Sinteza derivata 3-acetilkumarina potpomognuta ultrazvukom i mehanokemijskom metodom

Sušjenka, Martina

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Martina Sušjenka

Rad je izraĎen na Zavodu za primijenjenu kemiju i ekologiju Prehrambeno-tehnološkog fakulteta u Osijeku

Mentor: doc. dr. sc. Valentina Bušić

Neposredni voditelj: Melita Lončarić, mag. ing. proc.

Kratak sažetak završnog rada: Kako bi zaštitili okoliš od štetnih organskih otapala, sinteza derivata 3-actilkumarina provedena je „*zelenim metodama*“, ultrazvučnim postupkom bez otapala, mehanokemijskom metodom i konvencionalnom metodom uz miješanje. Sinteza željenih derivata provedena je Knoevenagelovom kondenzacijom različitih salicilaldehida i etil-acetoacetata, uz dodatak piperidina kao katalizatora. Rezultati ultrazvučne, mehanokemijske i konvencionalne sinteze 3-acetilkumarina pokazuju kako je za reakciju najpogodnija ultrazvučna metoda.

Jezik izvornika: engleski

Ključne riječi: kumarini, sinteza, eutektička otapala, zelena kemija, kolin-klorid, Knoevenagelova kondenzacija

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Ultrasound assisted and mechanochemical synthesis of 3-acetylcoumarin derivatives

Martina Sušjenka

Thesis performed at Department of Applied Chemistry and Ecology, Faculty of Food Technology, Josip Juraj Strossmayer University in Osijek

Supervisor: Valentina Bušić, PhD, Assistant Professor

Assistant supervisor: Melita Lončarić, mag. ing. proc.

Short abstract: In order to protect the environment from harmful organic solvents, the synthesis of 3-actylcoumarin derivatives was carried out by "green methods", solvent-free ultrasonic process, mechanochemical method and conventional method with stirring. The synthesis of the desired derivatives was carried out by Knoevenagel condensation of various salicylaldehydes and ethyl acetoacetate, with the addition of piperidine as a catalyst. The results of ultrasonic, mechanochemical and conventional synthesis of 3-acetylcoumarin show that ultrasonic method is the most suitable for the reaction.

Original in: english

Key words: Coumarins, synthesis, deep eutectic solvents, green chemistry, choline chloride, Knoevenagel condensation

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1. UVOD

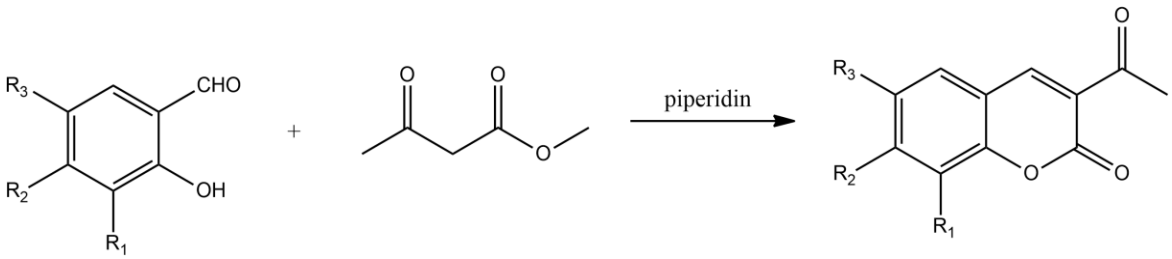
Kumarini su heterociklički spojevi koji produkti sekundarnog metabolizma biljaka gdje se pojavljuju u porodicama *Apiaceae, Asteraceae, Fabaceae, Rubiaceae, Rosaceae, Solanaceae, Rutaceae, Umbelliferae* (Molnar, Čačić, 2011), ali i kao produkti metabolizma u gljiva i bakterija (Revankar i sur., 2017). Kumarin je izoliran su godine 1820. iz biljke *Coumarouna odorata Aube* (*Dipteryx odorata*) te po istoj dobiva ime. Kumarin i njegovi derivati pokazuju razne biološke aktivnosti, uključujući antitumorsku, antibakterijsku, protuupalnu aktivnost (Borges i sur. 2005), prirodni protuupalni lijekovi, inhibitori DNA giraze (Rádl, 1990) te kao antikoagulansi (Rohini, Srikumar, 2014). Uz izolaciju iz prirodnih izvora poput biljaka, kumarini se sintetiziraju i u laboratoriju Perkinovom, Pechmannovom, Knoevenagelovom, Wittigovom, Kostanecki-Robinsonovom i Reformatsky reakcijom. Knoevenaglova kondeznacija odvija se najčešće reakcijom nukleofilne adicije aktivnih metilenskih spojeva s aldehidma kataliziranih slabim bazama (Molnar, Lončarić, Kovač, 2020) ili prikladnom kombinacijom amina ili karboksilnih ili Lewisovih kiselina (Borges i sur., 2005). U ovom radu derivati kumarina sintetizirani su pomoću različito supstituiranih salicilaldehida i etil-acetoacetata. Korištene su zelene metode: metoda mehanosinteze bez otapala, sinteze potpomognute ultrazvukom, te usporeĎene s konvencionalnom metodom uz miješanje.

2. MATERIJALI I METODE

Sve su kemikalije kupljene od komerijalnih dobavljača. Tankoslojna kromatografija (TLC-*thin-layer chroatography*) provedena je na fluorescirajućim pločicama presvučenima silika gelom (Merck, Darmstadt, Njemačka), a kao mobilna faza koristilo se otapalo benzen : aceton : octena kiselina (8 : 1 : 1). Masena spektrometrija provedena je na LC/MS/MS API 2000 spektrometru (Applied Biosystems/MDS SCIEX, Foster City, CA, SAD). Mehanosinteza je provedena na mlinu BeadRuptor 12 (Omni International, Kennesaw GA, SAD) uz dodatak staklenih kuglica. Svi derivati kumarina sintetizirani su putem Knoevenagelove kondenzacije, a kao reaktanti su korištene ekvimolarne količine supstituiranih salicilaldehida i odgovarajućeg karbonilnog spoja. Sinteza derivata 3-acetilkumarina provedena je reakcijom supstituiranih salicilaldehida (10 mmol) i etil-acetoacetata (10 mmol) s nekoliko kapi piperidina, nakon čega je smjesa podvrgnuta ultrazvučnoj kupelji ili mlinu (uz 1 gram staklenih kuglica) na odreĎeno vrijeme (30-60 minuta na ultrazvučnoj kupelji i magnetnoj mješalici te 2 minute na mlinu). Dobiveni produkti izolirani su dodatkom klorovodične kiseline i filtracijom.

3. REZULTATI I RASPRAVA

Derivati 3-acetilkumarina sintetizirani su Knoevenagelovom kondenzacijom „*zelenim*“ metodama iz supstituiranih salicilaldehida i etil-acetoacetata. Budući da korištenje eutektičkih otapala nije bilo pogodno za dobivanje 3-acetilkumarina, korištene su gore spomenute zelene metode za sintezu istih. Provedena je konvencionalna metoda bez uporabe otapala, ultrazvučna i mehanokemijska metoda. Korištene su ekvimolarne količine reaktanata, odnosno supstituiranih salicilaldehida i etil-acetoacetata uz nekoliko kapi piperidina kao katalizatora. (Shema 1.)

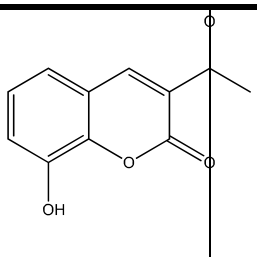
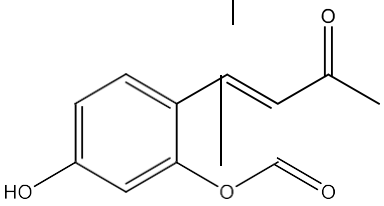
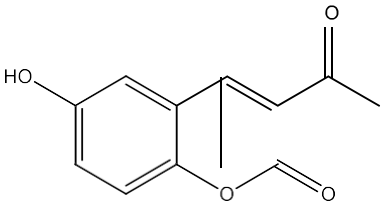
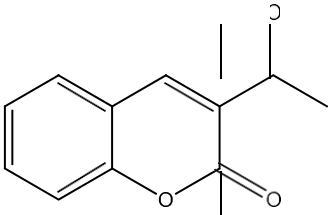
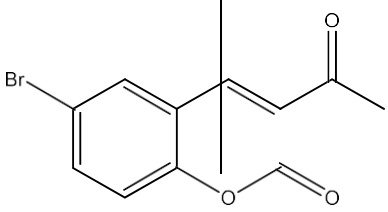


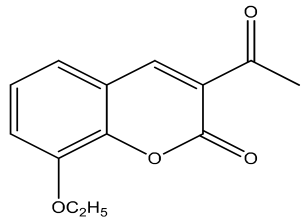
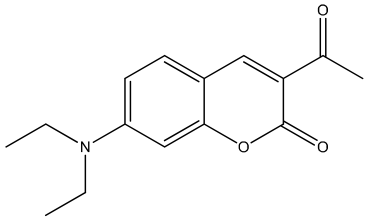
Shema 1: Sinteza derivata 3-acetilkumarina Knoevenagelovom kondenzacijom uz piperidin kao katalizator.

