Deep eutectic solvent mediated synthesis of pyrazolo[3,4-*b*]- and pyrimido[4,5-*b*]quinolines

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Abstract
Herein, this research explores the versatility and efficiency of choline chloride based deep eutectic solvent (DES) as a catalyst as well as reaction media for the cyclocondensation of pyrazolo[3,4-b]quinolines and pyrimido[4,5-b]quinolines. The eutectic solvent employed for this protocol is recyclable, non-toxic, non-volatile and biodegradable with high chemical and thermal stability, making it ideal for the sustainable synthesis of quinoline derivatives. These protocols are simple, straightforward, highly scalable and aligned with green chemistry principles. Additionally, these methods are eco-friendly, economical and outperform existing methodologies in operational efficiency.

Keywords: Deep eutectic solvent, pyrazolo[3,4-*b*]quinoline, pyrimido[4,5-*b*]quinoline, green synthesis.

Introduction

Heterocyclic scaffolds such as xanthenes, pyridines, pyrimidines, indoles, benzimidazoles and pyrazoloquinoline derivatives play a crucial role in medicinal, pharmaceutical, agrochemical and biochemistry fields due to their broad spectrum of therapeutic activities.[3,22,49] Synthesis of structurally diverse heterocyclic moieties and their structural modifications continues to yield promising new drug molecules. Nowadays, researchers face a serious challenge as many existing therapeutic agents are becoming ineffective due to microbial resistance. The search for new therapeutic agents that can overcome antimicrobial resistance is becoming increasingly important. Therefore, the synthesis of fused heterocycles incorporating a pyrrole or pyrimidine ring with quinoline moieties has gained significant scientific interest.

Fused heterocyclic compounds like pyrazolo[3,4-*b*]quinolines and pyrimido[4,5-*b*]quinolines are well known for their diverse pharmacological properties. Its fused structural framework is important for medicinal chemistry and drug discovery because of interaction with specific biological targets.[9,10,43] Pyrazole and quinoline derivatives and their fused heterocyclic scaffolds were explored as therapeutic agents like antituberculosis[25], antidepressant[30], anticancer[21], antimalarial[42], antibacterial[27], antihyperglycemic[23], antiviral[45] and antimalarial activities[42].

Pyrimido[4,5-*b*]quinolines hold remarkable potential as therapeutic agents because of their broad-spectrum of antibacterial activity, anti-inflammatory and antioxidant properties comparable to standard drugs. They also exhibit anticancer activity, which enhances their adaptability in drug development and designing.[15] The synthesis of pyrazoloquinolines was accomplished with the use of different catalysts such as cyclocondensation of 2-chloroquinoline-3-carbaldehyde with hydrazine hydrate or phenyl hydrazine in ethanol[34], *p*-toluene sulphonic acid assisted solvent-free microwave synthesis[36], water-catalysed baker yeast assisted synthesis[8], water-mediated microwave energy resource[28] and L-proline catalysed novel synthesis.[18]

Several efforts have also been made to develop fused pyrimido[4,5-*b*]quinolines derivatives such as glycolic acid supported cobalt ferrite[13], nano-[Fe_3O_4@SiO_2/N-propyl 1-(thiophen-2-yl)-ethanimine][$ZnCl_2$][12], [Zr-UiO-66-PDC-SO_3H]$FeCl_4$[19] nano [Fe_3O_4@-SiO_2@R-$NHMe_2$]-[H_2PO_4][50], [C_4(DABCO)$_2$].2OH[14], Fe_3O_4@Cellulose sulfuric acid[20], [H_2-DABCO]-[ClO_4][33] N, N-diethyl-N-sulfoethanaminium chloride[5], [bmim]Br[38] and agar-entrapped sulfonated DABCO.[29] Earlier reported methods exhibited one or more limitations. The scientific community has made several efforts to develop environment-friendly organic transformations aligned with green chemistry principles.

