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REVIEW article

Insight into the synthesis of warfarin and its promiscuous derivatives

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Abstract: Warfarin is the most widely used anticoagulant drug which reduces the risk of blood clots forming. This review aims to highlight the significant research on the synthesis of warfarin and its derivatives using numerous methods such as Michael reactions, green enantioselective, one-pot condensation, and catalytic synthesis. The synthesis of warfarin derivatives was discussed since they have proven to have higher biological activity than warfarin itself. Further, this review was carried out to figure out the shortcomings in the synthesis methods and shed light on the contribution of each research on the development and design of stereospecific synthesis of warfarin or its derivatives which were proven to be potent hits with an acceptable cost. Moreover, the contribution of some methods in green chemistry advancement has been investigated.

Introduction

Over the last two decades, the interest in chiral drugs has extremely increased due to the difference between the enantiomers in biological activity, mechanism, and toxicity [1]. This review focuses on warfarin which belongs to this category of drugs. Warfarin is one of the crucial coumarin derivatives because of its anticoagulant properties [2], which were reported for the first time in 1944 through the bioessay in rabbits [3]. Hence, it has been the most VKAs prescribed oral anticoagulant worldwide over 60 years [4-6], owing to it is low cost and once-daily also dosing for the numerous effects such as the antithrombotic effect attributed to its anticoagulant which in turn is mediated by inhibiting the carboxylation of vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X and of the natural anticoagulant proteins C and S [7, 8]. It has been demonstrated that this oral anticoagulant has a high efficacity in the prevention of strokes and recurrent Deep Vein Thrombosis and Pulmonary Embolism (DVT/PE) which are dangerous complications that can stroke patients suffer from DVT/PE [9-13]. Despite a range of limitations, warfarin is highly effective for stroke prevention in arterial fibrillation AF [14]. Although all these effects have been demonstrated this extensively used drug still has high interaction with food and herbal medicines and some xenobiotics [15]. Furthermore, this drug can be affected by co-administration of other medications that cause extensive disturbing in pharmacodynamics and pharmacokinetics which will affect its absorption or distribution or metabolism and excretion [16, 17]. However, there are some shortcomings while treating with warfarin; we can note the risk of bleeding complications or hemorrhage which requires normalise the INR, for example in a neuraxial block [18-22].

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Warfarin is also believed to affect sometimes the cognitive function in patients with arterial fibrillation [21]. Nevertheless, there is no need for that in minor dental, dermatological, and ophthalmological procedures [23]. Otherwise, it can increase bone turnover and stronger osteoclast activity [24]. Therefore, we decided to be a part of the improvement of the shortcomings that were reported previously by discussing some new and efficient synthesis methods in this review.

Synthesis of warfarin and its derivatives: Nowadays, warfarin is the most widely used anticoagulant. It is a vitamin K antagonist that inhibits the conversion of oxidized vitamin K epoxide into its reduced form, which is required for gamma-carboxylation of the coagulation factors and anticoagulant proteins C and S1. This increased use is due to its high efficacy in preventing embolic strokes in atrial fibrillation patients [25, 26]. It has been synthesized for years with a variety of reagents, solvents, and catalysts using several methods.

The first practical synthesis of warfarin and its derivatives: In fact, the first practical asymmetric synthesis of R and S-warfarin was developed by Andrea Robinson and Hui-Yin Li in 1996; where the preparation of enantiomeric pure warfarin involved the resolution of racemic warfarin via repeated recrystallization of quinidine/quinine salts [27] or chromatographic separations [28]. These methods are limited to small-scale preparation. In **Figure 1**, they have reported an efficient two-step process by using our chiral switch strategy for the preparation of either warfarin enantiomers via a highly efficient DuPHOS-Rh catalyzed asymmetric hydrogenation of an α-, β-unsaturated ketone as the key step. It was the first time a racemic ketone was "switched" to its pure enantiomers via a prochiral enone, as well as the first time a prochiral ketone was asymmetrically hydrogenated dehydrowarfarin 2 (R=H) is a recognized metabolite of rat hepatic microsomal metabolism of warfarin lb. It was first identified and produced by Kaminsky and co-workers by copper (I) - induced oxidation of racemic warfarin 1a (R=H) in pyridine [29]. The reported process proved unreliable in their hands, yielding only mediocre yields of oxidized product 2 (30.0%) at best. However, high yields of dehydrowarfarin 2b (90%-98%) were produced by maintaining a constant air stream across the reaction mixture and raising the reaction temperature (55-60°C) (90%-98%). Oxidation takes place in a stereoselective manner, yielding just E- alkene. The stability of this geometric isomer is owing to the formation of a hemiketal form which was confirmed by the X-ray crystal structure [30]. In this work, they have not noticed any improvement in enantioselectivity when the countercations were changed to lithium or potassium, or even when the reaction temperature was lowered. Acidification and single recrystallization of the crude hydrogenation products provided R- la and -lb warfarin in >98%ee.

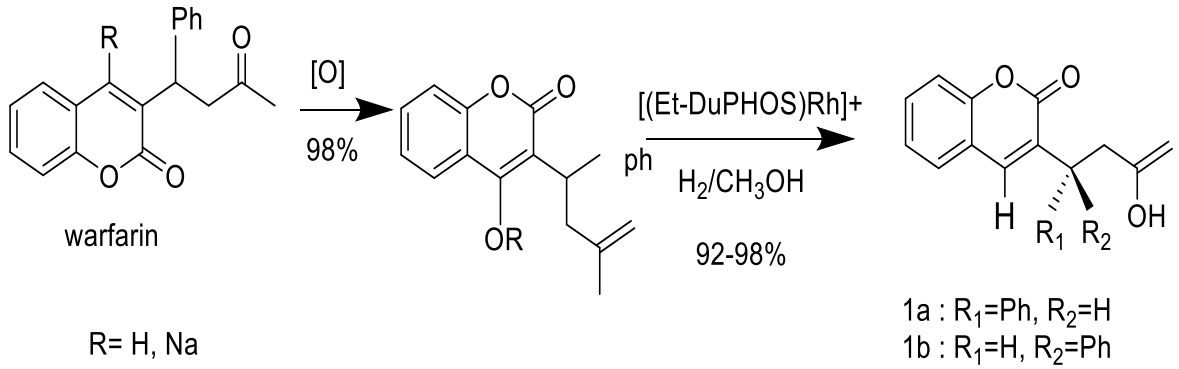

Figure 1: A highly efficient synthesis of both enantiomers of warfarin la and lb

The first organocatalytic preparation of warfarin and its derivatives: Interest in warfarin has highly increased in the last two decades. Wether, several types of reagents and catalysts especially organocatalysts have played a role in the synthesis of warfarin and its derivatives. In 2003, the research group of Jørgensen in Denmark reported for the first time that the imidazolidine catalyst was an efficient asymmetric catalyst for the formation of warfarin (3) from 4-hydroxycoumarin (1) and benzylideneacetone (2) (**Figure 2**) [31].

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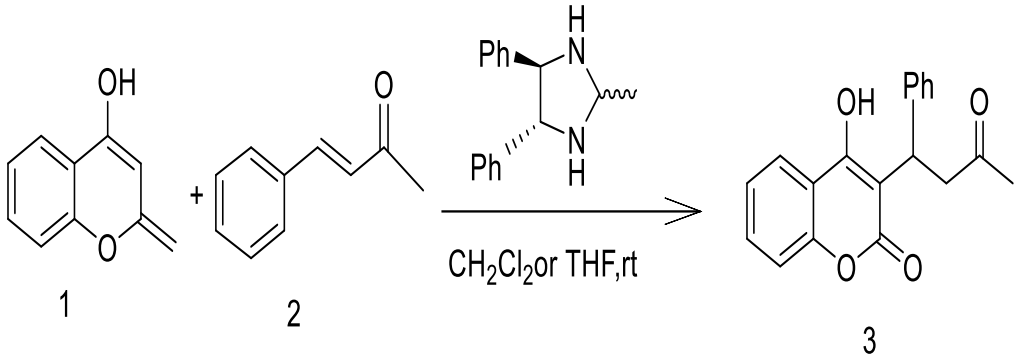
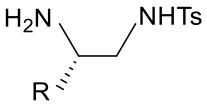
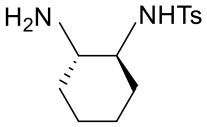
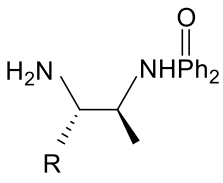
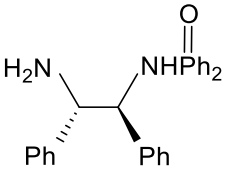
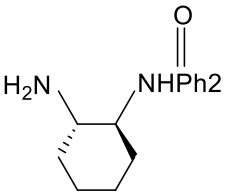


Figure 2: The first organocatalytic preparation of warfarin

Synthesis of warfarin and its derivatives using different types of amines: Natural products, medicines, and agrochemicals are all rich in chiral amines. It is the case of warfarin which has been synthesized using different amines, and diamines depending on the aim of the synthesis [32]. The use of primary amine-phosphinamide bifunctional catalysts (20 mol%) to catalyze the enantioselective Michael addition of 4-hydroxycoumarin (0.20 mmol), to α, β-unsaturated ketones (0.24 mmol) with toluene (1.5 mL) as additive at room temperature for 48 hrs has been developed after a screening of different sulfonamide and phosphinamide organocatalysts and several solvents as $CHCl_3$, EtOAc, Et_2O, and THF to have the best yield and enantioselectivity (**Table 1**).

Table 1: Yield and ee of several sulfonamide and phosphinamide organocatalysts

Catalyst		Yield (%)	ee (%)
	(S)-1a : R= *i*-Pr	86	41
	(S)-1b : R=*t*-Bu	87	57
	(S)-1c : R=Ph	80	45
	(S)-1d : R= Bn	95	25
	(S, S)-1e	48	32
	(S)-2a : R= *i*-Pr	4	/
	(S)-2b : R=*t*-Bu	45	47
	(S)-2c : R=Ph	99	68
	(S)-2d : R= Bn	21	25
	(S, S)-1e	72	88
	(S, S)-1e	3	/

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However, in Chen's paper, 20 mol% catalysts and 40 mol% TFA were utilized, resulting in a bigger and more expensive catalyst quantity. For the asymmetric Michael addition of 4-hydroxycoumarin to α, β-unsaturated ketones, Feng and colleagues designed C2-symmetric secondary amine-amide catalysts (see below). The relevant compounds were produced in high enantioselectivities and excellent yields (up to 99%) and (up to 89%ee). In comparison to these described organocatalysts, we used only 10 mol% phosphinamide catalysts and 20 mol% 4-methyl benzoic acid in our above catalytic system, making this methodology more cost-effective and appealing. The scope of this organocatalytic asymmetric Michael reaction was extended to variousα, β-unsaturated enones under optimum reaction conditions. Warfarin and its analogs had moderate to excellent yields (up to 99%) and good to outstanding enantioselectivities as a result of this reaction (up to 99% ee) [33]. In another study, 4-dimethylaminopyridine (DMAP, 2 mmol: 0.44 g) was used as a catalyst in the synthesis of warfarin (6.8 mmol; 2.1 g), dicyclohexylcarbodiimide (DCC, 9 mmol: 1.86 g) was added in small amounts to a solution of PEG2000-(COOH) (4.5 mmol: 5 g) in CH_2Cl_2. The dicyclohexyl urea (DCU) precipitate was filtered out, and the filtrate evaporated to dryness. The residue was extracted with CH_2Cl_2, filtered to remove DCU residue, and ether was used to precipitate the result. From ethanol, the product was recrystallized twice, 85% yield. The PEEG-warfarin prodrug exhibited some unique characteristics that made it appealing for anticoagulant drug delivery. In water, it was very soluble, and in physiological buffer, it was stable, although it was able to release medication consistently and effectively *in vivo* [34]. In a similar work, warfarin triflate 6 (0.858 g, 1.95 mmol) was added after N-Acetyl-L-cysteine (265 mg, 1.63 mmol) was dissolved in deoxygenated pyridine (5.0 mL). The resulting solution was heated to 90°C for 3 min, then cooled before adding 40 mL of ethylacetate and washing the organic phase with 2 M HCl (2×30 mL). The organic phase was extracted with $NaHCO_3$ (3×20 mL), the aqueous phase was acidified with H_3PO_4 to pH 2, and the extracted aqueous phase was extracted with ethylacetate (2×30 mL) and dried over $MgSO_4$. After removing the solvent, the residue was chromatographed (15% acetic acid/85% ethylacetate) to yield 200 mg (27%) of [10-R,S]-4-S-(N-Acetyl-L-cysteinyl)-3-(10-phenyl-30- oxobutyl)-2H-1-benzopyran-2-one « S-(N-Acetyl-L-cysteinyl)warfarin » as an off-white solid. Another derivative [10-R,S]-4-Chloro-3-(10-phenyl-30-oxobutyl)-2H-1-Benzopyran-2-one (4-Chlorowarfarin) was synthesized as follows: At 60°C, tetrabutylammonium chloride (2.58 g, 9.28 mmol) was dissolved in DMSO (4.0 mL). Warfarin triflate 6 (1.246 g, 2.83 mmol) was diluted in 4.0 mL pyridine and added right away. The liquid was agitated for 1 hr at 60°C, before being put onto a 5% H_3PO_4 surface (50 mL). It was extracted with ethylacetate (230 mL), then washed with 5% H_3PO_4 (30 mL), $NaHCO_3$ (2×20 mL), and brine (20 mL) before drying over $MgSO_4$ and removing the solvent. The residue was chromatographed twice (20% ethylacetate/80% n-heptane) to get 80 mg (8.6%) of 10 as a white solid, with a melting point of 134-135^{o}C [35]. Lately, in 2015, Talhi and co-workers have used the organobase catalytic procedure using 4-pyrrolidinopyridine (4-PPy) to generate a new series of warfarin analogs via typical 1,4-conjugate addition of 4-hydroxycoumarin (used in excess >2 equivalents) on chalcone derivatives 2a-j using $CHCl_3$ as a solvent in reflux for 24 hrs to generate a new series of warfarin analogs (**Table 2**). This simple procedure has proven to be versatile in producing a new library and structural variety of warfarin analogs 3a-j in modest yields [36].

