

Sinteza derivata 3-acetilkumarina potpomognuta ultrazvukom i mehanokemijskom metodom

Sušjenka, Martina

Undergraduate thesis / Završni rad

2020

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **Josip Juraj Strossmayer University of Osijek, Department of biology / Sveučilište Josipa Jurja Strossmayera u Osijeku, Odjel za biologiju**

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:181:466306>

Rights / Prava: [In copyright](#) / [Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-04-19**



**ODJEL ZA
BIOLOGIJU**
Sveučilište Josipa Jurja
Strossmayera u Osijeku

Repository / Repozitorij:

[Repository of Department of biology, Josip Juraj Strossmayer University of Osijek](#)



Sveučilište Josipa Jurja Strossmayera u Osijeku

Odjel za biologiju

Preddiplomski sveučilišni studij Biologija

Martina Sušjenka

**Sinteza derivata 3-acetilkumarina potpomognuta ultrazvukom i
mehanokemijskom metodom**

Završni rad

Osijek, 2020.

Sveučilište Josipa Jurja Strossmayera u Osijeku

Odjel za biologiju

Preddiplomski sveučilišni studij Biologija

Znanstveno područje: Prirodne znanosti

Znanstveno polje: Biologija

Sinteza derivata 3-acetilkumarina potpomognuta ultrazvukom i mehanokemijskom metodom

Martina Sušjenka

Rad je izrađen 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-acetilkumarina 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

Rad je pohranjen: na mrežnim stranicama Odjela za biologiju te u Nacionalnom repozitoriju završnih i diplomskih radova Nacionalne i sveučilišne knjižnice u Zagrebu.

Josip Juraj Strossmayer University of Osijek

Department of Biology

Undergraduate university study programme in Biology

Scientific Area: Natural sciences

Scientific Field: Biology

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

Thesis deposited: on the Department of Biology website and Croatian Digital Theses Repository of the National and University Library in Zagreb

Ovaj rad je sufinancirala Hrvatska zaklada za znanost projektom Zelene tehnologije u sintezi heterocikličkih spojeva (UIP-2017-05-6593).

SADRŽAJ

1. UVOD	1
2. MATERIJALI I METODE	2
3. REZULTATI I RASPRAVA	3
4. ZAKLJUČAK.....	6
5. LITERATURA	7

1. UVOD

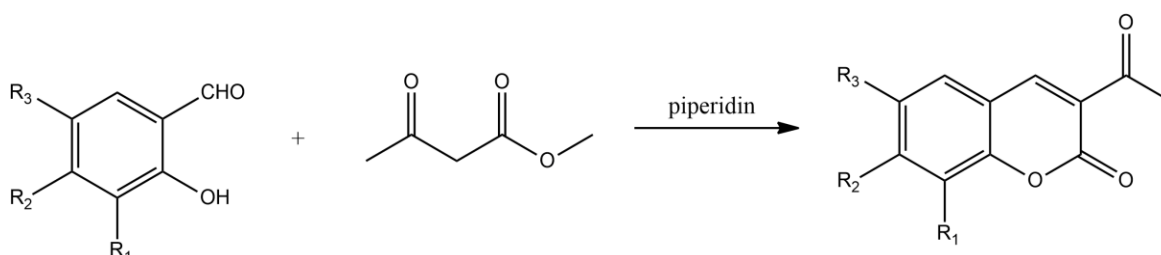
Kumarini su heterociklički spojevi koji su produkti sekundarnog metabolizma biljaka gdje se pojavljuju u porodicama *Apiaceae*, *Asteraceae*, *Fabaceae*, *Rubiaceae*, *Rosaceae*, *Solanaceae*, *Rutaceae*, *Umbelliferae* (Molnar, Čačić, 2011), ali i kao produkti metabolizma u gljiva i bakterija (Revankar 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 kondenzacija odvija se najčešće reakcijom nukleofilne adicije aktivnih metilenskih spojeva s aldehidima 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 uspoređene s konvencionalnom metodom uz miješanje.

2. MATERIJALI I METODE

Sve su kemikalije kupljene od komercijalnih dobavljača. Tankoslojna kromatografija (TLC-*thin-layer chromatography*) 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 određeno 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.)

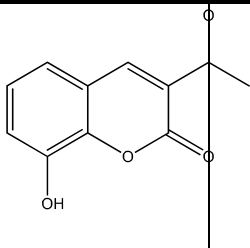
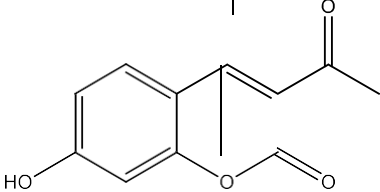
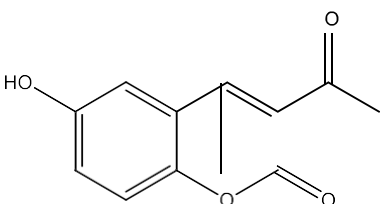
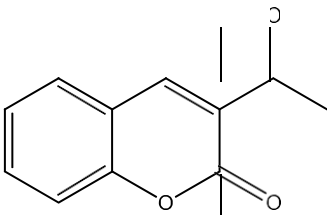
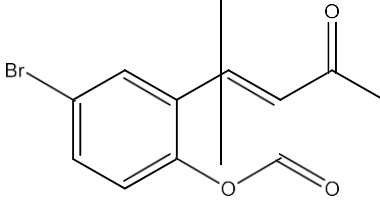


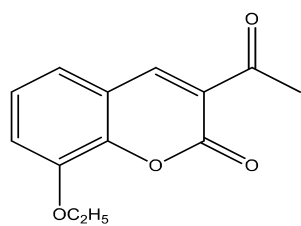
Shema 1: Sinteza derivata 3-acetilkumarina Knoevenagelovom kondenzacijom uz piperidin kao katalizator.

