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Synthesis of New dihydropyrimidinones catalysed by dicationic ionic liquid

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Abstract. A convenient multi step synthetic protocol for new dihydropyrimidinones bearing quinolynyl methoxy phenyl moiety has been developed from 2-chloro-3-formyl quinolines. The last step is one-pot Biginelli reaction of multicomponents, 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes, ethyl acetoacetate and urea mediated and catalysed by dicationic ionic liquid (3-methyl-1-[3-(methyl-1H-imidazolium-1-yl) propyl]-1H-imidazolium dibromide (C_3 [min]$_2$ 2 [Br^-])). Simple work-up procedures and moderate to good yields of the pyrimidinones and the intermediates are the merits of the route.

Keywords. Dihydropyrimidinones; quinoline; dicationic ionic liquid; ethereal linkage; Biginelli reaction.

1. Introduction

Dihydropyrimidinones (DHPMs) occupy special place in the realm of natural and synthetic organic chemistry, because of their therapeutic and pharmacological properties.[1] Dihydropyrimidinones scaffold emerged as an integral backbone of several drugs used as calcium channel blockers,[2] antihypertensive[3] and anticancer agents.[4] DHPMs also elicit antidiabetic activitiy.[5] Recently isolated marine alkaloids[6] concomitant with dihydropyrimidine-5-carboxylate core. Most noteworthy among the isolated marine alkaloids is batzelladine, a potent HIVgp-120- CD4 inhibitor.[7]

Quinolines are gaining importance in medicinal chemistry due to their elegant pharmacological properties like antibacterial,[8] antidepressant,[9] antimalerial[10] and hypoglycemic.[11] The ethereal linkage and 2,4-thiazoldinedione are essential in the molecular framework of various antidiabetic drugs[12] like, pioglitazone, troglitazone and rosiglitazone.

The most simple and straight forward procedure for the synthesis of DHPMs was reported by Biginelli[1c] in 1893. This involves one-pot condensation of ethylacetoacetate, aryl aldehydes and urea under strongly acidic conditions. One of the drawbacks of this method is low yields. Synthesis of DHPMs has attracted renewed attention and many improved procedures have been reported. Many of these reported methods employ catalysts such as H_2SO_4,[13] BF_3OEt_2,[14] polyphosphate esters,[15] montmorillonite KSF,[16] zeolites,[17] $FeCl_3.6H_2O$,[18] Yb $(OTf)_3$,[19] bismuth triflate,[20] cupric chloride,[21] zirconium chloride,[22] heteropoly acids,[23] ion exchange resins,[24] polymer-based solid acids,[25] chiral phosphoric acids,[26] $TaBr_5$,[27] propane phosphoric acid anhydride,[28] TMSCl,[29] $Cu(NO_3)_2H_2O$,[30] $InCl_3$,[31] $CeCl_3.7H_2O$,[32] chiral yetterbium[33] and ionic liquids.[34]

Recently Biginelli reaction has been catalysed by using t-BuOK.[35] The Biginelli one-pot condensation has also found to be accelerated by microwave,[36] ultrasonication[37] and solid fluorous phase.[38]

The above methods need expensive catalysts, strong acidic conditions, higher temperatures and prolonged reaction time. Most of the routes require costly reagents, toxic/hazardous organic solvents and tedious work-up. Hence chemists are putting more efforts to modify reaction conditions of the Biginelli protocol by employing some green tools.

Ionic liquids are emerging as a set of new green solvents to replace the volatile organic solvents.[39] The use of non-volatile organic solvents for chemical reactions is of ecological and economic concern. Ambient temperature of ionic liquids encompassing 1,3-dialkyl imidazolium cations are alternative to conventional organic solvents.[40] The important properties of these ionic liquids are low volatility, negligible vapour pressure, ease of handling, potential for recycling, and compatibility with various organic compounds and organometallic

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catalysts.[41] Ionic liquids have been found to be useful in various organic transformations.[42] The ionic liquids with wide range of combinations of cations and anions are well-explored as media and catalysts. The ionic components can be easily modified by specific functional groups to produce ionic liquids of useful applications.[43]

It has been reported that dicationic ionic liquids linked by alkyl chains show much higher thermal stability than that of most common ionic liquids.[44] Armstrong *et al* have synthesized dicationic ionic liquids containing dicationic imidazolium with halides possessing high thermal stability.[44] Literature survey reveals that there is scanty information on the use of such dicationic ionic liquids in the organic transformations.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[45] Multicomponent strategies offer significant advantages over conventional linear type syntheses.[45] The most useful MCRs have additional advantages of selectivity, synthetic convergancy and atom-economy.[45,46]

Considering the pharmacological importance of DHPMs, quinolines and ethereal linkage and the drawbacks of existing routes for the synthesis of DHPMs, here it was thought worthwhile to bring DHPMs, quinoline and ethereal linkage in one molecular framework using multicomponent one-pot safer route to obtain the new molecules with the hope that they may display intensified bioactivities.

In continuation of our earlier work, carried to develop convenient synthetic protocols for the synthesis of bioactive heterocycles[47] by employing green tools and considering the above urgent need to provide convenient rapid route for the DHPMs, here we report for the first time the Biginelli reaction by subjecting substituted quinoline methoxy benzaldehydes, ethyl acetoacetate and urea in dicationic ionic liquid (3-methyl-1-[3-(methyl-1H-imidazolium-1-yl) propyl]-1H-imidazolium dibromide (C_3 [min]$_2$ 2 [Br^-])), as medium and catalyst for obtaining new DHPMs.

2. Experimental

2.1 General

Chemicals and solvents required were from Merck, Spectorchem and SD fine meck. ^{1}H–NMR spectra were recorded at 400 MHz on Jeol and at 300 MHz on Bruker DRX-300. The mass spectra were recorded on Shimanzu GCMS and on JEOL – Accu TOF DART-MS- T 100 Lc. Elemental analyses were performed on Perkin Elmer elemental auto analyzer. The melting points were taken in open capillary and are uncorrected. Dicationic ionic liquid used here was prepared by reported methods.[44,51]

*2.2 Experimental procedure for the synthesis of Dihydropyrimidinone **5a***

A mixture of benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol) and urea (12 mmol) were heated in dicationic ionic liquid, C_3 [min] 2Br^- (10 mmol) at 80°C. The progress of the reaction was monitored by thin layer chromatography. After 2 h of the reaction, the reaction mass was allowed to cool to rt. and it was poured on ice cold water. Thus obtained solid mass was filtered, washed with water and dried. Similarly the other compounds, (**5 b–f**) of the series were synthesized.

