A rapid and green method for expedient multicomponent synthesis of N-substituted decahydroacridine-1,8-diones as potential antimicrobial agents

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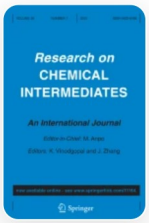

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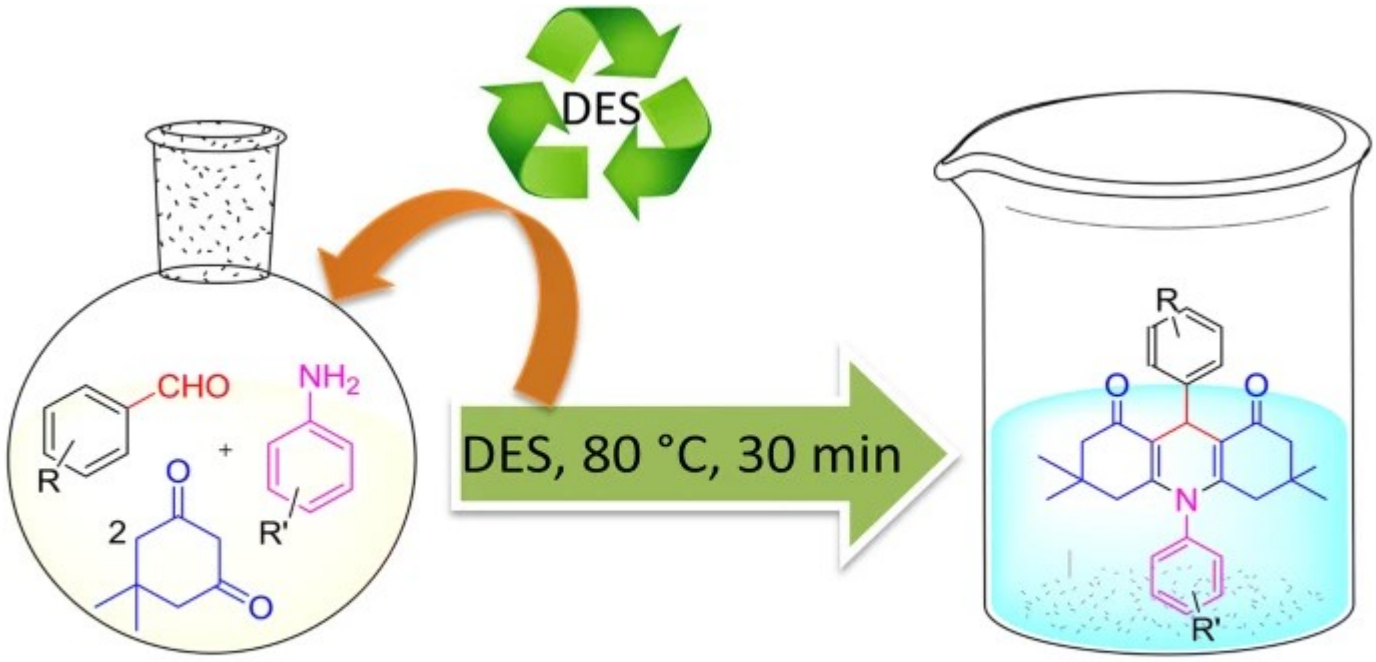
Abstract

An efficient, green, high yielding, and quick method for the synthesis of N-substituted decahydroacridine-1,8-diones was achieved by multicomponent reaction between various aromatic aldehydes (1a–q), dimedone (2), and various aromatic amines (2a–d) using

ChCl:Urea deep eutectic solvent as a recyclable organocatalyst and medium. The reaction conditions are relatively mild and do not require additional metals, acid catalysts, or organic solvents. The mild reaction conditions, experimental simplicity, straightforward purification procedures, excellent yields with short reaction times, as well as the application of green chemistry principles, are the advantages of this methodology. This simple ammonium deep eutectic solvent, easily synthesized from choline chloride and urea, is relatively inexpensive and biodegradable, making it applicable for industrial use. The deep eutectic solvent was easily separated and reused without loss of activity, and thus provides a good alternative. The synthesized 10-(substituted phenyl)-9-(substitutedphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-diones (4a–l) were screened for their in vitro antimicrobial activity against four bacterial Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and three fungal strains (*Candida albicans*, *Aspergillus niger and Aspergillus flavus*). Among them, the 9-(*N*,*N*-Dimethylphenyl)-3,3,6,6-tetramethyl-10-(3-pyridyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4f), 10-(4-Bromophenyl)-9-(3-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4i) and 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4k) show good antimicrobial activity.

Graphical Abstract



- Short reaction time, quantitative yield of products
- DES as greener and recyclable medium/catalyst
- Antimicrobial activity

Introduction

The development of an environmentally benign and efficient protocol for the synthesis of privileged molecular skeletons has been a challenging task for synthetic chemists [1, 2]. Among them, multi-component reactions (MCRs) have been shown to be a one of the most efficient tools in modern synthetic organic chemistry, since they have all the features that contribute to an ideal synthesis: high atom efficiency, quick and simple implementation, time and energy savings, environment-friendly, and they offer a target and diversity-oriented synthesis [3,4,5]. Therefore, the development of new multicomponent reactions towards

biomedical and industrial scaffolds is inevitable at the present time.

