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Facile and efficient synthesis of 3,4,5-substituted furan-2(5*H*)-ones by using β-cyclodextrin as reusable catalyst

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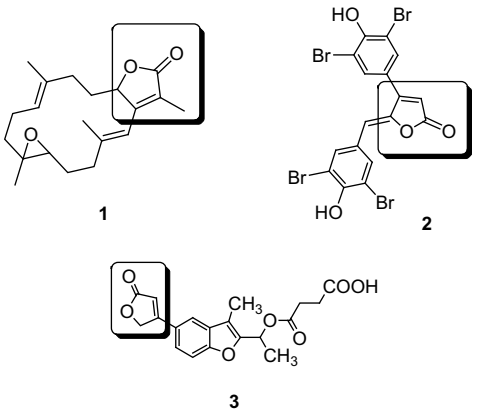
ABSTRACT

3,4,5-Substituted furan-2(5*H*)-one derivatives were synthesized by using β-cyclodextrin as a catalyst in water via biomimetic approach. β-Cyclodextrin can be recovered and reused.

1. Introduction

Furan-2(5*H*)-ones have attracted the attention of several organic chemists as valuable targets due to their presence as a subunit in many natural products isolated from a variety of sources like sponges, algae,[1] animals,[2] plants[3] and insects.[4] According to the literature reports this subunit is present in as many as more than 13,000 natural products.[5] This core unit is the key structure to induce a wide range of biological activities like antimicrobial,[6] antifungal,[7] anti-inflamatory,[8] anticancer[9] and anti-viral HIV-1.[10] Butenolide synthon is the core structural unit found in many bioactive natural products such as sarcophine **1** and rubrolide **2**, which is isolated from the colonial tunicate *Ritterela rubra*,[11,12] as well as in synthetic drug benfurodil hemisuccinate **3** (Eucilat®).



In view of the biological activity associated with butenolide synthon researchers have developed a number of methodologies to construct substituted furan-2(5*H*)-one unit. Domschke et al. developed a methodology for the synthesis of 2(5*H*)-furanone, which describes the method in short.[13] Liu et al. described the synthesis of 2(5*H*)-furanone by refluxing furfural with hydrogen peroxide followed by oxidation leading to a mixture of 2(3*H*) and 2(5*H*)-furanones.[14] Chunling Fu et al. developed a protocol for the synthesis of 4-iodofuran-2(5*H*)-ones from iodolactonisation of allenoates with molecular iodine.[15]

Sweeney et al. reported the first preparation of 3,4-bistributylstannyl 2(5*H*)-furanones by reacting TBS as well as THP protected butynoate with hexabutylditin in the presence of $PdCl_2(PPh_3)_2$ leading to substituted acrylate intermediate, which upon treating under a variety of conditions yielded desired furanone synthon.[16] More recently Mauro et al. described the construction of furanone system via ring-closing metathesis catalyzed by the first generation Grubbs' catalyst.[17] The above-mentioned methodologies suffer from certain limitations like multistep strategies, use of costly metal catalysts and highly volatile solvents. Thus, in view of these shortcomings there is need to develop mild and environmentally benign methodology to synthesize furanones, by replacing organic solvents with water using a recyclable activator as a part of green chemical approach.

Presently organic reactions in aqueous phase have attracted attention because of the added advantages of water as an environmentally benign and economically affordable solvent. However the fundamental problem in performing the reaction in water is that many organic substrates are hydrophobic and insoluble in water. In continuation of our efforts towards developing biomimetic approaches,[18] through supramolecular catalysis and also to overcome the drawbacks of the existing methodologies for the synthesis of furanones, we report herein, the synthesis of furanones in presence of β-cyclodextrin, as recyclable supramolecular catalyst.

