Catalysis Communications 152 (2021) 106289

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short communication

The first efficient biocatalytic route for the synthesis of Kojic acid derivatives in aqueous media

Kiran S. Dalal [a], Mangal A. Chaudhari [a], Dipak S. Dalal [b,*], Bhushan L. Chaudhari [a,*]

[a] School of Life Sciences, Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon 425 001, Maharashtra, India
[b] School of Chemical Sciences, Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon 425 001, Maharashtra, India

ARTICLE INFO

Keywords:
Aspergillus niger
Lipase
Biocatalysis
Kojic acid derivatives

ABSTRACT

The first efficient biocatalytic route for the synthesis of kojic acid derivatives was developed in presence of an enzyme. In this process, benzaldehydes, malononitrile and kojic acid were used as starting materials while lipase from *Aspergillus niger* was the promiscuous biocatalyst giving high conversion (82–95%) of kojic acid derivatives in aqueous medium. The probable enzymatic mechanism is proposed here. The lipase was reused till three consecutive cycles without a significant loss of activity. This efficient bioprocess has potential to replace the existing chemical catalytic processes to produce heterocyclic anti-tyrosinase compounds that prevents hyperpigmentation.

1. Introduction

Kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, KA) is a natural product synthesized by many fungi and bacteria such as *Aspergillus*, *Penicillium* and *Acetobacterium* sp. [1]. It is a polyfunctional heterocycle, with several important reaction centers, used in many types of reactions, involving addition, alkylation, acylation, oxidation, ring opening, and nucleophilic and electrophilic substitution reactions [2]. KA is generally used as an antioxidant in food to act as a preservative, an additive for preventing enzymatic discoloration of vegetables, crabs, shrimps and as a skin lightening or bleaching agent in cosmetic preparations [3]. The melanin pigment is an important molecule which is generally found in the microorganisms, plants and animals. Despite of high importance, the overproduction of melanin is observed in several hyperpigmentation disorders, such as freckles, senile lentigines and melasma [4]. KAand its derivatives are used to inhibit tyrosinase activity in synthesis of melanin or block the formation of pigment by melanocytes that prove to be the most popular lighteners among the cosmetic product [5]. Besides its role as a whitening agent, kojic acid shows a wide range of biological activities such as antibacterial and antifungal activities [6], anti-inflammatory [7], antineoplastic [8], depigmenting agents [9], anticonvulsant, antiviral [10] and anti-HIV activities [11]. Due to the importance of KA in industry, the synthesis of its derivatives is of great importance to organic chemists.

The kojic acid was commercially produced and marketed by Charles Pfizer and Compancy, USA in 1955 . Rapid growth of various industries due to the potential uses of kojic acid and its derivatives generated great demands for this product. According to FDA, kojic acid derivatives are used in a about 16 products [12]. The kojic acid is the most studied inhibitor of the tyrosinase enzyme. The synthesis of kojic acid derivatives has become a challenge for academic and industrial researchers due to its wide range of biological, industrial, and synthetic applications. Many biocatalysts (enzymes/whole cells) can replace chemo-catalysts in synthetic routes which are more efficient and more sustainable [13,14]. In this perspective, lipases were used in several important chemical transformations that works well in aqueous medium as well as non-conventional medium [15]. Lipases have gained attention due to their general ease of handling, being inexpensive, broad substrate tolerance, high stability towards a wide range of temperatures and solvents while the most important aspect is its commercial availability [16]. Bora et al. reported the synthesis of dihydropyrano(2,3-*c*)pyrazoles using lipase from *Aspergillus niger* as a biocatalyst [17]. It catalyzed the Henry (nitroaldol) reaction, which is an important C—C bond formation reaction between aromatic aldehydes and nitroalkanes in organic/aqueous medium [18]. Recently, this lipase was used in the synthesis of butyl butyrate [19]. But, this enzyme has not been studied in depth in organic synthesis.

Various chemical methods have been reported in the literature towards the synthesis of kojic acid derivatives. Generally, these derivatives were synthesized by multi-component reaction of kojic acid,

* Corresponding authors.
E-mail addresses: dsdalal2007@gmail.com (D.S. Dalal), blchaudhari@nmu.ac.in (B.L. Chaudhari).

https://doi.org/10.1016/j.catcom.2021.106289
Received 8 September 2020; Received in revised form 30 January 2021; Accepted 31 January 2021
Available online 3 February 2021
1566-7367/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

aldehydes and malononitrile. Recently, some environment compatible catalyst like MCM-41-SO_3H [20], Cobalt nanoparticles [21], Cuprous oxide-Zeolite clinoptilolite nanoparticles [22], Fe_3O_4@SiO_2-BenzIm-Fc (Cl)/$ZnCl_2$ [23], nano Fe_3 O_4@SiO_2-IL-Fc [24], NH_4Cl [25], Fe_3O_4@-SiO_2-*s*-triazinium chloride [26], Ultrasonic irradiation [27] and β-Cyclodextrin [28] were also used to achieve this transformation. Lajis et al. reported the enzymatic method for the synthesis of kojic acid based KAD (7-O-kojic acid monopalmitate) using immobilized lipase N435 at 80 °C for 4 h in bioreactors (reaction volume 0.12 L) using palmitic acid and kojic acid as a substrate [29]. Although these methods show good results, exhibit some limitations such as low conversion rate, high temperature, toxic reagents and use of strong catalysts. Therefore, it is important to explore newer biocatalyst with good activity to avoid toxic chemical catalysts and reagents in the reaction. In continuation of our work for the synthesis and characterization of promising heterocyclic compounds [30], we recently developed a new methodology for the synthesis of ortho-aminocarbonitriles using lipase as a biocatalyst [31]. To the best of our knowledge, there is no report on enzyme-catalyzed synthesis of kojic acid derivatives using multicomponent reaction of aromatic aldehydes, malononitrile and kojic acid.

