Research article

A vitamin C-based natural deep eutectic solvent for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives

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ABSTRACT

Efficient and green protocols were reported to synthesize 2,3-dihydroquinazolin-4(1H)-one derivatives in natural deep eutectic solvent (NADES). NADES was prepared from ascorbic acid (AA) and choline chloride (ChCl) with reduced or null toxicity, biocompatibility, and low cost. The ChCl/AA NADES was successfully used in the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives via the condensation reaction of aldehydes with 2-aminobenzamide and the three-component reactions of aldehydes, isatoic anhydrides and ammonium salts under solvent-free conditions. The scope of this method was evaluated by employing various aromatic, heterocyclic, and aliphatic aldehydes. The desired products were achieved in 85–97 % yield in a short reaction time. Also, the deep eutectic solvent ChCl/AA showed good recyclability and reusability.

1. Introduction

Quinazolinones and its derivatives are an important class of heterocyclic compounds that have attracted much attention in organic and medicinal chemistry due to their wide presence in various natural alkaloids and bioactive natural products [1,2]. In particular, 2,3-dihydroquinazolin-4(1H)-one scaffolds as the central unit show a wide range of biological and pharmacological activities such as antimicrobial [3], antifungal [4], antibiotic [5], antihistamine [6], antidiabetic and antioxidant [7], analgesic [8], vasodilating [9], diuretic [10], antifibrillator [11] and antitumor [12] (Fig. 1). Due to the importance of these compounds, several strategies have been developed for their synthesis [13–16]. One of the simplest protocols is the cyclocondensation of 2-aminobenzamide with carbonyl analogs using an acid catalyst. Furthermore, they can be synthesized through three-component reactions of aldehydes, isatoic anhydrides, amines, or ammonium salts in the presence of various acid catalysts, which has attracted the attention of many researchers interested in multicomponent reactions [17]. Accordingly, a large number of catalysts have been employed for the synthesis of 2,3-dihydroquinazolin-4(1H)-one quinazolinone derivatives under different conditions, including: indium chloride [18], zirconium (IV) chloride [19], $ZnCl_2$ [20], Amberlyst A26-OH [21], choline hydroxide [22], indium bromide [23], $CoFe_2O_4@SiO_2$-CPTES-Guanidine-Cu(II) [24], [C12Py] [FeCl_3Br] ionic liquid [25], gallium (III) triflate [26]. Although the described methods have significant merits and advantages, most of these methods suffer from one or more limitations, such as the use of toxic organic solvents, difficulties in catalyst preparation, laborious work-up procedure, high temperature, long reaction times, and low yields.

According to the principles of green chemistry, chemical and industrial processes must be designed to minimize the amount of final waste and avoid hazardous or toxic solvents [27]. More recently, a new type of solvent has emerged called deep eutectic solvents (DES) [28]. The use of DESs as cost-effective ionic liquid analogs has attracted increasing attention [29]. DESs are formed by two or more
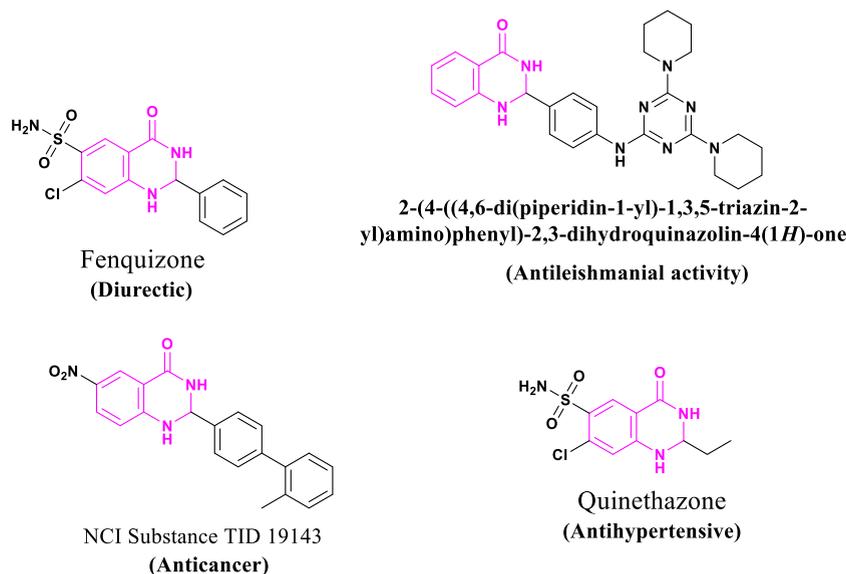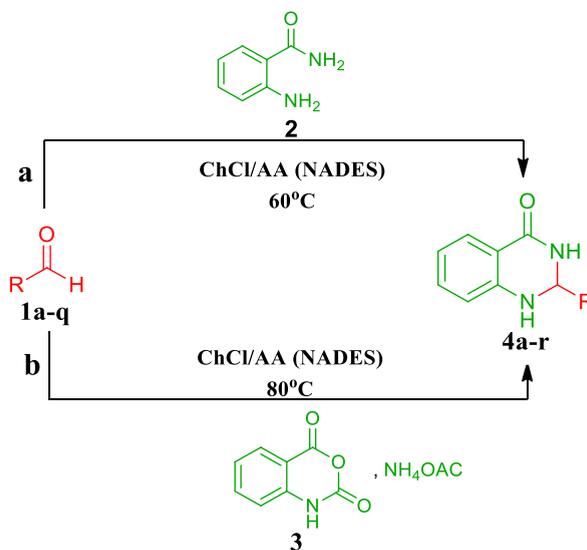
Fig. 1. Examples of biologically active 2, 3-dihydroquinazolin-4(1H)-one derivatives.