Reakcije potpomognute ultrazvukom izvođene 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 izvođena 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 izuzetak 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. Uspoređujući 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-dihidroksibenzaldehid za koji produkt uopće nije nastao konvencionalnom metodom.

Također, 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.

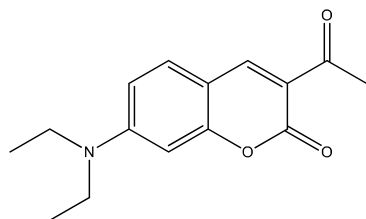
PRODUKT	Konvencionalna metoda	Ultrazvučna metoda	Mehanokemijska metoda
	$\eta=69\%$ $t=30$ min	$\eta=90\%$ $t=30$ min	$\eta=66\%$ $t=2 \times 1$ min
	-	$\eta=19\%$ $t=3$ dana	$\eta=36\%$ $t=2 \times 1$ min
	$\eta=51\%$ $t=30$ min	$\eta=95\%$ $t=30$ min	$\eta=22\%$ $t=4 \times 0,5$ min
	$\eta=90\%$ $t=30$ min	$\eta=98\%$ $t=30$ min	$\eta=38\%$ $t=4 \times 0,5$ min
	$\eta=88\%$ $t=30$ min	$\eta=93\%$ $t=30$ min	$\eta=22\%$ $t=2 \times 1$ min



$\eta=94\%$
t=30 min

$\eta=94\%$
t=30 min

$\eta=47\%$
t=4x0,5 min



$\eta=55\%$
t=60 min

$\eta=85\%$
t=60 min

$\eta=51\%$
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. Uspoređujući 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-dihidroksibenzaldehid.
- Postupci bez prisustva otapala pokazali su se pogodnima za ovakve sinteze.

5. LITERATURA

Borges, F., Roleira, F., Milhazes, N., Santana, L., Uriarte, E. (2005). Simple Coumarins and Analogues in Medical Chemistry: Occurrence, Synthesis and Biological Activity. *Current Medical Chemistry*. 12:887-916

Molnar, M., Čačić, M. (2011). Biološka aktivnost derivata kumarina – pregledni rad. *Croatian Journal of Food Science and Technology*. 3:55-64

Molnar, M., Lončarić, M., Kovač, M. (2020). Green Chemistry Approaches to the Synthesis of Coumarin Derivatives. *Current Organic Chemistry*. 24:4-43

Rohini, K., Srikumar, P.S. (2014). Therapeutic Role of Coumarins and Coumarin-Related Compounds. *Journal of Biofertilizers and Biopesticides*. 5:5-7

Rádl, S. (1990) Structure activity Relationships in DNA gyrase Inhibitors. *Pharmacology and Therapeutics*. 48:1-17

Revankar, H. M., Bukhari, S. N. A., Kumar, G. B., Qin, H.-L. (2017). Coumarins Scaffolds as COX inhibitors. *Bioorganic Chemistry*. 71:146-159

RESEARCH ARTICLE

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

Melita Lončarić¹, Martina Sušjenka² and Maja Molnar^{1,*}¹Josip Juraj Strossmayer University of Osijek, Faculty of Food Technology Osijek, Franje Kuhaca 18, 31000 Osijek, Croatia;²Department of Biology, Josip Juraj Strossmayer University of Osijek, Cara Hadrijana 8/A, 31000 Osijek, Croatia

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 chloride: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.

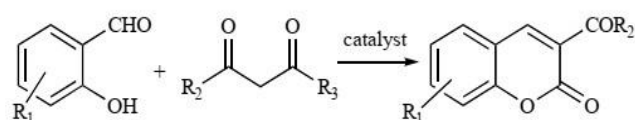
Keywords: Coumarins, synthesis, deep eutectic solvents, green chemistry, choline chloride, Knoevenagel condensation.

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 performed a Knoevenagel 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 Deep Eutectic 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,

*Address correspondence to this author at the Department of Applied Chemistry and Ecology, Faculty of Food Technology Osijek, Josip Juraj Strossmayer University of Osijek, P.O. Box: 31000, Osijek, Croatia; Tel: +38531224342; E-mails: Maja.Molnar@ptfos.hr

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 : <i>N</i> -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 : <i>trans</i> -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:acetic acid (8:1:1) as eluent using fluorescent silica gel plates F₂₅₄ (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-*d*₆ (DMSO-*d*₆). Mechanochemistry 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