2. Experimental section

2.1. General information

Lipase from *Aspergillus niger* (200 U/g), Lipase from *Candida rugosa* (2 U/mg), Lipase from porcine pancreas Type II (100–500 U/mg) and Acylase I from *Aspergillus melleus* (0.5 U/mg) were purchased from Sigma-Aldrich. All other chemicals including aldehydes, kojic acid and malononitrile were purchased from Spectrochem and Sigma-Aldrich, India and used without further purification. The reactions were monitored by thin-layer chromatography (Hexane: Ethyl acetate, 3:7) using silica gel-coated plates and EtOAc/hexane solution as the mobile phase. The spots were visualized under UV light. Melting points of compounds were recorded in open glass capillary method and were uncorrected. The NMR spectra were recorded on Bruker Avance-II spectrophotometer operating at 500, 400 MHz and 125, 100 MHz. Infrared (IR) spectra were obtained on Shimadzu IR-Affinity spectrometer using KBr pellets.

2.2. General procedure for the synthesis of kojic acid derivatives (4a-4 k)

In a 25 ml round bottom flask containing aromatic aldehyde (1.0 mmol), malononitrile (66 mg, 1.0 mmol), kojic acid (142 mg, 1.0 mmol) and enzyme (50 mg, 10 U) were added in the mixture of H_2O (5 ml) and ethanol (5 ml) and then stirred at room temperature (RT). Completion of reaction was confirmed by TLC and the crude solid products were extracted by adding 10 ml of ethyl acetate to the reaction mixture, followed by filtration and evaporation of solvent. The enzyme was filtered off and washed with acetone. Isolated products were further recrystallized from ethanol to achieve the pure products. The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, Mass Spectrometry.

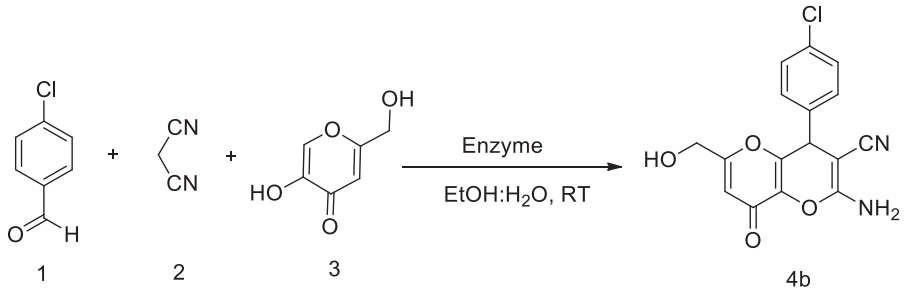
3. Results and discussion

3.1. Screening of enzymes

In initial phase, the kojic acid (1.0 mmol), malononitrile (1.0 mmol) and 4-chloro benzaldehyde (1.0 mmol) were used as the model substrates to optimize the reaction conditions (Scheme 1). In order to carry out the model reaction, different enzymes were tested for the synthesis of 2-amino-4,8-dihydropyrano [3,2-b]pyran-3-carbonitrile and the results are shown in Table 1. The results showed that only 20% yield of product was obtained when the reaction was carried out in the control with absence of catalyst (**entry 1,** Table 1). When lipase from Porcine pancreas and *Candida rugosa* were used, the target compound **4b** was obtained with 63% and 69%, yields respectively (**entry 2 and 3,** Table 1). The best yield of 95% was achieved using lipase from *Aspergillus niger* (**entry 4,** Table 1). Under the same condition, the Acylase I from *Aspergillus melleus* was used as a catalyst which resulted in low yield of 50% (entry 5, Table 1). To determine the catalytic effects coming from enzyme, the control experiments were performed using denatured lipase that obtained the yield of 21% (**entry 6,** Table 1). In next experiment, lipase samples pretreated with urea and PMSF were tested to confirm its role as enzyme in overall reaction system (**entry 7–8,** Table 1). The results indicated that the active ANL is the only enzymatic preparation capable of performing this reaction with good yield.

