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An Effective One-Pot Access to 2-Amino-4*H*-benzo[*b*]pyrans and 1,4-Dihydropyridines via γ-Cyclodextrin-Catalyzed Multi-Component Tandem Reactions in Deep Eutectic Solvent

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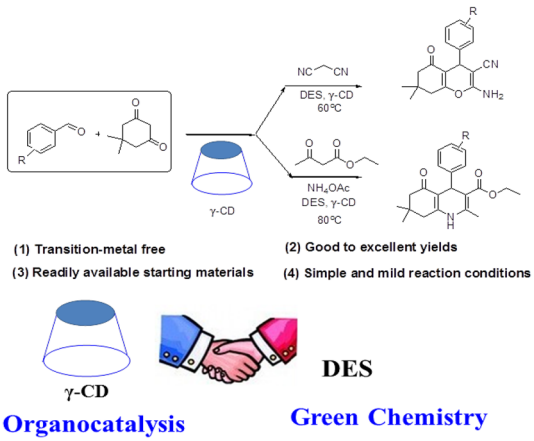
Abstract

A simple, highly efficient and green route for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans and 1,4-dihydropyridines has been developed by using γ-cyclodextrin (γ-CD) as catalyst in deep eutectic solvent (DES) of urea-choline chloride (urea-ChCl), for the first time, accomplished via a one-pot, three-component strategy. All the reactions were successfully carried out under mild conditions and gave good to excellent yields (86–98%) in 8–28 min in the presence of 5 mol% of the γ-CD catalyst. The short reaction time, green reaction medium, moderate reaction conditions, simple work-up procedure and use of easily available reagents are the attractive features of this novel synthetic method. More importantly, the urea-ChCl-γ-CD catalytic system was regenerated and reused up to 6 times with a slight drop in the product yields.

Graphical Abstract



Keywords γ-Cyclodextrin · Multi-component reaction · Supramolecular catalyst · Deep eutectic solvent

1 Introduction

2-Amino-4*H*-benzo[*b*]pyrans and 1,4-dihydropyridines are two important nitrogen-containing heterocyclic compounds, which exist widely in numerous natural compounds. Both of them exhibit good biological activities and they are widely used as antiallergic, antitumor, and antibacterial agents in the pharmaceutical field [1–3]. For example, 2-amino-4*H*-benzo[*b*]pyran derivatives have attracted great interest due

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to biological and pharmacological properties including treatment of human inflammatory TNF-mediated diseases, Parkinson's disease and so on [4, 5]. 1,4-Dihydropyridines also have good antitumor and antibacterial effects and can be commercially used as calcium channel blocker agents in the treatment of cardiovascular diseases [6–8]. Typically, the 1,4-dihydropyridine derivatives, such as nicardipine (I), nimodipine (II), nifedipine (III) can be commercially used as calcium channel blocker agents in the treatment of cardiovascular, cerebrovascular and high blood pressure diseases (Fig. 1).

Due to wide biological significance of 2-amino-4*H*-benzo[b]pyrans and 1,4-dihydropyridines, synthesis of these types of compounds have received a great deal of attention. Up to now, there are several conventional methods to synthesize them. In general, 2-amino-4*H*-benzo[*b*]pyrans are synthesized by three-component cycloaddition reaction of aldehydes, malononitrile, and cyclic 1,3-diketones in organic solvents. With the aim of efficient preparation of 2-amino-4*H*-benzo[*b*]pyrans, several catalysts have been employed in the synthesis process, such as carbon-based solid acids [9], proline [10], NaBr [11], per-6-amino-*β*-CD [12], silica supported sulphonic acid [13], 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [14], $H_6P_2W_{18}O_{62}{\cdot}18H_2O$ [15], P4VPy-CuI [16], aspartic acid [17], etc. The known procedure for the preparation of 1,4-dihydropyridines is Hantzsch reaction. A variety of catalysts, such as I_2 [18], Et_3N [19], nano-γ-Fe_2O_3-SO_3H [20], polyethylene glycol [21], magnetic guanidinylated chitosan [22], cellulose sulfuric acid [23], solid acid [24], chitosan [25], sulfated polyborate [26], Sm_2O_3/ZrO_2 [27], V_2O_5/ZrO_2 [28], MWCNTs@meglumine [29], poly(ionic liquid)-based nanozeolite [30], Fe_3O_4@silica sulfonic acid [31], etc., were found to catalyze this reaction. However, many of those reactions suffer from one or more limitations, such as tedious process of catalyst preparation, long reaction times and low yield, drastic reaction conditions and use of organic solvents. In addition, metal catalysts were also used in the synthesis process, which would lead to metal residues in the products, and limit their application in biomedicine [32, 33]. Therefore, a simple and green approach for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans and 1,4-dihydropyridines is still highly desired and in demand. The search continues for a better non-metallic catalytic system for the synthesis of them in terms of mild reaction conditions, environment-friendly reaction medium, and operational simplicity.

Green chemistry is the frontier of chemistry research, and the development of environmentally friendly synthetic methods has become one of the important goals in the field of organic chemistry. Solvents play an important role in organic reactions. Using green solvents is an effective way to solve environmental pollution. The chemistry of deep eutectic solvents (DESs) has attracted increasing attention because DESs are very green solvents [34, 35]. In general, DESs are prepared with two classes of compounds: hydrogen bond donors (polyols, sugars, and carboxylic acids) and hydrogen bond acceptors (quaternary ammonium salts) [36]. DESs are similar to ionic liquids (ILs) in many ways. However, DESs have several advantages over ILs, such as lower cost, simple preparation, non-toxic, and biodegradable [37]. Recently, much attention has been paid to the development of DESs because of their advantages and wide applications in the field of green and sustainable chemistry [38–46].

Cyclodextrins (CDs) are well known cyclic polysaccharides consisting of six, seven, or eight D-glucopyranoside units. It has a hydrophilic outer surface and a hydrophobic inner cavity, which can bind reactive substrates selectively via noncovalent interactions. Therefore, CDs and functional CDs are often used to catalyze many chemical reactions with high catalytic activity [12, 47–54]. In recent years, they have attracted great attention not only from academic research but also from industrial application. For example, sulphonic acid or amino-modified *β*-CD has been proved to be a highly efficient supramolecular catalyst for the synthesis of high-added value compounds. Unfortunately, a series of laborious, fiddly, and time-consuming process were needed during the preparation procedure of these functional *β*-CD catalysts. In continuation of our efforts to develop green and practical synthetic methods as well as our interest on the application of DESs in organic reactions [55–59], we report here an environmental-friendly and highly efficient route to synthesize 2-amino-4*H*-benzo[*b*]pyrans and 1,4-dihydropyridines by multi-component reaction in urea-ChCl with γ-CD as catalyst (Scheme 1). To the best of our knowledge, there are no reports on the use of urea-ChCl-γ-CD as a catalytic system for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans and 1,4-dihydropyridines via one-pot multi-component reaction.

