Asian Journal of Chemistry; Vol. 35, No. 5 (2023), 1089-1094

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.27612

A Catalyst Free and Sustainable Synthesis of Quinazolinones in Glycerol as Green Solvent

GAURAV PRAKASH[1], AJAY KUMAR DAS[1] and V.D. TRIPATHI[2,*]

[1]Department of Chemistry, M.L.T. College (Constituent unit of B.N. Mandal University, Madhepura), Saharsa-852201, India
[2]Department of Chemistry, C.M. Science College (Constituent unit of L.N. Mithila University, Darbhanga), Darbhanga-846004, India

*Corresponding author: E-mail: vdtmkclnmu@gmail.com

Received: 5 February 2023; *Accepted*: 28 March 2023; *Published online*: 28 April 2023; AJC-21214

In this article, glycerol was employed in a quest to develop an environmentally benign and sustainable synthetic protocol for synthesis of quinazolinone and spiro-quinazolinone derivatives. These studies were performed to investigate the effect of electron-rich and electronegative groups on the synthetic route of an established protocol. Different substituted isatin and benzaldehyde derivatives have been incorporated to synthesize analogues of two series of quinazolinones in order to investigate the efficacy of the developed methodology and substrate tolerance. A total of 12 derivatives were synthesized and characterized by spectroscopic techniques.

Keywords: Quinazolinones, Spiro, Green chemistry, Glycerol, Sustainable.

INTRODUCTION

The unavoidable environmental restrictions for consuming hazardous and toxic solvents or chemicals shifting the synthetic chemists towards the development of ecofriendly and sustainable synthesis for small organic molecules. This situation is creating an urgent need for designing new types of methodologies to be adopted by synthetic chemists. To avoid the use of toxic chemicals and solvents a number of alternative method are reported in literature among them ultrasonic irradiation mediated method, ball milling method, surfactant mediated synthesis, solid phase reactions, reactions in water as solvents, using supercritical fluids as solvents, ionic liquids as solvents for the reactions, glycerol as solvents, using carbohydrate based catalysts, organocatalyzed reactions are some frontline examples [1-8]. Although all these reported procedures are following principals to perform sustainable chemistry but there are certain restrictions associated with them, which renders them from using as a green alternative for conventional ways of synthesis. Scale up issues, tedious work up procedures, high temperature, low selectivity, narrow substrate scope, poor yields, toxic by-products after reaction are the main hurdles behind the use of various reported protocols [9-13]. Therefore, the need to search for better sustainable process is very important.

Quinazolinones and spiroquinazolinones constitute a class of heterocyclic molecules which is quite fascinating and interesting due to the broad range of biological properties associated with it [14-17]. The molecules showing in Fig. 1 exhibits the structure of certain quinazolinone based molecules with special biological potential. These molecules are associated with them the diverse range of biological properties like antibacterial, antifungal, antimycobacterial, anti-inflammatory, antidiabetic, anticancer, antimalarial, antileishmanial and anticonvulsant activities, which make them crucial in medicinal chemistry and drug discovery programs [18-23]. A number of synthetic protocols are reported in literature to construct the quinazolinone nucleus among them the multicomponent reactions are prominent [24, 25]. Transition metal catalyzed coupling reactions are also the most frequently used methodology for the synthesis of quinazolinones [26-28]. Apart from these, several other methods are reported with lot of limitations in terms of substrate scope and feasibility of the reactions. 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 [29,30].

In this direction, the application of green organic solvents for synthesis is an attractive choice for chemists and chemical industries also. Among various solvents used for green synthesis the water, glycerol, polyethylene glycol, ionic liquids, super-