3.2. Influence of solvents

The reaction medium has always been one of the important influencing factors. The solvents are known to affect the configuration of the enzyme and hence the enzyme promiscuity also. Several solvents were screened in this reaction using kojic acid, 4-chlorobenzaldehyde and malononitrile as a model reaction. As shown in Table 2, the experimental results demonstrate that this reaction went smoothly in the presence of various proportions of water and ethanol. When the reaction was carried out in acetonitrile, the yield was just 10% (**entry 1,** Table 2) while in ethanol it was 60% (**entry 2,** Table 2). Methanol gave lesser yield of 15% (**entry 3,** Table 2). When the reaction was performed in pure water, only 42% of yield was obtained. We speculated that the low yield might be due to poor solubility of the aldehyde in water and the corresponding Knoevenagel product. (**entry 4,** Table 2). Therefore, the model reaction was tested in a 50% aqueous ethanol, so that the solubility could be enhanced. Interestingly, when water and ethanol were used in equal concentration (1:1) for the reaction, the yield of the product enhanced dramatically up to 95% (**entry 5,** Table 2). Many



Scheme 1. Model reaction to prepare derivatives of kojic acid

Table 1
Screening of enzyme for synthesis of kojic acid derivatives[a].

Entry	Enzyme	Yield[b] (%)
1	Blank (without enzyme)	20
2	Lipase from Porcine pancreas[c] (PPL)	63
3	Lipase from *Candida rugosa*[d] (CRL)	69
4	Lipase from *Aspergillus niger* (ANL)	95
5	Acylase I from *Aspergillus melleus*[e]	50
6	Denatured lipase from *Aspergillus niger*[f]	21
7	ANL denatured with urea[g]	18
8	ANL pretreated with PMSF[h]	20

[a] Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol), Kojic acid (1.0 mmol), enzyme ANL (10 U, 50 mg), in H_2O (5 ml), ethanol (5 ml) at RT, 10 h,
[b] Isolated yield of product.
[c] Lipase from porcine pancreas (100–500 U, 20 mg).
[d] Lipase from *Candida rugosa* (20 U, 10 mg).
[e] Acylase from *Aspergillus melleus* (15 U, 30 mg).
[f] ANL denatured by heating it to 100 °C for 6 h in water.
[g] ANL denatured with 50 mg urea in 2 ml water (0.83 M) at 100 °C for 24 h.
[h] ANL pretreated with 50 mg PMSF in 2 ml THF (0.29 M) at 25 °C for 24 h.

polar aprotic solvents such as DMSO, DMF, and THF failed to show good yields (**entries 6–8,** Table 2). The combination of polar protic solvents such as water and ethanol gave best yield (**entry 5,** Table 2). The polarization of the solvent creates a field that polarizes the solute in the direction to enhance its dipole moment. Hence, the water and ethanol (1:1) was chosen as the most suitable medium for the said transformation.

3.3. Influence of water content

The effect of water molecule in presence of ethanol solvent was examined and the results are plotted in Fig. 1. When addition of water molecule was raised from 0 to 70%, the yield was increased from 60 to 95% while in ethanol it was 60%. When we added the water in the reaction (20, 30, 40, 50%), the yields of 67, 71, 77, 95% were obtained respectively. However, addition of water above 50%, the yield of reaction was decreased probably due to the insolubility of reactants/intermediates. The results showed that water was crucial for synthesis of kojic acid derivatives in organic medium. The performance of enzyme improved when binary mixture of ethanol and water was used in reaction medium possibly due to essential conformational flexibility of enzyme obtained in ethanol-water mixture necessary for catalytic activity of enzyme.

3.4. Reusability of enzyme

To investigate the reusability of lipase, the model reaction of 4-chlorobenzaldehyde, malononitrile and kojic acid were stirred in ethanol: water (1:1) solvent at room temperature for four hours. After completion of reaction, the lipase was separated via centrifugation. Even after three runs, the product isolated was good enough (95, 92 and 80% respectively) where the yield of the isolated compound was not affected in the second run but, in the third run the reactivity of lipase reduced considerably to obtain 80% yield of product.

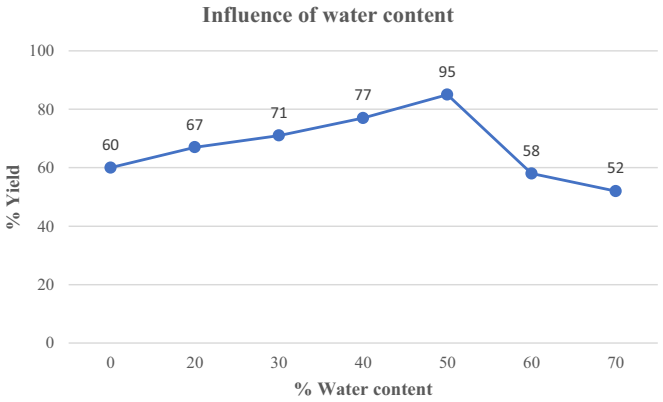


Fig. 1. Effect of concentration of ethanol: water binary mixture on lipase catalyzed kojic acid derivative (**4b**).
[a]Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol), kojic acid (1.0 mmol), enzyme ANL (10 U, 50 mg), H_2O /+ ethanol = 10 ml at RT, 10 h, [b]Isolated yield.