*2.3 Experimental procedure for the synthesis of (2-chloroquinolin-3-yl) methanol **8a***

To the solution of 2-chloro-3-formyl quinoline (10 g, 52 mmol) in methanol (100 mL), $NaBH_4$ (1.98 g, 52 mmol) was added portion-wise and then the mass was stirred at rt. The progress of the reaction was monitored by thin layer chromatography. After 30 min of stirring, solvent was removed from the reaction mass under vacuum and the residue was added in ice cold water. The obtained solid was filtered and washed with water and dried. Similarly the other compounds, (**8 b–h**) were synthesized by following the above procedure.

*2.3a (2-Chloroquinolin-3-yl) methanol **8a:*** White solid; m.p. 148–149°C; yield: 87%.; ^{1}H–NMR (300 MHz, DMSO$-d_6$): δ = 8.29 (s, 1H, quinoline), 8.04 (d, 1H, J = 8.4 Hz, Ar–H quinoline), 7.84 (d, 1H, J = 6.0 Hz, quinoline Ar–H), 7.76 (t, 1H, J = 6.0 Hz, quinoline Ar–H), 7.55 (t, 1H, J = 9.0 Hz, quinoline Ar–H), 3.49 (s, 1H, OH, exchangeable with D_2O), 2.08 (s, 2H, CH_2)ppm; DART-MS: (ESI^+, m/z) = 194 (M^+), 196 (M^++2).

*2.3b (2-Chloro-8-methylquinolin-3-yl) methanol **8b:*** White solid; m.p. 137–138°C; yield: 84%; ^{1}H–NMR (300 MHz, DMSO$-d_6$): δ = 8.22 (s, 1H, quinoline), 7.66 (d, 2H, J = 6.0 Hz, quinoline Ar–H), 7.55 (t, 1H, J = 6.0 Hz, quinoline Ar–H), 7.45 (t, 1H, J = 6.0 Hz,

quinoline Ar–H), 4.91 (s, 2H, CH_2), 3.49 (s, 1H, OH, exchangeable with D_2O), 2.76 (s, 3H, CH_3); DART-MS: (ESI^+, m/z) = 208 (M^+), 210 (M^++2).

2.3c (2-Chloro-7-methylquinolin-3-yl) methanol ***8c:*** White solid; m.p. 144–145°C; yield: 87%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 8.15 (s, 1H, quinoline Ar–H), 7.8 (d, 1H, J = 8.3 Hz, quinoline Ar–H), 7.58 (s, 1H, quinoline Ar–H), 7.41(d, 1H, J = 8.1 Hz, quinoline Ar–H), 4.92 (s, 2H, CH_2), 3.48 (s, 1H, OH, exchangeable with D_2O), 2.76 (s, 3H, CH_3); DART-MS: (ESI^+, m/z) = 208 (M^+), 210 (M^++2).

2.3d (2-Chloro-6-methylquinolin-3-yl) methanol ***8d:*** White solid; m.p. 124–125°C; yield: 86%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 8.10 (s, 1H, quinoline Ar–H), 7.60 (d, 1H, J = 7.50 Hz, quinoline Ar–H), 7.58 (s, 1H, quinoline Ar–H), 7.40 (d, 1H, J = 7.30 Hz, quinoline Ar–H), 4.93(s, 2H, CH_2), 3.51(s, 1H, OH, exchangeable with D_2O), 2.77 (s, 3H, CH_3); DART-MS: (ESI^+, m/z) = 208 (M^+), 210 (M^++2).

2.3e (2-Chloro-7-methoxyquinolin-3-yl) methanol ***8e:*** White solid; m.p. 197–198°C; yield: 85%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 8.01 (s, 1H, quinoline Ar–H), 7.26 (d, 1H, J = 8.50 Hz, quinoline Ar–H), 7.19 (d, 1H, J = 7.0 Hz, quinoline Ar–H), 7.02 (s, 1H, quinoline Ar–H), 5.03 (s, 2H, CH_2), 3.46 (s, 1H, OH, exchangeable with D_2O); GCMS: (ESI^+, m/z) = 224 (M^+), 226 (M^++2).

2.3f (2-Chloro-6-methoxyquinolin-3-yl) methanol ***8f:*** White solid; m.p. 145–146°C; yield: 87%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 7.80 (s, 1H, quinoline Ar–H), 7.25 (d, 1H, J = 8.50 Hz, quinoline Ar–H), 7.20 (d, 1H, J = 7.0 Hz, quinoline Ar–H), 7.03 (s, 1H, quinoline Ar–H), 4.80 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.47 (s, 1H, OH, exchangeable with D_2O) ppm; GCMS: (ESI^+, m/z) = 224 (M^+), 226 (M^++2).

2.3g (2-Chloro-6-ethoxyquinolin-3-yl) methanol) ***8g:*** White solid; m.p. 121–123°C; yield: 86%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 7.74 (s, 1H, quinoline Ar–H), 7.42 (s, 1H, quinoline Ar–H), 7.26 (d, 1H, J = 7.50 Hz, quinoline Ar–H), 7.20 (d, 1H, J = 7.20 Hz, quinoline Ar–H), 4.85 (s, 2H, CH_2), 4.11 (m, 2H, $-OCH_2CH_3$), 3.70 (s, 1H, OH, exchangeable with D_2O), 1.76 (t, 3H, J = 7.10 Hz, $-OCH_2CH_3$)ppm; GCMS: (ESI^+, m/z) = 238 (M^+), 240 (M^++2).

2.3h (2,7-Dichloroquinolin-3-yl)methanol ***8h:*** White solid; m.p. 105–106°C; yield: 88%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 8.5 (s, 1H, quinoline Ar–H), 8.3 (s, 1H, quinoline Ar–H), 7.80 (d, 1H, J = 8.10 Hz), 7.6 (d, 1H, J = 7.60 Hz, quinoline Ar–H), 5.10 (s, 2H, CH_2), 3.80 (s, 1H, OH, exchangeable with D_2O) ppm; GCMS: (ESI^+, m/z) = 228 (M^+), 230 (M^++2), 232 (M^++4).