In recent years, deep eutectic solvents (DESs) have emerged as a new generation of ionic liquids for economical and eco-friendly organic transformations and play a key role in various chemical processes.[4,26,32] Several attempts have been made in exploring eco-friendly DESs in numerous organic transformations.[11,24,37] These green and sustainable eutectic solvents are having unique physicochemical properties such as biodegradability, bio-renewability, relatively wide liquid range, negligible vapor pressure and nontoxicity.[1,2,41] The applicability of DES has been well demonstrated by its several applications in many important organic transformations, Knoevenagel condensation[7], spirooxindole synthesis[6], synthesis of thiazolidinones[47], Clauson-Kass reaction[44], regioselective synthesis of imidazoheterocycles[46], Pictet-Spengler reaction[17], n-alkylation of amines[40], synthesis of thiazolopyridines[48], Perkin reaction[31] and Paal-Knorr reactions.[16]

Though there are reports on these quinoline derivatives, however, no reports have been found for a synthesis of pyrimido[4,5-*b*] quinolines and pyrazolo[3,4-*b*]quinolines catalysed by DESs. Over the past few decades, 2-chloroquinoline-3-carbaldehydes and their structurally diverse derivatives have attracted more attention from the research community due to their diverse biological and

pharmacological properties.[35] They are readily available and exhibit high chemical reactivity due to the presence of chloride and aldehyde active functional moieties. This encouraged us for synthesis of quinoline derivatives using eco-friendly DES as a catalyst as well as the reaction media.

Material and Methods

All starting materials and components of deep eutectic solvents were commercially available and purchased from Spectrochem, Merck and Sigma Aldrich in high purity. Melting points of products were determined using the open capillary method and are uncorrected. IR spectra were recorded on Bruker 870 FTIR spectrometer (ATR, Alpha). ^{1}HNMR spectra were recorded on an AMX-400, 400MHz spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm). All the reactions were monitored by TLC. Elemental analysis of the product was conducted using a Perkin Elmer CHN analyzer.

Synthesis of DES: Choline chloride (100 mmol) and glycerol (200 mmol) were added to the flask, stirred and heated to 60 °C until a clear homogeneous liquid was formed. The resulted deep eutectic mixture, which is liquid at room temperature, was used further without purification.[47]

Synthesis of substituted pyrazolo[3,4-*b*]quinolines (3a-h): 2.0 g DES was added to the reaction flask containing a mixture of substituted 2-chloroquinoline-3-carbaldehydes 1a–h (1.0 mmol) and phenyl hydrazine (1.25 mmol) or hydrazine hydrate 2 (3.0 mmol). The reaction mixture was stirred continuously at 85°C for 70–75 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice. The obtained product was isolated using ethyl acetate extraction and subsequently purified through column chromatography.

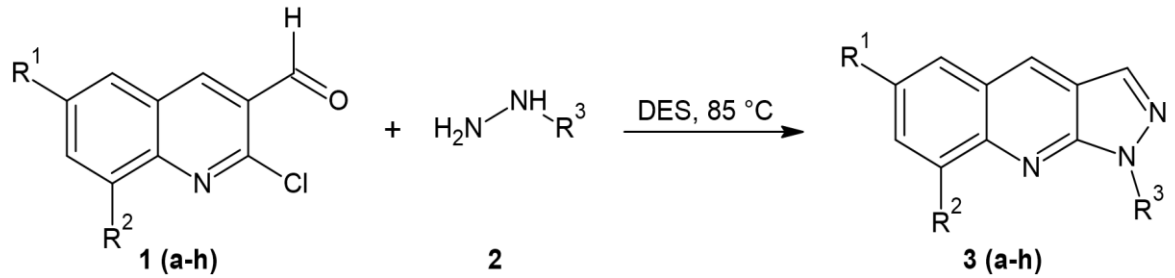
Synthesis of substituted pyrimido[4,5-*b*]quinolines (6a-g and 7a-g): 2-chloroquinoline-3-carbaldehydes (1.0 mmol), urea or thiourea (1.25 mmol) and DES (2.0 g) were taken in a 100 cm^3 round-bottom flask and mixed well. The reaction mixture was stirred continuously at 85°C for 65-70 minutes. The progress reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice. The observed product was extracted with ethyl acetate and purified using column chromatography.