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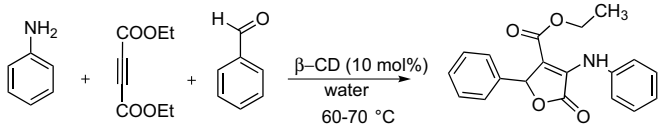
2. Results and discussion

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities. They are torus-like macro rings consisting of six (α-CD), seven (β-CD), eight (γ-CD) 1,4-linked α-D-glucopyranose units. Cyclodextrins and modified cyclodextrins have attracted much attention as aqueous based hosts for inclusion complex phenomenon with a wide variety of guests. Inclusion complex formation occurs as a result of interaction between hydrophobic cavity of CD and hydrophobic portion of guest. These bind the substrates selectively and catalyze the chemical reactions by supramolecular catalysis involving reversible formation of host–guest complex with the substrate by non-covalent bonding as seen in the enzyme complexation process. These features of CDs attracted us to investigate reactions, under biomimetic conditions.

In general, model reaction was carried by in situ formation of β-cyclodextrin complex of aniline in water at 50 °C, followed by successive addition of diethylacetylenedicarboxylate and benzaldehyde while stirring at 60–70 °C to yield corresponding 3,4,5-substituted furan-2(5*H*)-one in almost quantitative yield (Scheme 1) (Table 2, entry 1, 85%) after 12 h. Controlled reaction in water as well as in neat indicated no product formation, even after prolonged reaction times (24–30 h). Next, the scope of this novel transformation to construct 3,4,5-substituted furan-2(5*H*)-one



Scheme 1.

derivatives with various substituted anilines and substituted aldehydes was evaluated by keeping diethylacetylenedicaboxylate as a common substrate (Table 2). In general, all the reactions were very clean, and the 3,4,5-substituted furan-2(5*H*)-one derivatives were obtained in high yields with good amount of catalyst recovery. The results showed that the substitution group played a major role in governing the reactivity of the substrate as well as product yield. The reaction with electron donating group on aniline gave good yield (Table 2, entry 10, 88%), while with electron withdrawing groups, such as *para*-chloro and *para*-fluoro (Table 2, entries11 and 12), yields decreased due to electronic factors. With aliphatic amines such as benzylamines and *n*-alkylamines the reaction was very sluggish. All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectrometry. The catalytic activity of the β-CD was established by the fact that no lactone formation was observed in the absence ofβ-cyclodextrin even after longer reaction times. The evidence for the formation of 3,4,5-substituted furan-2(5*H*)-ones in presence of β-CD was supported by ^{1}H NMR studies of inclusion complex between aniline and β-CD. The hydrophobic environment of β-CD facilitates the formation of lactones via inclusion complex of aniline/diethylethylenedicarboxylate carbanion stabilized by the primary and secondary –OH groups of β-CD, which further reacts with aldehyde as indicated in Fig. 1.

Table 1
Recyclability of β-CD

Cycles	Yield (%)	Catalyst recovered (%)
Native	85	93
1	83	91
2	80	89
3	80	86

All reactions were carried out with a catalytic amount (10 mol %) of β-CD in water. But for NMR studies inclusion complex was prepared by taking β-CD and aniline in 1:1 ratio. A comparison of ^{1}H NMR spectra of aniline, β-CD and β-CD/aniline complex was done (Table 3).

In the ^{1}H NMR spectrum (in DMSO-d_6) of aniline, the aromatic protons from *ortho* position appear as a doublet at 6.61 ppm (J=8.2 Hz), while *meta* and *para* protons appear as triplets at 7.06 (J=7.4 Hz) and 6.55 (J=6.7 Hz), respectively. Amine protons in aniline appear as singlet at 5.05 ppm. The ^{1}H NMR spectrum of β-CD/aniline inclusion complex shows upfield shift of aromatic protons as well as amine protons of aniline. This upfield shift of aniline protons can be due to the inclusion of aniline inside β-CD cavity. Apart from the upfield shift of aniline protons due to the incorporation inside the β-CD cavity, the protons located in the β-CD cavity (C^3–H and C^5–H) are also shifted upfield due to magnetic anisotropy caused by the guest (aniline) molecule.[19] β-CD was recovered and reused. After the reaction, the reaction mass was cooled to room temperature and β-CD was filtered and washed with ice-cold water and dried. The recovered β-CD was further used with the same substrates as a catalyst and checked for the yields and catalytic activity of recovered catalyst (β-CD). As shown in Table 1, the yields of 3,4,5-substituted furan-2(5*H*)-one after two to three recycles were almost same (Table 1).

