RESEARCH ARTICLE

*European Journal of Advanced Chemistry Research*
*www.ej-chem.org*

# A Catalyst Free Surfactant Mediated Multicomponent Synthesis of Quinazolinone Derivatives in Aqueous Media

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**ABSTRACT**

**A versatile and green synthetic protocol has been developed for synthesis of substituted quinazolinone and spiroquinazolinone heterocycles effectively via a combined surfactant mediated system. The use of Surfactant, water as reaction medium, room temperature, high yield and ease of purification made the process very effective and ecofriendly in nature. To demonstrate the wide scope of reaction Isatoic anhydride and Isatin used as reactants in different sets of reactions that leads to formation of Quinazolinones and spiroquinazolinones. A total of 12 derivatives has been prepared and characterized by all the spectroscopic data. The developed protocol presents a better and environmentally efficient methodology to get these heterocycles.**

**Keywords:** Aqueous, Heterocyclic, Quinazolinones, Surfactant, Sustainable Chemistry.

**Published Online:** May 06, 2023

**ISSN**: 2684-4478

**DOI**: 10.24018/ejchem.2023.4.3.139

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## I. Introduction

Nitrogen based heterocyclic systems attracts special attention from scientific community due to the wide range of biological properties associated with them. In order to prepare heterocyclic frameworks at rapid speed synthetic medicinal chemists around the globe are facing heavy burden of development of environmentally benign protocols due environmental constraints. This situation has shifted the paradigm towards the developing green protocols to construct complex structures. In this direction multicomponent reactions provides a significant alternative over the other synthetic methodologies in terms of greenness and ease of purification [1]-[3]. The multicomponent reactions meet the criteria of green chemistry from the atom economical perspectives. Carrying out organic synthesis in water is not only limited up to green solvent but water as solvent is very crucial for selectivity, creativity, catalyst recovery and product isolation [4], [5]. The prime difficulty in using water as solvent is the insolubility of reactants and catalyst. This problem can be overcome by the "On Water" concept involving the use of surfactant to initiate the micelle-promoted reaction in aqueous medium [6]. Saito and Yamamoto also reported that presence of water increases the reactivity and stereoselectivity of the reaction [7]. Several heterocycles as furans, acridines, indoles, pyrazines, Pyrazolines, Pyridine, Pyrimidine, and Imidazole are known to be synthesized in aqueous medium [8]-[11]. The use of surfactants in concentrations exceeding the critical micelle concentration is an excellent alternative to mediate the organic reactions in aqueous conditions. The inner hydrophobic cavity of micelles traps the hydrophobic reactant molecules inside the cavity to bring them in close proximity resulting in product formation. We believe that this technique can be applied for multicomponent reactions too. In this scenario the discovery of any new green protocol for synthesis of therapeutically important molecule via a multicomponent synthetic procedure is of great need.

Quinazolinones and spiroquinazolinones represents very fascinating and interesting class of heterocyclic molecules due to wide range of biological properties associated with it [12]-[15]. These molecules are associated with them the diverse range of biological like antibacterial, antifungal, antimycobacterial, anti-inflammatory, antidiabetic, anticancer, antimalarial, antileishmanial and anticonvulsant activities which make them very crucial in medicinal chemistry and drug discovery programs [16],[17].