Results and Discussion

With the aforementioned interest in mind, we have developed a DES-catalysed approach for the synthesis of pyrazolo[3,4-*b*]quinolines (Scheme 1) and pyrimido[4,5-*b*]quinoline derivatives (Scheme 2). To study the reaction parameters for these fused heterocycles, a model reaction of 2-chloroquinoline-3-carbaldehyde 1 and phenyl hydrazine 2 was selected (Scheme 1). Initially, the reaction was conducted without any eutectic solvent, which resulted in a negligible amount of the desired product 3a even after refluxing for 600 minutes. Different choline chloride based DESs were employed at 60 °C and the desired product was obtained in low yield. The results are summarized in table 1. The deep eutectic mixture of choline chloride and glycerol (ChCl:Gly) in the ratio 1:2 was found to be a competent catalyst and produced a high yield of product (Table 1, Entry 15). The extensively strong hydrogen bonding between choline chloride and glycerol establishes a synergistic effect, which likely plays a crucial role in enhancing the reaction's efficiency and activity.

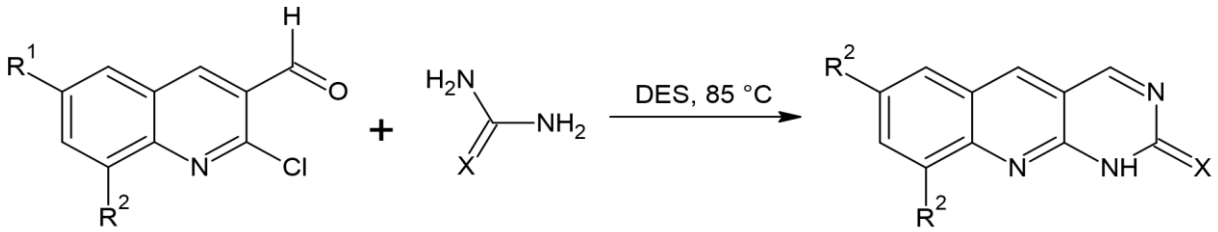
To determine the optimal concentration of DES, the same model reaction was studied by using 0.5 g, 1.0 g, 1.5 g, 2.0 g, 2.5 g and 3.0 g of DES ChCl:Gly (1:2) at 85°C. The corresponding yields were 36 %, 60 %, 80 %, 94 %, 94 % and 94 % respectively. These results show that 2.0 g of DES is sufficient to drive the reaction efficiently. Notably, in the absence of the eutectic solvent, no product formation was observed. Therefore, the most suitable reaction conditions were established.

When the reaction was carried out only in glycerol instead of DES, the product yield was 67%, whereas choline chloride alone produced no significant yield at 85 °C (Table 1, Entries 23 and 24). This shows that the enhanced reaction efficiency is due to the DES (ChCl:Gly) mixture rather than its individual components glycerol and choline chloride.



3a: R^1 = H, R^2 = H, R^3= H **3b:** R^1 = OMe, R^2 = H, R^3= H **3c:** R^1 = Me, R^2 = H, R^3= H
3d: R^1 = H, R^2 = Et, R^3= H **3e:** R^1 = H, R^2 = H, R^3= Ph **3f:** R^1 = OMe, R^2 = H, R^3= Ph
3g: R^1 = Me, R^2 = H, R^3= Ph **3h:** R^1 = H, R^2 = Et, R^3= Ph

Scheme 1: Synthesis of pyrazolo[3,4-b]quinolones



4 (a-g) **5** **6 (a-g) and 7 (a-g)**

6a: R^1=H, R^2=H **6b:** R^1=CH_3, R^2=H **6c:** R^1=H, R^2=CH_3 **6d:** R^1=OCH_3, R^2=H
6e: R^1=H, R^2=OCH_3 **6f:** R^1=Br, R^2=H **6g:** R^1=Cl, R^2=H **X** = O
7a: R^1=H, R^2=H **7b:** R^1=CH_3, R^2=H **7c:** R^1=H, R^2=CH_3 **7d:** R^1= OCH_3, R^2=H
7e: R^1=H, R^2=OCH_3 **7f:** R^1=Br, R^2=H **7g:** R^1=Cl, R^2=H **X** = S

