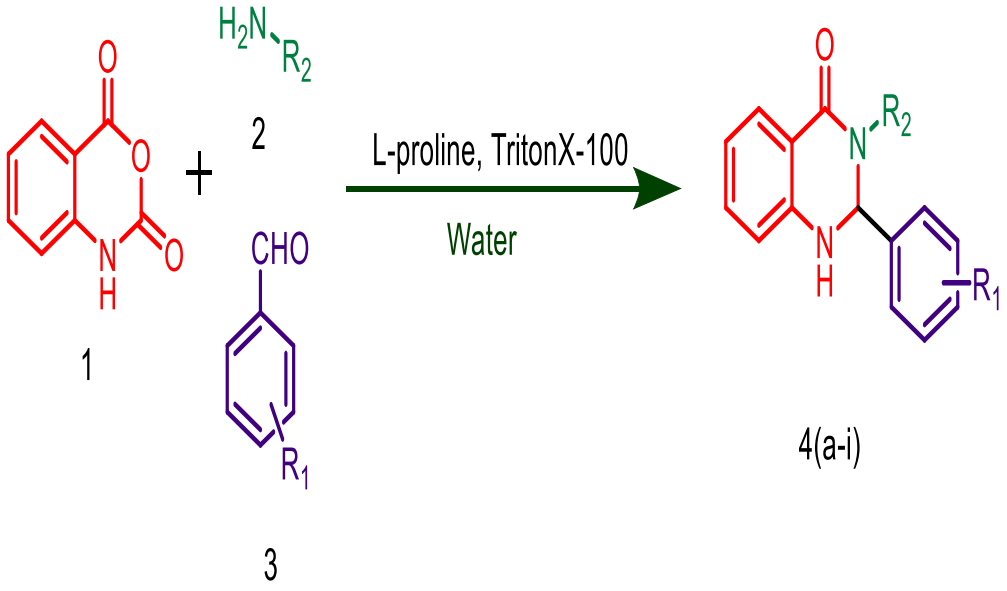
Entry	Organocatalyst	surfactant	Time	Yield[b] %
1	L-Proline	-	8h	32
2	L-Thiaproline	-	8h	15
3	L-hydroxy proline	-	8h	12
4	L-proline methyl ester	-	8h	15
5	L-proline long chain ester	-	8h	10
6	Cinchonidine	-	8h	20
7	None	Triton X-100	8h	15
8	L-Proline	Triton X-100	1h	90
9	L-Thiaproline	Triton X-100	1.5h	82
10	L-hydroxy proline	Triton X-100	1h	75
11	L-proline methyl ester	Triton X-100	2h	70
12	L-proline long chain ester	Triton X-100	1h	85
13	Cinchonidine	Triton X-100	1.5h	76
14	L-Proline	Triton X-114	2h	80

The optimized conditions involved L-proline (10 mol%) and Triton X-100 at room temperature in water. Under these conditions, different substituted aldehydes and amines were used successfully for synthesis of quinazolinones. It was observed that electron withdrawing groups like nitro group slowed down the reaction and reduced yield. On the other hand, halogen substituted aldehydes showed better reactivity and gave products in comparatively shorter time. Table 2 summarizes the reaction progress at different concentration of surfactant catalysts.

Table 2. Screening of Surfactant Concentration

Organo-catalyst	Surfactant	Time	Yield[d]
L-Proline	Triton X-100 at cmc	4h	91
L-Proline	Tween- 100 at below cmc	3h	25
L-Proline	Tween-20 at above cmc	2.5h	32

To further expand the scope of this synthetic methodology and examine the effect of substrate variation, several substituted primary amines and benzaldehydes were employed for the synthesis of quinazolinone analogues. In this protocol, L-proline was used as an organocatalyst while Triton X-100 acted as a surfactant in aqueous medium. It was noticed that benzaldehydes containing a nitro group at the para position significantly reduced the reaction progress, and even after prolonged reaction time the reaction did not go to completion, giving very low product yield. Interestingly, halogen-substituted benzaldehydes showed much better reactivity, and the reactions were completed within a shorter time (around 1.5 h).