A number of synthetic protocols has reported in literature to construct the quinazolinone nucleus among them the multicomponent reactions are very prominent [18],[19]. Transition metal catalyzed coupling reactions are also the most frequently used methodology for the synthesis of quinazolinones.[20] Apart from these several other methods are reported with lot of limitations in terms of substrate scope and feasibility of reactions [21]. Very few reports are present involving employment of multicomponent reactions for synthesis of quinazolinone nucleus which are not suitable from green chemistry perspective due to use of toxic metals, microwave reaction condition, high pressure conditions, high temperature, use of toxic solvents, large reaction time and problem of purification [22]. Our group is working in the area of development of multicomponent reactions for synthesis of biologically active heterocycle in ecofriendly manner [23]-[25]. We have shown earlier the first report regarding synthesis of quinazolinone heterocycles by using supramolecular catalysis potential of cyclodextrins in water at room temperature [26]. We have proposed the first green synthesis of quinazolinone based natural product Tryptanthrin [27]. In the continuation of our efforts to find the sustainable methodologies for synthesis involving multicomponent approach here we wish to report the first organocatalyzed, environment friendly synthesis of quinazolinone based heterocycles in water. Water as a solvent is proved to be a very effective alternative to carry out organic transformations. Water as a solvent always preferred over others due to its easy availability and cheap cost. Moreover, the non-toxic nature and nonflammable property make it right choice to perform tedious organic synthesis.

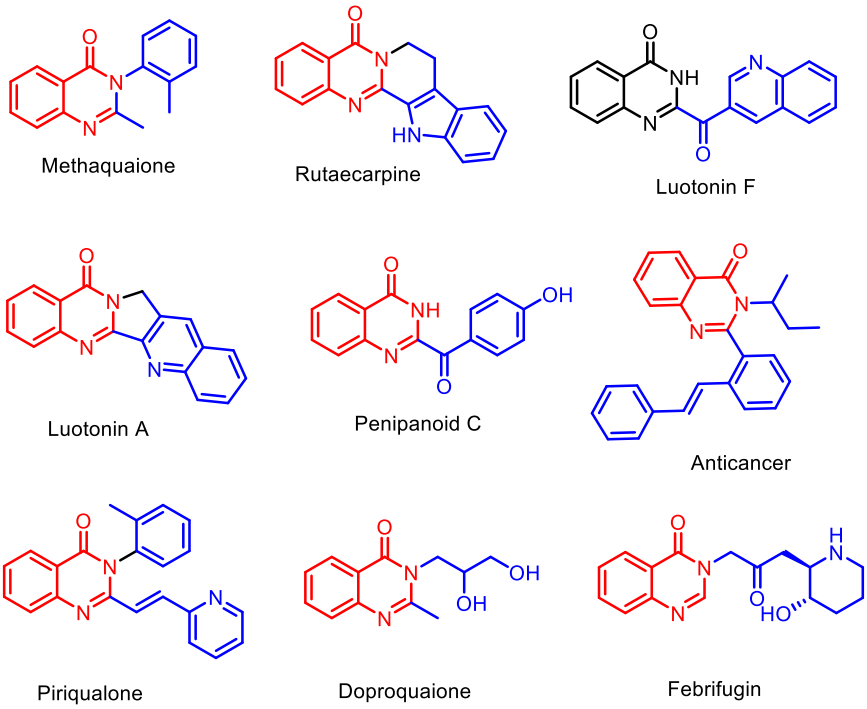


Fig. 1. Structure showing new quinazolinone based drug molecules.

## II. Experimental

Unless otherwise specified all the reagents were purchased from Sigma-Aldrich and were used without further any purification. The common organic solvents were purchased from Ranchem. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on 230-400 mesh silica gel. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates visualized under UV light, iodine or KMnO4 staining. 1H and 13C NMR spectra were recorded on a Brucker DRX -300 Spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Mass spectra (ESI MS) were obtained by Micromass Quattro II instrument. Melting points were obtained on a COMPLAB melting point apparatus and are uncorrected.

Synthesis of spiroquinazolinone derivatives: Isatoic anhydride (1 mmol), Isatin (1 mmol) and Primary amine derivative (1 mmol) were mixed in 100 ml round bottom flask in 15 ml water fitted with magnetic stirrer. L- Proline 10 mol% was added followed by addition of surfactant Triton X-100 2 ml. Reaction mixture was stirred at room temperature up to completion of reaction. Progress of reaction was monitored through TLC. After completion the solid mass filtered out from reaction mixture and washed twice with distilled water. Product was recrystallized with ethanol to afford the desired quinazolinone derivatives.