In another work, dl-proline (661 mg, 5.75 mmol) was added to a stirred solution of 4-bromobenzalacetone (2.59 g, 11.5 mmol) and 4-hydroxycoumarin (1.69 g, 11.5 mmol) in DMSO (23 mL) and the mixture was agitated for 24 hrs at room temperature. The mixed organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure after the combination was extracted twice with chloroform. The target chemical (4.03 g, 91.0%) was purified using flash chromatography with Wakosil C-200 as the stationaryphase and hexane-ethyl acetate (50: 50, v/v) as the mobile phase. The pure named substance (3-[1-(4-bromophenyl)-3-oxobutyl]-4-hydroxy-2H-1-benzopyran-2-one (BWF)) was obtained as a white crystal after recrystallization in chloroform and hexane; in moderate yield (2.55 g, 57.0%) [37]. The synthesis of (R)-Warfarin was also described by Sonsona and co-workers for the first time using primary aromatic diamines

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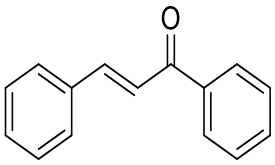
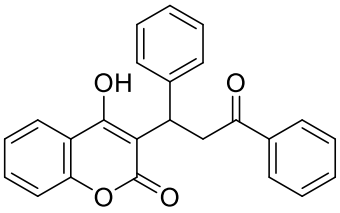
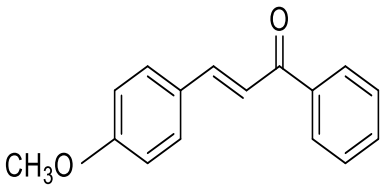
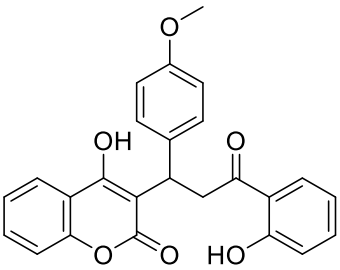
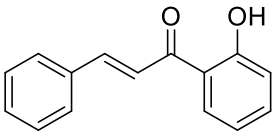
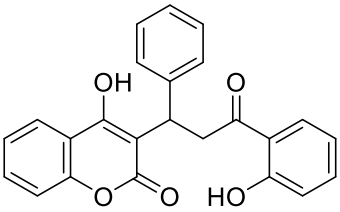
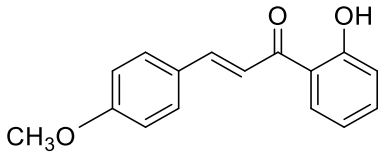
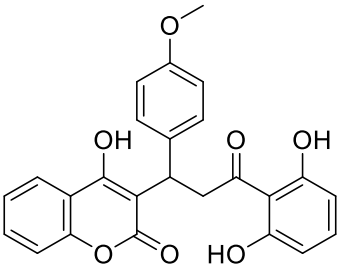
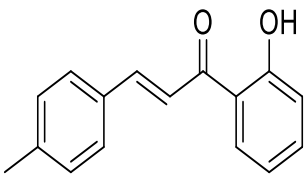
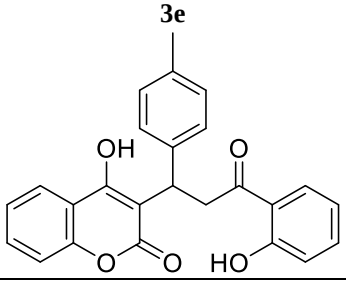
as organocatalysts [38]. Despite the long reaction time (3 days), the desired products were obtained with good to excellent yields of 68%-92% and moderate enantiomeric excesses of 50%-67%. The chiral primary amine thiourea bifunctional catalysts were used to induce highly asymmetric Michael addition of 4-hydroxycoumarin to α, β-unsaturated ketones, and a series of Michael adducts were produced in good yields (97%) and enantio-selectivities (up to 95%ee). After a single recrystallization, optically pure S-warfarin was easily obtained in 99%ee (**Figure 3**).

Table 2: Yield and products of the addition of 4-hydroxycoumarin on chalcone derivatives

Chalcone substrate	Product	Yield (%)
2a 	**3a** 	**62**
2b 	**3b** 	**67**
2c 	**3c** 	**34**
2d 	**3d** 	**54**
2e 	**3e** 	**65**

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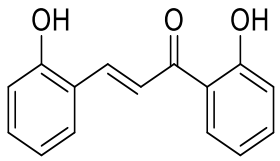
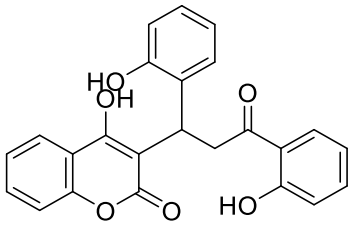
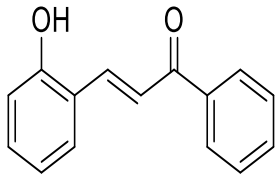
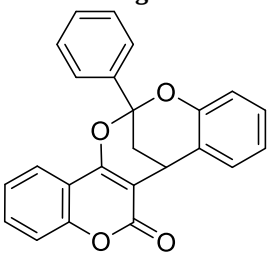
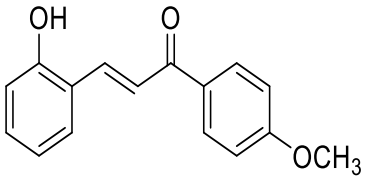
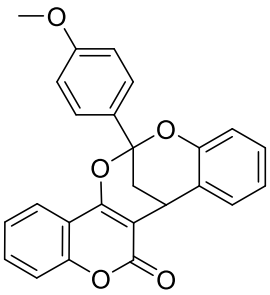
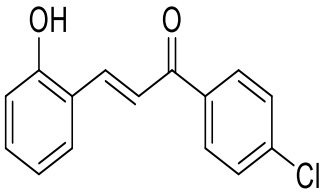
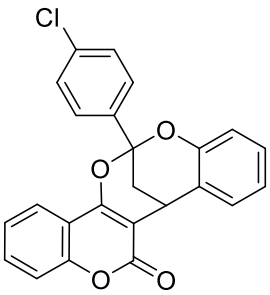
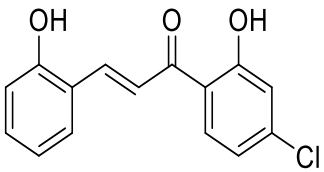
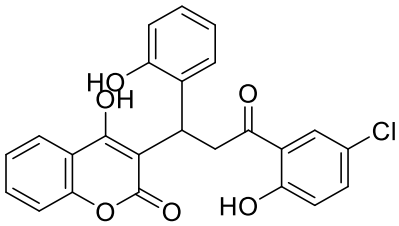
2f 	**3f** 	**46**
2g 	**3g** 	**41**
2h 	**3h** 	**71**
2i 	**3i** 	**52**
2j 	**3j** 	**55**

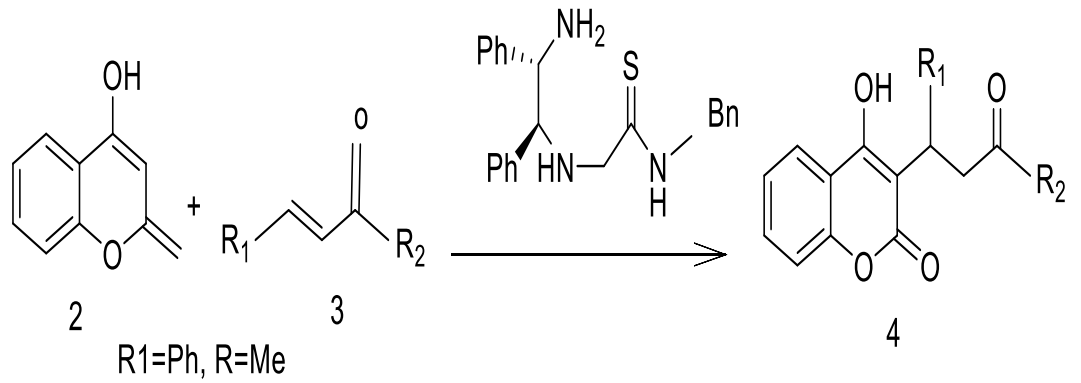


Figure 3: Warfarin preparation via Michael's addition

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Otherwise, the asymmetric reactions have been catalyzed by 1,2-diamines. In this study, it was shown that two substrates bound to the diamine catalyst control the stereoselectivity of warfarin synthesis (**Figure 4**).

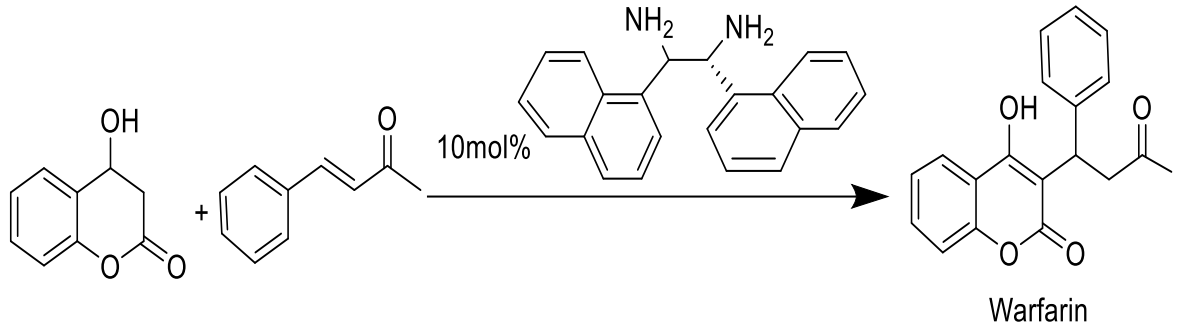

Figure 4: Asymmetric synthesis of warfarin

The undergraduate organic laboratory did a modern, one-step synthesis of warfarin by simply mixing the chemicals depicted in **Figure 4** with tetrahydrofuran and acetic acid in a vial and letting the components react at room temperature, with or without stirring. Thin-layer chromatography is used to compare the reaction mixture to a racemic warfarin standard, after which the solvent is withdrawn and the product is purified using column chromatography or mixed solvent recrystallization. Thin-layer chromatography, 1H NMR spectroscopy, and polarimetry are used to characterize the purified product. In the form of an Organic Letters manuscript, the keto-ketal ratio and enantiopurity of the warfarin product were reported. This technique often produces high yields of 40%-95% and enantiopurities (30%-90% after column chromatography or 80%-100% after recrystallization). The molecular details are extensive, including imine-iminium synthesis, keto-enol tautomerism, Michael addition, enamine hydrolysis, organocatalysis, enantioselectivity, and keto-ketal equilibrium, among other medically relevant ideas. This experiment provided an excellent opportunity to discuss green chemistry principles that have recently gotten a lot of interest, notably asymmetric organocatalytic reactions since it has many advantages, including short reaction times and inexpensive reagents, as well as great enantiomeric excess (**Figures 5** and **6)**. This reaction, for example, is carried out at room temperature and pressure and does not necessitate stirring or an inert environment. The reagents are cheap and can be utilized right away. The diamine (dpen) is utilized in catalytic amounts (5 or 10 mol%) and could theoretically be recovered through extraction. When the product is recrystallized, the atom economy of the reaction is remarkable and the enantiomeric excess is excellent. The process for isolating this reaction is significantly easier than it is for many other reactions. The reaction is not fast, but it can be run for a week. These and other factors can lead to in-depth critical evaluations [39].

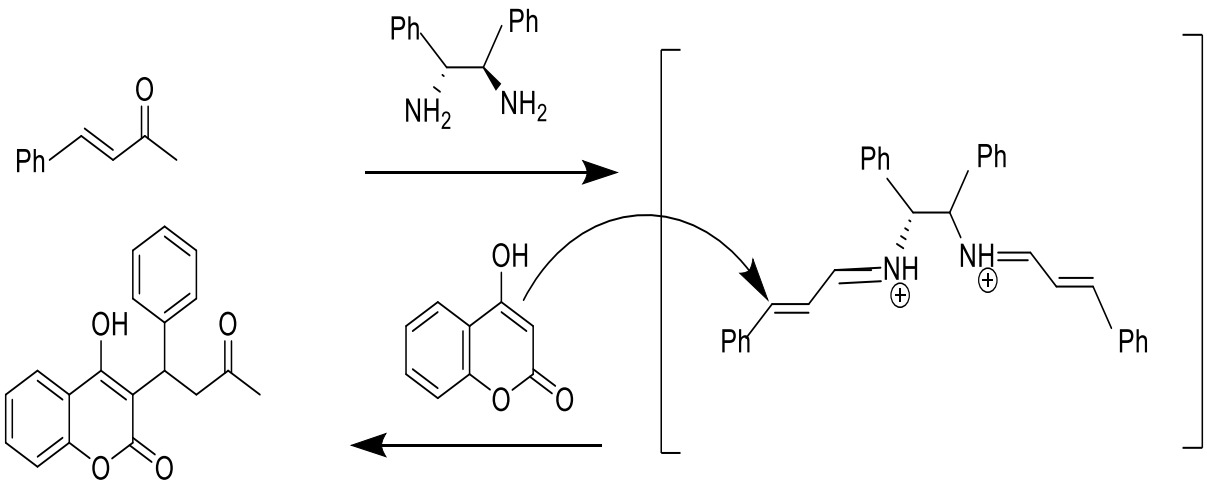

Figure 5: Proposed model for stereoinduction in the asymmetric, organocatalytic synthesis of (R)- or (S)-warfarin (dpen=diphenylethylenediamine).

