

The Study of DES via Sonochemistry method in Synthesis of 2,3-dihydroquinazolin-4(1H)- ones derivatives

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ABSTRACT

Deep eutectic solvents (DESs) have emerged as viable alternatives to ionic liquids (ILs) and conventional organic solvents for organic syntheses. DESs exhibit distinctive properties compared to traditional solvents and ILs, including a low vapor pressure, the ability to dissolve reagents that are insoluble in common organic solvents, and the capacity to alter the overall pH of the medium by substituting one of the components of the mixture. DESs can be synthesized by combining molecules derived from natural sources such as PEG-400 to ensure biodegradability. The initial study and synthesis of DESs was conducted by Ijardar [1,1.1]. The catalytic activity of the DES (PEG-400:TBAB) was evaluated in a reaction involving a series of aldehydes and 2-amino-benzamide under sonochemical conditions. DES (TBAB: PEG-400)(1:3) was synthesized using a straightforward method with readily available starting materials, and its structure was confirmed by FTIR (Fourier Transform Infrared Spectroscopy). This protocol was characterized by a green and efficient catalyst as well as solvent, ease of workup, simple separation without chromatography, and the reusability of the DES up to four cycles. These features suggest that it can find extensive applications in future research, green chemistry, and innovation.

Keywords: Green chemistry, Sonochemistry, 2,3-dihydroquinazolin-4(1H)-ones, DES, MCR

1. INTRODUCTION

Deep Eutectic Solvents (DESs) have attracted attention in green chemistry owing to their unique properties. These solvents are formed when a hydrogen bond donor (HBD) and acceptor (HBA) combine, creating a eutectic mixture with a lower melting point than its components. PEG-400 served as the HBD and TBAB as the HBA. DESs' physicochemical properties of DESs can be adjusted by varying their components and ratios. These biodegradable, low-toxicity solvents enhance the reaction rates and improve the yields of organic transformations. Their renewable source derivations make them attractive alternatives to traditional organic solvents, offering environmental benefits while maintaining the reaction efficiency [2].

Deep eutectic solvents (DESs) are environment-friendly solvents with low toxicity, biodegradability, and cost-effectiveness. PEG-400-and tetrabutylammonium bromide (TBAB)-based DESs have emerged as promising candidates owing to their physicochemical properties. DESs are mixtures of two or more components that form a eutectic mixture with a lower melting point than the individual components, involving a hydrogen bond donor (HBD) and acceptor (HBA). Common HBAs include quaternary ammonium salts such as TBAB, whereas HBDs include organic acids, amides, sugars, or polymers such as PEG-400. DESs are alternatives to ionic liquids, offering similar properties, but easier synthesis. PEG-400 is a polymeric liquid that functions as a hydrogen bond donor, whereas TBAB is a quaternary ammonium salt that acts as a hydrogen bond acceptor. When mixed in ratios of 1:1 to 3:1 PEG-400:TBAB, hydrogen bonding between the PEG hydroxy groups and bromide anions creates a homogeneous viscous liquid at RT. Abbott et al. introduced DESs in the early 2000s, with polymer-based DESs expanding since 2010s. PEG-400/TBAB systems offer advantages such as low volatility, non-toxicity, tunable viscosity, excellent solubility, and thermal stability. Applications include extraction, catalysis, electrochemistry, drug delivery, nanomaterial synthesis, and organic reactions. Recent studies have explored enzyme stabilization, CO₂ capture, and green synthesis, with FTIR analysis confirming strong hydrogen bonding [3,4,5,6].

Ultrasound has become a valuable tool for promoting chemical reactions in organic synthesis (sonication). This technique uses high-frequency sound waves (20 kHz to MHz) to enhance reaction rates and yields while following green chemistry principles. Sonochemistry relies on Acoustic Cavitation, the formation and collapse of microscopic bubbles in liquid media, generating extreme conditions: temperatures up to 5000 K, Pressures over 1000 atm, and rapid cooling rates (~10⁹ K/s) [7,8,9]. Sonochemical benefits include reduced reaction times through enhanced mass transfer, improved yields, mild conditions, and energy efficiency in organic synthesis applications such as C-C Bond formation,

oxidation, reduction, MCRs, heterocycle synthesis, and functional group transformations [10,11,12,13]. This eco-friendly technique reduces the use of harsh reagents and works synergistically with green solvents such as DESs in modern organic chemistry [14,15,16]. The 2,3-Dihydroquinazolin-4(1H)-one scaffold shows biological activity, with applications in anticancer, antileishmanial, neuroprotective, anticonvulsant, and antidiabetic treatments [17,18,19,20].

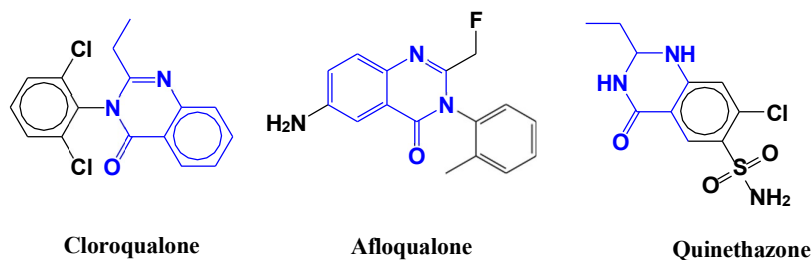


Figure 01 biological active molecules based on 2,3-Dihydroquinazolin-4(1H)-one (DHQ) scaffold.

MATERIALS AND METHODS:

Experimental section:

All essential raw materials were procured from the local chemical supplier, an analytical chemistry facility associated with the local testing laboratory for FT-IR and mass spectra. Additionally, NMR were conducted by Sathi-BHU.

Preparation of DES:

Deep Eutectic Solvents (DESs) were synthesized by combining tetrabutylammonium bromide (TBAB) and polyethylene glycol 400 (PEG-400) in molar ratios. The selected ratios of 1:2 and 1:3 was derived from literature [1], with PEG-400 functioning as the hydrogen bond donor (HBD) and TBAB as the hydrogen bond acceptor (HBA). Ultimately, a 1:3 molar ratio was chosen due to its superior dissolution properties and comprehensive solvent behaviour in the intended reaction. The preparation process, as outlined by Wang et al [2], involved weighing the HBA and HBD components in screw-capped bottles according to the selected molar ratio. The mixture was heated to 80 °C under ultrasonic agitation, resulting in a clear homogeneous liquid within 5 minutes. Following synthesis, the DESs underwent a vacuum drying process to ensure purity prior to physicochemical property measurements. The water content of the final DES product was determined using the Karl Fischer method a crucial step in characterizing the properties of the solvent and its potential applications.

General procedure for the synthesis of 2,3- dihydroquinazolin-4(1H)-ones

The described reaction protocol involves the synthesis of a product utilizing aldehyde and 2-aminobenzamide in eq-mol ratio take as reactants within a deep eutectic solvent (DES) system. DES fulfils a dual role, functioning as both the reaction medium and the catalyst. The reaction mixture underwent ultrasonic irradiation for a brief duration of 15 min under continuous conditions, and progress was monitored via thin-layer chromatography (TLC). This methodology illustrates the efficacy of employing DES as an environmentally benign alternative to conventional organic solvents, with the potential to reduce reaction times and enhance yields. Following each reaction cycle, in case of solid product formation filtered the reaction mass and washed by dry ether dry. Subsequently, In case of liquid product extract by dry ether. The DES was cleaned via dry ether extraction and reused in subsequent reaction cycles. Following ether removal, the purity of the isolated product was verified using various analytical techniques, proton and carbon NMR spectroscopy, and mass spectrometry. The recyclability of DES is emphasized by its recovery under mild vacuum conditions, allowing for its reuse in subsequent reaction cycles. This highlights the potential sustainability and cost-effectiveness of the synthetic method.

Spectral Data of Derivatives

1)2-phenyl-2,3-dihydroquinazolin-4(1H)-one: ^1H NMR:5.93 (1H), 6.94 (1H), 7.23-7.66 (9H),8.30(1H), ^{13}C NMR: δ 73.2 (1C), 112.0 (1C), 118.2 (1C), 120.8 (1C), 126.9 (2C), 127.3 (1C), 127.8 (1C), 128.5 (2C), 132.3 (1C), 138.3 (1C), 139.4 (1C), 161.6 (1C).Mass spectra:225.10(M+1).