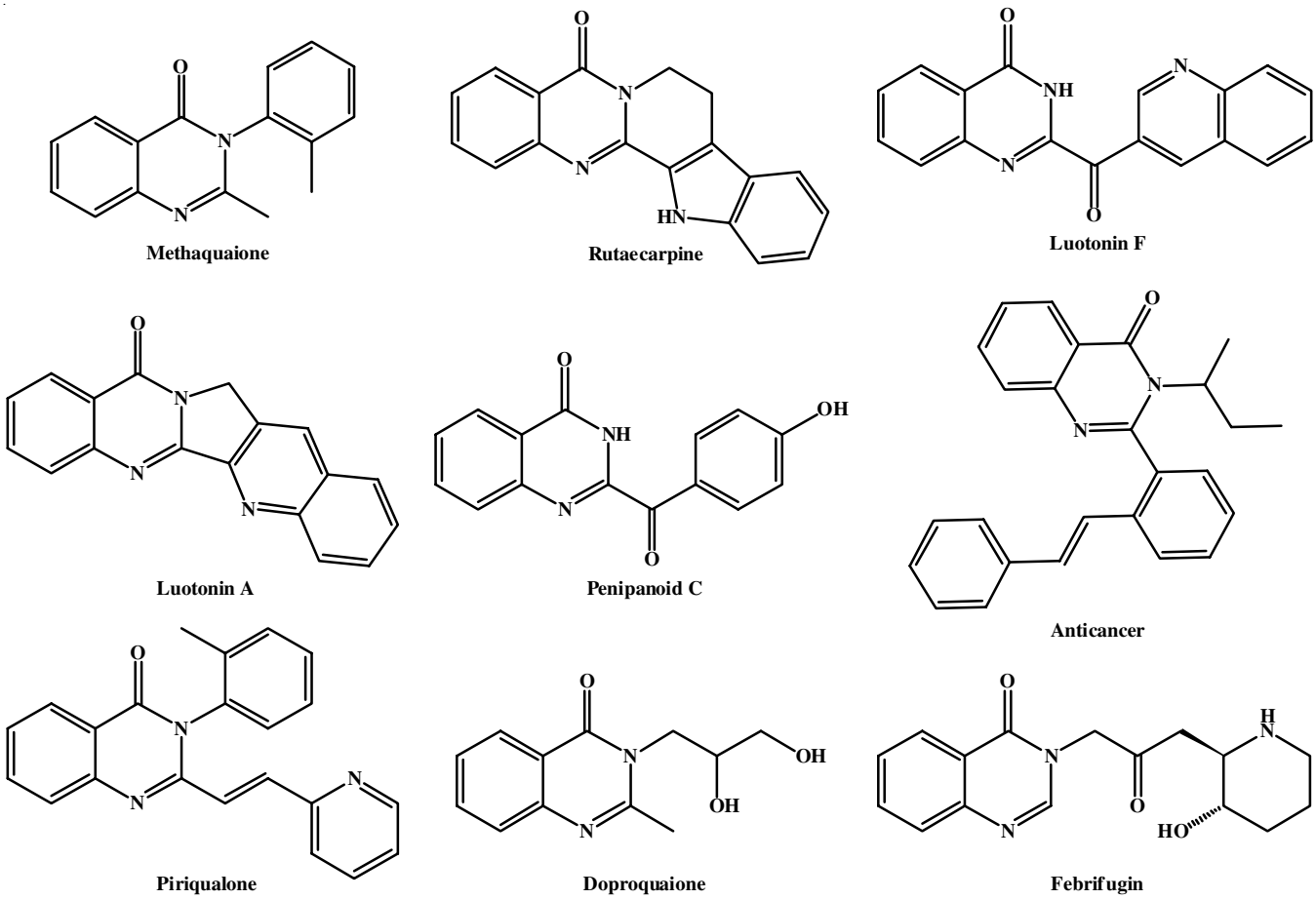


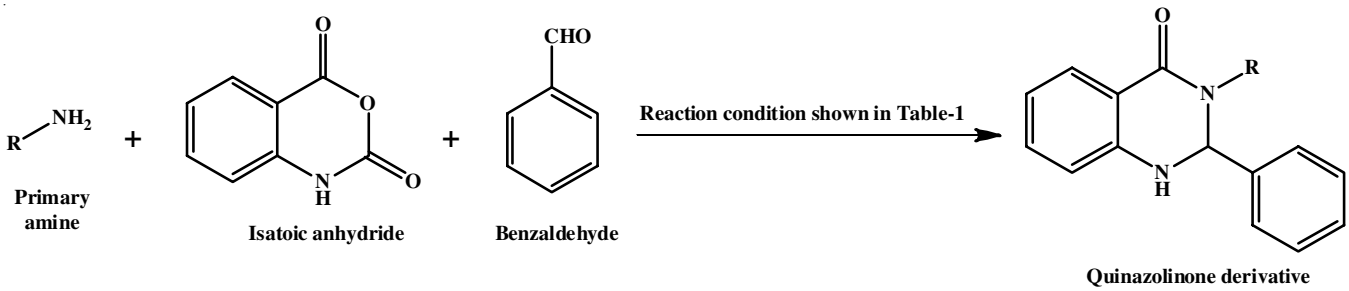
Fig. 1. Structure of some bioactive molecules based on quinazolinone core

