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ORIGINAL ARTICLE

# Triethylammonium acetate ionic liquid assisted one-pot synthesis of dihydropyrimidinones and evaluation of their antioxidant and antibacterial activities

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**KEYWORDS**

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Ionic liquid;
Triethylammonium acetate;
Antioxidant activity;
Reaction medium;
Antibacterial activity

**Abstract** A mild and efficient catalytic method has been developed to synthesize 3,4-dihydropyrimidinones in high yield by one-pot three component Biginelli condensation in the presence of triethylammonium acetate (TEAA) which acts as catalyst/reaction medium. Further, we have studied the antioxidant and antibacterial activities of these synthesized 3,4-dihydropyrimidinones. All the synthesized compounds reveal the significant antioxidant properties, these properties have been studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and cupric reducing antioxidant capacity (CUPRAC) assays. In addition, to this, these compounds also show the good antibacterial activity against four human pathogenic bacteria.


## 1. Introduction

In recent years, environmentally friendly chemical synthesis has been gaining substantial attention both in academia and industrial research (Anastas and Warner, 1998; Clark and Macquarie, 2002). In this context, surrogation of toxic and volatile organic solvents as reaction media with environmentally acceptable alternatives such as water, ionic liquids (ILs) is an area of tremendous importance in modern organic synthesis (Breslow, 1991; Grieco, 1998; Sheldon, 2001;

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Wasserscheid and Keim, 2000; Welton, 1999). ILs completely consist of weakly coordinating ions i.e., organic cation and inorganic/organic anion possessing desirable properties, and are liquids at or close to room temperature (Attri et al., 2010a,b, 2011a). An interesting aspect is that ILs do not influence the physicochemical properties of mixtures. ILs are emerging as more promising solvents in various fields such as organic synthesis, catalysis, materials science, electrochemistry and separation technology (Attri et al., 2010a,b, 2011a,b,c; Attri and Pal, 2010; Attri and Venkatesu, 2011; Karbalaei-Heidari et al., 2013; Parmar et al., 2013a,b; Verma et al., 2008). Notwithstanding the unique advantages of ILs as reaction media and catalysts, currently they have not been extensively implemented in industries (Attri and Pal, 2010; Grieco, 1998; Sheldon, 2001; Verma et al., 2008; Wasserscheid and Keim, 2000; Wang et al., 2006; Weng et al., 2006). The issues related to the less usage of ILs are most probably high cost, the difficulty in separation or recycling and the paucity of data with regard to their toxicity and biodegradability etc.

3,4-Dihydropyrimidinones, known as Biginelli compounds are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties, including anti-viral, anti-tumor, anti-bacterial and anti-inflammatory activities (Kappe, 2000a,b; Kappe and Falsone, 1998). Furthermore, these compounds have emerged as calcium channel blockers, anti-hypertensive agents and α-1a-adrenergic antagonists. Also, several alkaloids containing dihydropyrimidine nucleus isolated from marine sources have been found to possess interesting biological activities (Atwal et al., 1990, 1991). Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important challenge in current years. The Biginelli reaction, first reported in 1893, is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones by one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid (Biginelli, 1893). However, one serious drawback of this method is the low yield of the products, particularly in case of substituted aromatic and aliphatic aldehydes (Barleunga et al., 1989). This has led to the development of a multistep synthesis of Biginelli compounds that produce higher yields, albeit lacking the simplicity of the one pot synthesis. Thus, the Biginelli reaction involving one step cyclocondensation for the synthesis of dihydropyrimidinones has received renewed interest, and several improved protocols, mainly using Lewis acids as well as protic acids have been developed for accomplishing this reaction (Bigi et al., 1999; Ramalinga et al., 2001; Reddy et al., 2002). Nevertheless, use of toxic organic solvents, expensive catalysts and harsh reaction conditions in these protocols leave scope for further development of new environmentally clean synthesis. Recently, many researchers synthesized the dihydropyrimidinones using ILs (Chen and Peng, 2008; Garima et al., 2010; Peng and Deng, 2001; Sharma et al., 2012; Sajjadifar et al., 2013). Peng and Deng (2001) reported an efficient ionic liquid catalyzed Biginelli reaction using [bmim][$BF_4$] and [bmim][$PF_6$] as catalysts under solvent-free conditions. However, ILs especially imidazolium based systems containing $PF_6$ and $BF_4$ anions are toxic in nature as they liberate hazardous HF, and their high cost and disposability make their utility limited (Kamal et al., 2005). On the contrary, TEAA is inexpensive, thermally stable, non-toxic and recyclable; so has wide applications as catalysts/reaction medium (Attri and Pal, 2010; Parmar et al., 2013a,b; Verma et al., 2008; Wang et al., 2006). However, their potential as reaction media and promoter for organic reaction does not appear to be explored much. In order to extend application and show the effectiveness of the simple ammonium ILs, herein we have explained the preparation of 3,4-dihydropyrimidinones using TEAA under solvent free conditions. Further, we have also studied the antioxidant and antibacterial activities.