Scheme 1. Synthesis of 2,3-dihydroquinazolinone derivatives using ChCl/AA (NADES).

constituents via hydrogen bonds between hydrogen-bonding acceptor (HBA) and hydrogen-bonding donor (HBD), halogen bonds, π-π interactions, or electrostatic interactions [30,31]. Recently, Choi and co-workers reported natural deep eutectic solvents (NADES) [32]. NADES is a mixture of two or more components of natural origin, such as sugars, carboxylic acids, alcohols, and amino acids [33]. NADESs include constituents that are in our daily food, being thus cheap, sustainable, and safe [34]. So far, numerous chemical process such as extraction, gas adsorption, material synthesis and organic reactions have been carried out in NADES medium [35].

Accordingly, in continuation our previous works on the development of environmentally friendly synthesis methods [36–40], herein we report a completely environmentally friendly procedure for the preparation of 2,3-dihydroquinazolin-4(1H)-ones using NADES medium. Since the synthesis of 2,3-dihydroquinazolin-4(1H)-ones are often performed in the presence of acid catalysis, in this project we attempted to use ascorbic acid in DES, which is more environmentally friendly, biosafe, cheaper, and commercially available compared to many other carboxylic acids. As shown in Scheme 1, two environmentally friendly methods were presented for the synthesis of 2,3-dihydroquinazolinones using choline chloride/ascorbic acid (AA or vitamin C) as an efficient, inexpensive, and reusable catalyst under solvent-free conditions.
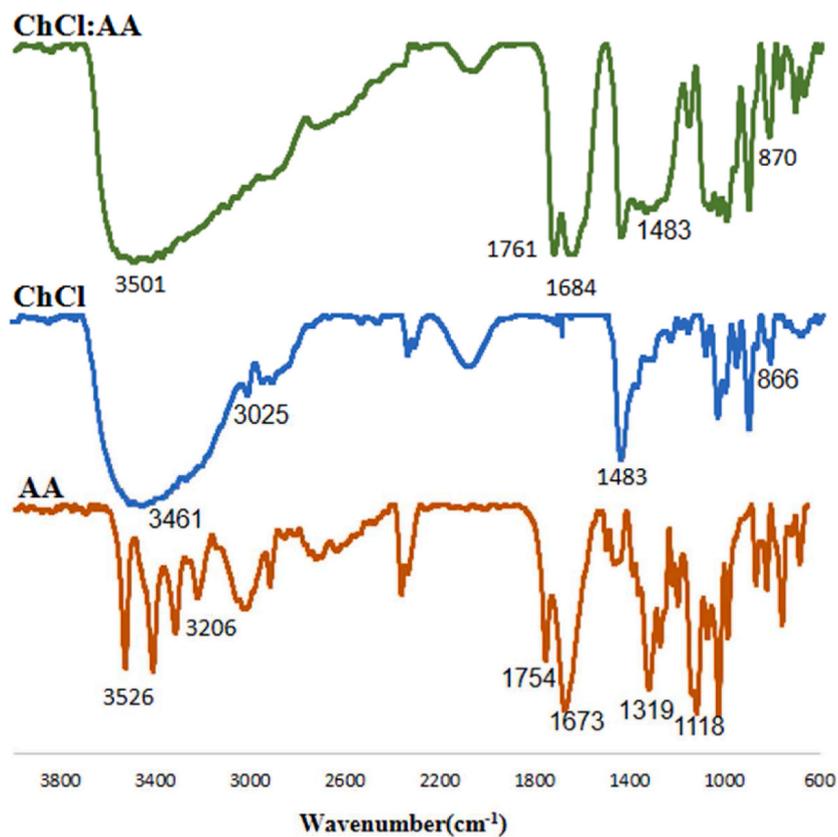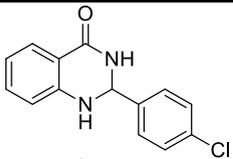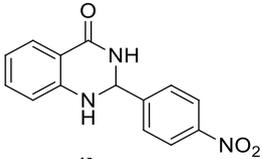
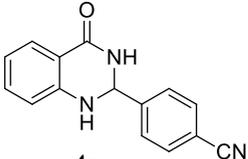**Fig. 2.** FT-IR spectra of ChCl, AA, and ChCl/AA.