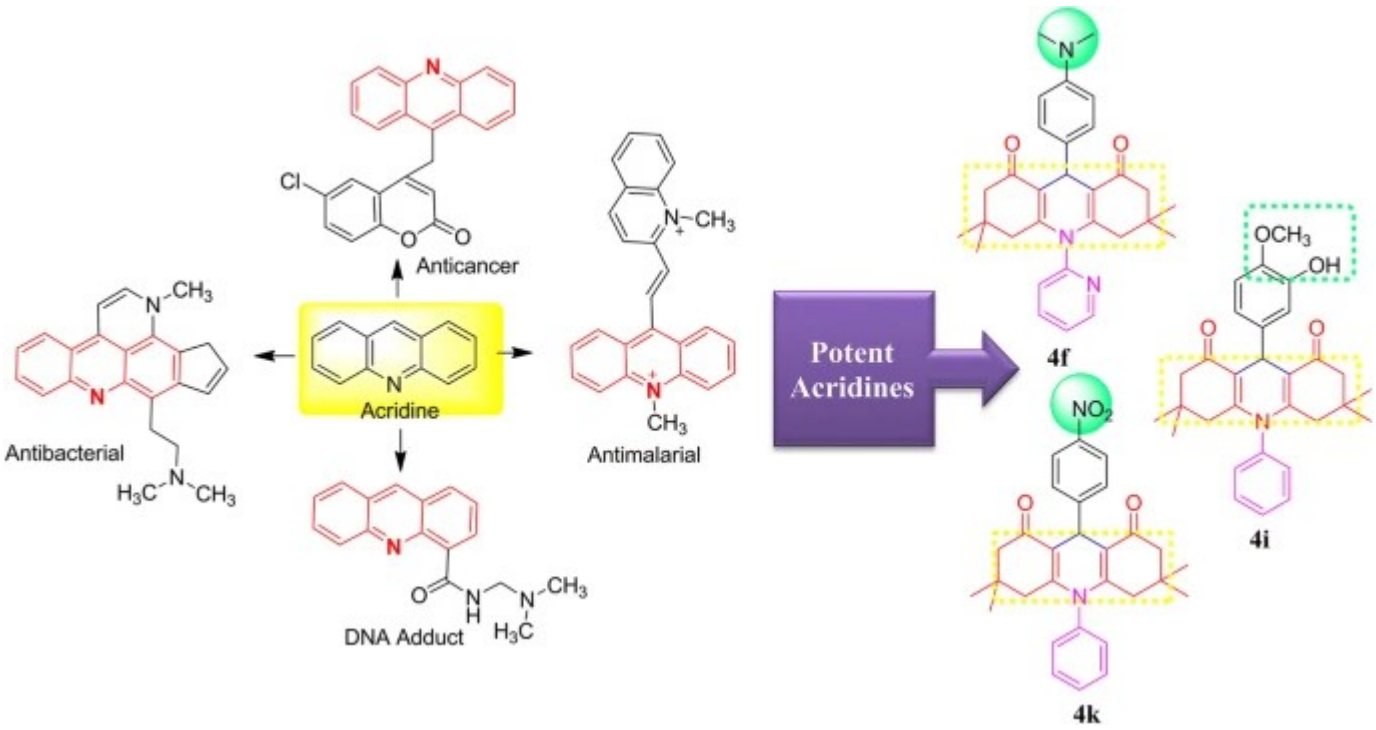
In the continuing effort to attain greener synthetic methods, reaction solvents have attracted a great deal of attention. Certainly this awareness is well justified as reaction solvents are generally the largest component of a reaction by volume/mass. They are also typically volatile, flammable, and toxic. A number of alternatives have been developed over the last two decades, including water, supercritical fluids and ionic liquids [6]. Each of these alternatives has its own strengths and weaknesses. Ionic liquids and deep eutectic solvents (DES) have been studied as an alternative to traditional solvents in many applications. The environmentally friendly and green, nature of these solvents, together with their tunable properties, has led to their promotion for use in organic, inorganic and electrochemistry processes [7, 8]. Very recently, the use of deep eutectic solvents (DES) has been explored in organic synthesis as a green alternative to VOCs and some ionic liquids (ILs).

DESs are commonly prepared from a eutectic mixture of Lewis or Brønsted acids and bases, which may contain a variety of anionic or cationic species, and possess a melting point much lower than either of the individual components [9,10,11]. The majority studied series of DESs are those prepared using choline chloride as a donor compound with components including urea, sugars, carboxylic acids, and ethylene glycol or M^{2+} ions. The most commonly employed is the 1:2 molar mixture of choline chloride and urea which affords a viscous liquid at room temperature. Advantages of this solvent are several-fold: it is relatively inexpensive, easily available; it is non-toxic, exhibits no detectable vapor pressure under ambient conditions, is based on biorenewable materials and is a recyclable catalyst for various organic transformations [9,10,11]. Due to interesting properties such as the ease of handling, excellent catalytic activity and simplicity in processing, ChCl:Urea have emerged as a promising green reaction media for organic transformations [12,13,14,15,16,17,18,19]. Combination of established multicomponent reactions with a deep eutectic mixture is highly desirable.

Fused polycyclic heterocyclic molecules are an important class of organic molecule because of their widespread applications as pharmaceutical candidates, optical materials and sensors [20,21,22]. Acridine is a fused polycyclic aromatic molecule, which is exhibited in numerous publications in organic, pharmaceutical and medicinal chemistry because of its potential biological activities and presence in a variety of significant natural products and synthetic

dye-stuffs [23,24,25,26]. Acridines are firstly used as antibacterial and antiparasite agents with planar aromatic structures that are capable of intercalating into DNA base pairs [27]. Furthermore, acridinedione derivatives are known to be biological agents with antimalarials [28], anti-fungal [29], anti-tumor [30], anti-cancer [31], cytotoxic [32] and anti-multidrug-resistant properties [33] (Fig. 1).

Fig. 1



Acridine containing biologically active molecules and synthesized potent antimicrobial acridines

There are various reports in the literature for the three-component Hantzsch-type condensation of aromatic aldehydes, anilines and dimedone via the traditional heating in organic solvents [34], under MW irradiation [35], and using catalysts, for example, *p*-toluenesulfonic acid [36, 37], *p*-dodecylbenzenesulfonic acid [38], Ceric ammonium nitrate (CAN) [39], InCl3-ionic liquid [40], montmorillonite [41], Fe_3O_4@SiO_2-MoO_3H nanoparticles [42], silica-bonded *N*-propyl sulfamic acid (SBNPSA) [43], amberlyst-15 [44], and benzyltriethylammonium chloride (TEBAC) [45], leading to acridines. However, many of these methods suffer from disadvantages such as low yields, toxic organic solvents, long

reaction times, expensive catalysts, the requirement of special apparatus, laborious workup procedures, and harsh reaction conditions. Thus, to avoid these limitations and to improve the reaction conditions available for the synthesis of acridinedione, the discovery of new methodologies using new green and reusable catalysts is still needed.