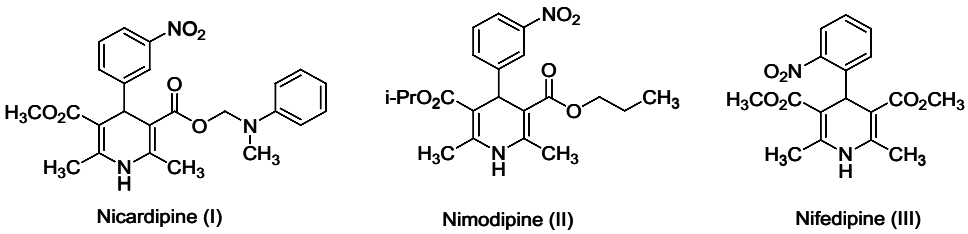
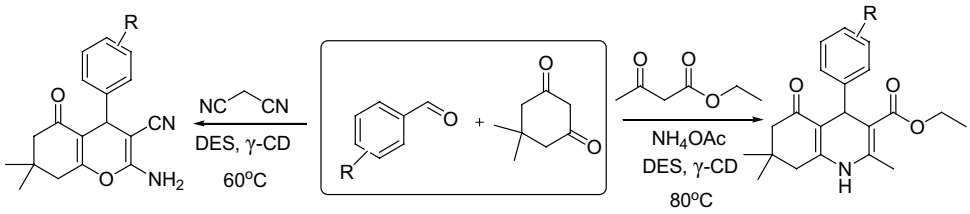


Fig. 1 Some examples of biologically active 1,4-dihydropyridines

Scheme 1 One-pot multi-component synthesis of 2-amino-4*H*-benzo[*b*]pyrans and 1,4-dihydropyridines



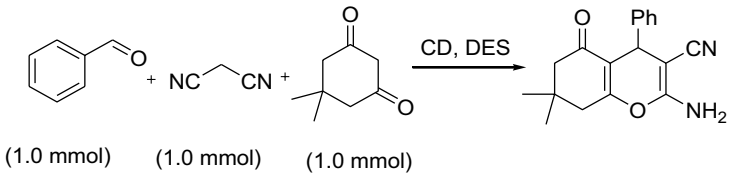
2 Results and Discussion

2.1 Influence of Different Amounts of CD Catalysts in Various Solvents on the Synthesis of 2-Amino-4H-benzo[b]pyrans

In order to get the best catalytic activity, reaction conditions were optimized by evaluating the influence of different amounts of CD catalysts in various solvents (such as H_2O, different DESs) on the model reaction in terms of reaction times, reaction temperatures and product yields. Firstly, we studied the effect of different kinds of CDs on the synthesis of 2-amino-4*H*-benzo[*b*]pyran from benzaldehyde, malonatrile and 5,5-dimethyl-1,3-cyclohexanedione (Table 1). Without adding CD catalyst, the reaction substrates were reacted in DES of urea-ChCl at 60 °C for 15 min, and the yield of the product was only 14%. When the reaction was continued to 240 min, and TLC result showed that the reaction was smoothly carried out, and the isolated yield of the product was 85%. Subsequently, 5 mol% of *α*-CD was added into the reaction mixture at 60 °C, we were surprised to find that the reaction time was obviously shortened from 4 h to 15 min, and the yield of the desired product was 75% (Table 1, entry 2). At the same condition, when 5 mol% of *β*-CD was added into the reaction mixture for 15 min, and the yield was up to 82% (Table 1, entry 3). To our delight, the reaction gave excellent yield of 98% in 15 min in the presence of 5 mol% of *γ*-CD as catalyst (Table 1, entry 4). Comparing the catalytic effects of three different CDs on the reaction, we found that the catalytic effects of *α*-CD, *β*-CD and *γ*-CD on the reaction were obviously different and the cavity diameter of CDs plays a crucial role in catalytic activity. The obtained results indicated that *γ*-CD showed the best catalytic activity.

In addition to DESs, water is also an ideal green reaction solvent. Thus, we tried to add 5 mol% of *γ*-CD into the aqueous phase to catalyze the reaction. Unfortunately, the aqueous phase yield was only 27% (Table 1, entry 5). Subsequently, the other DESs, such as ChCl: glycerol (1:2) and sorbitol: urea: NH_4Cl (7:2:1) were selected as reaction medium under the same condition. The yields of the desired product were 54% and 68%, respectively (Table 1, entries 6 and 7).

Table 1 Screening of different CD catalysts, solvents and temperature on the synthesis of 2-amino-4*H*-benzo[*b*]pyran



Entry	Additive (mol%)	Solvent	Temp (°C)	Time (min)	Isolated yield (%)
1	–	Urea: ChCl (2:1)	60	15	14
		Urea: ChCl (2:1)		240	85
2	α-CD (5)	Urea: ChCl (2:1)	60	15	75
3	β-CD (5)	Urea: ChCl (2:1)	60	15	82
4	**γ-CD (5)**	**Urea: ChCl (2:1)**	**60**	**15**	**98**
5	γ-CD (5)	H_2O	60	15	27
6	γ-CD (5)	ChCl: Glycerol (1:2)	60	15	54
7	γ-CD (5)	Sorbitol: Urea: NH_4Cl (7:2:1)	70	15	68
8	γ-CD (5)	Urea: ChCl (2:1)	80	15	98
9	γ-CD (10)	Urea: ChCl (2:1)	60	15	95

Finally, we explored the effect of reaction temperature and the catalyst dosage on the reaction. When the reaction temperature rose to 80 °C, the yield of the reaction did not change (Table 1, entry 8). Considering the energy consumption, we choose 60 °C as the optimized reaction temperature. Furthermore, no further improvement in the yield could be achieved, when the amount of γ-CD was increased up to 10 mol% at 60 °C, the yield decreased to 95% (Table 1, entry 9). This phenomenon may be caused by the amount of γ-CD. When the amount of γ-CD increases to a certain extent, γ-CD and reaction products form host–guest inclusions in the treatment process, resulting in a part of products dispersed into aqueous phase. In order to obtain the highest yield, we used 5 mol% of γ-CD as the catalyst dosage. Thus the optimal conditions for this reaction were found to be heating the reactants in DES of urea-ChCl at 60 °C for 15 min by using γ-CD as catalyst (5 mol%, Table 1, entry 4). As for the synthesis of 1,4-dihydropyridines, the optimal conditions were found to be heating the reactants in DES of urea-ChCl at 80 °C for 8 min by using γ-CD as catalyst (5 mol%, Table S1, entry 4).