2.4 Experimental procedure for the synthesis of (2-chloroquinolin-3-yl) methyl 4-methylbenzenesulfonate ***9a***

(2-Chloroquinolin-3-yl) methanol (7.0 g, 36 mmol) and triethyl amine (5.4 g, 51 mmol) were dissolved in DCM (100 mL) and the solution was stirred for 30 min. To this stirred solution *p*-toluene sulphonyl chloride (7.6 gm, 39 mmol) was added in portions at 0°C. Then the reaction mass was further stirred for 5–6 h at rt. The progress of reaction was monitored by thin layer chromatography. After the 6 h of the reaction, the solvent was removed from the mass under vacuum. The residue was then poured in ice cold water. The solid was obtained filtered, washed water and dried. It was used for the further reaction without any purification. Similarly the other compounds, (**9 b–h**) of the series were synthesized by following the above same procedure.

2.4a (2-Chloroquinolin-3-yl) methyl 4-methyl benzenesulfonates ***9a:*** White solid; m.p. 98–99°C; Yield: 82%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 8.29 (s, 1H, quinoline), 8.03 (d, 1 H, J = 6.0 Hz, quinoline Ar–H), 8.03 (d, 1H, J = 9.0 Hz, quinoline Ar–H),7.90 (d, 2H, J = 7.50 Hz, Ar–H), 7.85 (d, 1 H, J = 6.0 Hz, quinoline Ar–H), 7.77 (t, 1 H, J = 6.0 Hz, quinoline Ar–H), 7.75 (d, 2 H, J = 7.50 Hz, Ar–H), 7.58 (t, 1 H, J = 9.0 Hz, quinoline Ar–H), 4.85 (s, 2H, CH_2), 1.56 (s, 3H, CH_3) ppm; DART-MS: (ESI^+, m/z) = 348 (M^+), 350 (M^++2).

2.4b (2-Chloro-8-methylquinolin-3-yl) methyl 4-methyl benzenesulfonate ***9b:*** White solid; m.p. 78–79°C; yield: 76%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 8.23 (s, 1H, quinoline Ar–H), 7.80 (d, 2H, J = 7.1 Hz, Ar–H), 7.67 (d, 1H, J = 9.0 Hz, quinoline Ar–H), 7.60 (d, 2H, J = 7.60 Hz, Ar–H), 7.59 (d, 1H, J = 6.0 Hz, quinoline Ar–H), 7.48 (t, 1H, J = 12.0 Hz, quinoline Ar–H), 4.92 (s, 2H, CH_2), 2.77 (s, 3H, CH_3) ppm; DART-MS: (ESI^+, m/z) = 362 (M^+), 364 (M^++2).

2.4c (2-Chloro-8-methylquinolin-3-yl) methyl 4-methyl benzenesulfonate ***9c:*** White solid; m.p. 121–122°C; yield: 75%; ^{1}H–NMR (300 MHz, DMSO−d_6): $\delta = 8.15$ (s, 1H, quinoline Ar–H), 7.81 (d, 2H, $J = 7.72$ Hz, Ar–H), 7.70 (d, 1H, $J = 8.1$ Hz, quinoline Ar–H), 7.51 (d, 1H, $J = 7.90$ Hz, quinoline Ar–H), 7.67 (s, 1H, quinoline Ar–H), 7.51 (d, 1H, $J = 7.90$ Hz, quinoline Ar–H), 4.92 (s, 2H, CH_2), 2.76 (s, 3H, CH_3), 2.61 (s, 3H, CH_3) ppm; DART-MS: (ESI$^+$, m/z) = 362 (M^+), 364 (M^++2).

2.4d (2-Chloro-6-methylquinolin-3-yl) methyl 4-methylbenzenesulfonate ***9d:*** White solid; m.p. 101–102°C; yield: 87%; ^{1}H–NMR (300 MHz, DMSO−d_6): $\delta = 8.11$ (s, 1H, quinoline Ar–H), 7.80 (d, 2 H, $J = 7.70$ Hz, Ar–H), 7.69 (d, 1H, $J = 7.90$ Hz, quinoline Ar–H), 7.55 (s, 1H, quinoline Ar–H), 7.51 (d, 2H, $J = 7.58$ Hz, Ar–H), 7.41 (d, 1H, $J = 7.80$ Hz, quinoline Ar–H), 4.94 (s, 2H, CH_2), 2.77 (s, 3H, CH_3), 2.60 (s, 3H, CH_3) ppm; DART-MS: (ESI$^+$, m/z) = 362 (M^+), 364 (M^++2).

2.4e (2-Chloro-7-methoxyquinolin-3-yl) methyl 4-methyl benzenesulfonate ***9e:*** White solid; m.p. 124–125°C; yield: 83%; ^{1}H–NMR (400 MHz, DMSO−d_6): $\delta = 7.80$ (s, 1H, quinoline Ar–H), 7.73 (d, 2H, $J = 7.65$ Hz, Ar–H), 7.50 (d, 2H, $J = 7.65$ Hz, Ar–H), 7.24 (d, 1H, $J = 8.40$ Hz, quinoline Ar–H), 7.19 (d, 1H, $J = 7.60$ Hz, quinoline Ar–H), 7.03 (s, 1H, quinoline Ar–H), 4.60 (s, 2H, $-CH_2$-), 3.76 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3) ppm; GCMS: (MS^+, m/z) = 378 (M^+), 380 (M^++2).

2.4f (2-Chloro-6-methoxyquinolin-3-yl)methyl 4-methyl benzenesulfonate ***9f:*** White solid; m.p. 131–132°C; yield: 84%; ^{1}H–NMR (400 MHz, DMSO−d_6): $\delta = 7.81$ (s, 1H, quinoline Ar–H), 7.7 (d, 2H, $J = 7.65$ Hz, Ar–H), 7.40 (d, 2H, $J = 7.65$ Hz, Ar–H), 7.24 (d, 1H, $J = 8.5$ Hz, quinoline Ar–H), 7.21 (d, 1H, $J = 7.0$ Hz, quinoline Ar–H), 7.01 (s, 1H, quinoline Ar–H), 4.70 (s, 2H, $-CH_2$-), 3.80 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3) ppm; GCMS = (ESI$^+$, m/z): 378 (M^+), 380 (M^++2).

