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Synthesis of functionalized chromones through sequential reactions in aqueous media

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Abstract: An efficient sequential four-component reaction of chromone carbaldehydes, Meldrum's acid, 4-hydroxyl coumarin or 6-methyl-4-hydroxyl-pyrone and primary alcohols is reported which leads to **5a-i** in aqueous media. Replacing the primary alcohol with isopropyl alcohol and *tert*-butyl alcohol results in different products **10, 11**. The environmentally-friendly features, good to high yields and easy work-up are advantages of this approach.

Keywords: Meldrum's acid, Chromonyl Meldrum's acid, Four-component reaction, 4-Hydroxy coumarin, sequential reaction

Dedicated to Prof. Abbas Shafiee on the occasion of his 75th birthday

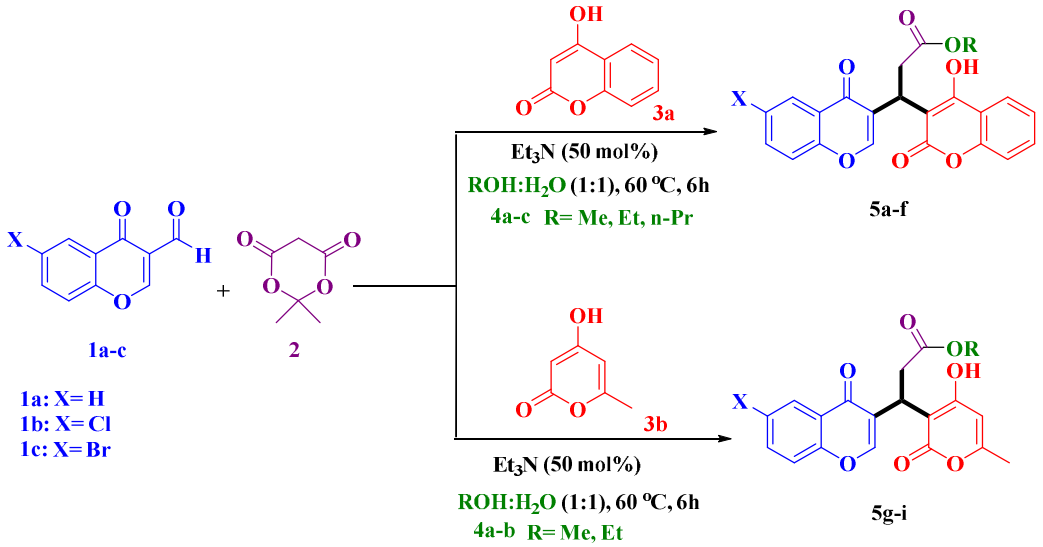
Introduction

Carrying out the organic reactions in aqueous media has attracted much attention due to its importance in green and sustainable chemistry.[1] Water has been used as a suitable media for the formation of C-C bond.[2] But, designing the new reactions based on multicomponent reactions (MCRs) and sequential one-pot combination for the coupling of two biologically active heterocyclic skeletons is an interesting subject in organic synthesis. One-pot multicomponent reactions have gained considerable interest for the synthesis of biologically active compounds.[3] Designing the new multicomponent and sequential reactions using readily available starting materials in aqueous media have gained widespread recognition among the organic chemists.[4] This approach could be categorized based on combining two or more distinct reactions into a single transformation, thereby producing cascade reactions as sequential reactions to form molecular diversity and complexity in natural and biologically relevant systems.[5] Employing water as green solvent, is an important approach in developing environmentally friendly approaches in the synthesis of biologically active compounds via MCRs and also sequential reactions.[6-10]

Coumarins and their derivatives are extensively found in different natural products and they have interesting biological activities. The coumarin structural motif is present in many naturally occurring compounds that display a wide range of biological activities.[11] Due to the activity of these compounds, the development of a facile approach to synthesize these heterocyclic skeletons in a molecule through C-C bond formation in aqueous media is highly desirable and valuable for medicinal chemistry and also green chemistry.[12] Meanwhile, chromones are present in nature, with wide variety of useful biological activities such as protein kinase C inhibitors,[13] antifungal,[14] antivirial,[15] anti-oxidant[16] and anticancer activities.[17] The chromones exist as efficient pharmacophores in some drugs and also in flavones.[18] Reaction of 3-formyl chromone with two equivalents of 4-hydroxy coumarin and their antimicrobial activity has been recently reported. [19] Furocoumarins and biscoumarins were also reported through designing of a three-componenet reaction of 3-formyl chromone, 4-hydroxy coumarin and isocyanide.[20] Due to the mentioned importance of these building blocks, we planned the preparation of chromones containing coumarin skeleton.

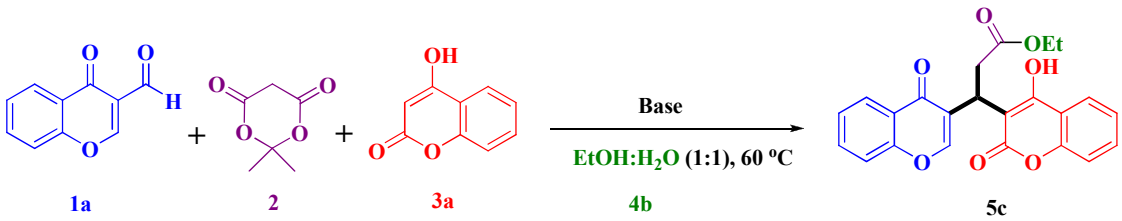
In continuation of our previous research works on the design of novel multicomponent reaction,[21] we wish to report herein a four-component reaction of 3-formyl chromone, Meldrum's acid, and 4-hydroxy coumarin or 6-methyl-4-hydroxy-2-pyrone in the mixture of

some primary alcohols and water (alcohol:water 1:1) in the presence of triethylamine (50%) to construct the products containing chromone and coumarin skeletons. (Scheme 1)



Scheme1. Synthesis of alkyl 3-chromonyl-3-chromemnylpropanoates **5a-i**

The study was started with designing a model four-component reaction of 3-formyl chromone **1**, Meldrum's acid **2** and 4-hydroxy coumarin **3a** in the mixture of ethanol and water (1:1) in the presence of various bases (Table 1). In all reaction conditions, the isolated product was compound **5c**.



