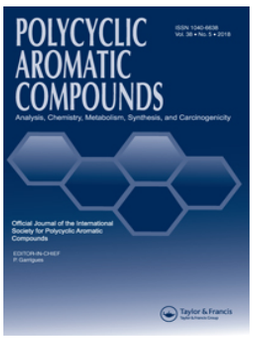

Polycyclic Aromatic Compounds

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Per-6-NH_2-β-CD as Supramolecular Host and Reusable Aminocyclodextrin Promoted Solvent-Free Synthesis of 2-Amino-4*H*-Chromene Scaffolds at Room Temperature

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ABSTRACT

Aminocyclodextrins are homogeneous CD derivatives modified by per substitution at the primary face with amino pendant groups, and this manifests combined hydrophobic and electrostatic binding of guest molecules relative to native CDs. A green multi-component tandem strategy for solvent-free synthesizing 2-amino-4*H*-chromene scaffolds by Knoevenagel-Michael cyclocondensation of aryl aldehydes, malononitrile and resorcinol is reported via supramolecular host and reusable per-6-amino-β-cyclodextrin at room temperature. The isolated products were checked for its purity by TLC. The final product was characterized by ^{1}HNMR spectrometry. This study paves the use of supramolecular host and reusable aminocyclodextrin for producing of 2-amino-4*H*-chromene scaffolds with use of the commercially accessible inexpensive preliminary substances, energy-effectiveness, reusable catalyst, excellent yields, operational simplicity, time-saving aspects of the reaction, easy work-up, solvent-free conditions, high atom economy, green reaction conditions thus meeting some features of sustainability and green chemistry. Also, per-6-amino-β-cyclodextrin was so stable that they were capable of being used for six consecutive times with no significant change in structure and any activity loss. These characteristics have caused this procedure to be highly beneficial in facing the environmental worries and industrial needs.

ARTICLE HISTORY
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KEYWORDS
2-amino-4*H*-chromene scaffolds; per-6-amino-β-cyclodextrin (per-6-NH_2-β-CD); reusable aminocyclodextrin; solvent-free; supramolecular host

Introduction

In green chemistry, the most notable objectives of Atomic saving include reduction of by-products, the number of stages of organic synthesis, energy costs, waste generated, and the use of non-hazardous reagents in catalytic protocols. One of the important factors of green chemistry in recent organic, synthetic pathways is green catalyst. According to, our recent researches have focused on the development of green catalysts[1–4] in organic synthesis.

Chromenes and their analogues have attracted attention to them because of their biological activities such as antiallergenic,[5,6] antimicrobial,[7] antifungal,[8] anti-inflammatory,[9] antibacterial,[10] antioxidant,[11] antileishmanial,[12] anti-HIV,[13,14] anticancer,[15,16] and hypotensive.[17] Some of these compounds could also be used as inhibitors.[18,19] Some of them are shown with biological characteristics in Figure 1.

Numerous approaches for synthesizing 2-amino-4*H*-chromene scaffolds using MCRs have been reported opposite different catalysts such as glycine,[20] mesolite,[21] potassium phthalimide,[22]