Through the versatility and green features of DES combined with the synthetic, biological attributes of acridinediones, and as a part of our research aimed at the development of synthetic methodologies using environmentally benign catalysts through MCRs [46,47,48,49,50], we decided to explore the use of a 1:2 mixture of choline chloride (ChCl) and urea as a medium and catalyst in the synthesis of N-substituted decahydroacridine-1,8-diones for the first time.

Experimental

General All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 and 75 MHz using DMSO and $CDCl_3$ solvents and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. The elemental analysis was done on a Thermofisher EA1112 series CHNS Elemental Analyser. The purity of each compound was checked by TLC using silica-gel, $60F_{254}$ aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

Preparation of choline chloride:Urea deep eutectic mixture

A mixture of choline chloride (50 mmol) and urea (100 mmol), that is, in the ratio of 1:2 was heated at 80 °C with stirring for 2 h. In the resulting eutectic solvent, the liquid was then allowed to cool to room temperature and was used for the synthesis of N-substituted decahydroacridine-1,8-diones.

General procedure for the synthesis of 10-(substituted phenyl)-9-(substitutedphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-diones 18 compounds

A mixture of substituted benzaldehydes (1a–q) (1 mmol), dimedone (2) (2 mol), and substituted anilines (2a–d) (1 mol) in Choline chloride:Urea (5 mL) was stirred at 80 °C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 30 min of stirring, the reaction mixture was allowed to cool to room temperature and poured on crushed ice. The thus obtained solid was filtered, dried and purified by crystallization using ethanol as solvent. Synthesized compounds were confirmed by melting point, IR, ^{1}H and ^{13}C NMR and were in good agreement with those reported in the literature [36, 37, 39].

Spectral analysis of compounds

4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10 (9H) yl) benzenesulfonohydrazide (4a)

White solid, Yield 91%. Melting point 197–199 °C. IR (ATR υ_{max} cm^{-1}): 737, 864, 1098, 1260, 1369, 1498, 1661, 2824, 2957. ^{1}H NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.88 (s, 6H, CH_3), 0.99 (s, 6H, CH_3), 2.20–2.28 (m, 4H, CH_2), 2.32 (dd, J = 17 Hz, 4H, CH_2), 4.90 (s, 1H), 7.08–7.16 (m, 5H, ArH), 7.20–7.39 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 26.92, 28.46, 32.42, 41.88, 50.13, 115.29, 125.36, 125.84 (2C), 127.59, 127.83 (2C), 127.91, 127.98, 128.62, 132.45, 137.07 (2C), 145.80, 150.47 (2C), 195.54 (2C).

4-(9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl) benzenesulfonohydrazide (4b)

White solid, Yield 93%. Melting point 232–235 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.87 (s, 6H, CH_3), 0.94 (s, 6H, CH_3), 1.84–2.06 (m, 4H, CH_2), 2.10–2.18 (m, 4H, CH_2), 3.71 (s, 3H, OCH_3), 5.24 (s, 1H), 7.23–7.29 (d, *J = 8.8 Hz*, 2H, ArH), 7.31–7.38 (m, 4H, ArH), 7.57–7.61 (d, J = 7.6 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 26.82, 29.79, 32.65, 41.86, 50.27, 57.32, 114.25 (2C), 119.87, 129.62 (4C), 129.89, 131.21, 138.93 (2C), 145.45 (2C), 150.09, 151.67, 195.83 (2C).

10-(4-Methoxyphenyl)-9-(4-flurophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

(4c)

White solid, Yield 86%. Melting point 223–225 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.84 (s, 6H), 0.97 (s, 6H), 1.80–1.83 (d, J = 17.4 Hz, 2H, CH_2), 2.05–2.21 (m, 6H), 3.51 (s, 3H, OCH_3), 5.17 (s, 1H), 7.08–7.23 (m, 4H, ArH), 7.39–7.42 (m, 4H, ArH). ^{13}C NMR(100 MHz, $CDCl_3$ δ_{ppm}): 23.45, 26.78, 29.64, 32.38, 41.72, 50.17, 56.78, 113.57, 116.59 (2C), 123.52, 128.81 (2C), 129.78, 138.29 (2C), 146.42 (2C), 148.71, 150.39, 152.96 (2C), 195.62(2C).

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4d)

White solid, Yield 91%. Melting point 245–246 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.83 (s, 6H, CH_3), 0.93 (s, 6H, CH_3), 1.60–1.98 (m, 4H, CH_2), 2.09–2.15 (m, 4H, CH_2), 5.20 (s, 1H), 7.06–7.10 (d, J = 7.2 Hz, 2H, ArH), 7.10–7.28 (m, 5H), 7.39–7.41 (m, 2H, ArH). ^{13}C NMR(100 MHz, $CDCl_3$ δ_{ppm}): 26.85; 28.91, 32.56, 40.97, 49.99, 115.6 (2C), 120.3, 127.0 (4C), 129.35, 132.2 (2C), 135.8, 143.67 (2C), 150.6, 153.0 (2C), 196.21 (2C).

9-(3,4-Dimethoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4e)

White solid, Yield 90%. Melting point 231–233 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.84 (s, 6H, CH_3), 0.93 (s, 6H, CH_3), 1.96–2.01 (m, 4H, CH_2), 2.09–2.18 (m, 4H, CH_2), 3.74 (s, 6H, OCH_3), 5.15 (s, 1H), 7.20–7.38 (m, 6H, ArH), 7.41–7.52 (m, 2H, ArH); ^{13}C NMR(100 MHz, $CDCl_3$ δ_{ppm}): 27.5, 28.8, 32.6, 40.1, 49.89, 57.29, 114.9 (2C), 116.5, 120.3, 127.7 (2C), 131.49, 132.0, 132.8 (2C), 135.8, 146.87 (2C), 154.36, 158.62, 163.2, 195.95 (2C).

9-(*N*,*N*-Dimethylphenyl)-3,3,6,6-tetramethyl-10-(3-pyridyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4f)

White solid, Yield 87%. Melting point 254–255 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}):0.89 (s, 6H, CH_3), 0.94 (s, 6H, CH_3), 1.81–1.86 (m, 4H, CH_2), 2.05–2.23 (m, 4H, CH_2), 2.79 (s, 6H, CH_3), 5.23 (s, 1H), 7.07–7.19 (m,

4H, ArH), 7.27–7.37 (m, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 27.45, 28.17, 32.49, 40.79, 41.72, 49.99, 115.43, 118.37, 123.09, 124.96, 127.17, 128.49 (2C), 135.77 (2C), 135.81 (2C), 149.59, 149.84, 153.46 (2C), 196.67 (2C).