Scheme 2. The model reaction for the synthesis of **5c**

As shown in table 1, triethylamine, piperidine, DABCO, diiopropylethylamine (DIPEA) and potassium carbonate were the investigated bases. The best yield (85%) of the desired product **5c** was obtained by using triethylamine as the base, and using of 10, 20, 40, and 50% of the base led to 20, 50, 65, and 85% yields, respectively. It was found that when the amount of

triethylamine was increased to 60%, the yield of product was still 85% which shows that further increasing of triethylamine did not improve the yield of product. It should be mentioned that the reaction didn't proceed in the absence of base catalyst and only the alkene was produced through reaction of 3-formyl chromone and Meldrum's acid. (Table **1**)

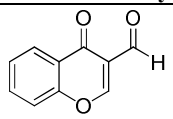
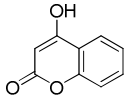
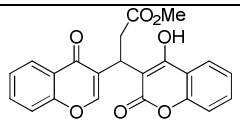
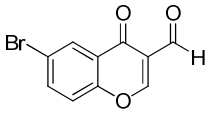
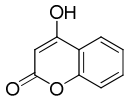
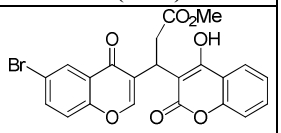
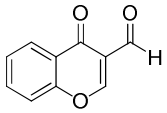
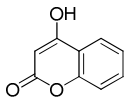
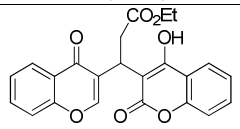
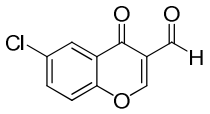
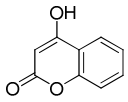
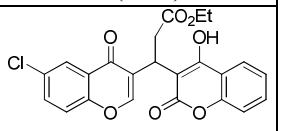
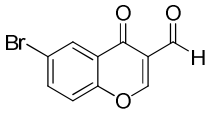
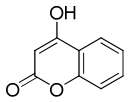
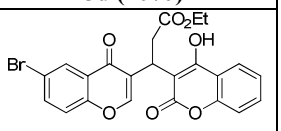
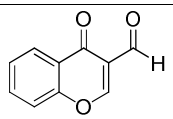
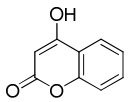
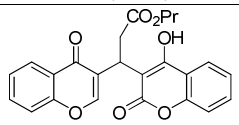
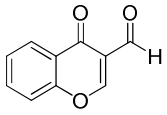
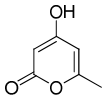
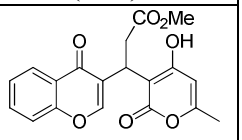
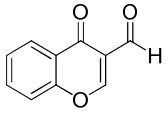
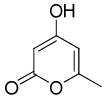
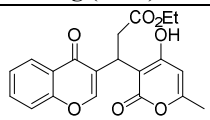
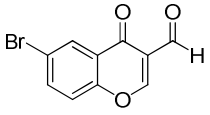
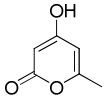
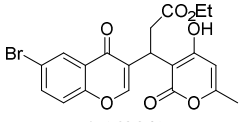
Table1. Optimization of the base for the synthesis of **5c**

entry	Base	Solvent	Time(h)	Yield(%)
1	Et_3N (10 mol%)	EtOH : H_2O(1:1)	6	20
2	Et_3N (20 mol%)	EtOH : H_2O(1:1)	6	50
3	Et_3N (40mol%)	EtOH : H_2O(1:1)	6	65
4	**Et_3N (50 mol%)**	**EtOH : H_2O(1:1)**	**6**	**85***
5	Et_3N (60mol%)	EtOH : H_2O(1:1)	6	85
6	Piperidine (50mol%)	EtOH : H_2O(1:1)	6	80
7	DABCO (50mol%)	EtOH : H_2O(1:1)	8	73
8	DIPEA (50mol%)	EtOH : H_2O(1:1)	7	80
9	K_2CO_3 (50mol%)	EtOH : H_2O(1:1)	6	80

*Reaction conditions, **1a** (1mmol, 174 mg) , **2** (1mmol, 144 mg), **3a** (1mmol, 162 mg), Et_3N(0.5 mmol, 50 mg) in 6 ml (EtOH, H2O) (1:1)

Meanwhile, to study the effect of temperature, the reaction was performed at different temperatures, *i.e.* 40, 50, 60, and 80 ˚C. The yields of the desired product **5c** were 62, 75, 85, and 80 % respectively. So, the suitable reaction temperature was 60 ˚C. After finding the optimized reaction conditions, the scope and limitations of this reaction were studied using different 3-formyl chromone **1a-c**, Meldrum's acid **2**, 4-hydroxy coumarin **3a** or 4-hydroxy-6-methyl pyrone **3b** in the mixture of some primary alcohol (methanol, ethanol and *n*-propyl alcohol) **4a-c** and water (1:1) to access the desired products **5a-i** under the optimized conditions. The results are summarized in table 2.