Reakcije potpomognute ultrazvukom izvoĎene su u ultrazvučnoj kupelji, 30 do 60 minuta na sobnoj temperaturi. Konvencionalnom su metodom reakcije provedene uz miješanje u trajanju od 30 do 60 minuta pri sobnoj temperaturi. Mehanosinteza izvoĎena je u mlinu, a jednake količine reaktanata pomiješane su s 1 gramom staklenih kuglica te se reakcija odvijala 2 minute u intervalima od 2x1 minuta ili 4x30 sekundi. Budući da se reakcijska smjesa zagrijavala, trajanje jednog intervala je skraćeno. Najbolja iskorištenja dobivena su sintezom potpomognutom ultrazvukom. U odnosu na mehanokemijsku sintezu i konvencionalnu metodu, za ovu metodu nije potrebna visoka temperatura koja bi utjecala na temperaturu same reakcijske smjese. Najmanja iskorištenja dobivena su mehanokemijskom sintezom, a razlog tomu mogu biti i nedovoljno isprani produkti sa staklenih kuglica i pregrijavanje reakcijske smjese. Produkt dobiven reakcijom salicilaldehida i etilacetoacetata ultrazvučnom metodom ima najveće iskorištenje (98%). Iskorištenja na ultrazvuku kreću se od 85% do 98%, ali izuzezak je 2,4-dihidroksibenzaldehid čije je iskorištenje samo 19%. Reakcijsko vrijeme na za ultrazvučnu metodu bilo je uglavnom 30 minuta te 60 minuta za 4-(dietilamino)salicilaldehid. UsporeĎujući konvencionalnu i ultrazvučnu metodu, reakcijska vremena su jednaka za sve spojeva, ali se iskorištenja kreću od 51% do 94% u konvencionalnoj metodi. Izuzetak je 2,4-dihidriksobenzaldehid za koji produkt uopće nije nastao konvencionalnom metodom.

TakoĎer, ovaj spoj pokazao je i najmanju reaktivnost, što je odstupanje od ostalih dihidroksida korištenih u ovim sintezama koji su pokazali visoka iskorištenja. Iskorištenja produkta i metoda prikazani su u Tablici 1.

Tablica 1. Dobiveni produkti i njihova iskorištenja.

PRODUKT	**Konvencionalna metoda**	**Ultrazvučna metoda**	**Mehanokemijska metoda**
	η=69% t=30 min	η=90% t=30 min	η=66% t=2x1 min
	-	η=19% t=3 dana	η=36% t=2x1 min
	η=51% t=30 min	η=95% t=30 min	η=22% t=4x0,5 min
	η=90% t=30 min	η=98% t=30 min	η=38% t=4x0,5 min
	η=88% t=30 min	η=93% t=30 min	η=22% t=2x1 min

	η=94% t=30 min	η=94% t=30 min	η=47% t=4x0,5 min
	η=55% t=60 min	η=85% t=60 min	η=51% t=2x1 min

4. ZAKLJUČAK

Derivati kumarina uspješno su sintetizirani putem Knoevenagelove kondenzacije koristeći postupke bez otapala. Iz provedenoga doneseni su sljedeći zaključci:

- Od korištenih zelenih metoda kao najbolja se pokazala ultrazvučna metoda zbog manjeg zagrijavanja reakcijske smjese i većih iskorištenja u odnosu na konvencionalnu i mehanokemijsku metodu
- Mehanokemijska metoda nije se pokazala kao dobra zelena metoda jer je došlo do pregrijavanja reakcijske smjese, zaostataka produkata na staklenim kuglicama i malih iskorištenja. UsporeĎujući ju s konvencionalnom metodom, pokazala se lošijom.
- Piperidin je dobar katalizator za ovakve reakcije jer se lako uklanja dodatkom klorovodične kiseline.
- Od svih spojeva, najveće je iskorištenje dao salicilaldehid, a najmanje 2,4-dihidroksibenzalehid.
- Postupci bez prisustva otapala pokazali su se pogodnima za ovakve sinteze.

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RESEARCH ARTICLE

An Extensive Study of Coumarin Synthesis *via* Knoevenagel Condensation in Choline Chloride Based Deep Eutectic Solvents

Melita Lončarić[1], Martina Sušjenka[2] and Maja Molnar[1,*]

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Abstract: ***Aim and Objective:*** In order to preserve the environment from harmful organic solvents, a synthesis of coumarin derivatives was performed in deep eutectic solvents, which are considered as "*green*" due to their characteristics.

Materials and Methods: Choline chloride based deep eutectic solvents (DESs) were employed, both as solvents and as catalysts, in the synthesis of coumarin derivatives *via* Knoevenagel condensation. In order to find the best DES for coumarin synthesis, 20 DESs were tested for the reaction of salicylaldehyde and dimethyl malonate at 80 °C.

Results: Among the twenty tested deep eutectic solvents only five were adequate for this kind of synthesis. The best DES for this reaction was found to be the one composed of choline chloride:urea (1:2). Most coumarin compounds were obtained in good to excellent yield. Compounds **1g**, **2g** and **2p** should be pointed out due to their yields of 85, 88 and 98 %, respectively. 3-Acetylcoumarins **5a**, **5c**, **5d**, **5e**, **5f** and **5g** were synthesized under ultrasound irradiation and were also obtained in excellent yields of 90, 95, 98, 93, 94 and 85 %, respectively.

***Conclusion*:** Series of coumarin derivatives were successfully synthesized, either in choline chloide:urea DES at 80 °C or in ultrasound-assisted reaction, from different salicylaldehydes and active methylene compounds. These "*green*" methods were found to be very effective in Knoevenagel condensation, while DES was recycled for several cycles without any significant influence on the product yield.

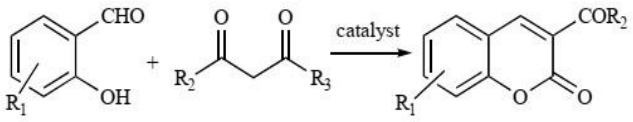
Keywords: Coumarins, synthesis, deep eutectic solvents, green chemistry, choline chloride, knoevenagel condensation.

1. INTRODUCTION

Coumarins are an important group of organic compounds that belong to the family of lactones, having 1-benzopyran-2-one system [1, 2]. Coumarins have found a wide range of use, as additives in food, perfumes, cosmetics, laser dyes, pharmaceutical and optical brighteners [3, 4]. Due to their biological activities, they have many health benefits like anticancer, analgesic, anti-inflammatory, bactericidal, antifungal, anticonvulsant, anti-tumour, anti-hypertensive, muscle relaxant, antioxidant, anti-HIV [1, 2, 5-11].

As naturally occurring compounds, coumarins could be isolated from various plants [12-14], as well as synthesized in the laboratory [2, 15, 16].

First, coumarins were synthesized *via* the Perkin reaction, but there are more methods for coumarin derivatives synthesis, like Pechmann condensation reaction, Wittig, Claisen, Reformatsky and Kontanecki-Robinson reaction [17, 18]. Throughout the years, Knoevenagel reaction (Scheme **1**) turned out to be the simplest and the most important method for coumarin derivatives synthesis [19, 20].



Scheme 1. Knoevenagel condensation in coumarin synthesis.

There are several solvent-free reactions described for this kind of synthesis, but they usually utilize piperidine as a catalyst [21, 22]. Some authors peformed a Knoeveangel condensation in solvent-free reactions under microwave irradiation, catalyzed by ammonium acetate [23]. Over the past years, many authors have reported coumarin synthesis in many different ionic liquids [24-27]. Ionic liquids have been used because of their favorable chemical and physical properties (non-volatility, non-flammability, thermal stability, controlled miscibility) [28]. Ionic liquids are described as "*green solvents*" due to their low vapor pressure, but investigations showed that many ionic liquids are dangerous environmental contaminants because of their high toxicity level [29, 30]. An alternative to ionic liquids are Deepeutectic Solvents (DESs), which may have an ionic character [31]. DES are mixtures of organic compounds (mostly natural compounds such as amino acids, organic acids, sugars, choline chloride and urea) with melting point significantly lower than that of either single component [31, 32]. Natural DESs have many advantages such as low price, chemical inertness with water, recyclable, most of them are biodegradable,

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Table 1. Product yields obtained in different choline chloride based deep eutectic solvents.

DES	Ratio ChCl:HBD	Time (h)	Y (%)
ChCl : Urea	1 : 2	6	50.5
ChCl : *N*-methylurea	1 : 3	7	45.1
ChCl : Thiourea	1 : 2	7	2.1
ChCl : Glucose	1 : 1	-	**
ChCl : Fructose	1 : 1	-	**
ChCl : Xylitol	1 : 1	-	**
ChCl : Sorbitol	1 : 1	-	**
ChCl : Butan-1,4-diole	1 : 2	-	**
ChCl : Ethan-1,2-diole	1 : 2	-	**
ChCl : Glycerol	1 : 2	-	**
ChCl : Acetamide	1 : 2	12	4.4
ChCl : Malic acid	1 : 1	-	**
ChCl : Citric acid	1 : 2	-	**
ChCl : Tartaric acid	1 : 1	-	**
ChCl : Malonic acid	1 : 1	-	**
ChCl : Oxalic acid	1 : 1	-	**
ChCl : 1,3-dimethylurea	1:2	9	42.2
ChCl : Lactic acid	1:2	-	**
ChCl : Levulinic acid	1:2	-	**
ChCl : *trans*-Cinnamic acid	1:1	-	**

***product was not obtained*

biocompatible and non-toxic [33-35]. Also, DESs could be used as solvents [36-38] as well as catalysts [39, 40].