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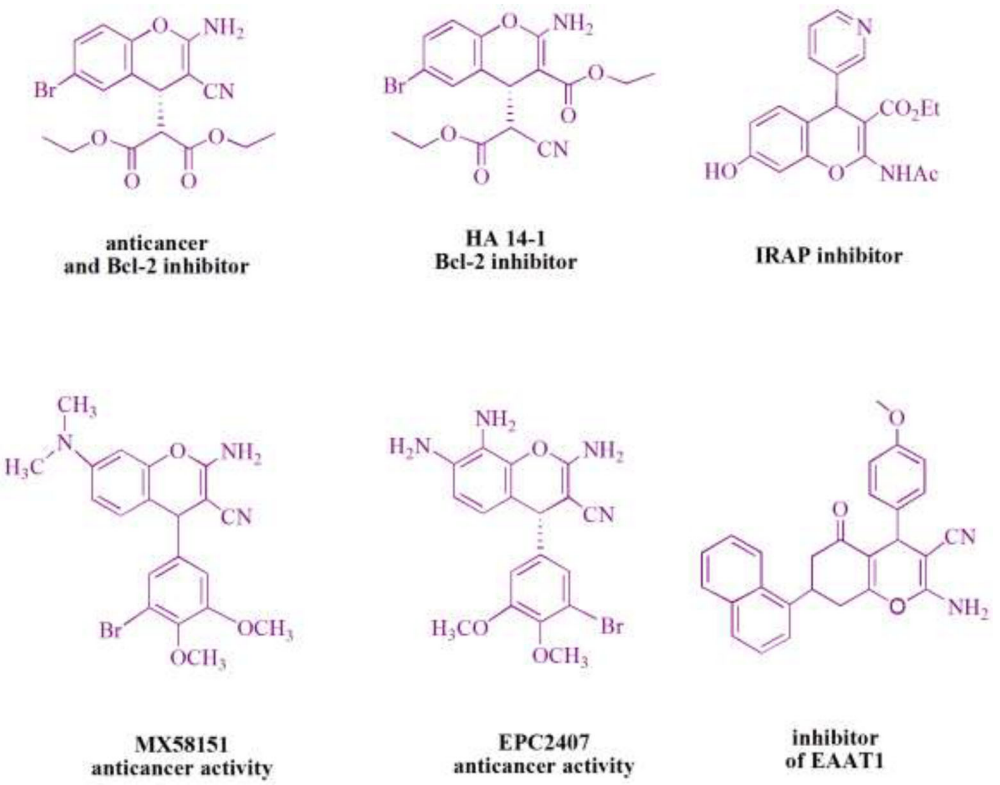


Figure 1. Medical compounds with chromene motifs.

$MgFe_2O_4$NPs,[23] POM@Dy-PDA,[24] P_4VPy-CuI,[25] nanozeolite clinoptilolite,[26] water extract of lemon fruit shell ash (WELFSA),[27] tungstic acid functionalized SBA-15,[28] MIL-101(Cr)-SO_3H,[29] $[Et_2NH(CH_2)_2CO_2H][AcO]$,[30] $\{[4,4'\text{-BPyH}][C(CN)_3]_2\}$[31] DBU,[32] hydrotalcite,[33] Fe_3O_4MNPs[34] and nano-cellulose-$OTiCl_3$.[35] These procedures resulted in numerous cases. Though, some of synthetic policies contain also restrictions regarding the metal catalyst, harsh reaction circumstances, expensive reagents, monotonous workup process, unacceptable yield, longer reaction time, environmental hazard, and using the homogeneous catalyst that is problematically detached from the mixture of reaction.

Composed of six, seven, or eight α-1,4-linked D-(+)- glucopyranose units, the cyclodextrins (α, β, and γ, respectively) are cyclic oligosaccharides which has an overall shape reminiscent of a lampshade or truncated cone.[36] Cyclodextrins (CDs) are cyclic oligosaccharides that can bind substrates and catalyze chemical reactions with high selectivity through the reversible formation of host – guest complexes.[37] They are successfully employed to improve the pharmacological properties of drugs.[38] The most significant characteristic of the cyclodextrins is their ability to form inclusion complexes in aqueous solutions with a wide variety of substrates. Since compounds that are complexed by an appropriate cyclodextrin often display much improved water solubilities, the cyclodextrins may act as enhancers of the aqueous solubilities of small organic molecules. In this context, cyclodextrins have found applications in the solubilization of organic compounds when organic solvents cannot be employed because of their toxicity, flammability, or expense.[36]

As a consequence of its good binding ability to ward aromatic units, as well as its ready availability, β-cyclodextrin has emerged at present as the naturally-occurring cyclodextrin with the highest commercial potential.[36] β-CD, among the multifarious cyclodextrins, is the most notable

catalyst because it is not only economically and environmentally beneficial, but also metabolically secure, nontoxic, and easily recoverable and reusable with β-cyclodextrin. It is, therefore, unfortunate that its aqueous solubility is so low. As a result, the extensive investigations into the chemical modifications of cyclodextrins have been concerned primarily with influencing their solubilities as well as with modifying their binding behaviors.[36]

Aminocyclodextrins are homogeneous CD derivatives modified by persubstitution at the primary face with amino pendant groups, and this manifests combined hydrophobic and electrostatic binding of guest molecules relative to native CDs. In addition, they can also act as ligands for various metal ions. As part of our continuing interest in developing an efficient method for the synthesis of useful compounds, we have recently successfully utilized per-6-amino-β-cyclodextrin (per-6-NH_2-β-CD) as useful catalyst as well as host.[37] Supramolecular host per-6-NH_2-β-CD and reusable aminocyclodextrin will be a useful tool and catalyst economically as well as environmentally.[38–40]