## III. CHARACTERIZATION DATA

**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.

**2-(4-nitrophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4c):** Light yellow solid, 247−249 °C; IR (KBr): 3411, 1635, 1608, 1585, 1551, 1485, 1365, 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, 2H), 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, 3H), 8.01 (dd, *J* = 7.5, 1.5 Hz, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm: 74.4, 113.9, 114.5, 114.8, 116.2, 119.6, 120.2, 126.4, 128.6, 129.2, 129.8, 132.2, 133.3, 136.1, 137.9, 145.6, 159.4, 163.1; Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17; O Found: C, 69.54; H, 4.40; N, 12.15

**2,3-diphenyl-2,3-dihydroquinazolin-4(1H)-one (4d):** 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), 6.61-6.72 (m, 3H), 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, 2H); 13C NMR (75 MHz, $CDCl_3$) δ ppm: 74.4, 113.6, 114.7, 114.9, 116.5, 119.8, 121.4, 126.1, 128.6, 129.4, 130.2, 132.2, 133.4, 136.7, 138.2, 144.1, 159.3, 163.8; Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33;. Found: C, 79.96; H, 5.35; N, 9.36

**2-(3,4-Dimethoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4e):** White solid, IR (KBr): 3411, 2932, 1635, 1616, 1508, 1485, 1463, 1390, 1267, 1236, 1137, 1120, 1068, 1029, 997, 952, 862, 694, 617 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 3.85 (s, 3H), 3.88 (s, 3H), 5.22 (s, 1H), 6.30 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.18−7.22 (m, 2H), 7.30−7.34 (m, 4H), 8.01 (d, *J* = 7.0 Hz, 1H); Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.18; H, 5.38; N, 7.88.

**3-Phenyl-2-m-tolyl-2,3-dihydroquinazolin-4(1H)-one (4f):** White solid, IR (KBr): 3303, 2927, 1635, 1616, 1512, 1487, 1446, 1400, 1346, 1317, 1298, 1176, 1114, 1068, 950, 864, 619 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.27 (s, 3H), 4.74 (s, 1H), 6.06 (s, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 7.13−7.20 (m, 6H), 7.27−7.31 (m, 3H), 8.03 (dd, *J* = 8.0, 1.5 Hz, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm: 21.4, 74.6, 114.8, 116.9, 119.5, 123.8, 126.7, 126.8, 127.3, 128.6, 129.0, 129.7, 133.8, 138.5, 139.8, 140.6,145.2, 163.1; Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 79.99; H, 5.90, N, 8.79.

**3-Phenyl-2-(3,4,5-trimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (4g):** White solid, IR (KBr): 3411, 2941, 1635, 1616, 1521, 1502, 1463, 1417, 1394, 1353, 1232, 1124, 1070, 1004, 952, 765, 613 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 3.72 (s, 6H), 3.81 (s, 3H), 4.87 (s, 1H), 6.04 (s, 1H), 6.56 (s, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 7.20−7.24 (m, 3H), 7.30−7.36 (m, 3H), 8.03 (d, *J* = 7.0 Hz, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm: 56.0, 60.8, 74.7, 114.8, 116.8, 119.5, 120.3, 120.5, 126.8, 127.0, 128.9, 133.9, 135.3, 138.2, 140.5, 145.5, 153.2, 163.1; Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.60; H, 5.85; N, 6.98.

**3-(2-cyclohexylethyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (4h):** Creamy White solid, IR (KBr): 3303, 2927, 1635, 1616, 1512, 1487, 1446, 1400, 1346, 1317, 1298, 1176, 1114, 1068, 950, 864, 619 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.61-1.38(m, 13H); 3.18(t, J = 8 Hz, 2H); 6.01(s, 1H); 6.29(s, 1H); 6.75(t, 1H); 7.019(d, 1H); 7.31-7.44(m, 6H); 7.61(d, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm:; 162.0, 145.3, 139.2, 83.2, 116.1, 113.3, 128.0, 126.9, 124.4, 128.5, 130.5, 116.9, 128.5, 127.1, 33.6, 33.3, 32.9, 25.8, 26.0, 42.4, 32.7 Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38; Found: C, 79.08; H, 79.06, N, 8.34.