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On the other hand, simple enantiomerically pure C2-symmetric quinoline (isoquinoline) derived 1,2-diamines have been synthesized and used in the efficient green synthesis of enantiomers warfarin in aqueous medium using catalysts 8e in combination with (R)- or (S)-mandelic acid, respectively. They achieved high enantioselectivity (up to 99%ee) for this bioactive compound for the first time under these conditions using known catalysts. Furthermore, the main advantage of this study was that the designed aqueous catalytic system has the benefit of not producing parasitic by-products and being able to be recovered and reused in the asymmetric reaction.

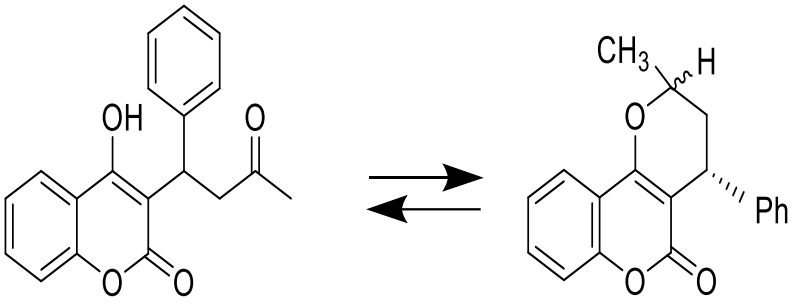

Figure 6: Keto-Ketal isomerism of warfarin

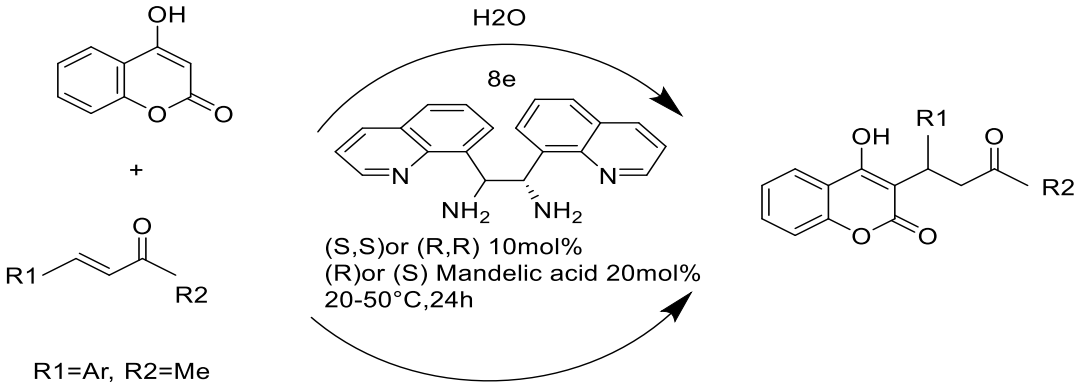

Figure 7: Asymmetric catalytic syntheses of warfarin in pure water [40, 41]

In the other hand, primary diamines I–III provided the best yield and enantiomeric purity of the drug product (>90%ee) (**Figure 1**). Thus, it has been predicted that chiral primary amines with the squaramide fragment would be suitable promotors for asymmetric synthesis of warfarin. Several studies demonstrated the high stereocontrolling potential of the fragment [42-44]. Novel C2-symmetric N,N'-bis(2-amino-1,2-diphenylethyl)squaramides with 1,2-di(pyridin-2-yl)ethane and 1,2-diphenylethane spacer groups have recently been developed and applied in asymmetric additions of 4-hydroxycoumarin and 4-hydroxy-6-methyl-2H-pyran-2-one to α,β-unsaturated ketones (**Figure 8**). These latters could be especially valuable. They are easier to make, and the amount of squaramide groups inserted will be increased, perhaps increasing reaction selectivity. As a result, up to 96% yield and 96%ee enantiomers of the anticoagulant warfarin and its analogs have been prepared (**Figures 9** and **10)**.

The results of different conditions of this reaction are listed in **Table 3**.

Table 3: Warfarin's yield and ee using catI-III

Catalyst	Yield	ee	Time (hr)	Temperature
Cat I (TFA, DCM)	88%	96%	96	0
	90%	92%	12	12
Cat II(DCM)	97%	95%	55	Rt
Cat III (mandelic acid, H_2O)	86%	91%	24	Rt

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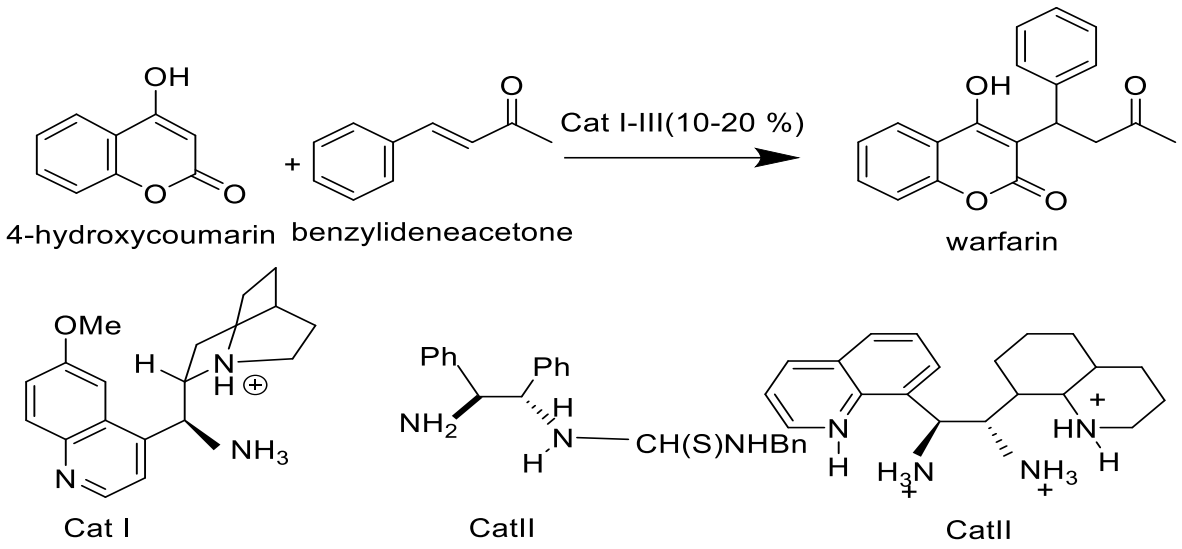

Figure 8: The catalysts used for asymmetric addition of 4-hydroxycoumarin to α, β-enones

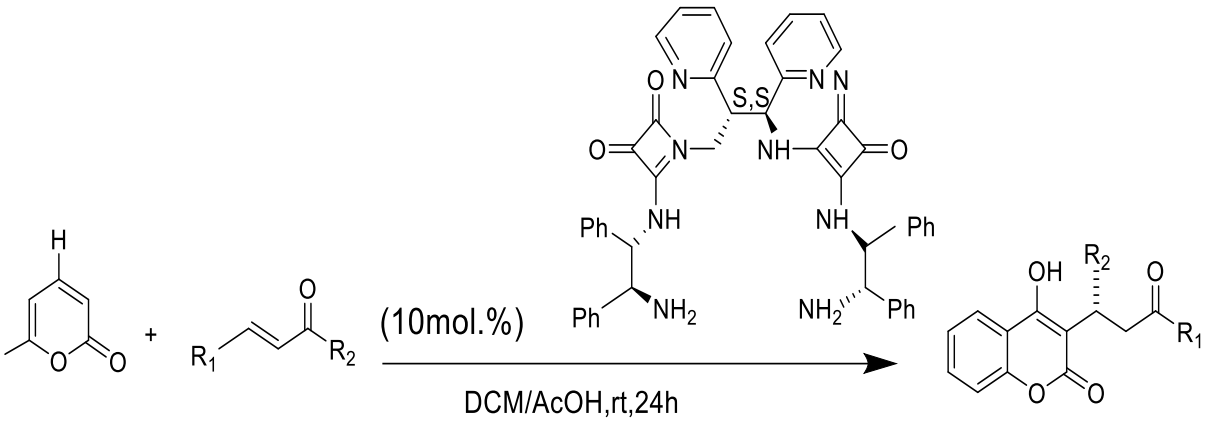

Figure 9: Asymmetric synthesis of warfarin analogs

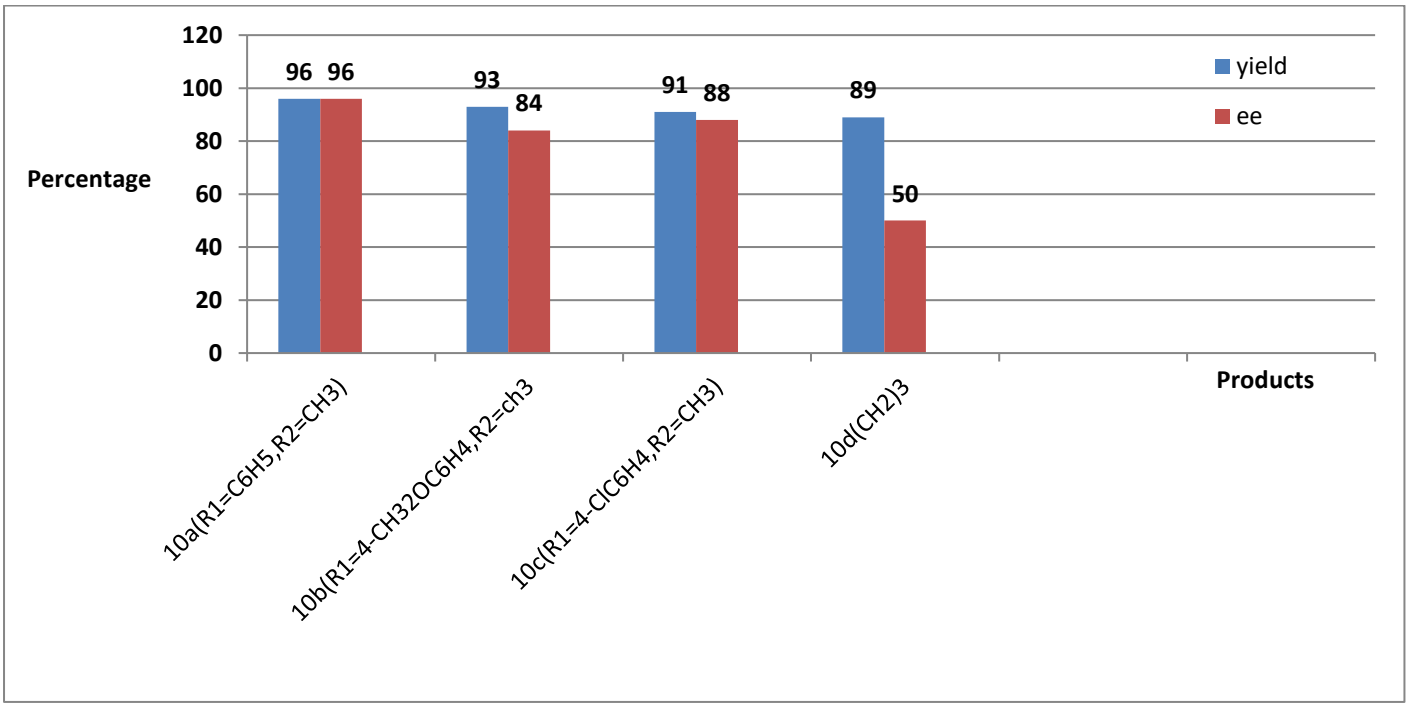

Figure 10: Yield and ee of warfarin analogs

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In **Figure 11**, selective acylation of warfarin 10a (0.154 g, 0.5 mmol) with bioactive acids (0.5 mmol), namely acetylsalicylic (12a), 5,9-dimethyldeca-4,8-dienoic (12b), and 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoic (12c), in the presence of DCC/DMAP, indicated the synthetic usefulness of the obtained compounds. The precipitate was filtered out and washed with 3.0 mL of DCM. To get ester 13, the mixed organic washings were evaporated, and the residue was purified using column chromatography on silica gel (eluent: n-hexane/EtOAc, 4: 1-2: 1). Corresponding chiral esters 13a-c were produced in high yields of 75-86% and had the same enantiomeric purity as starting compound 10a (HPLC data: Daicel Chiralcel AS-H; n-hexane/2-propanol, 99: 1; flow rate = 0.8 mL min; λ= 254 nm at these conditions the first was retained at 22.22 min and the second at 24.19). In, **Table 4** Because the esters 13a-c bind to separate cellular receptors selectively, they exhibit unusual pharmacological profiles that correspond to their two preferred pharmacophoric groups [45].

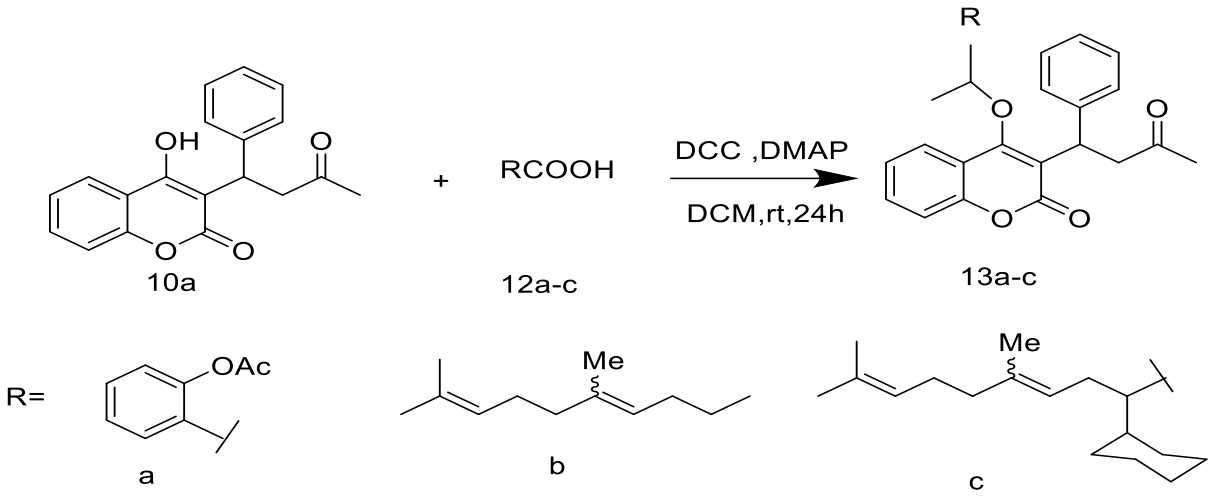

Figure 11: Derivatization of warfarin with bioactive carboxylic acids

Table 4: Properties of the synthesised warfarin derivative

Warfarin dereivative	Aspect	Yield
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-acetoxybenzoate (13a)	Colorless oil	0.2 g (85%).
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 5,9-dimethyldeca-4,8-dienoate (13b)	Colorless oil,	0.21 g (86%).
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoate (13c)	Colorless oil	0.21 g (75%).