2.4g (2-Chloro-6-ethoxyquinolin-3-yl)methyl-4-methyl benzenesulfonate ***9g:*** White solid; m.p. 110–111°C; yield: 83%; ^{1}H–NMR (400 MHz, DMSO−d_6): $\delta = 7.77$ (s, 1H, quinoline Ar–H), 7.60 (d, 2H, $J = 7.68$ Hz, Ar–H), 7.41 (s, 1H, quinoline Ar–H), 7.30 (d, 2H, $J = 7.40$ Hz, Ar–H), 7.25 (d, 1H, $J = 7.40$ Hz, quinoline Ar–H), 7.19 (d, 1H, $J = 7.60$ Hz, quinoline Ar–H), 4.80 (s, 2H, $-CH_2$-), 4.10 (q, 2H, $J = 7.60$ Hz, CH_2CH_3), 2.53 (s, 3H, CH_3), 1.37 (t, 3H, $J = 7.11$ Hz, CH_2CH_3) ppm; GCMS: (ESI$^+$, m/z) = 392 (M^+), 394 (M^++2).

2.4h (2,7-dichloroquinolin-3-yl)methyl 4-methyl benzene sulfonate ***9h:*** White solid; m.p. 97–98°C; yield: 80%; ^{1}H–NMR (400 MHz, DMSO−d_6): $\delta = 8.40$ (s, 1 H, quinoline Ar–H), 8.1 (s, 1H, quinoline Ar–H), 7.90 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.70 (d, 1H, $J = 8.10$ Hz, quinoline Ar–H), 7.50 (d, 1H, $J = 7.90$ Hz, quinoline Ar–H), 7.20 (d, 2H, $J = 8.0$ Hz, quinoline Ar–H), 4.91 (s, 2H, CH_2), 2.61 (s, 3H, CH_3) ppm; GCMS: (ESI$^+$, m/z) = 382 (M^+), 384 (M^++2), 386 (M^++4).

2.5 Experimental procedure for the synthesis of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehyde ***10a***

A mixture of 4-hydroxybenzaldehyde (1.82 g, 15 mmol) and potassium carbonate (2.71 g, 20 mmol) was stirred in DMF (60 mL) for 20 min. at 80 °C. To this, (2-chloroquinolin-3-yl) methyl 4-methylbenzenesulfonate (**9a**) (5 g, 14 mmol) was added and further the mass stirred for 3 h at 80°C. The progress of the reaction was observed by thin layer chromatography. After 3 h of the reaction, the reaction mass was allowed to cool at rt. and poured on crushed ice. The obtained solid crude was filtered, washed with water and crystallized by using ethanol. Similarly the other compounds, (**10 b–h**) of the series were synthesized by following the same synthetic procedure.

2.5a 4-((2-Chloroquinolin-3-yl) methoxy) benzaldehydes ***10a:*** White solid; m.p. 118–119°C; yield: 83%; ^{1}H–NMR (300 MHz, DMSO−d_6): $\delta = 9.90$ (s, 1H, CHO), 8.64 (s, 1H, quinoline Ar–H), 8.08 (d, 1H, $J = 6.0$ Hz, quinoline Ar–H), 7.99 (d, 2H, $J = 9.0$ Hz, Ar–H), 7.92 (d, 1H, $J = 9.0$ Hz, quinoline Ar–H), 7.85 (t, 1H, $J = 6.0$ Hz, quinoline Ar–H), 7.69 (t, 1H, $J = 9.0$ Hz, quinoline Ar–H), 7.32 (t, 1H, $J = 9.0$ Hz, quinoline Ar–H), 5.43 (s, 2H, CH_2) ppm; DART-MS: (ESI$^+$, m/z) = 298 (M^+), 300 (M^++2).

2.5b 4-((2-Chloro-8-methylquinolin-3-yl) methoxy) benzaldehyde ***10b:*** White solid; m.p. 135–136°C; yield: 87%; ^{1}H–NMR (300 MHz, DMSO−d_6): $\delta = 9.89$ (s, 1H, CHO), 8.59 (s, 1H, quinoline Ar–H), 7.90 (t, 2H, $J = 9.0$ Hz, quinoline Ar–H), 7.69 (d, 2H, $J = 6.0$ Hz, Ar–H), 7.56 (t, 1H, $J = 6.0$ Hz, quinoline Ar–H), 7.32 (d, 2H, $J = 9.0$ Hz, Ar–H), 5.42 (s, 2H, CH_2),

2.67 (s, 3H, CH_3) ppm; DART-MS: (ESI^+, m/z) = 312 (M^+), 314 (M^++2).

2.5c 4-((2-Chloro-7-methylquinolin-3-yl) methoxy) benzaldehyde ***10c:*** White solid; m.p. 138–139°C; yield: 82%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 9.83 (s, 1H, CHO), 8.61 (s, 1H, quinoline Ar–H), 7.92 (d, 2H, J = 8.6 Hz, Ar–H), 7.63 (d, 1H, J = 8.0 Hz, quinoline Ar–H), 7.51 (d, 1H, J = 7.9 Hz, quinoline Ar–H), 7.11 (d, 2H, J = 6.8 Hz, Ar–H), 5.13 (s, 2H, CH_2), 2.77 (s, 3H, CH_3) ppm; DART-MS: (ESI^+, m/z) = 312 (M^+), 314(M^++2).

2.5d 4-((2-Chloro-6-methylquinolin-3-yl) methoxy) benzaldehyde ***10d:*** White solid; m.p. 140–141°C; yield: 87%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 9.85 (s, 1H, CHO), 8.30 (s, 1H, quinoline Ar–H), 7.90 (d, 2H, J = 8.60 Hz, Ar–H), 7.60 (d, 1H, J = 8.10 Hz, quinoline Ar–H), 7.60 (s, 1H, quinoline Ar–H), 7.48 (d, 1H, J = 7.80 Hz, quinoline Ar–H), 7.20 (d, 2H, J = 7.20 Hz, Ar–H), 5.10 (s, 2H, CH_2), 2.76 (s, 3H, CH_3) ppm; DART-MS :(ESI^+, m/z) = 312 (M^+), 314(M^++2).

2.5e 4-((2-Chloro-7-methoxyquinolin-3-yl) methoxy) benzaldehyde ***10e:*** White solid; m.p. 128–129°C; yield: 86%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 9.89 (s, 1H, CHO), 7.81 (s, 1H, quinoline Ar–H), 7.77 (d, 2H, J = 8.20 Hz, Ar–H), 7.28 (d, 1H, J = 8.60 Hz, quinoline A–H), 7.23 (d, 1H, J = 8.20 Hz, quinoline Ar–H), 7.12 (d, 2H, J = 6.9 Hz, Ar–H), 5.17 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3) ppm; GCMS: (ESI^+, m/z) = 328 (M^+), 330 (M^++2).