**3-(4-hydroxyphenethyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (4i):** Dark Brown solid, IR (KBr): 3303, 2927, 1635, 1616, 1512, 1487, 1446, 1400, 1346, 1317, 1298, 1176, 1114, 1068, 950, 864, 619 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.85(t, 2H); 3.53(t, 2H); 6.01(t, 1H); 6.29(s, 1H); 6.75-6.689(m, 3H); 7.00-7.02(m, 3H); 7.32-7.44(m, 6H); 7.67(d, 1H); 9.06(s, 1H); 13C NMR (75 MHz, $CDCl_3$) δ ppm:;

162.0, 155.7, 83.2, 145.3, 116.1, 139.2, 132.3, 115.8, 113.3, 128.0, 126.9, 130.2, 128.5, 126.3, 130.3, 128.4, 127.0, 45.9, 34.1 Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; Found: C, 76.78; H, 5.88, N, 8.10.

**3'-(4-hydroxyphenethyl)-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione(6a):** Orange powder; IR (KBr) ($\nu_{max}$, $cm^{-1}$): 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) ($\nu_{max}$, $cm^{-1}$): 3361, 3254, 2946, 1712, 1650, 1503; $^1$H 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.

**1-methyl-3'-phenyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6c):** Orange powder; IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3361, 3254, 2946, 1712, 1650, 1503; $^1$H NMR (300MHz, DMSO-$d_6$): δ ppm 3.42(s, 3H), 7.26-7.10 (m, 4H), 7.74-7.65 (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 $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82; Found: C, 74.29; H, 4.86; N, 11.78

**1-ethyl-3'-phenyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6d):** Yellow powder; IR (KBr); ($\nu_{max}$, $cm^{-1}$): 3372, 3268, 2970, 1710, 1648, 1505; $^1$H NMR (300MHz, DMSO-$d_6$): δ ppm 1.40 (t, *J* =6.47Hz, 3H); 4.36 (q, *J*=6.3Hz, 2H); 6.74-6.63 (m, 5H); 7.17-7.10 (m, 4H); 7.29-7.24 (m, 2H); 7.48-7.41 (m, 1H); 7.94 (d, *J* =8.3Hz,1H); 10.23 (s, 1H); $^{13}$C NMR ( 75MHz, DMSO-$d_6$): δ ppm 13.71, 41.33, 93.11, 110.36, 113.37, 114.26, 115.17, 118.34, 128.44, 129.88, 129.91, 132.16, 134.15, 135.21, 135.69, 138.81, 141.44, 145.93, 163.81, 175.64; MS (ESI) m/z = 370 $(M+H)^+$; Anal. Calcd for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37; Found: C, 74.80; H, 5.21; N, 11.34.

**3'-Phenyl-1-propyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6e)** Cream powder; IR (KBr); ($\nu_{max}$, $cm^{-1}$): 3380, 3298, 2972, 1721, 1650, 1503; $^1$H NMR (300MHz, DMSO-$d_6$): δ ppm; 0.79 (t, *J* =Hz, 3H), 1.45-1.40 (m, 2H), 3.36-3.27 (m, 1H), 3.72-3.59 (m, 1H), 6.96 (t, *J* =8.22 Hz, 2H), 7.04-6.97 (m, 4H), 7.18-7.03 (m, 3H), 7.32(t, *J* =Hz, 1H), 7.35-7.19 (m, 2H), 7.49 (d, *J* =10.2Hz, 1H), 8.21 (d, 1H, *J* =8.9Hz); $^{13}$C NMR (75MHz, DMSO-$d_6$): δ ppm 11.51, 20.4, 42.47, 109.66, 114.14, 114.24, 114.96, 117.34, 123.84, 129.44, 130.81, 130.15, 134.13, 134.21, 136.69, 137.61, 141.44, 146.27, 163.91, 175.64; MS (ESI) m/z = 384 $(M+H)^+$; Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96; Found: C, 75.14; H, 5.49; N, 10.97

