RSC Advances

PAPER

View Article Online
View Journal | View Issue

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Check for updates

Cite this: *RSC Adv.*, 2024, **14**, 6225

Iodine-PEG as a unique combination for the metal-free synthesis of flavonoids through iodonium-triiodide ion-pair complexation†

Naveen Kumar,[a] Navneet Sharma,[b] Vijay Kumar,[a] Vinay Kumar,[a] Kailash Jangid,[ac] Bharti Devi,[a] Ashish Ranjan Dwivedi,[cd] Kousik Giri,[b] Rakesh Kumar[a] and Vinod Kumar *[a]

Received 24th December 2023
Accepted 8th February 2024

DOI: 10.1039/d3ra08810c

rsc.li/rsc-advances

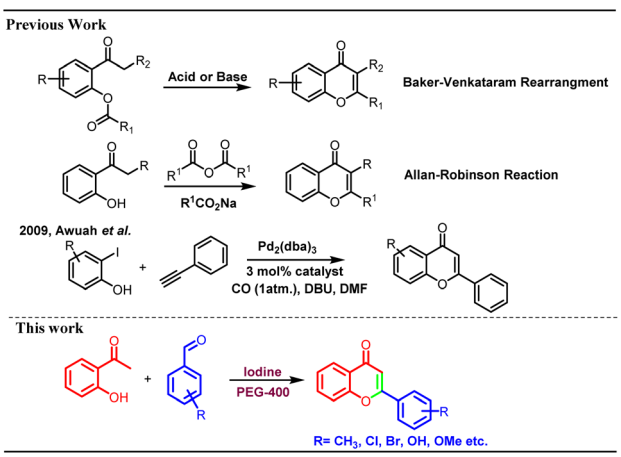
An efficient metal-free single-step protocol has been developed for the direct synthesis of flavones from 2-hydroxyacetophenone and substituted benzaldehydes. This chemical transformation is exclusively promoted by the iodonium-triiodide ion couple formed through iodine and PEG-400 complexation. The triiodide anion not only helps in the abstraction of a proton from the acetophenone but also promotes the cyclization of intermediate chalcone to the corresponding flavones. The flavones were obtained in very high yields without using any toxic metal catalysts or harsh reaction conditions. The reaction mechanism was established through a series of test reactions and entrapping of reaction intermediates. The developed protocol provides direct access to flavones in high yields under milder reaction conditions with great substrate compatibility, including hydroxylated derivatives.

Introduction

Flavonoids are secondary metabolites widely distributed in many plants, fruits, and vegetables.[1] These play a crucial role in the defence mechanism of plants against various pathogens and fungal attacks.[2] Polyhydroxy flavonoids impart attractive colours to the flowers and help in the process of pollination by attracting various pollinating agents. Flavonoids are part of the core structural units of many biologically and pharmacologically important moieties.[3] Several flavonoids have been reported to possess antioxidant, antimicrobial, anticancer, anti-psychotic, anti-inflammatory, and antiallergic properties.[4] Because of the diverse biological properties and numerous pharmacological activities, many flavonoid derivatives have been prepared utilizing various synthetic strategies.

Synthesis of flavonoids is carried out through different methods, including Baker–Venkataraman rearrangement,[5] Claisen–Schmidt condensation,[6] Allan–Robinson reactions,[7] coupling reactions, and cyclization through chalcones, *etc.* Many coupling reactions have been reported involving several metal catalysts[8] however, most of these suffers with limitations such as use of toxic metal catalysts, tedious work up and formation of many side products (Scheme 1).

Baker–Venkataraman method has been extensively used for the synthesis of flavonoids[9] including total synthesis of dirchromone and related 2-substituted chromones.[10] Yatabe *et al.* synthesized a library of flavones using gold nanoparticles supported on a layered double hydroxide catalyst.[11] Kunde *et al.* described catalytic synthesis of chalcones and flavanones using Zn–Al hydrotalcite adhere ionic liquids however, lower yields were reported.[12] In another metal-based protocol, thermally regulated molybdate-based ionic liquids were used for the



Scheme 1 Previous synthetic schemes and present work.

[a]Laboratory of Organic and Medicinal Chemistry, Department of Chemistry, Central University of Punjab, Bathinda, Punjab, India-151401. E-mail: vpathania18@gmail.com; vinod.kumar@cup.edu.in; Tel: +911642864214

[b]Department of Computational Sciences, Central University of Punjab, Bathinda, Punjab, India-151401

[c]Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Bathinda, Punjab, India-151401

[d]Gitam School of Pharmacy, Hyderabad, Telangana, 502329, India

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ra08810c

© 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

molecular oxygen generation and one pot oxidative cascade process furnished variety of flavones.[13] Similarly, palladium has been used as catalyst for the synthesis of chromones/flavanones through cyclo-carbonylation of *ortho*-iodophenols with terminal acetylenes in phosphonium salt ionic liquids.[14] Awuah *et al.* reported microwave-assisted one pot synthesis of flavones through Sonogashira-carbonylation-annulation reactions of aryl halides with iodophenols in the presence of palladium catalyst.[15] There are many reports for the formation of chalcones in the presence of iodine only.[16] Cyclization of 2-hydroxy chalcones can lead to the formation of chromones and other flavonoids under strong basic conditions.[17] Chalcones are also cyclized to corresponding flavones using number of oxidizing agents such as DDQ,[18] NH_4I,[19] $InBr_3/InCl_3$.[20] In addition, molecular I_2 (ref. 21) and other iodine-mediated catalytic systems such as I_2-DMSO,[18,22] I_2-SiO_2 (ref. 23) and I_2–Al_2O_3 (ref. 24) were explored for the cyclization of chalcones into flavones. Kavala *et al.* reported iodine catalysed one pot synthesis of flavanones and tetrahydropyrimidines from benzaldehyde, aniline and 2-hydroxyacetophenones *via* Mannich type reaction however, no flavone formation was reported in this research article.[25] Naik *et al.* reported synthesis of flavones through pyrrolidine and iodine catalysed aldol-Michael-dehydrogenative reaction. In this transformation, pyrrolidine was found to be indispensable and it was observed that no product formation could occur in the absence of pyrrolidine.[26] The iodine-PEG combination was utilised in several other valuable transformations.[27] We did not come across any report for the single pot synthesis of flavones from 2-hydroxyacetophenone and benzaldehydes exclusively using molecular iodine only under milder conditions. Most of the reported protocols suffer with the disadvantages like use of strong acidic or basic conditions, use of toxic reagents/catalysts, formation of mixture of products such as flavones, flavanones, aurones *etc.* Thus, there is a scope for the development of efficient protocol for the synthesis of flavones under mild conditions without use of toxic metal catalysts. In the current research work, a single-pot synthesis of flavones is reported from the 2-hydroxy acetophenone and benzaldehydes using molecular iodine in polyethylene glycol. No other supporting reagent or catalyst was used for this transformation. The developed methodology provides direct access to the pharmaceutically important flavonoids/chromones in high yields. The possible mechanism of this chemical transformation was explored, and it was found to be facilitated by iodonium-triiodide anion pair formation through iodine-PEG 400 complexation.