Multi-component responses (MCRs)[41–43] have developed as effective and effective apparatuses for the era of profoundly differing and complex items in tall immaculateness and fabulous yields from promptly accessible beginning materials in a single operation, without separation of intermediates, in negligible time, with greatest selectivity and atom-economy. Given the above considerations and our interest in developing the 2-amino-4*H*-chromenes production, the study of eco-safe and reusable catalyst under green circumstances for the proper synthesis of these oxygen-containing heterocyclic compounds via multi-component reactions has been an important goal. Encouraged by these efforts and aiming to demonstrate the efficiency and generality of these aminocyclodextrins as catalysts further,[37] we have utilized this catalyst for the synthesis of 2-amino-4*H*-chromene scaffolds from simple and easily available starting materials under much milder reaction conditions.

Here, supramolecular host and reusable aminocyclodextrin provided producing of 2-amino-4*H*-chromene scaffolds. The phenomenal yields, short reaction times were procured by anticipated products in which might solve some expense issues in industry. However, the supramolecular aminocyclodextrin can be recycled minimum six times with no crucial decline in catalytic activity to beneficially address the industrial needs and environmental trepidations.

Experimental

General

Using a 9100 electro-thermal device, the melting points of all compounds were found. In addition, the nuclear magnetic resonance recording, the spectrum (^{1}H NMR) was performed on a Bruker (DRX-300) instruments using DMSO-d_6 as solvent. We bought the entire reagents from the chemical companies called Fluka, Merck, and Acros and used without additional treatment.

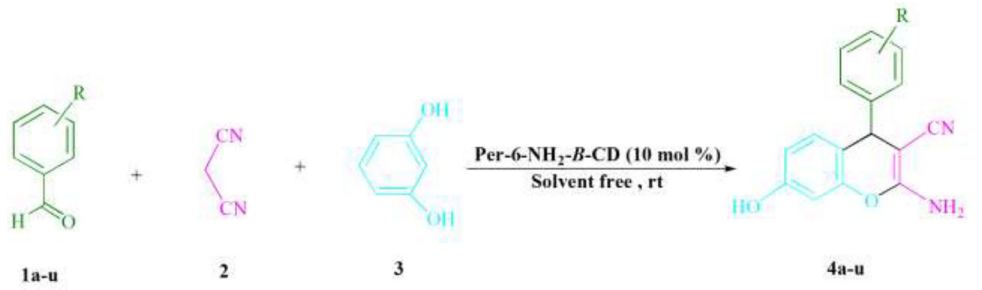
Synthesis of per-6-NH_2-β-CD

Per-6-NH_2-β-CD synthesized according to the literature.[36] ^{1}HNMR data of per-6-NH_2-β-CD are represented below:

M.p. 207–209 °C; ^{1}HNMR (300 MHz, D_2O): 3.34 (7H, dd, $J = 7.6$, 10.4 Hz,), 3.51 (7H, dd, $J = 8.4$, 10.4 Hz), 3.66 (7H, d, $J = 7.6$ Hz), 3.70 (7H, dd, $J = 7.6$, 8.4 Hz), 4.08 (7H, dd, $J = 7.2$, 8.8 Hz), 4.23 (7H, t, $J = 11.2$ Hz,), 5.27 (7H, dd, $J = 8.0$, 9.6 Hz).

Producing of 4a-u

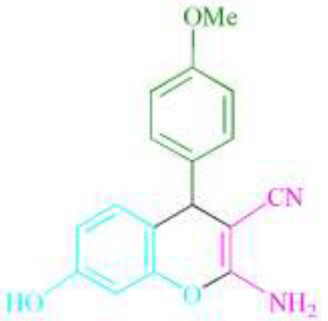
Combination malononitrile (**2**, 1.0 mmol), aryl aldehyde derivatives (**1**, 1.0 mmol), and resorcinol (**3**, 1.0 mmol) and per-6-NH_2-β-CD (10 mol %) in solvent-free conditions was reacted at rt



Scheme 1. Synthesis of 2-amino-4*H*-chromene scaffolds.