3.5. Influence of substrate

After optimizing all parameters, the scope and generality of the method was explored with respect to various aromatic aldehydes under the optimal conditions of which the results are summarized in Table 3, **4a–k**. The electron-rich aromatic aldehydes such as benzaldehyde, 4-chloro, 4-methyl, and 3-methoxy benzaldehydes reacted efficiently with kojic acid and malononitrile to bring good yields of 94, 95, 94 and 90% respectively within 4 h. The aromatic aldehydes with electron withdrawing groups such as 2-nitro, 4-nitro, and 3-nitro benzaldehydes reacted efficiently to give 82, 84, and 86% yield respectively within 5 h. The -NO_2 group shows strong electron withdrawing effect (i.e., negative effect) when substituted at ortho and para position that affects the yield. Again, 2-nitrobenzaldehyde is insoluble in water whereas 4-nitrobenzaldehyde is slightly soluble in water that perhaps decreases the yield of product. The 4-chlorobenzaldehyde gave highest yield 95% whereas 4-fluorobenzaldehyde required the highest reaction time of 5 h among other tested halides. The substituents present on the aromatic ring as well as solubility of reactants had shown some effect on the conversion. In all cases, the conversion was completed within 2–5 h with good to excellent yields of desired products without forming any by-products.

4. Proposed mechanism

Based on literature studies [32–35], the promiscuous reactions by hydrolases are known to proceed through the activation of the Michael acceptor through binding of its heteroatom functionality with the oxyanion hole of the enzyme. The proposed plausible mechanism is stated in Fig. 2. The intermediate (I) forms promptly by condensation of benzaldehyde and malononitrile, bound with the oxyanion hole of the lipase. Then kojic acid bound with lipase undergoes activation to form complex (II). The complex (II) possibly undergoes Michael type addition with the activated enzyme intermediate (I). Then a lipase catalyzed cyclization results in the formation of kojic acid derivative **4a**.