Thus, in Michael/hemiketalization reactions of 4-hydroxycoumarines with two types of enones, the catalytic effectiveness of different amine-squaramides was investigated (**Figure 12**). When α, β-unsaturated-ketoesters were utilized as Michael acceptors, tertiary amine-squaramide organocatalysts produced the greatest results in terms of both activity and enantioselectivity (yields up to 98%, enantioselectivities up to 90%ee). The main amine-squaramides, on the other hand, are the optimum choice for related reactions of 4-hydroxycoumarins with enones. The pyrano [3,2-c]chromen-5-on compounds with good enantiomeric purity were produced (up to 96%). When green solvent 2-MeTHF and catalyst (S, S)-C8 (13 mg, 0.025 mmol) and $LiClO_4$ (2,7 mg, 0,025 mmol) were used in the Michael addition of 4-hydroxycoumarin (1.0 mmol) to 4-phenylbut-3-en-2-on (0.3 mmol). This procedure produced chiral anticoagulant medication (S)-warfarin (63 mg (81%), white solid, mp 160-161°C) in 92%ee. Furthermore, using an enantiomeric catalyst (R, R)-C8, (R)-warfarin was produced in 99% ee which is a satisfying result despite that the reaction took four days [46].

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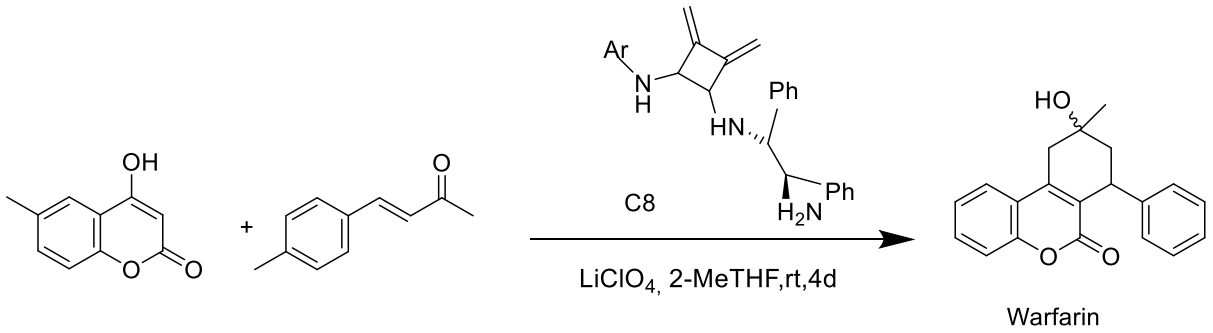

Figure 12: Michael/hemiketalization reactions of 4-hydroxycoumarines with two types of enones, the catalytic effectiveness of different amine-squaramides

In the same field, many methods for synthesizing optically active warfarin have been reported: To synthesize warfarin in moderate yield and enantiomeric excess, Demir et al. [47] performed a diastereoselective Michael addition in which chiral enamines of 4-hydroxycoumarin were treated with benzylideneacetone in the presence of LDA and superstochiometric quantities of Lewis acid. Cravotto and others [48] used a tandem Knoevenagel /hetero-Diels-Alder method to achieve diastereoselectivity; nevertheless, the protracted synthesis resulted in low yields. Nis Hallandand co-workers presented a simple, effective, and highly atom-economical synthesis of optically active warfarin from 4-hydroxycoumarin and benzylideneacetone in the presence of imidazolidine catalysts, where the reaction of various acyclic and cyclic nitroalkanes was found to proceed well with enantioselectivities up to 86%ee furnished [49]. Furthermore, the synthesis of several significant optically, physiologically, and pharmaceutically active molecules demonstrates the scope and potential of a new one-step, organocatalytic enantioselective Michael addition. The imidazolidine catalysts 4a-c [10] have been proposed as efficient catalysts for the addition of cyclic 1,3-dicarbonyl molecules toα, β-unsaturated carbonyl compounds (**Figure 13**).

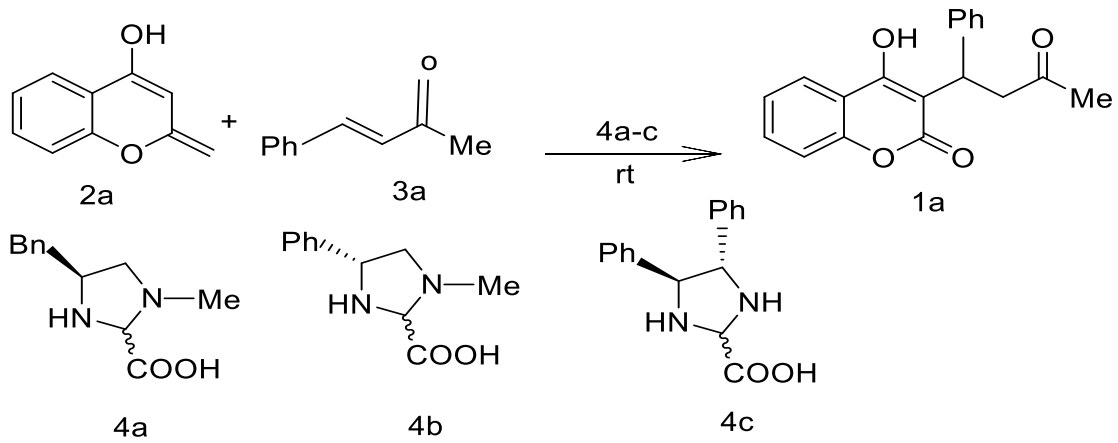

Figure 13: Organocatalytic asymmetric formation of warfarin

In high yields of up to 70%ee, optically active 1a was formed. Organocatalyst 4c, which is made by condensation of 1,2-diphenylethanediamine with glyoxylic acid, outperformed 4a, b and 1a was obtained with up to 82%ee. In these cases, the advantage is that the reaction proceeded smoothly at room temperature without the formation of any by-products in the absence of an external base. Starting from a sample with 79%ee and increasing to >99.9%ee, a single recrystallization from a water/acetone mixture provided the enantiopure, improving the enantiomeric purity of the Michael adduct when catalyzed by imidazolidine. This new organocatalytic asymmetric Michael reaction can be carried out on a kilogram scale with no loss of yield or enantioselectivity (**Table 5**). Recycling of the catalyst was also possible, as well as the very easy and inexpensive access to large quantities of enantiopure warfarin. In the next year, it was demonstrated that the Michael addition of 4-hydroxycoumarin to a number of α-, β-unsaturated enones that bear alkyl, branched

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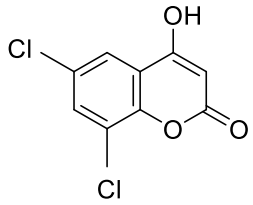
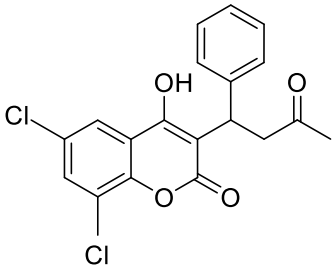
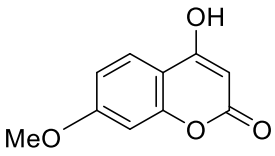
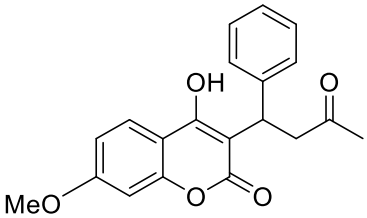
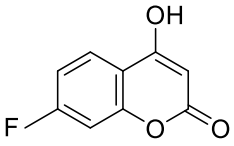
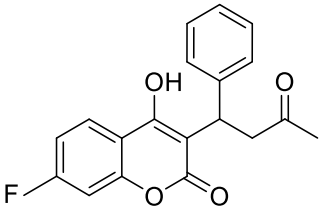
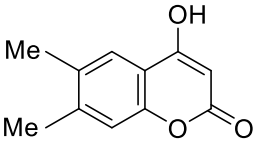
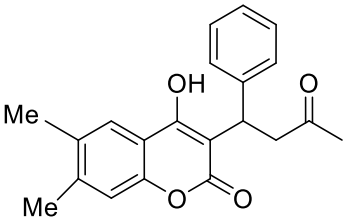
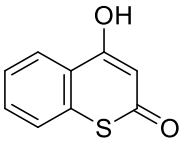
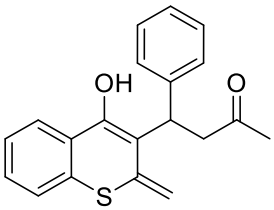
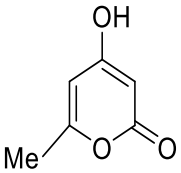
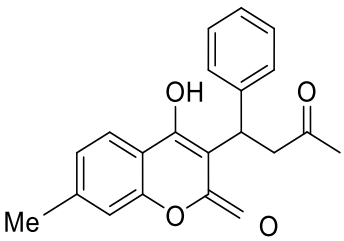
alkyl, as well as various aromatic and heteroaromatic substituents proceeds smoothly to afford Michael adducts in high yields and enantioselectivities. The ketone substituent (R2) could also be varied from methyl to ethyl and isopropyl; in this case, they obtained a slightly lower yield of the Michael adduct 1 k, and good enantioselectivities were maintained. In addition, to broaden the scope of the reaction, numerous cyclic 1,3-dicarbonyl compounds were used as Michael donors in the reaction with benzylideneacetone (3a) in the presence of catalyst 4c.

Table 5: Organocatalytic asymmetric Michael addition of Michael donors 2b–g to dibenzylideneacetone

Michael donor	Michael adduct	Yield%	%ee
		**6**	**79**
		**81**	**85**
		**68**	**83**
		**84**	**85**
		**84**	**78**
		**76**	**85**

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When utilizing 4-hydroxycoumarin carrying either electron-withdrawing or electron-donating substituents, as well as 1-thio-4-hydroxycoumarin 2 f and 4-hydroxy-6-methylpyrone 2.0 g as Michael donors, the Michael reaction proceeded in good yields and with high enantioselectivities. X-ray crystallographic analysis and a comparison of optical rotation for warfarin (1a) and acenocoumarin (1b) were used to identify the absolute configuration of the coumachlor. The stereochemical results of 4a-catalyzed reactions are consistent with previously suggested iminium-ion intermediates for the imidazolidine-catalyzed Michael reaction. Both an iminium-ion and an aminal intermediary species are possible for the imidazolidine catalyst. They have developed the first organocatalytic asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to α, β-unsaturated enones. In the presence of an easily available organic catalyst, this versatile and environmentally friendly Michael reaction generates warfarin and other Michael adducts in high yields and enantioselectivities even though it has taken a long time. It was also shown that enantiopure products may be obtained from a single recrystallization [31]. In 2006, a report argued convincingly that the efficiency of imidazolidine catalyst in the preparation of warfarin originated in its decomposition into chiral diamine and that this chiral diamine was the genuine catalyst for the transformation. Then, they employed this diamine directly, using acetic acid as a co-catalyst, and obtained similar or better results. Importantly, they postulated a diimine intermediate as essential for the high degree of asymmetric induction.

Interestingly, replacing diaryldiamine with alkyldiamine gave reduced stereoselectivity and a different reaction pattern, an effect that was attributed to the basicity difference. More recently, the combination of a chiral diamine and acid co-catalyst has also proven to be successful in the archetypical aldol reactions of substituted benzaldehydes with ketones, a manifestation of the growing utility of primary amine organocatalysts [50]. In 2007, a third report on the organocatalytic preparation of warfarin was published, this time by using the Cinchona-derived amines 9-amino-9-deoxyepiquinine [51] and 9-amino-9-deoxy-epicinchonine [52]. Iminium catalysts were previously developed by the same research group [53]. More than 90% ee was obtained by reaction in CH_2Cl_2 with CF_3CO_2H as co-catalyst, although still at 20 mol% of catalyst loading. Interestingly, in the original report for these Cinchona-derived amines, the authors also described a diarylamino alcohol derived from valine as a useful, but less selective catalyst for Michael addition to α, β-unsaturated ketones such Cinchona-derived primary amines have recently also proven useful for the Michael addition of 1,3- diaryl-1,3-propanedione to nitro olefins. Also, warfarin was prepared by adding 4-hydroxycoumarin (1, 81.1 mg, 0.50 mmol) to benzylideneacetone (2, 87.7 mg, 0.60 mmol) and the appropriate catalyst was charged into a tiny vial (0.10 mmol, 20 mol%). THF (1.0 mL) and a tiny magnetic stirring bar were added to the reaction mixture, which was stirred at room temperature for 24 hours. By flushing with compressed air, the volatiles were eliminated. The residue was refined using silica gel column chromatography with 15% EtOAc in hexanes to get pure warfarin as a white solid. HPLC examination of the purified product with an AD-H chiral column (20% iPrOH in isohexane, 1.0 mL/min, =254 nm, minor enantiomer tR=6.5 min, and major enantiomer tR=6.5 min) was used to detect the enantiomeric excess (**Figure 14**).