Scheme 1: Synthesized Quinazolinone derivatives using Bezaldehyde

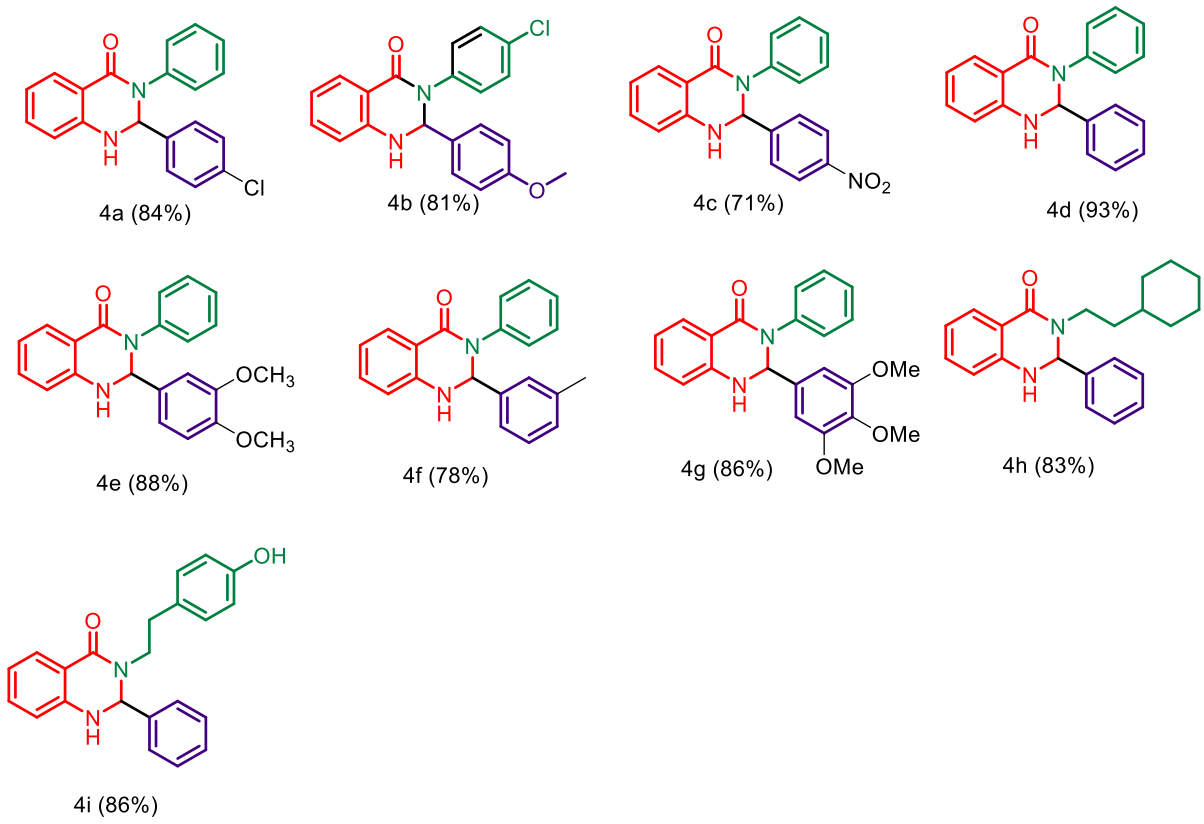
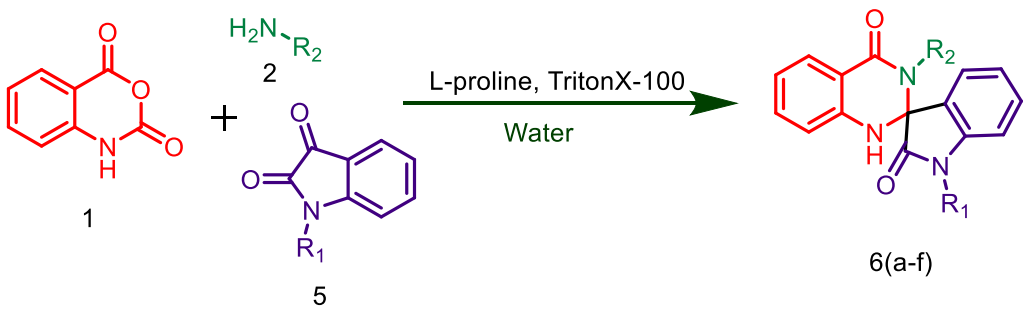


Figure 2: Synthesized quinazolinones structures.