## 2. Experimental

### 2.1. General procedure

Quercetin, Gallic acid, Neocuprine, 1,1-di-phenyl-2-picrylhydrazyl (DPPH), copper (II) chloride tryptone soya agar were procured from Sigma Aldrich. Glacial acetic acid, hydrochloric acid, hexane, methanol, tris buffer and sodium acetate were procured from Merck India Ltd., and ready-made Nutrient agar and broth was purchased from Hi-Media Lab, New Delhi. Bacterial culture *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 3160), *Pseudomonas aeruginosa* (MTCC 2581) and *Klebsiella pneumoniae* (MTCC 7028) were procured from the microbial type culture collection and gene bank, Institute of Microbial Technology, Chandigarh. All the reagents used were of AR grade. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. $^1$H (400 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Jeol 400 NMR spectrometer in $CDCl_3$ (with TMS for $^1$H and chloroform-*d* for $^{13}$C as internal references) unless otherwise stated. Mass spectra were recorded on a Hybrid Quadrupole-TOF LC\MS\MS mass spectrometer (Q. Star XL). The reactions were monitored by Thin Layer chromatography (TLC) using aluminum sheets with silica gel 60 $F_{254}$ (Merck).

### 2.2. Synthesis of triethyl ammonium acetate (TEAA)

The synthesis of IL was carried out in a 250 mL round-bottomed flask, which was immersed in a water-bath and fitted with a reflux condenser. Acetic acid (1 mol) was dropped into the triethyl amine (1 mol) at 70 °C for 1 h. The reaction mixture was then heated at 80 °C with stirring for 2 h to ensure that the reaction had proceeded to completion. The reaction mixture was further dried at 80 °C until the weight of the residue remained constant. The sample was analyzed by Karl Fisher titration, which revealed very low levels of water (below 70 ppm). The yield of TEAA was found to be 98 %. $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 0.78 (t, 9H), 1.47 (s, 3H), 2.58 (m, 6H), 11.00 (s, 1H).

### 2.3. General procedure for the preparation of 3,4-dihydropyrimidinones

In a typical experimental procedure, a mixture of three components was added in a round bottom flask containing aldehyde (1 mmol), urea (1.6 mmol), β-dicarbonyl compound (1 mmol) and TEAA (2 mL) and stirred thoroughly for 45 min at 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, dichloromethane

(5 mL × 3) was added and the reaction mixture was washed with saturated sol. of $NaHCO_3$, water, and then dried over $Na_2SO_4$. The solvent was removed and the residue was purified by recrystallization or silica gel chromatography. The reaction products were analyzed with $^1H$ and $^{13}C$ NMR spectroscopy.

In addition to this the NMR data of the synthesized compounds are given in supporting information.