3. Conclusion

In conclusion we have demonstrated an elegant and simple method for the synthesis of furanone synthon in one pot by using β-cyclodextrin as a reusable catalyst and water as a reaction medium. This methodology also overcomes the formation of unwanted products, lower yields, high temperature etc., thus making an ecofriendly procedure, which will be a useful addition to green chemistry.

4. Experimental

4.1. General

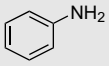
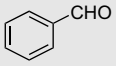
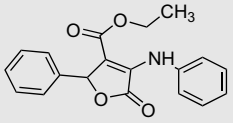
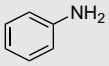
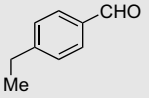
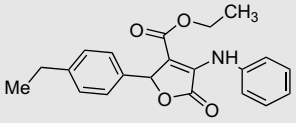
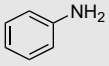
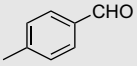
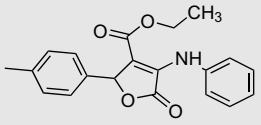
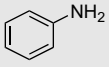
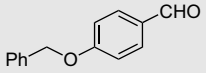
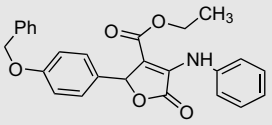
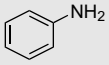
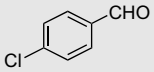
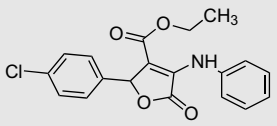
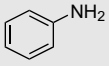
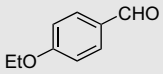
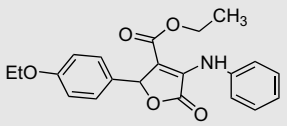
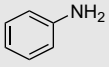
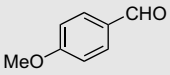
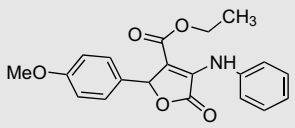
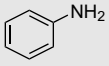
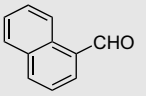
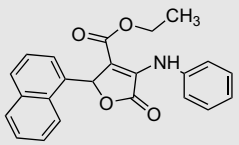
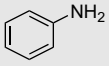
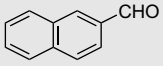
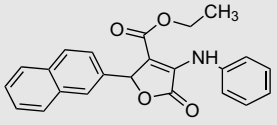
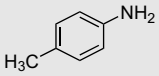
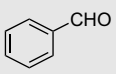
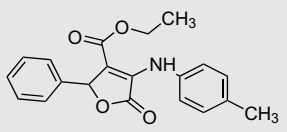
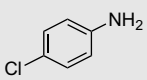
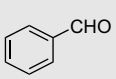
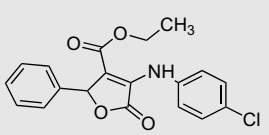
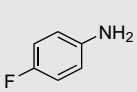
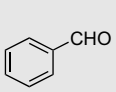
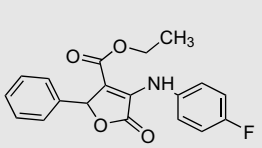
^{1}H NMR spectra were recorded on Brucker's Gemini-200 MHz or Varian's Avance-300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded on Finnigan MAT 1020 mass spectrometer operating at 70 eV. IR spectra were recorded using Thermo Nicolet Nexus 670 FT-IR spectrometer. Elemental analyses were carried out by using Elementar-Vario MICRO Cube model available at IICT, Hyderabad.