Results and discussion

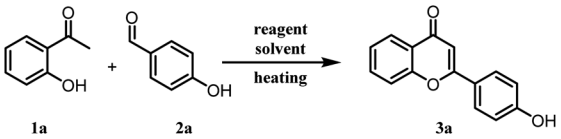
2-Hydroxy acetophenone and benzaldehydes are usually converted into flavones/chromones in a two-step process.[28] In the first step, chalcones are synthesized under strong basic, acidic, or other conditions and the second step involves the cyclization of 2-hydroxy chalcones to the corresponding flavones under different catalytic conditions. From the literature search, we have realized that no synthetic methodology is available for the direct conversion of 2-hydroxy acetophenone and benzaldehydes into flavones. Hence, we got interested in the one-pot synthesis of flavones/chromones from the corresponding 2-hydroxy acetophenone and benzaldehydes under milder conditions. Initially, a mixture of 2-hydroxyacetophenone (**1a**), benzaldehyde (**2a**), and molecular iodine (0.5 equivalent) was refluxed in ethanol at 80 °C. Notably, the desired product flavone (**3a**) was obtained in 7% yield along with some other side products and unreacted starting material even after 72 h of refluxing. It was pleasant to see the direct formation of flavone in a single pot. Naik *et al.* in their report, could not observe the flavone formation under similar reaction conditions. It might be due to the use of low molar concentration (10 mol%) of molecular iodine and shorter reaction time.[26] To improve the product yield, we increased the amount of molecular iodine to one equivalent (100 mol%), which slightly improved the yield of **3a** (14%) after refluxing for 72 h. Thereafter, we tried different reaction conditions such as elevated temperatures and different solvents like acetonitrile, dimethyl sulfoxide, ethylene glycol, glycerine, toluene, *N*-methyl pyrrolidone and dimethylformamide (Table 1). However, no product formation could be observed with these solvents, and starting materials remained unreacted in most of the cases even after prolonged heating. Polyethylene glycol (PEG-400) was found to be compatible for this reaction and **3a** was obtained in 84% yield at 140 °C within 7 h of optimized reaction conditions (Table 1). It was interesting to see that only PEG as solvent provided the desired product in high yield and all the other solvents were found to be ineffective. The lower molar percentage of molecular iodine with PEG as solvent were also found ineffective (Table 1, entries 12, 13, 14). In addition, replacement of molecular iodine with NaI and CuI as iodine source in PEG yielded no product however KI provided lower yields of the product (Table 1, entries 15, 16, 17). From these test reactions, we concluded that it might be a specific I_2-PEG combination assisting this two-step single-pot transformation. Molecular iodine is reported to form a complex with PEG, and it generates an iodonium-triiodide anion pair ($PEG\text{-}I^+ \cdot I_3^-$). Thus, some more test reactions were performed to explore the role of triiodide anion in this chemical transformation. A catalyst combination of molecular iodine and KI was used for the generation of triiodide anion and the reaction was performed with different solvents like DMF (Table 1, entry 18), toluene (Table 1, entry 19), and ethanol (Table 1, entry 20). Interestingly, improved yield of the product was obtained with catalyst combination in ethanol as compared to reaction conditions reported in entry 2 (Table 1), and product formation was observed even with DMF and toluene as solvents, clearly demonstrating the involvement of triiodide anion in the facilitation of this reaction.

Thus, the optimized reaction conditions were extended to other substituted benzaldehydes. Different types of benzaldehydes containing electron-releasing and electron-withdrawing groups were used and found compatible with the developed reaction conditions. Chloro, bromo, and cyano substituents were found to be well tolerated under the developed reaction conditions. Most importantly, even mono, and di-hydroxy substituted benzaldehydes provided corresponding flavones in high yield.[29] A polyhydroxylated flavonoid derivative, 6,3′,4′-

 © 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 1 Optimization of reaction conditions for the synthesis of chromones[a]



Entry	Reagents (equiv.)	Solvents	Temp. (°C)	Time (h)	Yield[b] (%)
1	I_2 (0.5)	Ethanol	80	72	7
2	I_2 (1.0)	Ethanol	80	72	14
3	I_2 (1.0)	EG	140	72	nd
4	I_2 (1.0)	Acetonitrile	80	72	nd
5	I_2 (1.0)	Toluene	80	72	nd
6	I_2 (1.0)	EtOAc	80	72	nd
7	I_2 (1.0)	DMF	140	72	nd
8	I_2 (1.0)	NMP	140	72	nd
9	I_2 (1.0)	DMSO	140	72	nd
10	I_2 (1.0)	Xylene	140	72	nd
11	**I_2 (1.0)**	**PEG-400**	**140**	**7**	**84**
12	I_2 (0.1)	PEG-400	140	72	13
13	I_2 (0.3)	PEG-400	140	72	39
14	I_2 (0.5)	PEG-400	140	72	58
15	NaI (1.0)	PEG-400	140	72	nd
16	CuI (1.0)	PEG-400	140	72	nd
17	KI (1.0)	PEG-400	140	72	8
18	I_2 + KI (1.0)	DMF	140	72	28
19	I_2 + KI (1.0)	Toluene	80	72	32
20	I_2 + KI (1.0)	Ethanol	80	72	22
21	$PhI(OAc)_2$	PEG-400	140	48	nd

[a] Reagents and conditions: different reagents were screened as given in Table 1 with varied temp. and equivalencies. [b] Isolated yield, nd - not detected.

trihydroxyflavone (6,3′4′-HOFL) was synthesized with ease using this protocol. It is reported to possess good anti-oxidant and anti-inflammatory activities in 2D and 3D cell culture models.[30] It is worth mentioning that hydroxy benzaldehydes were not reported in the previous studies[25,26] and in other reports, reactions were performed by protecting the hydroxy functionality. In addition, the hydroxy-substituted benzaldehydes were reported to display low reactivity due to phenoxide formation and results in the formation of several side products.[31] The current protocol was also found to be compatible with 2-thiophenecarboxyaldehyde and nitrobenzaldehyde. However, no product formation was observed with aliphatic aldehydes, probably due to the low boiling points of aliphatic aldehydes. Aliphatic aldehydes have low electrophilicity as compared to the aromatic aldehydes and there is a possibility of self-addition products due to the presence of enolizable protons. Thus, it was concluded that the developed reaction conditions are selective for the aromatic aldehydes (Table 2).

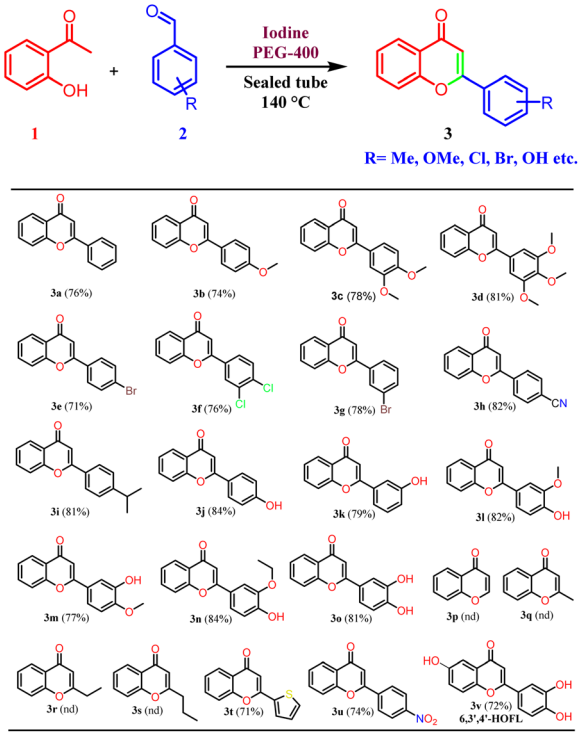
Plausible reaction mechanism

The current two-step single-pot chemical transformation is believed to proceed through triiodide anion formation. There are reports indicating that PEG-400 and higher can make a complex with neutral molecular iodine by trapping iodonium ion in a crown ethers-like cage and generating an iodide anion (I^-), which subsequently changes to triiodide anion (I_3^-) by reacting with another molecule of iodine (Fig. 1).[32]

