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ORIGINAL ARTICLE

# Inclusion complex of Isatoic anhydride with β-cyclodextrin and supramolecular one-pot synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones in aqueous media

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**Abstract** The inclusion complex of isatoic anhydride with β-cyclodextrin was formed as a result of intermolecular interaction between isatoic anhydride with β-CD. The inclusion complex was confirmed by IR spectroscopy, X-ray diffraction and DSC studies. From application of complex, herein we have described a simple and efficient protocol for synthesis of 2, 3-dihydroquinazoline-4(1*H*)-one derivatives by one pot condensation of isatoic anhydride, ammonium acetate or amine and aldehyde using β-CD as a supramolecular catalyst in aqueous media.

**Keywords** β-Cyclodextrin · Isatoic anhydride · Inclusion complex · IR spectroscopy · X-ray diffraction · Differential scanning calorimetry

## Introduction

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavity, which binds substrate selectively and catalyze chemical reactions with high selectivity. They catalyze reaction by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding as seen in enzymes [1, 2]. β-cyclodextrin is a cyclic heptamer composed of seven glucose units jointed head to tail by α 1,4-links. It is widely accepted that the binding forces involved in the inclusion complex formation are Vander Waals interactions, hydrophobic interactions between guest molecules and β-CD [3]. Because of such behavior β-CD is used as catalyst for varieties of organic reactions [4].

Isatoic anhydride is used for synthesis of racemic paraensine [5], its reaction with amine and amides [6] and in synthesis of diverse heterocycles [7]. 2,3-dihydroquinazolinone derivatives are an important class of heterocycles which shows a wide range of biological, antibiotic, antipyretic, analgesic, diuretic, antihistamine, antidepressant and vascodialating activities [8, 9]. The quinazolinone moiety is a building block for various naturally occurring alkaloids [10] such as glycosamine [11], luotonin [12] and deoxyvasicinone [13]. In addition 2,3-dihydroquinazolinones have been shown to act as potent tubulin inhibitors with the impressive antiproliferatrive activity against several human cancer cell lines [14].

Recently a number of classical methods for synthesis of 2,3-dihydroquinazolin-4(1*H*)-one have been reported in literature involving use of Ethylene diamine diacetate [15], silica sulfuric acid [16], ionic liquid/water [17], p-TsOH [18], $KAl(SO_4)_2{\cdot}12H_2O$ [19], gallium triflate [20], $[bimm]BF_4$ [21], Montmorillonite K-10 [22], $Al(H_2PO_4)_3$ [23], condensation of 2-aminobenzamides with aldehyde in presence of p-TsOH/DDQ [24], $CuCl_2$ [25], chiral phosphoric acid [26, 27], iodine [28], nano $Fe_3O_4$ [29], use of p-toluenesulphonic acid-paraformaldehyde copolymer [30], silica bonded N-propyl sulfamic acid [31], etc. However most of the reported methods involve the use of organic solvents, metal catalyst with tedious procedure and low yields of product. Therefore the development of simple, environmentally benign, high yielding and clean synthesis of 2,3-dihydroquinozolin-4(1*H*)-ones is demand. Water is safe, economical and environmentally benign

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solvent [32]. In connection with our previous work with cyclodextrin [33] and considering the application of inclusion complex of isatoic anhydride with $\beta$-CD [34], herein we have developed a simple methodology for formation of 2, 3-dihydroquinazolin-4(1*H*)-ones in aqueous media.

## Experimental

### Material and chemicals

$\beta$-CD purchased from Aldrich, isatoic anhydride, ammonium acetate, amines and aldehydes (analytical grade) purchased from Spectrochem and were used without purification.

### Methods and instruments

IR spectra were recorded in frequency range from 4000 to 400 cm-1 with IR affinity model-I (Schimadzu) using KBr. Powder X-ray diffraction patterns were obtained using a Philips X'pert MPD System. Differential scanning calorimetry (DSC) analyses were carried out in the temperature range from 30 to 500 °C in a stream of nitrogen atmosphere on DSC-50 thermal analyzer (Shimadzu, Japan). During experiments, aluminium crucibles were used. The heating rate was 10 °C/min, and the flow rate of nitrogen atmosphere was 50 ml/min. Both $^{1}$H NMR and $^{13}$C NMR were recorded on a Bruker Avance- II spectrophotometer operating at 500 MHz.