critical fluids and ethanol are of maximum used solvents [31, 32]. The poor aqueous solubility of non-polar organic molecules is one of the major restriction behind the use of water as solvents. Usage of surfactant in water may overcome this issue but surfactant is hazardous for aquatic environment. Use of ionic liquids suffers with the tedious work up procedures and toxic byproducts after the product isolation [33]. Use of supercritical fluids has scale up issues, expensive and not energy efficient process [34]. The glycerol proves to be one of the best use as a green alternative over these options due to the better solubility of organic molecules, low-cost and non-toxic nature [35]. The prime hurdle in using glycerol as solvent is the viscous nature of the liquid which might be overcome by increasing the temperature of reaction mixture. It is reported in the literature that the using glycerol as solvent to perform a reaction can be considered as organic water reaction medium [36]. The polar nature due to presence of three hydroxyl groups and strong hydrogen bonding ability make glycerol as potentially good substitute to perform organic of small heterocyclic molecules. Additionally, in comparison to water glycerol is preferred due to high boiling point and better solubility for organic molecules. Due to these benefits the glycerol has been used in the synthesis of many types of organic heterocycles like selanylpyridines, disulfides, arylbenzothiazoles, pyrazolines, imidazoles, tetrazoles, *etc*. [37]. However, quinazolinones are still not synthesized using glycerol based solvents.

EXPERIMENTAL

Unless otherwise specified all the reagents were purchased from Sigma-Aldrich and 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 & ^{13}C NMR spectra were recorded on a Brucker DRX-300 spectrometer. 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 quinazolinone and spiroquinazolinone derivatives: Isatoic anhydride (1 mmol), primary amine (1 mmol) and benzaldehyde analogue or isatin derivative (1 mmol) were mixed in 100 mL round bottom flask and 10 mL glycerol was added. Reaction mixture was heated upto 80 ºC and stirred at the same temperature upto completion of reaction. The reaction progress was monitored using thin layer chromatography in ethyl acetae and hexane mixture. After the completion reaction mixture was poured in ice cold water under stirring and filtered off to get the solid residue. The solid residue was further crystallized using ethanol to afford the desired product in quantitative yield (**Scheme-I**).



Scheme-I: Synthesis of quinazolinone derivatives

1-Methyl-3′-phenyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione (5a): Orange powder; yield: 82%; Time: 5 h, m.p.: 224 ºC; IR (KBr, ν_{max}, cm^{-1}): 3361, 3254, 2946, 1712, 1650, 1503; ^{1}H NMR (300 MHz, 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 (75 MHz, 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. (found) % for $C_{22}H_{17}N_3O_2$: C, 74.35 (74.33); H, 4.82 (4.85); N, 11.82 (11.80).

3′-Phenyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′-(3'*H*)-dione (5b): Orange powder; yield: 87%; Time: 5 h, m.p.: 208 ºC; IR (KBr, ν_{max}, cm^{-1}): 3361, 3254, 2946, 1712, 1650, 1503; ^{1}H NMR (300 MHz, 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 (75 MHz, 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. (found) % for $C_{21}H_{15}N_3O_2$: C, 73.89 (73.80); H, 4.43 (4.31); N, 12.31 (15.23).

1-Ethyl-3′-phenyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione (5c): Yellow powder; yield: 80%; Time: 5 h, m.p.: 234 ºC; IR (KBr, ν_{max}, cm^{-1}): 3372, 3268, 2970, 1710, 1648, 1505; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.40 (t, *J* = 6.47 Hz, 3H); 4.36 (q, *J* = 6.3 Hz, 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* = 8.3 Hz, 1H); 10.23 (s, 1H); ^{13}C NMR (75 MHz, 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. (found) % for $C_{23}H_{19}N_3O_2$: C, 74.78 (74.80); H, 5.18 (5.21); N, 11.37 (11.34).