Table 1
Optimization of reaction conditions of 2-aminobenzamide and 4-chlorobenzaldehyde[a].

Entry	Catalyst	Amount of the catalyst (mg)	Temp. (^{o}C)	Time (min.)	Yield[b] (%)
1	-	-	80	120	-[c]
2	ChCl/ AA	110	r.t	120	20
3	ChCl/ AA	110	40	50	90
4	**ChCl/ AA**	**110**	**60**	**10**	**97**
5	ChCl/ AA	220	60	10	98
6	ChCl/ AA	55	60	60	60
7	ChCl/ AA	55	80	60	65
8	AA	110	60	120	45[c]
9	ChCl	110	60	120	-[c]

[a] Reaction conditions: 4-chlorobenzaldehyde (0.5 mmol) and 2-aminobenzamide (0.5 mmol).
[b] Isolated yields.
[c] Reaction conditions: 4-chlorobenzaldehyde (0.5mmol) and 2-aminobenzamide (0.5 mmol) in EtOH.

Table 2
Preparation of 2,3-dihydroquinazolin-4(1H)-one derivatives [a].

Entry	R	product	Time (min)	Yield [b] (%)	M.P (°C)	
					Found	Reported
1	$4\text{-}ClC_6H_4$	**4a**	10	97	206-208	206-208 [21]
2	$4\text{-}NO_2C_6H_4$	**4b**	15	95	200-202	197-200 [44]
3	$4\text{-}CNC_6H_4$	**4c**	20	92	300>	350-352 [45]
4	C_6H_5	**4d**	20	92	222-224	221-223 [46]
5	$4\text{-}(CH3)_2NC_6H_4$	**4e**	20	91	208-205	205-208 [44]
6	$4\text{-}MeOC_6H_4$	**4f**	20	95	185-187	186-188 [46]
7	$4\text{-}HOC_6H_4$	**4g**	35	90	280-283	278-280 [21]
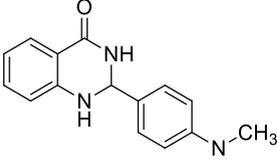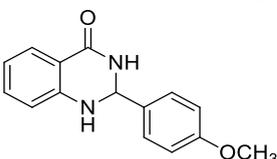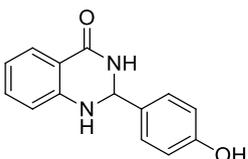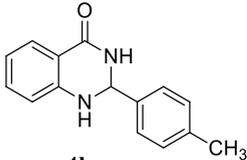
| 8 | 4-MeC₆H₄ | | 20 | 92 | 219-221 | 220-222 [47] |

4h
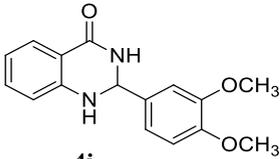
| 9 | 3,4-MeOC₆H₄ | | 35 | 90 | 210-212 | 211-214 [21] |

4i
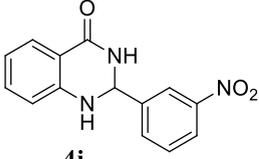
| 10 | 3-NO₂C₆H₄ | | 20 | 90 | 186-188 | 188-189 [24] |

4j
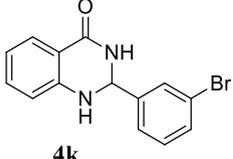
| 11 | 3-BrC₆H₄ | | 25 | 91 | 180-183 | 181-182 [24] |

4k
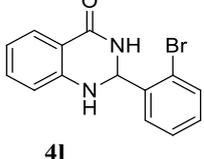
| 12 | 2-BrC₆H₄ | | 35 | 91 | 173-175 | 175-177 [48] |

4l
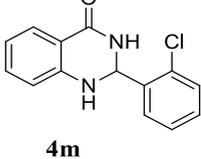
| 13 | 2-ClC₆H₄ | | 30 | 93 | 203-205 | 200-203 [44] |

4m
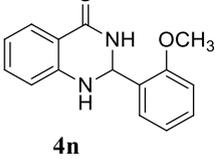
| 14 | 2-MeOC₆H₄ | | 30 | 90 | 173-175 | 171-173 [24] |

4n

15	C$_4$H$_3$O		30	85	165-168	165-167 [21]

4o

16	C$_4$H$_3$S		30	89	210-125	211-213 [44]

4p

17	C$_3$H$_7$		40	76	192-196	191-193 [49]

4q

18	Fe(C$_5$H$_5$)$_2$		20	95	**211-214**	-

4r

a Reaction conditions: aldehyde (0.5mmol) and 2-aminobenzamide (0.5 mmol) in ChCl/AA (110 mg) at 60 °C.
b Isolated yields.
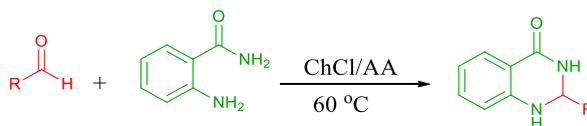
Scheme 2. Cyclocondensation of 2-aminobenzamide with aldehydes using ChCl/AA.