2.5f 4-((2-Chloro-6-methoxyquinolin-3-yl)methoxy) benzaldehyde ***10f:*** White solid; m.p. 126–127°C; yield: 83%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 9.88 (s, 1H, CHO), 7.80 (s, 1H, quinoline Ar–H), 7.75 (d, 2H, J = 8.20 Hz, Ar–H), 7.26 (d, 1H, J = 8.50 Hz, quinoline Ar–H), 7.22 (d, 1H, J = 7.10 Hz, quinoline Ar–H), 7.10 (d, 2H, J = 6.80 Hz, Ar–H), 7.02 (s, 1H, quinoline Ar–H), 5.14 (s, 2H, $-CH_2O$), 3.70 (s, 3H, OCH_3) ppm; GCMS: (ESI^+, m/z) 328 (M^+), 330 (M^++2).

2.5g 4-((2-Chloro-6-ethoxyquinolin-3yl)methoxy) benzaldehyde ***10g:*** White solid; m.p. 120–121°C; yield: 84%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 9.83 (s, 1H, CHO), 7.80 (s, 1H, quinoline Ar–H), 7.70 (d, 2H, J = 7.80 Hz, Ar–H), 7.42 (s, 1H, quinoline Ar–H), 7.28 (d, 1H, J = 7.50 Hz, quinoline Ar–H), 7.20 (d, 1H, J = 7.60 Hz, quinoline Ar–H), 7.15 (d, 2H, J = 7.10 Hz, Ar–H), 5.10 (s, 2H, $-CH_2O$), 4.10(m, 2H, OCH_2CH_3), 1.37 (t, 3H, J = 7.10 Hz, OCH_2CH_3) ppm; GCMS: (ESI^+, m/z) = 342 (M^+), 344 (M^++2).

2.5h 4-((2,7-Dichloroquinolin-3-yl)methoxy) benzaldehyde ***10h:*** White solid; m.p. 132–133°C; yield: 81%; ^{1}H–NMR (400 MHz, DMSO−d_6): δ = 9.93 (s, 1H, CHO), 8.50 (s, 1H, quinoline Ar–H), 7.93 (d, 2 H, J = 8.40 Hz, Ar–H), 7.80 (d, 1H, J = 8.10 Hz, quinoline Ar–H), 7.50 (d, 1H, J = 7.60 Hz, quinoline Ar–H), 7.30 (d, 2H, J = 8.10 Hz, Ar–H), 5.05 (s, 2H, CH_2) ppm; GCMS :(ESI^+, m/z) = 332 (M^+), 334 (M^++2), 336 (M^++4).

2.6 Experimental procedure for the synthesis of ethyl 4-(4-((2-chloroquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11a***

Multicomponent 4-((2-chloroquinolin-3-yl) methoxy) benzaldehyde (1 g, 3.4 mmol), ethyl acetoacetate (0.4 g, 3.7 mmol) and urea (0.27 g, 4.40 mmol) was heated in dicationic ionic liquid C_3[min] $2Br^-$ (1.26 g, 3.4 mmol) at 80°C. The progress of reaction was monitored by thin layer chromatography. After heating the reaction mass for 2 h, it was allowed to cool to rt. and poured on ice cold water. Thus solid mass was obtained filtered, washed with water and dried. Similarly the other compounds (**11 b–h**) of the series were synthesized.

2.6a Ethyl 4-(4-((2-chloroquinolin-3-yl) methoxy) phenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylates ***11a:*** White solid; m.p. 230–231°C; yield: 83%; ^{1}H–NMR (300 MHz, DMSO−d_6): δ = 11.95 (s, 1 H, NH, exchangeable with D_2O), 9.13 (s, 1H, NH, exchangeable with D_2O), 7.97 (s, 1H, quinoline Ar–H), 7.69 (t, 1H, J = 7.8 Hz, Ar–H quinoline), 7.49 (t, 1H, J = 6.0 Hz, quinoline Ar–H), 7.19 (d, 2H, J = 6.0 Hz, Ar–H), 7.15 (d, 1H, J = 6.0 Hz, quinoline Ar–H), 5.10 (s, 1H, −CH-), 5.02 (s, 2H, CH_2), 3.97 (q, 2H, J = 6 Hz, −CO CH_2 CH_3), 2.67 (s, 3H, CH_3), 1.09 (t, 3H, J = 9.0 Hz, −CO CH_2 CH_3) ppm; Anal. Cald for $C_{24}H_{22}ClN_3O_4$: C 63.79, H 4.91, N 9.30, Found: C 62.18, H 4.77, N 9.18. GCMS: (ESI^+, m/z) = 452 (M^+), 454 (M^++2).

2.6b Ethyl 4-(4-((2-chloro-8-methylquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11b:*** White solid; m.p. 237–238°C; yield: 82%; ^{1}H–NMR (400 MHz, DMSO$-d_6$): $\delta = 11.21$ (s, 1H, -NH exchangeable with D2O), 9.14 (s, 1H, exchangeable with D_2O), 8.62 (s, 1H, quinoline Ar–H), 7.90 (t, 1H, $J = 9.0$ Hz, quinoline Ar–H), 7.70 (d, 1H, $J = 8.10$ Hz, quinoline Ar–H), 7.28 (d, 1H, $J = 9.0$ Hz, quinoline Ar–H), 6.99 (d, 2H, J = 7.30 Hz, Ar–H), 5.13 (s, 2H, $-CH_2O$), 5.0 (s, 1H, −CH-), 3.96 (q, 2H, $J = 7.10$ Hz, $-COCH_2CH_3$), 2.78 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.06 (t, 3H, $J = 7.10$ Hz, $-COCH_2CH_3$) ppm; Anal. Cald for $C_{25}H_{24}ClN_3O_4$: C 64.44, H 5.19, N 9.02, Found: C 63.98, H 5.13, N 8.96. GCMS: (ESI$^+$, m/z) = 466 (M^+), 468 (M^++2).