3′-Phenyl-1-propyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione (5d): Cream powder; yield: 78%; Time: 5 h, m.p.: 242 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3298, 2972, 1721, 1650, 1503; ^{1}H NMR (300 MHz, 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* = 10.2 Hz, 1H), 8.21 (d, 1H, *J* = 8.9 Hz); ^{13}C NMR (75 MHz, 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. (found) % for $C_{24}H_{21}N_3O_2$: C, 75.18 (75.14); H, 5.52 (5.49); N, 10.96 (10.97).

3′-(2-Cyclohexylethyl)-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione (5e): Yellow powder; yield: 75%; Time: 6 h, m.p.: 226 ºC; IR (KBr, ν_{max}, cm^{-1}): 3372, 3268, 2970, 1710, 1648, 1505; ^{1}H NMR (300 MHz, 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 (75 MHz, 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. (found) % for $C_{23}H_{25}N_3O_2$: C, 73.57 (73.60); H, 6.71 (6.73); N, 11.19 (11.15).

2-(4-Chlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (6a): Light yellow solid, yield: 82%; Time: 6 h, m.p.: 179 ºC; IR (KBr, ν_{max}, cm^{-1}): 3411, 1635, 1608, 1585, 1508, 1485, 1390, 1298, 1245, 1159, 1068, 1029, 956, 835, 601; ^{1}H 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); ^{13}C 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. (found) % for $C_{20}H_{15}N_2OCl$: C, 71.75 (71.72); H, 4.52 (4.54); N, 8.37 (8.35).

3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (6b): Light yellow solid; yield: 80%; Time: 5 h, m.p.: 186 ºC; IR IR (KBr, ν_{max}, cm^{-1}): 3411, 1635, 1608, 1585, 1508, 1485, 1390, 1298, 1245, 1159, 1068, 1029, 956, 835, 601; ^{1}H 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); ^{13}C 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. (found) % for $C_{21}H_{17}N_2O_2Cl$: C, 69.14 (69.19); H, 4.70 (4.74); N, 7.61 (7.65).

2-(4-Nitrophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (6c): Light yellow solid; yield: 72%; Time: 10 h, m.p.: 216 ºC; IR (KBr, ν_{max}, cm^{-1}): 3411, 1635, 1608, 1585, 1551, 1485, 1365, 1298, 1245, 1159, 1068, 1029, 956, 835, 601; ^{1}H 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); ^{13}C 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. (found) % for $C_{20}H_{15}N_3O_3$: C, 69.56 (69.54); H, 4.38 (4.40); N, 12.17 (12.15).

2,3-Diphenyl-2,3-dihydroquinazolin-4(1*H*)-one (6d): Light yellow solid; yield: 76%; Time: 6 h, m.p.: 174 ºC; IR (KBr, ν_{max}, cm^{-1}): 3411, 1635, 1608, 1585, 1508, 1485, 1390, 1298, 1245, 1159, 1068, 1029, 956, 835, 601; ^{1}H 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); ^{13}C 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. (found) % for $C_{20}H_{16}N_2O$: C, 79.98 (79.96); H, 5.37 (5.39); N, 9.33 (9.31).

2-(3,4-Dimethoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (6e): White solid; yield: 82%; Time: 5 h, m.p.: 192 ºC; IR (KBr, ν_{max}, cm^{-1}): 3411, 2932, 1635, 1616, 1508, 1485, 1463, 1390, 1267, 1236, 1137, 1120, 1068, 1029, 997, 952, 862, 694, 617; ^{1}H 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. (found) % for $C_{22}H_{20}N_2O_3$: C, 73.32 (73.18); H, 5.59 (5.38); N, 7.77 (7.88).

3-Phenyl-2-*m*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (6f): White solid; yield: 80%; Time: 5 h, m.p.: 158 ºC; IR (KBr, ν_{max}, cm^{-1}): 3303, 2927, 1635, 1616, 1512, 1487, 1446, 1400, 1346, 1317, 1298, 1176, 1114, 1068, 950, 864, 619; ^{1}H 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); ^{13}C 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. (found) % for $C_{21}H_{18}N_2O$: C, 80.23 (79.99); H, 5.77 (5.90); N, 8.91 (8.79).