To further extend the synthetic applicability of the developed methodology, Isatin, Isatoic anhydride, and different primary amines were utilized for the synthesis of spiro quinazolinone analogues. Tyramine, aniline, and cyclohexylethyl amine were selected in order to achieve wider substrate variation. Fortunately, the reaction proceeded smoothly under the optimized conditions and the desired spiro analogues were obtained in good yields. Altogether, 6 different analogues were synthesized as presented in Figure 3. In this way, a small library of spiro quinazolinone derivatives was successfully prepared. All the synthesized quinazolinone and spiroquinazolinone analogues were properly characterized by using ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, and IR spectral analysis. The formation of spiroquinazolinone derivatives was mainly confirmed by the appearance of the characteristic quaternary carbon signal in their spectra.



Scheme 2: Synthesis of Quinazolinones using Isatin Derivatives

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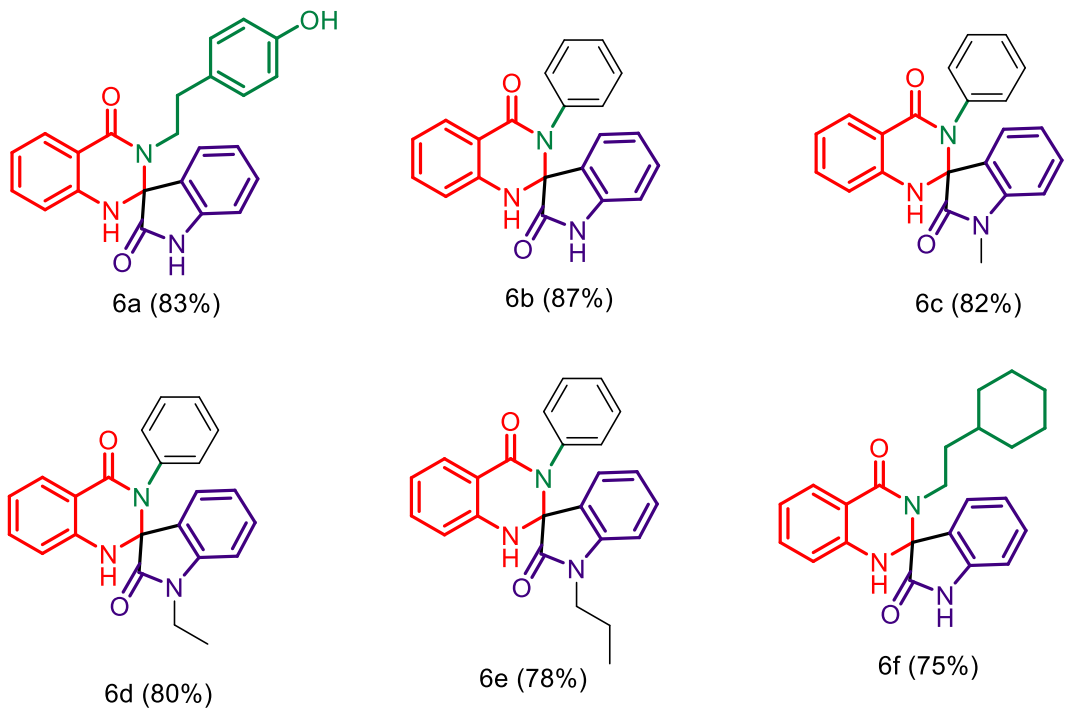


Figure 3: Synthesized spiroquinazolinones structures.

The plausible mechanistic pathway of reaction has also been proposed which is schematically depicted in figure **4**. Since the reactants (Isatoic anhydride, Benzaldehydes or Isatins and Amine derivatives) were insoluble, therefore the reaction was not efficient. Applying surfactant at the CMC leads to the formation of micelle in the reaction medium. Which form a hydrophobic cavity and lipophilic reactants molecules were trapped inside cavity, which triggers the efficient reaction and facilitates the product conversion