Knoevenagel condensation is usually performed in different organic solvents and catalyzed by bases [41] or acids [42]. An application of DESs for Knoevenagel condensation was described by some authors and found to be very efficient [42-44]. Knoevenagel condensation into coumarin derivatives employing DESs was investigated by Harishkumar *et al*., where they used only one DES, choline chloride (ChCl):Urea (U), as a catalyst [17]. Phadatre *et al*. successfully employed choline chloride:urea DES in the synthesis of coumarin dyes [45]. Combination of choline chloride:zinc chloride DES in coumarin synthesis was investigated by Keshavarzipour and Tavakol [19].

Therefore, the above-mentioned authors have performed different research, which can be considered as pioneering in the area of application of some DESs in the coumarin synthesis. Our research can be considered as a continuation of such studies, where, for the first time, an extensive investigation of coumarin synthesis *via* Knoevenagel condensation in a number of various choline chloride based deep eutectic solvents, as green and environmentally acceptable method, was performed. Unlike Harishkumar *et al*., hereby we performed a screening of different DESs, in order to find the most suitable one for this reaction, as well as the synthesis of 3-acetyl coumarin derivatives employing different green synthetic methods. DES components, recyclability, 100% atom efficiency, minor demands for postsynthetic handling and no use of catalysts designate this method as green, compared to other methods described in this kind of synthesis.

2. MATERIALS AND METHODS

2.1. General

All chemicals were purchased from commercial suppliers. Melting points were determined on Electrothermal melting point apparatus (Electrothermal Engineering Ltd., Rochford, UK). Thin-Layer Chromatography (TLC) was performed in benzene:acetone:acetic acid (8:1:1) as eluent using fluorescent silica gel plates F_{254} (Merck, Darmstadt, Germany). Mass spectra were recorded on LC/MS/MS API 2000 spectrometer (Applied Biosystems/MDS SCIEX, Foster City, CA, USA). NMR spectra were recorded on Bruker Avance 600 MHz NMR Spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany) at 293 K in dimethylsulfoxide-d6 (DMSO-d6). Mechanosynthesis was performed on BeadRuptor 12 ball mill (Omni International, Kennesaw GA, USA), using acid-washed glass beads (425-600 μm, 30-40 U.S. sieve).

2.2. Synthetic Procedures

2.2.1. General Procedure for the Synthesis of Deep Eutectic Solvents

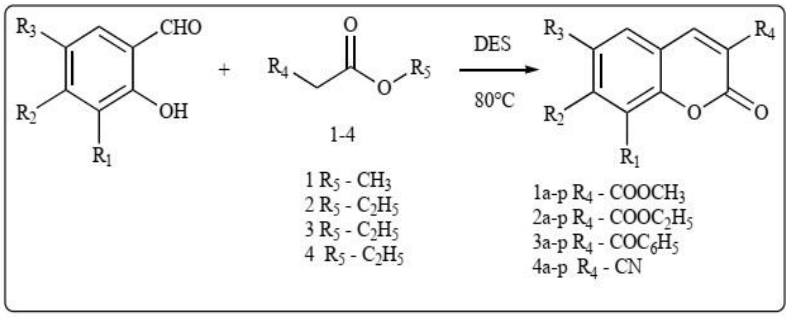
Choline chloride based deep eutectic solvents were prepared by mixing choline chloride, as a Hydrogen Bond Acceptor (HBA), with different Hydrogen Bond Donors (HBDs), as listed in Table **1**. A mixture of HBA and HBD was heated until a clear liquid was formed and used for further reactions as such.

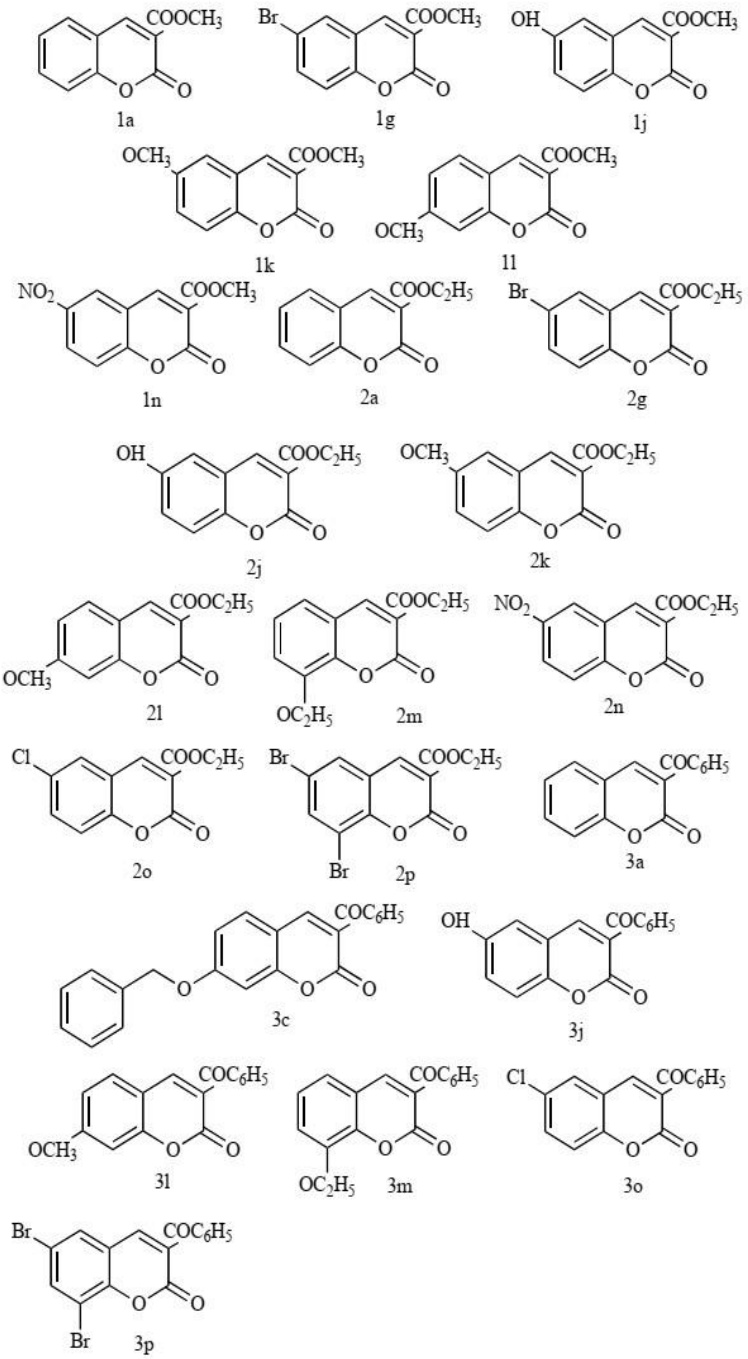
2.2.2. General Procedure for Synthesis of Coumarin Derivatives (1-4a-p) A

Coumarin derivatives were synthesized *via* Knoevenagel condensation. A mixture of an equimolar amount of substituted salicylaldehyde and a corresponding carbonyl compound was added to the DES and stirred until full consumption of reactants, monitored by TLC. Upon completion of the reaction, water was added and the precipitated product was filtered.

2.2.3. General Procedure for the Synthesis of 3-acetylcoumarin Derivatives (5a-g) B

3-Acetylcoumarin derivatives were synthesized *via* Knoevenagel condensation. A mixture of substituted





Scheme 2. Synthesized coumarin derivatives in ChCl:U DES at 80 °C.

salicylaldehyde (10 mmol) and ethyl acetoacetate (10 mmol), with a few drops of piperidine, was stirred/subjected to ultrasound/ball-milled (with 1 g of glass beads) for a certain time (30-60 min for ultrasound and stirring and 2 min for ball-milling), monitored by TLC. Products were isolated upon acidification and filtration.

3. RESULTS AND DISCUSSION

A series of coumarin derivatives were synthesized *via* Knoevenagel condensation in DESs, starting from various substituted salicylaldehydes and active methylene compounds, such as ethyl acetoacetate, ethyl cyanoacetate, dimethyl malonate, diethyl malonate, ethyl benzoylacetate, respectively (Scheme **2** and **3**). The structures of all compounds were confirmed by different spectral methods (Supplementary materials).

First, a screening of 20 choline chloride based DESs for coumarin synthesis, *via* Knoevenagel condensation, was performed. We chose one model reaction for the screening experiments, a reaction between salicyladehyde and dimethylmalonate at 80 °C (Table **1**). A model reaction was performed in order to find the best DES for coumarin synthesis *via* Knoevenagel condensation.

Temperature of 80 °C was chosen, since some DESs, such as ChCl:glucose, ChCl:fructose, ChCl:xylitol, do not remain liquid or are too viscous at lower temperatures. The best solvent for this kind of reaction was chosen upon the highest reaction yield. As evident from the Table **1**, ChCl:U 1:2 was shown to be the most convenient for this type of synthesis. After finding the best DES, we investigated the effect of temperature on the reaction yield. In that manner, we performed the same model reaction at two different temperatures, 40 °C and 80 °C, namely. As expected, the higher temperature of 80 °C gave better results regarding reaction time and product yield. Our other attempt to perform this model reaction using DES ChCl:U as a catalyst, according to Harishkumar et al. [17], provided much lower yields than we expected. Therefore, we decided to use a ChCl:U DES as a solvent in all further reactions.