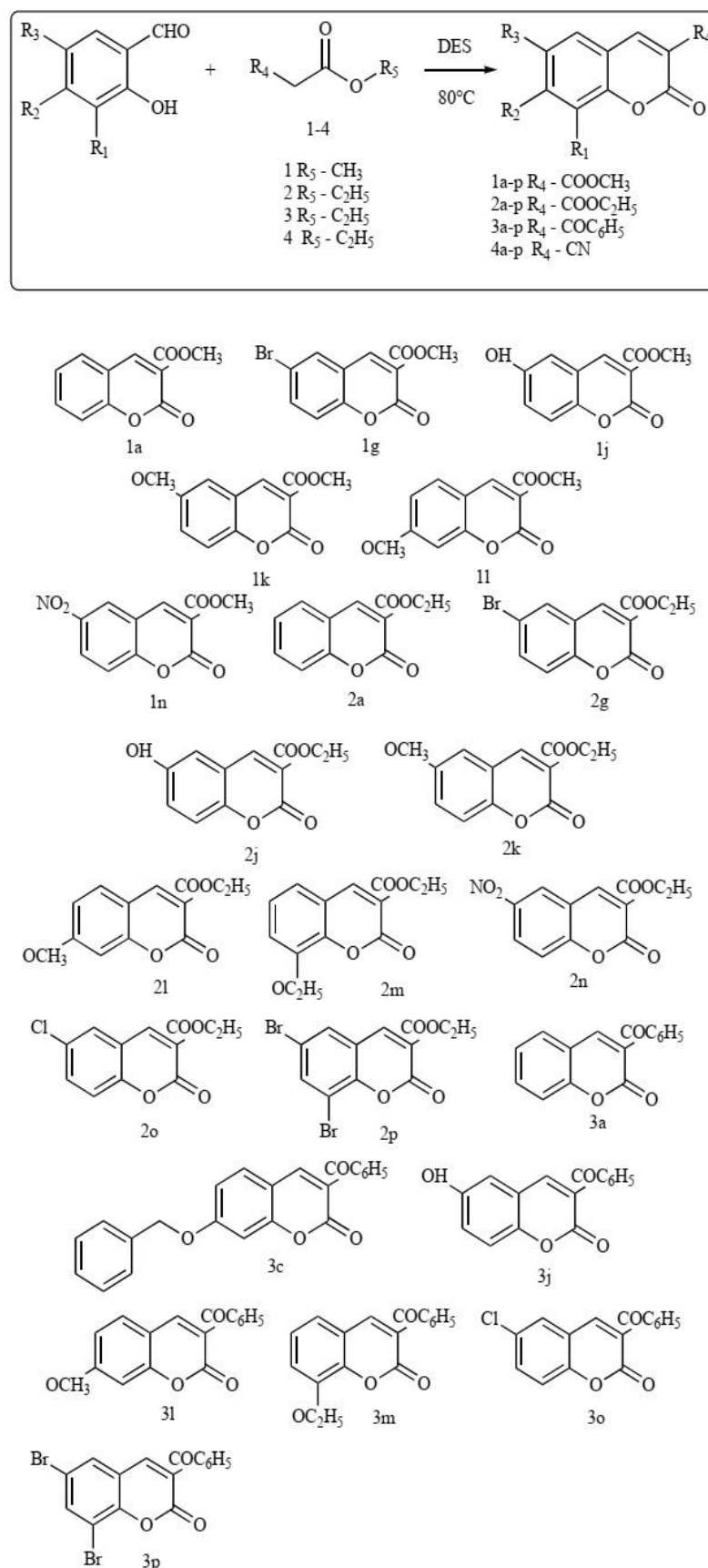
Choline chloride based deep eutectic solvents were prepared by mixing choline chloride, as a Hydrogen Bond Acceptor (HBA), with different Hydrogen Bond Donors (HBDs), as listed in Table 1. A mixture of HBA and HBD was heated until a clear liquid was formed and used for further reactions as such.

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 salicylaldehyde 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 salicylaldehydes were reacted with different methylene active compounds (1-5), to obtain the desired coumarin derivatives

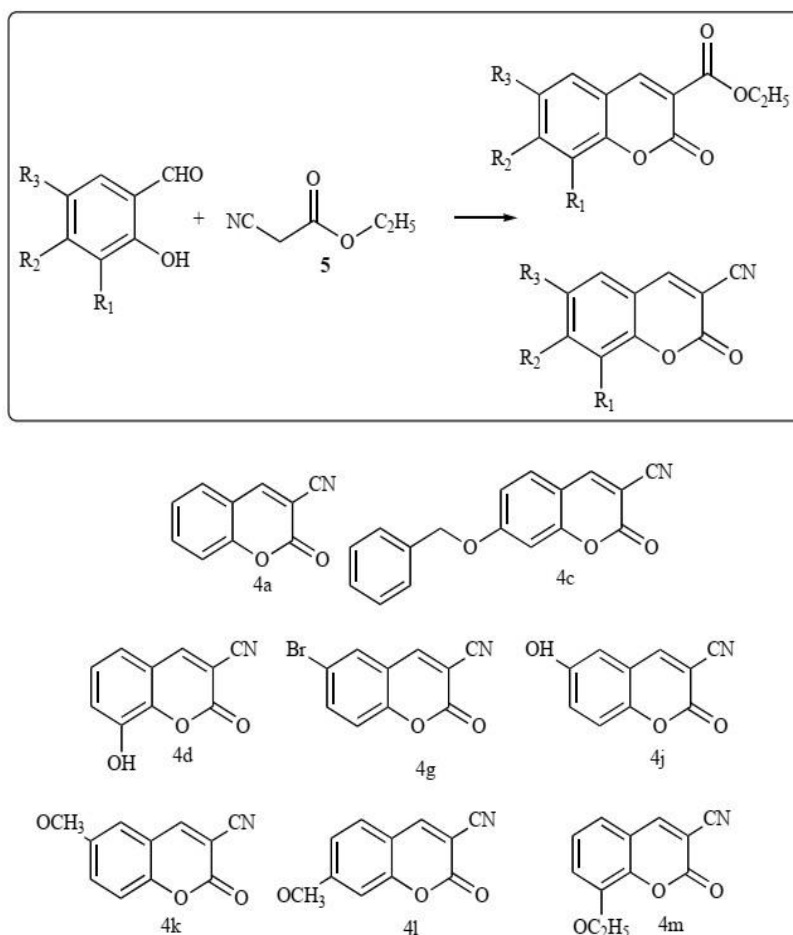
Table 2. Influence of DES recycle of final product yield shown for model reaction.

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

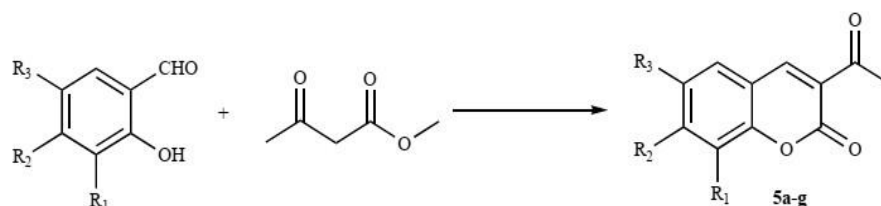
(Schemes 2 and 3). All reactions were monitored by TLC and quenched with water upon the disappearance of all the reactants on TLC. The addition of water to the reaction mixture precipitated the crude product, which was then collected by filtration and dried.