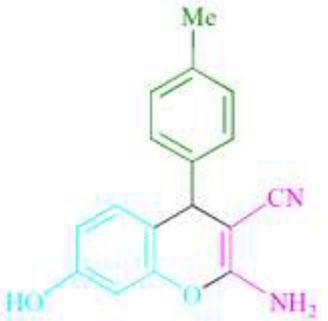
(Scheme 1). Monitoring of reaction progress was conducted by TLC. After reaction, we filtered the obtained solid and washed with ethanol. Finally, the recrystallization occurred in the crude solid from ethanol to bring the pure material with no need for further purification (**4a-u**). The products were classified after the comparison of spectroscopic information (^{1}H NMR). Spectra data some of known products are represented below:

2-Amino-3-cyano-7-hydroxy-4-(4-methoxyphenyl)-4H-chromene (4c)



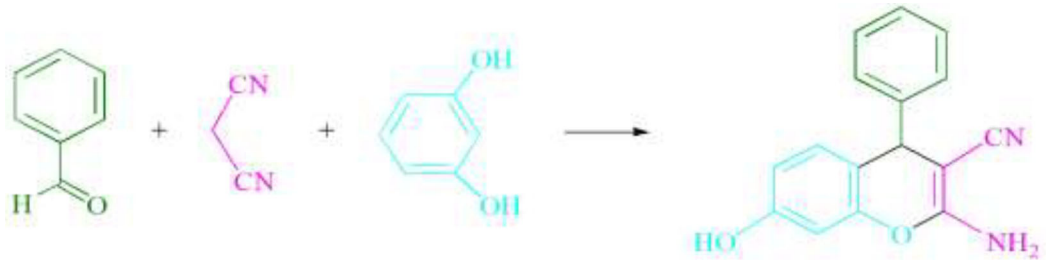
Yield: 89%; M.p. 212–214 °C; ^{1}HNMR (300 MHz, DMSO-d_6): 3.71 (3H, s, OCH_3), 4.53 (1H, s, CHAr), 6.18 (1H, d, $J = 8.8$ Hz, ArH), 6.45 (1H, dd, $J = 7.2$, 2.4 Hz, ArH), 6.77 (1H, d, $J = 8.4$ Hz, ArH), 6.84 (2H, s, NH_2), 7.25 (2H, d, $J = 8.4$ Hz, ArH), 7.83 (2H, d, $J = 9.2$ Hz, ArH), 9.78 (1H, s, OH).

2-Amino-3-cyano-7-hydroxy-4-(4-methylphenyl)-4H-chromene (4d)



Yield: 96%; M.p. 187–189 °C; ^{1}HNMR (300 MHz, DMSO-d_6): 2.51 (3H, s, CH_3), 4.72 (1H, s, CHAr), 6.21 (1H, d, $J = 9.6$ Hz, ArH), 6.70 (1H, d, $J = 9.6$ Hz, ArH), 6.84 (1H, d, $J = 10.4$ Hz,

Table 1. Optimization table for the synthesis of **4a**.[a]



Entry	Per-6-NH_2-β-CD (mol %)	Solvent	Time (min)	Isolated Yields (%)
1	Catalyst free	Solvent free	120	trace
2	5	Solvent free	10	72
3	**10**	**Solvent free**	**3**	**94**
4	10	H_2O	50	87
5	10	H_2O/EtOH (1:1)	65	83
6	10	EtOH	55	81
7	10	MeOH	70	59
8	10	DMF	85	68
9	10	DMSO	85	77
10	10	THF	80	74
11	10	CH_3CN	70	62
12	15	Solvent free	3	94

[a]Reaction condition: benzaldehyde (1 mmol), malononitrile (1 mmol), resorcinol (1 mmol) under various solvents and molar catalyst.

ArH), 7.03 (2H, s, NH_2), 7.17 (2H, d, $J = 9.6$ Hz, ArH), 7.48 (2H, d, $J = 9.6$ Hz, ArH), 9.63 (1H, s, OH).