3) 2-(2-Methylphenyl)-2,3-dihydroquinazolin-4(1H)-one : ^1H NMR :3.73-3.78 (3H), 5.95 (1H), 6.72–6.61 (2H), 7.03 (1H), 7.22–7.14 (3H), 7.35–7.33 (2H), 7.58–7.56 (1H),8.2 (1H), ^{13}C NMR: 19.35(1C).

65.29(1C),115.06(1C), 115.71(1C), 117.81(1C), 126.49(1C), 128.02(2C), 129.05(1C), 131.25(1C), 133.81(1C), 136.68(1C), 138.62(1C), 149.12(1C),164.70(1C),, Mass Spectra(M+1):239.11

4)2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one:¹H NMR : 5.70 (1H), 6.66–6.63 (1H), 6.73–6.71 (1H), 7.12 (1H), 7.24–7.19 (1H), 7.49–7.41 (4H), 7.59–7.57 (1H), δ 8.37 (1H), , ¹³C NMR: 66.31(1C), 115.11(1C), 115.14(1C), 115.17(1C), 117.83(1C), 128.00, (2C),128.25(2C),129.30(1C),133.95(1C),141.17(1C),148.20(1C),164.06,(1C),Mass Spectra(M+2):260.05

5)2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one:¹H NMR:5.70(1H),6.69-6.75(2H),7.09(1H), 7.23–7.19 (1H), 7.42–7.39 (2H), 7.58–7.54 (3H), 8.28 (1H) ,δ ¹³C NMR : 66.34(1C). 114.99(1C), 115.17(2C), 117.82(1C), 122.08(1C), 127.89(2C), 129.61(1C), 131.76(1C), 133.93(1C), 141.65(1C), 148.15, (1C) , 164.00(1C), Mass Spectra:303.80(M+1)

6)2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one: ¹H NMR: δ 3.76 (3H),4.934(2H), 5.93 (1H), 6.83-7.00 (3H),7.23-7.41 (3H), 7.48-7.66 (2H), ¹³C NMR: δ 55.9 (1C), 73.2 (1C), 113.3 (1C), 114.6 (2C), 115.6 (1C), 126.6 (1C), 127.7 (2C), 128.5-128.7 (2C), 138.3 (1C), 139.4 (1C), 159.7 (1C), 161.5 (1C).Mass Spectra:255.80(M+1)

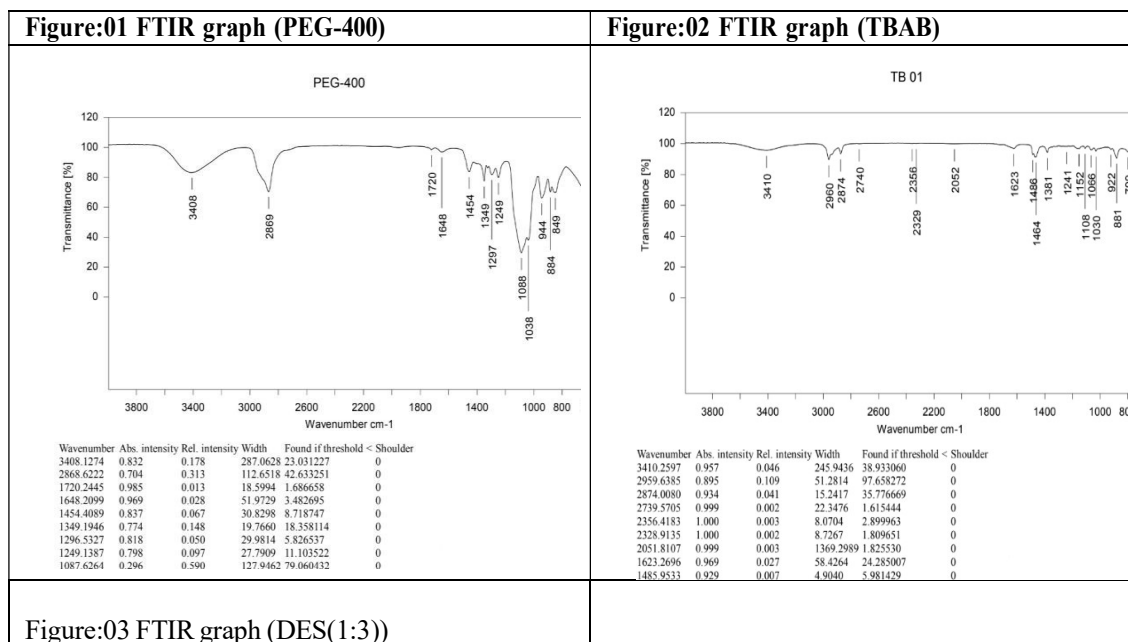
7)2-(4-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one : ¹H NMR: δ:4.9(3H), 5.92 (1H), 6.65 (2H), 6.94 (1H), 7.16-7.37 (3H), 7.48-7.66 (2H)). ¹³C NMR: δ 73.2 (1C), 113.3 (1C), 115.5-115.6 (3C), 126.6 (1C), 127.7 (2C), 128.5-128.7 (2C), 138.3 (1C), 139.4 (1C), 157.2 (1C), 161.5 (1C).Mass Spectra:241.12(M+1).

Table-04 Recovery of DES :

Entry	Cycle Num	Yield
01	1	96
02	2	95
03	3	93
04	4	93
05	5	60

As observed during the recovery of the DES , a DES of up to 4 cycles gave a constant yield after each cycle DES clean by dry ether once, DES reduced the efficiency after cycle-4.

2.0 RESULTS AND DISCUSSION



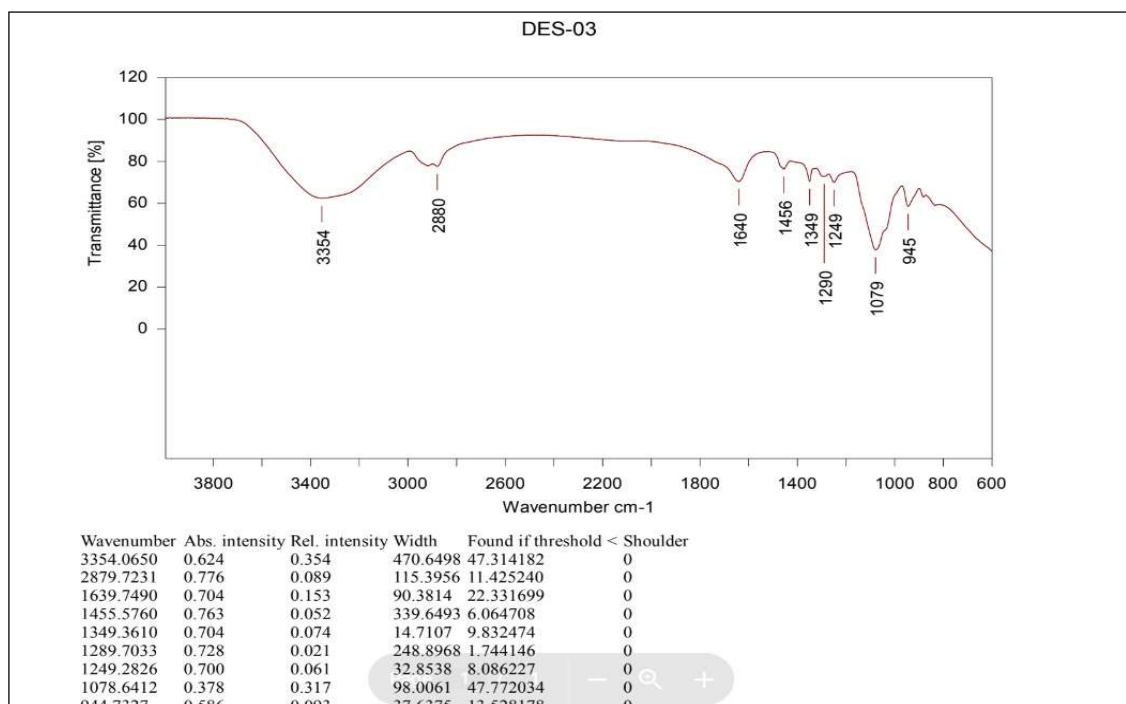


Figure01 FTIR graph (PEG-400): Indicates the 3408cm^{-1} (O-H stretch), 2869cm^{-1} (C-H Stretching), 1454cm^{-1} , 1349cm^{-1} (CH_2 bending), 1297cm^{-1} , 1249cm^{-1} (CH_2 twisting/torsion), 1088cm^{-1} , 1038cm^{-1} (C-O-C Stretching), 944cm^{-1} (CH_2 medium)

Figure02 FTIR graph (TBAB): Indicates the 3410cm^{-1} (Moisture contamination), 2960cm^{-1} , 2874cm^{-1} (C-H stretching (asymmetric and symmetric) in $-\text{CH}_2$ and $-\text{CH}_3$ groups), 1623cm^{-1} (C-H bending vibrations), 1486cm^{-1} , 1464cm^{-1} (C-H stretching), 1381cm^{-1} (CH_2 -wagging), 1108cm^{-1} (C-N Weak), 737cm^{-1} (CH_2 rocking (butyl chains)).