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-bromobenzaldehyde and both dimethylmalonate (85%) and diethylmalonate (88%). Other yields could be considered as moderate. 5-Tert-butyl-salicylaldehyde, 4-diethylaminosalicylaldehyde, 5-fluoro-salicylaldehyde 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-2H-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). ¹H 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, OCH₃). ¹³C 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 C₁₁H₈O₄ [M+H]⁺: 204.17, found 205.10. (Suupl. Mat. Fig. 1).

4.2. Methyl 6-bromo-2-oxo-2H-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). ¹H 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, -OCH₃). ¹³C 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 C₁₁H₇BrO₄ [M+H]⁺: 283.07, found 283.0. (Suupl. Mat. Fig. 3).

4.3. Methyl 6-hydroxy-2-oxo-2H-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). ¹H 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, OCH₃). ¹³C 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 C₁₁H₈O₅ [M+H]⁺: 220.17, found 221.10. (Suupl. Mat. Fig. 5).

4.4. Methyl 6-methoxy-2-oxo-2H-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). ¹H 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, -OCH₃), 3.84 (s, 3H, -OCH₃). ¹³C

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 C₁₂H₁₀O₅ [M+H]⁺: 234.20, found 235.10. (Suupl. Mat. Figs. 7-9).

4.5. Methyl 7-methoxy-2-oxo-2H-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). ¹H 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, -OCH₃), 3.82 (s, 3H, -OCH₃). ¹³C 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 C₁₂H₁₀O₅ [M+H]⁺: 234.20, found 235.10. (Suupl. Mat. Figs. 10, 11).

4.6. Methyl 6-nitro-2-oxo-2H-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). ¹H 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, -OCH₃). ¹³C 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 C₁₁H₇NO₆ [M-H]⁻: 249.17, found 247.90.

4.7. Ethyl 2-oxo-2H-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). ¹H 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, -CH₂CH₃), 1.31-1.34 (t, 3H, -CH₂CH₃). ¹³C 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 C₁₂H₁₀O₄ [M+H]⁺: 218.20, found 219.0.

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

Using 2-hydroxy-5-bromobenzaldehyde (2.03 g, 10 mmol) and diethylmalonate (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). ¹H 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, -CH₂CH₃), 1.30-1.32 (t, 3H, *J* = 6.97 Hz, CH₂CH₃). ¹³C 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 C₁₂H₉BrO₄ [M+H]⁺: 297.1, found 297.10.

4.9. Ethyl 6-hydroxy-2-oxo-2H-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). ¹H 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, -CH₂CH₃), 1.29-1.31 (m, 3H, -CH₂CH₃). ¹³C 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 C₁₂H₁₀O₅ [M-H]⁻: 234.20, found 232.90.

4.10. Ethyl 6-methoxy-2-oxo-2H-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). ¹H 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, -CH₂CH₃), 3.81 (s, 3H, -OCH₃), 1.31–1.35 (t, 3H, *J* = 6.97 Hz, -CH₂CH₃). ¹³C 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 C₁₃H₁₂O₅ [M+H]⁺: 248.23, found 249.10.

4.11. Ethyl 7-methoxy-2-oxo-2H-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). ¹H 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, -CH₂CH₃), 3.89 (s, 3H, OCH₃), 1.29–1.32 (m, 3H, -CH₂CH₃). ¹³C 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 C₁₃H₁₂O₅ [M+H]⁺: 248.23, found 249.20.

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

Using 3-ethoxysalicylaldehyde (1.71 g, 10 mmol) and diethylmalonate (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). ¹H 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, -CH₂CH₃), 4.19–4.18 (q, 2H, *J* = 7.34 Hz, -CH₂CH₃), 1.43–1.40 (m, 3H, -CH₂CH₃), 1.34–1.31 (m, 3H, -CH₂CH₃). ¹³C 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 C₁₄H₁₄O₅ [M+H]⁺: 262.25, found 263.20.

4.13. Ethyl 6-nitro-2-oxo-2H-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). ¹H 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, -CH₂CH₃), 1.32–1.34 (m, 3H, CH₂CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 162.0, 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 C₁₂H₉NO₆ [M+H+Na]⁺: 263.20, found 286.10.

4.14. Ethyl 6-chloro-2-oxo-2H-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). ¹H 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, -CH₂CH₃), 1.30–1.35 (t, 3H, *J* = 6.97 Hz, -CH₂CH₃). ¹³C 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 C₁₂H₉ClO₄ [M+H]⁺: 252.65, found 253.0.

4.15. Ethyl 6,8-dibromo-2-oxo-2H-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). ¹H 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, -CH₂CH₃), 1.30–1.33 (m, 3H, -CH₂CH₃). ¹³C 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 C₁₂H₈Br₂O₄ [M+H]⁺: 375.99, found 377.0.

4.16. 3-Benzoyl-2H-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). ¹H 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.). ¹³C 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 C₁₆H₁₀O₃ [M+H]⁺: 250.24, found 251.10.

4.17. 3-Benzoyl-7-(benzyloxy)-2H-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). ¹H 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, -CH₂-). ¹³C 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 C₂₃H₁₆O₄ [M+H]⁺: 356.37, found 357.10.

4.18. 3-Benzoyl-6-hydroxy-2H-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). ¹H 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.). ¹³C 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 C₁₆H₁₀O₄ [M+H]⁺: 266.24, found 266.90.