### 2.4. Antioxidant activity

#### 2.4.1. DPPH free radical scavenging activity

The working solutions of test extracts and standards were prepared in methanol. Querctin and Gallic acid (1–100 μg/ml) solution was used as standard and DPPH solution (0.1 mM, 1 mL) as blank. Different concentrations (12.5, 25, 50 and 100 μg/mL) of test compounds were pipetted to the test tubes and volume was adjusted to 3 mL with methanol. 1 mL of DPPH (0.1 mM) solution was mixed with 1 mL of sample and standard solution separately. The samples were vortexed, incubated in the dark at room temperature for 30 min. and the absorbance measured at 517 nm against blank samples in a spectrophotometer (Gulcin et al., 2004). The absorbance was recorded and radical scavenging activity was expressed as percentage inhibition of DPPH radical and was calculated by the following equation:

$$\%\ \text{Inhibition} = (\text{Absorbance of control} - \text{Absorbance of sample}/\text{Absorbance of control}) \times 100$$

#### 2.4.2. Cupric reducing antioxidant capacity (CUPRAC) assay

The CUPRAC reagent solution was prepared by mixing 1 mL of $1.0 \times 10^{-2}$ M copper (II) chloride, 1 mL of $7.5 \times 10^{-3}$ M neocuprine solution and 1 mL of ammonium acetate buffer at pH 7.0. Sample solution ($x$ mL) and distilled water ($1-x$) were added and well mixed to obtain a total volume of 4.0 mL. The absorbance of the Cu (I)-chelate was measured at 450 nm. The increased absorbance of the reaction mixture indicates the increased reduction capability (Talaz et al., 2009).

### 2.5. Antibacterial activity

#### 2.5.1. Disk diffusion assay

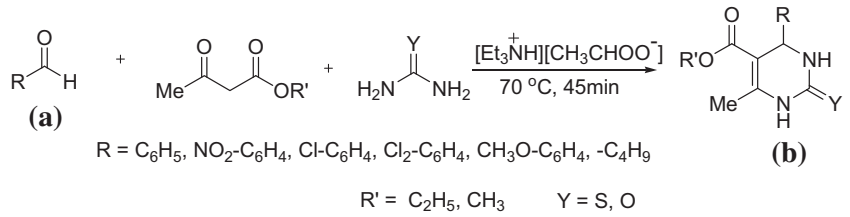
The antimicrobial potential of synthesized compounds was tested using a disk diffusion assay. Briefly the nutrient agar medium (25 mL) was poured into Petri dishes (90 cm in diameter) under aseptic conditions in a laminar flow hood. The plates were kept in the laminar flow chamber for solidification of the media. After solidification, 100 μL of fresh culture (log phase) was spread on the surface of the solidified medium with the help of a spreader. The plates were then kept in laminar flow for drying. Once dried, five plain sterile disks were placed in the plate and 5 μL of the test solution of different concentrations (*250.000–15.625 ppm) was loaded on each disk. Commercially procured ampicillin (10 μg/disk) was used in the control plate. The plates were then kept at 37 °C for 24 h in the incubator and then were taken out from the incubator and zone of inhibition (in mm) was recorded for all the tested compounds and commercial antibiotic. All experiments were in triplicate for each treatment against each bacterium.

#### 2.5.2. Determination of minimum inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC), defined as the lowest concentration of material that inhibits the growth of an organism (Tripathi et al., 2012), was determined based on the serial dilution method by varying the concentration of test compounds ranging from 200.000 to 15.625 μg/ml. The test compound of required concentration was added to all sterile Erlenmeyer flasks (100 mL), each containing 10 mL nutrient broth and was sonicated for 10 min. Subsequently, the flasks were inoculated with 1 mL of the freshly prepared bacterial suspension in order to maintain the initial bacterial concentration 103–104 CFU $mL^{-1}$, and then incubated in an orbital shaker at 200 rpm and 37 °C. Bacterial growth was monitored using a spectrophotometer as indicated by an increase in absorbance at 600 nm. The experiments also included a positive control (flask containing test compound and nutrient media, devoid of inoculum) and a negative control (flask containing inoculum and nutrient media, devoid of test compound). The negative controls indicated the microbial growth profile in the absence of test compounds. The absorbance values for positive controls were subtracted from the experimental values (Williams et al., 2006). All the experiments were carried out in triplicate.