Table 2. Synthesis of 3-chromenyl or (3-pyranyl)-3-coumarinylpropanoate **5a-i** through one-pot four-component reaction

Entry	Chromone aldehyde	Pyrone	Solvent	Products
1	 **1a**	 **3a**	$MeOH:H_2O$ **4a**	 **5a (85%)**
2	 **1c**	 **3a**	$MeOH:H_2O$ **4a**	 **5b (62%)**
3	 **1a**	 **3a**	$EtOH:H_2O$ **4b**	 **5c (85%)**
4	 **1b**	 **3a**	$EtOH:H_2O$ **4b**	 **5d (70%)**
5	 **1c**	 **3a**	$EtOH:H_2O$ **4b**	 **5e (70%)**
6	 **1a**	 **3a**	n-$PrOH:H_2O$ **4c**	 **5f(72%)**
7	 **1a**	 **3b**	$MeOH:H_2O$ **4a**	 **5g (63%)**
8	 **1a**	 **3b**	$EtOH:H_2O$ **4b**	 **5h (65%)**
9	 **1c**	 **3b**	$EtOH:H_2O$ **4b**	 **5i (63%)**

The structure of compounds **5a-i** was deduced from their ^{1}H and ^{13}C NMR spectroscopic data and also ESI-HRMS spectrometric data. For compound **5c** as a representative example, the ^{1}H NMR spectrum of **5c** consisted of a doublet of doublet for the C-H in prochiral centers with the distinguished peak at δ 4.88 ppm, and also a doublet of doublet for the -CH_2 as the diastereotopic protons. The olephinic proton of chromone resonated at 8.45 ppm. The hydroxyl group resonated at δ 12.0 ppm which is related to intramolecular hydrogen bonding. The proton decoupled ^{13}C NMR spectrum of **5c** showed 22 distinct resonances in agreement with the proposed structure. The carbonyl group of unsaturated ketone and also two esters resonated at δ 180.2, 171.6 and 163.0 ppm, respectively. Meanwhile, the structure of **5c** was subsequently confirmed by single-crystal X-ray crystallographic data (Fig. 1). As shown in Fig. 1 the orientation of two coumarin and chromone skeletons allows an intramolecular hydrogen bridge between $C{=}O^{12}\ldots\ {}^{22}H\text{-}{}^{22}O$ group.

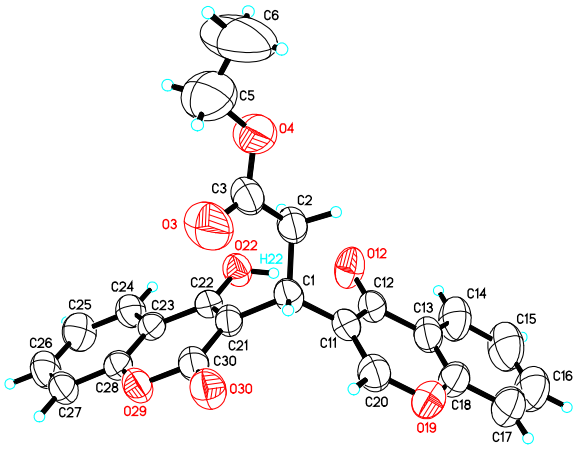
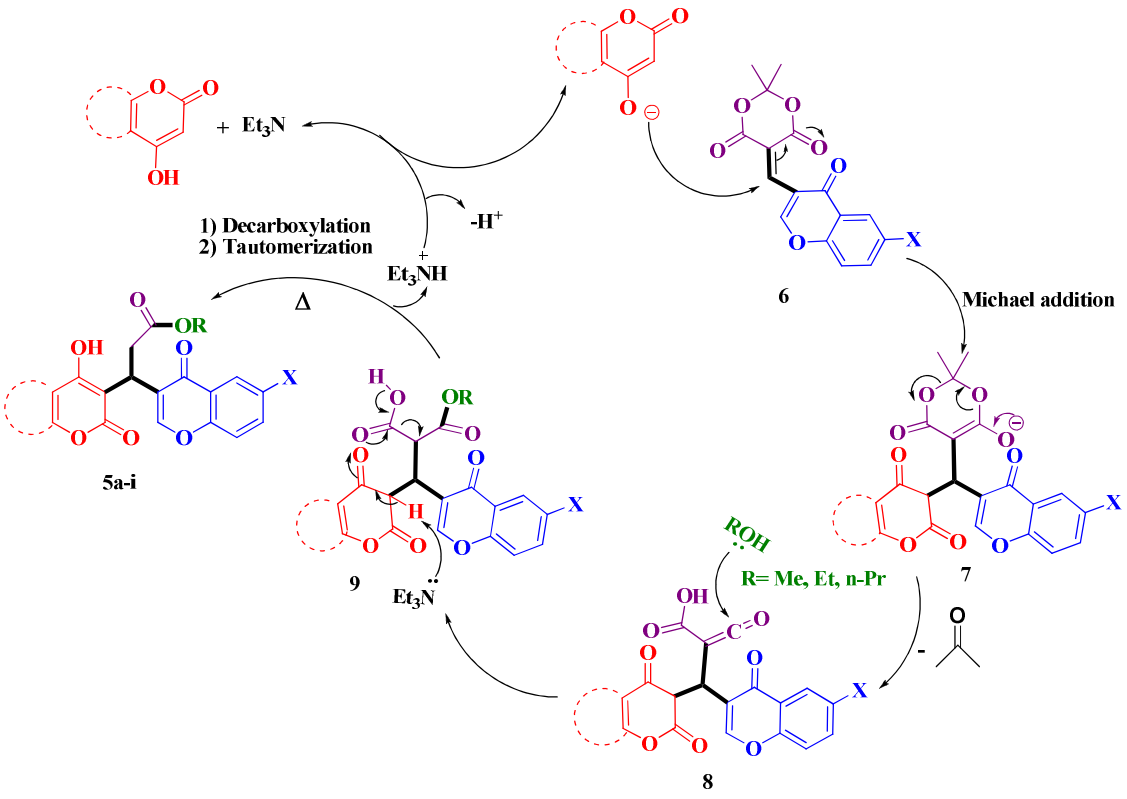


Figure 1. ORTEP structure of compound **5c**.