Disproportionation of two molecules of molecular iodine also leads to the formation of triiodide anion.[33] It has been found that the negative charge of the triiodide anion is highly localized on the terminal iodine atom, resulting in the formation of two kinds of iodine–iodine bonds based on the bond lengths. The shorter I–I bond (approx. 2.8708 Å) dissociates in the excited state, whereas the longer one (approx. 3.0048 Å) dissociates in the ground state.[34] The disproportionation in the bond length of these I–I bonds explains the electron acceptor as well as the electron-donating nature of the triiodide anion.[35] Further, Rogachev and group also explained the potential acceptor and donor nature of I_3^- anion through the localized highest occupied molecular orbital (HOMO) and low-lying lowest unoccupied molecular orbital (LUMO) of the anion.[36] We have confirmed the formation of triiodide anion in the reaction mixture through UV absorption bands near 290 nm and 360 nm (Fig. 2A).[37] As evident from Fig. 2, no peaks were observed for the formation of triiodide anion when molecular iodine was used with THF, NMP, ethanol, ethylene glycol, ethylacetate, DMSO, DMF, AcCN, xylene, toluene, and only a band for molecular iodine was observed at 500 nm. While strong bands were observed at 290 nm and 360 nm with PEG-400. In Fig. 2B, the addition of KI along with molecular iodine in other

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 2 Substrate scope[a]



[a] Reagents and conditions: acetophenones, benzaldehydes, I_2, PEG-400, 140 °C, 4–7 h.

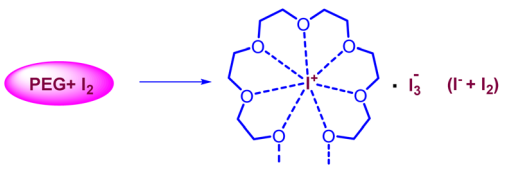


Fig. 1 Formation of I_3^- anion from iodide and molecular iodine.

solvents (ethylene glycol, DMF, ethanol) promoted triiodide anion formation, and bands were observed at 290 nm and 360 nm. It was also observed that the band for molecular iodine completely disappeared after 15 min of heating (Fig. 2B), and the whole of the iodine converted into triiodide anion.

It was hypothesized that due to disproportionation, the I_3^- anion abstracts the proton through the longer iodine–iodide bond.[38] In addition, iodine plays an active role in the polarization of carbonyl and olefinic bond during the cyclization of intermediate chalcones to the corresponding chromones. Deshidi and group demonstrated the polarisation of oxygen (C=O bond) molecule by molecular iodine through halogen bond formation for the synthesis of α-ketoamides[39] while Liang *et al.* showed the keto–enol tautomerization of cyclohexanone through interaction with iodonium ion.[40] It is reported that iodine also plays a central role in α,β-dehydrogenation reactions.[41] Thus, it was proposed that the reaction is initiated and assisted by the formation of PEG-

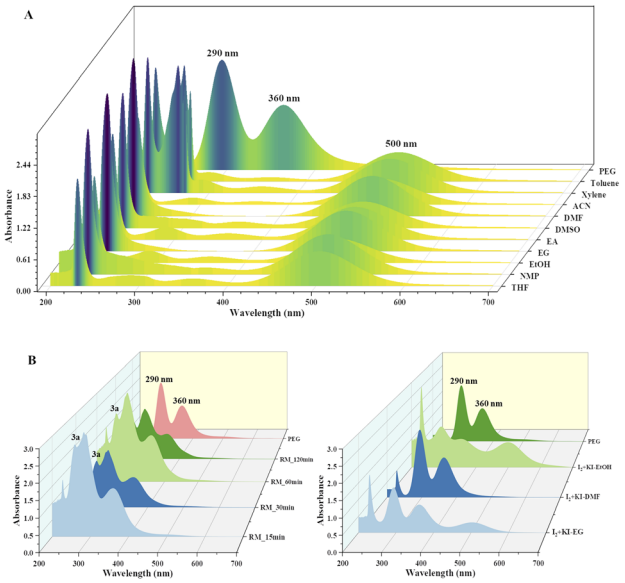


Fig. 2 UV-visible spectrum of (A) various iodine and solvent mixtures depicting the formation of I_3^- anion, peaks at 290 nm and 360 nm for the I_3^- and peak at 500 nm for I_2; (B) formation of I_3^- anion by the reaction of iodine and KI in solvents and in reaction mixture (PEG) at different time intervals.

iodonium-triiodide ion pair. Acetophenones and benzaldehydes condense to form chalcones as intermediates, which, through oxidative cyclization, convert to corresponding chromones. To get the mechanistic insights, we performed some controlled reactions. In a first test reaction, a mixture of 2-hydroxy acetophenone, benzaldehyde, molecular iodine, and PEG-400 was refluxed at 140 °C for one hour, and the reaction was stopped and quenched to trap and identify the intermediates. The reaction mixture was subjected to EIMS analysis, and four intermediates were identified as shown in Fig. 3. The quenched reaction mixture was worked up and purified through column chromatography. The two reaction intermediates (chalcone, **B**, and flavanone, **C**) were isolated, purified, and characterized through ^{1}H and ^{13}C NMR (see ESI† for details). Given below are some of the mass spectra of the identified intermediates.

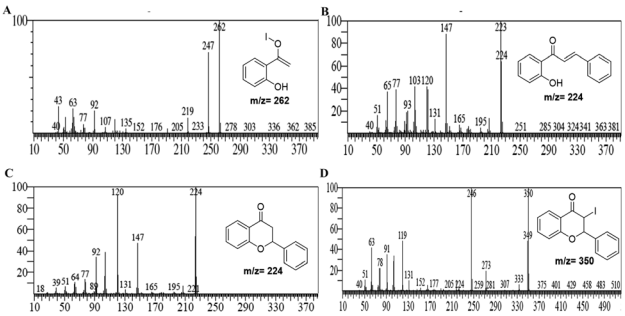


Fig. 3 Mass spectra of the identified intermediates; (A) formation of 1-(2-hydroxyphenyl)vinylhypoiodite intermediate; (B) formation of chalcone intermediate; (C) formation of chromanone intermediate; (D) formation of 3-iodo-chromanone intermediate.

 © 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

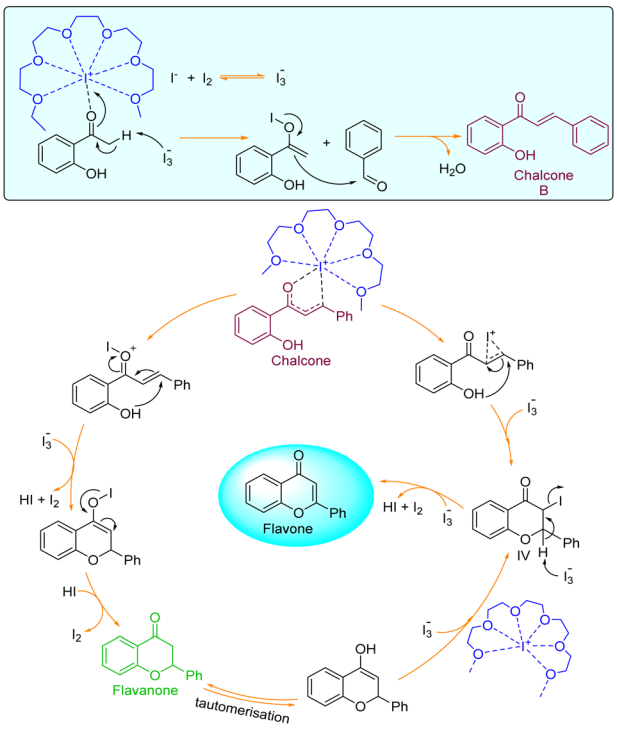


Fig. 4 Plausible mechanism for the formation of flavones.