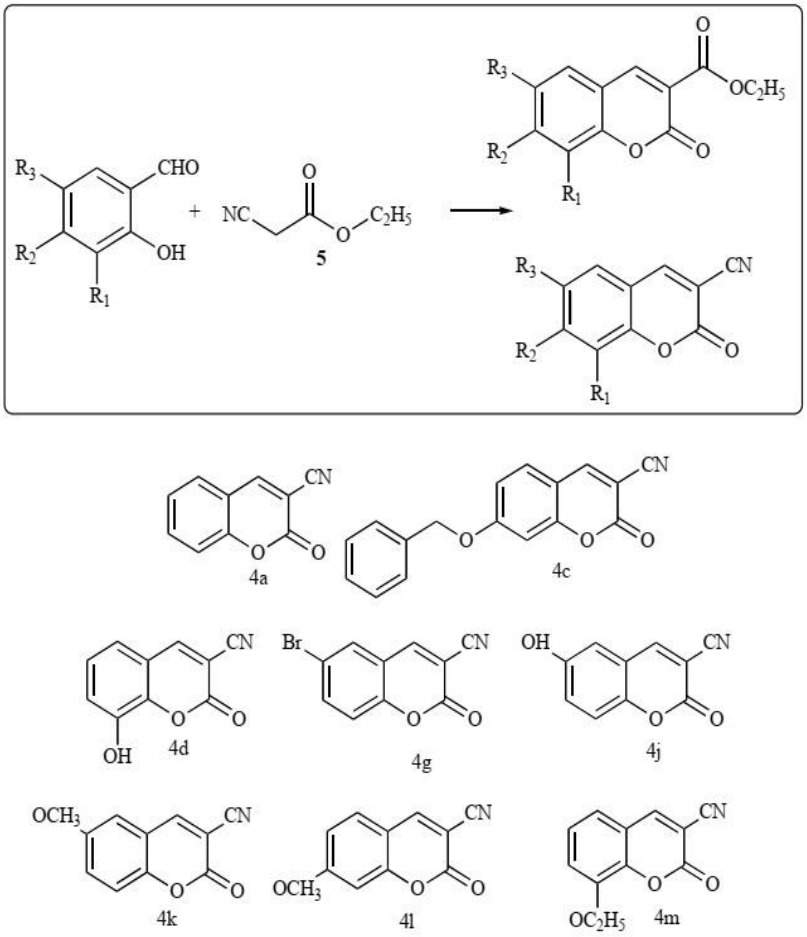
With the optimized conditions in hands, various substituted salicyladehydes were reacted with different methylene active compounds (**1**-**5**), to obtain the desired coumarin derivatives (Schemes **2** and **3**). All reactions were monitored by TLC and quenched with water upon the disappearance of all the reactants on TLC. The addition of water to the reaction mixture precipitated the crude product, which was then collected by filtration and dried.

Table 2. Influence of DES recycle of final product yield shown for model reaction.

Solvent	Yield (%)
choline chloride/urea	98
1st recycle	98
2nd recycle	97
3rd recycle	96
4th recycle	97
5th recycle	96

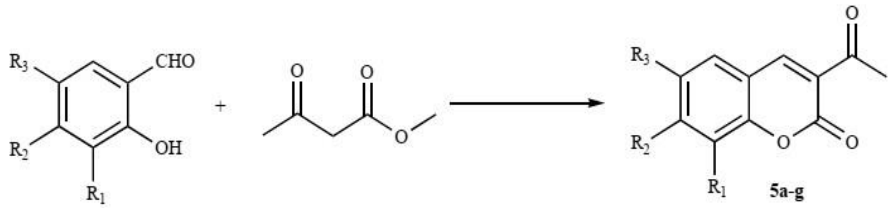
The type of salicylaldehyde, as well as the active methylene compound, greatly influenced the reaction yield. The highest yield was observed in a reaction of 3,5-dibromosalicylaldehyde and diethyl malonate where the obtained product yield was 98%. An excellent yield was also obtained with 2-hydroxy-5-bromo-benzaldehyde and both dimethylmalonate (85%) and diethyl-malonate (88%). Other yields could be considered as moderate. 5-Tert-butyl-salycilaldehyde, 4-diethylaminosalicyladehyde, 5-fluoro-salycilaldehyde and 3-iodo-5-chlorosalicylaldehyde were not reactive under these conditions, and reactions with any of these active methylene compounds yielded no products.

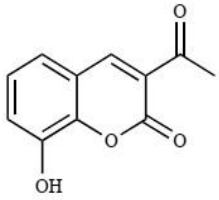
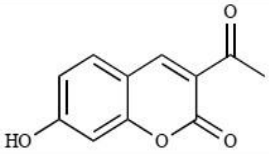
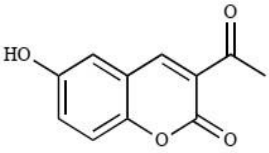
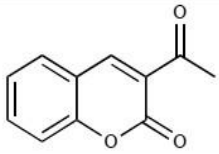
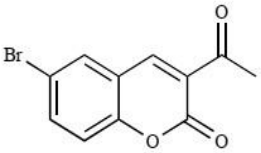
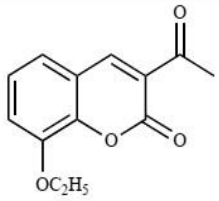
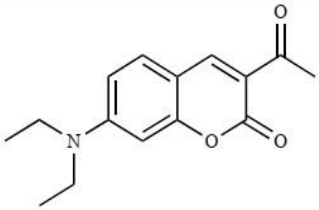
Furthermore, when ethylcyano acetate was employed as an active methylene compound, a mixture of 3-cyano coumarin



Scheme 3. Knoevenagel condensation of various salicylaldehydes with ethyl cyanoacetate.

Table 3. Comparison of different synthetic methods in the synthesis of 3-acetylcoumarins.



Entry	Product	Stirring	Ball-milling	Ultrasound
5a		Y = 69% t= 30 min	Y = 66% t= 2x1 min	Y = 90% t= 30 min
5b		-	Y = 36% t= 2x1 min	Y = 19% t= 3 days
5c		Y = 51% t= 30 min	Y = 22% t= 4x0.5 min	Y = 95% t= 30 min
5d		Y = 90% t= 30 min	Y = 38% t= 4x0.5 min	Y = 98% t= 30 min
5e		Y = 88% t= 30 min	Y = 22% t= 2x1 min	Y = 93% t= 30 min
5f		Y = 94% t= 30 min	Y = 47% t= 4x0.5 min	Y = 94% t= 30 min
5g		Y = 55% t= 60 min	Y = 51% t= 2x1 min	Y = 85% t= 60 min

derivatives (**4a-m**) and 3-coumarinyl-ethylacetate derivatives (**2a-m**) was formed (Scheme **3**). This is the main reason for lower yields of the desired 3-cyanocoumarins. This was also reported by Sugino and Tanaka, where, depending on the reaction conditions, different derivatives were formed [21].

Our procedure for the synthesis of coumarin derivatives using DESs is the first extensive report on the screening of different choline chloride based DESs for this purpose. It fits the green chemistry concept, since no toxic solvents or catalysts were added, components of DES are biodegradable, non-toxic, cheap, easy to handle [29, 46] and furthermore, it is possible to reuse the same solvent for a few times.

To demonstrate this assumption, a recyclability of the DES was also investigated, on a model reaction between 3,5-dibromosalicylaldehyde and diethyl malonate. Recyclability is performed upon isolation of the product and water evaporation. This is an energy consuming process, but the same DES could be used for the same reaction up to 5 times without decreasing reaction yield (Table **2**).

Since this method, performed in the DES, was not suitable for obtaining 3-acetylcoumarins (**5a**-**g**) we decided to explore other green methods for their synthesis.

Hereby, we decided to employ different solvent-free reactions: under stirring, ultrasound promoted reactions and mechanosynthesis, to find the best conditions for this kind of condensation. Generally, an equimolar amounts of reactants were mixed and a few drops of piperidine were added. Ultrasound promoted reactions were performed on an ultrasonic bath, for 30-60 minutes at room temperature (Table **3**). The same was also performed when the reaction mixtures were only stirred at room temperature. When ball-mill was used to perform a mechano-synthesis of desired compounds, equimolar amounts of reactants were mixed with 1 g of glass beads and ball-milled for 2 minutes (intervals of 2x1 min or 4x30 s). Reaction time for ball-milling was shorter due to the overheating of the mixture. The best results were obtained when ultrasound was employed, where all yields were over 90%, except for 2,4-dihydroxybenzaldehyde (Table **3**). 2,4-Dihydroxybenzaldehyde was the least reactive aldehyde in all methods (compound 5b), providing a very low product yields, while the reaction under stirring using this aldehyde, yielded no product.

4. EXPERIMENTAL

4.1. Methyl 2-oxo-2*H*-chromene-3-carboxylate (1a)

Using salicylaldehyde (1.06 mL, 10 mmol) and dimethylmalonate (1.15 mL, 10 mmol), in accordance with the General Procedure A, the title compound 1a was obtained (1.03 g, 50 % yield) as a pale yellow solid (m.p. 102 – 105 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.79 (s, 1H, coum.), 7.91 (m, J = 2.0 Hz, 1H, arom.), 7.75 (m, J = 1.6, 8.0 Hz, 1H, arom.), 7.41-7.45 (m, 2H, arom.), 3.84 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.1, 155.9, 154.5, 148.9, 134.5, 130.3, 125.7, 117.7, 116.1, 52.36. LC/MS/MS for $C_{11}H_8O_4$ [M+H]+: 204.17, found 205.10. (Suupl. Mat. Fig. **1**).