## 3. Results and discussion

In our earlier research paper, we elucidated the role of TEAA in various applications (Attri et al., 2010a, 2011b,c; Attri and Pal, 2010; Attri and Venkatesu, 2011; Verma et al., 2008). In the present report, we investigated the additional applicability of simple ammonium acetate ILs as catalyst/reaction medium for the solvent free synthesis of 3,4-dihydropyrimidinones. In addition to this, we also studied the antioxidant and antibacterial activities for all derivatives of 3,4-dihydropyrimidinones. A variety of aldehydes, β-dicarbonyl compounds and urea/thiourea are made to react chemically under reaction conditions to yield the corresponding 3,4-dihydropyrimidinones as presented in Scheme 1. Further, to study the effect of TEAA as catalyst, we have used benzaldehyde, ethylacetoacetate and urea which leads to the formation of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2a). The standardized results are represented in Tables 1 and 2. Through a deep look in Tables 1 and 2, we observed that most judicious, economical, optimized temperature, time and amount of TEAA for reaction was found to be 70 °C, 45 min and 2 mL of TEAA. A variety of aromatic aldehydes containing both electron donating and withdrawing groups are converted to their corresponding 3,4-dihydropyrimidinones in excellent yields under mild reaction conditions, as demonstrated in Table 3 (Eynde et al., 1997; Folkers et al., 1932; Folkers and Johnson, 1933; Fu et al., 2002; Gupta et al., 1995; Kappe and Falsone, 1998; Lu and Ma, 2000; Ma et al., 2000; Ranu et al., 2000; Singh et al., 1999). It is well documented that both β-ketoesters (ethyl and methylacetoacetate) and 1,3-dicarbonyl compound (acetylacetone) react with greater ease under these reaction conditions. Furthermore, the use of thiourea in place of urea yielded corresponding




**Scheme 1** Synthesis of 3,4-dihydropyrimidinones from aldehyde (1 mmol), urea (1.6 mmol), β-dicarbonyl compound (1 mmol) catalyzed by TEAA (2 mL) for 45 min at 70 °C.

**Table 1** The Biginelli of compound 1b with ethylacetoacetate, urea, benzaldehyde and TEAA.

| Entry | Solvent | Temperature (°C) | Time for complete conversion | Yield (%) |
|---|---|---|---|---|
| 1 | No solvent | 70 | 24 h | No product |
| 2 | TEAA (1 mL) | 70 | 45 min | 30.0 |
| 3 | TEAA (1.5 mL) | 70 | 45 min | 70.0 |
| 4 | TEAA (2 mL) | 70 | 45 min | 90.0 |
| 5 | TEAA (2.5 mL) | 70 | 45 min | 90.3 |
| 6 | TEAA (2 mL) | 70 | 24 h | 91.0 |

**Table 2** The Biginelli of compound 1b with ethylacetoacetate, urea, benzaldehyde and TEAA (2 mL).

| Entry | Solvent | Temperature (°C) | Time for complete conversion | Yield (%) |
|---|---|---|---|---|
| 1 | No solvent | 25 | 24 h | No product |
| 2 | TEAA | 25 | 24 h | 15.0 |
| 3 | TEAA | 30 | 24 h | 40.0 |
| 4 | TEAA | 70 | 45 min | 90.0 |
| 5 | TEAA | 70 | 24 h | 90.2 |
| 6 | TEAA | 90 | 45 min | 91.2 |
| 7 | TEAA | 90 | 24 h | 92.3 |

3,4-dihydropyrimidinones-2(1*H*)-thiones in comparable amount, as shown in Table 3, entries (10–12). To evaluate the effect of TEAA, a mixture of benzaldehyde, urea and ethyl acetoacetate in molar ratio (1:1.6:1) was stirred at 70 °C for 24 h in the absence of TEAA. It was found that the reaction did not proceed, indicating TEAA to be an essential catalyst for this reaction. The efficiency of TEAA in comparison to other ILs is shown in Table 4 revealing more catalytic activity of TEAA as compared to the other existing ILs.