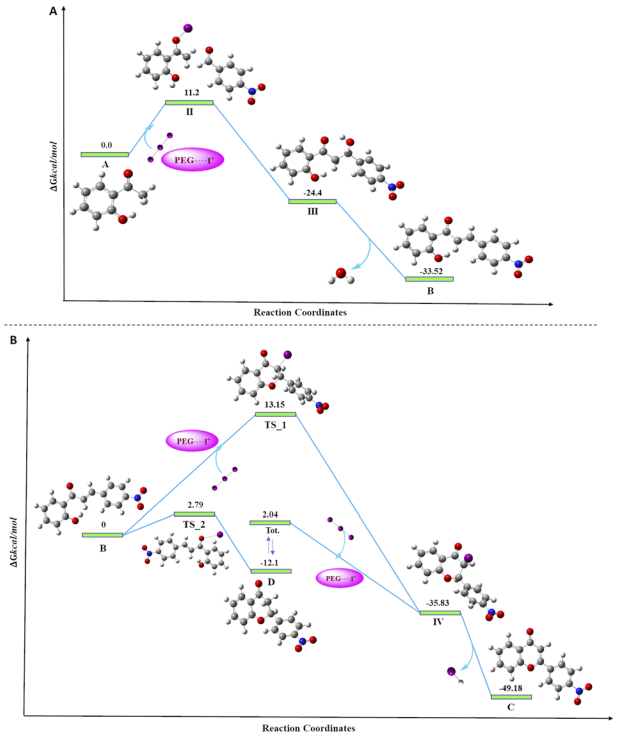


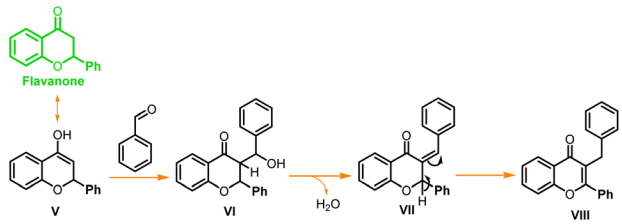
Fig. 5 Free energy diagram for the progress of the reaction, (A) the formation of chalcone; (B) the formation of flavone from chalcone.

In the 2nd test reaction, chalcone was synthesized through Claisen–Schmidt condensation of 2-hydroxy acetophenone and benzaldehyde. Thereafter, the chalcone was treated with molecular iodine in PEG-400 at 140 °C. After completion of the reaction, the flavone was successfully obtained thus further confirming that the reaction might be proceeding through the formation of chalcone-intermediate. Based on the results obtained from all the test reactions and the UV-visible spectra of the reaction and solvent mixtures in iodine, we proposed a reaction mechanism as given below (Fig. 4).

DFT studies

To access the feasibility of the reaction progression and to support the reaction mechanism, DFT calculations were performed using ORCA 5.0.3 software with PBE0 functional. Herein, it shows that the 1st step of the reaction proceeds with the formation of stable intermediate B (chalcone, $\Delta G^S = -33.52$ kcal mol^{-1}) through an exergonic aldol condensation reaction. It is also evidenced that the formation of major product flavone (C) may proceed through two pathways. The first is through oxidative cyclization of chalcone to flavone ($\Delta G^S = -49.18$ kcal mol^{-1}) directly *via* transition state TS_1 ($\Delta G^S = 13.15$ kcal mol^{-1}). Secondly, it may change to another stable intermediate flavanone (D, $\Delta G^S = -12.10$ kcal mol^{-1}), which subsequently converts to flavone through a barrierless transformation. This transformation of chalcone to either flavanone or flavone is exergonic in nature in both cases, but the energy barrier of the transformation through TS_1 to flavone is 10.36 kcal mol^{-1} more as compared to TS_2 to flavanone. This showed that the major product, flavone (C), is 37.08 kcal mol^{-1} lower in energy than flavanone, which is untimely converted to flavone by dehydrohalogenation. Transformation of both, the chalcone and flavanone to flavone proceeds through a common intermediate (IV, $\Delta G^S = -35.83$ kcal mol^{-1}) with the loss of HI. The DFT analyses concur the formation of the final product through two stable intermediates (chalcone and flavanone), with the overall release of energy (Fig. 5).

In a similar test reaction, when 2-hydroxy acetophenone was reacted with *p*-methoxy benzaldehyde under the same reaction conditions, and it was quenched after one hour, two new side products (Scheme 2, VII, and VIII) were obtained along with the expected chalcone and flavone. Compounds VII and VIII were purified through column chromatography and characterized through ^{1}H and ^{13}C NMR (ESI†). These side products were formed through double addition of *para*-methoxy-benzaldehyde and both side products were found to be isomers. In another test reaction with *para* hydroxybenzaldehyde, flavone was obtained as a major product while chalcone was obtained as



Scheme 2 Plausible mechanism for the formation of side products from flavanone.

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

a minor product when the reaction was stopped within an hour. Similarly, with *para* nitro-benzaldehyde flavanone and chalcone were obtained as intermediate products after one hour of the reaction time. The spectroscopic data of all these intermediates (chalcone and flavanone) from unsubstituted benzaldehyde, *p*-OH, and *p*-NO_2 substituted benzaldehydes are reported in the ESI.†

Conclusion

Flavones are an important class of compounds, and limited protocols are reported for their synthesis. Most of the synthetic methodologies for the flavones make use of toxic metal catalysts. In the current research article, a single-step synthesis of flavones was achieved from inexpensive and abundantly available acetophenones and benzaldehydes. Molecular iodine was used as a mild reagent in PEG-400 as solvent. The developed conditions were found to be compatible with range of substituted benzaldehydes including hydroxy-substituted derivatives. A reasonable mechanism has been proposed for this two-step single-pot chemical transformation through a series of test reactions. The iodine-PEG-400 combination was anticipated to play a crucial role in this reaction. UV-visible spectra showed the formation of the PEG iodonium-triiodide anion complex. The reaction proceeds through the formation of stable intermediates chalcone and flavanone. The DFT studies also supported the proposed mechanism. Thus, the developed protocol provides an efficient route for the direct excess of flavones with great tolerability for different substrates and can be explored for the synthesis of new library of medicinally important chromone derivatives.