Figure 15 shows that, like classic secondary amine organocatalysts, most of these amino alcohols show no promise in the synthesis of warfarin. However, the phenylglycine-derived amino alcohol 15 is very successful in this transformation, yielding good yields and about 80%ee in only 24 hrs. There was hope in this research; that adding sterically more demanding side chains like cyclohexylglycine or tert-leucine (amino alcohols 16-17) would improve enantioselectivity even further, however, this idea was debunked by experiment. The presence of an aromatic moiety is critical [54]. 2-aminoDMAP/prolinamide is a novel chiral sec-amine/amidine-base hybrid catalyst that can catalyze the conjugate addition of 4-hydroxycoumarin and different benzylideneacetones, yielding anticoagulant warfarin and its analogs with high yields (70%-87%) and enantioselectivities (58%-72%), **Figure 16**, [55].

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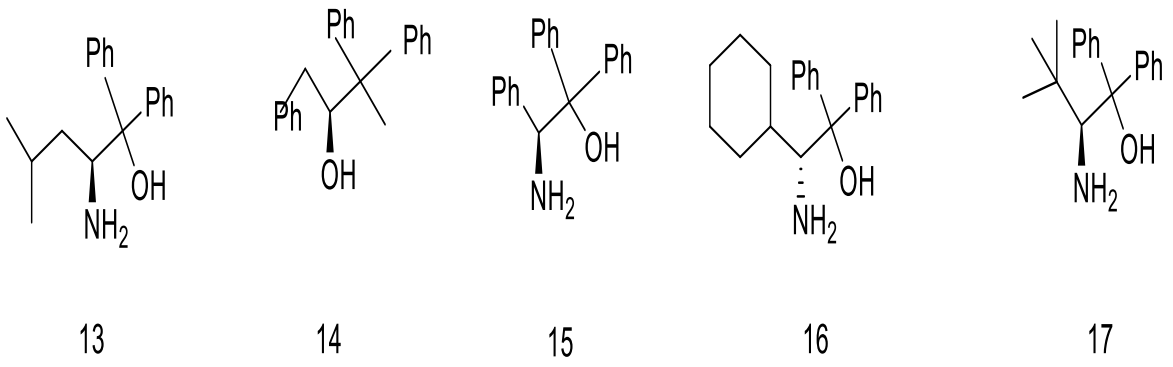

Figure 14: Bulky amino alcohols 13-17

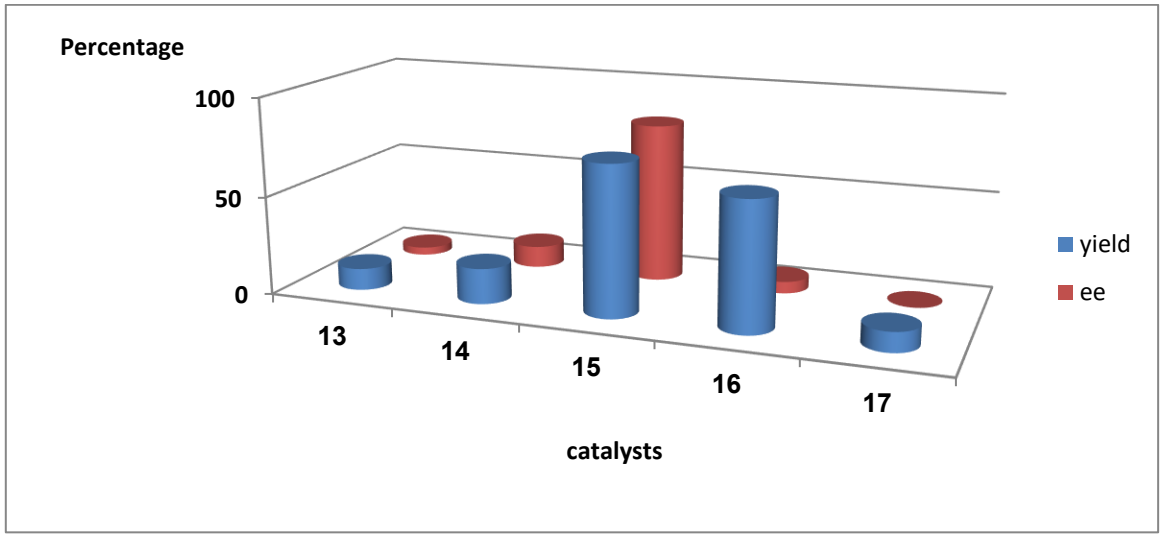

Figure 15: Time, yield, and ee of bulky amino alcohols

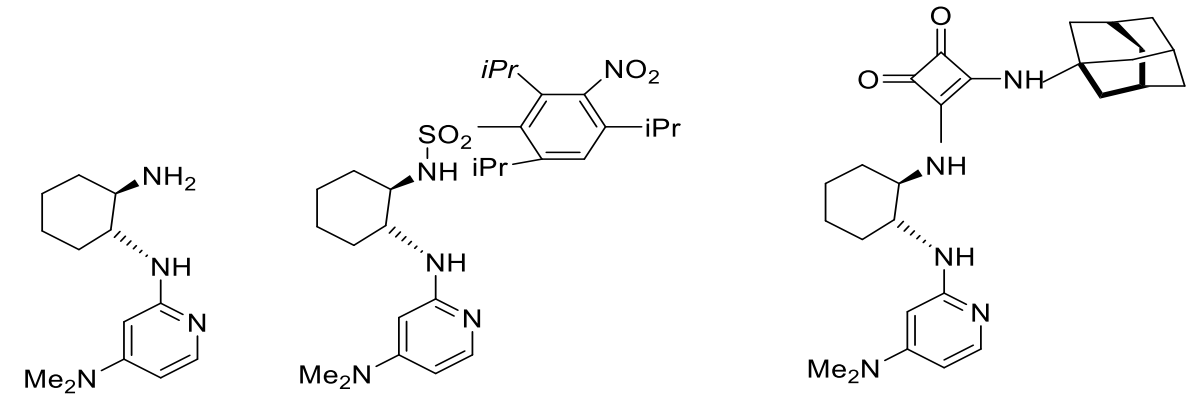

Figure 16: 2-Amino DMAP based organocatalysts

In another work, warfarin (18.31 g, 59.4 mmol) and triethylamine (6.31 g, 62.4 mmol) were added to 50 mL of $CHCl_3$ and agitated until completely dissolved under nitrogen. The solution was chilled to 5.0°C, and then trifluoromethanesulfonic acid was added with anhydride (17.59 g, 62.3 mmol) over 30 min at a rate that did not surpass the temperature of 0°C. The solution was then allowed to reheat to a temperature of 25°C. The solvent has been eliminated. The ether (400 mL) was added to the solution. 2.0 M HCl (2100 mL) was used to wash away the residue. 260 mL $NaHCO_3$ and brine (100 mL). The solvent was removed when the phase was dried over $MgSO_4$ and chromatographed the residue (15% ethylacetate/85% n-heptane) to yield 16.23 g

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(62%) of warfarin triflate [10-R,S]-3-(10-Phenyl-30-oxobutyl)-2H-1-benzopyran-2-one-4-trifluoro-methane-sulfonate as the final product. The latter (1.97 g, 4.46 mmol) was dissolved in pyridine (10 mL) and immediately added to sodium hydrosulfide hydrate (500 mg of NaHS. H_2O) was dissolved in deoxygenated water (10 mL) and warmed under nitrogen to 80°C. The agitated mixture was cooled, and the organic phase was washed with percent H_3PO_4 (2×40 mL), $NaHCO_3$ (2×40 mL), ethylacetate (40 mL), brine (20 mL), and 5% H_3PO_4 (20 mL). The solvent was removed when the organic phase was dried on $MgSO_4$. Chromatography was performed on the residue (35 ethylacetate/65% n-heptane) 800 mg (55%) of 4-Sulfhydrylwarfarin [10-R,S]-4-Sulfhydryl-3-(10-phenyl-3- oxobutyl)-2H- 1-benzopyran-2-one as a result mp 183-185°C; beige solid [35]. The one-pot reaction of aryl glyoxal with benzamide and 4-hydroxycoumarins resulted in a simple and environmentally friendly synthesis of warfarin analogs. A small amount of ZnO nanorods efficiently catalyzed the reactions (NRs). Some properties of the current approach stand out, such as the lack of a solvent, excellent product yields, and the catalyst's recyclability. Because the size of the catalytic particle has a substantial influence on its activity in various heterogeneous catalysis processes, nanostructured catalysts have received considerable research in recent years with the goal of finding useful applications in the chemical industries. In general, nanoparticles can be well disseminated in a reaction mixture, resulting in a wide surface area that substrate molecules can easily reach. They can also be easily separated from the rest of the system. Metal oxide nanostructures, such as zinc, have garnered a lot of attention as they have been shown to work in ultraviolet (UV) lasers [56] nanogenerators, UV photodiodes and especially organic reactions as catalysts [57] which their bulk counterparts can't generally do. Nanocatalytic organic reactions, on the other hand, have lately emerged as a strong synthetic tool for creating highly functionalized molecules [58].

Synthesis of warfarin and its derivatives using microwaves: In 2001, an efficient synthesis of warfarin acetals on montmorillonite clay K-10 with microwaves was realised by Kristi et al. [59] in continuation of the synthesis of coumarin derivatives investigation, the synthesis of heterocyclic condensed 4-hydroxycoumarin derivatives has been described in their article. Montmorillonite clay has been used as a catalyst for this reaction owing to its several advantages such as strong acidity, non-corrosive, nontoxic properties, cheapness, mild reaction conditions, high yields and selectivity and the ease of set-up and work-up; which is not the case in the classical acids. Thus, it has been the catalyst of choice for the formation of acetals in the preparation of a variety of multifunctional organic molecules; using microwave heating which has widely been used in organic synthesis12 ("MORE" chemistry=Microwave Oven-induced Reaction). More recently, the emphasis has shifted in favour of microwave-assisted methods under solvent-free conditions, which have a special appeal as they provide an opportunity to work with open vessels, thus avoiding the risk of the development of high pressure. To begin with, unlike traditional heating, the bulk temperature in the case of microwaves is no longer reflective of the reaction conditions. Second, when compared to traditional procedures, a significant improvement in yields and a reduction in reaction times were seen. They were able to remove the acetals from the support in high quantities. The cyclic acetals 2 or 3 were the only products found under the conditions used, and their characteristics are stated below (**Table 6**).

Table 6: Warfarin acetals properties

Derivative	Aspect	Yield	Melting point	IR(KBr) cm^{-1}
(2) 2-Methoxy-2-methyl-4-phenyl-3,4-dihydro-2H-pyrano3, 2-chromen-5-one	White needles	0.82 g (90%)	165-166°C	1708, 1625, 1611, 1493, 1379, 1142, 1102, 1054, 730, 690
2-Ethoxy-2-methyl-4-phenyl-3,4-dihydro-2H-pyrano3, 2-chromen-5-one (3)	White needles	0.59 g (67%)	174-176°C	1710, 1629, 1607, 1490, 1377, 1142, 1102, 1054, 730, 690

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When compared to conventional heating, there appears to be a significant rate enhancement for some reactions when using such non-conventional reaction conditions, beginning with a reduction in typical thermal degradation and/or improved selectivity. There also appears to be a significant rate enhancement for some reactions when using such non-conventional reaction conditions, particularly under heterogeneous conditions. Pharmacologically, warfarin is one of the most important blood anticoagulants, however, cyclic acetals 2 or 3 are more potent. In general, microwave-assisted intra-cyclodehydration of warfarin with methanol or ethanol to the corresponding acetals 2 or 3 in the presence of montmorillonite clay K-10 as a catalyst is a more efficient way than older methods [60, 61]. In 2021, microwaves have been a part of the synthesis of warfarin where 4-hydroxy coumarin, 1,3-diketone with α, β-unsaturated carbonyl compounds, microwave-assisted one-pot conjugate Michael addition followed by annulation of nucleophiles, deep eutectic solvent (DES) catalyzed (chalcones) in the direction of benzopyran, pyranocoumarin, xanthene, dihydrofuran, and it has proven possible to create4- hydroxy-coumarin (warfarin analogs) derivatives. A clean, one-pot, solvent-free, metal-free, and green chemical method with high regio, stereo selectivities, and yields under gentler conditions MW-irradiation. The DES catalyst is easily recovered, and the reaction is environmentally beneficial. The current technique has several noticeable advantages. They have successfully developed a green chemical approach to various benzo-fused oxygen-heterocycles using DESs as a catalyst and reaction medium with high regio, stereo selectivities, and yields where the reaction conditions were as follows: di((E)-benzylidene) cyclohexan-chalcone (1.0 mmol), 4-hydroxy coumarin (1.0 mmol) /1,3-cyclohexane dione (1.0 mmol) and DMU-Malonic acid DES (70: 30) as an additive for reaction medium, under microwave irradiation, (90˚C, 15 min, 350 W, closed vessel) (**Figure 17**). In this case, the microwave has various advantages over traditional heating techniques, including rapid reaction and quantitative yields, but it also has limitations, such as greater batch production in the industrial setting, which we may be able to solve in the future. Furthermore, optimization investigations demonstrated that the DES has intrinsic catalytic activity in terms of metal-free, mild reaction, easily recoverable catalyst, and so on. The suggested chemical pathway can take a novel approach to the production of several oxygen-containing heterocycles [62].

