Indian Journal of Advances in Chemical Science

Research Article

Sustainable Synthesis of Quinazolinone Scaffolds in Aqueous Media: A Surfactant-Promoted Approach

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ABSTRACT

A versatile and green synthetic protocol has been developed for the synthesis of substituted quinazolinone and spiroquinazolinone heterocycles effectively through 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 eco-friendly in nature. To demonstrate the wide scope of the reaction, isatoic anhydride and isatin are used as reactants in different sets of reactions that lead to the formation of quinazolinones and spiroquinazolinones. A total of 12 derivatives have been prepared and characterized by all the spectroscopic data. The developed protocol presents a better and environmentally efficient methodology to get these heterocycles.

Key words: Aqueous, Heterocyclic, Quinazolinones, Surfactant, Sustainable chemistry.

1. INTRODUCTION

Nitrogen-based heterocyclic systems attract special attention from the scientific community due to the wide range of biological properties associated with them. To prepare heterocyclic frameworks at rapid speed, synthetic medicinal chemists around the globe are facing the heavy burden of developing environmentally benign protocols due to environmental constraints. This situation has shifted the paradigm toward developing green protocols to construct complex structures. In this direction, multicomponent reactions provide 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 perspective. Carrying out organic synthesis in water is not only limited to green solvents, but water as a solvent is very crucial for selectivity, creativity, catalyst recovery, and product isolation [4,5]. The prime difficulty in using water as a solvent is the insolubility of reactants and catalysts. 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]. Nakadai *et al*. also reported that the presence of water increases the reactivity and stereoselectivity of the reaction [7]. Several heterocycles, such as furans, acridines, indoles, pyrazines, pyrazolines, pyridine, pyrimidine, and imidazole, are known to be synthesized in an 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 to multicomponent reactions, too. In this scenario, the discovery of any new green protocol for the synthesis of therapeutically important molecules through a multicomponent synthetic procedure is of great need.

Quinazolinones and spiroquinazolinones represent a very fascinating and interesting class of heterocyclic molecules due to the wide range of biological properties associated with it [12-15]. These molecules are associated with a diverse range of biological such as antibacterial, antifungal, antimycobacterial, anti-inflammatory, antidiabetic, anticancer, antimalarial, antileishmanial, and anticonvulsant activities, [Figure 1] which make them very crucial in medicinal chemistry and drug discovery programs [16,17]. A number of synthetic protocols have been reported in the 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 a lot of limitations in terms of substrate scope and feasibility of reactions [21]. Very few reports are present involving the employment of multicomponent reactions for the synthesis of quinazolinone nucleus, which are not suitable from a green chemistry perspective due to the use of toxic metals, microwave reaction conditions, high-pressure conditions, high temperature, use of toxic solvents, large reaction time and the problem of purification [22]. Our group is working in the area of the development of multicomponent reactions for the synthesis of biologically active heterocycles in an eco-friendly manner [23-25]. We have shown earlier the first report regarding the synthesis of quinazolinone heterocycles using the 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 sustainable methodologies for synthesis involving a multi-component approach here, we wish to report the first organocatalyzed, environment-friendly synthesis of quinazolinone-based heterocycles in water. Water as a solvent has proved to be a very effective alternative to carry out

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ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2025.1302003

Received: 01th April 2025;
Revised: 06th April 2025;
Accepted: 25th April 2025;
Published: 02nd May 2025;

organic transformations. Water as a solvent is always preferred over others due to its easy availability and cheap cost. Moreover, the non-toxic nature and non-flammable properties make it the right choice to perform tedious organic synthesis.

2. 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 $KMnO_4$ staining. ^1H and ^{13}C 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 the Micromass Quattro II instrument. Melting points were obtained on a COMPLAB melting point apparatus and were uncorrected.

2.1. Synthesis of Spiroquinazolinone Derivatives

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

2.2. Characterization Data

2.2.1. 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.

2.2.2. 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.

2.2.3. 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.

2.2.4. 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.

2.2.5. 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.

2.2.6. 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.

2.2.7.3-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.

2.2.8. 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.

2.2.9. 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.

2.2.10. 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.

2.2.11. 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; ^{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.