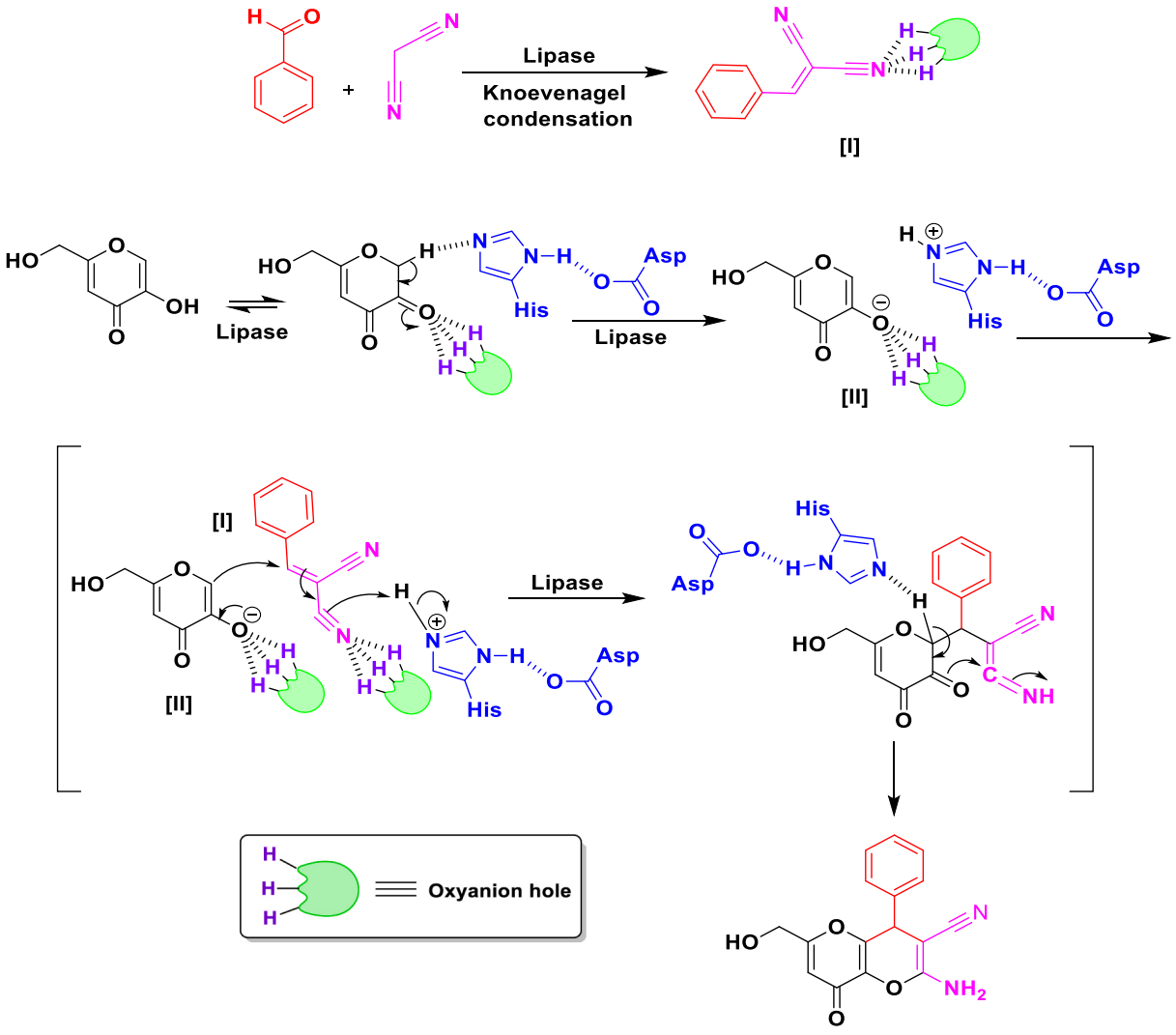
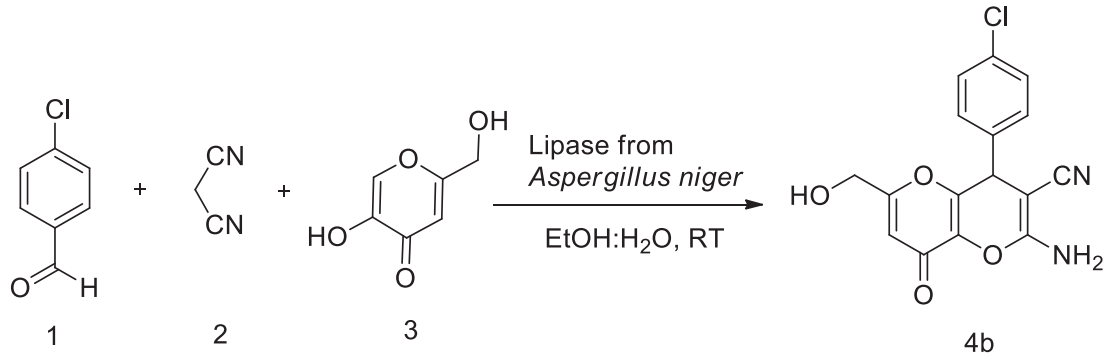
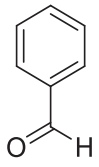
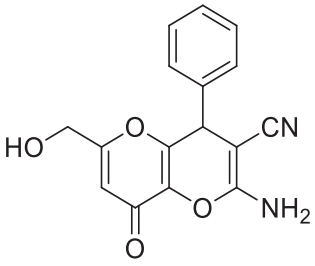
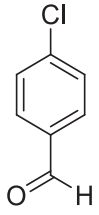
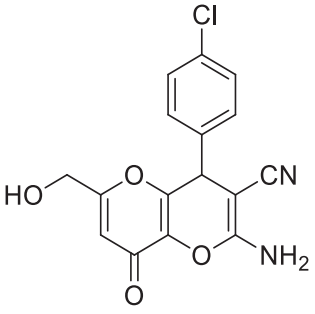
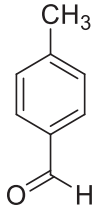
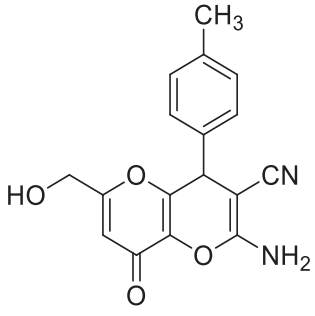
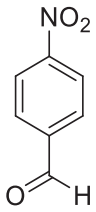
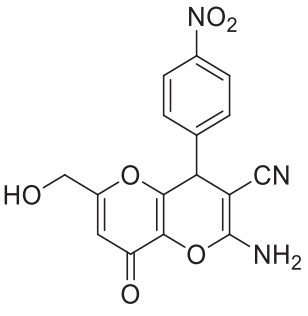
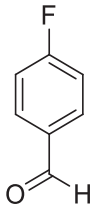
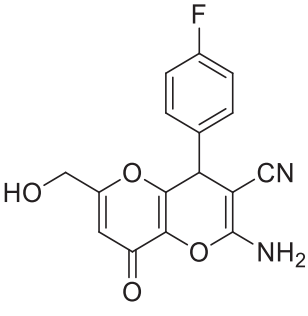
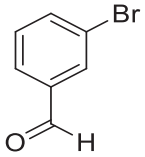
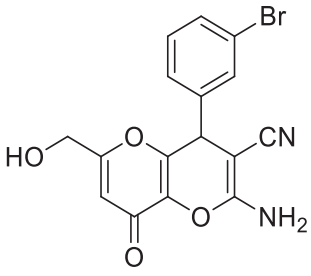
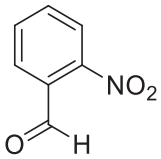
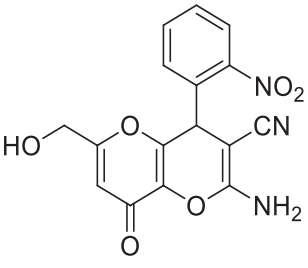
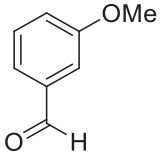
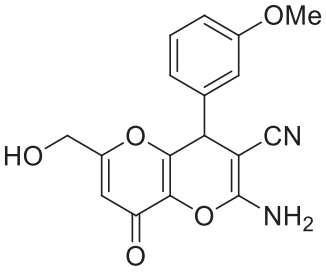