### Preparation of inclusion complex of isatoic anhydride with $\beta$-CD

The complex between isatoic anhydride and $\beta$-CD is prepared by coprecipitation method [35] from aqueous ethanol solution. To the clear solution of $\beta$-CD (1 mmol) in 25 mL of $H_2O$, isatoic anhydride (1 mmol) previously dissolved in ethanol added dropwise with stirring at room temperature and the resulting mixture allow to stir for 12 h. The white precipited obtained was filtered, washed gently with water and dried.

### General procedure for synthesis of 2,3-dihydroquinazolin-4(1*H*)-one

To a stir solution of $\beta$-CD (1 mmol) in 10 mL of $H_2O$, isatoic anhydride (5 mmol) previously dissolved in ethanol added dropwise and the resulting mixture was allowed to stir for 15 min. Then ammonium acetate (6 mmol) or amine (5 mmol) and aldehyde (5 mmol) (in case of solid previously dissolved in ethanol) added dropwise and reaction refluxed with stirring for appropriate time till reaction complete. The progress of reaction is monitored with TLC by extracting reaction mass in ethyl acetate. After completion of reaction, the reaction was cool and extracted with dichloromethane (10 mL). The aqueous layer washed thrice with dichloromethane (3 × 10 mL). The collected organic layer dried with anhydrous $Na_2SO_4$, evaporated in rotaevaporator leads to crude product which purified by recrystalization in ethanol. To the aqueous layer acetone added dropwise with stirring till white precipited formed, cool at lower temperature, filtered, washed with cold water and acetone, dried and recycled. All synthesized compounds have been characterized by IR, $^{1}$H NMR, $^{13}$C NMR and mass spectroscopy and compare with literature data.

## Result and discussion

The complex of isatoic anhydride and $\beta$-CD is studied by various physical methods. The evidence for association of isatoic anhydride and cyclodextrin provided by A. Kumar and et al. [34] by $^{1}$H NMR spectroscopy in which there is upfield shift of H-3 (0.034 ppm) and H-5 (0.058 ppm) of cyclodextrin in complex as compared to uncomplex $\beta$-CD indicating the formation of complex. Herein, we have studied IR, XRD and DSC of complex.

### Complex formation studied by IR spectroscopy

The formation of inclusion complex of $\beta$-CD and guest substances is accompanied by changes in their IR spectra as compared with individual components [35, 36]. Figure 1 shows the IR spectra of $\beta$-CD, isatoic anhydride, inclusion complex and physical mixture in solid state. Significance differences in CH and CO vibration modes were found. Peaks are not only shifted after complex formation but the shapes of peaks are also changed. The aliphatic CH of cyclodextrin 2,926 $cm^{-1}$ and in individual isatoic anhydride 1,728.22 $cm^{-1}$ shifted to 2,929.87 $cm^{-1}$ and 1,730.15 $cm^{-1}$ respectively. This is not observed in physical mixture suggesting an interaction between isatoic anhydride and $\beta$-CD. The absorption band at 767.61 $cm^{-1}$ of disubstituted benzene ring in individual isatoic anhydride shifted to 765.74 $cm^{-1}$ in inclusion complex, which was unaffected in physical mixture indicating phenyl ring interaction with $\beta$-CD.

### Complex formation studied by powder X-ray analysis

True inclusion complexes have its diffraction pattern altered from those of pure components [37]. The powder X-ray pattern for individual components, complex and

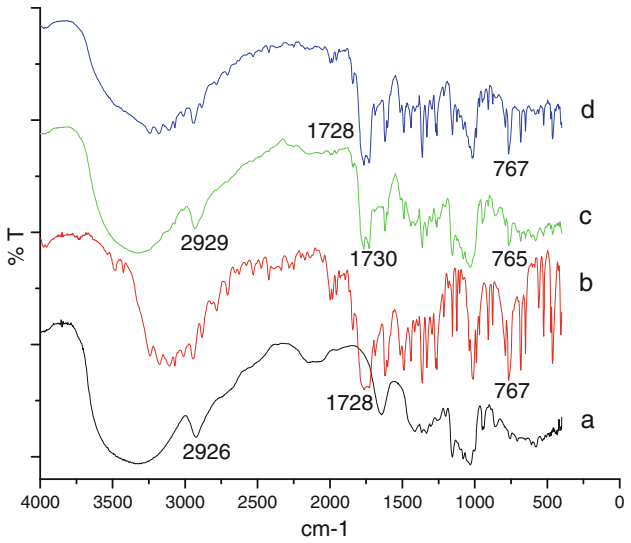



**Fig. 1** FTIR of **a** $\beta$-CD, **b** Isatoic anhydride, **c** $\beta$-CD-isatoic anhydride complex and **d** physical mixture