2.2.12. 1-methyl-3'-phenyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6c)

Orange powder; IR (KBr) (ν_{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

2.2.13. 1-ethyl-3'-phenyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6d)

Yellow powder; IR (KBr); (ν_{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.

2.2.14. 3'-Phenyl-1-propyl-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6e)

Cream powder; IR (KBr); (ν_{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.

2.2.15. 3'-(2-cyclohexylethyl)-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (6f)

Yellow powder; IR (KBr); (ν_{max}, cm^{-1}): 3372, 3268, 2970, 1710, 1648, 1505; ^{1}H NMR (300MHz, DMSO-d_6): 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), ^{13}C NMR (75MHz, DMSO-d_6): 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 $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19; Found: C, 73.60; H, 6.73; N, 11.15.

3. RESULT AND DISCUSSION

We wish to report this time the synthesis of a small library of quinazolinone library through 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 of 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 a model reaction [Scheme 1]. Several commonly used catalysts in an aqueous medium, such as L-proline, L-thiaproline, L-hydroxyproline, L-proline methyl ester, and cinchonidine selected based on their application in literature for the synthesis of heterocycles are screened for reaction and results are summarized in Table 1. It is evident from the table that the application of L-proline (10 mol%) in surfactant-mediated conditions proved to be the best reaction condition for this synthesis, which afforded the product 92% yield in just 1 h reaction time. Surprisingly, in the 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 to the poor solubility of reactant molecules in water. With the application of surfactant Triton X-100, the product yield increased substantially, and the reaction time was reduced up to 1 h. We observed that the best results were obtained by application of L-proline as an organocatalyst, as evident from Table 1 that 92% product yield was obtained with the reaction time as low as 1 h. By employing the surfactant to enhance the solubility of reactants through its micelle actin was proved to be a crucial step in this synthetic protocol. Hence, we decided to use L-proline as an organocatalyst and Triton X-100 as a surfactant to perform the multicomponent synthesis of quinazolinone derivatives [Figure 2].

Table 1: Screening of organocatalyst.

Entry	Organocatalyst	surfactant	Time	Yieldb %
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 performed the experiments regarding the selection of an appropriate solvent for the reaction. We screened the polar solvents such as ethanol, DMF, and water to facilitate the surfactant-mediated mechanism below CMC, CMC, and super CMC concentrations. The results are summarized in Table 2. We used two different variants of Triton (Triton X-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.

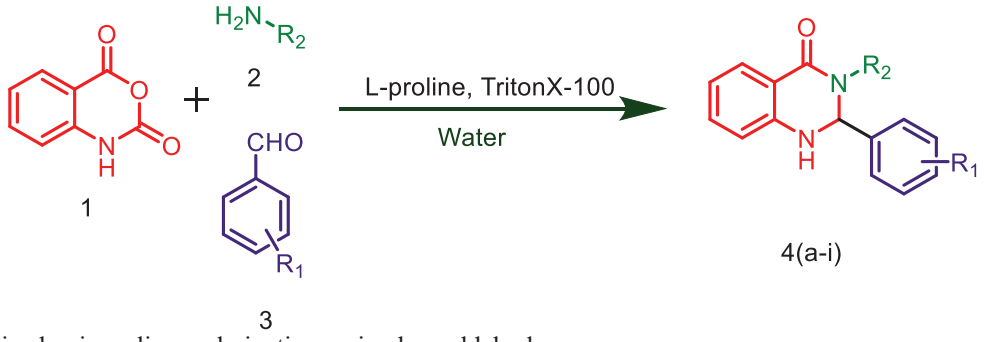
Now, to extend the scope of this synthetic methodology and study the substrate variation we used various substituted primary amines and benzaldehydes to prepare quinazolinone analogous. For this synthesis, the L-proline was used as an organocatalyst, and Triton X-100 as a surfactant in the aqueous medium.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

Table 2: Screening of surfactant concentration.

Organo-catalyst	Surfactant	Time	Yieldd
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 extrapolate the synthetic utility of our developed methodology, we used isatin, isatoic anhydride, and primary amines to synthesize spiro analogs of quinazolinones [Scheme 2]. Tyramine, aniline, and cyclohexylethyl amine were employed to archive maximum substrate variations. To our delight, the reaction was found to be smooth, and the desired spiro analogs were isolated with good yields. A total of six analogs have been synthesized, as shown in Figure 3. In this manner, we prepared a 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 atoms in spiroquinazolinone derivatives.