4.2. General procedure for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones

4.2.1. Typical example: synthesis of ethyl 2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)furan-3-carboxylate (Table 2, entry 1)

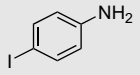
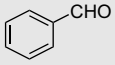
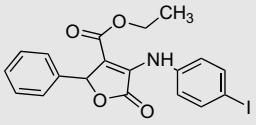
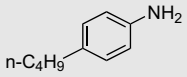
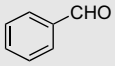
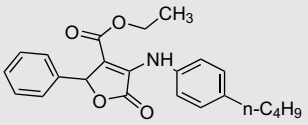
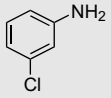
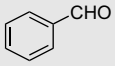
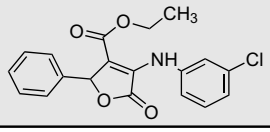
β-Cyclodextrin (0.113 g, 0.1 mmol (10 mol %)) was dissolved in water (15 mL). To this clear solution, aniline (0.093 g, 1.0 mmol) was added and stirred for 2 min, and then diethylacetylenedicarboxylate (0.170 g, 1.0 mmol) followed by benzaldehyde (0.106 g, 1.0 mmol) were added, after which the reaction mixture was heated at 60–70 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to the room temperature and β-CD was filtered, the aqueous phase was extracted with ethyl acetate (3×10 mL). The organic layers were washed with water, saturated brine solution and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the

Table 2
β-CD catalyzed synthesis of 3,4,5-substituted furan-2(5*H*)-ones

Entry	Anilines	Aldehydes	Products	Time (h)	Yield[a] (%)
1				12	85
2				13.5	81
3				13.5	81
4				14	81
5				13	80
6				12	81
7				15	80
8				16	78
9				15	80
10				12	88
11				13	80
12				12.5	79

(*continued on next page*)

Table 2 (*continued*)

Entry	Anilines	Aldehydes	Products	Time (h)	Yield[a] (%)
13				13	80
14				12	82
15				14	83

[a] Isolated yields.

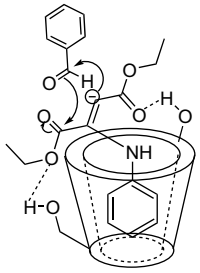


Figure 1. Plausible mechanistic pathway.

resulting crude product was purified by column chromatography by using ethyl acetate and hexane (7:3) as eluent to give the title compound (Table 2, entry 1) (0.274 g, 85%). Found: C, 70.49; H, 5.0; N, 4.29. $C_{19}H_{17}NO_4$ requires C, 70.58; H, 5.3; N, 4.33%. R_f (70% EtOAc/*n*-hexane) 0.25; ν_{max} (KBr) 3292, 1716, 1684, 1655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.19 (t, 3H, *J*=6.6 Hz, CH_2CH_3), 4.16 (q, 2H, *J*=7.3 Hz, OCH_2), 5.69 (s, 1H, benzylic), 7.03–7.32 (m, 5H, arom.), 7.45 (m, 5H, arom.); δ_C (300 MHz, $CDCl_3$) 13.9, 61.2, 113.1, 122.2, 125.8, 127.5, 128.5, 128.9, 135.0, 136.2, 156.3, 162.9, 165.1; HRMS *m*/*z* calcd for $C_{19}H_{17}NO_4$ ($[M+H]^+$): 324.1250, found 324.1235.

4.2.2. Ethyl 2-(4-ethylphenyl)-2,5-dihydro-5-oxo-4-(phenylamino)furan-3-carboxylate (**2**)

Yield 0.28 g (81%). Found: C, 71.72; H, 6.12; N, 3.92. $C_{21}H_{21}NO_4$ requires C, 71.78; H, 6.02; N, 3.99%. R_f (70% EtOAc/*n*-hexane) 0.22; ν_{max} (KBr) 3292, 1716, 1684, 1655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13–1.33 (m, 6H, $2CH_3$), 2.54 (q, 2H, *J*=8.0 Hz, CH_2), 4.18 (q, 2H, *J*=7.3 Hz, OCH_2), 5.65 (s, 1H, benzylic), 6.99–7.11 (m, 5H, arom.), 7.19–7.27 (m, 2H, arom.), 7.45 (d, *J*=8.0 Hz, 2H, arom.); δ_C (300 MHz, $CDCl_3$) 13.9, 15.1, 28.3, 61.2, 96.0, 122.1, 125.6, 127.3, 127.9, 128.8, 132.4, 137.1, 144.3, 156.2, 163.4, 165.0; MS *m*/*z* (ESI): 374 ($[M+Na]^+$).