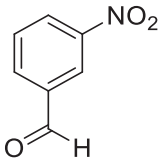
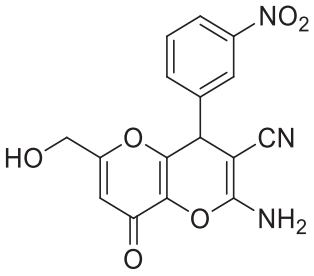
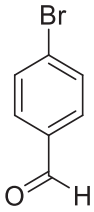
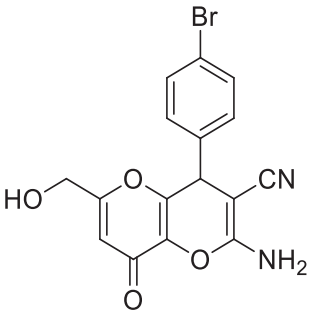
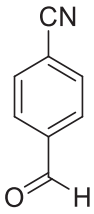
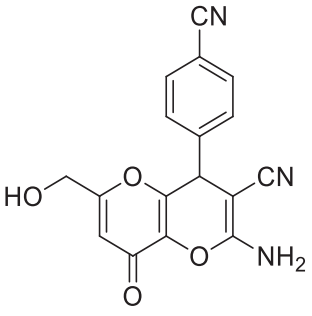
Fig. 2. Proposed mechanism of synthesis of kojic acid derivative **4a.**

Table 3
Synthesis of kojic acid derivatives[a].



Entry	Aldehyde	Product	Time (h)	Yield (%)	M.P. (°C)
1.		 **4a**	4	94	220-222
2.		 **4b**	4	95	206-208
3.		 **4c**	2	94	220-222

4.		 **4d**	5	84	232-234
5.		 **4e**	5	90	242-244
6.		 **4f**	3.5	89	240-242
7.		 **4g**	5	82	222-224
8.		 **4h**	4	90	236-238

9.		 **4i**	4.5	86	230-232
10.		 **4j**	3.5	88	232-234
11.		 **4k**	3.5	90	230-232

[a]Reaction conditions: aldehydes (1.0 mmol), malononitrile (1.0 mmol), kojic acid (1.0 mmol), enzyme (10 U, 50 mg), in H_2O (5 ml) + ethanol (5 ml) at RT, [b]Isolated yield.

[a]Reaction conditions: aldehydes (1.0 mmol), malononitrile (1.0 mmol), kojic acid (1.0 mmol), enzyme (10 U, 50 mg), in H_2O (5 ml) + ethanol (5 ml) at RT.
[b]Isolated yield.

Table 2
Selection of solvent for the model reaction for the formation of kojic acid derivative.[a]

Entry	Solvent	Yield[b] (%)
1	Acetonitrile	10
2	Ethanol	60
3	Methanol	15
4	H_2O	42
5	H_2O: Ethanol (1:1)	95
6	DMSO	60
7	DMF	55
8	THF	52

[a] Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol), kojic acid (1.0 mmol), enzyme ANL (10 U, 50 mg), in solvent (10 ml) at RT, 10 h.
[b] Isolated yield.

5. Conclusion

An efficient method has been developed for the synthesis of biologically relevant kojic acid derivatives using lipase from *Aspergillus niger* as a catalyst in aqueous ethanol medium. A total of eleven derivatives were prepared, where the highest 95% of yield was obtained for **4b** and **4a, 4c** have 94% yield while the lowest yield of 82% was found for **4g** after 5 h. Based on the literature studies, the plausible mechanism is proposed for the synthesis of kojic acid derivatives. This enzymatic route is new and has potential to replace conventional chemical methods. This study could be helpful in designing the new tyrosinase inhibitors for human use. Furthermore, this bio-based methodology has advantages, including short reaction time, high yields, recyclability of catalyst, simplicity in operations and safe reaction conditions.

Credit author statement

The below stated authors contributed in multiple roles as follows,

Sr No.	Authors name	Author contribution	Author categories
1.	Dr. Kiran Sharad Dalal	Methodology, formal analysis, validation	First Author
2.	Mr. Mangal Arun Chaudhari	Methodology, formal analysis	Second Author
3.	Dr. Dipak Sharadrao Dalal	Conceptualization, project administration, supervision, writing original draft	Corresponding Author
4.	Dr. Bhushan Liladhar Chaudhari	Conceptualization, administration, Editing the draft	Corresponding Author

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.

Acknowledgments

The authors are thankful to the Department of Science and Technology for infrastructural facilities under FIST Programme and Special Assistance Programme (SAP) of University Grants Commission, New Delhi to KBCNMU for financial support. BLC and DSD are thankful to Rajiv Gandhi Science & Technology Commission, Government of Maharashtra for financial support. Authors also thank SAIF-Punjab University, Chandigarh for characterization support to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.catcom.2021.106289.