The effect of substitution on the reaction progress has also been investigated during the synthesis of both series of compounds (with



Scheme 1: Synthesized quinazolinone derivatives using benzaldehyde.

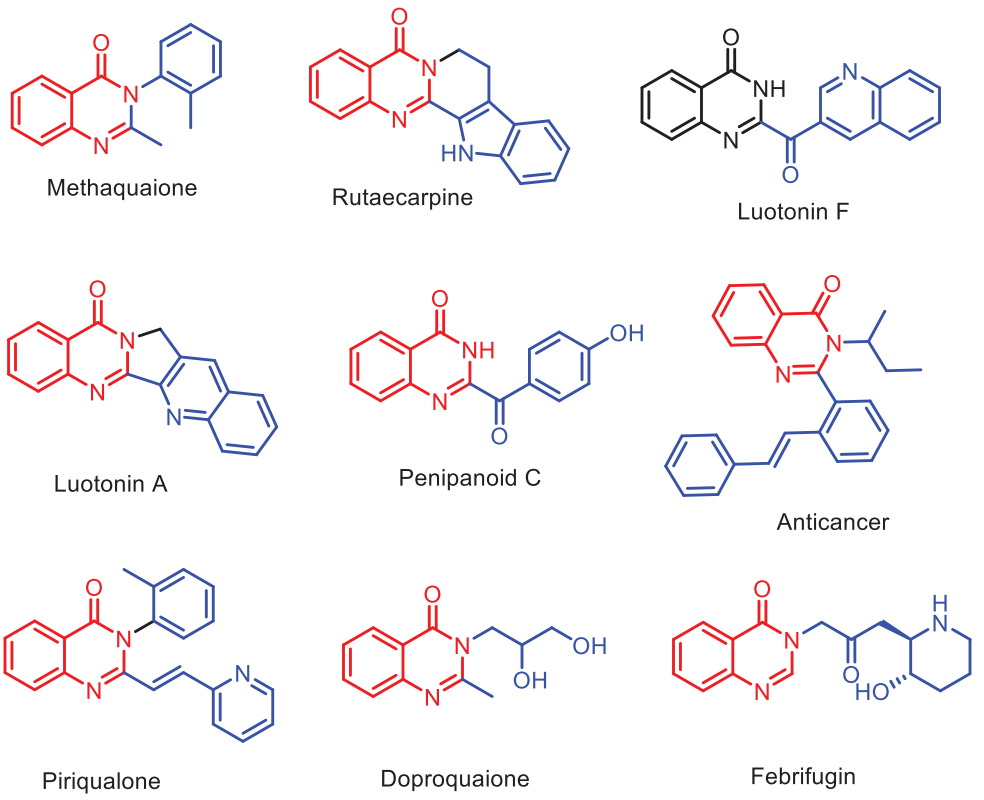
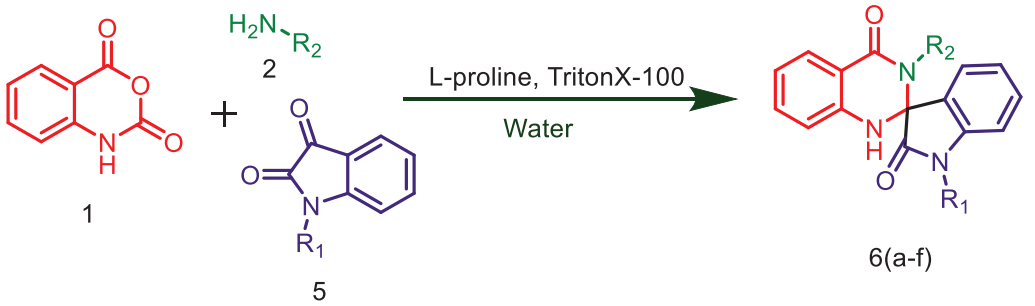


Figure 1: Structure shows new quinazolinone-based drug molecules.



Scheme 2: Synthesis of quinazolinones using isatin derivatives.