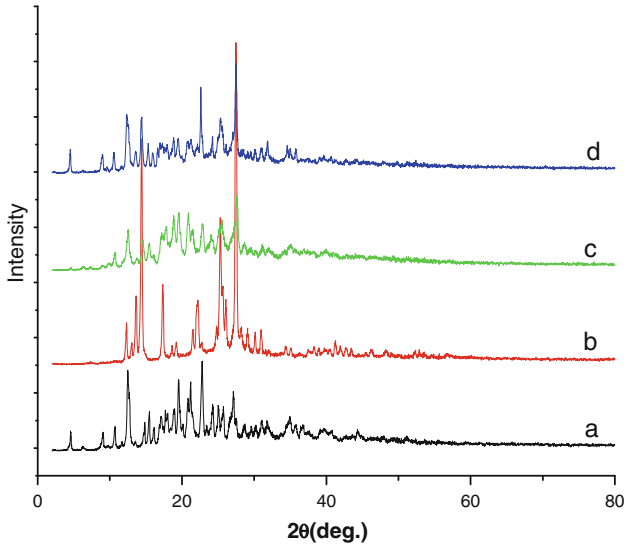



**Fig. 2** Powder X-ray diffraction patterns of **a** $\beta$-CD, **b** Isatoic anhydride, **c** $\beta$-CD-isatoic anhydride complex and **d** physical mixture

physical mixture is shown in Fig. 2. The diffraction pattern of complex was found to be different than diffraction pattern of pure $\beta$-CD and isatoic anhydride. Comparing the pattern for $\beta$-CD-isatoic anhydride complex with that of physical mixture reveals mark differences. In complex the new peaks were found and shift in peak position also found where as the physical mixture has the peaks which were superimposition of two individuals. Besides, it is also important to remarks that the peak intensities in complex were decreased with respect to the spectrum of $\beta$-CD, indicating the lower degree of crystallinity for the complex.

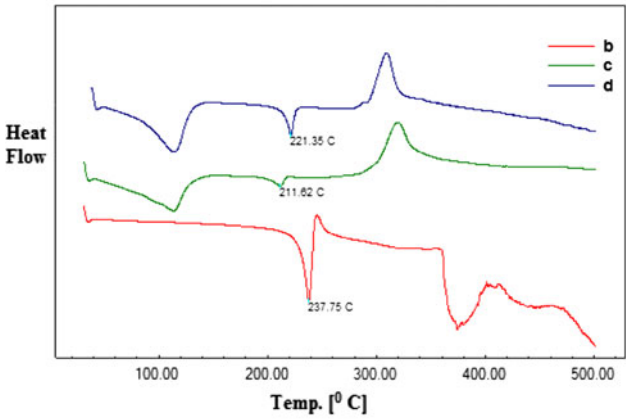


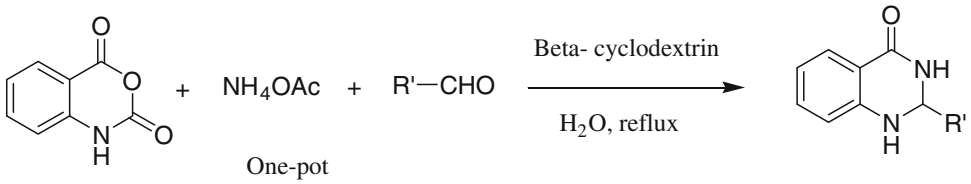

**Fig. 3** DSC of **b** Isatoic anhydride, **c** $\beta$-CD-isatoic anhydride complex and **d** physical mixture

## Complex formation studied by DSC

The DSC thermogram for isatoic anhydride, $\beta$-CD-isatoic anhydride complex and physical mixture is represented in Fig. 3. The thermogram of isatoic anhydride shows characteristic endothermic peak at 237.75 °C corresponding to its fussion peak. As regards with the analysis of $\beta$-CD-isatoic anhydride complex, the peak of isatoic anhydride found at 211.62 °C. Whereas in physical mixture, the peak of isatoic anhydride was found at 221.35 °C with less effect as compare to true inclusion complex clearly indicating an interaction between $\beta$-CD and isatoic anhydride. This lowering of melting of isatoic anhydride in complex state is due to variation of intermolecular forces amongst isatoic anhydride by $\beta$-CD. The second endothermic peak in isatoic anhydride occurs at 374.41 °C related to its decomposition. It disappears in 'c' and 'd' may be due to alteration with $\beta$-CD. The endothermic peak of $\beta$-CD-isatoic anhydride complex around 105-113 °C is associated to crystal water losses from $\beta$-CD. Owing to the association between isatoic anhydride and $\beta$-CD, the exothermic peak of $\beta$-CD in complex shifted to higher temperature of 319.72 °C than in physical mixture occurs at 309.43 °C. Alteration in these thermal properties due to intermolecular interactions supports the formation of inclusion complex.