Figure 03 FTIR graph (DES)

The Fourier-transform infrared (FT-IR) spectroscopy analysis reveals molecular interactions within the synthesized deep eutectic solvents (DESs) and the mixture of tetrabutylammonium bromide (TBAB) with polyethylene glycol 400 (PEG-400). The spectrum shows characteristic absorption bands for functional groups. 3354cm^{-1} (O-H stretching (broadened, PEG hydroxyls and H-bonding with TBAB)), 2880cm^{-1} (CH_2 asymmetric/symmetric stretching (TBAB butyl chains and PEG backbone)), 1640cm^{-1} (O-H bending (H-bonding artifacts)), 1456cm^{-1} (CH_2 scissoring (PEG and TBAB alkyl chains)), 1349cm^{-1} , 1290cm^{-1} , 1249cm^{-1} (CH_2 wagging (PEG and TBAB alkyl chains)), 1079cm^{-1} (C-O-C stretching (PEG ether) and C-N stretching (TBAB) overlapping).

Upon analysis, we deduce that the appearance of a new peak at 3354cm^{-1} (O-H stretching, broadened, associated with PEG hydroxyls and hydrogen bonding with TBAB) indicates the formation of H-bond between PEG-400 and TBAB. This confirmation of DES of TBAB and PEG-400. It is only physical mixing process not any chemical reaction take place. This results we confirmed by the previously reported DES related FTIR graph [1] S. Ijardar et al [1.1], Abdurrahman et al [1.2]

Table 1 Comparison of the catalytic efficiency of the DES-03(TBAB:PEG-400) with other various reported catalysts for the synthesis 2,3-Dihydroquinazolin-4(1H)-one derivatives

Entry	Catalyst	Solvent/condition	Time (min)	Yield (%)	Ref.
1	zinc oxide	Solvent free- 120°C	20	92%	21
2	ZnCl ₂ /urea eutectic solvent	DES/ 110°C	25	95%	22
3	zinc acetate dihydrate	Toluene/Reflux	150	90%	23
4	Fe ₃ O ₄ @nano-cellulose-OPO ₃ H	H ₂ O, EtOH/ Reflux	90	95%	24

5	oxalic acid	.EtOH: water(80°C)	44	90%	27
6	Iron oxide (Fe ₃ O ₄), Chitosan	Ethanol/RT	20	94%	28
7	Gr@SO ₃ H	Ethanol, reflux	35	92%	29
8	[Ce(L-Pro) ₂] ₂ (Oxa)	Ethanol	45-50	89%	30
9	Fe ₃ O ₄ @EDTA/CuI	Ethanol, reflux	20	97%	31
10	Nano preyssler catalyst	Water,Refluxe	210	95%	32
11	Bi(NO ₃) ₃ ·5H ₂ O:	Solvent free (80-100°C)	60-180	90-95%	33
12	Al-MCM-41	dual imidazolium ionic liquids nanocomposites (60°C)	60-180	95%	34
13	Phosphate Fertilizers	Ethanol/Reflux	40	96%	35
14	β-cyclodextrin-SO ₃ H	Water(RT-50°C)	25	96%	36
15	α-chymotrypsin	60°C/Ethanol	60	90%	37
16	Lactic acid	Solvent free-70°C	30-100	88-93%	38
17	NaHSO ₄	Ethanol/rt	40-240	97%	39
10	No added	DES-3(TBAB:PEG-400)/)))(Ultrasound)	15	96%	This Work
11	NO catalyst	No solvent /Sonication	60	Spot observed on TLC	This work

The synthesis of 2,3-Dihydroquinazolin-4(1H)-one was investigated using deep eutectic solvents (DES) as both catalyst and solvent. This study examined the influence of the presence of a catalyst, reaction time, and temperature on the synthesis process. The reaction employed a 1:1 molar ratio of aromatic aldehyde and 2-amino benzamide as the reactants.

The experimental findings indicated that extended sonication without any catalyst under ambient conditions resulted in suboptimal yields. Conversely, the introduction of the catalyst (10 equiv.) markedly increased yield to 96%. This result exceeds those of previous studies that reported yields of 82-96% using various metal oxides as solid acid catalysts, albeit with longer reaction times. The research team aimed to optimize the synthesis process by reducing the reaction time while maintaining or improving product yields. To this end, our team integrated sonochemical techniques into their methodology. This approach facilitates further optimization of key parameters such as the solvent ratio, temperature, and reaction time. The ultimate objective is to transform this conventional reaction into a more efficient click chemistry process, which offers advantages such as faster reaction rates, higher yields, and potentially milder reaction conditions. This innovative approach could have significant implications for the synthesis of 2,3-Dihydroquinazolin-4(1H)-one and related compounds in pharmaceutical and chemical industries. table 2. Subsequently, our team optimized the solvent ratio and reaction time for the formation of these derivatives.

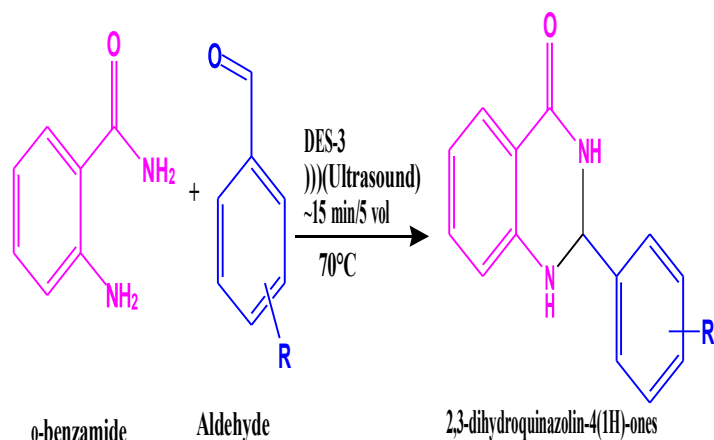
Table-02 Reaction Optimization condition at 40 kHz

Entry	DES in volume	Time (min)	Temperature (°C)	Yield (%) ^b
1	0	30	70°C	TLC spot observed
2	1	30	70°C	Conversion observed on TLC
3	3	30	70°C	81
4	5	10	70°C	96
5	8	10	70°C	94
6	11	10	70°C	94

Reaction conditions: 2-Amino acetamide (1 mmol), 4-methoxy benzaldehyde (1 mmol),
Isolated yield(%).