Experimental section

General information

All the chemicals were purchased from Sigma Aldrich and were used as received. The compounds synthesized by the general procedure described below and were characterised by mass spectrometry and ^{1}H and ^{13}C NMR spectra recorded on 600 MHz JEOL NMR spectrometer in either $CDCl_3$ or DMSO-d_6 with TMS as an internal reference at Central University of Punjab, Bathinda (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.5 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO-d_6 at 39.52 ppm). The spectroscopic data of all the synthesized compounds are consistent with the reported datas.[42]

General synthetic procedure for (3a–3v)

A mixture of 2-hydroxyacetophenone (0.5 g, 3.67 mmol), respective benzaldehyde (1 equiv.), and iodine (0.47 g, 3.67 mmol) were taken in a sealed tube in PEG-400 as solvent (2 ml) and heated at 140 °C for 4 to 7 hours. The completion of the reaction was checked by thin-layer chromatography. On completion of the reaction, it was cooled to room temperature, iodine was quenched by 10% sodium thiosulphate solution and extracted with ethyl acetate. As PEG-400 is soluble in water, the traces from the ethyl acetate layer were removed by several water washes. The crude product was purified on silica gel by column chromatography using pet. ether/ethyl acetate (3 : 1 to 6 : 1) as eluent to give the desired product (70–84% yield).

2-Phenyl-4*H*-chromon-4-one (3a). Off-white solid, 76% yield. M.pt.: 96–98 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (s, 1H), 7.41–7.44 (m, 1H), 7.51–7.55 (m, 3H), 7.58 (dd, J = 8.4, 1.2 Hz, 1H), 7.69–7.72 (m, 1H), 7.94 (dd, J = 7.8, 1.8 Hz, 2H), 8.24 (dd, J = 12.0, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 107.6, 118.1, 124.0, 125.2, 125.7, 126.3, 129.0, 131.6, 131.8, 133.7, 156.3, 163.43, 178.4. MS (EI, *m*/*z*): 222.

2-(4-Methoxyphenyl)-4*H*-chromen-4-one (3b). A white solid, 74% yield. M.pt.: 156–158 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.75 (s, 1H), 7.03 (dd, J = 6.6, 1.8 Hz, 2H), 7.40–7.42 (m, 1H), 7.55 (dd, J = 8.4, 1.2 Hz, 1H), 7.67–7.70 (m, 1H), 7.89 (dd, J = 6.6, 1.8 Hz, 2H), 8.23 (dd, J = 8.4, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.5, 106.2, 114.4, 117.9, 123.9, 124.0, 125.0, 125.6, 128.0, 133.5, 156.2, 162.4, 163.4, 178.4. MS (EI, *m*/*z*): 252.

2-(3,4-Dimethoxyphenyl)-4*H*-chrome-4-one (3c). A yellowish solid, 78% yield. M.pt.: 150–152 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 (s, 3H), 3.99 (s, 3H), 6.77 (s, 1H), 7.00 (d, J = 8.4, 1H), 7.42 (dd, J = 15.0, 7.2 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.68–7.71 (m, 1H), 8.23 (dd, J = 7.8, 0.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.0, 56.1, 106.5, 108.8, 111.1, 118.0, 120.0, 123.9, 124.2, 125.1, 125.6, 133.6, 149.3, 152.0, 156.2, 163.3, 178.3. MS (EI, *m*/*z*): 282.

2-(3,4,5-Trimethoxyphenyl)-4*H*-chromen-4-one (3d). A yellowish solid, 81% yield. M.pt.: 174–176 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.97 (s, 6H), 6.78 (s, 1H), 7.14 (s, 2H), 7.42–7.45 (m, 1H), 7.60 (dd, J = 8.4, 0.6 Hz, 1H), 7.72 (m, 1H), 8.24 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.3, 61.0, 103.6, 107.4, 118.0, 123.9, 125.3, 125.7, 127.0, 133.7, 141.2, 153.6, 156.2, 163.2, 178.4. MS (EI, *m*/*z*): 312.

2-(4-Bromophenyl)-4*H*-chromen-4-one (3e). Off-white solid, 71% yield. M.pt.: 178–180 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (s, 1H), 7.44 (m, 1H), 7.57 (dd, J = 8.4, 0.6 Hz, 1H), 7.67 (dd, J = 6.6, 1.8 Hz, 2H), 7.70–7.73 (m, 1H), 7.80 (dd, J = 6.6, 1.8 Hz, 2H), 8.23 (dd, J = 7.8, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 107.7, 118.0, 123.9, 125.4, 125.7, 126.3, 127.7, 130.7, 132.3, 133.9, 156.1, 162.3, 187.3. MS (EI, *m*/*z*): 300.

2-(3,4-Dichlorophenyl)-4*H*-chromen-4-one (3f). A yellowish solid, 76% yield. M.pt.: 196–198 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.59 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.44–7.46 (m, 1H), 7.50–7.52 (m, 2H), 7.64 (dd, J = 7.8, 1.2 Hz, 1H), 7.70–7.73 (m, 1H), 8.26 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 113.1, 118.2, 123.8, 125.5, 125.8, 127.6, 128.9, 131.5, 132.5, 134.0, 134.1, 134.5, 156.5, 162.3, 178.0. MS (EI, *m*/*z*): 290.

2-(3-Bromophenyl)-4*H*-chromen-4-one (3g). A brownish solid, 78% yield. M.pt.: 114–116 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.42–7.45 (m, 1H), 7.59 (dd, J = 8.4, 1.2 Hz, 1H), 7.67 (ddd, J = 6.6, 1.2 Hz, 1H), 7.70–7.73 (m, 1H), 7.83 (ddd, J = 6.6, 1.2 Hz, 1H), 8.08 (t, J = 1.8 Hz, 1H), 8.23 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 108.2, 118.1, 123.2, 123.9, 124.8, 125.4, 125.7, 129.2, 130.5, 133.8, 134.0, 134.4, 156.2, 161.7, 178.2. MS (EI, *m*/*z*): 300.

4-(4-oxo-4*H*-Chromen-2-yl)benzonitrile (3h). Off white solid, 82% yield. M.pt.: 218–220 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (s, 1H), 7.45–7.48 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.73–7.76 (m, 1H), 7.84 (dd, J = 6.6, 1.8 Hz, 2H), 8.05 (dd, J = 6.6, 1.8 Hz, 2H),

 © 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

8.25 (dd, J = 8.4, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 109.2, 115.0, 117.9, 118.1, 123.9, 125.7, 125.9, 126.8, 132.8, 134.3, 135.9, 156.1, 160.9, 178.0. MS (EI, m/z): 247.

2-(4-Isopropylphenyl)-4*H*-chromen-4-one (3i). A brownish liquid, 81% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (d, J = 7.2, 6H), 2.99 (h, J = 6.6 Hz, 1H), 6.80 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.39–7.42 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.67–7.70 (m, 1H), 7.86 (dd, J = 6.6, 1.8 Hz, 2H), 8.23 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.7, 34.1, 107.0, 118.0, 124.0, 125.1, 125.7, 126.4, 127.2, 129.3, 133.6, 153.0, 156.2, 163.6, 178.5. MS (EI, m/z): 264.

2-(4-Hydroxyphenyl)-4*H*-chromen-4-one (3j). A yellowish solid, 84% yield. M.pt.: 268–270 °C. ^{1}H NMR (600 MHz, DMSO) δ 6.87 (s, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.80–7.83 (m, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.04 (dd, J = 8.4, 2.4 Hz, 1H), 10.31 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 104.7, 115.8, 118.2, 121.4, 123.2, 124.6, 125.2, 128.2, 133.9, 155.4, 160.8, 162.9, 176.7. MS (EI, m/z): 238.