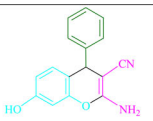
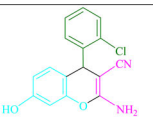
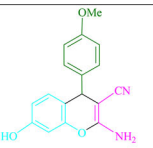
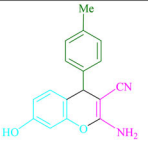
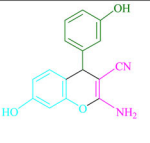
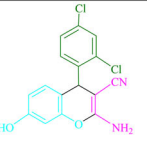
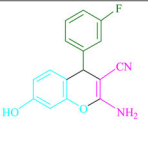
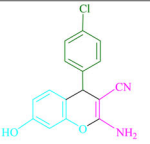
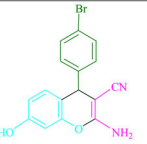
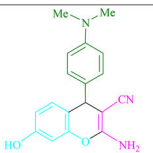
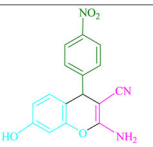
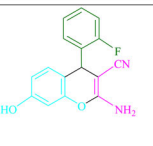
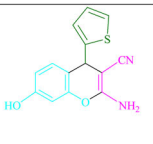
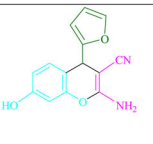
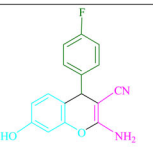
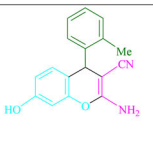
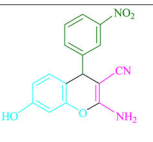
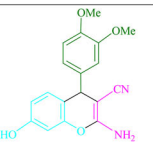
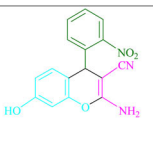
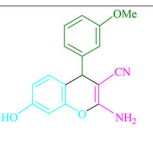
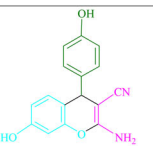
2-Amino-3-cyano-7-hydroxy-4-(3-nitrophenyl)-4H-chromene (4q)

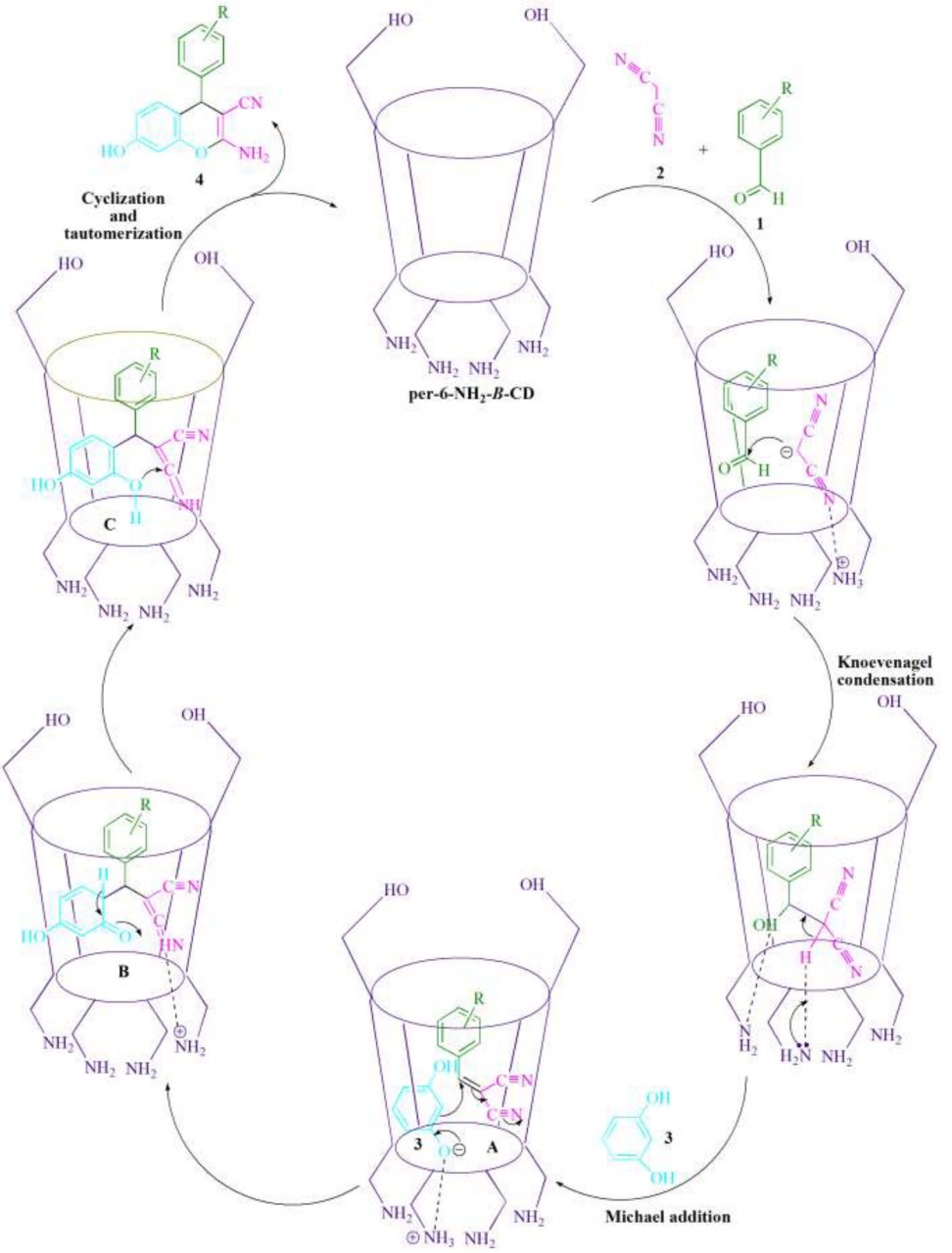
Yield: 95%; M.p. 169–171 °C; ^{1}HNMR (300 MHz, DMSO-d_6): 4.82 (1H, s, CHAr), 6.19 (1H, d, $J = 8.8$ Hz, ArH), 6.59 (1H, d, $J = 9.6$ Hz, ArH), 6.77 (1H, d, $J = 9.6$ Hz, ArH), 6.97 (2H, s, NH_2), 7.33 (2H, d, $J = 9.6$ Hz, ArH), 7.86 (2H, d, $J = 9.6$ Hz, ArH), 9.69 (1H, s, OH).