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-10-(3-pyridyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4g)

White solid, Yield 90%. Melting point > 300 °C. IR (ATR υ_{max} cm^{-1}): 734, 831, 1143, 1498, 1630, 1708, 2326, 2919, 3109. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.88 (s, 6H, CH_3), 0.94 (s, 6H, CH_3), 1.80–1.94 (m, 4H, CH_2), 2.06–2.22 (m, 4H, CH_2), 5.24 (s, 1H), 7.22–7.24 (m, 2H, ArH), 7.31–7.38 (m, 4H, ArH), 7.56–7.58 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 26.83, 29.80, 32.48, 41.88, 50.24, 114.23 (2C), 119.81 (2C), 129.61 (4C), 131.20 (2C), 138.97 (2C), 145.40 (2C), 150.04(2C), 195.88 (2C).

9-(2-Furyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4h)

White solid, Yield 75%. Melting point 245–247 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.88 (s, 6H, CH_3), 0.92 (s, 6H, CH_3), 1.25–1.46 (m, 4H, CH_2), 1.99–2.03 (m, 4H, CH_2), 5.70 (s, 1H), 6.83–6.97 (d, J = 8.4 Hz, 2H, ArH), 7.06–7.18 (m, 4H, ArH), 7.20–7.26 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 27.64, 29.60, 31.92, 40.96, 50.27, 109.34, 112.76, 116.43, 126.05 (2C), 132.17, 132.64, 135.90, 145.91, 148.24, 149.08, 152.98, 154.68 (2C), 195.42 (2C).

10-(4-Bromophenyl)-9-(3-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4i)

White solid, Yield 89%. Melting point > 300 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956, 3430. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.80 (s, 6H, CH3), 0.94 (s, 6H, CH3), 1.00–1.04 (d, 2H, CH2), 2.06–2.22 (m, 6H, CH2), 3.65 (s, 3H, OCH_3), 5.24 (s, 1H, CH), 7.22–7.26 (d, 2H, *J = 8 Hz*, Ar–H), 7.31–7.38 (m, 3H, Ar–H), 7.56–7.58 (m, 2H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 28.09, 29.16, 30.04, 40.42, 50.14, 56.98, 112.91 (2C), 119.07, 124.28 (2C), 128.29, 129.43(2C), 130.46 (2C), 145.81(2C), 150.40 (2C), 153.17 (2C), 194.98 (2C).

9-(4-Flurophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-

hexahydroacridine-1,8(2H,5H)-dione (4j)

White solid, Yield 87%. Melting point 272–273 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.86 (s, 6H, CH_3), 0.92 (s, 6H, CH_3), 1.62–1.88 (m, 4H, CH_2), 2.00 2.40 (m, 4H, CH_3), 5.06 (s, 1H), 6.63–7.09 (m, 4H, ArH), 7.17–7.37 (m, 5H, ArH); ^{13}C NMR(100 MHz, $CDCl_3$ δ_{ppm}): 26.89, 29.72, 31.90, 41.87, 50.24, 113.55 (2C), 114.82, 128.85 (2C), 129.48, 138.81, 139.14 (2C), 149.65 (2C), 153.45 (2C), 154.67 (2C), 157.7, 195.92 (2C).

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4k)

White solid, Yield 89%. Melting point 285–287 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): δ 0.92 (s, 6H, CH_3), 0.98 (s, 6H, CH_3), 1.23–1.37 (m, 4H, CH_2), 2.33–2.43 (m, 4H, CH_2), 5.54 (s, 1H), 7.08–7.18 (m, 5H, ArH), 7.24–7.29 (m, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 27.68, 29.02, 31.85, 41.34, 51.22, 110.19, 110.85, 116.53, 120.26 (2C), 126.91, 126.34, 125.98, 127.43, 139.88, 148.91, 144.63, 149.76, 155.34, 156.21, 194.37(2C).

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4l)

White solid, Yield 92%. Melting point 284–286 °C. IR (ATR υ_{max} cm^{-1}): 738, 864, 1094, 1370, 1664, 2297, 2879, 2956. ^{1}H-NMR (400 MHz, $CDCl_3$ δ_{ppm}): 0.87 (s, 6H, CH_3), 1.61–1.86 (m, 4H, CH_2), 2.0–2.17 (m, 4H, CH_2), 5.25 (s, 1H), 6.94–7.06 (m, 3H, ArH), 7.23–7.26 (m, 4H, ArH), 7.43–7.49 (d, 2H, ArH), 9.18 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$ δ_{ppm}): 27.51, 28.93, 31.59, 40.29, 50.94, 116.56 (2C), 118.71, 120.38, 127.81 (2C), 131.97, 133.09, 135.73, 141.67, 145.23, 150.65, 154.45 (2C), 155.23 (2C), 195.08 (2C).