When the reactions were carried out in a mixture of primary alcohol (MeOH, EtOH, *n*-propyl alcohol) and water (1:1), besides acting as a solvent, the alcohol could also be added as a nucleophile. This shows the more nucleophilicity of primary alcohol compared to water which is in accordance with the quantitative scales of solvent nucleophilicity for primary alcohols and water.[22] The model reaction was checked in ethanol as the solvent in the absence of water. At first, the alkene was formed through the reaction of 3-formyl chromone and Meldrum's acid with slow rate. The desired product **5c** was formed in lower yield (60%) in an oily form. In another try, the model reaction was investigated in the presence of triethylamine as the base and water as the solvent. The product was the carboxylic acid **11**. Water acts as a

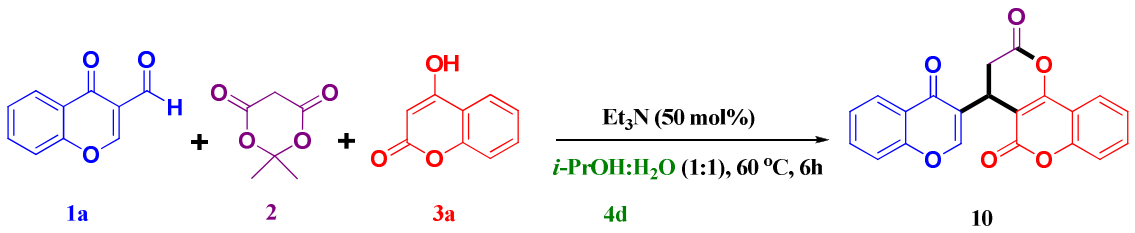
nucleophile and the product was appeared like oil. The yield of reaction was (60%) and accessing the product required extraction with organic solvents. This also shows that the primary alcohol has more nucleophilicity than water.

The possible mechanism for the synthesis of compounds **5a-i** is shown in Scheme 3. This conversion involves the initial Knoevenagel reaction of 3-formyl chromone and Meldrum's acid in the presence of triethylamine. The alkylidene Meldrum's acid **6** is an efficient intermediate as Michael acceptor which is used for post-transformation in the synthesis of some bioactive compounds.[23] The deprotonated form of 4-hydroxy coumarin or 6-methyl 4-hydroxy pyrone could be added to the alkene **6** and form the intermediate **7**. After removal of acetone, the ketene **8** is formed as an intermediate. The ketene intermediate is a suitable electrophile and nucleophilic addition of primary alcohol to ketene intermediate forms compound **9** which undergoes decarboxylation and tautomerization and finding leads to the desired product **5a-i**. The reaction has high bond forming efficiency and the three formed bonds has been specified in the molecular structure.



Scheme 3. Proposed mechanism for the synthesis of **5a-i**

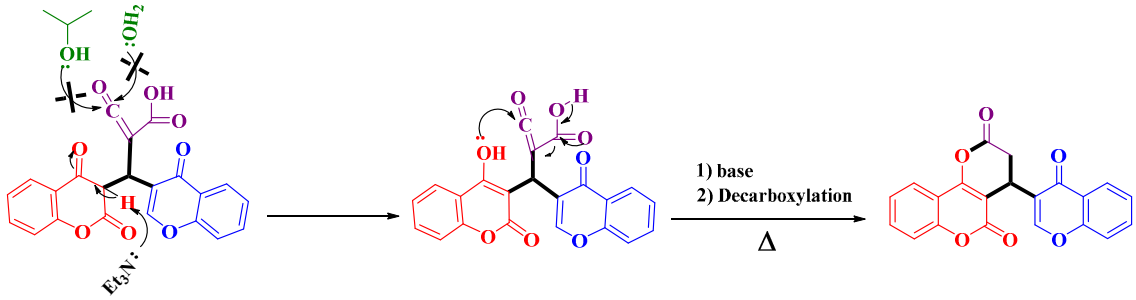
After these successful multicomponent reactions, the three-component reaction of 3-formyl chromone, Meldrum's acid and 4-hydroxy coumarin in the presence of triethylamine (50%) in a mixture of *i*-PrOH-H_2O (1:1) was also investigated and the sole product was compound **10**. (Scheme 4)



Scheme 4. Synthesis of chromonyl-dihydropyrano[3,2-*c*]chromene **10**

In this reaction condition, isopropyl alcohol could not act as a nucleophile and it didn't precipitate in the structure of the product. The desired ketene intermediate had good solubility in isopropyl alcohol, [18] but isopropyl alcohol couldn't be added as a nucleophile.In this case, the -OH group of coumarin acted as the intramolecular nucleophile in the presence of a base. The cyclized product, the lactone was an unusual product which could be formed through an intramolecular nucleophilic addition.[24]

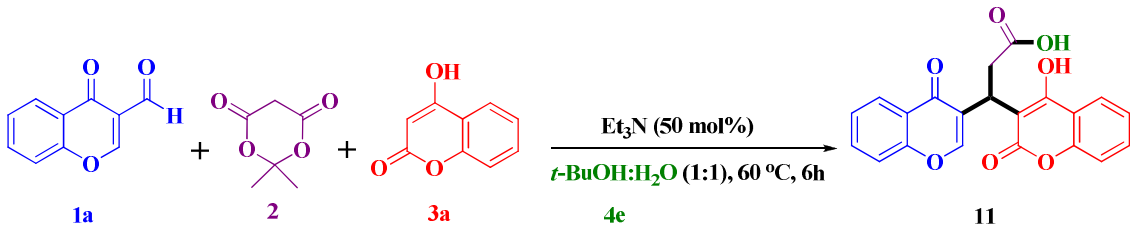
The proposed mechanism for the synthesis of compound **10** is summarized in Scheme 5. Due to low nucleophilicity of isopropyl alcohol, and low solubility of the intermediate in water, triethylamine could abstract the acidic proton and the internal nucleophilic addition to ketene after decarboxylation led to product **10.**



Scheme 5. Proposed mechanism for the synthesis of **10**

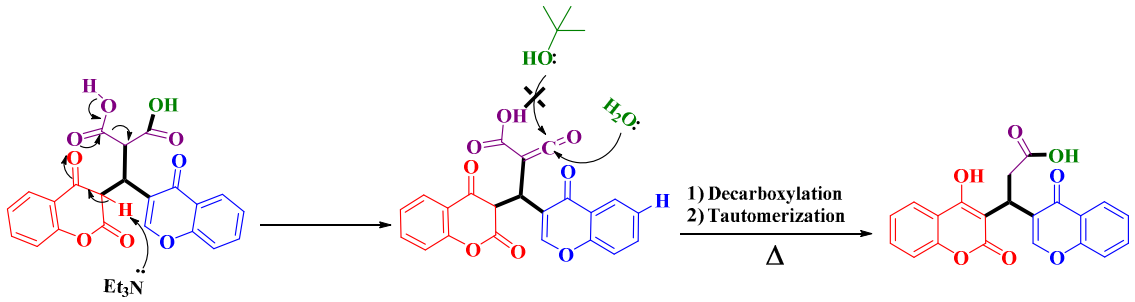
Our investigation was followed by a three-component reaction of 3-formyl chromone, Meldrum's acid and 4-hydroxy coumarin in the presence of triethylamine (50%) in a mixture

of *t*-BuOH-H_2O (1:1) and the carboxylic acid **11** was formed as the sole product. *Tert*-Butyl alcohol has lower nucleophilicity than water, and in this reaction condition, water could act as the nucleophile and the carboxylic acid **11** was formed as the product.