4.2. Methyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (1g)

Using 2-hydroxy-5-bromosalicylaldehyde (2.03 g, 10 mmol) and dimethylmalonate (1.15 mL, 10 mmol), in accordance with General Procedure A, the title compound 1g was obtained (2.41 g, 85 % yield) as a white solid (m.p. 180 -185 °C, ref. [19] m.p. 180-182 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (s, 1H, arom.), 8.17 (s, 1H, arom.), 7.86-7.89 (m, 1H, arom.), 7.39-7.42 (m, 1H, arom.), 3.84 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 154.0, 148.1, 137.1, 132.6, 120.1, 119.1, 116.7, 53.0. LC/MS/MS m/z for $C_{11}H_7BrO_4$ [M+H]+: 283.07, found 283.0. (Suupl. Mat. Fig. **3**).

4.3. Methyl 6-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (1j)

Using 2,5-dihydroxybenzaldehyde (1.38 g, 10 mmol) and dimethylmalonate (1.15 mL, 10 mmol), in accordance with the General Procedure A, the title compound 1j was obtained (1.21 g, 55% yield) as a dark red solid (m.p. 185 - 190 °C, ref. [47] m.p. 195-196 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.94 (s, 1H, OH), 8.69 (s, 1H, coum.), 7.15-7.30 (m, 3H, arom.), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.8, 156.7, 154.4, 149.2, 148.4, 123.1, 118.7, 117.8, 117.5, 114.4, 52.8. LC/MS/MS for $C_{11}H_8O_5$ [M+H]+: 220.17, found 221.10. (Suupl. Mat. Fig. **5**).

4.4. Methyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (1k)

Using 2-hydroxy-5-methoxybenzaldehyde (0.4 mL, 3.2 mmol) and dimethylmalonate (0.38 mL, 3.2 mmol), in accordance with the General Procedure A, the title compound 1k was obtained (0.29 g, 39% yield) as a yellow solid (m.p. 155 - 157 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.74 (s, 1H, coum.), 7.50 (s, 1H, arom.), 7.40-7.36 (m, 2H, arom.), 3.87 (s, 3H, -OCH_3), 3.84 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, CDCl3) δ 163.6, 156.2, 149.2, 122.9, 118.6, 118.0, 117.7, 112.4, 111.4, 56.2, 52.9. LC/MS/MS m/z for $C_{12}H_{10}O_5$ [M+H]+: 234.20, found 235.10. (Suupl. Mat. Figs. **7**-**9**).

4.5. Methyl 7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (1l)

Using 4-methoxy-2-hydroxybenzaldehyde (0.5 g, 3.3 mmol) and dimethyl malonate (0.39 mL, 3.3 mmol), in accordance with the General Procedure A, the title compound 1l was obtained (0.44 g, 56% yield) as a dark yellow solid (m.p. 200 - 202 °C, ref. [48] m.p. 201-203 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.82 (m, 1H, arom.), 7.00-7.03 (m, 2H, arom.), 3.90 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.8, 163.4, 157.11, 156.2, 149.4, 131.6, 113.2, 111.4, 100.3, 56.2, 52.1. LC/MS/MS m/z for $C_{12}H_{10}O_5$ [M+H]+: 234.20, found 235.10. (Suupl. Mat. Figs. **10, 11**).

4.6. Methyl 6-nitro-2-oxo-2*H*-chromene-3-carboxylate (1n)

Using 2-hydroxy-5-nitrobenzaldehyde (0.51 g, 3.1 mmol) and dimethyl malonate (0.4 mL, 3.1 mmol), in accordance with the General Procedure A, the title compound 1n was obtained (0.32 g, 42% yield) as a light brown solid (m.p. 210 - 213 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H, coum.), 8.88 (s, 1H, arom.), 8.47 (dd, J=9.23, 2.83 Hz, 1H, arom.), 7.61-7.64 (d, J=9.42 Hz, 1H, arom.), 3.84 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 158.5, 155.4, 148.4, 144.1, 129.1, 126.6, 119.7, 118.6, 118.2, 53.2. LC/MS/MS (ESI-TOF) m/z for $C_{11}H_7NO_6$ [M-H]-: 249.17, found 247.90.

4.7. Ethyl 2-oxo-2*H*-chromene-3-carboxylate (2a)

Using salicylaldehyde (1.06 mL, 10 mmol) and diethyl malonate (1.53 mL, 10 mmol), in accordance with the General Procedure A, the title compound 2a was obtained (1.1 g, 50 % yield) as a pale yellow solid (m.p. 92 – 94 °C, ref. [28] m.p. 93 °C]). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (s, 1H, coum.), 7.92-7.94 (dd, J = 7.70, 1.83 Hz, 1H, arom.), 7.73-7.76 (m, 1H, arom.), 7.41-7.45 (m, 2H, arom.), 4.30-4.33 (q, 2H, -$\underline{CH_2}CH_3$), 1.31-1.34 (t, 3H, -$CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.6, 155.9, 154.5, 148.6, 134.4, 130.2, 124.8, 117.8, 116.1, 61.2, 14.0. LC/MS/MS m/z for $C_{12}H_{10}O_4$ [M+H]+ : 218.20, found 219.0.

4.8. Ethyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (2g)

Using 2-hydroxy-5-bromobenzaldehyde (2.03 g, 10 mmol) and diethylamlonate (1.53 mL, 10 mmol), in accordance with the General Procedure A, the title compound 2g was obtained (2.63 g, 88% yield) as a white solid (m.p. 164 – 169 °C, ref. [49] m.p. 164-166 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (s, 1H, coum.), 8.17 (s, 1H, arom.), 7.87 (dd, J = 8.80, 1.47 Hz, 1H, arom.), 7.40 (m, 1H, arom.), 4.29-4.32 (q, 2H, J = 6.60 Hz, -$\underline{CH_2}CH_3$), 1.30-1.32 (t, 3H, J = 6.97 Hz, $CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.3, 155.5, 153.5, 147.2, 136.6, 132.3, 119.6, 118.8, 118.4, 116.2, 61.4, 14.00. LC/MS/MS m/z for $C_{12}H_9BrO_4$ [M+H]+: 297.1, found 297.10.

4.9. Ethyl 6-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (2j)

Using 2,5-dihydroxybenzaldehyde (1.38 g, 10 mmol) and diethylmalonate (1.53 mL, 10 mmol) in accordance with the General Procedure A, the title compound 2j was obtained (1.24 g, 52% yield) as a black solid (m.p. 170 – 173 °C, ref. [47] m.p. 174-175 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.90 (br.s, 1H, OH), 8.64 (s, 1H, arom.), 7.28 (d, 1H, J = 8.80 Hz, arom.), 7.28 (d, J = 8.80 Hz, 1H, arom.), 7.16 (m, 1H, arom.), 4.26-4.29 (q, 2H, J = 7.34 Hz, -$\underline{CH_2}CH_3$), 1.29-1.31 (m, 3H, -$CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.7, 156.3, 153.9, 148.4, 147.9, 122.6, 118.2, 117.8, 117.0. 113.7, 61.1, 14.0. LC/MS/MS m/z for $C_{12}H_{10}O_5$ [M-H]-: 234.20, found 232.90.

4.10. Ethyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (2k)

Using 2-hydroxy-5-methoxybenzaldehyde (0.4 mL, 3.2 mmol) and diethyl malonate (0.5 mL, 3.2 mmol), in accordance with General Procedure A, the title compound 2k was obtained (0.39 g, 48% yield) as a yellow solid (m.p. 145 – 148 °C, ref. [50] m.p. 140-142 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (s, 1H, coum.), 7.46 (d, 1H, J = 2.93 Hz, arom.), 7.36-7.38 (m, 1H, arom.), 7.32 (m, 1H, arom.), 4.29-4.32 (q, 2H, J = 6.85 Hz, -$\underline{CH_2}CH_3$), 3.81 (s, 3H, -OCH_3), 1.31-1.35 (t, 3H, J = 6.97 Hz, -$CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.6, 155.7, 148.9, 122.2, 118.1, 117.2, 115.5, 111.9, 110.8, 61.2, 55.7, 14.00. LC/MS/MS m/z for $C_{13}H_{12}O_5$ [M+H]+: 248.23, found 249.10.

4.11. Ethyl 7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (2l)

Using 2-hydroxy-4-methoxybenzaldehyde (0.5 g, 3.3 mmol) and diethylmalonate (0.51 mL, 3.3 mmol), in accordance with the General Procedure A, the title compound 2l was obtained (0.42 g, 50% yield) as a light brown solid (m.p. 157 – 160 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.71 (s, 1H, coum.), 7.82 (d, J = 8.80 Hz, 1H, arom.), 7.02 (d, 1H, J = 2.20 Hz, arom.), 6.99 (m, 1H, arom.), 4.26-4.29 (q, 2H, J = 6.85 Hz, -$\underline{CH_2}CH_3$), 3.89 (s, 3H, OCH_3), 1.29-1.32 (m, 3H, -$CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.8, 162.8, 156.9, 156.2, 149.1, 131.6, 113.3, 111.4, 100.3, 60.8, 56.2, 14.1. LC/MS/MS m/z for $C_{13}H_{12}O_5$ [M+H]+: 248.23, found 249.20.

4.12. Ethyl 8-ethoxy-2-oxo-2*H*-chromene-3-carboxylate (2m)

Using 3-ethoxysalicylaldehyde (1.71 g, 10 mmol) and diethylamlonate (1.53 mL, 10 mmol), in accordance with the General Procedure A, the title compound 2m was obtained (1.65 g, 62% yield) as a white solid (m.p. 98 – 100 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.71 (s, 1H, coum.), 7.45-7.39 (m, 2H, arom.), 7.33-7.31 (d, 1H, arom.), 4.3-4.30 (q, 2H, J = 7.34 Hz, -$\underline{CH_2}CH_3$), 4.19-4.18 (q, 2H, J = 7.34 Hz, -$\underline{CH_2}CH_3$), 1.43-1.40 (m, 3H, -$CH_2\underline{CH_3}$), 1.34-1.31 (m, 3H, -$CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.5, 155.7, 148.9, 145.4, 143.9, 124.7, 121.1, 118.4, 117.7, 117.3, 64.5, 61.2, 14.5, 14.0. LC/MS/MS m/z for $C_{14}H_{14}O_5$ [M+H]+:262.25, found 263.20.