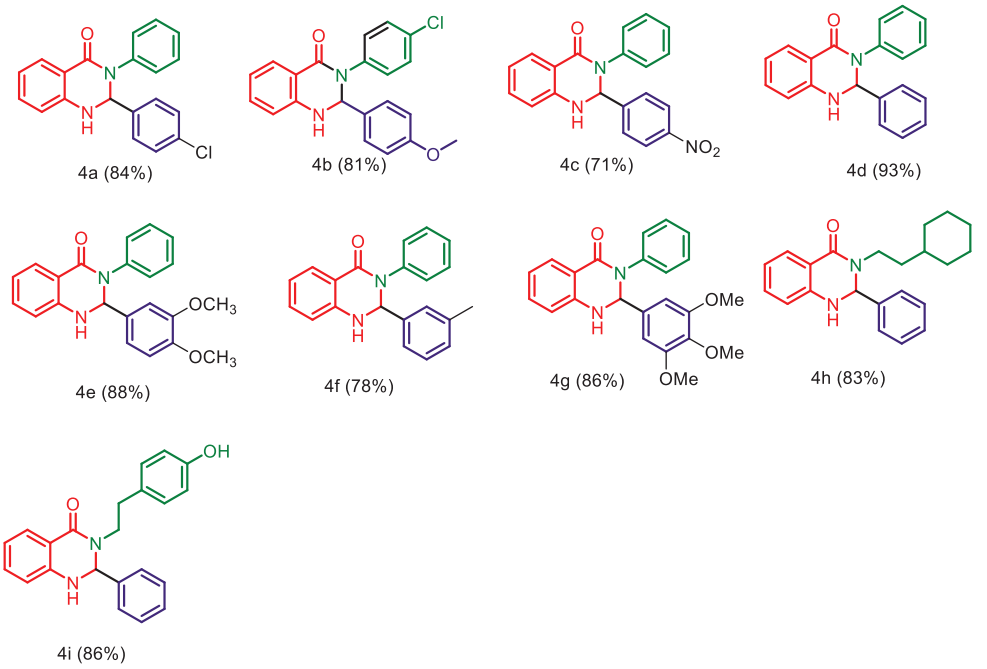


Figure 2: Synthesized quinazolinones structures.

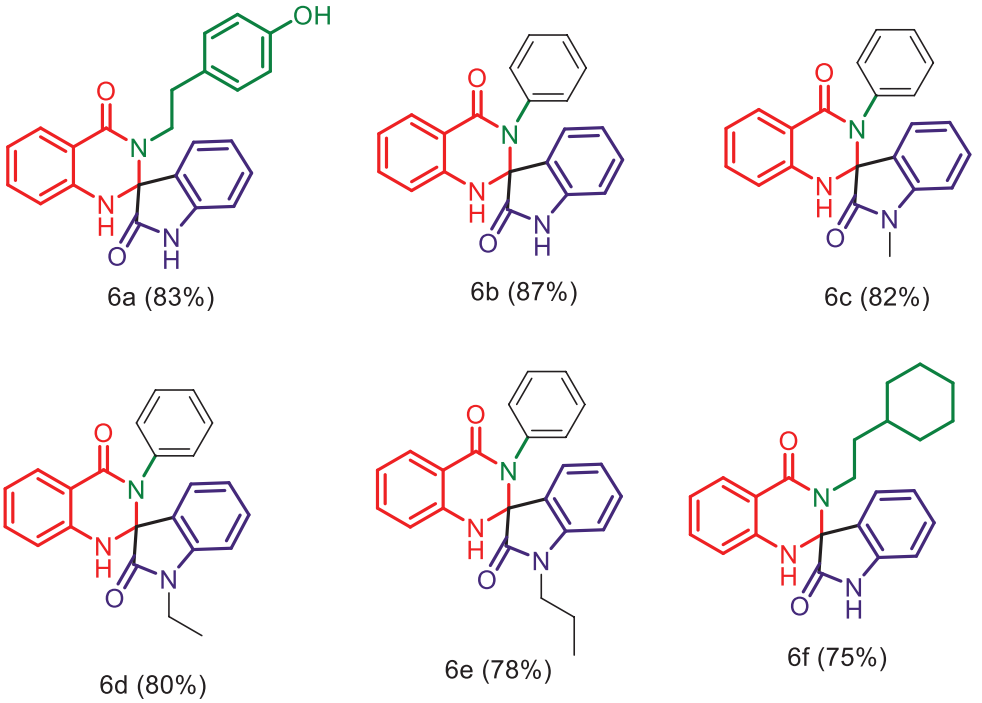
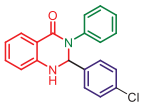
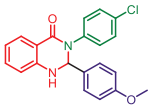
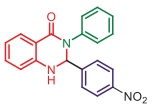
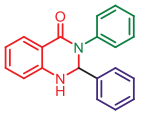
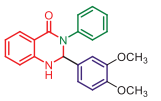
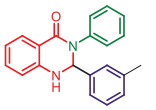
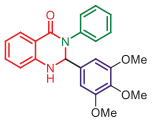
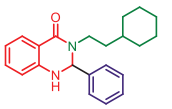
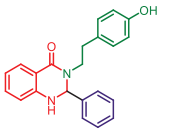
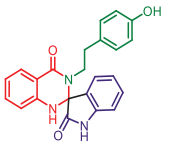
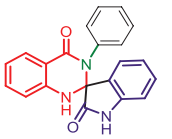
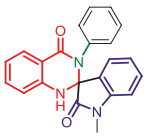
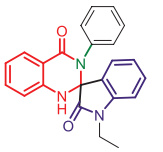