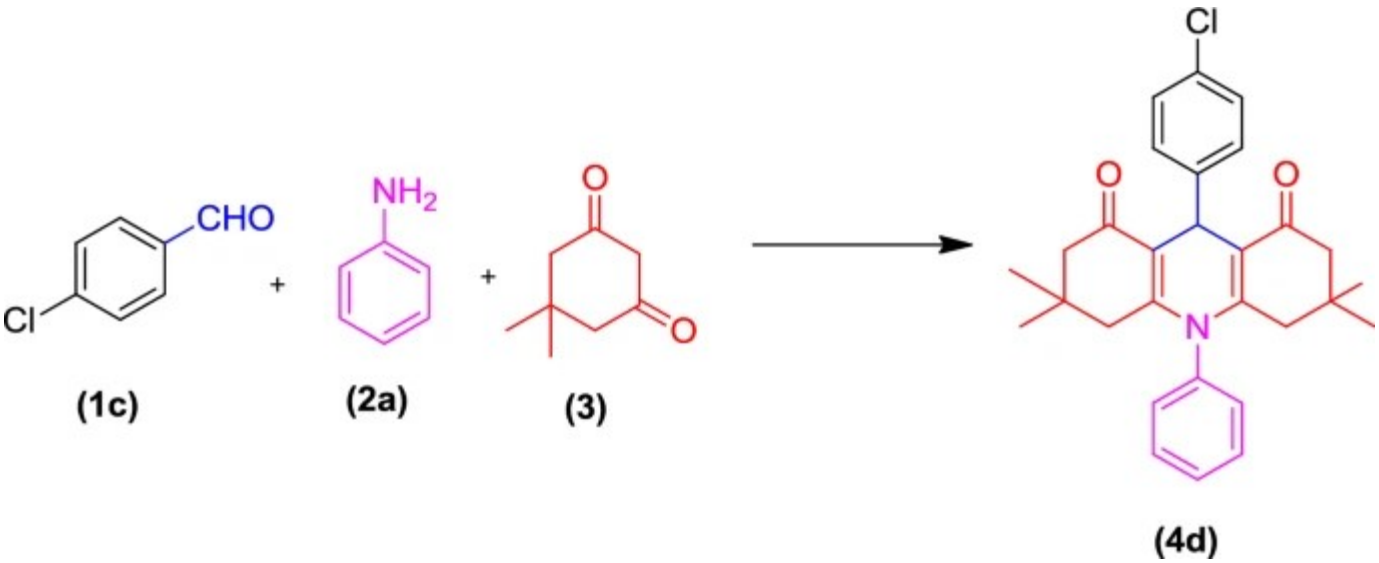
Results and discussion

Optimization of reaction conditions

In search of the best experimental reaction conditions, the reaction of 4-chloro benzaldehyde (1 mmol), cyclohexadione (2) (2 mmol) and aniline (3a) (1 mmol) in the presence of ChCl:Urea

as a deep eutectic medium was considered as a standard model reaction (Scheme 1). The reaction conditions were optimized on the basis of the catalyst, solvent and different temperature for the synthesis of N-substituted decahydroacridine-1,8-diones. This reaction was firstly examined in different catalysts and solvents such as CAN, *p*-TSA, and Acetic acid as reported catalyst. It was observed that formation of product 4d takes place after a long reaction time and obtained with poor yield (Table 1, entries 1–3). Considering the drawbacks of the volatile hazardous organic solvent, we have screened the model reaction in green solvents like *N*-Methyl pyridinium tosylate, DIPEAc, dicationinic ionic liquid, ChCl:Urea and ChCl:Glycerol (Table 1, entries 4–7). Among these solvents, ChCl:Urea as a prominent deep eutectic medium was used which fulfilled the requirements of excellent yields with high purity in short reaction time (30 min) (Table 1, entry 12).

Scheme 1



Synthesis of 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10 hexahydroacridine-1,8(2H,5H)-dione (4d)

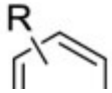
Table 1 Screening of reaction media and catalyst for the synthesis of compound 4[a]

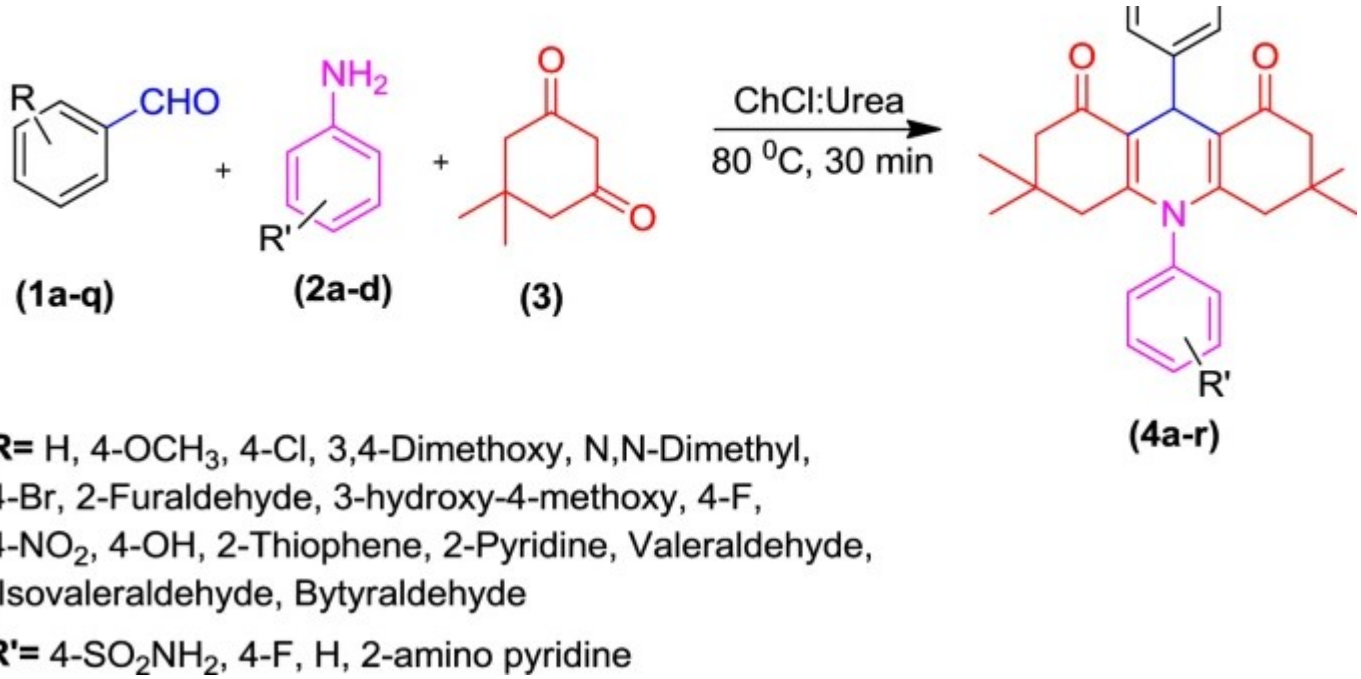
To confirm the role of ChCl:Urea as a catalyst, a model reaction was separately attempted in media, viz., ethanol, methanol, acetonitrile and water in the presence of 20 mol% of ChCl:Urea at reflux temperature (Table 1, entries 7–10). The compound 4d obtained in good yields 85, 75 and 71% in ethanol, methanol and acetonitrile respectively. The 20 mol% of ChCl:Urea in water gave the poor yield of desired product. However, time required for these condensations was 2 h (Table 1, entries 7–10). It was observed that, in absence of ChCl:Urea, condensation could not occur in media EtOH (Table 1, entry 13). This observation is in agreement with the idea that ChCl:Urea plays a role not only as a medium but also as a catalyst in this cyclocondensation. Therefore, ChCl:Urea was chosen as the medium and organocatalyst of choice for further optimization studies.