3-(2-Cyclohexylethyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (6g): Creamy white solid; yield: 83%; Time: 6 h, m.p.: 142 ºC; IR (KBr, ν_{max}, cm^{-1}): 3303, 2927, 1635, 1616, 1512, 1487, 1446, 1400, 1346, 1317, 1298, 1176, 1114, 1068, 950, 864, 619; ^{1}H 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); ^{13}C 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. (found) % for $C_{22}H_{26}N_2O$: C, 79.00 (79.08); H, 7.84 (7.04); N, 8.38 (8.34).

RESULTS AND DISCUSSION

Initially, the suitable conditions for synthesis of quinazoline analogues was first work out. To achieve this objective, the reaction of isatin, isatoic anhydride and bezaldehyde as model reaction was selected (**Scheme-I**). The viscous nature of glycerol requires temperature above 40 ºC for better stirring and mixing of reactant molecules. In order to compare the capability of other solvents for the synthesis of heterocycles over the glycerol, we screened the solvents like, ethanol, water, methanol, water-ethanol mixture, acetonitrile and glycerol at room temperature and higher temperatures and the results are summarized in Table-1.

TABLE-1
SCREENING OF DIFFERENT SOLVENTS FOR SYNTHESIS OF QUINAZOLINONES

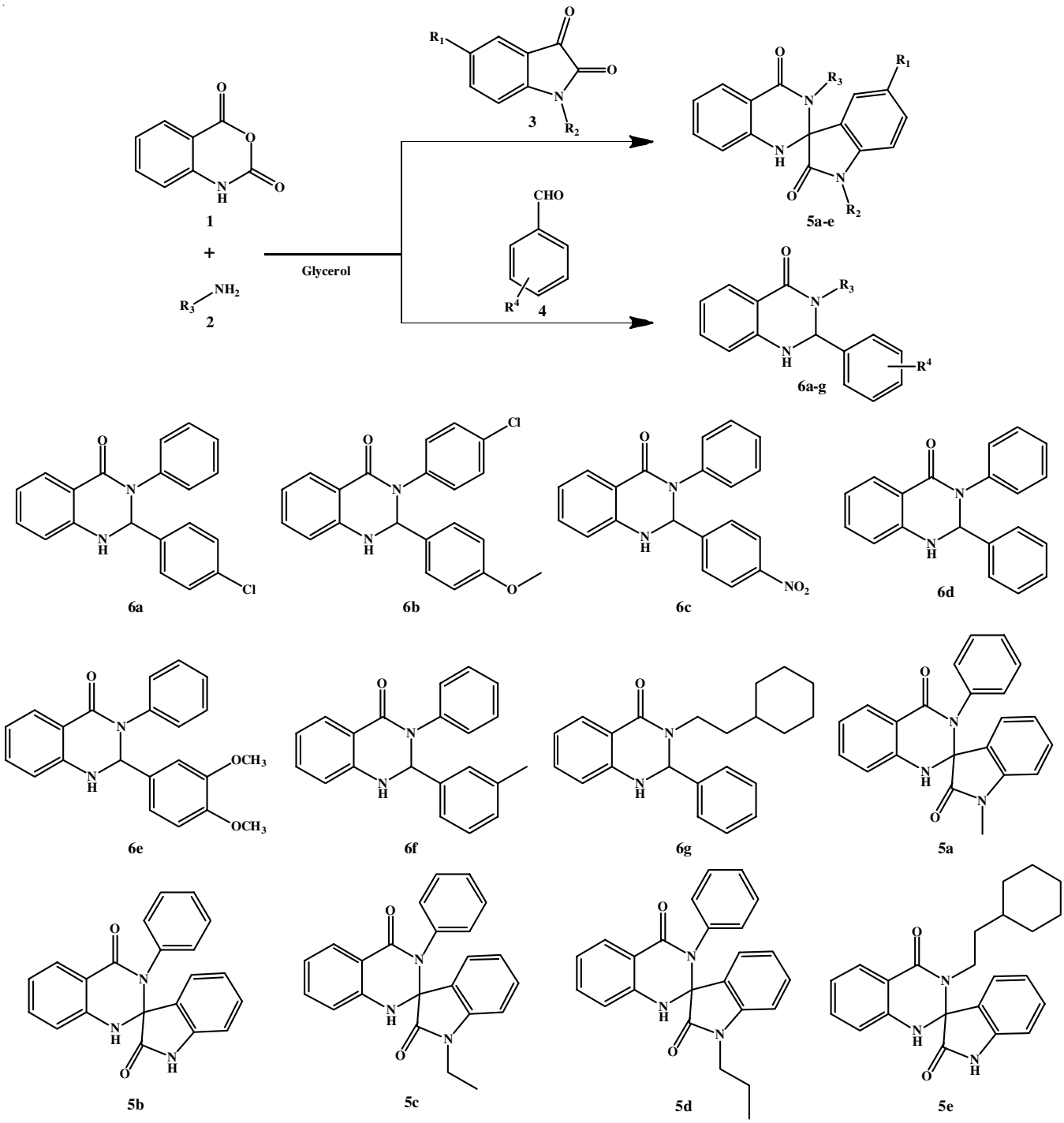
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	Ethyl acetate	Reflux	10	32
2	Methanol	Reflux	10	52
3	H_2O	Reflux	10	Trace
4	Acetonitrile	Reflux	10	25
5	Dichloromethane	Reflux	10	Trace
6	Chloroform	Reflux	10	Trace
7	Glycerol	Room temp.	10	39
7	Glycerol	40	7	58
8	Glycerol	60	3	77
9	Glycerol	70	2.5	87
10	Glycerol	80	2	92