2. Experimental

2.1. Reagents and materials

All chemicals and solvents were purchased from Merck and Aldrich companies and used without further purification. Reaction monitoring was accomplished by thin layer chromatography (TLC) on silica-gel Polygram SILG/UV254 plates. Melting points were measured on an Electrothermal 9100 apparatus. FT-IR spectra were recorded on a Bruker vector 22 spectrophotometer using KBr pills in the 600–4000 cm^{-1} region. NMR spectra were recorded on a Bruker Avance DPX-300 MHz and Bruker Avance III 400 MHz spectrometer in DMSO-d6.

2.2. Synthesis of ChCl/AA

The NADES was prepared by mixing 0.176 g (1 mmol) of ascorbic acid (AA) and 0.28 g (2 mmol) of choline chloride (ChCl) in a round-bottomed flask and heated in a water bath at 60 °C for 30 min until a clear and homogeneous liquid obtained.

2.3. General procedure for synthesis of 2,3-dihydroquinazolin-4(1H)-one

The effects of parameters such as reaction temperature (r.t, 40, 60 and 80 °C), reaction time (reactions were monitored from 5 to 120 min) and catalyst amount (55, 110 and 220 mg) were investigated to achieve optimal reaction conditions.
Two strategies have been developed for the synthesis of 2,3-dihydroquinazolin-4(1H)-one.
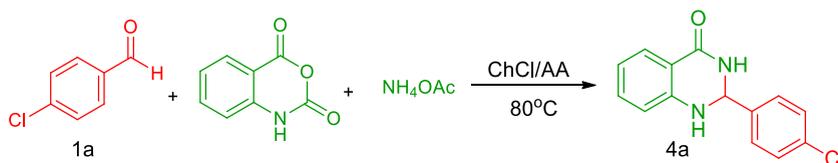
Scheme 3. Synthesis of 2,3-dihydro-4(1H)-quinazolinone via three-component reaction of aldehydes, isatoic anhydrides and ammonium acetate using ChCl/AA (NADES).

Table 3
Optimization of reaction conditions of isatoic anhydride, 4-chlorobenzaldehyde, and ammonium acetate.[a]

Entry	Catalyst	Amount of the catalyst (mg)	Temp. (°C)	Time (min.)	Yield[b] (%)
1	–	–	80	120	-[c]
2	ChCl/AA	110	r.t	120	–
3	ChCl/AA	110	40	120	40
4	ChCl/AA	110	60	120	70
5	**ChCl/AA**	**110**	**80**	**30**	**93**
6	ChCl/AA	110	100	30	93
7	ChCl/AA	220	80	30	94
8	ChCl/AA	55	80	120	65
9	ChCl	110	80	120	-[c]
11	AA	110	80	120	30[c]

[a] Reaction conditions: Isatoic anhydride (0.5 mmol), 4-chlorobenzaldehyde (0.5 mmol) and ammonium acetate (0.5 mmol).
[b] Isolated yields.
[c] Reaction conditions: Isatoic anhydride (0.5 mmol), 4-chlorobenzaldehyde (0.5 mmol) and ammonium acetate (0.5 mmol).in EtOH.

a) A mixture of aldehyde (0.5 mmol) and 2-aminobenzamide (0.5 mmol) in 110 mg ChCl/AA was stirred at 60 °C for an appropriate time. The progress of the reaction was monitored by TLC using *n*-hexane: EtOAc (15:5) as mobile phase. After the reaction was complete, the resulting mixture was allowed to cool to room temperature and water was added (when 2-aminobenzamide was present in the reaction mixture, hot water was used to remove it). The resulting solid was separated by filtration.

b) 110 mg NADES was added to the mixture of isatoic anhydride (0.5 mmol), aldehyde (0.5 mmol), and ammonium acetate (0.5 mmol) and heated at 80 °C for a suitable time. After completion of the reaction, under TLC monitoring, the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture (when 2-aminobenzamide was present in the reaction mixture, hot water was added), while stirring, and the obtained solid was collected by filtration.

The structure of products was characterized by NMR and melting point compared with those reported in the literature. NMR characterization data and spectra of the synthesized compounds (Fig. S1−S24) and IR spectra of DES (S25-S28) are provided as Supplementary materials.

2.4. Recovery of the NADES

After completing the preparation of 2,3-dihydroquinazolin-4(1H)-one, the resulting mixture was allowed to cool to room temperature, water (5 mL) was added, and the resulting mixture was stirred for 10 min. The product was then filtered as a precipitate using Whatman Grade 1 quality filter papers. NADES was obtained from the aqueous solution by water evaporation in vacuo at 80 °C. The yield was mostly quantitative.