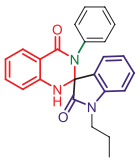
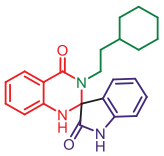
Figure 3: Synthesized spiroquinazolinones structures.

Table 3: Synthesis of quinazolinones and spiroquinazolinones.

Entry	Compound no.	Structure	Yield (%)	Reaction time (h.)	Melting point (°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

(Contd...)

Table 3: *(Continued).*

Entry	Compound no.	Structure	Yield (%)	Reaction time (h.)	Melting point (°C)
14	**6e**		78	5	242
15	**6f**		75	6	226

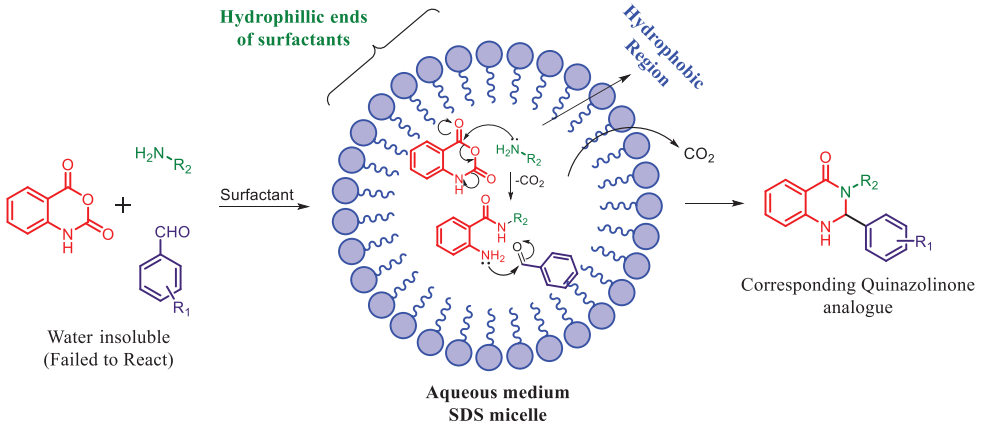


Figure 4: Plausible mechanistic pathway for reaction.

benzaldehyde and with isatin). It was noticed and also listed in Table 3 that the electron-withdrawing substitution, such as the NO_2 group, decreases the reaction rate significantly, whereas the halogen substitution supported the reaction as the progress of the reaction was very fast. 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 forms a hydrophobic cavity, and lipophilic reactant molecules are trapped inside the cavity, which triggers the efficient reaction and facilitates the product conversion, as shown in Figure 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 ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy. In IR Spectra, the character stick peaks were obtained at 3,411 cm^{-1} from the amine group. For newly formed methylene proton singlet was observed in proton NMR spectra near to 4.8 ppm region.

4. 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 effective for the synthesis of quinazolinones and spiroquinazolinones. Being privileged structures (quinazolinones) in the field of medicinal chemistry we have a firm opinion that these molecules can become important in drug discovery programs in the near future.