Scheme 2: Synthesis of pyrimido[4,5-b]quinolones

Table 1
Optimization of reaction conditions[a]

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1.	-	60	600	Trace
2.	ChCl:$FeCl_3$ (1:2)	60	95	22
3.	ChCl:$ZnCl_2$ (1:2)	60	95	18
4.	ChCl:$_L$(+) Tartaric Acid (2:1)	60	60	33
5.	ChCl:Citric Acid (2:1)	60	50	48
6.	ChCl:$LaCl_3$ (2:1)	60	60	20
7.	ChCl:Urea(1:2)	60	65	70
8.	ChCl:Malic Acid (1:1)	60	60	35
9.	ChCl:Adipic Acid (1:1)	60	60	28
10.	ChCl:Penyl Acetic Acid (1:1)	60	85	42
11.	ChCl:Thiourea(1:2)	60	65	68
12.	ChCl:Fumaric Acid (1:1)	60	70	33
13.	ChCl:Succinic Acid(1:1)	60	75	43
14.	ChCl:Malonic Acid(1:1)	60	90	45
15.	ChCl:Glycerol (1:2)	60	90	79
16.	ChCl:Glycerol (1:3)	60	90	72
17.	ChCl:Glycerol (1:2)	70	85	83
18.	ChCl:Glycerol (1:2)	75	72	88
19.	ChCl:Glycerol (1:2)	80	65	90
20.	**ChCl:Glycerol (1:2)**	**85**	**70**	**94**
21.	ChCl:Glycerol (1:2)	90	70	94
22.	ChCl:Glycerol (1:2)	95	70	94
23.	Glycerol	85	90	70
24.	ChCl	85	90	10

[a]**Reaction conditions:** 2-chloroquinoline-3-carbaldehyde **1a** (1mmol), Phenyl hydrazine **2** (1.25 mmol) and DES (2.0 g).
[b]**Isolated yields.**

This effect is attributed to the extensive hydrogen bonding between the choline chloride and glycerol. When glycerol is mixed with choline chloride in varying ratios, the resulting DES demonstrates slightly higher polarity than individual glycerol, along with an enhanced hydrogen bond donor ability and improved dipolarity-polarizability.[26] For the synthesis of structurally diverse pyrazolo[3,4-*b*]quinolines and pyrimido[4,5-*b*]quinoline derivatives, DES ChCl:Gly (1:2) emerged as the superior catalyst as well as solvents in both cases, ensuring excellent product yields. The optimal reaction parameters for this methodology were determined as 2-chloroquinoline-3-carbaldehyde 1a-h (1 mmol) and phenyl hydrazine (1.25 mmol) or hydrazine hydrate 2 (3 mmol) or urea or thiourea 3 (1.25 mmol) in 2.0 g DES at 85°C for 65-75 minutes (Table 1, Entry 20).

After optimization, this protocol was evaluated for the synthesis of structurally diverse pyrazolo[3,4-*b*]quinolines and pyrimido[4,5-*b*]quinoline derivatives. The results hint that DES ChCl:Gly (1:2) outperforms other deep eutectic solvents in terms of reaction time and yield of the desired pyrazolo[3,4-*b*]quinolines (Table 2).

Table 2
Synthesis of pyrazolo[3,4-*b*]quinolines(3a-h) and pyrimido[4,5-*b*]quinolines(6a–g & 7a–g).