Table 3
400 MHz ^1H chemical shifts of aniline and β-CD protons in free and complexed state[a]

Protons	Aniline	β-CD	β-CD/aniline complex	Δδ
H-*ortho*	2646		2612	34
H-*meta*	2826		2800	26
H-*para*	2621		2594	27
$-NH_2$	2015		1932	83
C_1		1926	1980	−54
C_2		1346	1339	7
C_3		1464	1461	−4
C_4		1327	1321	−6
C_5		1442	1444	−2
C_6		1448	1452	−4
O_2		2292	2293	−1
O_3		2272	2273	−1
O_6		1796	1793	3

[a] Chemical shifts expressed in hertz with reference to DMSO-d_6.

4.2.3. Ethyl 2,5-dihydro-5-oxo-4-(phenylamino)-2-p-tolylfuran-3-carboxylate (**3**)

Yield 0.27 g (81%). Found: C, 71.12; H, 5.59; N, 4.21. $C_{20}H_{19}NO_4$ requires C, 71.20; H, 5.68; N, 4.15%. R_f (70% EtOAc/*n*-hexane) 0.25; ν_{max} (KBr) 3397, 2922, 1718, 1683, 1586, 1492, 1244 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (t, 3H, *J*=8.0 Hz, CH_2CH_3), 2.24 (s, 3H, CH_3), 4.11 (q, 2H, *J*=7.3 Hz, OCH_2), 5.61 (s, 1H, benzylic), 6.98–7.34 (m, 9H, arom.); δ_C (300 MHz, $CDCl_3$) 13.9, 20.8, 61.9, 122.2, 127.6, 128.0, 128.2, 129.3, 134.0, 135.2, 165.9, 169.1; MS *m*/*z* (ESI): 360 ($[M+Na]^+$).

4.2.4. Ethyl 2-(4-(benzyloxy)phenyl)-2,5-dihydro-5-oxo-4-phenylamino)furan-3-carboxylate (**4**)

Yield 0.34 g (81%). Found: C, 71.03; H, 5.49; N, 4.19. $C_{26}H_{23}NO_5$ requires C, 71.71; H, 5.40; N, 3.26%. R_f (70% EtOAc/*n*-hexane) 0.21; ν_{max} (KBr) 3159, 2922, 1719, 1684, 1548, 1496, 1266 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (t, 3H, *J*=6.0 Hz, CH_2CH_3), 4.11 (q, 2H, *J*=6.7 Hz, OCH_2), 4.91 (s, 2H, $OCH_2C_6H_5$), 6.77 (s, 1H, benzylic), 7.07–7.46 (m, 14H, arom.); δ_C (300 MHz, $CDCl_3$) 14.7, 61.8, 70.2,111.3, 114.5, 118.2, 122.5, 126.2, 127.0,127.5,128.9, 132.3, 139.2, 144.9, 160.3, 166.9, 169.2; MS *m*/*z* (ESI): 452 ($[M+Na]^+$).