It is demonstrated that water as a solvent does not feasible for the reaction as only traces of quinazolinone formation was observed. The results were similar with chloroform and dichloromethane as solvent. Ethyl acetate showed 32% product formation while 25% coversion was observed with acetonitrile at room temperature. The product yield was 52% with methanol as solvent which was more superior than water, acetonitrile and ethylacetate. Glycerol was also tested as solvent and 39% conversion observed at room temperature. The viscous nature of glycerol was considered as prime hurdle behind proper stirring. To enhance the efficacy, the reaction temperature was increased and checked the product conversion at 40, 60, 70 and 80 ºC. It was found that 92% product was obtained by performing the synthesis at 80 ºC. Probably increased temperature facilitated the reaction by effective stirring. Since, the best product formation was observed at 80 ºC with glycerol, therefore we finalized the optimum reaction condition to perform the synthesis of quinazolinone derivatives.

After finalizing the reaction conditions, efforts were made for the synthesis of various derivatives of quinazolinones. Also to prove the utility of present synthetic protocol, we introduced substrate variation in place of aldehydes by using substitution on benzene ring. 5-Substituted isatin was used to widen the substrate scope of designed methodology. As shown in **Scheme-II**, 10 quinazolinones were prepared and characterized using the spectroscopic techniques. To include the substrate variation differently substituted aldehydes were used for the synthesis of quinazolines.

Both electron donating and electron withdrawing groups on benzaldehyde were explored and observed the effect of substituent on the reaction time. It was found that the electron withdrawing substitution tends to increase the reaction time probably due to decreasing the rate of reaction. The reaction involving benzaldehydes with electron donating substitution took less time for completion.

In another reaction sequence isatin was used instead of benzaldehyde derivatives under similar reaction conditions. It was found that the reaction proceeds very smoothly leading to the formation of spiro analogues of quinazolinones. Compared



Scheme-II: Glycerol mediated synthesis of quinazolinones

to conventional techniques of quinazolinone preparation, our developed protocol is a highly efficient green option due to the wide range of substrate variation and presence of glycerol for the effective synthesis. The presence of quaternary carbon in the product structure was found to be characteristic feature for the characterization of synthesized spiro analogues. This quaternary carbon was confirmed in ^{13}C NMR spectroscopy, which appear near to 100 ppm in the spectrogram. Further all the synthesized molecules were fully characterized using mass, ^{1}H NMR, IR and elemental analysis.

Conclusion

In summary, an ecofriendly and efficient protocol is developed leading to the preparation of biologically significant quinazolinones and spiro quinazolinones analogues using isatoic anhydride, primary amines and benzaldehydes or isatin in glycerol as solvent. The developed synthetic protocol exhibits wide range of substrate tolerance and environmentally benign strategy to get quinazolinones and spiro quinazolinones analogues. All the synthesized molecules were isolated in excellent yields and characterized. The effect of electron withdrawing

and electron donating groups on reaction were also established using different types of substitutions in the reactant molecules.

ACKNOWLEDGEMENTS

Two of the authors, Gaurav Prakash and Ajay Kumar Das, are highly thankful to M.L.T. College, Saharsa and B.N. Mandal University, Madhepura, India to necessary support and funding for the research work carried out.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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