Results and discussion

The preparation of **4a** was studied in various solvents opposite different molars of per-6-NH_2-β-CD at rt. Table 1 illustrates the results. Without per-6-NH_2-β-CD, trace amount **4a** was seen at rt for 120 min. As this table shows, products were produced in H_2O, H_2O/EtOH (1:1), EtOH, MeOH, DMF, DMSO, THF and CH_3CN solvents at higher reaction times and lower yields and a great enhancement in solvent-free conditions (Table 1, entry 3). We recognized the optimized conditions by different molars of catalyst (5, 10 and 15 mol %). Also, the best results were

Table 2. Per-6-NH_2-β-CD as catalyst for synthesis of 2-amino-4*H*-chromene scaffolds.

 **4a** (3 min, 94%) Mp. 230-232 °C Lit. 232-234 °C [25]	 **4b** (7 min, 88%) Mp. 190-192 °C Lit. 189-191 °C [25]	 **4c** (5 min, 89%) Mp. 212-214 °C Lit. 210-212 °C [27]
 **4d** (3 min, 96%) Mp. 187-189 °C Lit. 186-188 °C [26]	 **4e** (10 min, 84%) Mp. 220-222 °C Lit. 219-221 °C [31]	 **4f** (12 min, 86%) Mp. 256-258 °C Lit. 257-259 °C [25]
 **4g** (2 min, 95%) Mp. 147-149 °C Lit. 148-150 °C [27]	 **4h** (10 min, 81%) Mp. 160-162 °C Lit. 162-163 °C [25]	 **4i** (7 min, 85%) Mp. 222-224 °C Lit. 222-224 °C [22]
 **4j** (5 min, 93%) Mp. 195-197 °C Lit. 194-196 °C [22]	 **4k** (3 min, 91%) Mp. 165-167 °C Lit. 166-168 °C [21]	 **4l** (2 min, 92%) Mp. 202-204 °C Lit. 200-202 °C [32]
 **4m** (3 min, 94%) Mp. 208-210 °C Lit. 210-212 °C [22]	 **4n** (3 min, 92%) Mp. 191-193 °C Lit. 190-192 °C [30]	 **4o** (2 min, 97%) Mp. 190-192 °C Lit. 188-190 °C [25]
 **4p** (2 min, 91%) Mp. 231-233 °C Lit. 228-231 °C [23]	 **4q** (3 min, 95%) Mp. 169-171 °C Lit. 168-170 °C [30]	 **4r** (7 min, 88%) Mp. 225-227 °C Lit. 227-229 °C [31]
 **4s** (2 min, 94%) Mp. 163-165 °C Lit. 162-163 °C [32]	 **4t** (5 min, 86%) Mp. 181-183 °C Lit. 180-182 °C [31]	 **4u** (10 min, 80%) Mp. 252-254 °C Lit. 250-252 °C [21]