Water is safe, economical and environmentally benign solvent; however the fundamental problem in with performing reactions in water is that many organic substrates are hydrophobic and insoluble in water. This difficulty is solved by inclusion formation characteristic of $\beta$-CD that enhances the solubility of guest molecule in water. By taking the advantage of inclusion complex ability of $\beta$-CD with isatoic anhydride we report the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from reaction of isatoic anhydride, ammonium acetate or amine and aldehyde in aqueous media (Scheme 1, 2). For optimization the reaction has been carried

**Scheme 1** $\beta$-CD catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-one from isatoic anhydride, ammonium acetate and aldehyde




**Scheme 2** $\beta$-CD catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-one from isatoic anhydride, primary amine and aldehyde

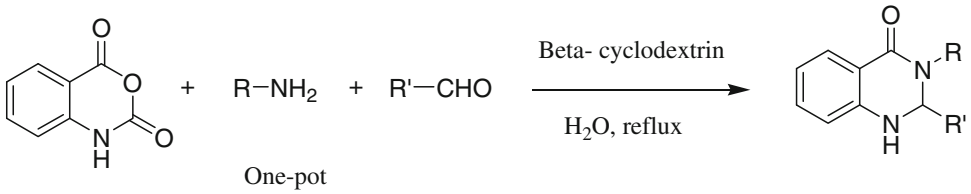



**Table 1** Formation of 2,3-dihydroquinazoline-4-one under different reaction condition

| Entry | $\beta$-CD (mmol) | Solvent | Condition | Yield (%)[a] |
|---|---|---|---|---|
| 1 | – | $H_2O$ | Reflux, 6 h | 60 |
| 2 | 0.1 | $H_2O$ | Reflux, 2 h | 82 |
| 3 | 0.2 | $H_2O$ | Reflux, 2 h | 86 |
| 4 | 0.4 | $H_2O$ | Reflux, 2.5 h | 85 |
| 5 | 0.6 | $H_2O$ | Reflux, 2.5 h | 85 |
| 6 | 0.8 | $H_2O$ | Reflux, 5 h | 83 |
| 7 | 1 | $H_2O$ | Reflux, 5 h | 85 |
| 8 | 0.2 | $H_2O$ | 27 °C, 12 h | – |
| 9 | 0.2 | $H_2O$ | 60 °C, 6 h | 80 |
| 10 | 0.2 | $H_2O$ | 80 °C, 4.5 h | 82 |
| 11 | 0.2 | Ethanol | Reflux, 4 h | 76 |
| 12 | 0.2 | DMF | Reflux, 4 h | 62 |
| 13 | 0.2 | DMSO | 100 °C, 6 h | 52 |
| 14 | 0.2 | Acetonitrile | Reflux, 6 h | 30 |
| 15 | 0.2 | DCM | Reflux, 8 h | 32 |

Isatoic anhydride (1 mmol), $NH_4OAc$ (1.2 mmol) and Benzaldehyde (1 mmol), solvent (2 mL)