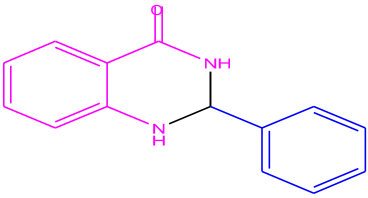
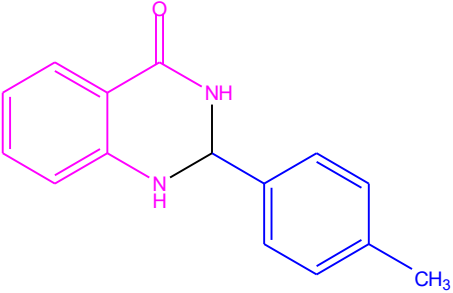
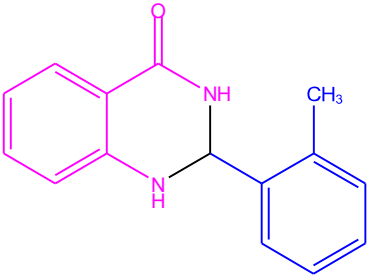
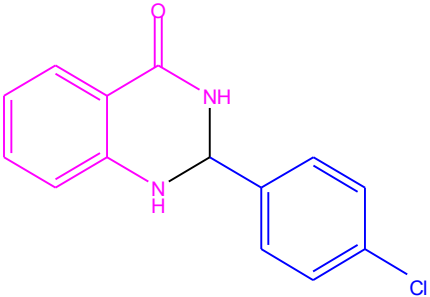
Optimization of the solvent conditions for the reaction under sonication at ambient temperature provided significant insights into the role of deep eutectic solvents (DES) in enhancing the reaction efficiency. Initially, the absence of the DES resulted in no reaction progress, even at elevated temperatures. However, a marked improvement was observed as the DES volume increased incrementally, accompanied by a corresponding increase in temperature. This adjustment led to a substantial yield of 81% (entry-3), demonstrating the synergistic effect of the DES volume and temperature on the reaction kinetics. Further experiments focused on fine-tuning the DES volume while maintaining a constant temperature. A notable breakthrough occurred when the DES volume was increased by five units, resulting in an impressive increase in yield 96%(entry-04). This finding underscores the critical importance of optimizing the DES volume to maximize the reaction yield. Subsequent trials with slightly varied DES volumes (increased by three units) yielded comparable results, consistently achieving yields above 94%(entry-5,6). These outcomes collectively informed the decision to adopt the conditions from Entry-04 as the optimal parameters for future reactions involving various aromatic aldehydes, highlighting the potential for the broader applicability of this optimized methodology.

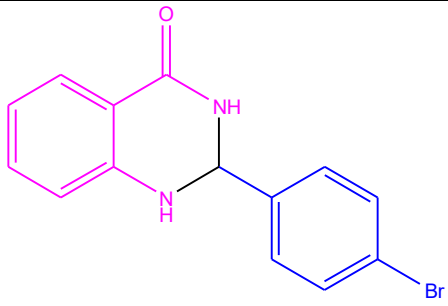
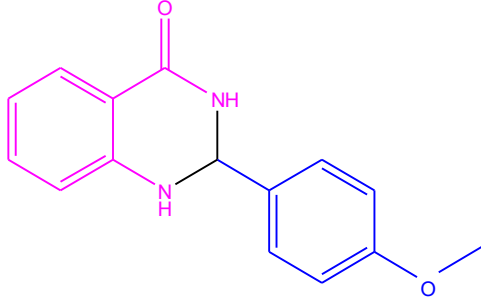
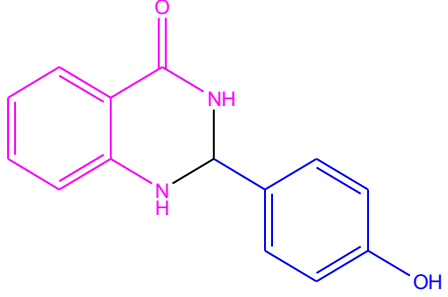
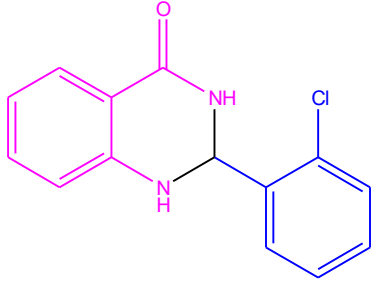
Scheme-01

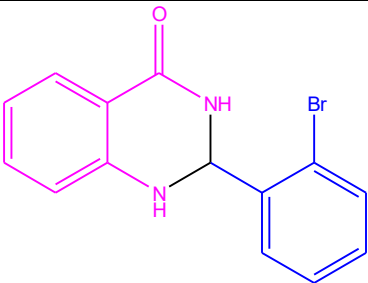
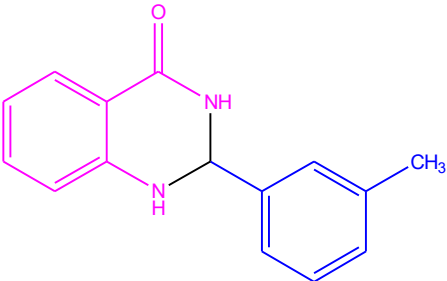
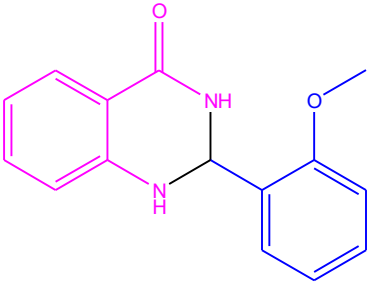
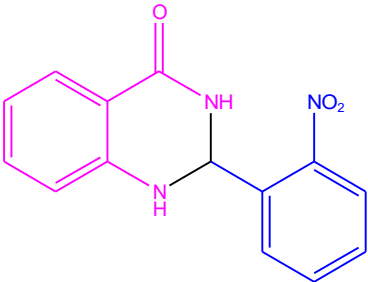


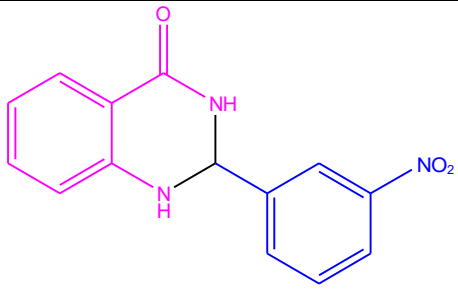
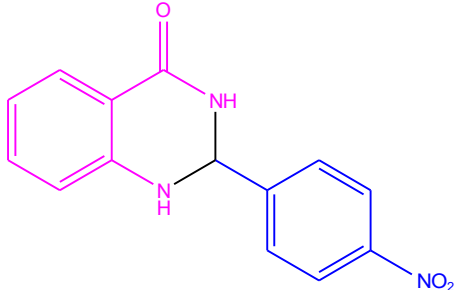
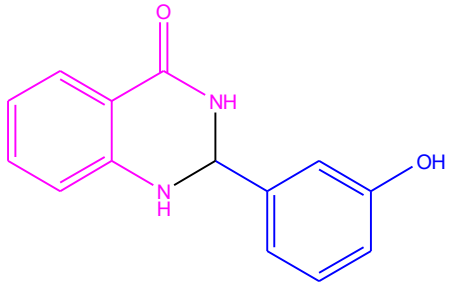
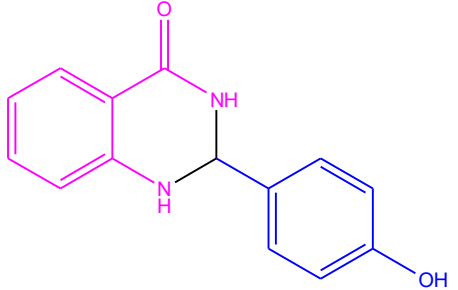
R-H,NO₂,OCH₃,F,Cl,Br,CH₃,OH

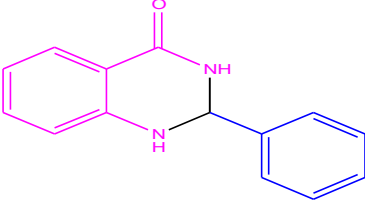
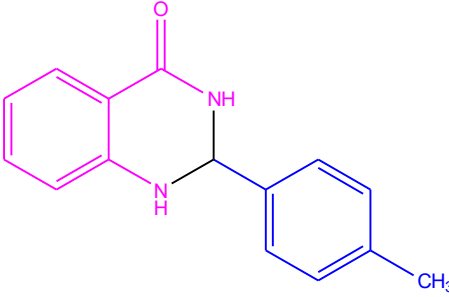
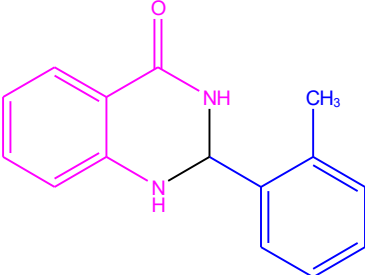
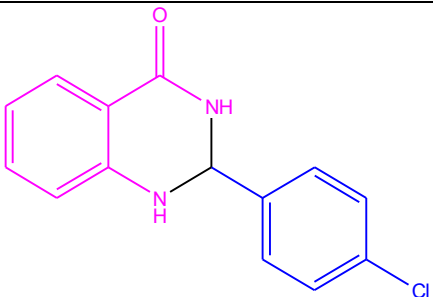
Table03: 2,3-dihydroquinazolin-4(1H)-ones Derivatives