**3'-(2-cyclohexylethyl)-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6f):** Yellow powder; IR (KBr); (vmax, cm-1): 3372, 3268, 2970, 1710, 1648, 1505; 1H NMR (300MHz, DMSO-d6): δ ppm 1.38-1.62(m, 13H), 3.28(t, 2H); 6.75(t, 1H), 7.00(d, 1H); 7.17-7.44(m, 5H), 7.67(d, 1H), 8.28(s, 1H), 13C NMR (75MHz, DMSO-d6): δ ppm 167.8, 141.1, 106.2, 130.7, 162.0, 147.3, 115.2, 122.8, 116.1, 113.3, 127.8, 137.2, 128.2, 130.5, 116.9, 33.6, 33.3, 33.1, 25.8, 25.6, 26.2, 39.2, 32.3, MS (ESI) m/z = 376 (M+H)+; Anal. Calcd for C23H25N3O2: C, 73.57; H, 6.71; N, 11.19; Found: C, 73.60; H, 6.73; N, 11.15.

## IV. Result and Discussion

We wish to report this time the synthesis of small library of Quinazolinone library via a combined catalytic system of organocatalyst and surfactant. To the best of our belief this will be the first report of surfactant-organocatalyzed mediated synthesis of this type heterocycles. To begin our synthetic journey, we first tried to find out the best organocatalyst in water for this synthesis. To perform this investigation, we took the reaction of Isatoic anhydride, benzaldehyde and aniline as model reaction. Several commonly used catalysts in aqueous medium such as as L-Proline, L-Thiaproline, L-Hydroxyproline, L-Proline methyl ester and cinchonidine selected on the basis of their application in literature for synthesis of heterocycles are screen for reaction and results are summarized in Table-1. It is evident from the table that application of L-proline (10 mol%) in surfactant mediated condition proved to be best reaction condition for this synthesis which afforded the product in 92% yield in just 1 hour reaction time. Surprisingly in absence of surfactant the formation of desired quinazolinone was detected but the product yield was very low even after long hours of stirring. This can be attributed due to poor solubility of reactant molecules in water. With the application of surfactant Triton X-100.

The product yield increased substantially, and the reaction time reduced up to 1 hour. We observed that the best results were obtained by application of L-proline as organocatalyst, as evident from the table 1 that 92% product yield was obtained with the reaction time as low as 1 hour. By employing the surfactant to enhance the solubility of reactants via its micelle actin was proved to be a crucial step in this synthetic protocol. Hence, we decided to use L-proline as organocatalyst and Triton X-100 as surfactant to perform the multicomponent synthesis of quinazolinone derivatives.

TABLE I: 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 |

Next, we have performed the experiments regarding selection of appropriate solvent for the reaction. We screened the polar solvents like ethanol, DMF and water to facilitate the surfactant mediated mechanism at below CMC, CMC and super CMC concentrations. The results are summarized in Table II. We used two different variants of Triton (TritonX-100 and Triton-114) at three different concentrations (at 0.5[c], Sub-cmc[c] and Super-cmc[c]). We found that the application of Triton-100 surfactant at CMC in water gives the best results.

TABLE II: 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 |

Now to extend the scope of this synthetic methodology and study the substrate variation we used various substituted primary amines and benzaldehydes to prepare quinazolinone analogous. For this synthesis the L-proline used as organocatalyst and Triton X-100 as surfactant in aqueous medium. It was observed that the presence of nitro group at para position in benzaldehyde diminishes the reaction and reaction does not complete even after long reaction time and product yield was found to be very low. Surprisingly with the halogen substituted benzaldehyde's reaction took less time (1.5 h) to complete.