2.2 Synthesis of 2-Amino-4H-benzo[b]pyrans and 1,4-Dihydropyridines by Using γ-CD as Catalyst in DES of Urea: ChCl (2:1)

With the optimized condition in hand for the multi-component reaction, we proceeded to screen a wide range of different aromatic aldehydes (carrying electron-withdrawing or electron-donating groups on benzene ring), 5,5-dimethyl-1,3-cyclohexanedione, and malononitrile.

All the reactions have proceeded smoothly without the formation of any side products. The results of these reactions revealed that all of the aromatic aldehydes tested were converted efficiently (15–28 min) to the corresponding 2-amino-4*H*-benzo[*b*]pyrans in good to excellent yields (86–98%) under the optimized condition. The observed results are presented in Table 2. The obtained results show that some common functional groups such as –Cl, –OH, $–NO_2$, $–N(CH_3)_2$, etc. do not affect the high efficiency of the reaction. It was observed that aromatic aldehydes carrying electron-donating groups could be smoothly converted into the desired products in 20 min (Table 2, entries 1–4). Benzaldehydes carrying electron-withdrawing groups need much more time to complete their transformation (Table 2, entries 5 and 6). Interestingly, for the aromatic aldehydes containing heteroatoms, such as furaldehyde, the reaction can be carried out in 10 min, and the desired product can be synthesized in 93% yield (Table 2, entry 7). Similarly, the aromatic aldehydes tested were converted efficiently (8–25 min) to the corresponding 1,4-dihydropyridines in good to excellent yields (89–98%) under the optimized condition (Table 2, entries 8–14). It is worth mentioning that no by-product in Biginelli reaction was found in the final crude product. The main reason is that the hydrogen bond between urea and choline chloride greatly reduces the reactivity of urea.

2.3 γ-CD Catalyst Recycling

In the field of green chemistry, the recyclability and recycling of catalyst is an important aspect to evaluate its performance. To check the recyclability and reusability of the catalytic system, we studied the reaction of benzaldehyde, malononitrile and 5,5-dimethyl-1,3-cyclohexanedione under the optimized condition.

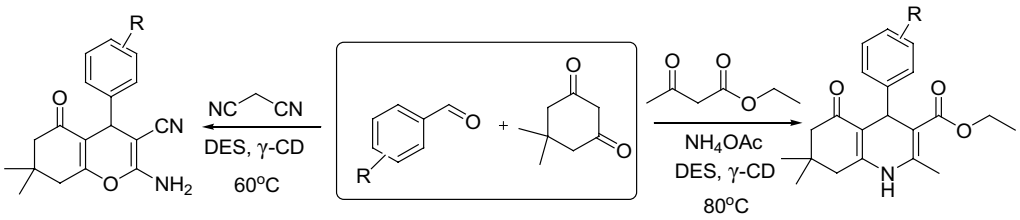
When the first reaction was completed, the reaction was heated by adding a certain amount of hot deionized water. After the crude product was filtered out and the water in the mixture was removed by rotary evaporator, the urea-ChCl-γ-CD catalytic system could be directly used in the subsequent experiments without further treatment. As shown in Fig. 2, the catalytic system could be recycled and reused at least 6 times without a noticeable drop in the product yield and its catalytic activity. The slight decrease of catalytic activity should be due to the normal loss of the γ-CD catalyst during the work-up stage. In the same way, as for the synthesis of 1,4-dihydropyridine, the catalytic system could also be recycled and reused at least 6 times without a noticeable drop in the product yield and its catalytic activity (Fig. S1).

2.4 Plausible Reaction Mechanism

During the course of synthesis of 2-amino-4*H*-benzopyrans and 1,4-dihydropyridines, DES of urea-choline chloride itself exhibited a certain catalytic activity. The experimental results showed that when the reaction was continued to 240 min, the isolated yield of the desired 2-amino-4*H*-benzopyran was 85%. Due to the hydrophobic inner cavity structure, γ-CD can effectively encapsulate small organic molecules, which can significantly promote the 2-amino-4*H*-benzopyran formation in the one-pot three-component reaction. Base on the above results and related literatures, we propose a mechanism of γ-CD catalyzed one-pot three-component reaction for the synthesis of 2-amino-4*H*-benzo[b]pyrans as shown in Scheme 2.

In the first step, arylidenemalononitrile is formed by Knoevenagel condensation between benzaldehyde and malononitrile. Subsequently, Michael addition of 5,5-dimethyl-1,3-cyclohexanedione to arylidenemalononitrile takes place followed by cyclization and to give the desired product 2-amino-4*H*-benzo[b]pyran. The high catalytic activity observed in steps of Knoevenagel condensation, Michael addition, and tautomerization could be attributed to the fact that, in DES of urea: ChCl (2:1), hydrophobic central cavities of γ-CD catalyst act as microvessels and accommodate

Table 2 One-pot multi-component synthesis of 2-amino-4H-benzo[b]pyrans and 1,4-dihydropyridines under the optimized condition in DES of urea: ChCl (2:1)