4.2.5. Ethyl 2-(4-chlorophenyl)-2,5-dihydro-5-oxo-4-(phenylamino)furan-3-carboxylate (**5**)

Yield 0.28 g (80%).Found: C, 63.71; H, 4.46; N, 3.93. $C_{19}H_{16}ClNO_4$ requires C, 63.78; H, 4.51; N, 3.91%. R_f (70% EtOAc/*n*-hexane) 0.25; ν_{max} (KBr) 3286, 2924, 1680, 1539, 1238 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.19 (t, 3H, *J*=6.7 Hz, CH_2CH_3), 4.20 (q, 2H, *J*=6.7 Hz, OCH_2), 5.71 (s, 1H, benzylic), 7.11–7.45 (m, 9H, arom.); δ_C (300 MHz, $CDCl_3$) 14.0, 60.8, 114.6, 122.2, 126.0, 129.0, 133.8, 134.2, 135.9, 137.2, 146.3, 165.0, 169.1; MS *m*/*z* (ESI): 380 ($[M+Na]^+$).

4.2.6. Ethyl 2-(4-ethoxyphenyl)-2,5-dihydro-5-oxo-4-(phenylamino)furan-3-carboxylate (**6**)

Yield 0.29 g (81%). Found: C, 68.62; H, 5.71; N, 3.80. $C_{21}H_{21}NO_5$ requires C, 68.65; H, 5.76; N, 3.81%. R_f (70% EtOAc/*n*-hexane) 0.20; ν_{max} (KBr) 3443, 2924, 1681, 1595, 1240 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.07 (t, 3H, *J*=6.7 Hz, CH_2CH_3), 1.30 (t, 3H, *J*=6.7 Hz, CH_2CH_3), 4.10 (q, 2H, *J*=6.7 Hz, OCH_2), 4.18 (q, 2H, *J*=6.7 Hz, OCH_2), 6.01 (s, 1H,

benzylic), 6.89 (d, 2H, J=7.5 Hz, arom.), 7.04 (t, 1H, J=6.7 Hz, arom.), 7.21–7.38 (m, 2H, arom.), 7.49–7.52 (m, 2H, arom.), 7.66 (d, 2H, J=7.5 Hz, arom.); δ_C (300 MHz, $CDCl_3$) 14.3,14.8, 61.1, 64.8, 114.1, 116.2, 119.5, 125.6, 126.3, 126.9, 127.9, 132.2, 144.9, 145.2, 156.1, 164.9, 169.7; MS m/z (ESI): 390 ($[M+Na]^+$).

4.2.7. Ethyl 2,5-dihydro-2-(4-methoxyphenyl)-5-oxo-4-(phenylamino)furan-3-carboxylate (**7**)

Yield 0.28 g (81%).Found: C, 67.92; H, 5.46; N, 3.91. $C_{20}H_{19}NO_5$ requires C, 67.98; H, 5.42; N, 3.96%. R_f (70% EtOAc/n-hexane) 0.21; ν_{max} (KBr) 3291, 2928, 1719, 1676, 1548, 1496 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.20 (t, 3H, J=6.7 Hz, CH_2CH_3), 3.71 (s, 3H, OCH_3), 4.19 (q, 2H, J=6.7 Hz, OCH_2), 5.63 (s, 1H, benzylic), 6.70 (d, 2H, J=8.3 Hz, arom.), 6.98–7.10 (m, 2H, arom.), 7.21–7.29 (m, 3H, arom.), 7.45 (d, 2H, J=7.5 Hz, arom.); δ_C (300 MHz, $CDCl_3$) 14.3, 55.7, 61.5, 114.6, 124.8, 127.3, 128.9, 141.8, 145.2, 150.6, 167.3, 171.9; MS m/z (ESI): 376 ($[M+Na]^+$).

4.2.8. Ethyl 2,5-dihydro-2-(naphthalen-1-yl)-5-oxo-4-(phenylamino)furan-3-carboxylate (**8**)

Yield 0.29 g (78%).Found: C, 73.95; H, 5.10; N, 3.74. $C_{23}H_{19}NO_4$ requires C, 73.98; H, 5.13; N, 3.75%. R_f (70% EtOAc/n-hexane) 0.25; ν_{max} (KBr) 3239, 2936, 1720, 1678, 1547, 1496 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.25 (t, 3H, J=5.8 Hz, CH_2CH_3), 3.87 (br s, NH), 4.09 (q, 2H, J=6.6 Hz, OCH_2), 6.63 (s, 1H, benzylic), 6.93–7.82 (m, 12H, arom.), 8.35 (d, 2H, J=8.0 Hz, arom.); δ_C (200 MHz, $CDCl_3$) 13.3, 60.9, 121.1, 122.7, 123.4, 125.4, 126.3,128.8,128.9,132.2, 133.8, 136.4, 144.1, 165.7, 169.7; MS m/z (ESI): 396 ($[M+Na]^+$).