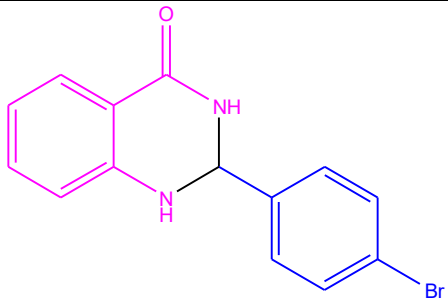
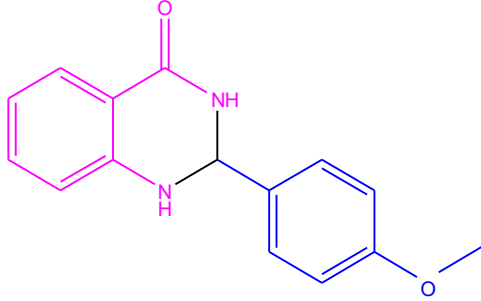
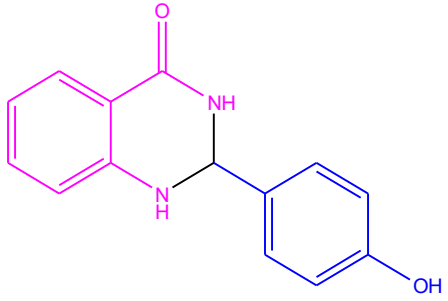
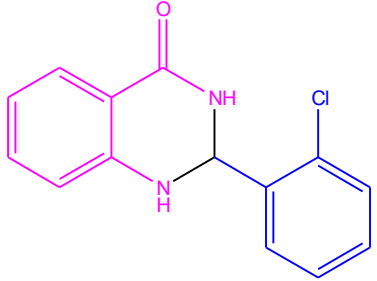
Sr Num	Aldehyde	Derivative	Yield	Time	State
Table03: 2,3-dihydroquinazolin-4(1H)-ones Derivatives					
1	Benzaldehyde	 <chem>O=C1NC(=O)C2=CC=CC=C2N1C3=CC=CC=C3</chem>	89	12	White solid
2	4-Methyl Benzaldehyde	 <chem>CC1=CC=C(C=C1)C2=CC=CC=C2N1C(=O)NC3=CC=CC=C31</chem>	96	08	White solid
3	2-Methyl Benzaldehyde	 <chem>CC1=CC=C(C=C1)C2=CC=CC=C2N1C(=O)NC3=CC=CC=C31</chem>	93	15	liquid
4	4-Chloro Benzaldehyde	 <chem>ClC1=CC=C(C=C1)C2=CC=CC=C2N1C(=O)NC3=CC=CC=C31</chem>	92	10	Solid

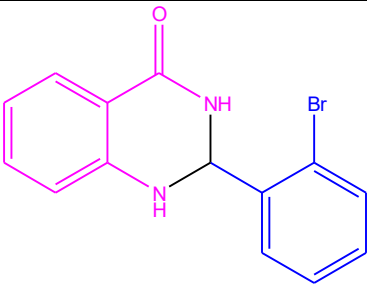
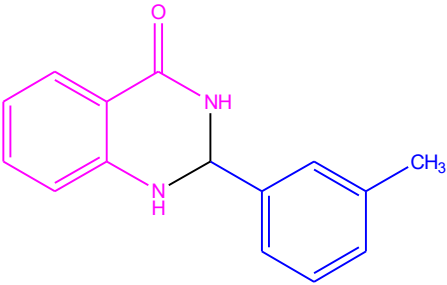
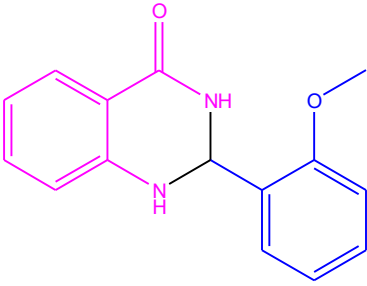
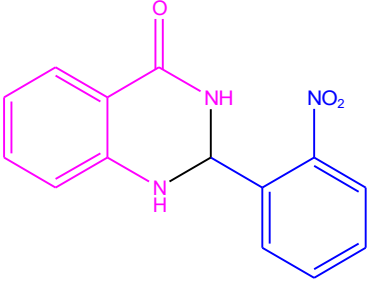
5	4-Bromo Benzaldehyde		92	08	Solid
6	4-Methoxy Benzaldehyde		91	10	Solid
7	4-Hydroxy Benzaldehyde		93	12	White solid
8	2-Chloro Benzaldehyde		89	15	Liquid e

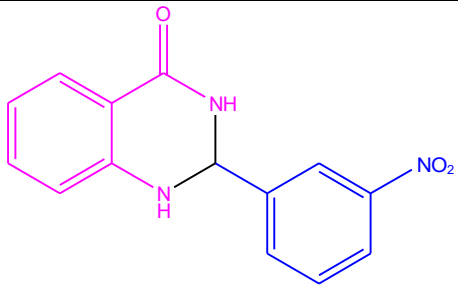
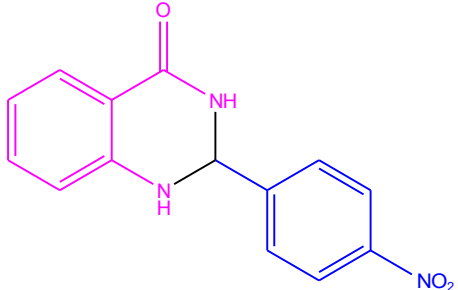
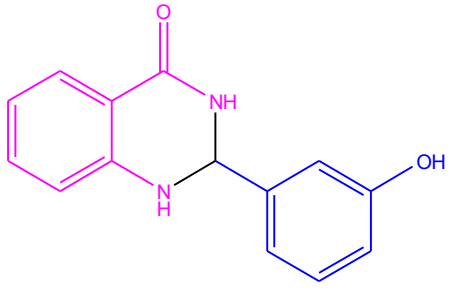
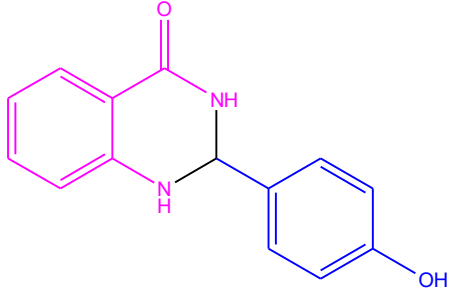
9	2-Bromo Benzaldehyde		89	15	Liquid e
10	3-Methyl Benzaldehyde		89	15	Liquid e
11	2-Methoxy Benzaldehyde		87	15	Liqide
12	2-Nitro Benzaldehyde		84	15	Yellow solid

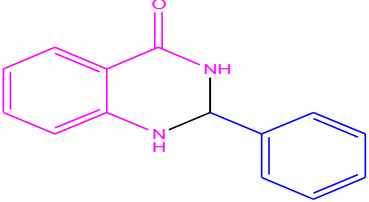
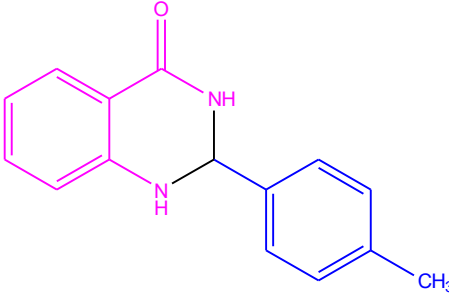
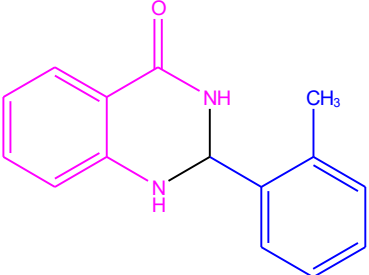
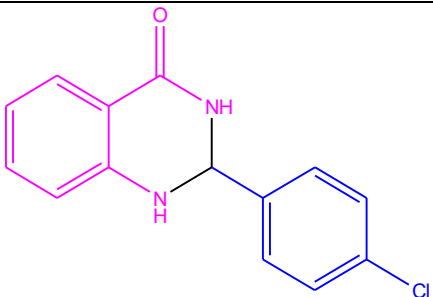
13	3-Nitro Benzaldehyde		87	15	Yellow soli
14	4-Nitro Benzaldehyde		93	10	Yellow solid
15	3-Hydroxy Benzaldehyde		92	15	White solid
16	4-Hydroxy Benzaldehyde		85	15	White solid