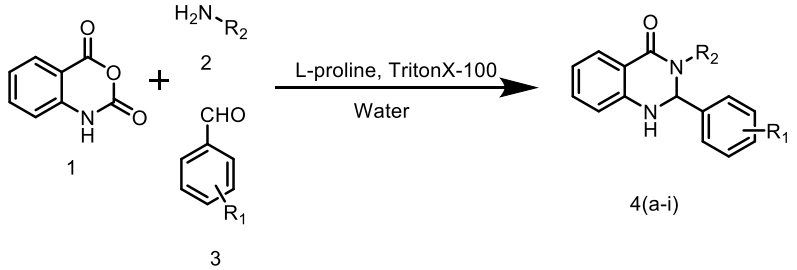


Fig. 2. Synthesized Quinazolinone derivatives using Bezaldehyde.

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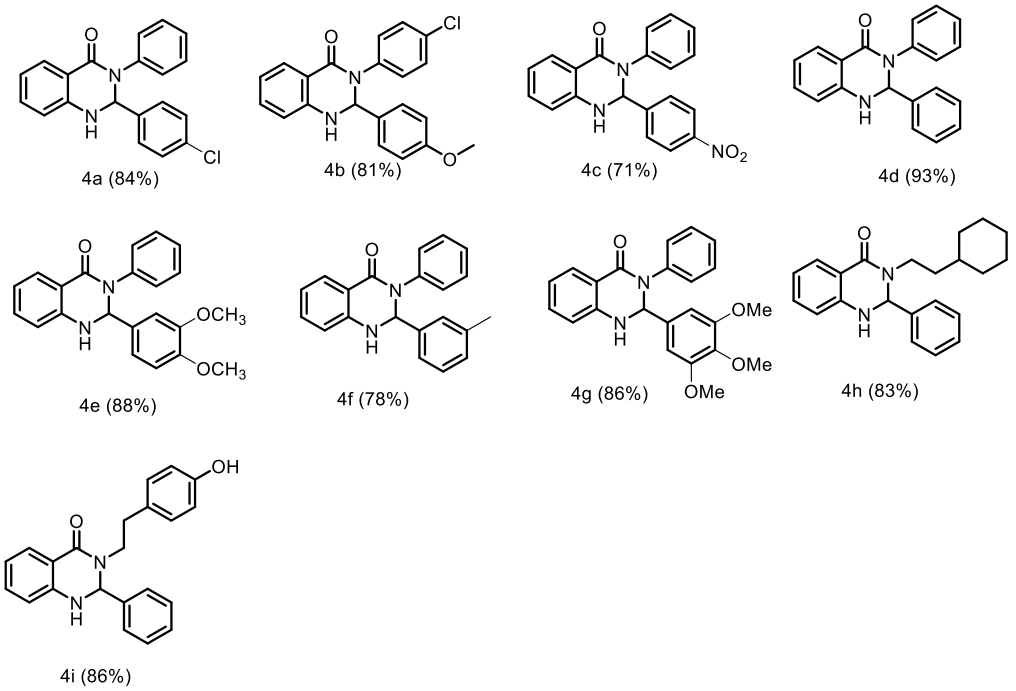


Fig. 3. Synthesized quinazolinones structures.

To further extrapolate the synthetic utility of our developed methodology we used Isatin, Isatoic anhydride and primary amines to synthesize spiro analogues of quinazolinones. Tyramine, aniline and cyclohexylethyl amine were employed to archive maximum substrate variations. To our delight the reaction was found to smooth and the desired spiro analogues were isolated in good yields. A total of 6 analogues has been synthesized shown in Fig. 5. In this manner we prepared the small library of spiro quinazolinone derivatives. All the synthesized quinazolinone and spiroquinazolinone analogous were well characterized using 1H NMR, 13C NMR, Mass Spectra and IR spectroscopy. The products were identified by the presence of quaternary carbon atom in spiroquinazolinone derivatives.