4.2.9. Ethyl 2,5-dihydro-2-(naphthalen-3-yl)-5-oxo-4-(phenylamino)furan-3-carboxylate (**9**)

Yield 0.29 g (80%). Found: C, 73.96; H, 5.14; N, 3.73. $C_{23}H_{19}NO_4$ requires C, 73.98; H, 5.13; N, 3.75%. R_f (70% EtOAc/n-hexane) 0.25; ν_{max} (KBr) 3236, 2931, 1723, 1670, 1621, 1490 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.23 (t, 3H, J=6.9 Hz, CH_2CH_3), 4.12 (q, 2H, J=7.1 Hz, OCH_2), 5.84 (s, 1H, benzylic), 6.97–7.75 (m, 12H, arom.); δ_C (300 MHz, $CDCl_3$) 14.5, 61.4, 116.8, 122.5, 126.7, 127.3, 129.3, 131.2, 133.7, 135.1, 144.3, 144.9, 166.7, 171.3; MS m/z (ESI): 396 ($[M+Na]^+$).

4.2.10. Ethyl 4-(p-tolylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**10**)

Yield 0.29 g (88%).Found: C, 71.18; H, 5.63; N, 4.09. $C_{20}H_{19}NO_4$ requires C, 71.20; H, 5.68; N, 4.15%. R_f (70% EtOAc/n-hexane) 0.25; ν_{max} (KBr) 3297, 1712, 1687, 1642 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.27 (t, 3H, J=6.6 Hz, CH_2CH_3), 2.24 (s, 3H, CH_3), 4.11 (q, 2H, J=7.3 Hz, OCH_2), 5.61 (s, 1H, benzylic), 6.98–7.34 (m, 9H, arom.); δ_C (200 MHz, $CDCl_3$) 13.9, 20.8, 61.9, 122.2, 127.6, 128.0, 128.2, 129.3, 133.9, 135.2, 165.5, 171.3; MS m/z (ESI): 360 ($[M+Na]^+$).

4.2.11. Ethyl 4-(4-chlorophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**11**)

Yield 0.28 g (80%).Found: C, 63.76; H, 4.51; N, 3.89. $C_{19}H_{16}ClNO_4$ requires C, 63.78; H, 4.51; N, 3.91%. R_f (70% EtOAc/n-hexane) 0.25; ν_{max} (KBr) 3293, 2918, 1681, 1586, 1239 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.20 (t, 3H, J=6.9 Hz, CH_2CH_3), 4.23 (q, 2H, J=8.0 Hz, OCH_2), 5.71 (s, 1H, benzylic), 7.29–7.57 (m, 9H, arom.); δ_C (300 MHz, $CDCl_3$) 14.2, 61.7, 114.3, 115.3, 117.4,123.9, 126.3, 127.3, 128.3, 129.2, 140.3, 145.3, 167.8, 171.4; MS m/z (ESI): 380 ($[M+Na]^+$).

4.2.12. Ethyl 4-(4-fluorophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**12**)

Yield 0.26 g (79%). Found: C, 66.83; H, 4.74; N, 4.08. $C_{19}H_{16}FNO_4$ requires C, 66.86; H, 4.72; N, 4.10%. R_f (70% EtOAc/n-hexane) 0.24; ν_{max} (KBr) 3392, 2935, 1709, 1680, 1584, 1486 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (t, 3H, J=7.2 Hz, CH_2CH_3), 4.10 (q, 2H, J=7.1 Hz, OCH_2), 5.58 (s, 1H, benzylic), 6.89–7.39 (m, 9H, arom.); δ_C (300 MHz, $CDCl_3$) 14.4, 61.9, 116.1, 117.3, 123.5, 127.6, 132.9, 140.3, 145.1, 153.6, 167.4, 170.1; MS m/z (ESI): 364 ($[M+Na]^+$).