Scheme 2. Recommended mechanistic path for synthesizing 2-amino-4*H*-chromene scaffolds.

opposite per-6-NH_2-β-CD (10 mol %) (Table 1, entry 3). No important change in reaction time and yield was observed with the increase in the amount of catalyst to 15 mol % (Table 1, entry 12). The best outcomes were found opposite per-6-NH_2-β-CD (10 mol %) at rt. Table 2 and Scheme 1 show that this technique can function in multifarious substrates.

Scheme 2 indicates recommended mechanism. We provoked reaction by devising an inclusion in the intermediate ylidenemalononitrile (cyano olefin) **A** was devised in situ from Knoevenagel condensation between active methylene **2** compound and arylaldehyde **1** oppositein front of per-

Table 3. Comparison of the catalytic ability of some of the catalysts in the manuscript for producing of 2-amino-4*H*-chromene scaffolds.[a]

Entry	Catalyst	Conditions	Time/Yield (%)	TON	TOF	References
1	Glycine	H_2O, sonic condition	9 min/94	6.2	0.6	[20]
2	Potassium phthalimide	ball milling, rt	17 min/97	19.4	1.14	[22]
3	POM@Dy-PDA	EtOH/H_2O, reflux	15 min/95	9.5	0.6	[24]
4	MIL-101(Cr)-SO_3H	H_2O, 100 °C	180 min/82	221.6	1.2	[29]
5	$[Et_2NH(CH_2)_2CO_2H][AcO]$	solvent-free, 60 °C	12 min/92	4.6	0.3	[30]
6	DBU	MW, EtOH, 50 °C	3 min/94	18.8	6.2	[32]
7	Hydrotalcite	H_2O, 60 °C	240 min/95	6.3	0.02	[33]
8	Fe_3O_4MNPs	H_2O, rt	25 min/98	14	0.5	[34]
9	per-6-NH_2-β-CD	solvent-free, rt	3 min/94	9.4	3.1	This work

[a]Based on the three-component reaction of benzaldehyde, malononitrile and resorcinol.

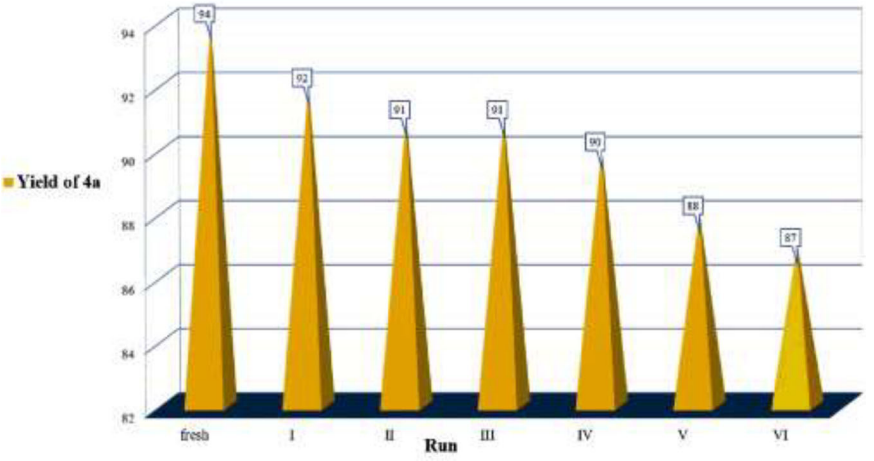


Figure 2. The recyclability of per-6-NH_2-β-CD in the preparation of **4a**.

6-NH_2-β-CD. We can show this via the arylaldehydes' steric impacts on the reaction (Table 2). Per-6-NH_2-β-CD also catalyzed the resorcinol **3** attack on intermediate **A** as Michael acceptor to give **B**, which aftercyclizing and tautomerizing aims the objective products **4**.