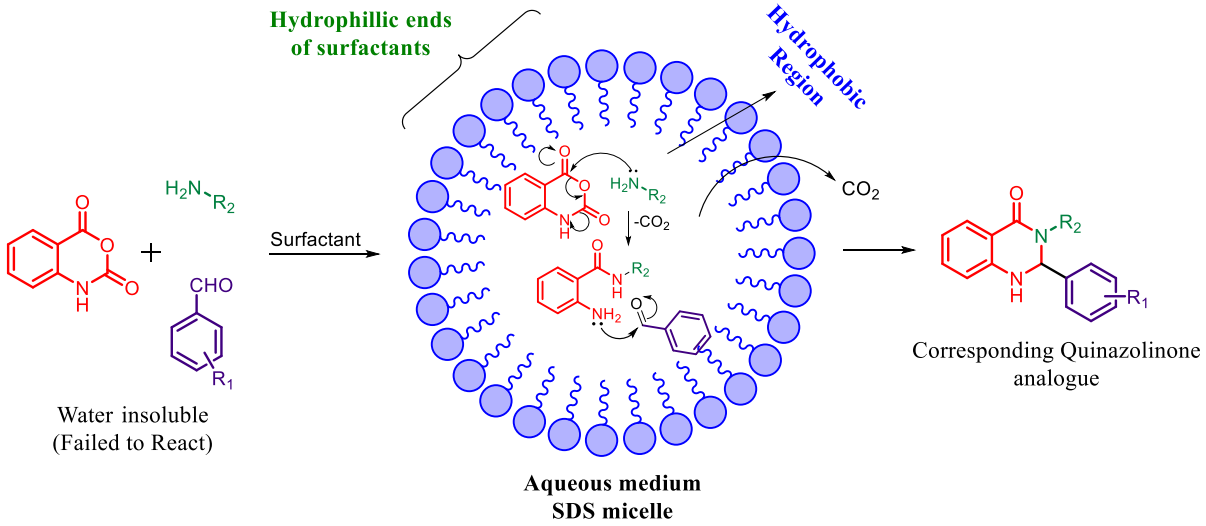
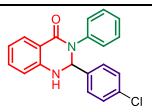
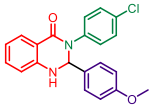
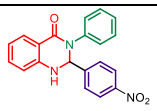
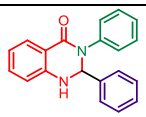
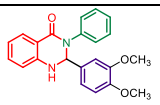
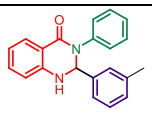
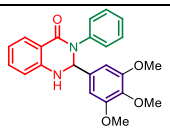
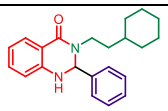
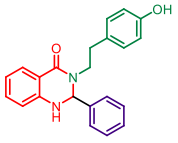
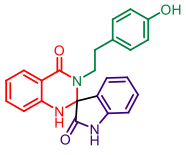
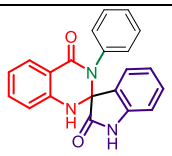
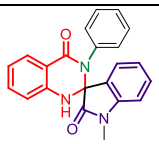
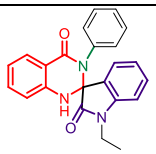
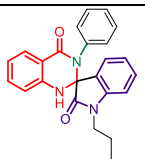
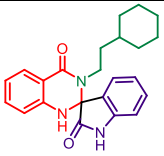


Figure 4: Plausible mechanistic pathway for reaction.

Table 3. Synthesis of Quinazolinones and Spiroquinazolinones.

Entry	Compound No.	Structure	Yield (%)	Reaction Time (h.)	Melting Point (^{0}C)
1	4a		82	6	179
2	4b		80	5	186
3	4c		72	10	216
4	4d		76	6	174
5	4e		82	5	192
6	4f		80	5	158
7	4g		86	4	186
8	4h		83	6	142
9	4i		86	6	196
10	6a		83	5	210

11	6b		82	5	224
12	6c		87	5	208
13	6d		80	5	234
14	6e		78	5	242
15	6f		75	6	226

Conclusion

A simple and greener protocol has been developed for synthesis of quinazolinone and spiroquinazolinone derivatives using water as reaction medium. The use of surfactant Triton X-100 and organocatalyst L-proline allowed the reactions to proceed under mild conditions without use of toxic solvents or expensive catalysts. The method offers several advantages including easy workup, moderate to high yields, room temperature conditions and environmentally safer reaction process. The synthesized quinazolinone derivatives may be useful for future medicinal chemistry studies because quinazolinone scaffold is already known for various biological activities.

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