4.19. 3-Benzoyl-7-methoxy-2H-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). ¹H 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, OCH₃). ¹³C 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 C₁₇H₁₂O₄ [M+H]⁺: 280.27, found 281.20.

4.20. 3-Benzoyl-8-ethoxy-2H-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). ¹H 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, CH₂CH₃), 1.45-1.39 (t, 3H, *J* = 6.97 Hz, -CH₂CH₃). ¹³C 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 C₁₈H₁₄O₄ [M+H]⁺: 294.3, found 294.90.

4.21. 3-Benzoyl-6-chloro-2H-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). ¹H 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.). ¹³C 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 C₁₆H₉ClO₃ [M+H]⁺: 284.69, found 284.90.

4.22. 3-Benzoyl-6,8-dibromo-2H-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). ¹H 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.). ¹³C 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 C₁₆H₈Br₂O₃ [M-H]⁻: 408.04, found 406.90.

4.23. 2-Oxo-2H-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). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.95 (s, 1H, coum.), 7.80 (m, 2H, arom.), 7.49 (m, 2H, arom.). ¹³C 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 C₁₆H₈Br₂O₃ [M-H]⁻: 171.15, found 169.9.

4.24. 7-(Benzyloxy)-2-oxo-2H-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). ¹H 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, -CH₂). ¹³C 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 C₁₇H₁₁NO₃ [M-H]⁻: 277.27, found 278.10.

4.25. 8-Hydroxy-2-oxo-2H-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). ¹H 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). ¹³C 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 C₁₇H₁₁NO₃ [M+H]⁺: 187.15, found 187.90.

4.26. 6-Bromo-2-oxo-2H-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). ¹H 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). ¹³C 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/MS *m/z* calcd. for C₁₀H₄BrNO₂ [M-H]⁻: 250.04, found 247.80.

4.27. 6-Hydroxy-2-oxo-2H-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). ¹H 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). ¹³C 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 C₁₀H₅NO₃ [M-H]⁻: 187.15, found 185.80.

4.28. 6-Methoxy-2-oxo-2H-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). ¹H 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, OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 157.0, 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 C₁₁H₇NO₃ [M-H]⁻: 201.17, found 199.9.

4.29. 7-Methoxy-2-oxo-2H-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). ¹H 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, OCH₃). ¹³C 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 C₁₁H₇NO₃ [M-H]⁻: 201.18, found 200.90.

4.30. 8-Ethoxy-2-oxo-2H-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). ¹H 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, CH₂CH₃), 1.41 (t, *J* = 6.97 Hz, 3H, CH₂CH₃). ¹³C 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 C₁₁H₇NO₃ [M-H]⁻: 215.20, found 213.90.

4.31. 3-Acetyl-8-hydroxy-2H-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). ¹H NMR (600 MHz, DMSO-*d*₆) 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, CH₃). ¹³C 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 C₁₁H₈O₄ [M-H]⁻: 204.17, found 202.80.

4.32. 3-Acetyl-7-hydroxy-2H-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). ¹H NMR (600 MHz, DMSO-*d*₆) 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, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 194.6, 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 C₁₁H₈O₄ [M-H]⁻: 204.17, found 202.80.

4.33. 3-Acetyl-6-hydroxy-2H-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). ¹H 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, CH₃). ¹³C 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 C₁₁H₈O₄ [M-H]⁻: 204.17, found 202.80.

4.34. 3-Acetyl-2H-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). ¹H 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, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 134.9, 131.2, 125.4, 116.6, 30.4. LC/MS/MS *m/z* calcd. for C₁₁H₈O₃ [M+H]⁺: 188.17, found 188.90.

4.35. 3-Acetyl-6-bromo-2H-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). ¹H NMR (300 MHz, DMSO-*d*₆) 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, CH₃). ¹³C 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-2H-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). ¹H NMR (300 MHz, DMSO-*d*₆) ppm 8.61 (s, 1H, C-4), 7.26 - 7.57 (m, 3H, arom.), 4.19 (q, *J*=7.16 Hz, 2H, CH₂CH₃), 2.59 (s, 3H, CH₃), 1.16-1.49 (m, 3H, CH₂CH₃). ¹³C 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 C₁₃H₁₂O₄ [M+H]⁺: 232.23, found 233.00.

4.37. 3-Acetyl-7-(diethylamino)-2H-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 (mill)) as a dark yellow solid (m.p. 153 – 156 °C, ref. [22] m.p. 152-153 °C). ¹H NMR (600 MHz, DMSO-*d*₆) 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, CH₂CH₃), 2.51 - 2.68 (m, 3H, CH₃), 1.12 - 1.24 (m, 6H, CH₂CH₃). ¹³C 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 C₁₅H₁₇NO₃ [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 salicylaldehydes 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.

FUNDING

This work has been supported in part by Croatian Science Foundation under the project "Green Technologies in Synthesis of Heterocyclic Compounds" (UIP-2017-05-6593).