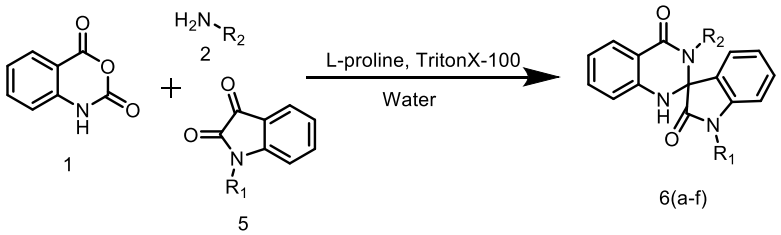


Fig. 4. Synthesis of Quinazolinones using Isatin Derivatives.

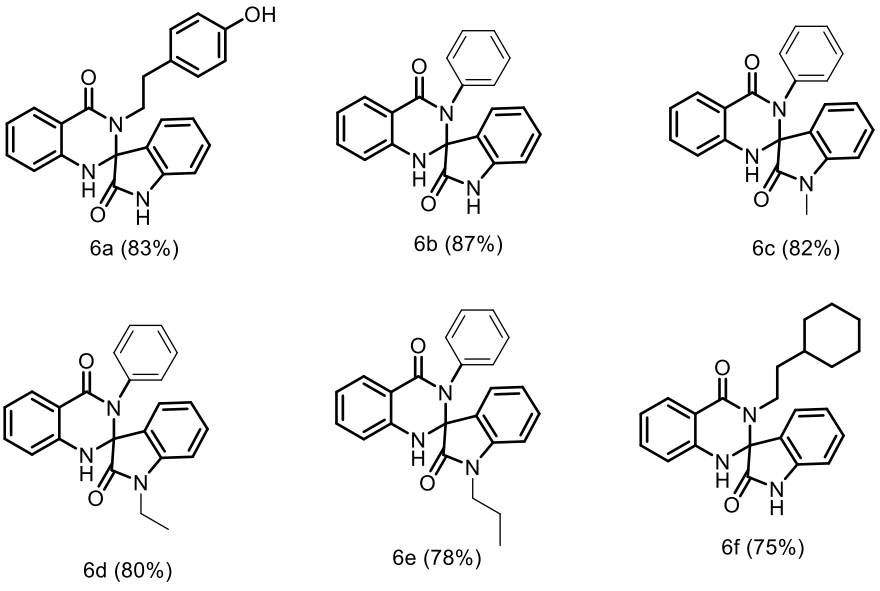


Fig. 5. Synthesized spiroquinazolinones structures.