Results obtained indicate that a raised temperature accelerates the reaction rate and favors the exclusive yield of titled product 4d. Raising the temperature up to 80 °C facilitates the homogenization of the reaction mixture. Due to the viscosity of the solvent, the reactions at lower temperature gave low poor yields of product. Accordingly, a set of reactions were conducted at varying the temperatures of 40, 60, 80 and 100 °C and obtained the product yield 67, 86, 95, 95% (Table 1, entry 12). Therefore, further reactions were carried out at 80 °C using 5 mL of ChCl:Urea.

The scope and limitations of this reaction were explored by utilizing various aldehydes (1), dimedone (2), and various aniline derivatives (3) Scheme 2 (Table 2). As indicated in Table 2, the aromatic substituted decahydroacridine-1,8-diones were synthesized in higher yields (75–95%) with shorter reaction times (30 min) relative to the aliphatic substituted decahydroacridine-1,8-diones (Trace). Various benzaldehydes containing electron-donating, electron withdrawing, and halogen substituents were successfully applied to the reaction and afforded the decahydroacridine-1,8-dione heterocycles in good to excellent yields. Aromatic and hetryl anilines also show good to excellent yields of the products. The synthesized compounds were isolated, purified, and characterized by Fourier-transform infrared (FT-IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), spectrometric techniques.

Scheme 2



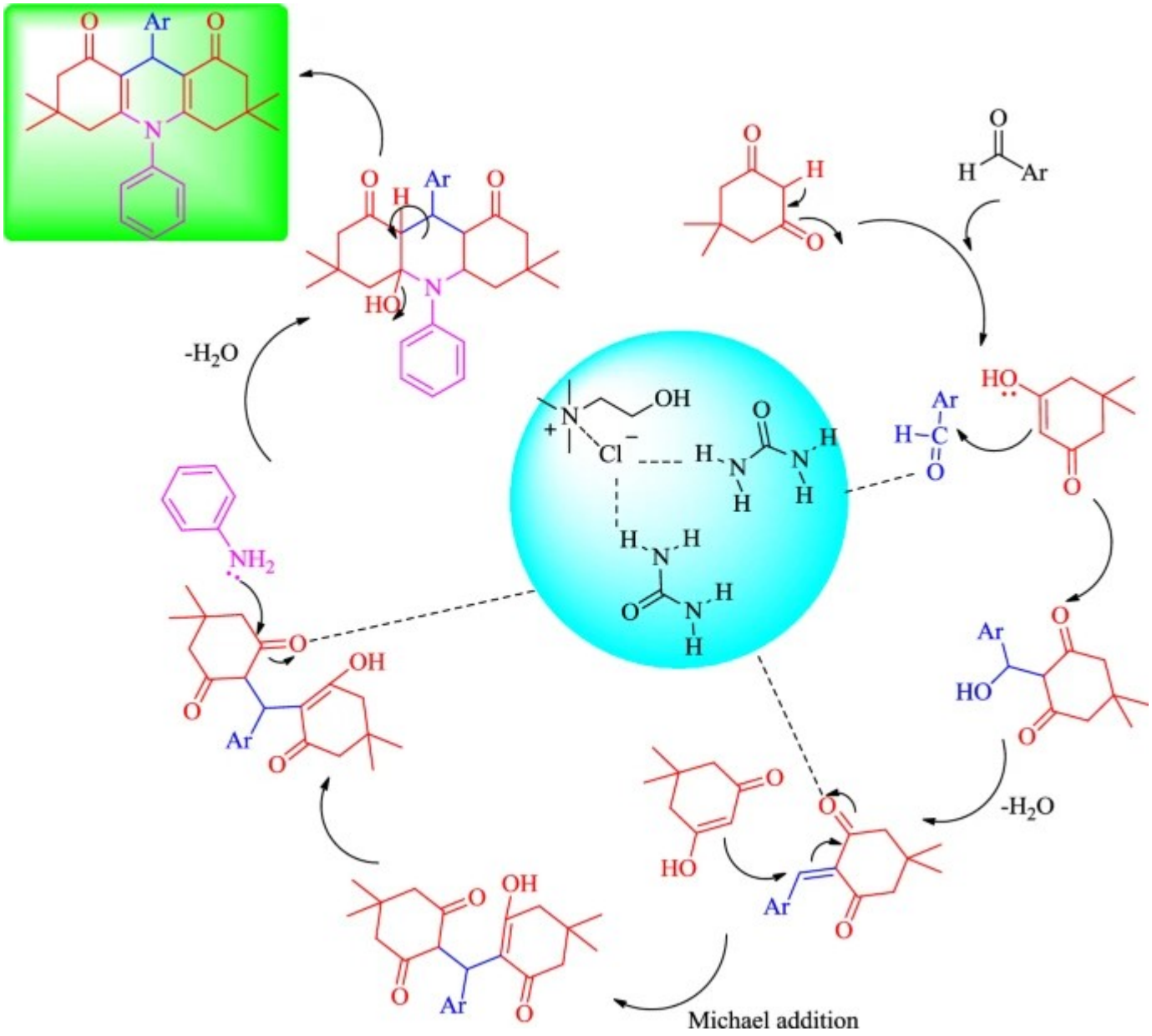


Synthesis of 10-(substituted phenyl)-9-(substitutedphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-diones (4a–r)

Table 2 Synthesis of N-substituted decahydroacridine-1,8-diones with a wide range of aldehydes and amines in ChCl:Urea as DES[a]

Hydrogen bonding and Bronsted basicity of urea are the main factors that influence the reactivity and selectivity of the process. We tentatively propose the mechanism of the present reaction to proceed in a manner similar to that described in the analogous ChCl:Urea catalyzed reactions outlined in Scheme 3. The reversible hydrogen bonding between urea and carbonyl groups giving substrate–solvent complex and activated aldehydes is depicted in Scheme 3. The initial condensation of carbonyl groups with activated dimedone with urea in the ChCl:Urea leads to the formation of arylidene dimedone with the loss of a water molecule. Then Micheal addition of the second molecule of enolizable dimedone to arylidene dimedone followed by intramolecular cyclization with aniline of the resulting species produces the N-substituted decahydroacridine-1,8-dione derivatives.