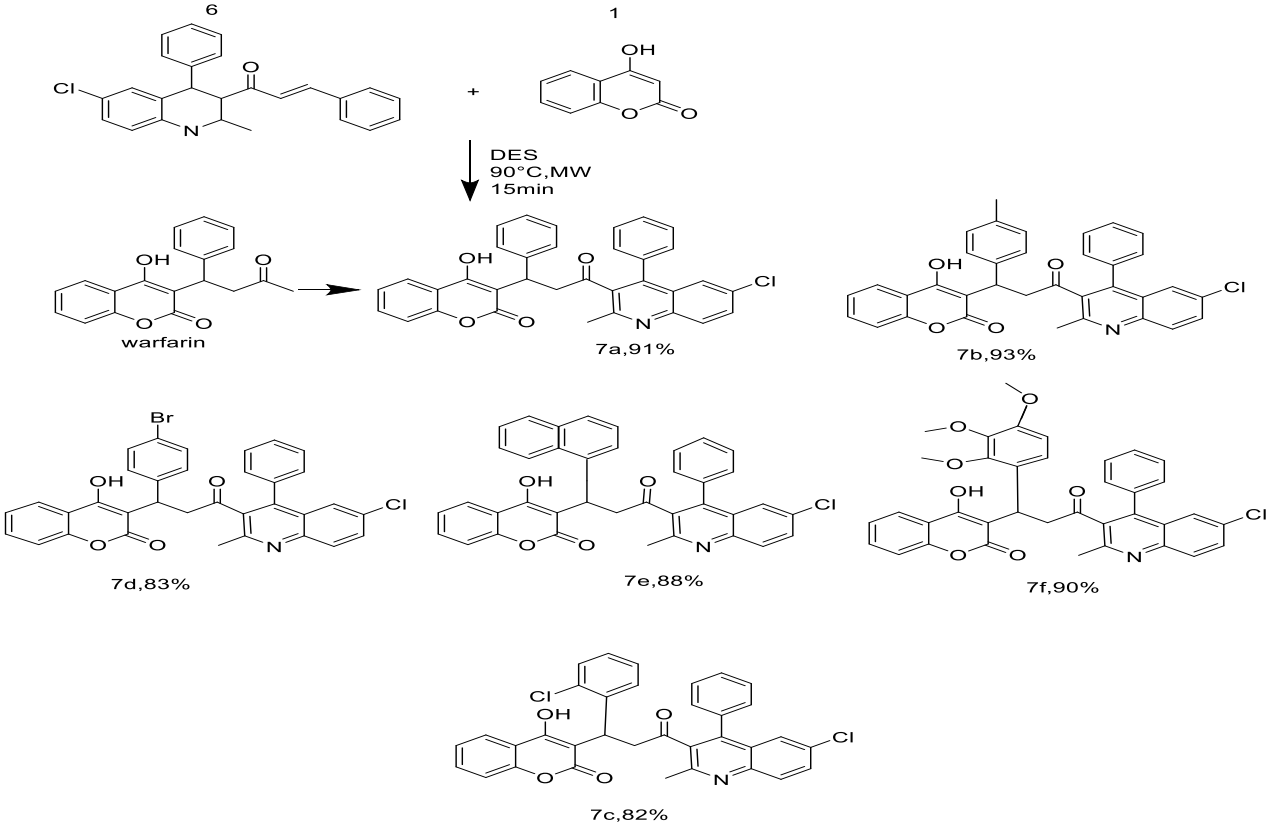

Figure 17: Green synthesis of warfarin derivatives using various benzo-fused oxygen-heterocycles and DES

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On water synthesis of warfarin and its derivatives: Using metal-free organic molecules as catalyst asymmetric organic synthesis is broadly recognised as a promising tool that easily meets green chemistry criteria. In the last decades, this approach known as organocatalysis has blossomed. This enabling technology of organo-catalysis is useful for the efficient synthesis of numerous biologically relevant molecules and drugs. Whether recent achievements in chemical efficiency have focused on the economic and ecological aspects of organocatalysis. From a green chemistry perspective, the use of water instead of even a small additive of organic solvent is preferred to decrease environmental contamination. “In water” and “On water” can be carried out through a good knowledge of the rectant's nature. These reactions are far more practical to separate substrates/products and water. Hence, organic liquids that remained separated from water in a clear organic phase were ideal reactants, but solids could also be used, although being conceptually more demanding. In 2006, Chin demonstrated that the application of 10 mol% of (R,R)- diphenylethylenediamine in THF resulted in the formation of (R)-warfarin in 94% yield after 48 hours (80%ee) [40]. Thus, the reaction in THF delivered warfarin in 64% yield after 24 hrs with 5.0 mol% of amine and metal salt combination. The disadvantage in this case was the use of harmful organic solvents which make any attempt at green chemistry is doomed to failure. Therefore, chiral warfarin synthesis has been offered using commercially available amines and Michael's addition of 4-hydroxycumarin to benzylideneacetone in water. First, a series of amine catalysts were screened at room temperature in homogenous solutions, including an aqueous environment, utilizing 4-hydroxycoumarin (0.50 mmol), and benzylideneacetone (0.55 mmol), **(Figure 18)**.

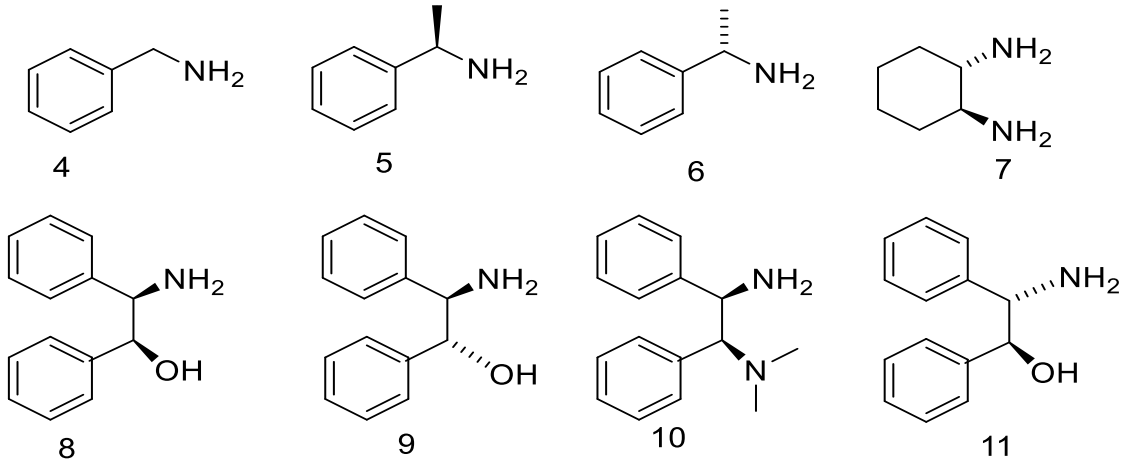

Figure 18: Chiral amines screening

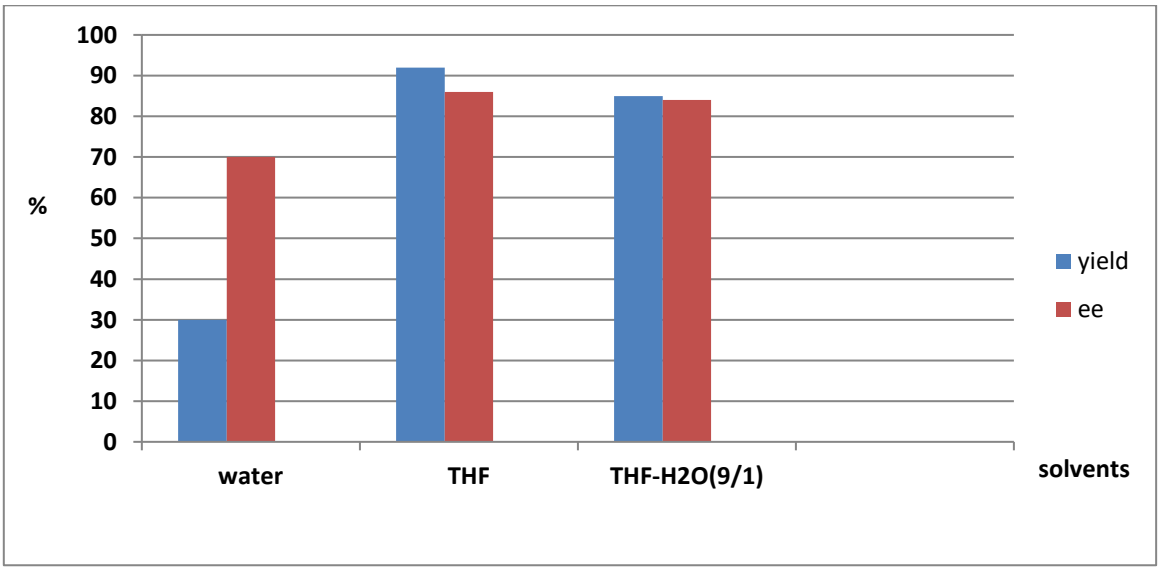

Figure 19: Yield and ee of different solvents

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In dry and aqueous THF solutions THF-H_2O (9/1) the structure of the main amine was found to be very important, and commercially available (S,S)- diphenylethylenediamine (11) displayed the best yield (98%) ee was 62%. Surprisingly, using acetic acid as an adjuvant allowed the reaction to proceed quickly and yield high ee in both dry and aqueous solvents. This conclusion, which contradicted prior findings [63], prompted us to remove organic solvents from the reaction mixture. Surprisingly, the reaction exhibited good enantio-selectivity (70%ee: 85% -S and 15% -R) when using pure water as a solvent, but careful reactant hunting was required for decent yields as shown in **Figure 19**.

The effectiveness of a reaction "on water" is dependent on proper contact between reactants, which is why vigorous mechanical stirring was used. When an ultrasonic bath was used for the reaction, it was discovered that the best reaction conditions were merely 2-5 mol% of the catalyst supported by acetic or better benzoic acid (**Figure 20**).

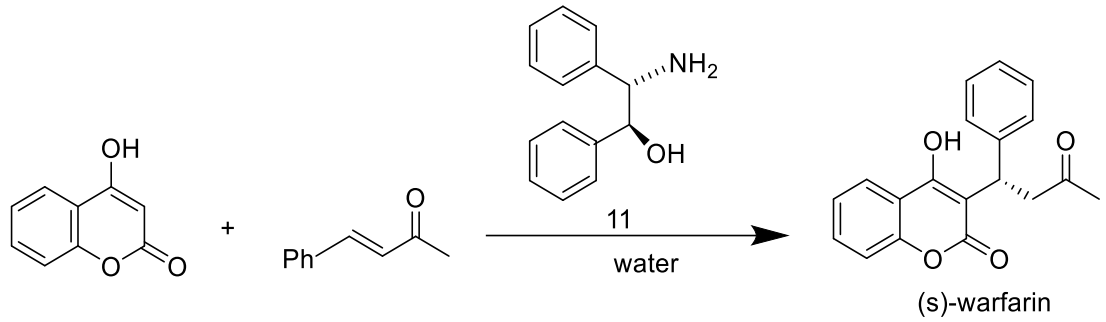

Figure 20: On water synthesis of warfarin using (S, S)-diphenylethylenediamine

Sonication allows particulates to disperse quickly on the water surface, allowing for improved contact between water and reactants. Ultrasound as a way of speeding up reactions is a key technique for green processes that is rapidly developing. Furthermore, excellent results were obtained in 10 hrs when the reaction was scaled up to 2.0 g with 2.0 mol% catalyst in an open vessel (**Figure 21**).

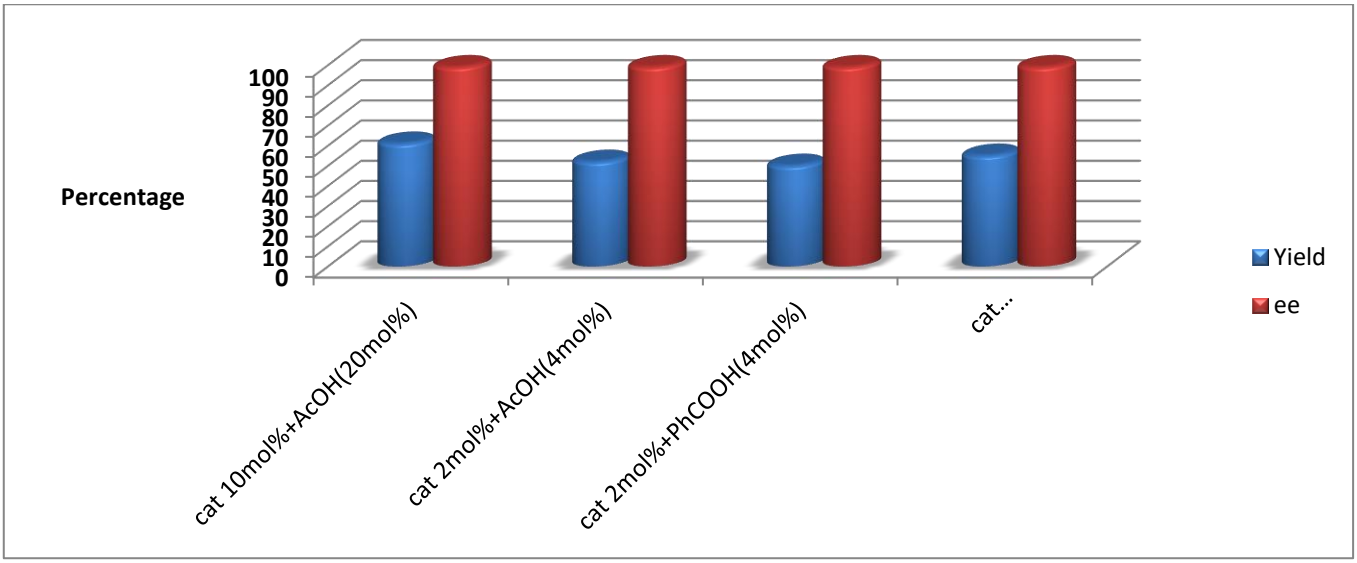

Figure 21: Yield and ee of several catalysts in accelerated reaction by ultrasound

To make use of the improved green technique, the solid product was isolated from the aqueous phase by filtration, and optically pure warfarin was provided after one crystallization from hexane. This approach avoided the use of costly silica gel chromatography, and the use of a small amount of hexane instead of chromatography eluents appears to be promising from the standpoint of green chemistry. In conclusion, using primary diamine as an organocatalyst, they have described a water-compatible and scalable protocol for the

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synthesis of (S)-warfarin. They were able to get warfarin with an outstanding ee under mild circumstances without using silica gel chromatography by changing the reaction parameters. Finally, they have demonstrated that by using a unique technique based on "solids on water," more advancements in the organocatalytic Michael reaction can be identified [64]. Thus, organic primary amines are claimed to catalyze the asymmetric Michael addition of a suspension of 4-hydroxycoumarin 1 (81.0 mg, 0.5 mmol), to α, β- unsaturated enone (0.6 mmol), on water without organic co-solvents (**Figure 22**). Through ultrasound-accelerated reactions, enantiomerically pure (S, S)-diphenylethylenediamine (0.05 mmol, 10 mol%) as the most effective catalyst which was chosen after a screening of different chiral primary amines. These conditions yielded a series of important pharmaceutically active compounds in good to excellent yields (73%-98%) and with good enantioselectivities (up to 76%ee). This research led to an efficient protocol for the formation of the anticoagulant warfarin in both enantiomeric forms using solids on water. The target medication is obtained in enantiomerically pure form using the suggested scalable and environmentally friendly organocatalytic technique which is one of the recommended advantages in green chemistry.