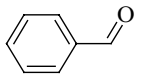
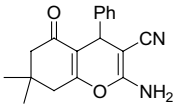
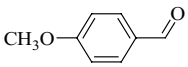
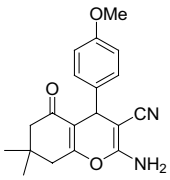
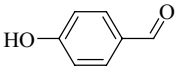
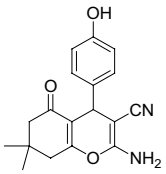
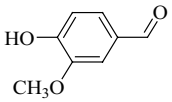
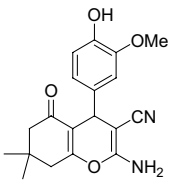
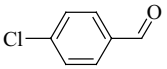
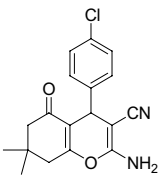
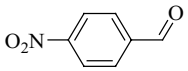
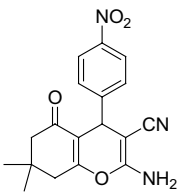
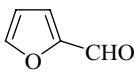
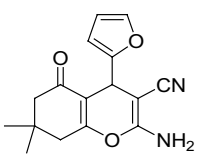
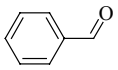
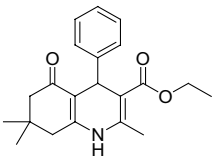
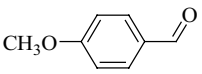
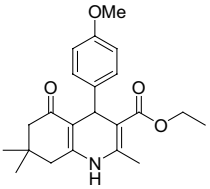
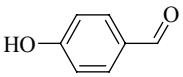
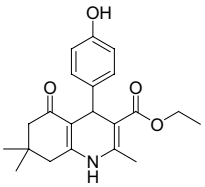
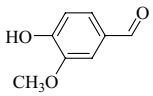
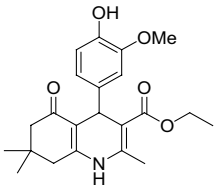
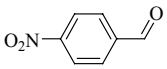
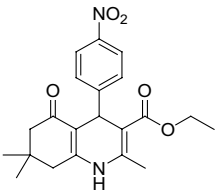
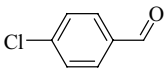
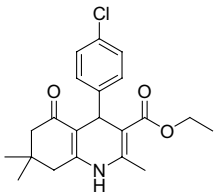
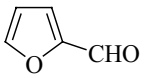
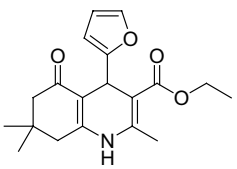
Entry	R-CHO	Product	Time (min)	Yield (%)
1			15	98
2			18	93
3			20	93
4			20	92
5			28	94
6			28	86
7			10	93

Table 2 (continued)

Entry	R-CHO	Product	Time (min)	Yield (%)
8			8	95
9			15	95
10			20	96
11			25	98
12			25	89
13			15	96
14			10	96

nonpolar benzaldehyde, malononitrile and 5,5-dimethyl-1,3-cyclohexanedione. The chemical reaction process was tracked by NMR technology. The results of ^{1}H NMR showed that the target compound was the main component in the crude product when the reaction lasted for 5 min and 10 min. Meanwhile, the evidence of the key intermediate 2-benzylidenemalononitrile could be found. As shown in Fig. 3, the peak at 7.90 ppm was assigned to the proton of CH_f=C in intermediate benzylidenemalononitrile. When the reaction was completed (15 min), the signal of the proton of CH_f=C disappeared. This result can indirectly prove the rationality of the mechanism.

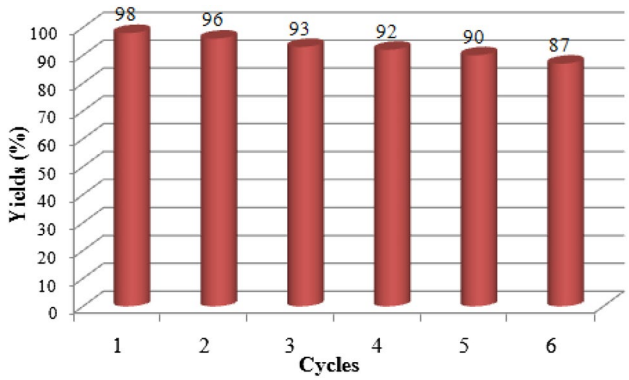


Fig. 2 γ-CD catalyst reusability

3 Conclusions

In summary, we have developed for the first time, a unique combination of DES and CD for highly efficient and green synthesis of 2-amino-4*H*-benzo[b]pyrans and 1,4-dihydropyridines. Sixteen derivatives of them were synthesized in just 8–28 min by the use of γ-CD and urea:ChCl (2:1) catalytic system as compared to conventional heating in urea:ChCl (2:1) that took 2–4 h. The cavity diameter of γ-CD catalyst plays a crucial role in catalytic activity. The γ-CD and urea: ChCl (2:1) catalytic system can be recycled and reused at least six times without a noticeable decrease in the product yield and its catalytic activity. This newly developed and environmentally friendly method not only can obviously shorten the reaction time without any byproduct by using nontoxic supramolecular γ-CD as catalyst, but also avoid the usage of toxic chemicals and volatile organic solvents. To sum up, the method is convenient, economical, time and energy-saving, eco-friendly and extremely efficient and thus has promising industrial applications.

4 Experimental

4.1 Materials and Instrumentation

All chemicals were purchased from Aladdin Reagent Company. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel plates.

The IR spectra were obtained using a FT-IR (4000–400 cm^{-1}) spectrometer (Nicolet Nexus FT-IR spectrometer, USA) at 4 cm^{-1} resolution and 32 scans. Samples were prepared using the KBr disc method. NMR spectra were acquired in $CDCl_3$ on a Bruker DMX-400 spectrometer at 400 MHz for ^1H NMR, the chemical shifts are given in δ values from TMS as an internal standard.

4.2 Typical Procedure for the Preparation of DES

Urea (0.2 mol) and ChCl (0.1 mmol) were mixed in a round-bottomed flask, then the mixture was heated at 80 °C with stirring until formation of a colorless homogeneous liquid with 100% atom economy. The DES of urea-ChCl was allowed to cool to room temperature, which was used directly for the synthesis of 2-amino-4*H*-benzo[b]pyrans and 1,4-dihydropyridines without any further purification.