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

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

REFERENCES

- [1] Ilango, K.; Biju, C.R. *In silico* docking investigation, synthesis and cytotoxic studies of coumarin substituted 1,3,4-oxadiazole derivatives. *J. Pharm. Res.*, **2012**, *5*, 1514-1517.
- [2] Nikhil, B.; Shikha, B.; Anil, P.; Prakash, N.B. Diverse pharmacological activities of 3-substituted coumarins: a review. *Inter. Res. J. Pharm.*, **2012**, *3*, 24-29.
- [3] Heravi, M.M.; Sadjadi, S.; Oskooie, H.A.; Shoor, R.H.; Bamoharram, F.F. The synthesis of coumarin-3-carboxylic acids and 3-acetyl-coumarin derivatives using heteropolyacids as heterogeneous and recyclable catalysts. *Catal. Commun.*, **2008**, *9*(3), 470-474. <http://dx.doi.org/10.1016/j.catcom.2007.07.005>
- [4] Phadtare, S.B.; Shankarling, G.S. Halogenation reactions in biodegradable solvent: Efficient bromination of substituted 1-aminoanthra-9, 10-quinone in deep eutectic solvent (choline chloride: urea). *Green Chem.*, **2010**, *12*(3), 458-462. <http://dx.doi.org/10.1039/b923589b>
- [5] Sharma, G.V.M.; Janardhan Reddy, J.; Sree Lakshmi, P.; Radha Krishna, P. An efficient ZrCl₄ catalyzed one-pot solvent free protocol for the synthesis of 4-substituted coumarins. *Tetrahedron Lett.*, **2005**, *46*(36), 6119-6121. <http://dx.doi.org/10.1016/j.tetlet.2005.06.166>
- [6] Bistović, A.; Stupanić, N.; Opačak-Bernardi, T.; Jukić, M.; Martínez, S.; Glavač-Obrovac, L.; Raić-Malić, S. Synthesis of 4-aryl-1, 2, 3-triazolyl appended natural coumarin-related compounds with antiproliferative and radical scavenging activities and intracellular ROS production modification. *New J. Chem.*, **2017**, *41*(15), 7531-7543. <http://dx.doi.org/10.1039/C7NJ01469D>
- [7] Hamdi, N.; Passarelli, V.; Romerosa, A. Synthesis, spectroscopy and electrochemistry of new 4-(4-acetyl-5-substituted-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl) methoxy-2H-chromen-2-ones as a novel class of potential antibacterial and antioxidant derivatives. *C. R. Chim.*, **2011**, *14*(6), 548-555. <http://dx.doi.org/10.1016/j.crci.2010.11.001>
- [8] Gouda, M.A.; Berghot, M.A.; Baz, E.A.; Hamama, W.S. Synthesis, antitumor and antioxidant evaluation of some new thiazole and thiophene derivatives incorporated coumarin moiety. *Med. Chem. Res.*, **2012**, *21*(7), 1062-1070. <http://dx.doi.org/10.1007/s00044-011-9610-8>
- [9] Al-Ayed, A.S. Synthesis, spectroscopy and electrochemistry of new 3-(5-aryl-4, 5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-2H-chromene-2-one 4, 5 as a novel class of potential antibacterial and antioxidant derivatives. *Int. J. Org. Chem. (Irvine)*, **2011**, *1*(03), 87-96. <http://dx.doi.org/10.4236/ijoc.2011.13014>
- [10] Svinayrov, I.; Bogdanov, M.G. One-pot synthesis and radical scavenging activity of novel polyhydroxylated 3-arylcoumarins. *Eur. J. Med. Chem.*, **2014**, *78*, 198-206. <http://dx.doi.org/10.1016/j.ejmech.2014.03.053> PMID: 24681984
- [11] Osman, H.; Arshad, A.; Lam, C.K.; Bagley, M.C. Microwave-assisted synthesis and antioxidant properties of hydrazinyl thiazolyl coumarin derivatives. *Chem. Cent. J.*, **2012**, *6*(1), 32. <http://dx.doi.org/10.1186/1752-153X-6-32> PMID: 22510146
- [12] Estévez-Braun, A.; González, A.G. Coumarins. *Nat. Prod. Rep.*, **1997**, *14*(5), 465-475. <http://dx.doi.org/10.1039/np9971400465> PMID: 9364778
- [13] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Curr. Med. Chem.*, **2005**, *12*(8), 887-916. <http://dx.doi.org/10.2174/0929867053507315> PMID: 15853704
- [14] Kulkarni, M.V.; Kulkarni, G.M.; Lin, C.H.; Sun, C.M. Recent advances in coumarins and 1-azacoumarins as versatile biodynamic agents. *Curr. Med. Chem.*, **2006**, *13*(23), 2795-2818. <http://dx.doi.org/10.2174/092986706778521968> PMID: 17073630
- [15] Paul, S.; Das, A.R. An efficient green protocol for the synthesis of coumarin fused highly decorated indenodihydropyridyl and dihydropyridyl derivatives. *Tetrahedron Lett.*, **2012**, *53*(17), 2206-2210. <http://dx.doi.org/10.1016/j.tetlet.2012.02.077>
- [16] Abdou, M.M. 3-Acetyl-4-hydroxycoumarin: Synthesis, reactions and applications. *Arab. J. Chem.*, **2017**, *10*, S3664-S3675. <http://dx.doi.org/10.1016/j.arabjc.2014.04.005>
- [17] Harishkumar, H.N.; Mahadevan, K.M.; Kumar, C.K.; Satyanarayan, N.D. A facile, choline chloride/urea catalyzed solid phase synthesis of coumarins via Knoevenagel condensation. *Org. Commun.*, **2011**, *4*(2), 26-32.
- [18] Wong, K.T.; Basar, N. Coumarins via Knoevenagel Condensation Reaction (KCR) and Pechmann condensation reaction. *J. Teknol.*, **2012**, *57*(1), 83-98.