Scheme 3

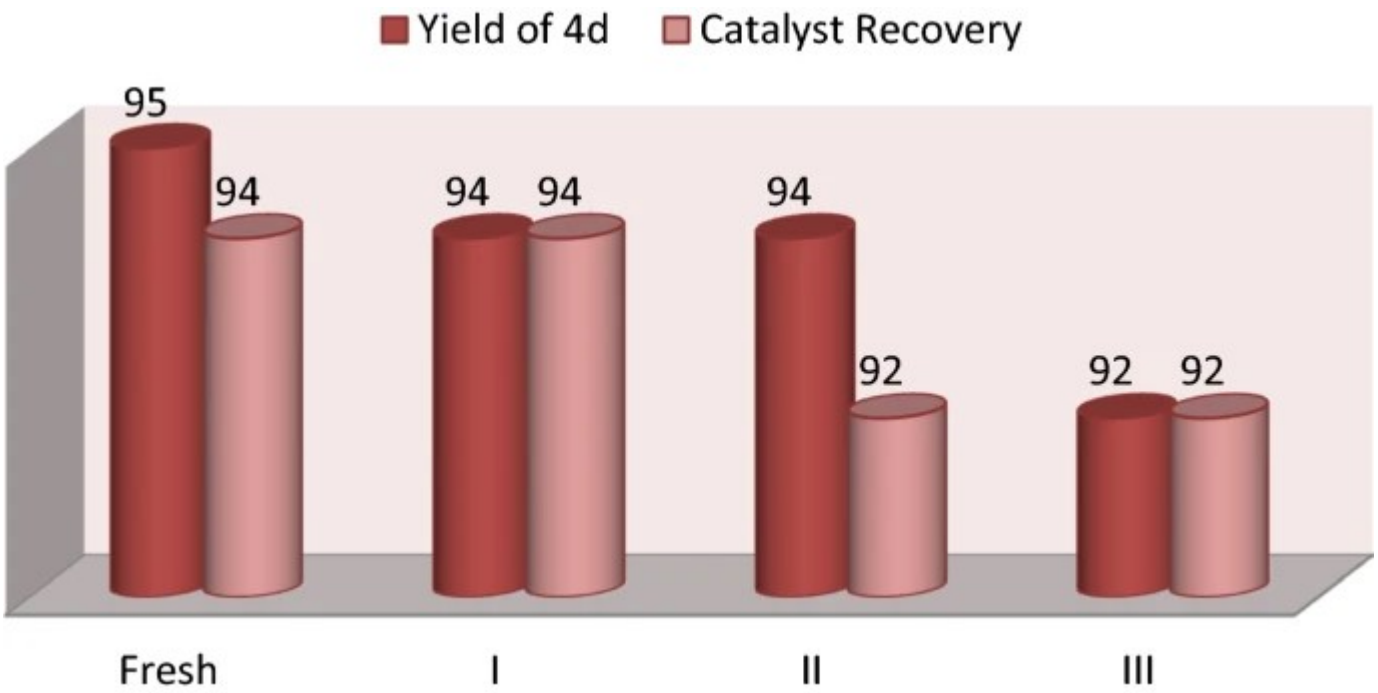


Plausible mechanism for the synthesis of N-substituted-1,8-dioxo-decahydroacridines

ChCl:Urea can play a dual role in this reaction: (1) as a medium/solvent and (2) as an organocatalyst which activates the carbonyl and intermediates functional groups via hydrogen bonding. The rate acceleration for the formation of N-substituted decahydroacridine-1,8-diones have been found to be enhanced by using ChCl:Urea as medium/solvent. ChCl:Urea might be helping to create a high initial concentration of the reactants in solvation at 80 °C.