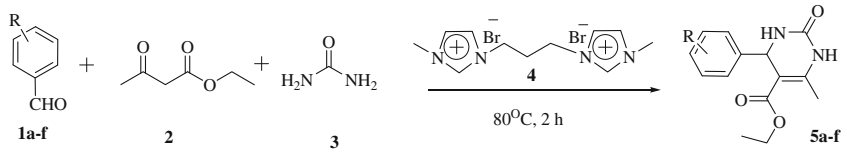
2.6c Ethyl 4-(4-((2-chloro-7-methylquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11c:*** White solid; m.p. 228–229°C; yield: 85%; ^{1}H–NMR (400 MHz, DMSO$-d_6$): $\delta = 11.12$ (s, 1H, -NH exchangeable with D_2O), 9.13 (s, 1H exchangeable with D_2O), 8.06 (s, 1H, quinoline Ar–H), 7.62 (d, 1H, $J = 8.0$ Hz, quinoline Ar–H), 7.52 (d, 1H, $J = 7.90$ Hz, quinoline Ar–H), 7.00 (d, 2H, $J = 8.40$ Hz, Ar–H), 5.05 (s, 1H, −CH-), 5.14 (s, 2H, CH_2O), 3.99 (q, 2H, $J = 7.1$ Hz, $-COCH_2CH_3$), 2.77 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.08 (t, 3H, $J = 7.20$ Hz, $-COCH_2CH_3$) ppm; Anal. Cald for $C_{25}H_{24}ClN_3O_4$,: C 64.44, H 5.19, N 9.02, Found: C 63.98, H 5.13, N 8.96. GCMS: (ESI$^+$, m/z) = 466 (M^+), 468 (M^++2).

2.6d Ethyl 4-(4-((2-chloro-6-methylquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11d:*** White solid; m.p. 211–212°C; yield: 84%; ^{1}H–NMR (400 MHz, DMSO$-d_6$): $\delta = 11.13$ (s, 1H, -NH exchangeable with D_2O), 9.14 (s, 1H exchangeable with D_2O), 7.67 (s, 1H, quinoline Ar–H), 7.54 (d, 1H, $J = 7.70$ Hz, quinoline Ar–H), 7.34 (d, 1H, $J = 7.0$ Hz, quinoline Ar–H), 7.17 (d, 2H, $J = 8.40$ Hz, Ar–H), 7.00 (d, 1H, $J = 8.40$ Hz, Ar–H), 5.10 (s, 2H, CH_2), 5.0 (s, 1H, −CH-), 3.98 (q, 2H, $J = 7.10$ Hz, $-COCH_2CH_3$), 2.44 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.09 (t, 3H, $J = 7.10$ Hz, $-COCH_2CH_3$) ppm; Anal. Cald. for $C_{25}H_{24}ClN_3O_4$, Calculated: C 64.44, H 5.19, N 9.02, Found: C 63.98, H 5.13, N 8.96. GCMS: (ESI$^+$, m/z) = 466 (M^+), 468 (M^++1).

2.6e Ethyl 4-(4-((2-chloro-7-methoxyquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11e:*** White solid; m.p. 225–226°C; yield: 87 %; ^{1}H–NMR (400 MHz, DMSO$-d_6$): $\delta = 11.80$ (s, 1H, -NH exchangeable with D_2O), 8.93 (s, 1H exchangeable with D_2O), 7.81 (s, 1H, quinoline Ar–H), 7.28 (d, 1H, $J = 8.60$ Hz, quinoline Ar–H), 7.20 (d, 1H, J = 7.20 Hz, quinoline Ar–H), 7.01 (s, 1H, quinoline Ar–H), 6.91 (d, 2H, $J = 8.90$ Hz, Ar–H), 5.18 (s, 1H, −CH-), 5.01 (s, 2H, CH_2O), 4.06 (m, 2H, −CO CH_2 CH_3), 3.79 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3), 1.14 (t, 3H, $J = 7.52$ Hz, −CO CH_2CH_3) ppm; Anal. Cald. for $C_{25}H_{24}ClN_3O_5$, : C 62.31, H 5.02, N 8.72, Found: C 62.27, H 4.98, N 8.68. GCMS: (ESI$^+$, m/z) = 482 (M^+), 484 (M^++2).

2.6f Ethyl 4-(4-((2-chloro-6-methoxyquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11f:*** White solid; m.p. 215–216°C; yield: 85%; ^{1}H–NMR (400 MHz, DMSO$-d_6$): $\delta = 11.82$ (s, 1H, -NH exchangeable with D_2O), 8.92 (s, 1H exchangeable with D_2O), 7.80 (s, 1H, quinoline Ar–H), 7.26 (d, 1H, $J = 8.50$ Hz, quinoline Ar–H), 7.21 (d, 1H, $J = 7.10$ Hz, quinoline Ar–H), 7.02 (s, 1H, quinoline Ar–H), 6.91 (d, 2H, $J = 8.50$ Hz, Ar–H), 6.80 (d, 2H, $J = 8.50$ Hz, Ar–H), 5.18 (s, 2H, $-CH_2$-), 4.99 (s, 1H, −CH-), 4.05-3.98 (m, 2H, $-COCH_2CH_3$), 3.8 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 1.15 (t, 3H, $J = 7.50$ Hz, $-COCH_2CH_3$) ppm; Anal. Cald for $C_{25}H_{24}ClN_3O_5$, : C 62.31, H 5.02, N 8.72, Found: C 62.27, H 4.98, N 8.68. GCMS: (ESI$^+$, m/z) = 482 (M^+), 484 (M^++2).

2.6g Ethyl 4-(4-((2-chloro-6-ethoxyquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11g:*** White solid; m.p. 218–219°C; yield: 83%; ^{1}H–NMR (400 MHz, DMSO$-d_6$): $\delta = 11.78$ (s, 1H, -NH exchangeable with D_2O), 8.92 (s, 1H exchangeable with D_2O), 7.76 (s, 1H, quinoline Ar–H), 7.40 (s, 1H, quinoline Ar–H), 7.26 (d, 1H, $J = 7.50$ Hz, quinoline Ar–H), 7.20 (d, 1H, $J = 7.50$ Hz, quinoline Ar–H), 6.90 (d, 2H, $J = 7.90$ Hz, Ar–H), 6.83 (d, 2H, $J = 7.60$ Hz, Ar–H), 5.19 (s, 1H, −CH-), 4.90 (s, 2H, $-CH_2$-), 4.11 (m, 2H, $-OCH_2CH_3$), 4.10 (m, 2H, $-OCOCH_2CH_3$), 2.23 (s, 3H, CH_3), 1.37 (t, 3H, $J = 7.1$ Hz, $-OCH_2$ CH_3), 1.16 (t, 3H, $J = 7.1$ Hz, −O CO CH_2CH_3) ppm; Anal. Cald for $C_{26}H_{26}ClN_3O_5$, : C 62.97, H 5.28, N 8.47, Found: C 62.93, H 5.27, N 8.43. GCMS: (ESI$^+$, m/z) = 496 (M^+), 498 (M^++2).