- [19] Keshavarzipour, F.; Tavakol, H. The synthesis of coumarin derivatives using choline chloride/zinc chloride as a deep eutectic solvent. *J. Iran. Chem. Soc.*, **2016**, *13*(1), 149-153. <http://dx.doi.org/10.1007/s13738-015-0722-9>
- [20] Abdel-Wahab, B.F.; Mohamed, H.A.; Farhat, A.A. Ethyl coumarin-3-carboxylate: synthesis and chemical properties. *Org. Commun.*, **2014**, *7*(1), 1-27. <http://dx.doi.org/10.1246/cl.2001.110>
- [21] Sugino, T.; Tanaka, T. Solvent-free coumarin synthesis. *Chem. Lett.*, **2001**, *30*(2), 110-111. <http://dx.doi.org/10.1007/s13738-015-0722-9>
- [22] Bogdal, D. Coumarins: Fast synthesis by Knoevenagel condensation under microwave irradiation. *J. Chem. Res.*, **1998**, *5*(8), 468-469. <http://dx.doi.org/10.1039/a801724g>
- [23] Balalaie, S.; Nemati, N. One-pot preparation of coumarins by Knoevenagel condensation in solvent-free condition under microwave irradiation. *Heterocycl. Commun.*, **2001**, *7*(1), 67-72. <http://dx.doi.org/10.1515/HC.2001.7.1.67>
- [24] Valizadeh, H.; Vaghefi, S. One-pot Wittig and Knoevenagel reactions in ionic liquid as convenient methods for the synthesis of coumarin derivatives. *Synth. Commun.*, **2009**, *39*(9), 1666-1678. <http://dx.doi.org/10.1080/00397910802573163>
- [25] Valizadeh, H.; Mahmoodian, M.; Gholipour, H.J. ZrCl₄/bmim] BF₄-catalyzed condensation of salicylaldehydes and malononitrile: Single-step synthesis of 3-cyanocoumarin derivatives. *Heterocyclic Chem.*, **2011**, *48*(4), 799-802. <http://dx.doi.org/10.1002/jhet.593>
- [26] Ranu, B.C.; Jana, V. Ionic liquid as catalyst and reaction medium—a simple, efficient and green procedure for Knoevenagel condensation of aliphatic and aromatic carbonyl compounds using a task-specific basic ionic liquid. *Eur. J. Org. Chem.*, **2006**, *16*, 3767-3770. <http://dx.doi.org/10.1002/ejoc.200600335>
- [27] Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. Lewis acidic ionic liquids for the synthesis of electrophilic alkenes via the Knoevenagel condensation. *Tetrahedron Lett.*, **2002**, *43*(6), 1127-1130. [http://dx.doi.org/10.1016/S0040-4039\(01\)02341-3](http://dx.doi.org/10.1016/S0040-4039(01)02341-3)
- [28] Phadtare, S.B.; Shankarling, G.S. Greener coumarin synthesis by Knoevenagel condensation using biodegradable choline chloride. *Environ. Chem. Lett.*, **2012**, *10*(4), 363-368. <http://dx.doi.org/10.1007/s10311-012-0360-8>
- [29] Smith, E.L.; Abbott, A.P.; Ryder, K.S. Deep eutectic solvents (DESs) and their applications. *Chem. Rev.*, **2014**, *114*(21), 11060-11082. <http://dx.doi.org/10.1021/cr300162p> PMID: 25300631
- [30] Burrell, A.K.; Sesto, R.E.D.; Baker, S.N.; McCleskey, T.M.; Baker, G.A. The large scale synthesis of pure imidazolium and pyrrolidinium ionic liquids. *Green Chem.*, **2007**, *9*(5), 449-454. <http://dx.doi.org/10.1039/b615950h>
- [31] Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R.L.; Duarte, A.R.C. Natural deep eutectic solvents—solvents for the 21st century. *ACS Sustain. Chem. Eng.*, **2014**, *2*(5), 1063-1071. <http://dx.doi.org/10.1021/sc500096j>
- [32] Kudlak, B.; Owczarek, K.; Namieśnik, J. Selected issues related to the toxicity of ionic liquids and deep eutectic solvents—a review. *Environ. Sci. Pollut. Res. Int.*, **2015**, *22*(16), 11975-11992. <http://dx.doi.org/10.1007/s11356-015-4794-y> PMID: 26040266
- [33] Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev.*, **2012**, *41*(21), 7108-7146. <http://dx.doi.org/10.1039/c2cs35178a> PMID: 22806597
- [34] Alonso, D.A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I.M.; Ramón, D.J. Deep eutectic solvents: the organic reaction medium of the century. *Eur. J. Org. Chem.*, **2016**, *2016*(4), 612-632. <http://dx.doi.org/10.1002/ejoc.201501197>
- [35] Lobo, H.R.; Singh, B.S.; Shankarling, G.S. Bio-compatible eutectic mixture for multi-component synthesis: A valuable acidic catalyst for synthesis of novel 2, 3-dihydroquinazolin-4(1H)-one derivatives. *Catal. Commun.*, **2012**, *27*, 179-183. <http://dx.doi.org/10.1016/j.catcom.2012.07.020>
- [36] Zhang, M.; Liu, P.; Liu, Y.H.; Shang, Z.R.; Hu, H.C.; Zhang, Z.H. Magnetically separable graphene oxide anchored sulfonic acid: a novel, highly efficient and recyclable catalyst for one-pot synthesis of 3, 6-di (pyridin-3-yl)-1 H-pyrazolo [3, 4-b] pyridine-5-carbonitriles in deep eutectic solvent under microwave irradiation. *RSC Advances*, **2016**, *6*(108), 106160-106170. <http://dx.doi.org/10.1039/C6RA19579B>
- [37] Zhang, M.; Liu, Y.H.; Shang, Z.R.; Hu, H.C.; Zhang, Z.H. Supported molybdenum on graphene oxide/Fe₃O₄: An efficient, magnetically separable catalyst for one-pot construction of spiro-oxindole dihydropyridines in deep