2-(3-Hydroxyphenyl)-4*H*-chromen-4-one (**3k**)

Off white solid, 79% yield. M.pt.: 206–208 °C. ^{1}H NMR (600 MHz, DMSO) δ 6.94 (s, 1H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 1.8 Hz, 1H), 7.53 (dd, J = 15.6, 7.2 Hz, 2H), 7.78 (d, J = 8.4, 1H), 7.83–7.86 (m, 1H), 8.07 (dd, J = 7.8, 1.2 Hz, 1H), 9.91 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 106.8, 112.7, 117.1, 118.4, 118.7, 123.2, 124.7, 125.4, 130.1, 132.3, 134.2, 155.5, 157.8, 162.6, 176.9. MS (EI, m/z): 238.

2-(4-Hydroxy-3-methoxyphenyl)-4*H*-chromen-4-one (3l). A brownish solid, 82% yield. M.pt.: 190–192 °C. ^{1}H NMR (600 MHz, DMSO) δ 3.98 (s, 3H), 6.73 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.43 (dd, J = 7.8, 0.6 Hz, 1H), 7.48 (dd, J = 8.4, 2.4 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.69–7.72 (m, 1H), 8.17 (dd, J = 7.8, 1.2 Hz, 1H), 9.11 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 56.0, 105.6, 109.3, 115.8, 118.0, 120.3, 122.7, 123.7, 125.0, 125.2, 133.5, 147.9, 150.4, 156.0, 163.7, 178.0. MS (EI, m/z): 268.

2-(3-Hydroxy-4-methoxyphenyl)-4*H*-chromen-4-one (3m). A yellowish solid, 77% yield. M.pt.: 148–150 °C. ^{1}H NMR (600 MHz, DMSO) δ 3.96 (s, 3H), 6.70 (s, 1H), 6.99 (dd, J = 6.0, 3.0 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.47–7.48 (m, 1H), 7.49 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.70–7.72 (m, 1H), 8.18 (dd, J = 7.8, 1.2 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 55.9, 106.0, 11.3, 113.0, 118.0, 118.5, 123.8, 124.2, 125.0, 125.3, 133.6, 146.8, 150.7, 156.1, 163.5, 178.1. MS (EI, m/z): 268.

2-(3-Ethoxy-4-hydroxyphenyl)-4*H*-chromen-4-one (3n). A yellow solid, 84% yield. M.pt.: 150–152 °C. ^{1}H NMR (600 MHz, DMSO) δ 1.39 (t, J = 6.6 Hz, 3H), 4.18 (q, J = 7.2 Hz, 2H), 6.98 (t, 4.5 Hz, 2H), 7.47–7.50 (m, 1H), 7.59–7.61 (m, 2H), 7.77 (dd, J = 8.4, 0.6 Hz, 1H), 7.80–7.82 (m, 1H), 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 14.6, 64.1, 105.0, 111.3, 115.7, 118.3, 120.1, 121.8, 123.2, 124.6, 125.1, 133.8, 147.1, 150.6, 155.5, 162.9, 176.8. MS (EI, m/z): 282.

2-(3,4-Dihydroxyphenyl)-4*H*-chromen-4-one (**3o**)

A brown solid, 81% yield. M.pt.: 242–244 °C. ^{1}H NMR (600 MHz, DMSO) δ 6.77 (s, 1H), 6.93 (d, J = 9.0 Hz, 1H), 7.47 (dt, J = 6.6, 1.8 Hz, 2H), 7.5 (d, J = 6.6 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.80–7.83 (m, 1H), 8.05 (dd, J = 7.8, 1.2 Hz, 1H), 9.44 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 104.7, 113.3, 115.9, 118.1, 118.7, 121.8, 123.2, 124.6, 125.2, 133.9, 145.6, 149.3, 155.4, 136.1, 176.6. MS (EI, m/z): 254.

2-(Thiophen-2-yl)-4*H*-chromen-4-one (3t). A yellowish solid, 71% yield. M.pt.: 98–100 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.70 (s, 1H), 7.18 (dd, J = 4.2, 1.2 Hz, 1H), 7.41 (t, J = 8.4 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.57 (dd, J = 4.2, 1.2 Hz, 1H), 7.67–7.69 (m, 1H), 7.72 (dd, J = 3.0, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.2, 117.9, 124.0, 125.2, 125.7, 128.4, 128.5, 130.2, 133.74, 135.2, 155.9, 159.0, 177.8. MS (EI, m/z): 228.

2-(4-Nitrophenyl)-4*H*-chromen-4-one (3u). A yellowish solid, 74% yield. M.pt.: 244–246 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 7.8 Hz, 1H), 8.39 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 109.6, 118.1, 123.9, 124.2, 125.7, 125.9, 127.2, 134.3, 137.6, 149.4, 156.2, 160.5, 177.9. MS (EI, m/z): 267.

2-(3,4-Dihydroxyphenyl)-6-hydroxy-4*H*-chromen-4-one (3v). A off white solid, 72% yield. ^{1}H NMR (600 MHz, DMSO) δ 6.67 (s, 1H), 6.90 (d, J = 9.0 Hz, 1H), 7.23 (dd, J = 6.0 Hz, 3.0 Hz, 1H), 7.31 (d, J = 3.0 Hz, 1H), 7.41–7.43 (m, 2H), 7.58 (d, J = 9.0 Hz, 1H), 9.39–9.96 (s, 3H, OH); ^{13}C NMR (150 MHz, DMSO) δ 104.4, 108.1, 113.7, 116.5, 119.1, 120.0, 122.7, 123.2, 124.7, 146.2, 149.7, 155.2, 163.3, 177.2. MS (EI, m/z): 270.

Spectroscopic data of some isolated intermediates/side products

2-(4-Nitrophenyl)-chroman-4-one. A yellowish solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.95 (dd, J = 13.2, 3.6 Hz, 1H), 3.02 (dd, J = 13.2, 3.6 Hz, 1H), 5.61 (dd, J = 9.6, 3.0 Hz, 1H), 7.09–7.11 (m, 2H), 7.55 (td, J = 7.2, 1.2 Hz, 1H), 7.68 (d, J = 9.0, 2H), 7.94 (dd, J = 6.0, 1.8 Hz, 1H), 8.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 44.6, 78.3, 118.0, 120.9, 122.2, 124.1, 126.8, 127.2, 136.5, 145.8, 148.0, 160.9, 190.6.

(*E*)-1-(2-Hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one. A yellowish solid, ^{1}H NMR (600 MHz, DMSO) δ 7.02 (dd, J = 6.0, 2.4 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.88 (d, J = 15.6 Hz, 1H), 8.17 (t, J = 13.8 Hz, 3H), 8.22 (d, J = 7.8 Hz, 1H), 8.28 (d, J = 8.4 Hz, 2H), 12.21 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO) δ 118.2, 119.8, 121.5, 124.4, 126.8, 130.5, 131.5, 137.0, 141.4, 141.9, 148.7, 162.1, 193.7.

(*E*)-1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one. A white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.93 (dd, J = 6.0, 1.2 Hz, 1H), 6.95 (dd, J = 4.8, 1.8 Hz, 2H), 7.02 (dd, J = 7.2, 1.2 Hz, 1H), 7.49 (td, J = 6.6, 1.8 Hz, 1H), 7.54 (d, J = 15.6 Hz, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.90 (d, J = 12.0 Hz, 1H), 7.92 (dd, J = 4.8, 1.8 Hz, 1H), 12.93 (s, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.4, 114.5, 117.6, 118.6, 118.7, 120.1, 127.3, 129.5, 130.5, 136.1, 145.3, 162.0, 163.5, 193.7.