4.13. Ethyl 6-nitro-2-oxo-2*H*-chromene-3-carboxylate (2n)

Using 2-hydroxy-5-nitrobenzaldehyde (0.5 g, 3.1 mmol) and diethyl malonate (0.47 mL, 3.1 mmol), in accordance with the General Procedure A, the title compound 2n was obtained (0.22 g, 27% yield) as a yellow solid (m.p. 198 – 203 °C, ref. [51] m.p. 192-193 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.92 (s, 2H, arom.), 8.49-8.51 (d, J = 9.17, J = 2.57 Hz, 1H, arom.), 7.64-7.66 (d, J = 8.80 Hz, 1H, arom.), 4.31-4.35 (m, 2H, -$\underline{CH_2}CH_3$), 1.32-1.34 (m, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ162.0, 158.0, 147.6, 143.6, 128.5, 126.0, 119.5, 118.2, 117.7, 61.5, 14.0. LC/MS/MS m/z calcd. for $C_{12}H_9NO_6$ [M+H+Na$^+$]+: 263.20, found 286.10.

4.14. Ethyl 6-chloro-2-oxo-2*H*-chromene-3-carboxylate (2o)

Using 2-hydroxy-5-chlorobenzaldehyde (0.51 g, 3.3 mmol) and diethylmalonate (0.5 mL, 3.3 mmol), in accordance with the General Procedure A, the title compound 2o was obtained (0.46 mg, 57% yield) as a pale yellow solid (m.p. 167 – 172 °C, ref. [51] m.p. 174-175 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (s, 1H, coum.), 8.04 (d, 1H, J = 2.26 Hz, arom.), 7.75 (dd, J = 8.85, 2.45 Hz, 1H, arom.), 7.46 (d, J = 8.67 Hz, 1H, arom.), 4.28-4.35 (q, 2H, J = 7.16 Hz, -$\underline{CH_2}CH_3$), 1.30-1.35 (t, 3H, J = 6.97 Hz, -$CH_2\underline{CH_3}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.8, 156.0, 153.6, 147.8, 134.3, 129.5, 128.9, 119.6, 118.7, 62.6, 14.5. LC/MS/MS m/z for $C_{12}H_9ClO_4$ [M+H]+: 252.65, found 253.0.

4.15. Ethyl 6,8-dibromo-2-oxo-2*H*-chromene-3-carboxylate (2p)

Using 3,5-dibromosalicylaldehyde (2.8 g, 10 mmol) and diethylmalonate (1.53 mL, 10 mmol), in accordance with General Procedure A, the title compound 2p was obtained (3.72 g, 98% yield) as a light brown solid (m.p. 170 – 173 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H, coum.), 8.20 (s. 1H, arom.), 8.17 (s, 1H, arom.), 4.34-4.29 (m, 2H, -$\underline{CH_2}CH_3$), 1.30-1.33 (m, 3H, -$CH_2\underline{CH_3}$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.9, 154.8, 150.4, 147.0, 138.4, 131.7, 120.7, 119.4, 116.2, 110.0, 61.5, 13.9. LC/MS/MS m/z for $C_{12}H_8Br_2O_4$ [M+H]+: 375.99, found 377.0.

4.16. 3-Benzoyl-2*H*-chromen-2-one (3a)

Using salicylaldehyde (0.14 mL, 1.3 mmol) and ethyl benzoylacetate (0.23 mL, 1.3 mmol), in accordance with the General Procedure A, the title compound 3a was obtained (0.12 g, 36% yield) as a pale yellow solid (m.p. 100 – 103 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H, coum.), 7.96 (m, 2H, arom.), 7.86 (m, 1H, arom.), 7.71-7.74 (m, 2H, arom.), 7.43-7.58 (m, 4H, arom.). ^{13}C NMR (75 MHz, DMSO-d_6) δ 192.2, 158.5, 154.6, 145.8, 136.5, 134.4, 134.1, 130.4, 130.3, 129.2, 126.8, 125.4, 118.7, 116.8. LC/MS/MS m/z for $C_{16}H_{10}O_3$ [M+H]+ : 250.24, found 251.10.

4.17. 3-Benzoyl-7-(benzyloxy)-2*H*-chromen-2-one (3c)

Using 4-(benzyloxy)salicylaldehyde (0.15 g, 0.64 mmol) and ethyl benzoylacetate (0.13 mL, 0.64 mmol), in accordance with the General Procedure A, the title compound 3c was obtained (0.12 g, 49% yield) as a brown solid (m.p. 140 – 143 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.39 (s, 1H, coum.), 7.88-7.90 (m, 2H, arom.), 7.79-7.81 (d, J = 8.80 Hz, 1H, arom.), 7.67-7.68 (m, 1H, arom.), 7.53-7.55 (m, 2H, arom.), 7.50-7.51 (m, 2H, arom.), 7.41-7.44 (m, 2H, arom.), 7.37-7.38 (m, 1H, arom.), 7.19 (m, 1H, arom.), 7.10-7.12 (dd, 1H, J = 8.44, 2.57 Hz, arom.), 5.29 (s, 2H, -CH_2-). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.0, 163.0, 158.2, 156.3, 146.2, 136.5, 136.0, 133.5, 131.2, 129.4, 128.6, 128.5, 128.2, 127.9, 122.4, 113.7, 111.9, 101.5, 70.1. LC/MS/MS m/z for $C_{23}H_{16}O_4$ [M+H]+: 356.37, found 357.10.

4.18. 3-Benzoyl-6-hydroxy-2*H*-chromen-2-one (3j)

Using 2,5-dihydroxybenzaldehyde (0.18 g, 1.3 mmol) and ethyl benzoylacetate (0.23 mL, 1.3 mmol), in accordance with the General Procedure A, the title compound 3j was obtained (0.16 g, 45% yield) as a brown solid (m.p. 227 – 230 °C, ref. [52] 224-225 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.88 (br.s, 1H, OH), 8.34 (s, 1H, coum.), 7.91 (m, 2H, arom.), 7.68-7.71 (m, 1H, arom.), 7.53-7.56 (m, 2H, arom.), 7.33-7.34 (d, 1H, J = 9.54 Hz, arom.), 7.17 (m, 1H, arom.), 7.15 (d, 1H, arom.). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.9, 158.2, 154.0, 145.1, 136.1, 133.9, 129.6, 128.7, 126.4, 121.6, 118.7, 117.2, 113.5. LC/MS/MS m/z for $C_{16}H_{10}O_4$ [M+H]+: 266.24, found 266.90.

4.19. 3-Benzoyl-7-methoxy-2*H*-chromen-2-one (3l)

Using 2-hydroxy-4-methoxybenzaldehyde (0.18 g, 1.2 mmol) and ethyl benzoylacetate (0.2 mL, 1.2 mmol), in accordance with the General Procedure A, the title compound 3l was obtained (0.14 g, 43% yield) as a white solid (m.p. 140 – 143 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H, coum.), 7.87 (m, 2H, arom.), 7.78 (m, 1H, arom.), 7.65 (t, J = 7.35 Hz, 1H, arom.), 7.51 (t, J = 7.54 Hz, 2H, arom.), 7.10 (s, 1H, arom.), 7.01-7.05 (m, 1H, arom.), 3.91 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 192.3, 164.6, 158.7, 156.9, 146.7, 137.0, 133.9, 131.8, 130.1, 129.1, 122.7, 113.6, 112.3, 101.1, 56.5. LC/MS/MS m/z for $C_{17}H_{12}O_4$ [M+H]+: 280.27, found 281.20.

4.20. 3-Benzoyl-8-ethoxy-2*H*-chromen-2-one (3m)

Using 3-ethoxy salicylaldehyde (0.19 g, 1.2 mmol) and ethyl benzoylacetate (0.2 mL, 1.2 mmol), in accordance with the General Procedure A, the title compound 3m was obtained (0.12g, 36% yield) as a pale yellow solid (m.p. 102 – 105 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H, coum.), 7.95-7.92 (m, 2H, arom.), 7.70-7.65 (m, 1H, arom.), 7.57-7.52 (m, 2H, arom.), 7.40-7.33 (m, 3H, arom.), 4.22-4.20 (q, 2H, *J* = 7.16 Hz, $\underline{CH_2}CH_3$), 1.45-1.39 (t, 3H, *J* = 6.97 Hz, -$CH_2\underline{CH_3}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 192.2, 158.3, 146.1, 136.5, 134.4, 130.1, 130.0, 129.2, 126.9, 125.3, 121.2, 119.4, 117.0, 64.9, 15.1. LC/MS/MS m/z for $C_{18}H_{14}O_4$ [M+H]+: 294.3, found 294.90.