2.5. Selected data for the products

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (**4a**): White solid; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H: 8.37 (s, NH, 1H), 7.62 (d, $J = 7.2$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H) 7.27 (td, $J = 7.5$, 1.2 Hz, 1H), 7.17 (s, NH, 1H), 6.76 (d, $J = 8.1$ Hz,1H), 6.70 (t, $J = 7.5$ Hz,1H), 5.79 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) (ppm): δ_C: 164, 148.1, 141.1, 133.9, 133.5, 130.1, 129.2, 127.9, 117.8, 115.5, 115, 66.3.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**4b**): White solid; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H: 8.58(s, NH, 1H), 8.30 (d, $J = 8.7$ Hz, 2H), 7.79 (d, $J = 8.7$ Hz, 2H), 7.66 (d, $J = 7.5$ Hz, 1H), 7.39 (s, NH, 1H), 7.31 (td, $J = 7.5$,1.2 Hz, 1H), 6.81 (d, $J = 8.1$ Hz,1H), 6.74 (t, $J = 7.5$ Hz,1H), 5.98 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C:163.8, 149.8, 147.9, 147.7, 134.1, 128.5, 129, 127.9, 124.1, 117.9, 115.3, 115, 65,7.

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**4f**): White solid;^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 8.20 (s, NH, 1H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.25 (td, $J = 7.2$, 1.5 Hz, 1H), 7.03 (s, NH, 1H), 6.96 (d, $J = 8.7$ Hz,1H), 6.75 (d, $J = 8.1$ Hz,1H), 6.69 (t, $J = 7.5$ Hz,1H), 5.72 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 164.2159.9, 148.5, 133.9, 133.7, 128.7, 127.7, 117.5, 115.4, 114.9114.1, 66.7, 55.6.

Table 4

Preparation of 2,3-dihydroquinazolin-4(1H)-one derivatives via a three-component reaction[a].

Entry	R	product	Time (min)	Yield[b] (%)	M.P (°C) Found	Reported
1	4-ClC₆H₄	**4a**	30	93	203-206	206-207 [21]
2	4-NO₂C₆H₄	**4b**	20	94	195-198	197-200 [44]
3	C₆H₅	**4d**	35	91	223-225	221-223 [46]
4	4-MeOC₆H₄	**4f**	45	91	180-183	186-188 [46]
5	4-MeC₆H₄	**4h**	40	90	222-225	224-222 [47]
6	3-BrC₆H₄	**4k**	35	90	183-186	181-182 [24]
7	2-BrC₆H₄	**4l**	45	84	171-174	175-177 [49]
8	C₄H₃S	**4p**	50	80	209-211	211-213 [44]
9	C₃H₇	**4q**	65	76	190-192	191-193 [49]