Entry	Compound	Time (min)	Yield (%)	Melting point (°C) (observed)	Melting Point (°C) (reported)
1.	3a	70	94	202-204	202-204[28]
2.	3b	70	93	217-219	217-218[28]
3.	3c	75	94	175(d)	176 (d) [28]
4.	3d	75	92	164-166	164-166[28]
5.	3e	70	91	172-174	171-172[28]
6.	3f	70	93	150-151	149-151[28]
7.	3g	70	91	179-180	179-181[28]
8.	3h	75	90	175-177	175-176[28]
9.	6a	65	93	214-216	214-215[36]
10.	6b	65	94	278-280	278-280[36]
11.	6c	65	92	229-231	229.5-230[36]
12.	6d	65	93	214-216	214-216[36]
13.	6e	65	90	246-248	246.5-248[36]
14.	6f	70	91	240-242	240-242[36]
15.	6g	70	93	257-259	258-260[36]
16.	7a	65	93	201-203	201-202[36]
17.	7b	65	92	198-200	199-200[36]
18.	7c	65	93	206-207	205-207[36]
19.	7d	65	94	216-218	215-218[36]
20.	7e	65	95	227-229	225-230[36]
21.	7f	70	89	222-224	222-223[36]
22.	7g	70	90	218-219	219-220[36]

[a]**Reaction conditions:** 2-chloroquinoline-3-carbaldehyde **1a** (1mmol), Phenyl hydrazine **2** (1.25 mmol) or hydrazine hydrate **2** (3.0 mmol) urea or thiourea **5** (1.25 mmol) and DES (2.0 g), at 85°C for 65-75 minutes. [b]**Isolated yields.**

The co-existence of glycerol and choline chloride through strong hydrogen bonding exhibits a strong synergistic effect on the reaction, which is likely to be a decisive factor contributing to its outstanding catalytic activity.

Spectral Analysis

1H-Pyrazolo[3,4-*b*]quinoline (3a): Melting point: 202-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.65 (t, 1H, J = 8 Hz), 7.78 (t, 1H, J = 8 Hz), 8.10 (d, 1H, J = 8 Hz), 8.20 (d, 1H, J = 8 Hz), 8.46 (s, 1H), 8.86 (s, 1H), 13.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 115.44, 123.66, 124.05, 127.34, 129.22, 131.13, 131.14, 134.73, 147.19, 153.59; HRMS (ESI$^+$): 170.0320 (M+H)$^+$.

6-Methoxy-1H-pyrazolo[3,4-*b*]quinoline (3b): Melting point: 217-219 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.10 (s, 3H), 7.19–7.68 (m, 2H), 7.99 (d, 1H, J = 8 Hz), 8.58 (s, 1H), 8.87 (s, 1H), 13.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 53.90, 106.18, 115.34, 125.41, 124.37, 129.61, 129.47, 132.46, 144.53, 151.22, 155.32; HRMS (ESI$^+$): 200.0211(M+H)$^+$.

6-Methyl-1H-pyrazolo[3,4-*b*]quinoline (3c): Melting point: 175(d); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.14 (s, 3H); 7.41 (t, 1H, J = 1.2 Hz and J = 8 Hz); 7.87 (d, 1H, J = 6.4 Hz); 7.92 (d, 1H, J = 8 Hz); 8.38 (s, 1H); 8.88 (s, 1H); 13.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 18.27, 115.10, 122.88, 123.89, 128.11, 130.21, 130.81, 134.22, 134.77, 146.55, 152.29; HRMS (ESI$^+$): 184.0869 (M+H)$^+$.

2-Oxopyrimido[4,5-*b*]quinoline (6a): Melting point: 214-216 °C; IR (KBr cm^{-1}): (N-H) 3200–3000, (C=O)1685; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.25 (t, 1H), 7.36 (d, 1H), 7.66 (t, 1H), 7.92 (d, 1H), 8.50 (s, 1H), 10.25 (s, 1H), 12.21 (s, 1H); Anal. Calcd $C_{11}H_7N_3O$: C, 67.00; N, 21.32; H, 3.58; Found: C, 67.15; N, 21.33; H, 3.50; HRMS (ESI$^+$):198.0692 (M+H)$^+$.