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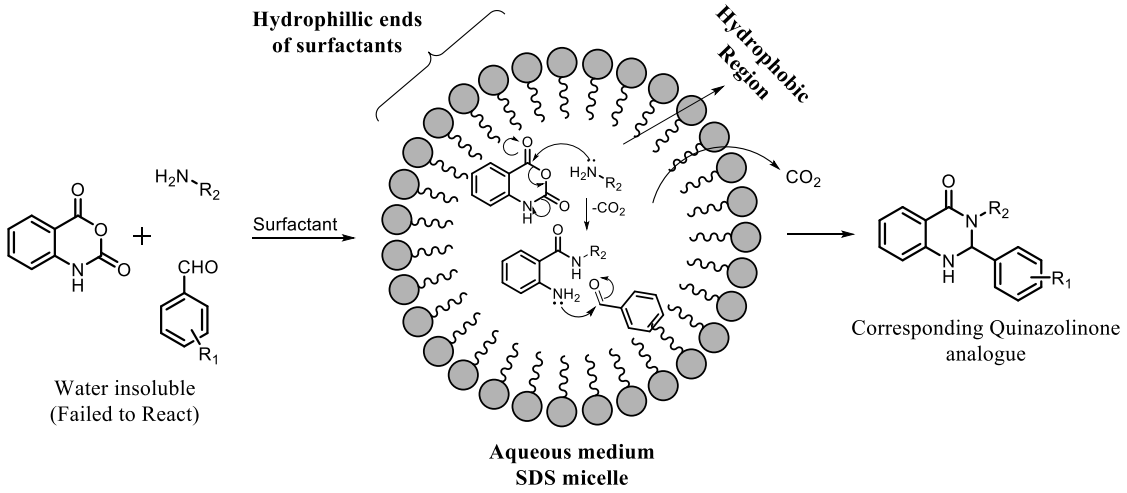
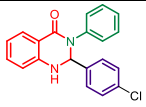
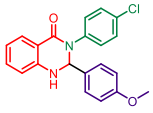
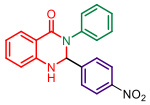
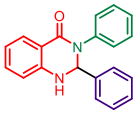
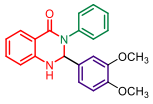
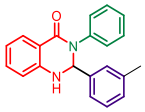
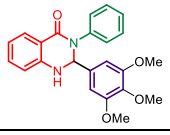
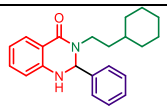
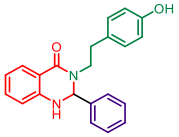
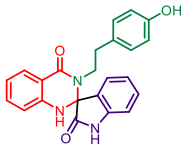
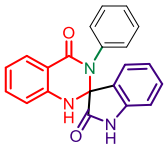
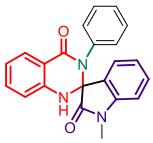
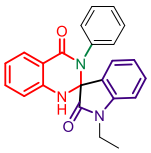
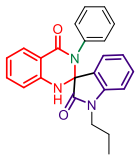
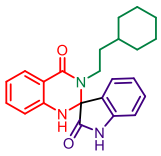



Fig. 6. Plausible mechanistic pathway for reaction.

The effect of substitution on the reaction progress have also been investigated during the synthesis of both series of compounds (with benzaldehyde and with Isatin). It was noticed and also listed in Table III that the electron withdrawing substitution like $NO_2$ group decreases the reaction rate significantly, while the halogen substitution supported the reaction as progress of reaction was very fast. The plausible mechanistic pathway of reaction has also been proposed which is schematically depicted in Fig. 6. 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 as shown in the Fig. 3. After completion the surfactant can be easily removed by extraction method. By applying similar conditions 15 molecules have been synthesized which were fully characterized by applying 1H NMR, 13C NMR, IR and mass spectroscopy. In IR Spectra the character stick peaks were obtained at 3411 $cm^{-1}$ form amine group. For newly formed methylene proton singlet was observed in proton NMR spectra near to 4.8 ppm region.

TABLE III: 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 |

| Entry | Compound No. | Structure | Yield (%) | Reaction Time (h.) | Melting Point ($^0$C) |
|---|---|---|---|---|---|
| 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

In the present work we have developed an efficient and effective protocol for the preparation of Quinazolinones and spiroquinazolinones in excellent yields. Our developed synthetic methodology involves aqueous medium using surfactant Triton X-100 as the reaction mediator. Two series of quinazolinones have been prepared to prove the wide range of substrate scope and functional group tolerance of the developed protocol. All the synthesized molecules were characterized by spectroscopic techniques. Based on the assumptions a plausible mechanistic pathway has been suggested for the product formation. The aqueous reaction medium, room temperature, cost effectiveness and environmentally benign nature of the reported methodology make this protocol an effective for synthesis of quinazolinones and spiroquinazolinones. Being privileged structures (Quinazolinones) in the field of medicinal chemistry we have firm opinion that these molecules can become important one in drug discovery program in near future.

## ACKNOWLEDGMENT

Authors acknowledge the necessary support from Lalit Narayna Mithila University Darbhanga and C. M. Science college Darbhanga. Authors also acknowledge IIT patna for helping in characterization data.

## FUNDING

Financial Support for this work was provided by Lalit Narayan Mithila University, Darbhanga, Bihar India.

## CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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