[a] Reaction conditions: Isatoic anhydride (0.5 mmol), aldehyde (0.5 mmol) and ammonium acetate (0.5 mmol) in ChCl/AA (110 mg) at 80 °C; [b] Isolated yields.
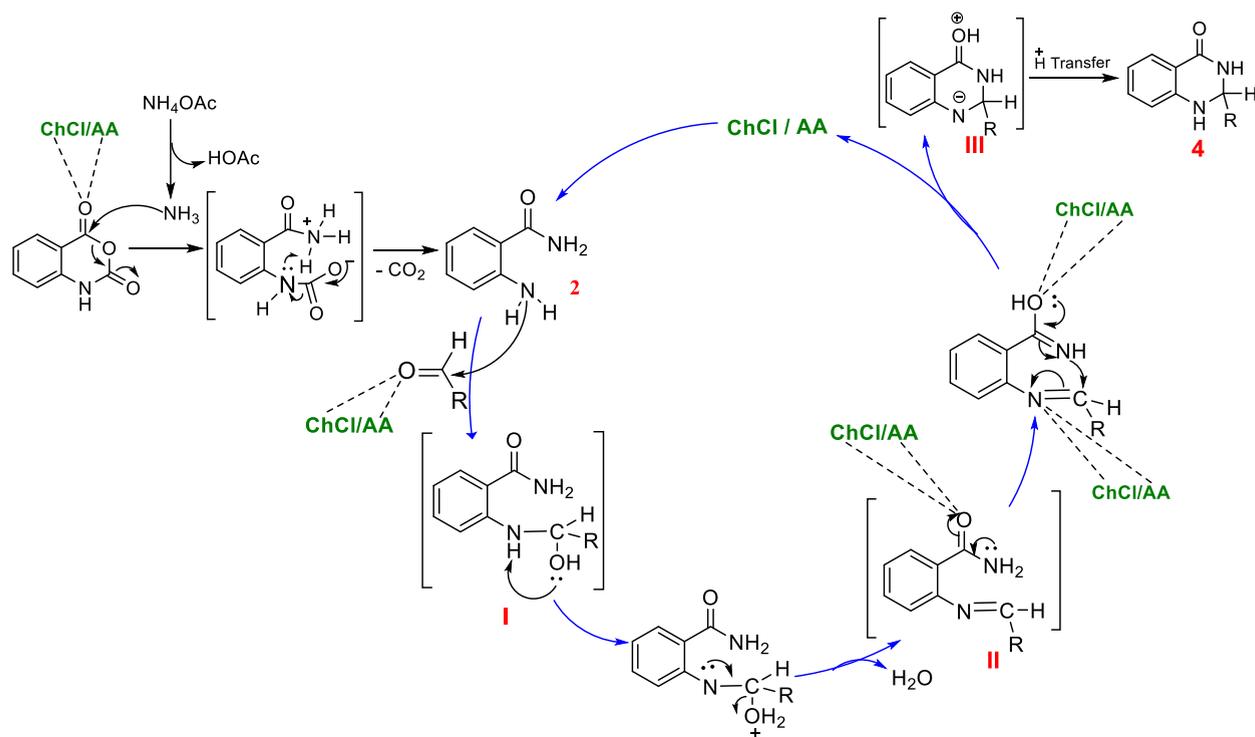
Scheme 4. Plausible mechanism for the synthesis of 2,3-dihydroquinazoline-4-(1H)-ones.
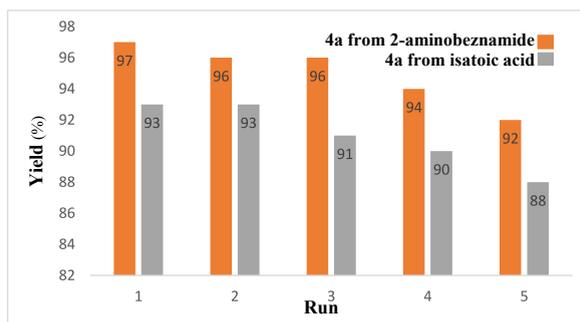
Fig. 3. Recycling study of ChCl/AA (NADES) for the model reaction of 4-chlorobenzaldehyde and 2-aminobenzamide or 4-chlorobenzaldehyde isatoic acid and ammonium acetate.

2-(Thiophene-2-yl)-2,3-dihydroquinazolin-4(1H)-one (**4p**): White solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 8.51 (s, NH, 1H), 7.66 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.51(dd, $J = 5.1, 0.9$ Hz, 1H), 7.35-7.29 (m, 2H, (NH, 1H)), 7.17 (d, $J = 3.0$ Hz, 1H), 7.03 (dd, $J = 3.6, 1.2$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz,1H), 6.73 (t, $J = 7.5$Hz,1H), 6.07 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 163.6, 147.7, 146.9, 133.9, 127.8, 126.9, 126.4, 126.2, 118, 115.6, 115.1, 63.

2-Ferrocene-2,3-dihydroquinazolin-4(1H)-one (**4r**): Light brown solid; FT-IR (KBr) 3343, 3052, 2921, 1641, 1511, 1447,1382 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 8.10 (s, NH, 1H), 7.61 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.22 (td, $J = 8.4, 1.6$ Hz, 1H), 6.77 (s, NH, 1H), 6.75 (d, $J = 5.2$ Hz,1H), 6.64 (t, $J = 7.6$ Hz,1H), 5.57 (s, 1H), 4.21-4.17 (m, 7H), 4.10 (d, J = 3.6 Hz, 2H),^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 163.1147.3, 133.1, 128.9, 127.1, 116.7, 115.0,114.3, 90.3, 69.6, 68.5, 67.6, 67.3, 66.0, 65.9, 62.8; Anal. Calcd. for C$_{18}$H$_{16}$FeN$_2$O: C, 65.08; H, 4.86; N, 8.43; Found: C, 65.18; H, 5.01; N, 8.54.

3. Results and discussion

NADES was prepared from choline chloride/ascorbic acid according to the reported method [41]. FT-IR spectroscopy shows the presence of characteristic peaks of the prepared NADES (Fig. 2). To better understand the presence of different functional groups, the IR spectra of ChCl, AA, and ChCl/AA are shown together in Fig. 2 for comparison. O–H stretching vibrations (3461 cm^{-1}), C-H stretching vibrations (3025 cm^{-1}), alkyl group vibrations bands (1483 cm^{-1}), and C-N$^+$(CH$_3$)$_3$ symmetric stretching vibrations (866
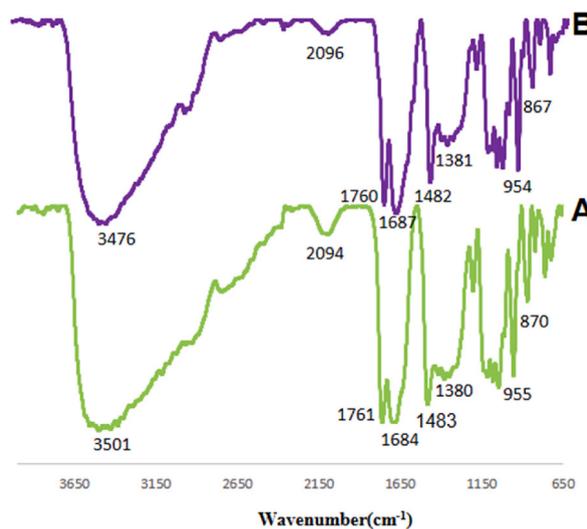
Fig. 4. FT-IR spectra of **A)** ChCl/AA NADES, **B)** reused ChCl/AA NADES.