The probable mechanism for the Biginelli condensation is shown in Scheme 2. In this probable mechanism, the [$Et_3$NH][$CH_3COO^-$]-catalyzed Biginelli condensation *via* acyl imine intermediate is presented in Scheme 2. The reaction of the aldehydes and urea generates an acylimine intermediate, which further reacts with the activated 1,3-dicarbonyl compound producing an open-chain ureide undergoing subsequent cyclization and dehydration to give the corresponding product. The exact role played by TEAA in this reaction remains imprecise and needs to be further explored. So, this study reveals that TEAA has shown its extraordinary potential to be an alternative cheap, cost effective, eco-friendly reagent/catalyst for the industries (as also employed as a catalyst for the Biginelli reaction), in addition to excellent yield in the reaction with both urea and thiourea.

Further, we monitored the antioxidant and antibacterial activities of these compounds. The antioxidant activity is determined by using DPPH and CUPRAC assay. Due to its simplicity and accuracy, DPPH assay is the most widely used method to assess antioxidant potential of compounds. Therefore, the antiradical activities of test compounds have been determined using DPPH assay. During this assay, antioxidant is used to reduce the alcoholic solution of DPPH resulting in the formation of the non-radical form DPPH-H in the reaction. And, the dark colored DPPH radical solution in the presence of an antioxidant compound turned yellow-colored diphenylpicrylhydrazine in the presence of antioxidants and thus absorbance of the solution decreases. The results of DPPH assay are revealed in Fig. 1.

The DPPH assay is commonly used to assess free radical scavenging activity of antioxidants. Fig. 1 shows a noteworthy decline in the concentration of DPPH radical in terms of % inhibition due to the scavenging ability of test compounds. The change in absorbance was measured at 517 nm. The inhibition percentage of all tested samples showed a concentration-dependent pattern as evident from Fig. 1. The inhibition percentages of the test compounds range from 64.4% to 17.3%. The standard gallic acid and quercetin exhibited inhibition percentages of 92.4% and 82.3% at 100 ppm concentration whereas compound 6 showed highest inhibition percentage as 64.4% in comparison to all test compounds at 100 ppm. Similarly, gallic acid and quercetin also exhibited inhibition percentages of 62.4% and 55.3% at concentration

**Table 3** TEAA promoted synthesis of 3,4-dihydropyrimidinones as Scheme 1.

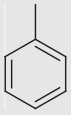
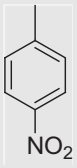
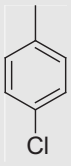
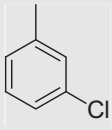
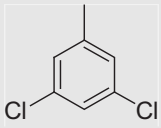
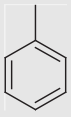
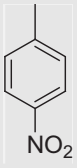
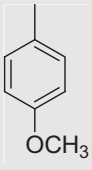
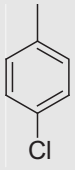
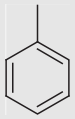
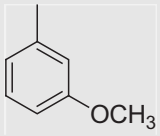
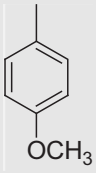
| Entry | R | R′ | Y | Yield%[a] | Mp (°C) | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported |
| 1 |  | $-C_2H_5$ | O | 90 | 202–203 | 201–203 |
| 2 |  | $-C_2H_5$ | O | 91 | 206.5–207 | 207–208.5 |
| 3 |  | $-C_2H_5$ | O | 89 | 214–215 | 213–215 |
| 4 |  | $-C_2H_5$ | O | 85 | 193–194 | 192–193 |
| 5 |  | $-C_2H_5$ | O | 85 | 223–224 | 222–223 |
| 6 |  | $-CH_3$ | O | 96 | 208–210 | 209–210 |
| 7 |  | $-CH_3$ | O | 89 | 235–238 | 236–237 |
| 8 |  | $-CH_3$ | O | 84 | 193–194 | 192–194 |