Scheme 6. Synthesis of product **11** using mixture of *t*-BuOH/H_2O

The proposed mechanism is summarized in scheme 7. After nucleophilic addition of 4-hydroxy coumarin to arylmethylidene Meldrum's acid and removal of acetone, the desired ketene was formed. Water has more nucleophilicity than *tert*-butanol, and nucleophilic addition of water to the ketene followed by the decarboxylation and tautomerization led to product **11**.



Scheme 7. Proposed mechanism for the synthesis of **11**

The isotopic hydrogen exchange was checked for the specified reaction using addition of D_2O to the solvent. The protons of carboxylic acid and also the hydroxyl group were exchanged with deuterium.

All of the above mentioned reactions could proceed through tandem reactions. During the initial effective reaction, the Knoevenagel product of Meldrum's acid and 3-formyl chromone was formed, then three reactions were done to access the desired product as follows: Michael/decarboxylation/nucleophilic addition. The nucleophilic addition of alcohol was the determining step for the selection of the product.

In conclusion, we have developed a facile four-component reaction of 3-formyl chromones, Meldrum's acid and 4-hydroxy coumarin or 6-methyl 4-hydroxy pyrone and primary alcohols in water to construct three C-C bond for connection of chromone and coumarin skeletons. In these reactions, alcohol could act as a nucleophile. When *iso*-propanol and *tert*-butyl alcohol were used as both solvent and reagent in the reaction, chromenyl-dihydropyrano[3,2-*c*] chromene **10** and also functionalized carboxylic acid **11** were formed. Synthesis of functionalized compounds, good to high yields, using of readily available starting materials, carrying out the reaction in a one-pot operation, environmentally friendly character and easy work-up are advantages of this approach.

Experimental section:

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal*9100 apparatus and are uncorrected. IR spectra were obtained on an ABB FTIR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-300 AVANCE spectrometers at 300 MHz for ^{1}H NMR, and 75 MHz for ^{13}C NMR. DMSO-d_6 and $CDCl_3$ was used as solvent. High resolution mass spectra were recorded on Mass-ESIPOS (Apex Qe-FT-ICR instrument) spectrometer.

General procedure for the synthesis of compounds **5a-i**, **10** and **11**.

To a solution of 3-formyl chromone **1**(174 mg, 1 mmol), Meldrum's acid **2 (**1 mmol, 144 mg**)** in 6 ml of mixture of (primary alcohol: H_2O) (1:1) was added. The mixture was stirred for 3 hours at ambient temperature. Then 4-hydroxy coumarin **3a** (1mmol, 162 mg) or 6-methyl-4-hydroxy pyrone **3b** (1mmol, 126 mg) and triethylamine (0.5 mmol, 50 mg) was added to the mixture of reaction and the mixture of reaction was heated at 60 ˚C for 3 hours. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 1:2), the alcohol was removed under vacuum, and the residue was precipitated. The precipitate was filtered off by addition of 3 mL of H_2O. Then, the precipitate was washed with 3mL hot ethanol (**5a-5f, 10, 11**). But for purification of products **5g-5i,** the aqueous phase was extracted with EtOAc (2×30ml). The combined organic phase separated, dried over sodium sulfate, filtered, and concentrated dryness in vacuum. Further purification was done using column chromatography. [*n*-hexane: ethyl acetate (2:1)]

Methyl 3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(4-oxo-4*H*-chromen-3- yl)propanoate(5a). white powder; m.p. 174-176 ^{o}C; IR (KBr, cm^{-1}) υ:3076, 2948, 1737, 1701, 1621; ^{1}HNMR (300 MHz, DMSO-d_6) δ_H: 3.20 (s, 2H, CH_2), 3.52 (s, 3H, OCH_3), 4.93 (s, 1H, C*H*), 7.30-7.33 (m, 2H, ArH), 7.43-7.50 (m, 1H,ArH), 7.58-7.64 (m, 2H, ArH), 7.78-7.85 (m, 1H,ArH), 7.90- 8.00 (d, 1H, *J*=6.6 Hz, ArH), 8.39 (s, 1H, =C*H*), 11.9 (brs, 1H, O*H*);^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 28.5, 33.8, 51.4, 103.8, 116.1, 116.4, 118.3, 122.7, 122.9, 123.6, 123.9, 125.1, 125.5, 132.0, 134.4, 152.2, 155.3, 155.6, 161.6, 161.7, 171.9, 176.8; ESI-MS *m/z*393[M+H]$^{+}$; HRMS (ESI) calc. for $C_{22}H_{17}O_7$ [M+H]$^{+}$ 393.09722 , found 393.09715; ESI-MS *m/z*415 [M+Na] $^{+}$; HRMS (ESI)calc. for $C_{22}H_{16}NaO_7$ [M+Na] $^{+}$ 415.07919, found 415.07912.