- eutectic solvent under microwave irradiation. *Catal. Commun.*, **2017**, *88*, 39-44.
<http://dx.doi.org/10.1016/j.catcom.2016.09.028>
- [38] Zhang, W.H.; Chen, M.N.; Hao, Y.; Jiang, X.; Zhou, X.L.; Zhang, Z.H. Choline chloride and lactic acid: A natural deep eutectic solvent for one-pot rapid construction of spiro [indoline-3, 4'-pyrazolo [3, 4-b] pyridines]. *J. Mol. Liq.*, **2019**, *278*, 124-129.
<http://dx.doi.org/10.1016/j.molliq.2019.01.065>
- [39] Ma, C.T.; Liu, P.; Wu, W.; Zhang, Z.H. Low melting oxalic acid/proline mixture as dual solvent/catalyst for efficient synthesis of 13-aryl-13H-benzothiazolo [2, 3-b] buinazoline-5, 4-diones under microwave irradiation. *J. Mol. Liq.*, **2017**, *242*, 606-611.
<http://dx.doi.org/10.1016/j.molliq.2017.07.060>
- [40] Ge, G.; Ping, W.; Peng, L.; Weihong, Z.; Liping, M.; Zhanhui, Z. Deep eutectic solvent catalyzed one-pot synthesis of 4, 7-dihydro-1H-pyrazolo [3, 4-b] pyridine-5-carbonitriles. *Youji Huaxue*, **2018**, *38*(4), 846-854.
<http://dx.doi.org/10.6023/cjoc201711014>
- [41] Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. Montmorillonite KSF as an inorganic, water stable, and reusable catalyst for the Knoevenagel synthesis of coumarin-3-carboxylic acids. *J. Org. Chem.*, **1999**, *64*(3), 1033-1035.
<http://dx.doi.org/10.1021/jo981794r> PMID: 11674183
- [42] Liu, S.; Ni, Y.; Wei, W.; Qiu, F.; Xu, S.; Ying, A. Choline chloride and urea based eutectic solvents: effective catalytic systems for the Knoevenagel condensation reactions of substituted acetonitriles. *J. Chem. Res.*, **2014**, *38*(3), 186-188.
<http://dx.doi.org/10.3184/174751914X13926483381319>
- [43] Sonawane, Y.A.; Phadtare, S.B.; Borse, B.N.; Jagtap, A.R.; Shankarling, G.S. Synthesis of diphenylamine-based novel fluorescent styryl colorants by Knoevenagel condensation using a conventional method, biocatalyst, and deep eutectic solvent. *Org. Lett.*, **2010**, *12*(7), 1456-1459.
<http://dx.doi.org/10.1021/ol902976u> PMID: 20199063
- [44] Liu, P.; Hao, J.W.; Mo, L.P.; Zhang, Z.H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. *RSC Advances*, **2015**, *5*(60), 48675-48704.
<http://dx.doi.org/10.1039/C5RA05746A>
- [45] Phadtare, S.B.; Jarag, K.J.; Shankarling, G.S. Greener protocol for one pot synthesis of coumarin styryl dyes. *Dyes Pigments*, **2013**, *97*(1), 105-112.
<http://dx.doi.org/10.1016/j.dyepig.2012.12.001>
- [46] Abbott, A.P.; Boothby, D.; Capper, G.; Davies, D.L.; Rasheed, R.K. Deep eutectic solvents formed between choline chloride and carboxylic acids: versatile alternatives to ionic liquids. *J. Am. Chem. Soc.*, **2004**, *126*(29), 9142-9147.
<http://dx.doi.org/10.1021/ja048266j> PMID: 15264850
- [47] Bisht, S.; Peddinti, R.K. Domino reactions of alkenyl p-benzoquinones: Access to aryl sulfide derivatives of coumarins. *Tetrahedron*, **2017**, *73*(18), 2591-2601.
<http://dx.doi.org/10.1016/j.tet.2017.03.030>
- [48] Shaabani, A.; Ghadiri, R.; Rahmati, A.; Rezayan, A.H. Coumarin synthesis via Knoevenagel condensation reaction in 1, 1, 3, 3-N, N, N', N'-tetramethylguanidinium trifluoroacetate ionic liquid. *J. Iran. Chem. Soc.*, **2009**, *6*(4), 710-714.
<http://dx.doi.org/10.1007/BF03246160>
- [49] Srikrishna, D.; Tasqueeruddin, S.; Kumar Dubey, P. Synthesis of 3-substituted Coumarins: An Efficient Green Approach Using L-proline as Catalyst in Triethanolamine Medium. *Lett. Org. Chem.*, **2014**, *11*(8), 556-563.
<http://dx.doi.org/10.2174/1570178611666140512215136>
- [50] Bao, W.; Wang, Z.; Li, Y. Coumarin synthesis via Knoevenagel condensation in moisture stable room temperature ionic liquids. *J. Chem. Res.*, **2003**, *2003*(5), 294-295.
<http://dx.doi.org/10.3184/030823403103173868>
- [51] He, X.; Shang, Y.; Zhou, Y.; Yu, Z.; Han, G.; Jin, W.; Chen, J. Synthesis of coumarin-3-carboxylic esters via FeCl₃-catalyzed multicomponent reaction of salicylaldehydes, Meldrum's acid and alcohols. *Tetrahedron*, **2015**, *71*(5), 863-868.
<http://dx.doi.org/10.1016/j.tet.2014.12.042>
- [52] Secci, D.; Carradori, S.; Bolasco, A.; Chimenti, P.; Yáñez, M.; Ortuso, F.; Alcaro, S. Synthesis and selective human monoamine oxidase inhibition of 3-carbonyl, 3-acyl, and 3-carboxyhydrazido coumarin derivatives. *Eur. J. Med. Chem.*, **2011**, *46*(10), 4846-4852.
<http://dx.doi.org/10.1016/j.ejmech.2011.07.017> PMID: 21872365
- [53] Liu, X.H.; Fan, J.C.; Liu, Y.; Shang, Z.C. L-Proline as an efficient and reusable promoter for the synthesis of coumarins in ionic liquid. *J. Zhejiang Univ. SC. B*, **2008**, *9*(12), 990-995.