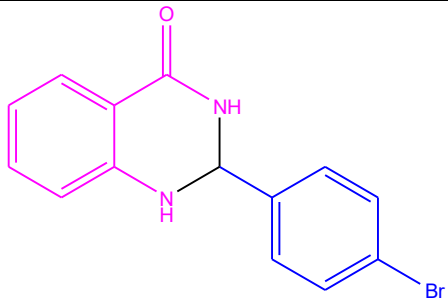
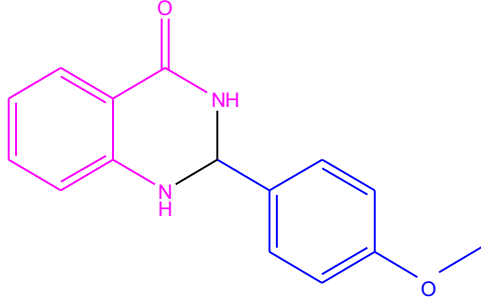
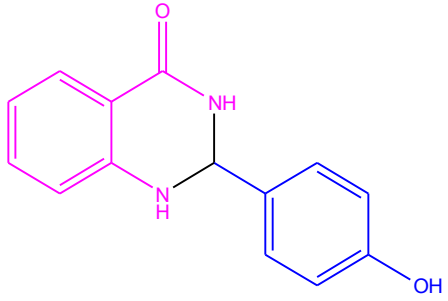
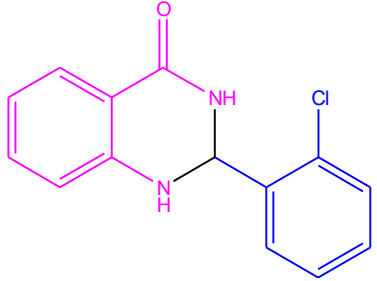
Sr Num	Aldehyde	Derivative	Yield	Time	State
Table03: 2,3-dihydroquinazolin-4(1H)-ones Derivatives					
1	Benzaldehyde		89	12	White solid
2	4-Methyl Benzaldehyde		96	08	White solid
3	2-Methyl Benzaldehyde		93	15	liquid
4	4-Chloro Benzaldehyde		92	10	Solid

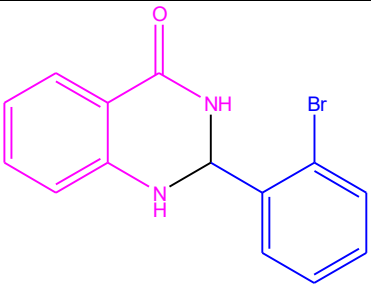
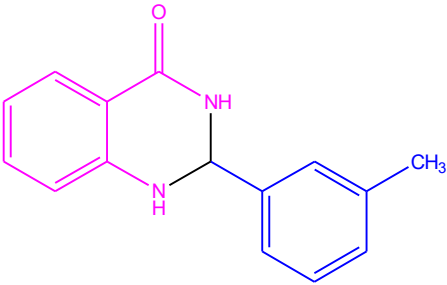
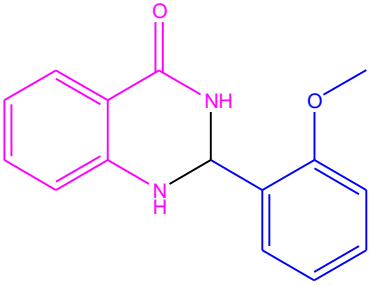
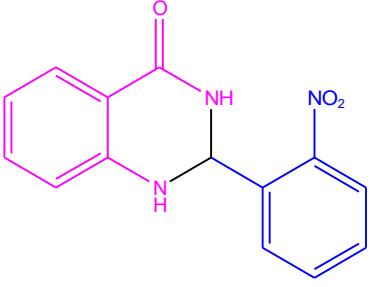
5	4-Bromo Benzaldehyde	 <p>The structure shows a benzamide core (a benzene ring fused to a five-membered hydrazide ring with a carbonyl group). The nitrogen of the hydrazide ring is substituted with a 4-bromophenyl group.</p>	92	08	Solid
6	4-Methoxy Benzaldehyde	 <p>The structure shows a benzamide core substituted with a 4-methoxyphenyl group.</p>	91	10	Solid
7	4-Hydroxy Benzaldehyde	 <p>The structure shows a benzamide core substituted with a 4-hydroxyphenyl group.</p>	93	12	White solid
8	2-Chloro Benzaldehyde	 <p>The structure shows a benzamide core substituted with a 2-chlorophenyl group.</p>	89	15	Liquid e

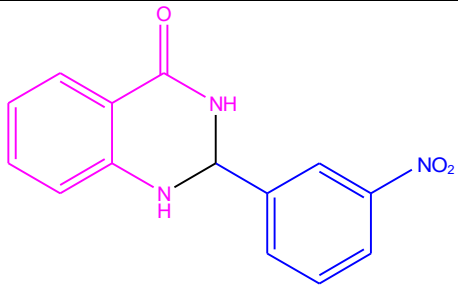
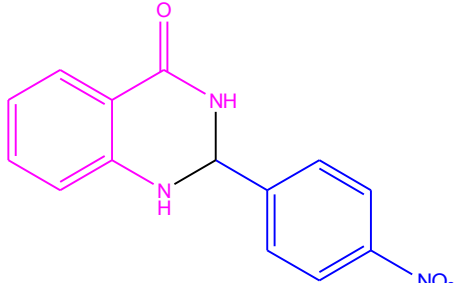
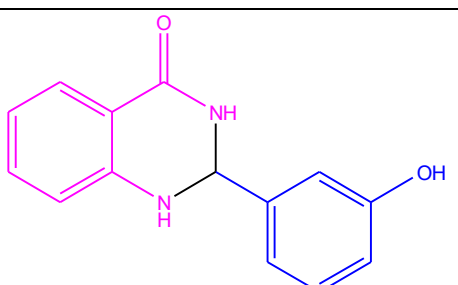
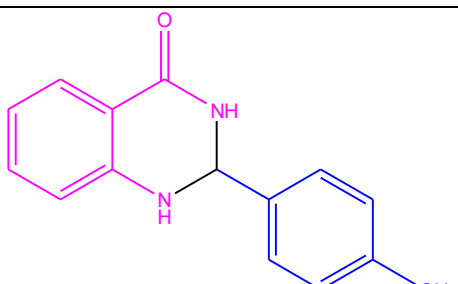
9	2-Bromo Benzaldehyde		89	15	Liquid e
10	3-Methyl Benzaldehyde		89	15	Liquid e
11	2-Methoxy Benzaldehyde		87	15	Liquide
12	2-Nitro Benzaldehyde		84	15	Yellow solid

13	3-Nitro Benzaldehyde		87	15	Yellow soli
14	4-Nitro Benzaldehyde		93	10	Yellow solid
15	3-Hydroxy Benzaldehyde		92	15	White solid
16	4-Hydroxy Benzaldehyde		85	15	White solid

Sr Num	Aldehyde	Derivative	Yield	Time	State
Table03: 2,3-dihydroquinazolin-4(1H)-ones Derivatives					
1	Benzaldehyde	 <chem>O=C1NC(C2=CC=CC=C2)NC3=CC=CC=C13</chem>	89	12	White solid
2	4-Methyl Benzaldehyde	 <chem>CC1=CC=C(C=C1)C2=NC(=O)NC3=CC=CC=C23</chem>	96	08	White solid
3	2-Methyl Benzaldehyde	 <chem>CC1=CC=C(C=C1)C2=NC(=O)NC3=CC=CC=C23</chem>	93	15	liquid
4	4-Chloro Benzaldehyde	 <chem>ClC1=CC=C(C=C1)C2=NC(=O)NC3=CC=CC=C23</chem>	92	10	Solid