Methyl 3-(6-bromo-4-oxo-4*H*-chromen-3-yl)-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)propanoate (5b).Isolated as a white powder; m.p. 182-183 ^{o}C; IR (KBr, cm^{-1}) υ: 3091, 2949, 1726, 1694, 1625; ^{1}HNMR (300 MHz, DMSO-d_6) δ_H: 3.08-3.19 (m, 2H, CH_2), 3.52 (s, 3H, OCH_3), 4.94 (t, 1H, *J* = 7.5 Hz,C*H*), 7.33 (t, 2H, *J* = 8.5 Hz, ArH), 7.58 (t, 1H, *J* = 7.8 Hz, ArH), 7.62 (d, 1H, J = 7.8 Hz, ArH), 7.62(d, 1H,*J*= 9.0 Hz, ArH), 7.87-8.05 (m, 2H, ArH), 8.09 (d, 1H, *J*= 2.0 Hz, ArH), 8.39 (s, 1H, =C*H*), 11.9 (brs, 1H, O*H*);^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 28.4, 33.7, 51.4, 103.5, 116.1, 116.3, 117.8, 121.0, 123.1, 123.6, 123.9, 124.3, 127.2, 132.1, 136.9, 152.2, 154.5, 155.5, 161.5, 161.7, 171.8, 175.2; ESI-MS m/z 471[M+H]$^{+}$; HRMS (ESI)calc. for $C_{22}H_{16}{}^{79}BrO_7$ [M+ H]$^{+}$; 471.00737 , found 471.00736; HRMS (ESI)calc. for $C_{22}H_{16}{}^{81}BrO_7$ [M + H]$^{+}$ 473.00529 , found 473.00530.

Ethyl 3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(4-oxo-4*H*-chromen-3-yl) propanoate (5c).
Isolated as a white powder: m.p.135-137°C; IR(KBr, cm^{-1}) ν^{-1}:3085, 2978, 1734, 1701, 1622, ^{1}H NMR(300 MHz, $CDCl_3$) δ_H: 1.16 (t, 3H, *J*=7.1 Hz, CH_3), 3.24 (dd, 1H, *J* = 16.5, 7.1 Hz, C*H*), 3.50 (dd, 1H, *J* = 16.5, 8.9 Hz, C*H*), 4.07 (q, 2H, *J*=7.1 Hz, CH_2), 4.88 (dd, 1H, *J*= 8.3, 7.1 Hz, C*H*), 7.26 (td, 2H,*J*= 8.1, 1.7 Hz, ArH), 7.42-7.49 (m, 2H, ArH), 7.52 (d, 1H, *J*=8.5 Hz, ArH), 7.73(td, 1H, *J*=7.1, 1.6 Hz, ArH), 7.98 (dd, 1H, *J* =7.8, 1.1 Hz, ArH), 8.25 (dd, 1H, *J* =8.1, 1.3 Hz, ArH), 8.45(s, 1H, =C*H*), 12(brs, 1H, O*H*); ^{13}C NMR(75 MHz, $CDCl_3$)δ_C: 14.1, 34.1, 60.7, 104.8, 116.1, 117.2, 118.4, 122.6, 123.4, 123.8, 124.2, 125.7, 125.9, 131.9, 134.7, 152.6, 156.5, 163.0, 171.6, 180.2; ESI-MS m/z 407 [M + H]$^{+}$;HRMS (ESI) calc. for $C_{23}H_{19}O_7$ [M + H]$^{+}$ 407.11325 , found 407.11311; HRMS (ESI) calc. for $C_{23}H_{18}NaO_7$ [M+Na]$^{+}$ 429.09538 , found 429.09521; HRMS (ESI) calc. for $C_{23}H_{18}KO_7$ [M+K]$^{+}$ 445.06919 , found 445.06937.colourless crystal (polyhedron), dimensions 0.43 x 0.31 x 0.08 mm^3, crystal system monoclinic, space group C2/c, Z=8, a=18.6832(15) Å, b=9.6574(8) Å, c=22.636(3) Å, alpha=90 deg, beta=108.894(3) deg, gamma=90 deg, V=3864.1(6) Å^3, rho=1.397 g/cm^3, T=199(2) K, Theta$_{max}$= 21.61 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.54and a completeness of 99.3% to a resolution of 0.96Å, 10455 reflections measured,

2226 unique (R(int)=0.0315), 1877 observed (I >2σ(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[1] based on the Laue symmetry of the reciprocal space, mu=0.10mm^{-1}, T_{min}=0.96, T_{max}=0.99, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package[2], 283 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.05 for observed reflections, final residual values R1(F)=0.061, wR(F^2)=0.150 for observed reflections, residual electron density -0.20 to 0.52 eÅ^{-3}. CCDC 990174 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Ethyl 3-(6-chloro-4-oxo-4*H*-chromen-3-yl)-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)propanoate (5d). Isolated as a yellow powder;m.p.145-148 °C; IR (KBr, cm^{-1})ν^{-1}:3104, 2972, 1731,1695, 1619; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.17 (t, 3H, *J* =7.1 Hz, C*H*$_3$), 3.24 (dd, 1H, *J* = 16.7, 6.9Hz, C*H*), 3.50 (dd, 1H, *J*= 16.7, 8.9 Hz, C*H*), 4.1 (q, 2H, *J* =7.1 Hz, C*H*$_2$), 4.87(dd, 1H, *J* = 8.5, 6.9 Hz, C*H*), 7.25 (d, 1H, *J*= 8.2 Hz, ArH), 7.27 (t, 1H, *J* = 7.7 Hz, ArH), 7.48-7.53(m, 2H, ArH), 7.67 (dd, 1H, *J* = 8.9, 2.5 Hz, ArH), 7.98 (dd, 1H, *J*= 7.8, 1.2 Hz, ArH), 8.21 (d, 1H, *J* = 2.4 Hz, ArH), 8.45(s, 1H, =C*H*), 11.6 (brs, 1H, O*H*);^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.1, 34.0, 60.8, 104.6, 116.1, 117.0, 120.1, 123.5, 123.6, 124.0, 124.2, 125.2, 131.8, 132.0, 135.0, 152.6, 154.8, 163.0, 171.5, 179.1; ESI-MS m/z 441 $[M + H]^+$; HRMS (ESI) calc. for $C_{23}H_{18}{}^{35}ClO_7$ $[M+ H]^+$ 441.07447 , found 441.07430.