4.2.13. Ethyl 4-(4-iodophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**13**)

Yield 0.35 g (80%). Found: C, 50.78; H, 3.7; N, 3.14. $C_{19}H_{16}INO_4$ requires C, 50.80; H, 3.59; N, 3.12%. R_f (70% EtOAc/n-hexane) 0.23; ν_{max} (KBr) 3289, 2922, 1724, 1679, 1651 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.25 (t, 3H, J=7.5 Hz, CH_2CH_3), 4.11 (q, 2H, J=6.7 Hz, OCH_2), 5.57 (s, 1H, benzylic), 7.16–7.47 (m, 9H, arom.); δ_C (200 MHz, $CDCl_3$) 14.1, 61.9, 80.7, 114.9, 117.6, 123.4, 125.8, 127.5, 128.1, 129.7, 134.8, 136.5, 137.4, 141.2, 149.7, 166.3, 169.7; MS m/z (ESI): 472 ($[M+Na]^+$).

4.2.14. Ethyl 4-(4-butylphenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**14**)

Yield 0.31 g (82%).Found: C, 72.74; H, 6.62; N, 3.61. $C_{23}H_{25}NO_4$ C, 72.80; H, 6.64; N, 3.69%. R_f (70% EtOAc/n-hexane) 0.25; ν_{max} (KBr) 3321, 2923, 2853, 1680, 1593, 1238 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.87 (t, 3H, J=6.7 Hz, $(CH_2)_3CH_3$), 1.26 (m, 5H, $(CH_2)_2CH_2CH_3$+OCH_2CH_3), 1.49 (m,2H, $CH_2CH_2CH_2CH_3$), 2.47 (t, 2H, J=6.7 Hz, $CH_2(CH_2)_2CH_3$), 4.13 (q, 2H, J=6.7 Hz, OCH_2), 5.67 (s, 1H, benzylic), 7.02–7.35 (m, 9H, arom.); δ_C (300 MHz, $CDCl_3$) 14.1 22.6, 34.3, 35.7, 61.6, 114.6, 118.9, 126.8, 127.4, 129.6, 132.3, 134.2, 140.1, 145.2, 147.3,165.9, 170.6; MS m/z (ESI): 402 ($[M+Na]^+$).

4.2.15. Ethyl 4-(3-chlorophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**15**)

Yield 0.29 g (83%).Found: C, 63.74; H, 4.48; N, 3.90. $C_{19}H_{16}ClNO_4$ requires C, 63.78; H, 4.51; N, 3.91%. R_f (70% EtOAc/n-hexane) 0.25; ν_{max} (KBr) 3393, 2919, 1686, 1593, 1240 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (t, 3H, J=7.0 Hz, CH_2CH_3), 4.05 (q, 2H, J=7.0 Hz, OCH_2), 5.72 (s, 1H, benzylic), 6.98–7.35 (m, 5H, arom.), 7.68–7.71 (m, 4H, arom.); δ_C (300 MHz, $CDCl_3$) 14.4, 61.2, 114.3, 115.6, 117.8, 123.6, 126.3, 127.4, 128.9, 135.2, 140.3, 145.1, 167.3, 170.1; MS m/z (ESI): 380 ($[M+Na]^+$).

4.3. Preparation of β-CD/aniline inclusion complex

β-CD (1.135 g, 1 mmol) was dissolved in water (15 mL) by warming at 60 °C to get clear solution Aniline (0.093 g, 1 mmol) was added drop wise, the mixture was allowed to stir for 30 min at 60 °C and then cooled to room temperature. It was further cooled overnight in refrigerator. The obtained solid was filtered, dried and analyzed by ^1H NMR spectroscopy.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.081.

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