7-Methyl-2-oxopyrimido[4,5-*b*]quinoline (6b): Melting point: 278-280 °C; IR (KBr cm^{-1}): (N-H) 3250–3000, (C=O)1683; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H) 7.29–8.41 (m, 4H) 10.24 (s, 1H), 12.14 (s, 1H); Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; N, 19.90; H, 4.29; Found: C, 68.22; H, N,19.89; 4.28; HRMS (ESI$^+$): 212.0822 (M+H)$^+$.

2-Thiopyrimido[4,5-*b*]quinoline (7a): Melting point: 201-203 °C; IR (KBr cm^{-1}): (N-H) 3300–2900, (C=S)1340; ^{1}H NMR(400 MHz, DMSO-d_6, δ ppm): 7.20–8.41 (m, 5H) 10.21 (s, 1H), 11.90 (s, 1H); Anal. Calcd for $C_{11}H_7N_3S$: C, 61.97; N, 19.71; H, 3.31; Found: C, 61.94; N, 19.69; H, 3.30; HRMS (ESI$^+$): 214.418 (M+H)$^+$.

7-Methyl-2-thiopyrimido[4,5-*b*]quinoline (7b): Melting point: 298-200 °C; IR (KBr cm^{-1}): (N-H) 3200–2900, (C=S) 1343; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.32 (s, 3H) 7.21–8.40 (m, 4H) 10.25 (s, 1H), 11.84 (s, 1H); Anal. Calcd for $C_{12}H_9N_3S$: C, 63.43; N, 18.50; H, 3.99; Found: C, 63.41; H, 3.97; N, 18.53; HRMS (ESI$^+$): 228.0572 (M+H)$^+$.

Recyclability: Scale-up and recycling studies for this methodology were conducted for the model reaction of 2-chloroquinoline-3-carbaldehyde 1a **(**1 mmol) and phenyl hydrazine 2 (1.25 mmol) in 2.0 g DES under the optimized reaction conditions. The reaction was monitored by TLC. After completion of the reaction, used eutectic solvent was fully recovered by isolating it from the products. It is then recovered by evaporating the water content under vacuum and reused for subsequent cycles (Figure 1). The DES was recycled up to five times without any considerable loss in activity or efficiency, consistently yielding high product yields. The deep eutectic solvent (DES) employed in this protocol demonstrates excellent recyclability. The reaction was successfully scaled up to 5 g, based on a model reaction and optimising reaction conditions.

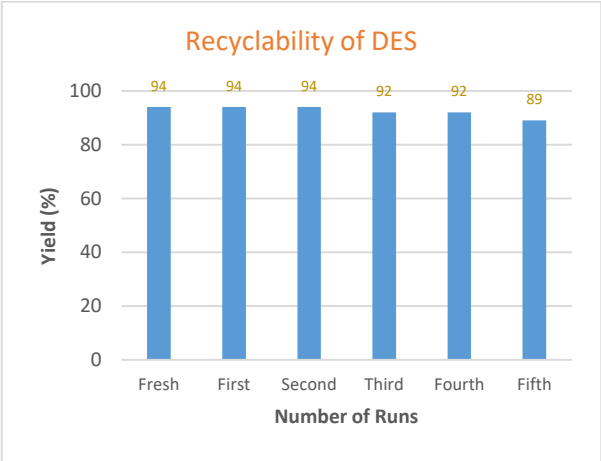


Fig. 1: Recyclability of DES ChCl:Gly

Conclusion

In conclusion, a simple, straightforward and efficient green methodology for the synthesis of pyrazolo[3,4-*b*]quinolines and pyrimido[4,5-*b*]quinolines has been developed, utilizing choline chloride-based deep eutectic solvent ChCl:Gly. It offers several advantages like excellent yield of desired quinoline derivatives and use of non-toxic, inexpensive, biodegradable, non-flammable eutectic solvent. The DES used in this protocol is recyclable and can be reused for up to five cycles, maintaining a consistent yield of the desired products throughout all cycles. Thus, the synthesis of a new diversified quinoline heterocyclic scaffold has been demonstrated.

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(Received 12th March 2025, accepted 15th May 2025)