Ethyl 3-(6-bromo-4-oxo-4*H*-chromen-3-yl)-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)propanoate (5 e). Isolated as a white powder; m.p. 182-184 ^{o}C; IR (KBr, cm^{-1}) ν^{-1}: 3101, 2972, 1731, 1695; ^{1}HNMR (300 MHz, DMSO-*d*$_6$) δ_H: 1.03 (*t*, 3H, *J*= 7.1 Hz, C*H*$_3$), 3.05-3.24 (*m*, 2H, C*H*$_2$), 3.95 (*q*, 2H, *J*=6.75 Hz,OC*H*$_2$),4.93 (*t*, 1H, *J*= 7.1 Hz, C*H*), 7.33 (*t*, 2H, *J*= 7.7 Hz, ArH), 7.57 (*d*, 1H, *J*= 7.2 Hz, ArH), 7.63 (*d*, 1H, *J*= 7.2 Hz, ArH), 7.95 (*t*, 2H, *J*= 8.1 Hz, ArH), 8.09 (*s*, 1H,ArH),8.38 (*s*, 1H, =C*H*),11.8 (brs, 1H, O*H*); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ_C: 13.9, 28.5, 34.0, 59.9, 103.4, 116.1, 116.3, 117.8, 121.1, 123.1, 123.6, 123.9, 124.3, 127.2, 132.1, 136.9, 152.2, 154.5, 155.5, 161.5, 161.7, 171.3, 175.3;ESI-MS m/z 486 $[M+H]^+$;HRMS (ESI) calc. for $C_{23}H_{18}{}^{79}BrO_7$ $[M+ H]^+$ 485.02400 , found 485.02384.

Propyl 3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(4-oxo-4*H*-chromen-3-yl)propanoate (5f).Isolated as a white powder; m.p. 200-202 ^{o}C; IR (KBr, cm^{-1}): ν^{-1}: 3443, 3068, 1729, 1626; ^{1}HNMR (300 MHz, DMSO-*d*$_6$)δ_H:0.70 (*t*, 3H,*J*= 7.3 Hz, C*H*$_3$), 1.37-1.45 (*m*, 2H, C*H*$_2$), 3.02- 3.24 (*m*, 2H, C*H*$_2$), 3.78-3.85 (*m*, 2H, C*H*$_2$), 4.98-5.02 (*m*, 1H, C*H*), 7.08-7.12 (*m*, 2H, ArH), 7.30-7.42 (*m*, 2H,ArH), 7.45-7.55 (*m*, 1H, ArH), 7.48-7.56 (*m*, 1H, ArH), 7.65-7.75 (*m*, 1H,ArH), 7.80- 7.95 (*m*, 2H, ArH), 8.27 (*s*, 1H, =C*H*); 12 (brs, 1H, O*H*);^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ_C: 10.1, 21.5, 27.9, 35.0, 64.9, 98.2, 115.4, 118.2, 121.5, 122.0, 122.9, 124.7, 125.0, 125.1, 130.2, 133.9, 153.2, 155.3,

155.5, 163.5, 169.7, 172.1, 176.8; ESI-MS m/z 421 $[M+H]^+$; HRMS (ESI) calc. for $C_{24}H_{21}O_7$ $[M+H]^+$ 421.12885 , found 421.12882; ESI-MS *m/z*443 $[M+Na]^+$; HRMS (ESI) calc. for $C_{24}H_{20}NaO_7$ $[M+Na]^+$ 443.11089 , found 443.11075.

Methyl 3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-(4-oxo-4*H*-chromen-3-yl)propanoate (5g). Isolated as a Red powder; m.p. 144-146 °C; IR (KBr, cm^{-1}): ν^{-1};3140, 2950, 1740, 1693, 1616; ^{1}HNMR (300 MHz, DMSO-d_6) δ_H:2.11 (*s*, 3H, C*H*$_3$), 2.89-3.08 (*m*, 2H, C*H*$_2$), 3.52 (*s*, 3H, OC*H*$_3$), 4.78 (*t*, 1H, *J* = 7.6 Hz, C*H*), 5.97 (*s*, 1H, =C*H*), 7.45 (*t*, 1H, *J* = 7.3 Hz, ArH), 7.58 (*d*, 1H, *J*= 8.2 Hz, ArH), 7.76 (*t*, 1H, *J* = 7.5 Hz, ArH), 8.15 (*d*, 1H, *J* = 7.8 Hz, ArH), 8.14 (*s*, 1H, =C*H*),11.6 (brs, 1H, O*H*);^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 19.2, 27.2, 34.4, 51.3, 99.3, 100.4, 118.3, 123.0, 123.5, 125.1, 125.3, 134.0, 154.5, 155.5, 161.0, 163.8, 167.1, 171.9, 175.8. ESI-MS m/z 357 $[M+H]^+$HRMS (ESI) calc. for $C_{19}H_{17}O_7$ $[M+1]^+$ 357.09676 , found 357.09671; ESI-MS *m/z*379 $[M+Na]^+$; HRMS (ESI) calc. for $C_{19}H_{16}NaO_7$ $[M+Na]^+$ 379.07867 , found 379.07862; ESI-MS *m/z*395 $[M+K]^+$;HRMS (ESI) calc. for $C_{19}H_{16}KO_7$ $[M+K]^+$ 395.05260 , found 395.05255.

Ethyl 3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-(4-oxo-4*H*-chromen-3-yl)propanoate (5h).