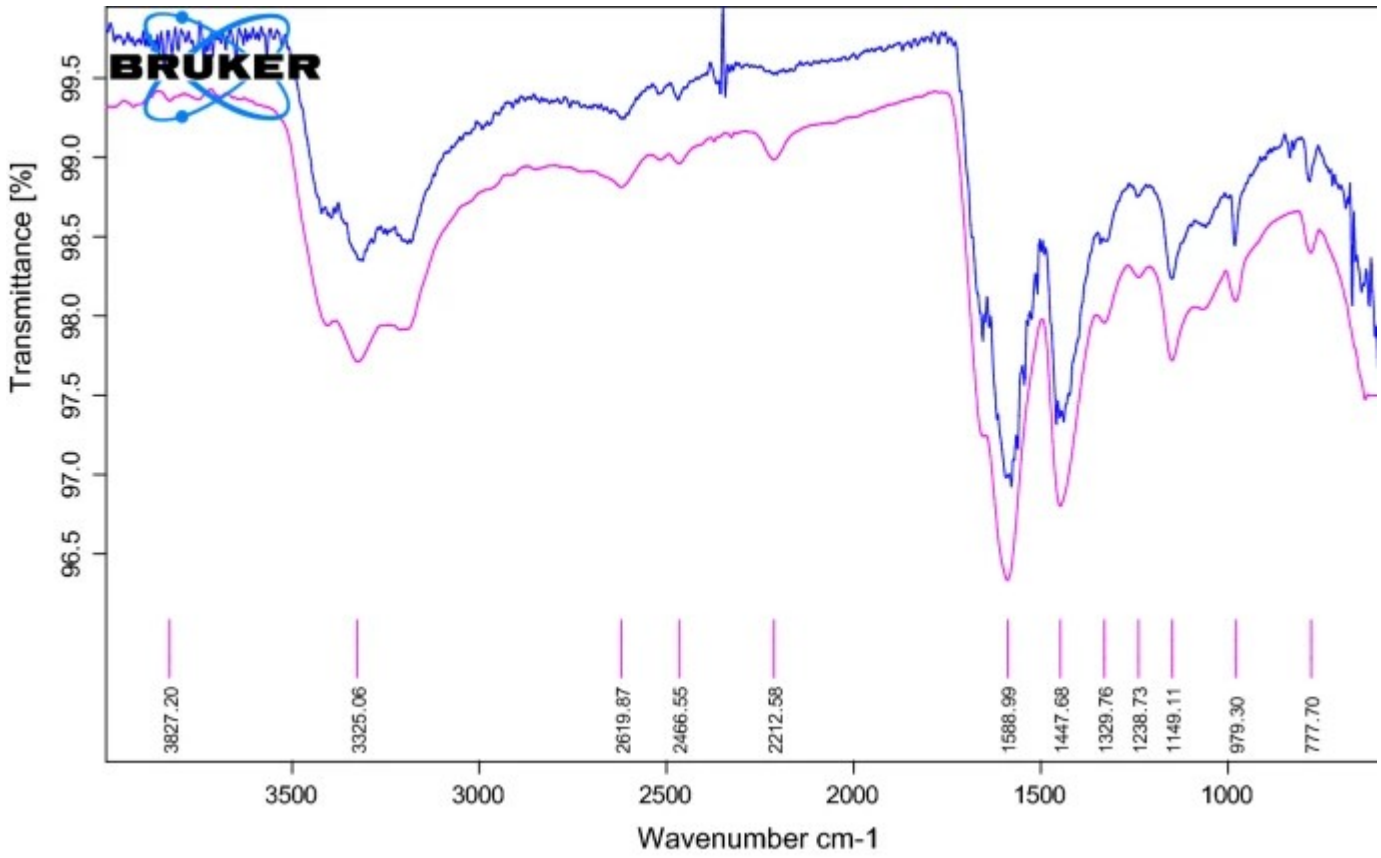
Another advantage of using ChCl:Urea is their ability to act as a recyclable reaction media/catalyst [51,52,53]. The reaction mixture, including the ChCl:Urea and 4a, was dissolved in water and the insoluble crude product was filtered off. The ChCl:Urea was recovered from water by evaporation at 80 °C under vacuum, recycled, and reused for three reaction runs without a significant loss of catalytic activity (Fig. 2). Recycled ChCl:Urea was confirmed by a FT-IR spectrum which resolved structural information about the molecule. There is no change observed in the IR spectra of the ChCl:Urea before the reaction and after third recycle (Fig. 3). The compound having the covalent bond absorbs various frequencies of electromagnetic radiation in the infrared region of the electromagnetic spectrum. The absorption peak at around 3425 cm^{-1} and 3325.06 is characteristic of N–H and O–H stretching vibration, respectively. The bands at 2212.58 and 1238.73 cm^{-1} result from the C–N and C–O stretching (Fig. 3).

Fig. 2



Recycle and recovery of ChCl:Urea and its effect on yield

Fig. 3



FT-IR spectra of ChCl:Urea. Below pink color: fresh ChCl:Urea, above blue color: after III recycle recovered ChCl:Urea. (Color figure online)

Biological activity

The in vitro antimicrobial activities for the newly synthesized decahydroacridine-1,8-dione compounds were evaluated for Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungal strains (*Candida albicans*, *Aspergillus niger and Aspergillus flavus*). Minimum inhibitory concentration (MIC, mg/mL) values of all the compounds were determined using the standard agar dilution method as per CLSI guidelines [54]. All the experiments were performed in triplicate, and the mean reading was taken as the final reading. The 5% DMSO was used as a negative control, along with ampicillin and fluconazole as the standard antibacterial and antifungal drugs, respectively (Table 3).

Table 3 Antibacterial and antifungal screening of N-substituted decahydroacridine-1,8-diones (4a–l)

Antimicrobial activity

The in vitro antibacterial evaluations of decahydroacridine-1,8-diones demonstrated that many of the synthesized compounds display prominent antibacterial activity against the tested strains. Some title compounds showed broad-spectrum activity while some compounds were narrow spectrum active against only one bacterial strain. As seen in Table 3, all the screened decahydroacridine-1,8-diones (4a–l) exhibited prominent activity compared to the standard drug ampicillin against Gram-positive bacteria (*S. aureus* and *B. subtilis*). Compound 4f having *N*,*N*-dimethyl substitution at the para position showed good inhibitory activity against Gram-positive bacteria (*S. aureus* and *B. subtilis*) MIC values 100 ± 0.67 and 112.5 ± 0.45, respectively. Among the whole series (4a–l), compound 4i with 3-hydroxy, 4-methoxy substitution exhibited excellent activity against all tested bacterial strains (*E. coli*, *P. aeruginosa* and *S. aureus*). Compound 4k with nitro group substitution at the para position showed the antibacterial activity against Gram-positive bacteria (*S. aureus* and *B. subtilis*) MIC values 112.1 ± 0.21 and 137.5 ± 0.43, respectively. According to the in vitro antifungal activity data (Table 3), most of the decahydroacridine-1,8-diones derivatives from the series (4a–l) exhibited poor inhibitory activities against *A. Niger and A. flavus*. All the synthesized compounds exhibited less antifungal activity against the fungal strain *A. flavus*.

Conclusion

In summary, we found ChCl:Urea as an effective and environmentally safe, recyclable catalyst, which successfully catalyzed to produce N-substituted decahydroacridine-1,8-diones from aromatic aldehydes, a dimedone and amines. High catalytic activity, high yields, a clean process, simple catalyst preparation, easy workup procedure and green conditions are advantages of these protocols. The synthesized compounds 10-(substituted phenyl)-9-(substitutedphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-diones (4a–l) evaluated for their in vitro antibacterial and antifungal activities and excellently

inhibited the four bacterial and three fungal strains. Compounds 9-(*N*,*N*-Dimethylphenyl)-3,3,6,6-tetramethyl-10-(3-pyridyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4f), 10-(4-Bromophenyl)-9-(3-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4i) and 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4k) showed excellent antimicrobial activity.

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Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary material 1 (DOCX 346 kb)

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