References

[1] T. Yabuta, The constitution of kojic acid, a γ-pyrone derivative formed by *Aspergillus oryzae* from carbohydrates, J. Chem. Soc. Trans. 125 (1924) 575–587.
[2] J. Brtko, L. Rondahl, M. Fickova, D. Hudecova, V. Eybl, M. Uher, Kojic acid and its derivatives: history and present state of art, Cent. Eur. J. Public Health 12 (2004) S16–S17.
[3] G.A. Burdock, M.G. Soni, I.G. Carabin, Evaluation of health aspects of kojic acid in food, Regul. Toxicol. Pharmacol. 33 (1) (2001) 80–101.
[4] S. Kumari, S.T. Thng, N.K. Verma, H.K. Gautam, Melanogenesis inhibitors, Acta Derm. Venereol. 98 (9–10) (2018) 924–931.
[5] Y.H. Cho, J.H. Kim, S.M. Park, B.C. Lee, H.B. Pyo, H.D. Park, New cosmetic agents for skin whitening from Angelica dahurica, J. Cosmet. Sci. 57 (1) (2006) 11–21.
[6] B.S. Reddy, M.R. Reddy, C.H. Madan, K.P. Kumar, M.S. Rao, Indium (III) chloride catalyzed three-component coupling reaction: a novel synthesis of 2-substituted aryl (indolyl) kojic acid derivatives as potent antifungal and antibacterial agents, Bioorg. Med. Chem. Lett. 20 (24) (2010) 7507–7511.
[7] H.S. Rho, S.M. Ahn, D.S. Yoo, M.K. Kim, D.H. Cho, J.Y. Cho, Kojyl thioether derivatives having both tyrosinase inhibitory and anti-inflammatory properties, Bioorg. Med. Chem. Lett. 20 (22) (2010) 6569–6571.
[8] L. Novotný, P. Rauko, M. Abdel-Hamid, A. Vachalkova, Kojic acid–a new leading molecule for a preparation of compounds with an anti-neoplastic potential, Neoplasma 46 (2) (1999) 89–92.
[9] J.C. Cho, H.S. Rho, H.S. Baek, S.M. Ahn, B.Y. Woo, Y.D. Hong, J.W. Cheon, J. M. Heo, S.S. Shin, Y.H. Park, K.D. Suh, Depigmenting activity of new kojic acid derivative obtained as a side product in the synthesis of cinnamate of kojic acid, Bioorg. Med. Chem. Lett. 22 (5) (2012) 2004–2007.
[10] M.D. Aytemir, B. Ozçelik, A study of cytotoxicity of novel chlorokojic acid derivatives with their antimicrobial and antiviral activities, Eur. J. Med. Chem. 45 (9) (2010) 4089–4095.
[11] R. Tanaka, H. Tsujii, T. Yamada, T. Kajimoto, F. Amano, J. Hasegawa, Y. Hamashima, M. Node, K. Katoh, Y. Takebe, Novel 3α-methoxyserrat-14-en-21β-ol (PJ-1) and 3β-methoxyserrat-14-en-21β-ol (PJ-2)-curcumin, kojic acid, quercetin, and baicalein conjugates as HIV agents, Bioorg. Med. Chem. Lett. 17 (14) (2009) 5238–5246.
[12] C.L. Burnett, W.F. Bergfeld, D.V. Belsito, R.A. Hill, C.D. Klaassen, D.C. Liebler, J. G. Marks, R.C. Shank, T.J. Slaga, P.W. Snyder, F.A. Andersen, Final report of the safety assessment of kojic acid as used in cosmetics, Int. J. Toxicol. 29 (6) (2010) 244S–273S.
[13] H. Bernhard, Embracing nature's catalysts: a viewpoint on the future of biocatalysis, ACS Catal. 10 (15) (2020) 8418–8427.
[14] J.P. Adams, M.J. Brown, A. Diaz-Rodriguez, R.C. Lloyd, G.D. Roiban, Biocatalysis: a pharma perspective, Adv. Synth. Catal. 361 (11) (2019) 2421–2432.
[15] B.P. Dwivedee, S. Soni, M. Sharma, J. Bhaumik, J.K. Laha, U.C. Banerjee, Promiscuity of lipase-catalyzed reactions for organic synthesis: a recent update, ChemistrySelect 3 (9) (2018) 2441–2466.
[16] A.C.L.M. Carvalho, T.D.S. Fonseca, M.C. Mattos, M.D.C.F. Oliveira, T.L.G. Lemos, F. Molinari, D. Romano, I. Serra, Recent advances in lipase-mediated preparation of pharmaceuticals and their intermediates, Int. J. Mol. Sci. 16 (2015) 29682–29716.
[17] P.P. Bora, M. Bihani, G. Bez, Multicomponent synthesis of dihydropyrano [2, 3-*c*] pyrazoles catalyzed by lipase from *Aspergillus niger*, J. Mol. Catal. B Enzym. 92 (2013) 24–33.
[18] Z.G. Le, L.T. Guo, G.F. Jiang, X.B. Yang, H.Q. Liu, Henry reaction catalyzed by lipase A from *Aspergillus niger*, Green Chem. Lett. Rev. 6 (4) (2013) 277–281.
[19] B.M. Travalia, M. Galvao, A.S. Lima, C.M.F. Soares, N. Narain, L.C.L. de Aquino Santana, Effect of parameters on butyl butyrate synthesis using novel *Aspergillus niger* lipase as biocatalyst, Acta Sci. Technol. 40 (1) (2018), e35999.