Isolated as a Yellow powder;m.p.136-138 °C; IR (KBr,cm^{-1}) υ^{-1}: 3065, 2984, 1737, 1650 cm^{-1}; ^{1}HNMR(300 MHz, DMSO-d_6) δ_H: 1.07 (t, 3H, *J* = 7.1 Hz, C*H*$_3$), 2.11 (s, 3H, C*H*$_3$), 2.90 (dd, 1H, *J* = 15.2, 6.6 Hz, C*H*), 3.02 (dd, 1H, *J* =15.2, 9.4 Hz, C*H*), 3.97 (q, 2H, *J* =7.1 Hz, OC*H*$_2$), 4.78 (dd, 1H, *J* = 9.2, 6.9 Hz, C*H*), 5.98 (ss, 1H, =C*H*), 7.413-7.46 (m, 1H, ArH), 7.57 (d, 1H, *J* = 8.3 Hz, ArH), 7.72-7.8 (m, 1H, ArH), 8.02 (dd, 1H, 6.4, 1.5 Hz, ArH), 8.14 (s, 1H, =C*H*), 11.6 (brs, 1H, O*H*); ^{13}CNMR (75 MHz, DMSO-d_6) δ_C: 14.0, 19.2, 27.2, 34.6, 59.7, 99.4, 100.0, 118.2, 123.0, 123.4, 125.0, 125.2, 134.0, 154.5, 155.5, 161.1, 163.7, 166.6, 171.3, 175.7; ESI-MS m/z 371 $[M+H]^+$; HRMS (ESI) calc. for $C_{20}H_{19}O_7$ $[M+H]^+$ 371.11300 , found 371.11290; ESI-MS *m/z*393 $[M+Na]^+$; HRMS (ESI) calc. for $C_{20}H_{18}NaO_7$ $[M+Na]^+$ 393.09542 , found 393.09523.

Ethyl-3-(6-bromo-4-oxo-4*H*-chromen-3-yl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl) propanoate (5i). Isolated as a Yellow powder; m.p. 169-171°C; IR (KBr,cm^{-1}): υ^{-1}: 3239, 2983, 1733, 1689 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6) δ_H: 1.07 (t, 3H, *J*= 7.1 Hz, C*H*$_3$), 2.11 (s, 3H, C*H*$_3$), 2.85-3.05 (m, 2H, C*H*$_2$), 3.97 (q, 2H, *J*= 7.0 Hz, OC*H*$_2$), 4.76 (dd, 1H, *J*= 9.1, 6.7 Hz, C*H*), 5.97 (s, 1H, =C*H*), 7.58 (d, 1H, *J*= 8.9 Hz, ArH), 7.90 (dd, 1H, *J*= 2.5, 2.5 Hz, ArH), 8.08 (m, 1H, ArH), 7.57 (d, 1H, *J*= Hz, ArH), 8.18 (s, 1H, =C*H*), 11.6 (brs, 1H, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 14.0, 19.2, 27.2, 34.6, 59.7, 99.1, 100.1, 117.6, 121.0, 123.6, 124.5, 127.2, 136.6, 154.4, 154.8, 161.1, 163.7, 166.7, 171.2, 174.5; ESI-MS m/z 449 $[M + H]^+$; HRMS (ESI) calc. for $C_{20}H_{18}{}^{79}BrO_7$ $[M+H]^+$ 449.02347 , found 449.02339.

4-(4-Oxo-4*H*-chromen-3-yl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione(10).Isolated as a Yellow powder; m.p. 230-232 °C; IR (KBr, cm^{-1}) ν^{-1}:3039, 2927, 1719, 1639; ^{1}HNMR (300 MHz,

DMSO-d_6) δ_H : 2.89 (*d*, 1H, *J*= 16.8 Hz, C*H*), 3.5 (*AB quartet*, 1H, *J* = 16.8 Hz, 9.4 Hz, C*H*), 4.13 (*d*, 1H, *J*= 9.1 Hz, C*H*), 7.44 (*m*, 3H, ArH), 7.62 (*d*, 1H, *J*= 8.4 Hz, ArH), 7.68 (*t*, 1H, *J*= 7.4 Hz, ArH), 7.77 (*t*, 1H, *J*= 7.4 Hz, ArH), 7.87 (*d*, 1H, *J*= 7.6 Hz, ArH), 7.96 (*d*, 1H, *J*= 7.6 Hz, ArH), 8.52 (*s*, 1H, =C*H*), ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 30.0, 32.6, 101.9, 113.5, 116.6, 118.4, 122.0, 122.5, 123.0, 124.8, 124.9, 125.6, 132.9, 134.5, 152.4, 155.5, 155.7, 156.8, 160.3, 163.7, 176.6;ESI-MS m/z 383[M + Na]$^+$; HRMS (ESI) calc. for $C_{21}H_{12}NaO_6$ [M+Na]$^+$ 383.05300 , found 383.05292; HRMS (ESI) calc. for $C_{42}H_{24}NaO_{12}$ [2M+Na]$^+$ 743.11638 , found 743.11633.

3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(4-oxo-4*H*-chromen-3-yl) propanoic acid (11).Isolated as a Yellow powder; m.p.138-140 ^oC; IR (KBr,cm^{-1}) υ^{-1}: 3084, 2927, 1803, 1719, 1639 cm^{-1}; ^{1}H NMR(300 MHz, DMSO-d_6) δ_H: 3.13 (d, 2H, *J*= 7.5 Hz, CH_2), 4.89 (t, 1H, *J*= 7.5 Hz, C*H*), 7.33 (t, 2H, *J*= 7.8 Hz, ArH), 7.46 (t, 1H, ArH), 7.56 (d, 1H, *J*=7.8 Hz, ArH), 7.62 (d, 1H, *J*= 8.4 Hz), 7.62 (d, 1H, *J* = 8.4 Hz, ArH), 7.78 (t, 1H, *J*= 7.4 Hz, ArH), 7.95 (d, 1H, *J*= 7.7 Hz, ArH), 8.05 (d, 1H,*J*= 7.8 Hz, ArH), 8.40 (s, 1H, =C*H*), 12.03 (brs, 2H, COO*H*,O*H*); ^{13}CNMR (75 MHz, DMSO-d_6) δ: 28.6, 34.0, 54.9, 104.2, 116.0, 116.4, 118.3, 122.6, 123.1, 123.5, 123.9, 125.1, 125.5, 132.0, 134.4, 152.1, 155.3, 161.5, 161.6, 172.9, 177.0; ESI-MS m/z 379 [M + H]$^+$; HRMS (ESI) calc. for $C_{21}H_{15}O_7$ [M+ H]$^+$ 379.08118 , found 379.08116.

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Graphical Abstract

Synthesis of functionalized chromones through sequential reactions in aqueous media

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