[a] Isolated yield

**Table 2** $\beta$-Cyclodextrin catalyzed one-pot synthesis of 2,3-dihydroquinazolinones in water

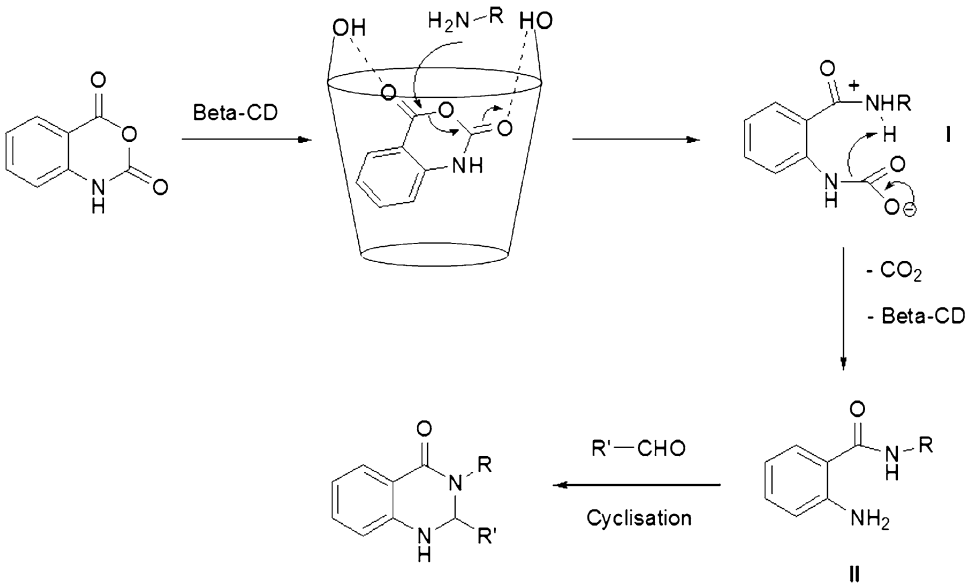
| Entry | Ammonium salt/amine (R) | R′ | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | $NH_4OAc$ | $C_6H_5$ | 2 | 86, 85[b] |
| 2 | $NH_4OAc$ | 3-$NO_2C_6H_4$ | 3 | 85 |
| 3 | $NH_4OAc$ | 2-$ClC_6H_4$ | 2.25 | 92 |
| 4 | $NH_4OAc$ | 3-$BrC_6H_4$ | 1.5 | 87 |
| 5 | $NH_4OAc$ | 4-$CH_3C_6H_4$ | 2.5 | 91 |
| 6 | $NH_4OAc$ | 4-$OCH_3C_6H_4$ | 4 | 90 |
| 7 | $NH_4OAc$ | 3, 4-$(OCH_3)_2C_6H_3$ | 4.5 | 84 |
| 8 | $NH_4OAc$ | 3, 4-$(CH_2O_2)C_6H_3$ | 3.5 | 90 |
| 9 | $C_6H_5$ | $C_6H_5$ | 3 | 84 |
| 10 | $C_6H_5$ | 3-$BrC_6H_4$ | 2.5 | 78 |
| 11 | $C_6H_5$ | 4-$OCH_3C_6H_4$ | 5 | 84 |
| 12 | 4-$BrC_6H_4$ | $C_6H_5$ | 4 | 78 |
| 13 | 4-$C_2H_5C_6H_4$ | $C_6H_5$ | 5 | 88 |
| 14 | $C_2H_5$ | $C_6H_5$ | 1.5 | 87 |
| 15 | $CH_3$ | $C_6H_5$ | 1.5 | 86 |

Isatoic anhydride (5 mmol), $NH_4OAc$ (1.2 mmol) or amine (5 mmol), Benzaldehyde (5 mmol), $\beta$-CD (1 mmol) and $H_2O$ (10 mL)

[a] Isolated yield based on isatoic anhydride; [b] Yield after third recycle

out under various conditions; the results are mentioned in Table 1. The better result was obtained when 0.2 mmol of $\beta$-CD used with short reaction time of 2 h and yield of 86 % (Table 1, entry 3). The other organic solvents like ethanol, DMF, DMSO, acetonitrile and DCM does not show significant results. Increase in amount of catalyst also not show improvement in results. The reaction also performed using other ammonium salts like ammonium carbonate gives 73 % of yield in 3 h where as with ammonium chloride affords only 46 % and with long reaction time of 8 h.

To explore generality and scope of $\beta$-CD as a supramolecular catalyst, additional reaction of isatoic anhydride, ammonium acetate or amines and benzaldehyde were attempted. The result obtain are listed in Table 2. The array of aldehyde bearing either electron donating or electron withdrawing groups on aromatic ring was investigated. The reaction time was found to be short for aliphatic amines with good to moderate yield of product (Table 2, entry 14, 15). The plausible general mechanistic pathway is shown in Scheme 3. First the isatoic anhydride is activated with microenvironment of $\beta$-CD cavity by the formation of hydrogen bonding with carbonyl group followed by nucleophilic attack of amine on the carbonyl group to give intermediate-I. Then decarboxylation resulting into the formation of intermediate-II followed by subsequent cyclisation with aldehyde. $\beta$-CD was recovered in good quantity with 95, 92 and 88 % for first, second and third recycle respectively.




**Scheme 3** Plausible mechanistic pathway for synthesis of 2,3-dihydroquinazolin-4(1*H*)-one

## Conclusion

In conclusion, the complex of isatoic anhydride and $\beta$-CD was prepared by co-precipitation method. The inclusion phenomena of isatoic anhydride with $\beta$-CD were successfully characterized by FTIR, XRD and DSC methods. Based on this, we have developed a simple and ecofriendly protocol for one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in aqueous media using $\beta$-CD as a catalyst. The advantage of procedure includes simplicity of operation, good yields, low cost and recyclability of catalyst.

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