**Table 3** (*continued*)

| Entry | R | R′ | Y | Yield%[a] | Mp (°C) | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported |
| 9 |  | $-CH_3$ | O | 92 | 205–206 | 204–207 |
| 10 |  | $-C_2H_5$ | S | 88 | 206–207 | 207–209 |
| 11 |  | $-C_2H_5$ | S | 85 | 151–152 | 150–152 |
| 12 |  | $-C_2H_5$ | S | 86 | 152–153 | 151–153 |
| 13 | $-C_4H_9$ | $-C_2H_5$ | S | 85 | 155–157 | 157–158 |

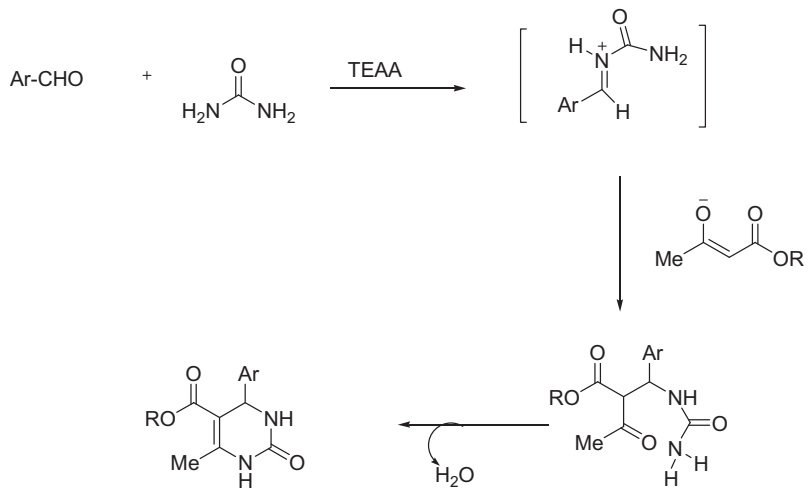
[a] Yields determined by GC analysis

**Table 4** Comparison of catalytic ability of ionic liquids for compound methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound No. 6b).

| Entry | Ionic liquids | Time (min) | Condition | Yield | References |
|---|---|---|---|---|---|
| 1 | [MSEI][Cl] | 30 | 80 °C, solvent free | 93 | Sajjadifar et al. (2013) |
| 2 | [BMIM][$FeCl_4$] | 120 | 90 °C, solvent free | 90 | Chen and Peng (2008) |
| 3 | [BMIM][$BF_4$] | 30 | 100 °C, solvent free | 99 | Peng and Deng (2001) |
| 4 | [HMIM][$HSO_4$] | 90 | 90 °C, solvent free | 96 | Garima et al. (2010) |
| 5 | $glyNO_3$ | 10 | MW, ethanol | 84 | Sharma et al. (2012) |
| 6 | TEAA | 45 | 70 °C, solvent free | 96 | |

12.5 ppm respectively, whereas all the test compounds show lower percentage inhibition at this concentration and the lowest inhibition percentage of 17.3% was observed for compound 5. Overall all the compounds showed moderate antioxidant activity in comparison to the standard compound and among all the compounds, compound 8 is found to be promising antioxidant.