5. ACKNOWLEDGMENT

Authors acknowledge the necessary support from Lalit Narayna Mithila University Darbhanga and C. M. Science College Darbhanga. The authors also acknowledge IIT Patna for helping in the characterization of data.

6. CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. C. K. Z. Andrade, L. M. Alves, (2005) Environmentally benign solvents in organic synthesis, ***Current Organic Chemistry***, **9:** 195-218.
2. A. Chanda, V. V. Fokin. (2009) Organic synthesis “On water”, ***Chemical Reviews***, **109:** 725-748.
3. U. M. Lindstrom, (2002) Stereoselective organic reactions in water, ***Chemical Reviews***, **102:** 2751-2772.
4. M. Shiri, M. A. Zolfigol, (2009) Surfactant-type catalysts in organic reactions, ***Tetrahedron***, **65:** 587-598.
5. A. Tuch, S. Wallé, (2002) Multicomponent reactions. In: K. C. Nicolaou, R. Hanko, W. Hartwig, (Eds.), ***Handbook of Combinatorial Chemistry***, Vol. 2. Weinheim, Germany: Wiley-

VCH, p685-705.
6. D. Guo, D. Zhu, X. Zhou, B. Zheng, (2015), Understanding "on-water" catalysis of organic reactions, ***Langmuir***, **31(51)**: 13759-13763.
7. M. Nakadai, S. Saito, H. Yamamoto, (2002) Diversity-based strategy for discovery of environmentally benign organocatalyst: Diamine-protonic acid catalysts for asymmetric direct aldol reaction, ***Tetrahedron Letters***, **58(41)**: 8167-8177.
8. A. Domling, I. Ugi, (2000) Multicomponent reactions with isocyanides, ***Angewandte Chemie***, **39:** 3168.
9. A. Domling, (2006) Recent developments in isocyanide based multicomponent reactions in applied chemistry, ***Chemical Reviews***, **106:** 17.
10. N. Hossain, J. Rozenski, E. P. Clercq, P. Herdewijn, (1997) Synthesis and antiviral activity of the alpha-analogues of 1,5-anhydrohexitol nucleosides, ***The Journal of Organic Chemistry***, **62(8)**: 2442-2447.
11. S. L. Hargreaves, B. L. Pilkington, S. E. Russell, P. A. Worthington, (2000) The synthesis of substituted pyridylpyrimidine fungicides using palladium catalysed cross-coupling reactions, *Tetrahedron Letters*, **41:** 1653-1656.
12. S. Bhanudas Zangade. ***Quinazoline Based Synthesis of some Heterocyclic Schiff Bases***, London: Intech Open.
13. Y. Jang, S. B. Lee, J. Hong, S. Chun, J. Lee, S. Hong, (2020) Synthesis of 2-aryl quinazolinones via iron-catalyzed cross-dehydrogenative coupling (CDC) between N-H and C-H bonds, ***Organic and Biomolecular Chemistry***, **18(28)**: 5435-5441.
14. D. Zhan, T. Li, H. Wei, W. Weng, K. Ghandi, Q. Zeng, (2013) A recyclable CuO-catalyzed synthesis of 4(3H)-quinazolinones, ***RSC Advances***, **3(24)**: 9325-9329.
15. A. V. A. Gholap, S. Maity, C. Schulzke, D. Maiti, A. R. Kapdi, (2017) Synthesis of Cu-catalysed quinazolinones using a Csp3-H functionalisation/cyclisation strategy, ***Organic and Biomolecular Chemistry***, **15(34)**: 7140-7146.
16. Y. Qian, G. Allegretta, J. Janardhanan, Z. Peng, K. V. Mahasenan, M. M. N. Gozun, S. Tejera, V. A. Schroeder, W. R. Wolter, R. Feltzer, M. Chang, (2020) Exploration of the structural space in 4(3H)-quinazolinone antibacterials, ***Journal of Medicinal Chemistry***, **63(10)**: 5287-5296.
17. U. A. Kshirsagar, (2015) Recent developments in the chemistry of quinazolinone alkaloids, ***Organic and Biomolecular Chemistry***, **13:** 9336-9352.
18. I. I. Khan, A. Ibrar, N. Abbas, A. Saeed, (2014) Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications, ***European Journal of Medicinal Chemistry***, **76:** 193-244.
19. N. C. Desai, A. M. Dodiya, (2014) Synthesis, characterization and antimicrobial screening of quinoline based quinazolinone-4-thiazolidinone heterocycles, ***Arabian Journal of Chemistry***, **7(6)**: 906-913.
20. A. Mishra, U. Mukherjee, T. K. Upasana, T. K. Vats, I. Deb, (2018) Ir(III)/MPAA-catalyzed mild and selective C-H amidation of N-Sulfonyl ketimines: Access to benzosultam-fused quinazolines/quinazolinones, ***Journal of Organic Chemistry***, **83(7)**: 3756-3767.
21. D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, (2005) Synthesis of quinazolinones and quinazolines, ***Tetrahedron***, **61(43)**: 10153-10202.
22. V. D. Tripathi, A. M. Jha, (2018) Design and synthesis of heterocyclic curcumin analogues as filarial topoisomerase II inhibitors, ***Journal of Biological and Chemical Chronicles***, **4:** 59-64.
23. V. D. Tripathi, A. K. Shukla, (2018) Design and synthesis of novel heterocyclic curcumin analogues as anticancer agents and filarial topoisomerase II inhibitors, ***Asian Journal of Organic and Medicinal Chemistry***, **3(4)**: 164-170.
24. A. Kumar, P. Kumar, V. D. Tripathi, S. Srivastava, (2012) A novel access to indole-3-substituted dihydrocoumarins in artificial sweetener saccharin based functional ionic liquids, ***RSC Advances***, **2:** 11641-11644.
25. V. D. Tripathi, A. K. Shukla, H. S. Mohammed, (2019) Regioselective three component domino synthesis of polyhydrospiro[indoline-3,3'-pyrrolizine]-2-one via [3+2] cycloaddition reaction, ***Asian Journal of Chemistry***, **31:** 613-616.
26. V. D. Tripathi, (2020) B-Cyclodextrin mediated multicomponent synthesis of spiroindole derivatives in aqueous medium, ***Asian Journal of Chemsitry***, **32(2)**: 293-296.
27. A. Kumar, V. D. Tripathi, P. Kumar, (2011) β-Cyclodextrin catalysed synthesis of tryptanthrin in water, ***Green Chemistry***, **13:** 51-54.