4.3 Typical Procedure for the Synthesis of 2-Amino-4H-benzo[b]pyrans

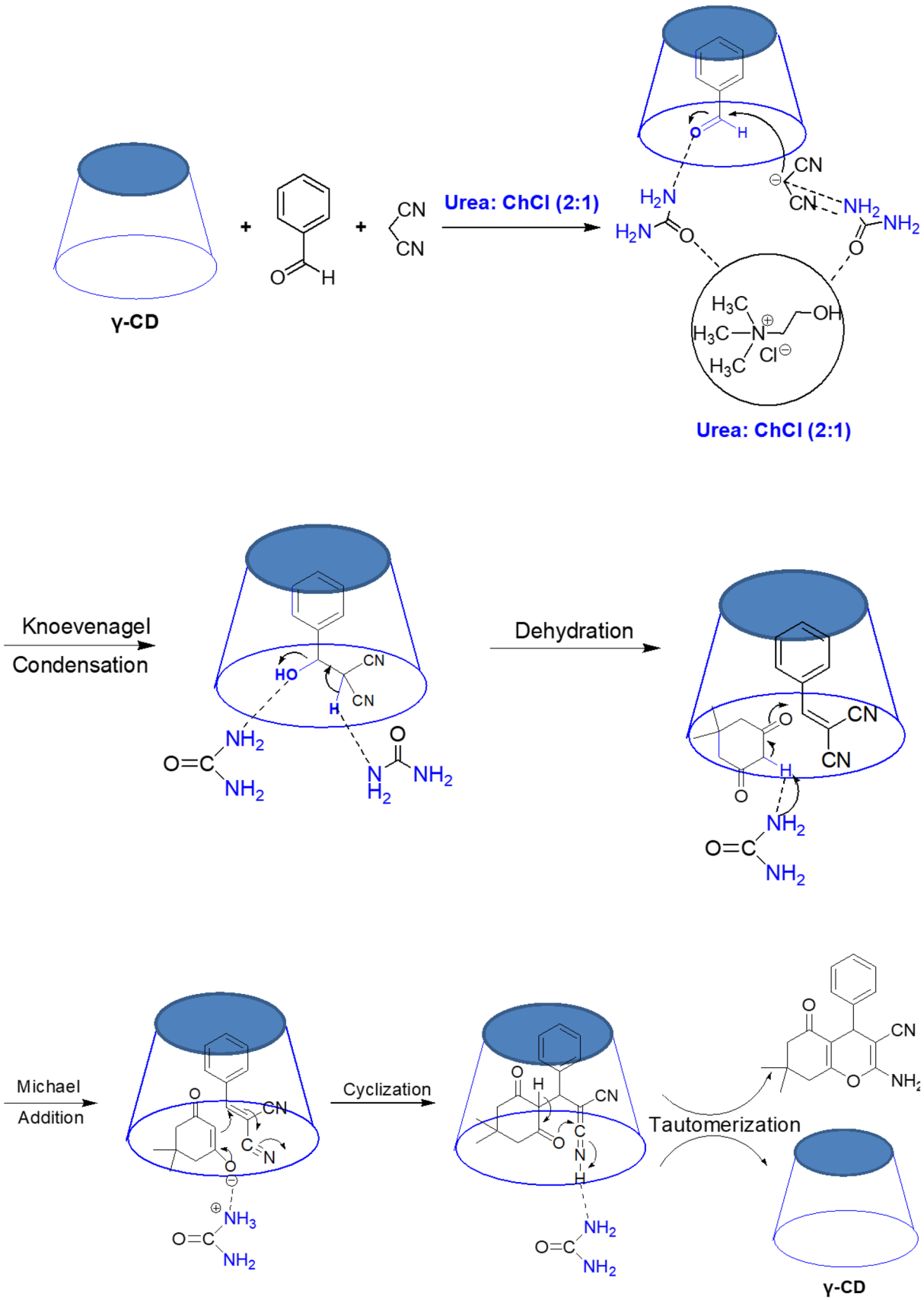
In a typical reaction, aldehyde (1.0 mmol), malononitrile (1.0 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol) are added to the reaction flask containing DES of urea-ChCl (2.0 mL), and γ-CD (5.0 mol%) is added to the reaction flask and then the reaction mixture was heated to 60 °C in an oil bath for 15–28 min. After completion of reaction, as detected by TLC, hot distilled water (5.0 mL) was added to the reaction mixture. The resulting mixture was stirred vigorously for several minutes until a lot of white solids appeared. The crude products were finally obtained through filtering and washing. The crude products were then recrystallized by anhydrous ethanol and then got pure products.

4.4 Typical Procedure for the Synthesis of 1,4-Dihydropyridines

In a typical reaction, aldehyde (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol), and ethyl acetoacetate malononitrile (1.0 mmol) are added to the reaction flask containing DES of urea-ChCl (2.0 mL), and γ-CD (5.0 mol%) is added to the reaction flask and then the reaction mixture was heated to 80 °C in an oil bath for 8–25 min. After completion of reaction, as detected by TLC, hot distilled water (5.0 mL) was added to the reaction mixture. The resulting mixture was stirred vigorously for several minutes until a lot of white solids appeared. The crude products were finally obtained through filtering and washing. The crude products were then recrystallized by anhydrous ethanol and then got pure products.

4.5 Spectroscopic Data of the Obtained Products

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-*4H*-chromene-3-carbonitrile (**1**): m. p. 226–227 °C. FT-IR (KBr disc) cm^{-1}: 3392, 3325, 3250, 2962, 2926, 2885, 2200, 1680, 1660, 1604, 1370, 1247, 1210, 1158, 1033. ^1H NMR (400 MHz, $CDCl_3$): δ: 7.31 (dd, $J = 12.2$,



Scheme 2 Plausible mechanism for the synthesis of 2-amino-4*H*-benzo[b]pyran catalyzed by γ-CD in DES of urea: ChCl (2:1)