Table 5
Comparison of the catalytic activity of ChCl/AA NADES with selected reported catalysts for the synthesis of **4d.**

Entry	catalyst	conditions	Time (min)	Yield	Ref.
1	[$C_{12}Py$] [$FeCl_3Br$]	Solvent free/60 °C	120	99 %	[25]
2	Tartaric acid-N, N'/Dimethylurea	solvent free/90 °C	24h	25 %	[49]
3	$ZnFe_2O_4@SiO_2$-ascorbic acid	EtOH/Reflux	100	90 %	[46]
4	$CoFe_2O_4@Pr$[a]	EtOH/Reflux	120	92 %	[48]
5	$ZrCl_2$	EtOH/rt	25	95 %	[53]
6	TCT[b]	CH_3CN, rt	10	96 %	[54]
7	**ChCl/AA**	**solvent free/60°C**	**20**	**92 %** [c]	**This work**
8	MNPs-Pec-Met/ChCl	Solvent free/70 °C	60	88 %	[44]
9	Nano-indium oxide	water/ethanol/80 °C	4h	89 %	[50]
10	SiO_2-(acac)}$_3Fe^{III}$]Cl_3	water/80 °C	60	98 %	[51]
11	Fe_3O_4/SBA-15	EtOH/Reflux	3.5h	75 %	[52]
12	$Ce(SO_4)_2.4H_2O$	Solvent free/120 °C	45	95 %	[55]
13	Amberlyst-15	Solvent-free, MWI	3	78 %	[56]
14	**ChCl/AA**	**solvent free/80°C**	**35**	**91 %** [d]	**This work**

[a] Praseodymium (III) anchored on $CoFe_2O_4$ MNPs.
[b] Trichlorotriazine (cyanuric chloride).
[c] Reaction of benzaldehyde and 2-aminobenzamide in the presence of catalyst.
[d] Reaction of Isatoic anhydride, benzaldehyde and ammonium acetate in the presence of catalyst.

cm^{-1}) confirms the characteristic peaks of choline chloride [42]. O–H stretching vibrations (3526, 3206 cm^{-1}), C=O stretching vibrations (1754 cm^{-1}) and C=C stretching vibrations (1673 cm^{-1}), corresponding to the specification of ascorbic acid [43]. The shifting of the O–H stretching vibration from 3461 cm^{-1} in the choline chloride spectrum to 3501 cm^{-1} and the broadening of absorption bands of ascorbic acid in the range of 3206 cm^{-1} to 3526 cm^{-1} in the NADES spectrum, suggests the formation of hydrogen bonding between the choline chloride and ascorbic acid when the NADES is formed [41]. According to visual observations and data obtained from FT-IR spectroscopy, ChCl/Ascorbic acid NADES has been successfully prepared.

In the next step, choline chloride/ascorbic acid NADES was evaluated as a green catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones through the cyclocondensation of 2-aminobenzamide with 4-chlorobenzaldehyde as a model reaction. The effects of parameters such as reaction temperature, reaction time and catalyst amount were investigated to achieve optimal reaction conditions (Table 1). The catalytic activity of NADES is confirmed by the fact that no product was observed without the catalyst (Table 1, entry 1). When the reaction was carried out in the presence of 110 mg NADES at room temperature, a yield of 20 % was achieved in 120 min (Table 1, entry 2). Increasing the temperature to 40 °C decreases the reaction time and increases the yield of the product (Table 1, entry 3). Noteworthy, increasing the temperature to 60 °C, a yield of 97 % was obtained in 10 min (Table 1, entry 4). The effect of NADES amount on the reaction was also investigated at 60 °C. Increasing NADES to 220 mg showed no significant effect on the yield and reaction time, but reducing NADES to 55 mg significantly decreased the reaction yield even when the temperature increased to 80 °C (entries 5–7). Furthermore, ChCl and ascorbic acid alone were tested as catalysts. When ascorbic acid was used, the desired product was produced in 45 % yield after 120 min (Table 1, entry 8), and in the presence of ChCl, no product was formed after 120 min (Table 2, entry 9).