***Bibliographical Sketch**

Dr. V. D. Tripathi, born in Lucknow, Uttar Pradesh, is a prominent medicinal chemist with a distinguished career in organic synthesis and drug discovery. He completed his Graduation and Post-Graduation from the University of Lucknow in 2003 and 2006, respectively. Demonstrating early academic excellence, he qualified for the CSIR NET-JRF and commenced his research journey at the prestigious CSIR (Central Drug Research Institute) in Lucknow. He was awarded a Ph.D. degree by Jawaharlal Nehru University, New Delhi, in 2012, marking a significant milestone in his academic career. Dr. Tripathi's professional journey is marked by his contributions to several esteemed organizations, including Jubilant Chemsys Noida, Zydus Cadila Healthcare Limited, LCC Toulouse France, and University Paul Sabatier. A highlight of his career was his role as a leading team member in the development of Lipaglyn, the first indigenous antidiabetic molecule by Zydus Cadila. This achievement underscores his expertise and significant contributions to medicinal chemistry. In 2015, Dr. Tripathi was honored with the prestigious CEFIPRA Indo-French Research Fellowship by DST, Government of India, allowing him to gain invaluable experience in dendrimer synthesis at CNRS-LCC Toulouse, France. Currently, Dr. Tripathi serves as an Assistant Professor in the Department of Chemistry at C.M. Science College, Darbhanga. His academic portfolio is impressive, with over 35 research publications in reputed national and international journals. He has authored six books and five book chapters, further establishing his authority in the field. Additionally, he holds three patents and has delivered more than a dozen invited talks. His editorial work includes the book 'Future Science for Sustainable Development,' showcasing his commitment to advancing scientific knowledge and education. Dr. Tripathi's extensive experience in teaching organic chemistry to undergraduate and postgraduate students highlights his dedication to nurturing the next generation of chemists.