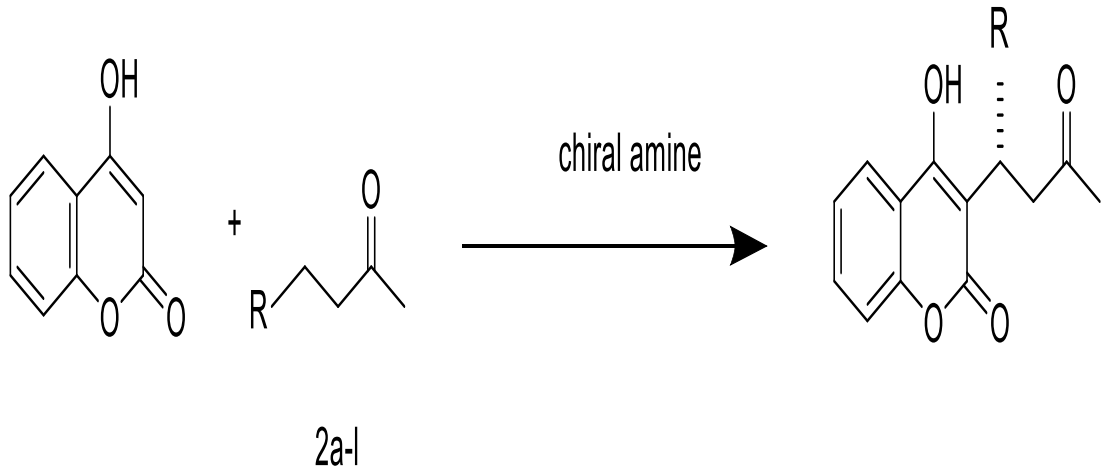

Figure 22: 'On water' catalytic Michael reaction using chiral amines

After determining the best reaction conditions, they looked at a range of α, β-unsaturated ketones 2a-l, to see if this 'on water' catalytic Michael reaction might be used in other situations. The reaction was carried out in an ultrasonic bath with 10 mol% catalyst 9 at room temperature for 10 hrs. Excellent results were obtained with all of the investigated ketones containing aromatic or aliphatic substituents substituents for the reaction of 4-hydroxycoumarin. For all sets of substrates, high yields and adequate enantioselectivities were reported, demonstrating that the improved 'on water' technique is substrate-independent, **Table 7**, [65].
In another manuscript a cooperative catalysis was found in an asymmetric primary amine-catalyzed Michael reaction, leading to the discovery of many cooperative catalytic complexes combining Lewis acid and primary amine, such as $LiClO_4$/DPEN. The cooperative catalyst system ($LiClO_4$/DPEN) resulted in greater levels of stereoselectivity in this Michael reaction of 4-hydrocoumarin (up to 94%ee) [66]. In a previous study, it has been shown that the Ts- DPEN Noyori ligand may be used as an enantioselective organocatalyst in the Michael addition of 1,3-dicarbonyl compounds to nitroolefins, and that the main amine group is important in determining the enantioselectivity in this Michael reaction [67]. However, when this catalyst is used to prepare chiral warfarin asymmetrically, only moderate enantioselectivity (64%ee) and low yield are produced. They have expected that iron salts would drive the reaction efficiently with higher enantioselectivity due to their favored chelation effects and preparative benefits in the Michael addition of 1,3-dicarbonyl compounds, such as user-friendly, affordable, and nearly non-toxic metal catalysts (**Figure 23**).

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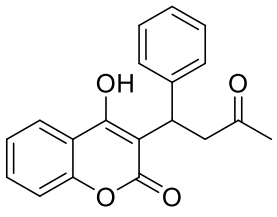
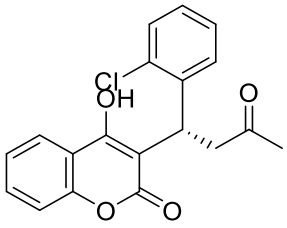
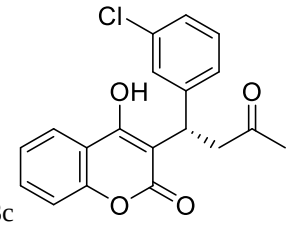
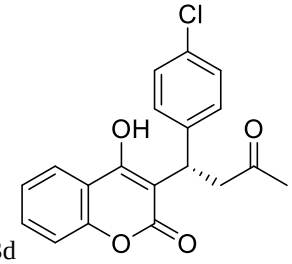
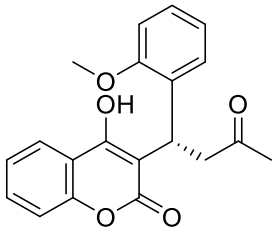
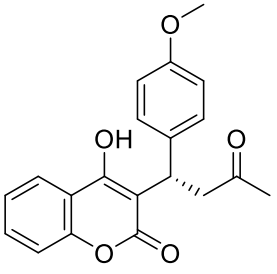
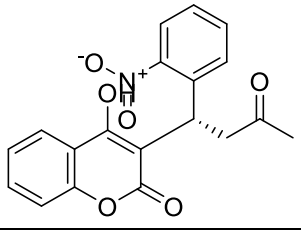
Table 7: The substrates of the developed procedure

R	Product	Yield/ee (%)	IR (cm^{-1})
Ph=2a	 3a	98/72	3409, 3029, 2839, 2738, 1719, 1548, 1456, 1380, 759, 698
2-ClC_6H_4=2b	 3b	90/68	3364 (br), 3066, 2969, 2933, 1689, 1621, 1570, 1492, 1382, 1072,756
3- ClC_6H_4=2c	 3c	93/67	2958, 2929, 2852, 1686, 1623, 1575, 1495, 1381, 1071, 759
4- ClC_6H_4=2d	 3d	89/72	3377, 2984, 2934, 2855, 1686, 1608, 1565, 1490, 1385, 1377, 1071
2-$MeOC_6H_4$=2e	 3e	92/76	3034, 2935, 2838, 1681, 1619, 1571, 1492, 1394, 1063, 748
4- $MeOC_6H_4$=2f	 3f	94/71	2987, 2937, 2837, 1683, 1608, 1512, 1377, 1250, 1070, 764
2-$NO_2C_6H_4$= 2g	 3g	93/66	3336 (br), 3073, 2938, 2868, 1687, 1622, 1572, 1526, 1384, 1176, 1079, 760

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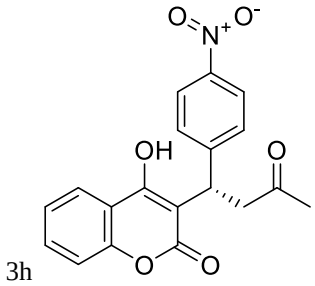
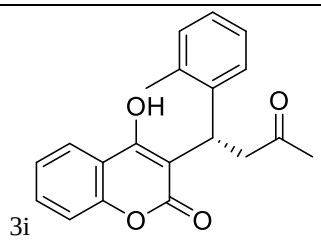
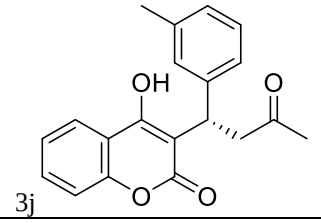
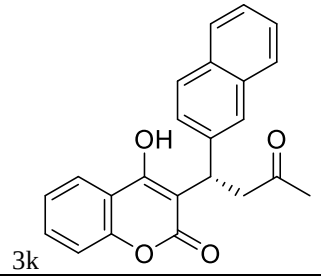
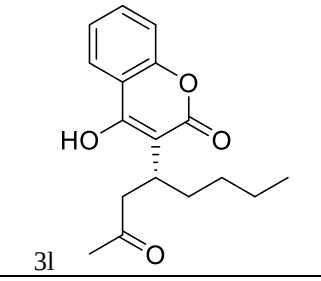
4- $NO_2C_6H_4$=2h	 3h	93/60	3326 (br), 3076, 2934, 2852, 1688, 1619, 1515, 1346, 1068, 759
2-$CH_3C_6H_4$=2i	 3i	91/76	3377 (br), 3080, 2961, 2926, 2871, 1712, 1681, 1615, 1569, 1492, 1385, 1046, 757
3- $CH_3C_6H_4$=2j	 3j	92/73	3299 (br), 2985, 2960, 2933, 1721, 1689, 1625, 1575, 1495, 1380, 1073, 759
2-Naftyl=2k	 3k	97/70	3321 (br), 3050, 2931, 1717, 1686, 1621, 1572, 1492, 1381, 1072, 759
C_4H_9= 2l	 3l	81/74	3374 (br), 2958, 2929, 2861, 1710, 1684, 1619, 1572, 1493, 1393, 1108

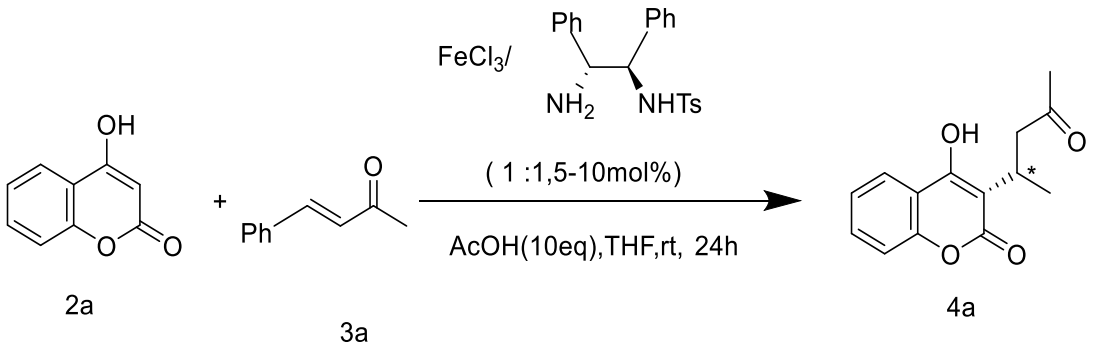


Figure 23: Asymmetric synthesis of chiral warfarin catalyzed by cooperative iron/primary amine catalyst

They have discovered that decreasing the catalytic quantity of iron and primary amine to 5.0 mol percent resulted in acceptable yield and enhanced enantioselectivity (81%ee, = +17%ee) in this reaction. Based on these findings, it is decided to conduct a preliminary set of experiments utilizing (R, R)-1,2-diphenylethylene-diamine (DPEN) as an organocatalyst under ideal conditions and just changing the metal salts. Surprisingly,

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depending on the type of metal salts, considerable differences in stereoselectivity were detected. Enantioselectivities of Ca(II), Li(I), Mg(II), Sn(II), and In(III) salts were found to be promising (>90%ee). Even with larger amounts of DPEN, no product or only a trace amount of the Michael adduct was detected when the salts of Bi(III), Cu(II), Ce (III), Ni(II), Ru(III), and Au(III) were used (10 mol%). They have discovered that $LiClO_4$ resulted in preferential enantioselectivity and yield of chiral warfarin, given the comprehensive synergistic effect of metal salt and DPEN in conversion and enantioinduction. This astonishing result produced in THF with $LiClO_4$/DPEN shows a tremendous salt effect when compared to that obtained with only DPEN catalysts, demonstrating that the concept of combining metal catalysis and organocatalysis is viable. The solvent effect was next investigated in the enantioselective chiral warfarin synthesis via the Michael reaction. The solvent had a substantial impact on the overall yields and stereoselectivity of the reaction; 1,4-dioxane provided a small increase in enantioselectivity (92%ee, = +8%ee), **Figure 24**.

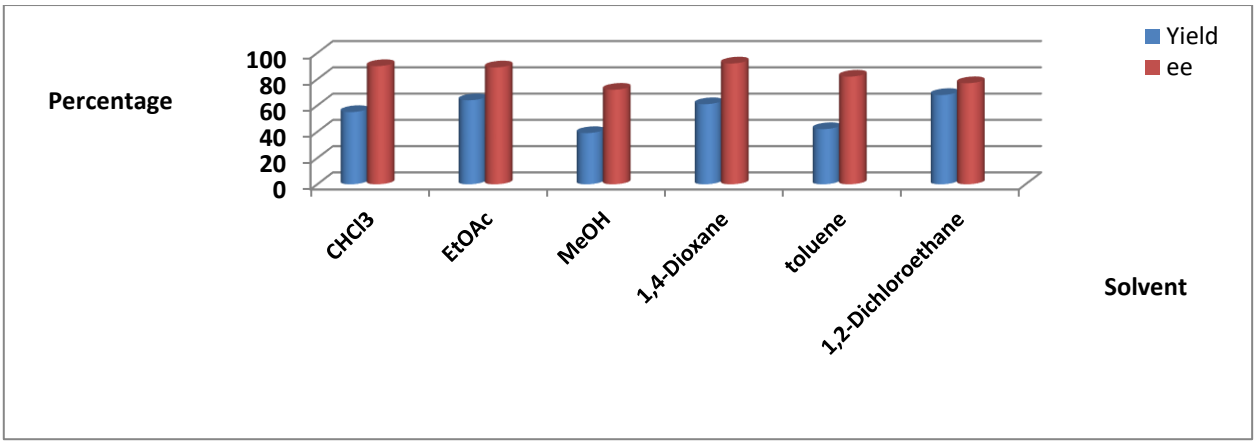

Figure 24: Solvent effect on the enantioselective synthesis of warfarin

In **Figure 25**, with these results in hand, they focused on the general Michael addition of substituted 4-hydrocoumarin to enones under ideal reaction circumstances. In the presence of the simple cooperative $LiClO_4$/primary amine catalysts.