(*Z*)-3-(4-Methoxybenzylidene)-2-(4-methoxyphenyl)chroman-4-one. A white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.80 (s, 3H), 6.61 (s, 1H), 6.83 (dd, J = 4.8, 1.8 Hz, 2H), 6.87 (dd, J = 4.8, 1.8 Hz, 2H), 6.89 (dd, J = 7.2, 1.2 Hz, 1H), 6.93–6.95 (m, 1H), 7.24 (dd, J = 4.8, 1.8 Hz, 2H), 7.36–7.38 (m, 1H), 7.39 (dd, J = 8.4, 0.6 Hz, 2H), 7.92 (dd, J = 6.0, 1.8 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.2, 55.4, 77.7, 114.2, 114.4, 118.6, 121.6, 122.3, 126.8, 127.6, 129.1, 130.2, 130.5, 132.2, 135.9, 139.1, 158.8, 159.8, 161.0, 182.7.

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one. A white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.87 (s, 3H), 3.92 (s, 2H), 6.77 (dt, J = 4.8, 1.8 Hz, 2H), 6.97 (dt, J = 4.8, 1.8 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 7.38–7.40 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.53 (dt, J = 4.8, 1.8 Hz, 2H), 7.64–7.66 (m, 1H), 8.24 (dd, J = 6.6, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.5, 55.2, 55.4, 113.8, 113.9, 117.8, 120.3, 123.0, 124.7, 125.6, 126.1, 129.0, 130.2, 132.4, 133.4, 156.1, 157.8, 161.2, 162.7, 178.3.

(*E*)-1-(2-Hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one. A white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (d, J = 9.0 Hz, 2H), 6.94 (m, 1H), 7.02 (dd, J = 7.2, 1.2 Hz, 1H), 7.48–7.50 (m, 1H), 7.54 (d, J = 15.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 15.6 Hz, 1H), 7.92 (dd, J = 6.6, 1.8 Hz, 1H), 12.92 (s, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 116.1, 117.8, 118.6, 118.8, 120.20, 127.6, 129.6, 130.8, 136.2, 145.3, 158.3, 136.6, 193.8.

2-Phenylchroman-4-one. A white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.90 (dd, J = 13.8, 3.0 Hz, 1H), 3.09 (dd, J = 13.2, 3.6 Hz, 1H), 5.49 (dd, J = 10.2, 3.0 Hz, 1H), 7.06 (m, 2H), 7.39 (tt, J = 3.6, 1.2 Hz, 1H), 7.44 (m, 2H), 7.49 (dd, J = 7.2, 1.2 Hz, 2H), 7.51 (dt, J = 5.4, 1.8 Hz, 1H), 7.94 (dd, J = 6.6, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 44.7, 79.6, 118.1, 120.9, 121.6, 126.1, 127.0, 128.8, 128.8, 136.2, 138.7, 161.5, 191.9.

DFT calculations

All the DFT calculations were performed using the ORCA 5.0.3 software.[43] Density functional theory was employed with PBE0 functional,[44] dispersion corrections based on tight binding partial charges (D4)[45] along with Ahlrichs and co-workers balanced polarised double zeta basis set (def2-svp).[46] RIJ-COSX[47] approximation was used throughout to speed up the calculations. Transition states were calculated by implementing Nudged-Elastic-Band method of Asgeirsson *et al.*[48] All minima on the potential energy surface were verified by calculating the vibrational frequencies using the same level of theory. Furthermore, for refinement in results, a higher valence polarised triple zeta basis set (def2-tzvp) was employed with PBE0 functional to calculate the single point-energy of the whole system. The solute–solvent interaction is described by the conductor-like polarizable continuum model (CPCM).[49] The dielectric constant & refractive index of PEG-400 is taken as 11.6 and 54, respectively.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

VK is thankful to the Council of Scientific and Industrial Research New Delhi for the financial grant No. 02/(0354)/19/EMRII. NK, NS, and Vijay Kumar are thankful to the University Grant Commission for providing Senior Research Fellowship. Vinay Kumar is thankful to CSIR for SRF. KJ and ARD are thankful to ICMR (45/29/2022-/BIO/BMS) and DST-SERB, respectively, for their fellowship grants.

Notes and references

1 N. Shen, T. Wang, Q. Gan, S. Liu, L. Wang and B. Jin, *Food Chem.*, 2022, **383**, 132531.
2 D. Treutter, *Environ. Chem. Lett.*, 2006, **4**, 147–157.
3 S. K Sharma, S. Kumar, K. Chand, A. Kathuria, A. Gupta and R. Jain, *Curr. Med. Chem.*, 2011, **18**, 3825–3852.
4 (*a*) J. Reis, A. Gaspar, N. Milhazes and F. Borges, *J. Med. Chem.*, 2017, **60**, 7941–7957; (*b*) M. Irfan, S. ul Hassan and U. Saleem, *Pharm. Chem. J.*, 2020, **54**, 241–257; (*c*) L. K. Tsou, M. Lara-Tejero, J. RoseFigura, Z. J. Zhang, Y.-C. Wang, J. S. Yount, M. Lefebre, P. D. Dossa, J. Kato and F. Guan, *J. Am. Chem. Soc.*, 2016, **138**, 2209–2218; (*d*) M. Singh, M. Kaur and O. Silakari, *Eur. J. Med. Chem.*, 2014, **84**, 206–239.
5 D. Ameen and T. J. Snape, *Synth.*, 2015, **47**, 141–158.
6 (*a*) D. A. Williams, C. Smith and Y. Zhang, *Tetrahedron Lett.*, 2013, **54**, 4292–4295; (*b*) S. Patel and U. Shah, *Synth.*, 2017, **10**, 403–406.
7 J. J. Li, in *Name Reactions*, Springer, 2014, pp. 8–9.
8 (*a*) N. Anitha, K. V. Reddy and Y. J. Rao, *Heterocycl. Commun.*, 2014, **20**, 129–132; (*b*) W. Mansour, M. Fettouhi and B. El Ali, *ACS Omega*, 2020, **5**, 32515–32529.
9 (*a*) B. P. Reddy and G. D. Krupadanam, *J. Heterocycl. Chem.*, 1996, **33**, 1561–1565; (*b*) A. Fougerousse, E. Gonzalez and R. Brouillard, *J. Org. Chem.*, 2000, **65**, 583–586; (*c*) N. Thasana and S. Ruchirawat, *Tetrahedron Lett.*, 2002, **43**, 4515–4517.
10 A. St-Gelais, J. Alsarraf, J. Legault, C. Gauthier and A. Pichette, *Org. Lett.*, 2018, **20**, 7424–7428.
11 T. Yatabe, X. Jin, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2015, **54**, 13302–13306.
12 L. B. Kunde, S. M. Gade, V. S. Kalyani and S. P. Gupte, *Catal. Commun.*, 2009, **10**, 1881–1888.
13 Z. Song, W. Huang, Y. Zhou, Z.-Q. Tian, Z.-M. Li and D.-J. Tao, *Green Chem.*, 2020, **22**, 103–109.
14 (*a*) X. Zhao, J. Zhou, S. Lin, X. Jin and R. Liu, *Org. Lett.*, 2017, **19**, 976–979; (*b*) Q. Yang and H. Alper, *J. Org. Chem.*, 2010, **75**, 948–950.
15 E. Awuah and A. Capretta, *Org. Lett.*, 2009, **11**, 3210–3213.
16 (*a*) K. V. Sashidhara, J. N. Rosaiah and A. Kumar, *Synth. Commun.*, 2009, **39**, 2288–2296; (*b*) D. Kakati and J. C. Sarma, *Chem. Cent. J.*, 2011, **5**, 1–5; (*c*) H. Wang and J. Zeng, *Can. J. Chem.*, 2009, **87**, 1209–1212.
17 H. Chawla and S. Sharma, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1987, **26**, 1075–1077.
18 P. Venkatesan and T. Maruthavanan, *Bull. Chem. Soc. Ethiop.*, 2011, **25**, 419–425.
19 P. S. Kulkarni, D. D. Kondhare, R. Varala and P. K. Zubaidha, *J. Serb. Chem. Soc.*, 2013, **78**, 909–916.
20 N. Ahmed, H. Ali and J. E. van Lier, *Tetrahedron Lett.*, 2005, **46**, 253–256.
21 K. V. Sashidhara, M. Kumar and A. Kumar, *Tetrahedron Lett.*, 2012, **53**, 2355–2359.
22 M. Masih, T. Banerjee, B. Banerjee and A. Pal, *Int. J. Pharm. Pharm. Sci.*, 2011, **3**, 51–54.