[20] Y. Sarrafi, E. Mehrasbi, S.Z. Mashalchi, MCM-41-SO_3H: an efficient, reusable, heterogeneous catalyst for the one-pot, three-component synthesis of pyrano [3, 2-*b*] pyrans, Res. Chem. Intermediat. (2015) 1–13.
[21] S.H. Banitaba, A mild protocol for the preparation of 2-amino-dihydropyrano [3, 2-*b*] pyran-3-carbonitriles via cobalt nanoparticles-catalyzed multi-component reaction in water Iran, Chem. Commun. 6 (4) (2018) 389–401.
[22] S.M. Baghbanian, Synthesis, characterization, and application of Cu_2O and NiO nanoparticles supported on natural nanozeolite clinoptilolite as a heterogeneous catalyst for the synthesis of pyrano [3, 2-*b*] pyrans and pyrano [3, 2-*c*] pyridones, RSC Adv. 4 (103) (2014) 59397–59404.
[23] M. Gholamhosseini-Nazari, S. Esmati, K.D. Safa, A. Khataee, R. Teimuri-Mofrad, Fe_3O_4@ SiO_2-BenzIm-Fc [Cl]/$ZnCl_2$: a novel and efficient nano-catalyst for the one-pot three-component synthesis of pyran annulated bis-heterocyclic scaffolds under ultrasound irradiation, Res. Chem. Intermediat. 45 (4) (2019) 1841–1862.
[24] R. Teimuri-Mofrad, S. Esmati, M. Rabiei, M. Gholamhosseini-Nazari, Efficient synthesis of new pyrano [3, 2-*b*] pyran derivatives via Fe_3O_4@ SiO_2-IL-Fc catalyzed three-component reaction, Heterocycl. Commun. 23 (6) (2017) 439–444.
[25] K.O. Aghbash, N.N. Pesyan, B. Notash, The clean synthesis and confirmatory structural characterization of new 2-amino-4, 8-dihydropyrano [3, 2-*b*] pyran-3-cyano based on Kojic acid, Monatsh Chem. 149 (11) (2018) 2059–2067.
[26] D. Azarifar, H. Ebrahimiasl, R. Karamian, M. Ahmadi-Khoei, *S*-Triazinium-based ionic liquid immobilized on silica-coated Fe_3O_4 magnetic nanoparticles: an efficient and magnetically separable heterogeneous catalyst for synthesis of 2-amino-4, 8-dihydropyrano [3, 2-*b*] pyran-3-carbonitrile derivatives for antioxidant and antifungal evaluation studies, J. Iran. Chem. Soc. 16 (2) (2014) 341–354.
[27] S.H. Banitaba, J. Safari, S.D. Khalili, Ultrasound promoted one-pot synthesis of 2-amino-4, 8-dihydropyrano [3, 2-*b*] pyran-3-carbonitrile scaffolds in aqueous media: a complementary 'green chemistry' tool to organic synthesis, Ultrason. Sonochem. 20 (1) (2013) 401–407.
[28] E.A. Kataev, M.R. Reddy, G.N. Reddy, V.H. Reddy, C.S. Reddy, B.V. Reddy, Supramolecular catalysis by β-cyclodextrin for the synthesis of kojic acid derivatives in water, New J. Chem. 40 (2) (2016) 1693–1697.
[29] A.F.B. Lajis, M. Hamid, S. Ahmad, A.B. Ariff, Lipase-catalyzed synthesis of kojic acid derivative in bioreactors and the analysis of its depigmenting and antioxidant activities, Cosmetics 4 (3) (2017) 22.
[30] K.S. Dalal, Y.A. Tayade, Y.B. Wagh, D.R. Trivedi, D.S. Dalal, B.L. Chaudhari, Bovine serum albumin catalyzed one-pot, three-component synthesis of dihydropyrano [2, 3-*c*] pyrazole derivatives in aqueous ethanol, RSC Adv. 6 (18) (2016) 14868–14879.
[31] K.S. Dalal, S.A. Padvi, Y.B. Wagh, D.S. Dalal, B.L. Chaudhari, Lipase from porcine pancreas: an efficient biocatalyst for the synthesis of *ortho*-aminocarbonitriles, ChemistrySelect 3 (37) (2018) 10378–10382.
[32] M. Lopez-Iglesias, V. Gotor-Fernández, Recent advances in biocatalytic promiscuity: hydrolase-catalyzed reactions for nonconventional transformations, Chem. Rec. 15 (4) (2015) 743–759.
[33] M. Kapoor, M.N. Gupta, Lipase promiscuity and its biochemical applications, Process Biochem. 47 (4) (2012) 555–569.
[34] C. Branneby, P. Carlqvist, A. Magnusson, K. Hult, T. Brinck, P. Berglund, Carbon–carbon bonds by hydrolytic enzymes, J. Am. Chem. Soc. 125 (4) (2003) 874–875.
[35] M. Svedendahl, K. Hult, P. Berglund, Fast carbon-carbon bond formation by a promiscuous lipase, J. Am. Chem. Soc. 127 (51) (2005) 17988–17989.