Under the optimum reaction conditions (Table 1, entry 4), the scope and limitations of the cyclocondensation of 2-aminobenzamide with various aldehydes were subsequently investigated (Scheme 2). As represented in Table 2, a wide variety of benzaldehydes bearing either electron-accepting substituents ($-Cl$, $-NO_2$ and $-CN$) and electron-donating substituents ($-OCH_3$, $-CH_3$, $-OH$ and - N $(CH_3)_2$) on the aryl ring were successfully reacted. The results showed that the electron withdrawing or donating groups had no significant influence on the reaction efficiency. However, the presence of the electron-accepting group somewhat reduces the reaction time (Table 2, entries 1–7). Although the substitution in the *meta* position on the aryl ring does not significantly affect the reaction efficiency, the presence of substitutions in the *ortho* position increases the reaction time due to steric hindrance (Table 2, entries 9–13). Interestingly, the reaction with heterocyclic and aliphatic aldehydes produced the desired products in reasonable times and relatively good yields (Table 2, entries 15–17).

The promising results described above prompted us to test the choline chloride/ascorbic acid NADES in a three-component reaction for the synthesis of 2,3-dihydroquinazolin-4(1H)-one (Scheme 3). Screening reaction conditions for the reaction of isatoic anhydride, 4-chlorobenzaldehyde, and ammonium acetate, similar to those reported in Table 1, revealed that using 110 mg of NADES at 80 °C gave the highest yield of the desired product (4a, Table 3, entry 5). Further increasing the temperature did not improve reaction time or yield. The efficiency of this method was evaluated for the synthesis of various 2,3-dihydro-4(1H)-quinazolinones with aromatic, aliphatic and heteroaromatic aldehydes. The 2,3-dihydro-4(1H)-quinazolinones could be synthesized in 76–94 % yields within 20–65 min of reaction time (Table 4 entries 1–9).

A plausible mechanism for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives in the presence of choline chloride/ ascorbic acid NADES was proposed in Scheme 4 based on published studies [5,17]. Initially, the hydrogen bonding ability of NADES with carbonyl groups facilitates the nucleophilic attack of NH_4OAc on the carbonyl carbon of isatoic anhydride to produce 2-amino-benzamide (2) via decarboxylation. Then, intermediate I was formed from the reaction of 2-aminobenzamide and activated aldehyde by NADES via hydrogen bonding. After removal of a water molecule, an imine intermediate (II) was generated. Subsequently, the intermediate (III) was formed by an intramolecular nucleophilic attack of the amide nitrogen on the activated imine group by NADES. Finally, a proton transfers in intermediate (III) leads to the formation of the product 4.

The ability to recover and recycle can clearly demonstrate the productivity and stability of the catalyst. Therefore, the reusability of the NADES for the synthesis of 2-(4-chlorophenyl)-2,3- dihydroquinazolin-4(1H)-one (4a) was also investigated. After the reaction was completed, water was added, the mixture was stirred for 10 min and the product was filtered off. After removing the water under vacuum at 80 °C, the obtained NADES was utilized for five cycles with only a slight decrease in activity. As shown in Fig. 3, an acceptable yield of products was obtained even after the fifth run. Also, the IR spectrum of recovered NADES showed no significant changes in characteristic bands after fifth run (Fig. 4.).

To demonstrate the advantage of the present method, we compared the effectiveness of NADES ChCl/Ascorbic acid in the preparation of 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (**4d**) with previously reported catalysts (Table 5). According to the results summarized in Table 5, the reaction in the presence of DES (tartaric acid-N, N'/dimethylurea, entry 2) afforded the product **4d** in lower yield, even at higher temperature and longer reaction time. Although the reaction in the presence of TCT leads to higher product yields in a shorter reaction time (entry 6), it should be noted that cyanuric chloride is a toxic reagent. As can be seen, this method furnishes the product (**4d**) with very good efficiency under mild conditions compared to most other methods. Notably, the ChCl/ascorbic acid catalyst offers superior advantages over other reported systems in terms of avoiding the use of toxic solvents or reagents as well as its simplicity and cost-effectiveness (synthesis of the catalyst and work-up).

4. Conclusion

We have developed two green, efficient, metal-free and solvent-free methods for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones through the cyclocondensation of 2-aminobenzamide with aldehydes and the three-component reaction of aldehydes, isatoic anhydride and ammonium acetate using an acidic NADES. The advantages of these methods are simple operation and workup, inexpensive reagents and good to excellent yields of the products in a short reaction time. Moreover, The NADES was easily recycled and reused in five cycles without any significant loss of its activity. We believe that this approach could provide a valuable additional contribution to existing processes in the synthesis of heterocyclic compounds.

Disclosure statement

No potential conflict of interest was reported by the author(s)

Availability of data and materials

NMR, FT-IR spectra are included in the supplementary information file.

CRediT authorship contribution statement

Rahman Hosseinzadeh: Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Shiva Zarei:** Methodology, Investigation, Data curation. **Zohreh Valipour:** Writing – original draft, Visualization, Validation, Investigation, Data curation. **Behrooz Maleki:** Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37170.

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