 © 2024 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 19 February 2024. Downloaded on 11/5/2025 2:52:00 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

23 K. Rajesh Babu, K. Vijaya Kumar, M. Vijaya and V. Madhavarao, *Int. J. Pharm. Technol*, 2012, **4**, 3943–3950.
24 S. R. Sarda, W. N. Jadhav and R. P. Pawar, *Int. J. Chem. Tech. Res.*, 2009, **1**, 539–543.
25 V. Kavala, C. Lin, C.-W. Kuo, H. Fang and C.-F. Yao, *Tetrahedron*, 2012, **68**, 1321–1329.
26 M. M. Naik, S. G. Tilve and V. P. Kamat, *Tetrahedron Lett.*, 2014, **55**, 3340–3343.
27 (*a*) W. Lui, G. Lu, B. Xiao and C. Xie, *RSC Adv.*, 2018, **8**(54), 30860–30867; (*b*) D. Guttman and T. Higuchi, *J. Am. Pharm. Assoc.*, 1955, **44**, 668–678; (*c*) A. K. Pathan, P. Patil, A. Shinde and S. Zangade, *Curr. Green Chem.*, 2021, **8**(2), 166–173.
28 E. S. VH, S. Matsjeh, T. D. Wahyuningsih, M. Mustofa and T. Redjeki, *Indones. J. Chem.*, 2012, **12**, 146–151.
29 M. Mellado, A. Madrid, Ú. Martínez, J. Mella, C. O. Salas and M. Cuellar, *Chem. Pap.*, 2018, **72**, 703–709.
30 X. Wang, Y. Cao, S. Chen, X. Yang, J. Bian and D. Huang, *Antioxid*, 2023, **12**, 204.
31 (*a*) G. Sipos and F. Sirokman, *Nature*, 1964, **202**, 489; (*b*) P. Kulkarni, P. Swami and P. Zubaidha, *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.*, 2013, **43**, 617–620.
32 S. Hemalatha, B. Chandani and D. Balasubramanian, *Spectrosc. Lett.*, 1979, **12**, 535–541.
33 S. Aronson, P. Epstein, D. B. Aronson and G. Wieder, *J. Phys. Chem.*, 1982, **86**, 1035–1037.
34 J. Heo, J. G. Kim, E. H. Choi, H. Ki, D.-S. Ahn, J. Kim, S. Lee and H. Ihee, *Nat. Commun.*, 2022, **13**, 522.
35 E. Bartashevich, V. Batalov, I. Yushina, A. Stash and Y. Chen, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2016, **72**, 341–345.
36 A. Y. Rogachev and R. Hoffmann, *Inorg. Chem.*, 2013, **52**, 7161–7171.
37 A. Nimmrich, M. R. Panman, O. Berntsson, E. Biasin, S. Niebling, J. Petersson, M. Hoernke, A. Björling, E. Gustavsson and T. B. van Driel, *J. Am. Chem. Soc.*, 2023, **145**, 15754–15765.
38 (*a*) P. A. Sathe, K. S. Vadagaonkar, M. V. Vhatkar, L. Melone and A. C. Chaskar, *ChemistrySelect*, 2018, **3**, 277–283; (*b*) Y.-P. Zhu, M. Lian, F.-C. Jia, M.-C. Liu, J.-J. Yuan, Q.-H. Gao and A.-X. Wu, *Chem. Commun.*, 2012, **48**, 9086–9088; (*c*) Y. Cao, L. Liu, T. Huang and T. Chen, *New J. Chem.*, 2020, **44**, 8697–8701.
39 R. Deshidi, M. Kumar, S. Devari and B. A. Shah, *Chem. Commun.*, 2014, **50**, 9533–9535.
40 Y.-F. Liang, X. Li, X. Wang, M. Zou, C. Tang, Y. Liang, S. Song and N. Jiao, *J. Am. Chem. Soc.*, 2016, **138**, 12271–12277.
41 (*a*) Y. Cao, L. Lui, T. Huang and T. Chen, *New J. Chem.*, 2020, **44**, 8697–8701; (*b*) Q. Gao, M. Wu, K. Zhang, N. Yang, M. Lui, J. Li, L. Fang, S. Bai and Y. Xu, *Org. Lett.*, 2020, **22**, 5645–5649; (*c*) D. Li, *Asian J. Org. Chem.*, 2023, **12**, e202300012.
42 (*a*) M.-L. Ma, M. Li, J.-J. Gou, T. Y. Ruan, H.-S. Jin, L.-H. Zhang, L. C. Wu, X. Y. Li, Y. H. Hu and K. Wen, *Biomed. Chem.*, 2014, **22**(21), 6117–6123; (*b*) J. Y. An, H.-H. Lee, J. S. Shin, H. S. Yoo, J. S. Park, S. H. Son, S. W. Kim, J. Yu, J. Lee and K. T. Lee, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 2613–2616; (*c*) V. N. Badavath, S. Ciftci-Yabanoglu, S. Bhakat, A. K. Timiri, B. N. Sinha, G. Ucar, M. E. Soliman and V. Jayaprakash, *Bio. Chem.*, 2015, **58**, 72–80; (*d*) Z. Du, H. Ng, K. Zhang, H. Zeng and J. Wang, *Org. Biochem.*, 2011, **9**, 6930–6933; (*e*) X. Zhao, R. Fang, F. Wang, X. Kong and Y. Li, *JACS Au*, 2023, **3**, 185–194.
43 (*a*) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**(1), 73–78; (*b*) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2018, **8**(1), e1327.
44 C. Adamo and V. Barone, *J. Chem. Phys.*, 1999, **110**, 6158–6170.
45 (*a*) E. Caldeweyher, C. Bannwarth and S. Grimme, *J. Chem. Phys.*, 2017, **147**, 034112; (*b*) E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth and S. Grimme, *Chem. Phys.*, 2019, **150**, 154122.
46 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305.
47 F. Neese, F. Wennmohs, A. Hansen and U. Becker, *Chem. Phys.*, 2009, **356**(1–3), 98–109.
48 V. Ásgeirsson, B. O. Birgisson, R. Bjornsson, U. Becker, F. Neese, C. Riplinger and H. Jónsson, *J. Chem. Theory Comput.*, 2021, **17**, 4929–4945.
49 J. Tomasi, B. Mennucci and R. Cammi, Quantum mechanical continuum solvation models, *Chem. Rev.*, 2005, **105**(8), 2999–3094.