5	4-Bromo Benzaldehyde		92	08	Solid
6	4-Methoxy Benzaldehyde		91	10	Solid
7	4-Hydroxy Benzaldehyde		93	12	White solid
8	2-Chloro Benzaldehyde		89	15	Liquid e

9	2-Bromo Benzaldehyde		89	15	Liquid e
10	3-Methyl Benzaldehyde		89	15	Liquid e
11	2-Methoxy Benzaldehyde		87	15	Liquide
12	2-Nitro Benzaldehyde		84	15	Yellow solid

13	3-Nitro Benzaldehyde		87	15	Yellow soli
14	4-Nitro Benzaldehyde		93	10	Yellow solid
15	3-Hydroxy Benzaldehyde		92	15	White solid
16	4-Hydroxy Benzaldehyde		85	15	White solid

The synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives was accomplished under optimized reaction conditions, as depicted in Scheme 1. This process yielded excellent results across a variety of benzaldehydes (1-16). The synthetic pathway involves the reaction between 2-aminobenzamide (1) and aldehyde (2) within a deep eutectic solvent (DES) composed of PEG-400 and TBAB. The DES functions dually as both catalyst and solvent, enhancing the electrophilicity of the aldehydic carbon through interaction with the carbonyl oxygen. This interaction facilitates the formation of a Schiff base via water elimination. Subsequently, the amide nitrogen attacks the electrophilic carbon of the imine, followed by

proton transfer, culminating in the formation of 2,3-dihydroquinazolin-4(1H)-ones. This innovative approach signifies a substantial advancement in green chemistry methodologies for synthesizing 2,3-dihydroquinazolin-4(1H)-ones. The developed protocol addresses previous limitations by employing a one-pot synthesis utilizing 2-aminobenzamide and various aldehydes in the presence of DES. The reaction is conducted at 70 °C using sonochemistry techniques, as illustrated in Scheme 1. This method offers several advantages, including the use of environmentally benign solvents, enhanced reaction efficiency, and the potential for broader applicability in the synthesis of similar heterocyclic compounds. The recyclability of the deep eutectic solvent (DES) was further investigated through a scaled-up reaction process. The reaction was conducted on a larger scale using 10 mmol of reactants and seven volumes of DES. Following each reaction cycle, in case of solid product formation filtered the reaction mass and washed by dry ether dry. Subsequently, In case of liquid product extract by dry ether. The DES was cleaned via dry ether extraction and reused in subsequent reaction cycles.

This method proved to be an efficient and accessible approach for synthesizing 2,3-dihydroquinazolin-4(1H)-one derivatives under sonication. The catalyst exhibited mild Lewis acid properties due to the tetrabutylammonium bromide (TBAB) ion, demonstrating chemical stability without dissociation at elevated temperatures. The reaction was successful with various benzaldehydes, including those containing electron-donating (-Me, -OMe, -OH, and -allyloxy) and electron-withdrawing groups (-NO₂, -F, -Cl, and -Br), all of which yielded excellent results. The optimal reaction conditions were determined to be 70°C for 15 minutes under 40 kHz ultrasound, underscoring the efficiency and versatility of this synthetic method.

Conclusion: We present a novel and sustainable methodology for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones utilizing deep eutectic solvents (DES) composed of PEG-400 and TBAB through sonochemical processes. This approach represents a substantial advancement over conventional synthetic techniques, which frequently involve harsh conditions, hazardous reagents, and non-renewable energy sources. By employing ultrasonic energy and a biodegradable, readily available solvent, this study aligns with the principles of green chemistry, emphasizing waste reduction, energy efficiency, and the use of renewable resources. Under optimized sonication conditions (40 Hz) with a 5 vol. the method achieved a 96% yield within a less than 15 minutes, underscoring its efficiency and effectiveness. Furthermore, the study demonstrated that DES functions as an efficient green solvent and catalyst, with sonochemistry emerging as the most advantageous method. The successful synthesis of 2,3-dihydroquinazolin-4(1H)-one via various encompassing a wide range of substrates, further underscores the practicality of this approach. This environmentally friendly methodology offers a practical, scalable, and sustainable pathway to 2,3-dihydroquinazolin-4(1H)-one derivatives with diverse substitution patterns, thereby advancing the principles of green chemistry.

REFERENCE

- Ijardar, S. P. (2020). Deep eutectic solvents composed of tetrabutylammonium bromide and PEG: Density, speed of sound and viscosity as a function of temperature. *The Journal of Chemical Thermodynamics*, 140, 105897.
- Abdurrahman, A., Shuwa, S. M., Dabai, F. N., Orodu, O. D., Ogunkunle, F. T., Adamu, S. Y., & El-Yakubu, B. J. (2022). Performance Evaluation Of Tetrabutylammonium Bromide-Based Deep Eutectic Solvents in Enhanced Oil Recovery of Nigerian Heavy Oil. *Nigerian Society of Chemical Engineers Journal*, 37(1), 94-102. DOI:10.51975/22370109.som
- Zhang, H., Wang, Y., Zhou, Y., Xu, K., Li, N., Wen, Q., & Yang, Q. (2017). Aqueous biphasic systems containing PEG-based deep eutectic solvents for high-performance partitioning of RNA. *Talanta*, 170, 266-274.
- El Achkar, T., Fourmentin, S., & Greige-Gerges, H. (2019). Deep eutectic solvents: An overview on their interactions with water and biochemical compounds. *Journal of Molecular Liquids*, 288, 111028.
- Vanda, H., Dai, Y., Wilson, E. G., Verpoorte, R., & Choi, Y. H. (2018). Green solvents from ionic liquids and deep eutectic solvents to natural deep eutectic solvents. *Comptes Rendus Chimie*, 21(6), 628-638.
- Choi, Y. H., & Verpoorte, R. (2019). Green solvents for the extraction of bioactive compounds from natural products using ionic liquids and deep eutectic solvents. *Current Opinion in Food Science*, 26, 87-93.
- Zhou, Y., Wu, W., Zhang, N., Soladoye, O. P., Zhang, Y., & Fu, Y. (2022). Deep eutectic solvents as new media for green extraction of food proteins: Opportunity and challenges. *Food Research International*, 161, 111842.
- Mahida, J., & Patel, R. B. Green Reusable Catalyst For The Formation Diastereo Selective Synthesis Of Cyclohexanones By Condensation Reaction Acetoacetanilide With Different Aromatic Aldehydes At Variety Method Of Reaction.
- Mahida, J., & Patel, R. B. (2019). Application of Silica Supported Aluminium Hydroxide as a Low Cost Green Catalyst for the One Pot MCR Sythesis via Thermal Method. *Journal of Drug Delivery and Therapeutics*, 9, 43-47.
- Puri, S., Kaur, B., Parmar, A., & Kumar, H. (2013). Applications of ultrasound in organic synthesis-a green approach. *Current Organic Chemistry*, 17(16), 1790-1828.
- Chowdhury, P., & Viraraghavan, T. (2009). Sonochemical degradation of chlorinated organic compounds, phenolic compounds and organic dyes—a review. *Science of the total environment*, 407(8), 2474-2492.