Scheme 1. Synthesis of dihydropyrimidinones catalysed by dicationic ionic liquid.

2.6h Ethyl 4-(4-((2,7-dichloroquinolin-3-yl) methoxy) phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ***11h:*** White solid; m.p. 232–233°C; yield: 85%; ^{1}H–NMR (400 MHz, DMSO$-d_6$): δ = 11.90 (s, 1H, -NH exchangeable with D_2O), 9.01 (s, 1H exchangeable with D_2O), 8.4 (s, 1H, quinoline Ar–H), 7.90 (d, 1H, J = 8.0 Hz, quinoline Ar–H), 7.50 (d, 1H, J = 7.60 Hz, quinoline Ar–H), 7.30 (d, 2H, J = 8.10 Hz, Ar–H), 7.01 (d, 2H, J = 8.30 Hz, Ar–H), 5.18 (s, 1H, −CH-), 5.10 (s, 2H, CH_2O), 4.10 (m, 2H, −CO CH_2 CH_3), 2.32 (s, 3H, CH_3), 1.16 (t, 3H, J = 7.60 Hz, −$COCH_2CH_3$) ppm; Anal. Cald. for $C_{24}H_{21}Cl_2N_2O_4$: C 59.27, H 4.35, N 8.64, Found: C 59.25, H 4.33, N 8.64. GCMS: (ESI$^+$, m/z) = 486(M^+), 488 (M^++2). 490 (M^++4).

3. Results and discussion

We have developed an environmentally benign and eco-sustainabale one-pot synthetic protocol for the synthesis of known DHPMs (**5 a–f**) by allowing the interactions of aryl aldehydes (**1 a–f**), ethyl acetoacetate (**2**) and urea (**3**) in presence of freshly prepared dicationic ionic liquid, 3-methyl-1-[3-(methyl-1H-imidazolium-1-yl) propyl]-1H-imidazolium dibromide (C_3 [min]$_2$ 2 [Br^-]) (**4**) at 80°C for 2 h (scheme 1).

To investigate the choice of catalysts, we have attempted the Biginelli reaction of multicomponents, 4-methoxy benzaldehyde (**1b**), ethyl acetoacetate (**2**) and urea (**3**) as a model reaction to afford the DHPM (**5b**). Initially the reaction was run in the absence of catalyst and diluent. It was noted that after heating, the product yield obtained was relatively low. Then the above model reaction was carried under neat condition in the presence of various catalysts like *p*-toluene sulphonyl chloride (PTSA), acetic acid, boric acid and SiO_2Cl at 80°C for 2 h. The yields of DHPM (**5b**) are recorded in table 1. Keeping these results in mind, we then performed the model reaction in [C4 min] Br^- (1-Butyl-3-methyl-1*H*-imidazolium bromide) ionic liquid, and observed yield enhancement. Encouraged by these results, we focused our attention on the use of C_3 [min]$_2$ 2 [Br^-] (dicationic ionic liquids) as a catalyst and medium to perform the cyclocondensation of aforementioned model reaction at 80°C. It was found that the dicationic ionic liquid worked well and the condensation was found to take place rapidly giving excellent yield of DHPM (**5b**) (table 1).

With all the above optimized conditions in hand, we then applied this approach to various aromatic aldehydes, ethylacetoacetate and urea using the dicationic ionic liquid and obtained DHPMs with excellent yields (table 2). It is noteworthy to mention that the methodology worked-well to both electron donating and withdrawing substituent on aldehydes. To the best our knowledge, we have been reporting first time the use of dicationic ionic liquid mediated and catalysed one-pot Biginelli reaction for DHPMs (table 2).

The developed synthetic strategies for DHPMs have been found to be economic as the dicationic ionic liquid can be recovered and reused.

Table 1. Optimization of catalysts.

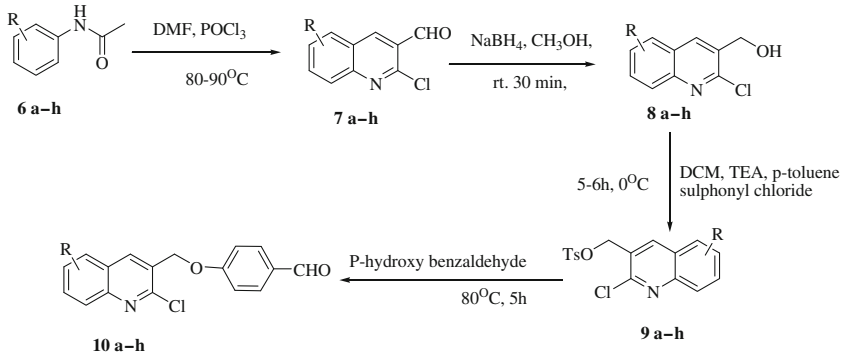
Sl. No.	Catalysts[a]	Time (h)[b]	Isolated yields[c]
1	None	2	61
2	PTSA	2	65
3	AcOH	2	68
4	Boric acid	2	73
5	SiO_2Cl	2	75
6	[C_4 min] Br	2	80
7	C_3 [min]$_2$ 2 [Br^-]	2	89

[a]Amount of catalyst required 100 mole %; [b]Reaction carried at 80°C; [c]Isolated yield

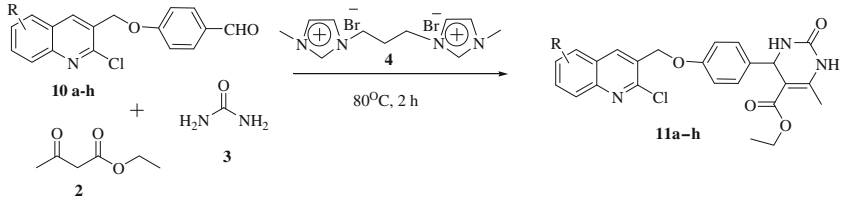
Table 2. Synthesis of known dihydropyrimidinones (scheme 2).