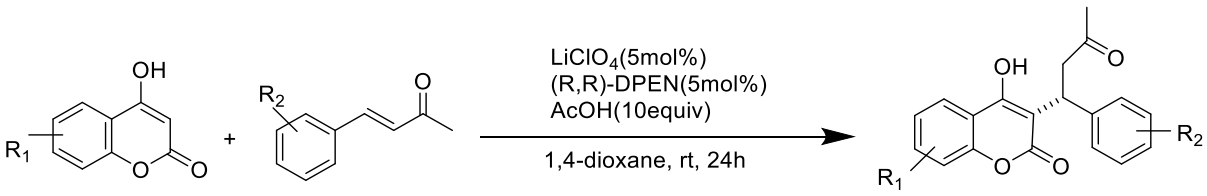

Figure 25: Michael's addition of substituted 4-hydrocoumarin to enones

In **Table 8**, all of the warfarin analogs were produced with good enantioselectivities (90%-94%ee). Surprisingly, while $NbCl_5$ yielded substantially greater yields for the investigated substrates than $LiClO_4$ under similar circumstances, the enantioselectivities were not as good (only 82%-90%ee).

Table 8: Yield and ee of warfarin derivatives using several substrates

R_1/R_2	Product	Yield/ee (%)
H/o-CH_3	4b	52/91
H/m-OCH_3	4c	64/90
H/p-CH_3	4d	75/90
H/p-Cl	4e	74/90
6-Cl	4f	61/94
6-Cl	4g	69/92
6-Cl	4h	62/91
6-Cl	4i	50/92

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Overall, this work leads to the discovery of several useful metal salts, such as $LiClO_4$, and increases reactivity and stereoselectivity. They were able to obtain warfarin with a superb 94%ee under mild circumstances by altering the reaction parameters. Finally, they have demonstrated that a novel cooperative strategy, in which the application of metal complexes or Lewis acid in tuning the reactivity of organic molecules-promoted reactions would be an efficient and privileged biomimetic catalytic process in asymmetric catalysis. These findings could lead to further improvements in stereoselectivity and reactivity [66]. In a similar research in 2013, a variety of new chiral porous metal-organic frameworks MOF organocatalysts efficiently catalyze the Michael reaction of cyclic 1,3-dicarbonyl compounds to α, β-unsaturated ketones with high yields and enantioselectivity. Notably, (S)-warfarin, a chiral anticoagulant medication, was synthesized directly employing CDMIL-4, an excellent MOF for heterogeneous catalysis including (1R, 2R)-DPEN as the best catalyst as well as the THF. Following the screening process, these conditions proved to be the best for giving the product higher enantioselectivities and yields, allowing for the production of warfarin on a gram-scale (up to 2.8 g) with high enantioselectivities (82%-90% ee) [68]. Aside from that, continuous flow processes have lately developed as a potent technique for executing chemical transformations since they offer various advantages over typical batch procedures, such as a faster reaction time [69-71]. (S)-warfarin has been synthesized by the nucleophilic addition of 4-hydroxy-coumarin (0.2 mmol, 32 mg) mixed in dry dioxane to fill syringe A (1.0 mL). Syringe B was loaded with a dry dioxane solution containing chiral primary amine 10 (0.02 mmol, 6.0 mg), trifluoroacetic acid (0.03 mmol, 3 L), and benzalacetone 9 (0.4 mmol, 58 mg) (1 mL). The reagents were pumped into microreactor II at the required flow rate (L/min) and temperature using syringes A and B linked to a syringe pump. To attain steady-state conditions, three reactor volumes were wasted before starting sample collection. As a result, they collected reaction results in a vial at room temperature and evaluated them using 1H-NMR. To determine conversion and enantiomeric excess, spectroscopy and HPLC were used [72, 73].

In **Figure 26**, there are two general approaches to organic synthesis when following the principles of green chemistry: (1) solvent-free and (2) alternate reaction media such as ionic liquid. Condensation reactions using solvent-free reaction procedures, such as Michael reactions, are increasingly becoming the preeminent synthetic approaches [74, 75]. Michael condensations of 4-hydroxycoumarin and benzalacetone in various reactions (**Table 9**).

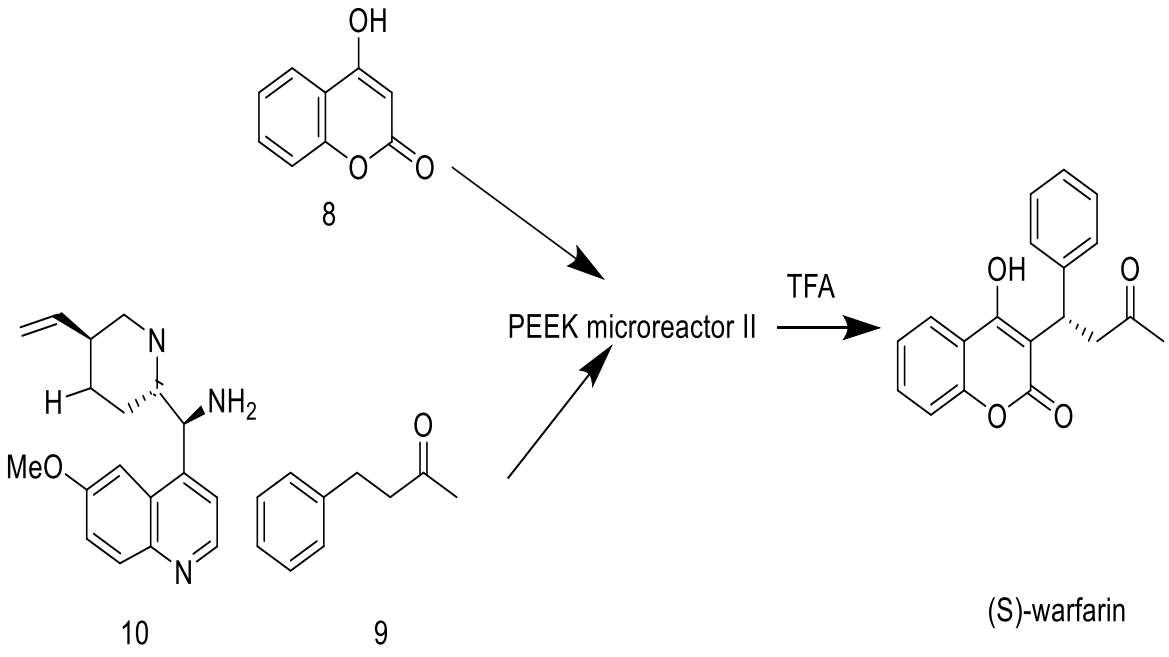

Figure 26: Synthesis of (*S*)-warfarin in flow

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Reaction 1: A combination of 4-hydroxycoumarin (1, 1 mmol), benzalacetone (2, 1 mmol), and [bmim] Br (1.0 mmol) was combined for 5 hrs at room temperature. After adding water, the product 3 was extracted with ethyl acetate (2x5 mL). They have an organic phase that has dried over anhydride Na_2SO_4. The solvent was then evaporated to extract warfarin in its purest form.

Reaction 2: At 50°C, 4-Hydroxycoumarin (1.0 mmol), benzalacetone (2.0 mmol), and BF_4 (1.0 mmol) were combined for around 8 hrs. Ethyl acetate was used to extract the resultant product 3 after adding 5.0 mL of water (2.5 mL). The organic phase was dried with Na_2SO_4 anhydride. Warfarin was delivered by evaporating the solvent.

Reaction 3: They combined 4-hydroxycoumarin (1, 5 g), benzalacetone (2, 5 g), 35cc H_2O, and 0.11cc ammonia in a flask with a reflux condenser and stirrer. The mixture was then boiled and kept at reflux for 2: 30 hrs, during which time a strong precipitate formed. They kept reflexing with strong agitation for an additional hour, and the reaction mixture was brought to room temperature. Filtration separated the solid crude product, which was then floated with fresh water and sucked as dry as feasible. The solid crude was suspended in benzene and refluxed with stirring for 45 min, then cooled, filtered, washed with fresh benzene on the filter, and sucked as dry as possible. The solids were dissolved in 5% NaOH at room temperature, then washed three times with CCl_4 and acidified to pH 1-3 using strong HCl. Warfarin was the final product. It was filtered out, washed with water to remove the chlorides, and dried.

Raction 4: 4-hydroxycoumarin (1.0 mmol), benzalacetone (1.0 mmol), and H_2O were charged into a flask fitted with a reflux condenser and stirrer. The reaction mixture was heated to boiling with stirring, formed at reflux for 12 hrs, and then cooled to 0°C overnight. A thick gum has formed. Decantation was used to remove the aqueous phase, which was then recrystallized from an acetone-water combination.

Table 9: Properties of warfarin derivatives resulting from the green synthesis

Reaction	Yield (%)	Melting point (°C)	IR(KBR) cm^{-1}	1HNMR	13CNMR
1	96	157-160	3300, 1680, 1610	δ= 2.32 (3H, s, CH3), 4.22 (2H, d, CH2), 4.31 (1H, t, CH), 7.01-7.94 (9H, m, 9CH).	δ= 34.8 (Me), 35.8 (CH), 43.1 (CH2), 104.6 (C), 117.1 (CH), 124.1 (CH), 124.4 (CH), 127.5 (CH), 128.7 (CH), 129.4
2	/	/	/	/	/
3	80	155-159.4	3300, 1700, 1640, 1600	δ= 2.28 (3H, s, Me), 3.33 (2H, d, CH2), 4.17 (1H, t, CH), 7.18 –7.93 (9H,m, 9CH).	δ= 30.9 (Me), 36.2 (CH), 46.0 (CH2), 104.9 (C), 117.5 (CH), 124.4 (CH), 124.9 (CH), 127.4 (CH), 128.8 (CH), 129.5 (2CH), 130.0 (2CH), 133.3 (C), 143.9 (C), 154.6 (C), 162.6 (CH), 167.2(C=O), 213.0 (C=O).
4	57.1	157-160	3300, 1680, 1610	δ= 2.27 (3H, s, Me), 3.30 (2H, d, CH2), 4.15 (1H, t, CH), 7.11-7.93 (9H, m, 9CH).	13CNMR: δ= 30.8 (Me), 36.1 (CH), 45.9 (CH2), 105.0 (C), 117.4 (CH), 124.4 (CH), 124.7 (CH), 127.3 (CH), 128.7 (CH), 129.4 (2CH), 130.0 (2CH), 132.8 (C), 144.0 (C), 153.7 (C), 159.7 (CH), 162.2 (C=O), 212.0 (C=O).

In terms of yields and reaction times, the RTIL Br was shown to be the optimal reaction solvent for synthesis. The reaction of 4-hydroxycoumarin, benzalacetone, and ammonia as catalysts with water as a solvent took 4: 30 hrs at refluxing temperature and yielded 80%, whereas at 50°C, the same product yielded 82% in 6 hrs. The first and second reactions with H_2O as the solvent took 12 hrs at refluxing temperature and yielded 57.1%, whereas the yield was 39.4% with pyridine as the catalyst and solvent took 24 hrs at refluxing temperature

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and yielded 39.4%. They next looked into the extent of the 4-hydroxycoumarin, benzalacetone condensation process in Br for the production of warfarin. All of the items were high-quality. The ionic liquid was recovered for the first and second reactions by extraction, followed by evaporation from water, washing with ethyl acetate, and drying with Na_2SO_4. They were able to reuse the ionic liquid numerous times after the ethyl acetate had evaporated, with no loss of activity. As a result, using room temperature ionic liquids (RTILs) in this reaction shortened the reaction time, which is a significant benefit. They discovered an effective and convenient approach for the synthesis of warfarin by employing ionic liquid as a novel solvent, which shortened reaction time and increased yield. The work-up methods were straightforward, and the products did not need to be purified any further [76].

In another manuscript, the lipase from porcine pancreas PPL-catalyzed Michael reaction of 4-hydroxycoumarin to α, β-unsaturated enones in DMSO/water have been described [77]. The established approach proved applicable to a wide range of α, β-unsaturated enones, including aromatic and heteroaromatic enones, as well as cyclic enones. Organic solvents, water content, temperature, and the molar ratio of substrates were all explored as reaction conditions. The control studies demonstrated PPL's unique catalytic impact. Warfarin, one of the most potent anticoagulants, was manufactured in one step with a decent yield of 87% and 22%ee using this biotransformation (R). Meanwhile, eight warfarin derivatives were synthesized with moderate to excellent yields (up to 95%) and enantioselectivities of up to 28%ee. It was the first time warfarin and derivatives were produced utilizing a biocatalyst, despite the limited enantioselectivity. Only a fraction of the many enzyme-catalyzed Michael additions reported so far have shown enantioselectivity. As a result, PPL's asymmetric Michael addition activity is a good example of enantioselective lipase catalytic promiscuity. More research on improving the enantioselectivity of the PPL-catalyzed transformation is currently being conducted [78].

Conclusion: Numerous synthesis methods of warfarin have been reported in this paper starting from the first asymmetric synthesis, organocatalytic synthesis, and green synthesis. Different catalysts have been used such as imidazolin, sulfonamides, phosphilamide as well as square amides. Showing higher anticoagulant activity; warfarin derivatives have been targeted to get synthesized green synthesis methods have been reported where alternative solvents and deep eutetic solvents have been used. On the water, water, and microwave synthesis have also been listed. Overall, the more efficient, cost-saving, and more importantly adheres to the green chemistry principles.

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