11. Shen, X., Hong, G., & Wang, L. (2025). Recent Advances in Green Multi-Component Reactions for Heterocyclic Compound Construction. *Organic & Biomolecular Chemistry*.
12. Boruah, D. J., Borkotoky, L., Newar, U. D., Maurya, R. A., & Yuvaraj, P. (2023). Transition-Metal-Free Synthesis of N-Heterocyclic Compounds via Multi-Component Reactions. *Asian Journal of Organic Chemistry*, 12(9), e202300297.
13. Сантра, С. (2024). Direct CC (X) coupling at an activated CHC (Y) bond in hetero-carbocycles as a green chemistry tool for the creation of promising biologically active molecules: Thesis for an academic degree doctor of chemical sciences: 1.4.3 (Doctoral dissertation, б. и.).
14. Ahmed, N., Siddiqui, Z. N., Khan, W. A., & Hamid, H. (2024). Catalytic Synthesis and Application of Heterocyclic and Heteroatom Compounds: Recent Advances. *Sustainable Green Catalytic Processes*, 79-96.
15. Zhang, L., Geng, M., Teng, P., Zhao, D., Lu, X., & Li, J. X. (2012). Ultrasound-promoted intramolecular direct arylation in a capillary flow microreactor. *Ultrasonics sonochemistry*, 19(2), 250-256.
16. Machado, I. V., Dos Santos, J. R., Januario, M. A., & Corrêa, A. G. (2021). Greener organic synthetic methods: Sonochemistry and heterogeneous catalysis promoted multicomponent reactions. *Ultrasonics sonochemistry*, 78, 105704.
17. Li, K., Wang, J., Zhao, P., McClements, D. J., Liu, X., & Liu, F. (2024). Effect of ultrasound-assisted Maillard reaction on glycosylation of goat whey protein: Structure and functional properties. *Food Chemistry*, 441, 138292.
18. Sun, M., Wang, J., Huang, X., Hang, R., Han, P., Guo, J., ... & Zhang, X. (2024). Ultrasound-driven radical chain reaction and immunoregulation of piezoelectric-based hybrid coating for treating implant infection. *Biomaterials*, 307, 122532.
19. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11110758/>
20. El-Sayed, N. N. E., Al-Otaibi, T. M., Barakat, A., Almarhoon, Z. M., Hassan, M. Z., Al-Zaben, M. I., ... & Ben Bacha, A. (2023). Synthesis and Biological Evaluation of Some New 3-Aryl-2-thioxo-2, 3-dihydroquinazolin-4 (1H)-ones and 3-Aryl-2-(benzylthio) quinazolin-4 (3H)-ones as Antioxidants; COX-2, LDHA, α -Glucosidase and α -Amylase Inhibitors; and Anti-Colon Carcinoma and Apoptosis-Inducing Agents. *Pharmaceuticals*, 16(10), 1392.
21. Hakimelahi, R., & Mousazadeh, M. H. (2018). The Synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones Using Zinc Oxide Nanotubes Modified by SiO₂ as a Catalyst with Recyclable effect. *Oriental Journal of Chemistry*, 34(1). DOI : <http://dx.doi.org/10.13005/ojc/340109>
22. Kumar, G., Khubone, L., Seboletswe, P., Manhas, N., Makhanya, T., Bhargava, G., & Singh, P. (2023). Serendipitous synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in ZnCl₂/urea deep eutectic solvent. *ARKIVOC: Online Journal of Organic Chemistry*, 2023. DOI: <https://doi.org/10.24820/ark.5550190.p012.167>
23. Turlapati, S. N., Chinta, B., & Gaddaguti, V. A. (2023). An efficient zinc acetate dihydrate-catalyzed green protocol for the synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones. *Organic Communications*, 16(2), 124. DOI:10.25135/acg.oc.149.2303.2742
24. Mirjalili, B. B. F., Zaghaghi, Z., & Monfared, A. (2020). Synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in the presence of Fe₃O₄@ nano-cellulose-OPO₃H as a bio-based magnetic nanocatalyst. *Journal of the Chinese Chemical Society*, 67(2), 197-201. DOI: <https://doi.org/10.1002/jccs.201900264>
25. Mou, J., Chen, N., Zhao, Y., Qi, H., Meng, S., Xiang, R., & Pei, D. (2020). An aqueous facile synthesis of 2, 3-dihydroquinazolin-4 (1H)-one derivatives by reverse zinc oxide micelles as nanoreactor. *Frontiers in Chemistry*, 8, 239. DOI:<https://doi.org/10.3389/fchem.2020.00239>
26. Katla, R., Chowrasia, R., da Silva, C. D., de Oliveira, A. R., dos Santos, B. F., & Domingues, N. L. (2017). Recyclable [Ce (I-Pro) 2] 2 (oxa) used as heterogeneous catalyst: one-pot synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in ethanol. *Synthesis*, 49(23), 5143-5148. DOI: 10.1055/s-0036-1590886; Art ID: ss-2017-m0378-op
27. Karhale, S., Survase, D., Bhat, R., Ubale, P., & Helavi, V. (2017). A practical and green protocol for the synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones using oxalic acid as organocatalyst. *Research on Chemical Intermediates*, 43(7), 3915-3924. <https://doi.org/10.1007/s11164-016-2855-6>
28. Maleki, A. (2016). Efficient synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in the presence of ferrite/chitosan as a green and reusable nanocatalyst. *International Journal of Nanoscience and Nanotechnology*, 12(4), 215-222.
29. Gajare, S., Jagadale, M., Naikwade, A., Bansode, P., Patil, P., & Rashinkar, G. (2020). An expeditious synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones using graphene-supported sulfonic acid. *Journal of Heterocyclic Chemistry*, 57(1), 89-102.
30. Katla, R., Chowrasia, R., da Silva, C. D., de Oliveira, A. R., dos Santos, B. F., & Domingues, N. L. (2017). Recyclable [Ce (I-Pro) 2] 2 (oxa) used as heterogeneous catalyst: one-pot synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in ethanol. *Synthesis*, 49(23), 5143-5148. DOI: 10.1055/s-0036-1590886; Art ID: ss-2017-m0378-op
31. Kohli, S., Rathee, G., Hooda, S., & Chandra, R. (2023). An efficient approach for the green synthesis of biologically active 2, 3-dihydroquinazolin-4 (1H)-ones using a magnetic EDTA coated copper-based nanocomposite. *RSC advances*, 13(3), 1923-1932.
32. Gharib, Ali, Hashemipour Khorasani, Bibi Robabeh, Jahangir, Manouchehr, Roshani, Mina, Safaee, Reza, Synthesis of Bis-2,3-dihydroquinazolin-4(1H)-ones and 2,3-Dihydroquinazolin-4(1H)-ones Derivatives with the Aid of Silica-Supported Preyssler Nanoparticles, *Organic Chemistry International*, 2013, 848237, 14 pages, 2013. <https://doi.org/10.1155/2013/848237>
33. Mohammadpoor-Baltork, I., Khosropour, A. R., Moghadam, M., Tangestaninejad, S., Mirkhani, V., Baghersad, S., & Mirjafari, A. (2011). Efficient one-pot synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones from aromatic aldehydes and their one-pot oxidation to quinazolin-4 (3H)-ones catalyzed by Bi (NO₃)₃·5H₂O: Investigating the role of the catalyst. *Comptes Rendus. Chimie*, 14(10), 944-952.
34. Hu, Y. L., Rong, Q., Chen, C., & Liu, X. B. (2023). Sustainable and efficient 2, 3-dihydroquinazolin-4 (1H)-ones production over heterogeneous and recyclable Al-MCM-41 supported dual imidazolium ionic liquids nanocomposites. *Journal of Saudi Chemical Society*, 27(1), 101588.
35. Merroun, Y., Chehab, S., Ghailane, T., Boukhris, S., Ghailane, R., Habbadi, N., ... & Souizi, A. (2018). An effective method to synthesize 2, 3-dihydroquinazolin-4 (1H)-One using phosphate fertilizers (MAP, DAP and TSP) as green heterogeneous catalysts. *Journal of the Turkish Chemical Society Section A: Chemistry*, 5(1), 303-316.
36. Wu, J., Du, X., Ma, J., Zhang, Y., Shi, Q., Luo, L., ... & Hu, D. (2014). Preparation of 2, 3-dihydroquinazolin-4 (1H)-one derivatives in aqueous media with β -cyclodextrin-SO₃H as a recyclable catalyst. *Green Chemistry*, 16(6), 3210-3217.
37. Zhang, S. G., Xie, Z. B., Liu, L. S., Liang, M., & Le, Z. G. (2017). Synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones catalyzed by α -chymotrypsin. *Chinese Chemical Letters*, 28(1), 101-104.

38. Zhaleh, S., Hazeri, N., & Maghsoodlou, M. T. (2016). Green protocol for synthesis of 2, 3-dihydroquinazolin-4 (1 H)-ones: Lactic acid as catalyst under solvent-free condition. *Research on Chemical Intermediates*, 42(7), 6381-6390.
39. Liu, X., Hu, D. H., & Shen, H. (2012). Efficient and mild synthesis of 2-aryl-substituted 2, 3-dihydroquinazolin-4 (1H)-ones catalyzed by NaHSO₄. *Asian Journal of Chemistry*, 24(3), 1365-1367