Entry	R	Products[a] [b]	Yield[b] (%)
1	H	5a	85
2	4-OCH_3	5b	89
3	4-Cl	5c	84
4	4-OH	5d	87
5	4-NO_2	5e	88
6	3-NO_2	5f	86

[a] All compounds are known and their spectroscopic data and melting point are in good agreement with literature [48]
[b]Isolated yields of products



Scheme 2. Synthesis of new 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes.



Scheme 3. Synthesis of new DHPMs using dicationic ionic liquid.

Keeping these results in mind, we then paid our attention to synthesize new dihydropyrimidinones bearing quinolines, catalysed by dicationic ionic liquid using new aldehydes and the details are given below.

New 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes (**10 a–h**), required precursors for the one-pot synthesis were freshly prepared by following the reaction sequence presented in (scheme 2). 2-Chloro-3-formyl quinolines (**7 a–h**), prepared by literature procedure[49] were first reduced[50] using sodium borohydride for getting corresponding (2-chloroquinolin-3-yl) methanols (**8 a–h**). The compounds, (**8 a–h**) when tosylated using *p*-toluene sulphonyl chloride and triethylamine gave (2-chloroquinolin-3-yl) methyl 4-methylbenzenesulfonates, (**9 a–h**). The sulphonates, (**9 a–h**) on condensation with *p*-hydroxy benzaldehyde in DMF in presence of potassium carbonate yielded the required 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes, (**10 a–h**) with good yields.

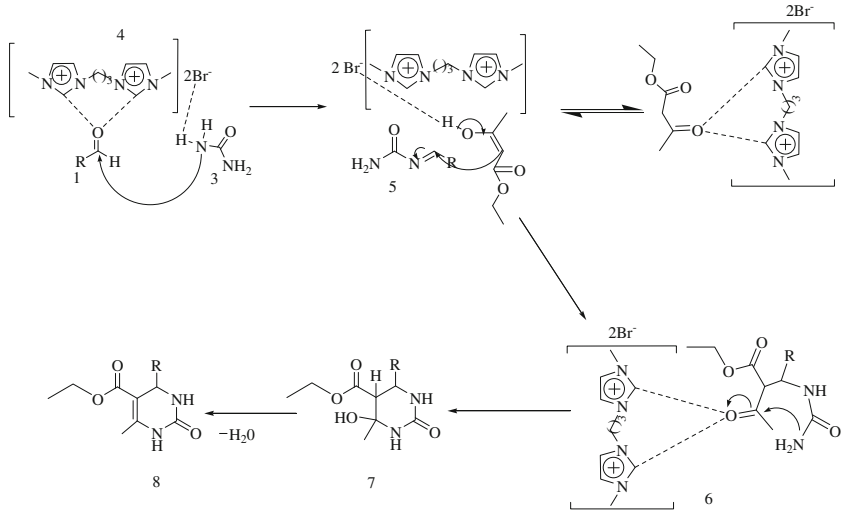
We have applied the above developed environmentally benign, ecosustaibale one-pot synthetic protocol for the synthesis of new DHPMs, (**11 a–h**) by carrying out the cyclocondensation of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes (**10 a–h**), ethyl acetoacetate (**2**) and urea (**3**) in dicationic ionic liquid, ([C3 min]$_2$ 2 Br $^-$) (**4**) at 80°C for 2 h (scheme 3). The cyclocondensation gave excellent yields of DHPMs (**11 a–h**), (table 3). This modified protocol was found to be better than any other reported for Biginelli reaction.

The dicationic ionic liquid encompasses two imidazole cations and two bromide ions. The ions might be useful for strong H-bondining with the substrate as compared with the traditional ionic liquids. It was also noted that dicationic ionic liquid has dual nature and the plausible mechanism for the formation of DHPMs using C_3 [min]$_2$ 2Br$^-$ has been depicted in (scheme 4). The electrophilic character of carbonyl carbon of the aldehydes (**1**) might be increased by forming intermolecular H- bonding between H atoms of imidazoles cations and carbonyl oxygen of the aldehydes and the nucleophilicity of N atom of urea (**3**) might be enhanced by forming the H bonding between H atom of urea and bromide ions of C_3[min]$_2$ 2Br$^-$ (**4**). Therefore, the

Table 3. Synthesis of new dihydropyrimidinones (scheme 3).

Entry	R	Products[a]	Yield[b] (%)
1	H	11a	83
2[t]	8-CH_3	11b	82
3	7-CH_3	11c	85
4	6-CH_3	11d	84
5	7-OCH_3	11e	87
6	6-OCH_3	11f	85
7	6-OCH_2CH_3	11g	83
8	7-Cl	11h	85

[a]All products were characterized by ^{1}H–NMR, Mass spectral and Elemental analyses
[b] Isolated yields of products



Scheme 4. Plausible mechanism for the synthesis of DHPMs using dicationic ionic liquid.

nucleophic addition of nitrogen atom of urea on the electrophilic carbonyl carbon might be enhanced and thus rate of acceleration of Mannich reaction was found to be increased to give intermediate *N*-acyliminium species (**5**). Further, the successive nucleophilic addition of enolic ethyl acetoacetate (**3**) on *N*-acylinium species would have occurred leading to intermediates (**6**). Thus obtained intermediates are being unstable which on successive dehydration would have helped to yield DHPMs (**8**). Thus, dicationic ionic liquid plays triple role other than as medium for obtaining DHPMs such as, (i) it might be enhancing the rate acceleration of Mannich addition of urea on aldehydes, (ii) it might be enhancing the nucleophilic addition of enolic ethylacetoacetate on *N*-acyliminium species and (iii) it would be useful for the successive dehydration of the intermediates for obtaining DHPMs.

4. Conclusion

We have developed safer, economic and one-pot synthetic protocol for the synthesis of DHPMs. Dicationic ionic liquid circumvents the problems associated with the organic solvents and also it minimizes the use of acetic acid and mineral acids. The synthetic strategy made more economic by recovering and recycling of dicationic ionic liquid. We have synthesized new DHPMs encompassing quinolines through ethereal link in four steps from known formyl quinolines. The fascinating scope of this synthetic strategy is that the products and intermediates obtained were from readily available materials and are unambiguous. The synthesized compounds are well-characterized by the spectral and elemental analyses.

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