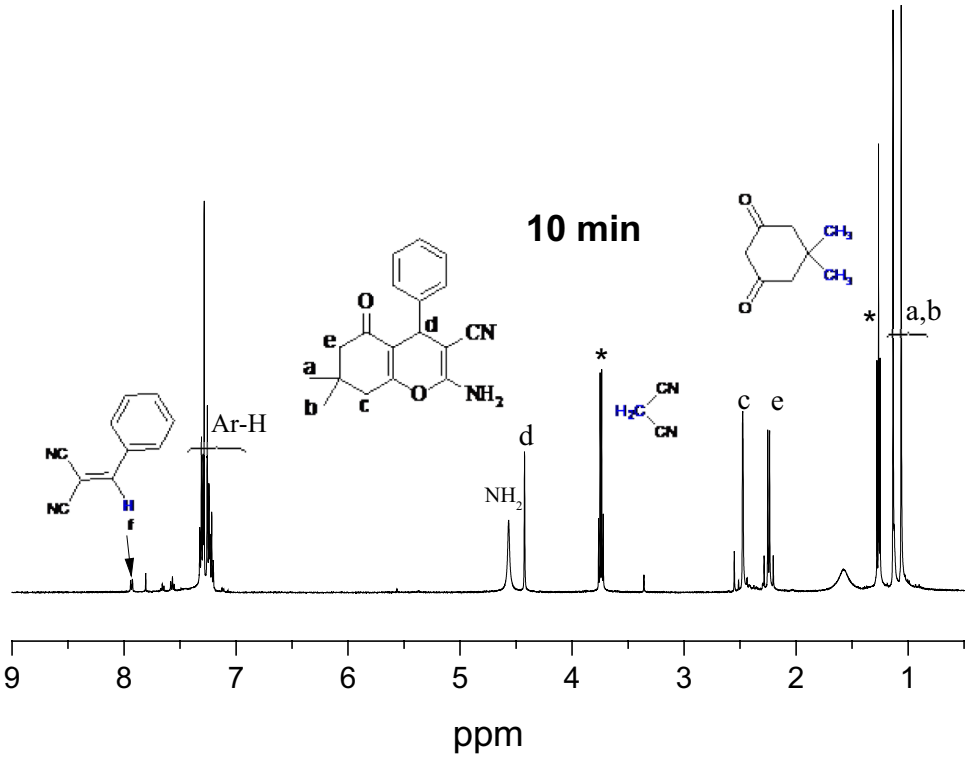


Fig. 3 ^{1}H NMR spectrum of the crude product (10 min)

4.8 Hz, 2H), 7.27–7.19 (m, 3H), 4.53 (s, 2H), 4.43 (s, 1H), 2.54–2.41 (m, 2H), 2.31–2.18 (m, 2H), 1.14 (s, 3H), 1.06 (s, 3H). ESI–MS calcd m/z 294.1, found 295.1 $[(M+1)]^{+}$.

2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (**2**): m. p. 196–197 °C. FT-IR (KBr disc) cm^{-1}: 3497, 3406, 3327, 2193, 1657, 1602, 1514, 1365. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21–7.14 (m, 2H), 6.87–6.81 (m, 2H), 4.50 (s, 2H), 4.39 (s, 1H), 3.79 (s, 3H), 2.46 (s, 2H), 2.31–2.15 (m, 2H), 1.13 (s, 3H), 1.06 (s, 3H). ESI–MS calcd m/z 324.1, found 325.1 $[(M+1)]^{+}$.

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-*4H*-chromene-3-carbonitrile (**3**): m. p. 207–208 °C. FT-IR (KBr disc) cm^{-1}: 3420, 3367, 3198, 2962, 2195, 1680, 1656, 1606, 1512, 1370, 1251, 1215, 1163, 1039, 850. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, $J=8.5$ Hz, 2H), 6.76 (d, $J=8.5$ Hz, 2H), 4.50 (s, 2H), 4.38 (s, 1H), 2.46 (s, 2H), 2.24 (d, $J=4.6$ Hz, 2H), 1.13 (s, 3H), 1.06 (s, 3H). ESI–MS calcd m/z 310.1, found 311.1 $[(M+1)]^{+}$.

2-Amino-4-(3-methoxy-4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-*4H*-chromene-3-carbonitrile (**4**): m. p. 228–229 °C. FT-IR (KBr disc) cm^{-1}: 3497, 3406, 3327, 3213, 2965, 2193, 1678, 1657, 1602, 1514, 1365, 1274, 1210, 1035. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, $J=7.8$ Hz, 2H), 6.67 (d, $J=8.1$ Hz, 1H), 4.49 (s, 2H), 4.36 (s, 1H), 3.92 (s, 3H), 2.47 (s, 2H), 2.25 (d, $J=2.7$ Hz, 2H), 2.04 (s, 1H), 1.14 (s, 3H), 1.07 (s, 3H). ESI–MS calcd m/z 340.1, found 341.1 $[(M+1)]^{+}$.

2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (**5**): m. p. 208–209 °C. FT-IR (KBr disc) cm^{-1}: 3398, 3325, 3260, 3210, 2958, 2930, 2193, 1740, 1683, 1654, 1602, 1410, 1370, 1250, 1210, 1039, 850. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, $J=2.1$ Hz, 1H), 7.27 (s, 1H), 7.20 (d, $J=8.5$ Hz), 4.55 (s, 2H), 4.41 (s, 1H), 2.47 (s, 2H), 2.31–2.17 (m, 2H), 1.14 (s, 3H), 1.05 (s, 3H). ESI–MS calcd m/z 328.1, found 329.1 $[(M+1)]^{+}$.

2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-*4H*-chromene-3-carbonitrile (**6**): m. p. 176–177 °C. FT-IR (KBr disc) cm^{-1}: 3390, 3327, 3254, 3210, 2960, 2925, 2198, 1680, 1660, 1602, 1371, 1250, 1215, 1160, 1140, 1035. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, $J=8.5$ Hz, 2H), 7.44 (d, $J=8.4$ Hz, 2H), 4.64 (s, 2H), 4.55 (s, 1H), 2.51 (s, 2H), 2.07 (s, 2H), 1.15 (s, 3H), 1.06 (s, 3H). ESI–MS calcd m/z 339.1, found 340.1 $[(M+1)]^{+}$.

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-*4H*-chromene-3-carbonitrile (**7**): m. p. 220–221 °C. FT-IR (KBr disc) cm^{-1}: 3398, 3329, 3254, 3215, 2966, 2930, 2875, 2196, 1681, 1660, 1604, 1502, 1363, 1247, 1217, 1160, 1140, 1037, 1012, 925. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (s, 1H), 6.29 (dd, $J=3.1$, 1.9 Hz, 1H), 6.21 (d, $J=3.2$ Hz, 1H), 4.60 (s, 1H), 4.57

(s, 2H), 2.46 (s, 2H), 2.30 (s, 2H), 1.13 (d, $J=7.8$ Hz, 3H), 1.10 (s, 3H). ESI–MS calcd m/z 284.1, found 285.1 $[(M+1)]^+$.