4.21. 3-Benzoyl-6-chloro-2*H*-chromen-2-one (3o)

Using 2-hydroxy-5-chlorobenzaldehyde (0.18 g, 1.2 mmol) and ethyl benzoylacetate (0.2 mL, 1.2 mmol), in accordance with the General Procedure A, the title compound 3o was obtained (0.11 g, 33% yield) as a white solid (m.p. 150 – 155 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.37 (s, 1H, coum.), 7.94-7.98 (m, 3H, arom.), 7.76-7.78(dd, *J* = 8.80, 2.20 Hz, 1H, arom.), 7.69-7.71 (m, 1H, arom.), 7.54-7.57 (m, 3H, arom.). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.3, 157.6, 152.8, 143.9, 135.8, 134.0, 132.9, 129.6, 128.7, 128.6, 127.4, 119.6. LC/MS/MS m/z for $C_{16}H_9ClO_3$ [M+H]+: 284.69, found 284.90.

4.22. 3-Benzoyl-6,8-dibromo-2*H*-chromen-2-one (3p)

Using 2-hydroxy-3,5-dibromobenzaldehyde (0.33 g, 1.2 mmol)) and ethyl benzoylacetate (0.2 mL, 1.2 mmol), in accordance with the General Procedure A, the title compound 3p was obtained (0.3 g, 62% yield) as a white solid (m.p. 200 – 202 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.35 (s, 1H, coum.), 8.26 (d, 1H, *J* = 2.20 Hz, arom.), 8.11 (d, 1H, *J* = 2.20 Hz,arom.), 7.97-7.99 (d, *J* = 7.34 Hz, 2H, arom.), 7.72 (m, 1H, arom.), 7.56 (t, 1H, *J* = 7.70 Hz, arom.). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.0, 157.0, 150.1, 143.6, 137.6, 135.7, 134.2, 131.2, 139.7, 128.8, 127.9, 121.2, 116.3, 110.3. LC/MS/MS m/z for $C_{16}H_8Br_2O_3$ [M-H]-: 408.04, found 406.90.

4.23. 2-Oxo-2*H*-chromene-3-carbonitrile (4a)

Using s salicylaldehyde (1.06 mL, 10 mmol) and ethyl cyanoacetate (1.09 mL, 10 mmol) in accordance with the General Procedure A, the title compound 4a was obtained (0.3 g, 14% yield) as a yellow solid (m.p. 181 – 182 °C, ref. [17] m.p. 180-182 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.95 (s, 1H, coum.), 7.80 (m, 2H, arom.), 7.49 (m, 2H, arom.). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.3, 154.5, 135.9, 130.5, 125.9, 117.9, 117.3, 115.1, 102.6. LC/MS/MS m/z for $C_{16}H_8Br_2O_3$ [M-H]-: 171.15, found 169.9.

4.24. 7-(Benzyloxy)-2-oxo-2*H*-chromene-3-carbonitrile (4c)

Using 4-(benzyloxy)salicylaldehyde (0.15 g, 0.6 mmol) and ethyl cyanoacetate (0.08 mL, 0.6 mmol), in accordance with the General Procedure A, the title compound 4c was obtained (0.16 g, 39% yield) as a yellow solid (m.p. 174 – 176 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.82 (s, 1H, coum.), 7.74 (d, *J* = 2.0 Hz, 1H, arom.), 7.47-7.48 (d, *J* = 8.80 Hz, 2H, arom.), 7.40-7.43 (d, *J* = 7.34 Hz, 2H, arom.), 7.36-7.37 (m, 1H, arom.), 7.20 (d, 1H, *J* = 2.20 Hz, arom.), 7.12-7.14 (dd, 1H, *J* = 8.07, 2.20 Hz, arom.), 5.28 (s, 2H, -CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 157.3, 156.4, 153.1, 135.8, 131.3, 128.7, 128.2, 127.9, 114.9, 114.4, 111.4, 101.9, 97.6, 70.4. LC/MS/MS m/z for $C_{17}H_{11}NO_3$ [M-H]- : 277.27, found 278.10.

4.25. 8-Hydroxy-2-oxo-2*H*-chromene-3-carbonitrile (4d)

Using 3-hydroxysalicylaldehyde (1.4 g, 10 mmol) and ethyl cyanoacetate (1.09 mL, 10 mmol), in accordance with the General Procedure A, the title compound 4d was obtained (0.79 g, 34% yield) as a dark brown solid (m.p. 218 – 222 °C, ref. [25] m.p. 228-230 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.55 (s, 1H, OH) 8.89 (s, 1H, C-4) 7.20-7.29 (m, 3H, arom). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.8, 153.9, 144.8, 142.6, 125.4, 121.6, 119.8, 118.4, 114.7, 101.9. LC/MS/MS m/z for $C_{17}H_{11}NO_3$ [M+H]+ : 187.15, found 187.90.

4.26. 6-Bromo-2-oxo-2*H*-chromene-3-carbonitrile (4g)

Using 5-bromosalicylaldehyde (2.03 g, 10 mmol) and ethyl cyanoacetate (1.09 mL, 10 mmol) in accordance with the General Procedure A, the title compound 4g was obtained (1.2 g, 40% yield) as a pale yellow solid (m.p. 199 – 201 °C, ref. [19] m.p. 200-201 °C). ^{1}H NMR (600 MHz, DMSO-d_6) ppm 8.84 (s, 1H) 8.04 (d, *J*=2.20 Hz, 1H) 7.94 (dd, *J*=8.80, 2.20 Hz, 1H) 7.48 (d, *J*=8.80 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 156.3, 153.1, 152.0, 137.5, 131.7, 119.0, 116.9, 114.3, 103.4. LC/MS/MSm/z calcd. for $C_{10}H_4BrNO_2$ [M-H]-: 250.04, found 247.80.

4.27. 6-Hydroxy-2-oxo-2*H*-chromene-3-carbonitrile (4j)

Using 5-hydroxysalicylaldehyde (1.4 g, 10 mmol) and ethyl cyanoacetate (1.09 mL, 10 mmol) in accordance with the General Procedure A, the title compound 4j was obtained (0.48 g, 20% yield) as a light brown solid (m.p. 231 – 234 °C, ref. [25] m.p. 237-238 °C). ^{1}H NMR (300 MHz, DMSO-d_6) ppm 10.07 (br. s., 1H, OH) 8.87 (s, 1H, C-4), 7.36 (d, *J*=9.04 Hz, 1H, arom.) 7.22 (dd, *J*=8.85, 2.83 Hz, 1H, arom.) 7.12 (d, *J*=3.01 Hz, 1H, arom). ^{13}C NMR (100 MHz, CDCl3) δ 157.6, 154.9, 153.9, 147.9, 124.1, 118.3, 115.2, 113.8, 102.5. LC/MS/MS m/z calcd. for $C_{10}H_5NO_3$ [M-H]-: 187.15, found 185.80.

4.28. 6-Methoxy-2-oxo-2*H*-chromene-3-carbonitrile (4k)

Using 5-methoxysalicylaldehyde (0.4 mL, 3.2 mmol) and ethyl cyanoacetate (0.35 mL, 3.2 mmol) in accordance with the General Procedure A, the title compound 4k was obtained (0.33 g, 41% yield) as a yellow solid (m.p. 230 – 232 °C). ^{1}H NMR (600 MHz, DMSO-d_6) ppm 8.84 (s, 1H), 7.46 (s, 1H, arom.) 7.38-7.40 (m, 1H, arom.) 7.32 (d, *J*=2.93 Hz, 1H, arom.), 3.82 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, CDCl3) δ157.0, 156.1, 153.1, 148.5, 123.2, 117.9, 114.6, 111.4, 102.4, 55.9. LC/MS/MS m/z calcd. for $C_{11}H_7NO_3$ [M-H]-: 201.17, found 199.9.

4.29. 7-Methoxy-2-oxo-2*H*-chromene-3-carbonitrile (4l)

Using 4-methoxysalicylaldehyde (0.5 g, 3.3 mmol) and ethyl cyanoacetate (0.36 mL, 3.3 mmol) in accordance with the General Procedure A, the title compound 4l was obtained (0.3 g, 37% yield) as a pale yellow solid (m.p. 222 – 225 °C, ref. [17] m.p. 221-223 °C). ^{1}H NMR (600 MHz, DMSO-d_6) ppm 8.82 (s, 1H, C-4), 7.72 (s, 1H, arom), 7.09 (d, *J*=2.20 Hz, 1H, arom.), 7.04 - 7.06 (m, 1H, arom), 3.90 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, CDCl3) δ 165.4, 157.3, 153.2, 131.3, 114.9, 113.9, 111.3, 101.0, 97.4, 56.4. LC/MS/MS m/z calcd. for $C_{11}H_7NO_3$ [M-H]-: 201.18, found 200.90.

4.30. 8-Ethoxy-2-oxo-2*H*-chromene-3-carbonitrile (4m)

Using 3-ethoxysalicylaldehyde (1.7 g, 10 mmol) and ethyl cyanoacetate (1.1 mL, 10 mmol) in accordance with the General Procedure A, the title compound 4m was obtained (0.16 g, 6% yield) as a yellow solid (m.p. 185 – 187 °C). ^{1}H NMR (300 MHz, DMSO-d_6) ppm 8.90 (s, 1H, C-4), 7.26 - 7.52 (m, 3H), 4.21 (q, *J*=7.16 Hz, 2H, $\underline{CH_2}CH_3$), 1.41 (t, *J*=6.97 Hz, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, CDCl3) δ 154.2, 125.9, 131.3, 119.1, 114.9, 102.7, 65.3, 14.9. LC/MS/MS m/z calcd. for $C_{11}H_7NO_3$ [M-H]-: 215.20, found 213.90.