CUPRAC assay has been extensively used to determine the total antioxidant capacity of antioxidant. The basic principal behind this assay is the redox reduction of Cu(II) to Cu(I) and which was monitored by change in absorbance at 450 nm. This redox reaction is a result of the CUPRAC reagent, Cu(II)-neocuproine ($Cu(Nc)_2^{2+}$), with an antioxidant (A-OH), to form the CUPRAC chromophore, Cu(I)-neocuproine ($Cu(Nc)^{2+}$) chelate (Apak et al., 2008). Also the results obtained from CUPRAC assay can easily be extended to possibly *in vivo* reactions of antioxidants. Further, the Cuprac assay was carried out at a pH (7.0) which is closer to the physiological pH. Thus, this assay is capable of monitoring the thiol-type antioxidants such as glutathione and non-protein thiols which are difficult to monitor by using other assays such as FRAP, (which do not detect –SH group antioxidants). The absorbance of the Cu (I)-chelate formed as a result of redox reaction with reducing antioxidant was measured at 450 nm. The color is possibly due to the formation of Cu (I)-Nc chelate. The increase in absorption indicates the higher antioxidant activity.




**Scheme 2** Mechanism for Biginelli condensation for the synthesis of 3,4-dihydro pyrimidinones using triethylammonium acetate.

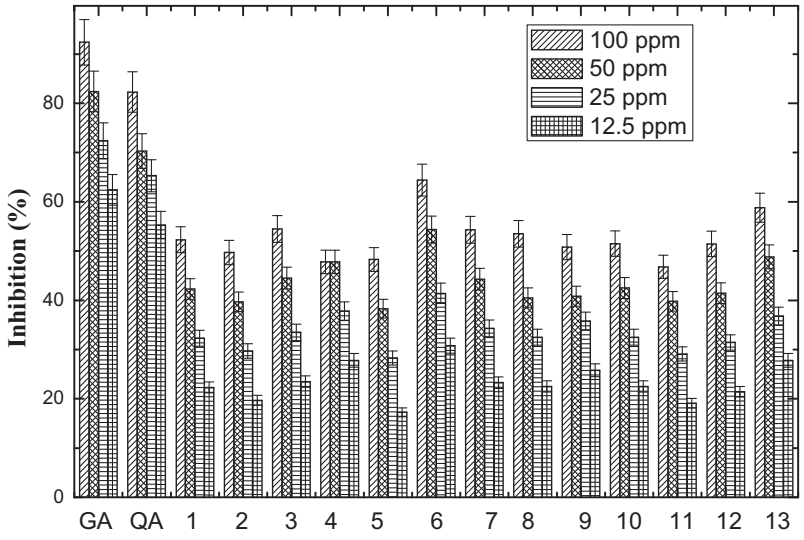



**Figure 1** DPPH radical scavenging activities of test compounds and standard antioxidant.

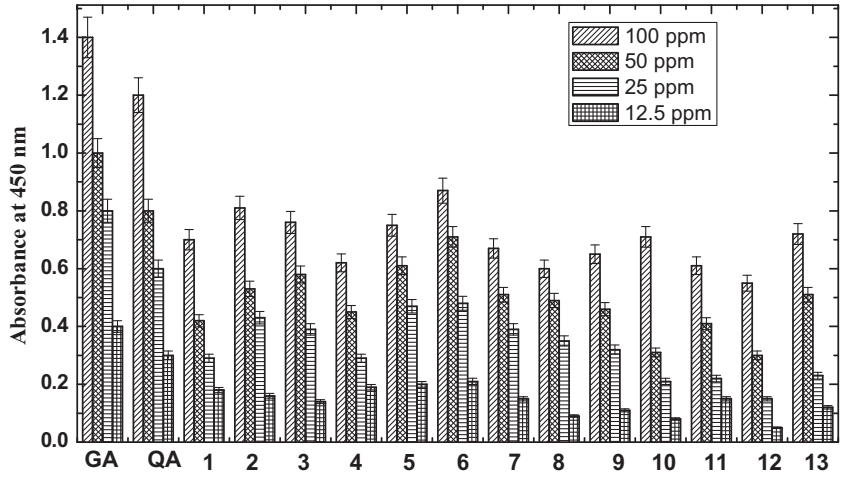



**Figure 2** Reducing power of standard antioxidants and test compounds by CUPRAC assay.

$$nCu(Nc)_2^{2+} + n - e \text{ reductant} \leftrightarrow nCu(Nc)_2^{2+} + n - e \text{ oxidized product} + nH^+$$