2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**8**): m.p. 208–209 °C. FT-IR (KBr disc) cm^{-1}: 3292, 3220, 3080, 2962, 2930, 1700, 1643, 1610, 1483, 1381, 1309, 1278, 1210, 1109, 1070. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, $J=7.3$ Hz, 2H), 7.21 (t, $J=7.5$ Hz, 2H), 7.11 (t, $J=7.3$ Hz, 1H), 5.83 (s, 1H), 5.08 (s, 1H), 4.13–4.01 (m, 2H), 3.75 (q, $J=7.0$ Hz, 2H), 2.40 (s, 2H), 1.31–1.24 (m, 3H), 1.21 (t, $J=7.1$ Hz, 3H), 1.10 (s, 3H), 0.96 (s, 3H). ESI–MS calcd m/z 339.1, found 340.1 $[(M+1)]^+$.

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**9**): m.p. 257–258 °C. FT-IR (KBr disc) cm^{-1}: 3277, 3244, 3207, 3078, 2963, 2936, 1705, 1647, 1604, 1491, 1381, 1309, 1280, 1215, 1190, 1167, 1153, 1107, 1072. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23 (t, $J=5.8$ Hz, 2H), 6.75 (t, $J=5.8$ Hz, 2H), 6.06 (s, 1H), 5.02 (s, 1H), 4.08 (q, $J=7.1$ Hz, 2H), 3.74 (d, $J=7.9$ Hz, 3H), 2.39 (s, 3H), 2.30–2.12 (m, 3H), 1.22 (t, $J=7.1$ Hz, 3H), 1.09 (s, 3H), 0.96 (s, 3H). ESI–MS calcd m/z 369.2, found 370.2 $[(M+1)]^+$.

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**10**): m.p. 245–246 °C. FT-IR (KBr disc) cm^{-1}: 3146, 3282, 3209, 3078, 2958, 1685, 1650, 1615, 1508, 1485, 1381, 1307, 1284, 1220, 1168, 1138, 1120. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, $J=8.3$ Hz, 2H), 6.67 (d, $J=8.4$ Hz, 2H), 5.96–5.86 (m, 1H), 5.00 (s, 1H), 4.08 (q, $J=7.1$ Hz, 2H), 2.41 (s, 3H), 2.33–2.14 (m, 4H), 1.22 (t, $J=7.1$ Hz, 3H), 1.10 (s, 3H), 0.96 (s, 3H). ESI–MS calcd m/z 355.1, found 356.1 $[(M+1)]^+$.

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-hydroxy-3-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**11**): m.p. 210–212 °C. FT-IR (KBr disc) cm^{-1}: 3398, 3298, 3072, 2955, 1700, 1643, 1591, 1510, 1485, 1381, 1310, 1273, 1215, 1168, 1128, 1070. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.95 (s, 1H), 6.74 (dd, $J=18.9$, 7.9 Hz, 2H), 5.86–5.72 (m, 1H), 5.00 (s, 1H), 4.10 (q, $J=6.8$ Hz, 2H), 3.88 (s, 3H), 2.42 (s, 3H), 2.26 (s, 4H), 1.24 (t, $J=7.1$ Hz, 3H), 1.11 (s, 3H), 0.99 (s, 3H). ESI–MS calcd m/z 385.2, found 386.2 $[(M+1)]^+$.

Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxoquinoline-3-carboxylate (**12**): m.p. 240–241 °C. FT-IR (KBr disc) cm^{-1}: 3443, 3275, 3192, 3074, 2966, 1703, 1650, 1606, 1518, 1492, 1381, 1345, 1307, 1280, 1215, 1189, 1150, 1109, 1070. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, $J=7.9$ Hz, 2H), 7.52 (t, $J=10.0$ Hz, 2H), 5.90 (s, 1H), 5.18 (s, 1H), 4.07 (q, $J=7.0$ Hz, 2H), 2.45 (s, 3H), 2.22 (dd, $J=37.9$, 15.9 Hz, 4H), 1.19 (t, $J=7.1$ Hz, 3H), 1.12 (s, 3H), 0.94 (s, 3H). ESI–MS calcd m/z 384.1, found 385.1 $[(M+1)]^+$.

Ethyl 4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**13**): m.p. 231–232 °C. FT-IR (KBr disc) cm^{-1}: 3275, 3207, 3076, 2960, 1705, 1645, 1602, 1489, 1381, 1280, 1215, 1107, 1080. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, $J=8.5$ Hz, 2H), 7.18 (d, $J=8.4$ Hz, 2H), 5.99 (s, 1H), 5.05 (s, 1H), 4.08 (q, $J=7.1$ Hz, 2H), 2.44–2.32 (m, 4H), 2.29–2.14 (m, 3H), 1.21 (t, $J=7.1$ Hz, 3H), 1.10 (s, 3H), 0.95 (s, 3H). ESI–MS calcd m/z 373.1, found 374.1 $[(M+1)]^+$.

Ethyl 4-(furan-2-yl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**14**): m.p. 247–248 °C. FT-IR (KBr disc) cm^{-1}: 3288, 3221, 3084, 2966, 2935, 2877, 1678, 1608, 1491, 1396, 1377, 1320, 1220, 1180, 1145, 1105, 1074, 1010, 927, 796. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.95 (s, 1H), 6.74 (dd, $J=17.4$, 8.2 Hz, 2H), 5.82 (s, 1H), 5.00 (s, 1H), 4.10 (q, $J=7.1$ Hz, 2H), 2.38 (d, $J=22.2$ Hz, 4H), 2.24 (q, $J=16.5$ Hz, 3H), 1.24 (t, $J=6.1$ Hz, 3H), 1.11 (s, 3H), 0.98 (s, 3H). ESI–MS calcd m/z 329.1, found 330.1 $[(M+1)]^+$.