4.31. 3-Acetyl-8-hydroxy-2*H*-chromen-2-one (5a)

Using 2,3-dihydroxybenzaldehyde (0.5 g, 3.6 mmol (stirrer and ultrasound); 0.05 g, 0.36 mmol (mill)) and ethyl acetoacetate (0.46 mL, 3.6 mmol (stirrer and ultrasound); 0.046 mL, 0.36 mmol (mill)), in accordance with the General Procedure B, the title compound 5a was obtained (0.51 g, 69% yield (stirrer); 0,67 g, 90% yield (ultrasound); 0.049 g, 66% yield (mill)) as a white solid (m.p. 257 – 259 °C, ref. [53] m.p. 253 °C). ^{1}H NMR (600 MHz, DMSO-*d6*) ppm 10.38 (br. s., 1H), 8.58 (s, 1H, C-4), 7.36 (dd, *J*=5.87, 2.93 Hz, 1H, arom.), 7.19 - 7.24 (m, 2H, arom.), 2.59 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl3) δ 195.2, 158.3, 147.4, 144.4, 143.2, 124.9, 124.3, 120.6, 119.0, 30.0. LC/MS/MS m/z calcd. for $C_{11}H_8O_4$ [M-H]-: 204.17, found 202.80.

4.32. 3-Acetyl-7-hydroxy-2*H*-chromen-2-one (5b)

Using 2,4-dihydroxybenzaldehyde (1 g, 7.2 mmol (ultrasound); 0.05 g, 0.36 mmol (mill)) and ethyl acetoacetate (0.92 mL, 7.2 mmol (ultrasound); 0.046 mL, 0.36 mmol (mill)), in accordance with the General Procedure B, the title compound 5b was obtained (0.2755 g, 19% yield (ultrasound); 0.0265 g, 36% yield (mill)) as a pale yellow solid (m.p. 237 – 240 °C). ^{1}H NMR (600 MHz, DMSO-*d6*) ppm 8.58 (s, 1H, C-4), 7.78 (d, *J*=8.80 Hz, 1H, arom.), 6.85 (dd, *J*=8.80, 2.20 Hz, 1H, arom.), 6.75 (d, *J*=2.20 Hz, 1H, arom.), 2.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl3) δ194.6, 164.2, 159.0, 157.2, 147.8, 132.6, 119.2, 114.2, 110.8, 101.7, 30.0. LC/MS/MS m/z calcd. for $C_{11}H_8O_4$ [M-H]-: 204.17, found 202.80.

4.33. 3-Acetyl-6-hydroxy-2*H*-chromen-2-one (5c)

Using 2,5-dihydroxybenzaldehyde (0.5 g, 3.6 mmol (stirrer and ultrasound); 0.05 g, 0.36 mmol (mill)) and ethyl acetoacetate (0.46 mL, 3.6 mmol (stirrer and ultrasound); 0.046 mL, 0.36 mmol (mill)), in accordance with the General Procedure B, the title compound 5c was obtained (0.3767 g, 51% yield (stirrer); 0.6995 g, 95% yield (ultrasound); 0.0164 g, 22% yield (mill)) as a light brown solid (m.p. 235 – 238 °C). ^{1}H NMR (600 MHz, DMSO-d_6) ppm 8.56 (s, 1H, C-4), 7.30 (d, *J*=8.80 Hz, 1H, arom.), 7.23 (d, *J*=2.93 Hz, 1H, arom.), 7.16 - 7.20 (m, 1H, arom.), 2.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl3) δ 195.3, 158.6, 154.0, 148.0, 146.9, 124.4, 122.7, 118.69, 117.0, 114.1, 30.0. LC/MS/MS m/z calcd. for $C_{11}H_8O_4$ [M-H]-: 204.17, found 202.80.

4.34. 3-Acetyl-2*H*-chromen-2-one (5d)

Using salicylaldehyde (1 mL, 9.4 mmol (stirrer and ultrasound); 0.05 g, 0.41 mmol (mill)) and ethyl acetoacetate (1.2 mL, 9.4 mmol (stirrer and ultrasound); 0.052 mL, 0.41 mmol (mill)), in accordance with the General Procedure B, the title compound 5d was obtained (1.5959 g, 90% yield (stirrer); 1.7293 g, 98% yield (ultrasound); 0.0289 g, 38% yield (mill)) as a yellow solid (m.p. 121 – 122 °C, ref. [28] m.p. 118 °C). ^{1}H NMR (300 MHz, DMSO-d_6) ppm 8.63 (s, 1H, C-4), 7.94 (dd, *J*=7.72, 1.70 Hz, 1H, arom.), 7.74 (ddd, *J*=8.57, 7.25, 1.88 Hz, 1H, arom.), 7.23 - 7.50 (m, 2H, arom.), 2.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl3) δ 147.4, 134.9, 131.2, 125.4, 116.6, 30.4. LC/MS/MS m/z calcd. for $C_{11}H_8O_3$ [M+H]+: 188.17, found 188.90.

4.35. 3-Acetyl-6-bromo-2*H*-chromen-2-one (5e)

Using 5-bromosalicylaldehyde (1 g, 4.9 mmol (stirrer and ultrasound); 0.05 g, 0.25 mmol (mill)) and ethyl acetoacetate (0.63 mL, 4.9 mmol (stirrer and ultrasound); 0.032 mL, 0.25 mmol (mill)), in accordance with the General Procedure B, the title compound 5e was obtained (1.1591 g, 88% yield (stirrer); 1.224 g, 93% yield (ultrasound); 0.0146 g, 22% yield (mill)) as a white solid (m.p. 229 – 232 °C, ref. [53] m.p. 231-233 °C). ^{1}H NMR (300 MHz, DMSO-*d6*) ppm 8.58 (s, 1H, C-4), 8.20 (d, *J*=2.64 Hz, 1H, arom.), 7.87 (dd, *J*=8.85, 2.45 Hz, 1H, arom.), 7.43 (d, *J*=8.67 Hz, 1H, arom.), 2.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl3) δ 195.4, 158.4, 154.1, 146.0, 137.0, 133.0, 118.9, 116.8, 30.34.

4.36. 3-Acetyl-8-ethoxy-2*H*-chromen-2-one (5f)

Using 3-ethoxysalicylaldehyde (1 g, 6.02 mmol (stirrer and ultrasound); 0.05 g, 0.26 mmol (mill)) and ethyl acetoacetate (0.77 mL, 6.02 mmol (stirrer and ultrasound); 0.038 mL, 0.3 mmol (mill)), in accordance with the General Procedure B, the title compound 5f was obtained (1.3157 g, 94 % yield (stirrer); 1.3245 g, 94% yield (ultrasound); 0.0331 g, 47% yield (mill)) as a pale yellow solid (m.p. 139 - 141 °C). ^{1}H NMR (300 MHz, DMSO-*d6*) ppm 8.61 (s, 1H, C-4), 7.26 - 7.57 (m, 3H, arom.), 4.19 (q, *J*=7.16 Hz, 2H, $\underline{CH_2}CH_3$), 2.59 (s, 3H, CH_3), 1.16-1.49 (m, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, CDCl3) δ 195.6, 158.7, 147.8, 145.9, 144.5, 125.3, 122.1, 119.3, 117.8, 64.9, 30.5, 15.0. LC/MS/MS m/z calcd. for $C_{13}H_{12}O_4$ [M+H]+: 232.23, found 233.00.

4.37. 3-Acetyl-7-(diethylamino)-2*H*-chromen-2-one (5g)

Using 4-(diethylamino) salicylaldehyde (0.5 g, 2.6 mmol (stirrer); 0.2 g, 1.03 mmol (ultrasound); 0.05 g, 0.26 mmol (mill)) and ethyl acetoacetate (0.33 mL, 2.6 mmol (stirrer); 0.13 mL, 1.03 mmol (ultrasound); 0.033 mL, 0.26 mmol (mill)), in accordance with the General Procedure B, the title compound 5g was obtained (0.3642 g, 55% yield (stirrer); 0.2244 g, 85% yield (ultrasound); 0.0336 g, 51% yield)) as a dark yellow solid (m.p. 153 – 156 °C, ref. [22] m.p. 152-153 °C). ^{1}H NMR (600 MHz, DMSO-*d6*) ppm 8.48 (s, 1H, C-4), 7.65 (d, *J*=8.80 Hz, 1H, arom.), 6.77 - 6.83 (m, 1H, arom.), 6.56 (d, *J*=2.20 Hz, 1H, arom.), 3.49 (q, *J*=7.34 Hz, 4H, $\underline{CH_2}CH_3$), 2.51 - 2.68 (m, 3H, CH_3), 1.12 - 1.24 (m, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl3) δ 194.2, 147.6, 132.4, 110.1, 107.5, 95.8, 44.4, 30.1, 12.3. LC/MS/MS m/z calcd. for $C_{15}H_{17}NO_3$ [M+H]+: 259.30, found 260.00.

CONCLUSION

We have successfully synthesized different coumarin derivatives *via* Knoevenagel condensation utilizing deep eutectic solvents. This green method for Knoevenagel condensation was proven very efficient in coumarin synthesis, without any need for catalysts, while the isolation of final products includes only the addition of water. Among 20 tested DESs, ChCl:U (1:2) was proved to be the best for this type of synthesis. Coumarin derivatives were synthesized at 80°C, from different salicylaldehides and active methylene compounds. ChCl:U DES was investigated on recyclability and it was found it can be used in at least five cycles without any decrease in product yield. A Knoevenagel condensation of different salicylaldehydes and ethyl acetoacetate yielded no products in DESs, therefore this condensation was performed solvent-free with stirring, ball-milling and ultrasound promoted. The highest yields were obtained using ultrasound in only 30-60 minutes.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available within the supplementary materials of this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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