Comparison of the catalytic capacity of a number of catalysts referred to in the present paper for the production of 2-amino-4*H*-chromene scaffolds has been shown in Table 3. It may find a wide range of applications, such as the use of supramolecular host and reusable aminocyclodextrin, short reaction time without any by-products. The marvelous atom-economic protocol is effective on a multi-gram scale and has important industrial applications. These products achieve both excellent performance and excellent purity. The atom economy has also done well with this response. TON and TOF is calculated in Table 3. The lower the amount of catalyst and the higher the yield, the higher the numerical value of the TON and TOF, and the higher the value, the more efficient the catalyst.

Reusability of the catalyst

Since the catalyst reusability is economically and environmentally important, the per-6-NH_2-β-CD catalyst reusability has been investigated over the next few periods. Recovery and reuse of the catalyst to prepare **4a** was examined.

At end reaction, the catalyst is filtered and washed using EtOH (3 × 3 mL). In the following, it dries in the vacuum and reuse. The per-6-NH_2-β-CD was reused for six rounds of recycling, while the detached product had sufficient potential to be affordable (Figure 2). In the first,

second, third, fourth, fifth and sixth reactions, there were very low reductions in yield (92%, 91%, 91%, 90%, 88%, and 87%, respectively).

Comparison of catalytic reusability some of catalysts reported in the literature for synthesis of 2-amino-4*H*-chromene scaffolds is studied. The recyclability of $MgFe_2O_4$NPs[23] was studied. $MgFe_2O_4$ nanocatalyst could be reused for 4 cycles with negligible loss of their activity. It was found that the P_4VPy-CuI[25] could be recycled up to five times with desired products obtained in high yields after each run. The reusability of the nano sized zeolite CP[26] was checked and nanozeolite clinoptilolite reused successively 5 times without any significant loss of activity. The reusability of the tungstic acid functionalized SBA-15[28] in the one-pot three component condensation reaction was examined. After recovery of the catalyst it has been employed for a further six additional repetitive reaction cycles. In all cases, the consistent catalytic activity over mesoporous TAFMC-1 has been observed, establishing the fact that the catalyst can be recycled and reused without any considerable loss of catalytic activity. The catalyst $[Et_2NH(CH_2)_2CO_2H][AcO]$[30] could be reused up to six times for catalyzing the selected reaction and is stable during the reaction. The recovered hydrotalcite[33] could be reused more than four reaction cycles with significant loss in catalytic activity. The Fe_3O_4MNPs[34] could be reused for the six cycle without any appreciable loss of its activity. Nano-cellulose-$OTiCl_3$[35] successfully recycled three times without significant loss of its activity. According to these results it was found that this present methodology is a fruitful one-pot approach under highly effective, mild and facile reaction conditions. Clean, avoiding the use of organic solvents, absence of tedious separation techniques, minimized amount of waste for each organic transformation, reasonable reaction times, solvent-free conditions, efficiency, green, reusability and economic availability of the organocatalyst are the other noticeable features of this procedure.

Conclusion

In summary, we have developed a green supramolecular host and reusable aminocyclodextrin-catalyzed one-pot three-component methodology for the synthesis of a variety of pharmaceutical interesting functionalized 2-amino-4*H*-chromene scaffolds in excellent yields, convenient approach and short reaction times under solvent-free conditions at room temperature. This approach is very simple from the experimental point of view and would permit easy access to large families of 2-amino-4*H*-chromene scaffolds. In comparison to the conventional methods, the remarkable advantages of this protocol are, the media doesn't require organic solvent, mild reaction condition, green catalyst and environmentally friendly and the isolated product is in purest form, it eliminates the use of chromatographic purification. The present method is found to be well tolerated for the arrays of substituted benzaldehydes. In future our research group is planning to extend to synthesize more efficient biologically active chromene derivatives. Moreover, this methodology is found to be fairly general and catalyst can be easily recovered and reused for six times without any apparent loss of activity for the reaction. These characteristics have caused this procedure to be highly beneficial in facing the environmental worries and industrial needs. The method described in this paper is mild and energy efficient and provides a very reliable procedure for the synthesis of 2-amino-4*H*-chromene derivatives.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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