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References

1. Wang JL, Liu D, Zhang ZJ, Shan S, Han X, Srinivasula SM, Croce CM, Alnemri ES, Huang Z (2000) Proc Natl Acad Sci USA 97:7124
2. Zhang G, Zhang Y, Yan J, Chen R, Wang S, Ma Y, Wang R (2012) J Org Chem 77:878
3. Stout DM, Meyers AI (1982) Chem Rev 82:223
4. Gourdeau H, Leblond L, Hamelin B, Desputeau C, Dong K, Kianicka I, Custeau D, Bourdeau C, Geerts L, Cai SX, Drewe J, Labrecque D, Kasibhatla S, Tseng B (2004) Mol Cancer Ther 3:1375
5. Kemnitzer W, Drewe J, Jiang S, Zhang H, Wang Y, Zhao J, Jia S, Herich J, Labreque D, Storer R, Meerovitch K, Bouffard D, Rej R, Denis R, Blais C, Lamothe S, Attardo G, Gourdeau H, Tseng B, Kasibhatla S, Cai SX (2004) J Med Chem 47:6299
6. Chandra KS, Ramesh G (2013) Indian Heart J 65:691
7. Sambongi Y, Nitta H, Ichihashi K, Futai M, Ueda I (2002) J Org Chem 67:3499
8. Valente S, Mellini P, Spallotta F, Carafa V, Nebbioso A, Polletta L, Carnevale I, Saladini S, Trisciuoglio D, Gabellini C, Tardugno M, Zwergel C, Cencioni C, Atlante S, Moniot S, Steegborn C, Budriesi R, Tafani M, Bufalo DD, Altucci L, Gaetano C, Mai A (2016) J Med Chem 59:1471
9. Moghaddas M, Davoodnia A (2015) Res Chem Intermed 41:4373
10. Elnagdi NMH, Hokbany NS (2012) Molecules 17:4300
11. Devi I, Bhujyan PJ (2004) Tetrahedron Lett 45:8625
12. Azath IA, Puthiaraj P, Pitchumani K (2013) ACS Sustain Chem Eng 1:174
13. Sharma P, Gupta M (2015) Green Chem 17:1100
14. Khurana JM, Nand B, Saluja P (2010) Tetrahedron 66:5637

15. Heravi MM, Jani BA, Derikvand F, Bamoharram FF, Oskooie HA (2008) Catal Commun 10:272
16. Albadi J, Mansournezhad A (2016) Res Chem Intermed 42:5739
17. Ahad A, Farooqui M (2017) Res Chem Intermed 43:2445
18. Ko S, Sastry MN, Lin VC, Yao CF (2005) Tetrahedron Lett 46:5771
19. Sun J, Xia EY, Wu Q, Yan CG (2010) Org Lett 12:3678
20. Otokesh S, Koukabi N, Kolvari E, Amoozadeh A, Malmir M, Azhari S (2015) S Afr J Chem 68:15
21. Pal S, Singh V, Das P, Choudhury LH (2013) Bioorg Chem 48:8
22. Maleki A, Firouzi-Haji R, Hajizadeh Z (2018) Inter J Bio Macro 116:320
23. Safari J, Banitaba SH, Khalili SD (2011) J Mol Catal A: Chem 335:46
24. Bamoniri A, Fouladgar S (2015) RSC Adv 5:78483
25. Safari J, Azizi F, Sadeghi M (2015) New J Chem 39:1905
26. Rekunge DS, Khatri CK, Chaturbhuj GU (2017) Tetrahedron Lett 58:1240
27. Shabalala S, Maddila S, Van Zyl WE, Jonnalagadda SB (2016) Catal Commun 79:21
28. Bhaskaruni SVHS, Maddila S, van Zyl WE, Jonnalagadda SB (2018) Catal Today 309:276
29. Moradi L, Zare M (2018) Green Chem Lett Rev 11:197
30. Amoli T, Baghbanian SM (2018) Res Chem Intermed 44:3389
31. Nasrollahi SMH, Ghasemzadeh MA, Zolfaghari MR (2018) Acta Chim Slov 65:199
32. Safaei-Ghomi J, Ziarati A, Teymuri R (2012) Bull Korean Chem Soc 33:2679
33. Viswanath IVK, Murthy YLN (2013) Chem Sci Trans 2:227
34. Abbott AP, Boothby D, Capper G, Davies DL, Rasheed RK (2004) J Am Chem Soc 126:9142
35. Paiva A, Craveiro R, Aroso I, Martins M, Reis RL, Duarte ARC (2014) ACS Sustain Chem Eng 2:1063
36. María P, Zaira M (2011) Curr Opin Chem Biol 15:220
37. Smith EL, Abbott AP, Ryder KS (2014) Chem Rev 114:11060
38. Gu YL, Jerome F (2013) Chem Soc Rev 42:9550
39. Liu P, Hao JW, Mo LP, Zhang ZH (2015) RSC Adv 5:48675
40. Xiong XQ, Han Q, Shi L, Xiao SY, Bi C (2016) Chin J Org Chem 36:480
41. Zhang ZH, Zhang XN, Mo LP, Li YX, Ma FP (2012) Green Chem 14:1502
42. Zhang M, Liu YH, Shang ZR, Hu HC, Zhang ZH (2017) Catal Commun 88:39
43. Zhang M, Liu P, Liu YH, Shang ZR, Hu HC, Zhang ZH (2016) RSC Adv 6:106160
44. Perrone S, Capua M, Messa F, Salomone A (2017) Tetrahedron 73:6193
45. Kafle A, Handy ST (2017) Tetrahedron 73:7024
46. Shaibuna M, Theresa LV, Sreekumar K (2018) Catal Lett 148:2359
47. Fihri A, Bouhrara M, Nekoueishahraki B, Basset JM, Polshettiwar V (2011) Chem Soc Rev 40:5181
48. Abbasi M (2017) J Chin Chem Soc 64:896
49. Natarajan M, Kasi P (2018) Chemistryselect 3:10886
50. Kanagaraj K, Pitchumani K (2013) J Org Chem 78:744
51. Kanagaraj K, Pitchumani K (2010) Tetrahedron Lett 51:3312
52. Ren YF, Zhang W, Lu J, Gao K, Liao XL, Chen XZ (2015) RSC Adv 5:79405
53. Ren YF, Yang B, Liao XL (2016) RSC Adv 6:22034
54. Ren YF, Yang B, Liao XL (2016) Catal Sci Tech 12:4283
55. Xiong XQ, Yi C, Liao X, Lai SL (2019) Tetrahedron Lett 60:402
56. Xiong XQ, Chen HX, Liao X, Lai SL, Gao LZ (2018) ChemistrySelect 3:8819
57. Xiong XQ, Tang ZK, Sun ZH, Meng XQ, Song SD, Quan ZL (2018) Appl Organometal Chem 32:e3946
58. Xiong XQ, Yi C, Han Q, Shi L, Li SZ (2015) Chin J Catal 36:237
59. Han Q, Xiong XQ, Li SZ (2015) Catal Commun 58:85