Fig. 2 shows reducing power of test compounds on copper ions using the CUPRAC assay. Similar to the DPPH assay, all the compounds show moderate activity in comparison to the standard compounds. In this assay, all test compounds again exhibited the ability of reducing copper ions from Cu(II) to Cu(I) in a concentration-dependent manner.

In this assay, standard gallic acid and quercetin depicted absorbance of 1.4 and 1.2 at 100 ppm concentration respectively, whereas in case of test compounds the highest absorbance (0.87) at same concentration was found for compound 6. This also showed the highest inhibition percentage in DPPH assay. At the lowest concentration of 12.5 ppm, standard gallic acid and quercetin showed absorbance of 0.4 and 0.3, whereas in case of test compounds the absorbance at same concentration ranged from 0.21 to 0.05, the lowest absorbance 0.05 was observed for compound 12. This trend indicates that at lower concentration the test compounds do not show antioxidant activity.

In order to explore the further potential of these compounds, we have investigated the antibacterial properties. The antibacterial potential of synthesized compounds was observed using the zone of inhibition method. Minimum inhibitory concentration (MIC) was determined with micro-dilution assay (Table 1S). The antibacterial activity of compounds was compared with the standard antibacterial drug ampicillin. All test compounds showed moderate to good inhibition activity. In case of *E. coli*, only compounds 3, 4, 5 and 6 showed good activities with MIC in the range of 31,250 to 15,625 ppm which is comparable to the standard. In *S. aureus*, compounds 4, 5 and 9 were active with MIC comparable to that of standard, whereas compounds 11, 12 and 13 were completely inactive with MIC values of 250 ppm and rest of the compounds were moderately active with MIC in the range of 62.5–125.0 ppm. Similarly in *P. aeruginosa*, compounds 1, 2, 3 and 5 showed good antibacterial activity with MIC value in the range of 15,625 to 31,250 ppm, while the compounds 4 and 11 showed moderate activities with MIC value of 62.5 ppm and rest of the compounds were inactive with MIC value of 250 ppm. For *K. pneumonia*, compounds 3, 4, 5, 7, 8, 9 and 12 showed moderate antibacterial activities with MIC 31.25–62.50 ppm and the rest of the compounds were found to be inactive. Overall compounds 3, 4 and 5 showed the good antibacterial activity against all bacteria which could possibly be due to the presence of halogen atom in them. And among these, compound 5 was found to be effective against bacteria with lower MIC in comparison to compound 3 and 4. This is suggested that the presence of two halogen atoms in compound 5 enhances the antibacterial activity. Thus, our results explicitly show that our synthesized 3,4-dihydropyrimidinones and their derivatives have potential for biomedical application.

## 4. Conclusions

In conclusion, TEAA is well documented as a catalyst/reaction medium for the synthesis of 3,4-dihydropyrimidinones under the solvent-free conditions. This procedure offers several advantages; (i) TEAA is a cost effective and environmentally benign reagent, (ii) green synthesis (avoiding hazardous and toxic organic solvents for work up), (iii) applicability to a wide range of substituted aldehydes and (iv) mild temperature reaction condition. Hence, simple reaction conditions with shorter reaction times, better yields, and easy work up make this a green, facile and superior method for the synthesis of 3,4-dihydropyrimidinones. The antioxidant potential of all the test compounds was determined using DPPH and CUPRAC assays. The results of these assays show that all the test compounds possess good to moderate antioxidant activity in comparison to the standard gallic acid and quercetin. Further, the antibacterial activity of these test compounds was monitored against four human pathogenic bacteria indicating moderate to good activity against all the bacteria.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2014.05.007.

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