



## A Review on the Methods of Preparing 1,4-dihydropyridine derivatives

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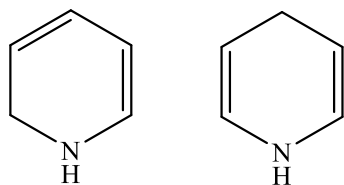
### Abstract

1,4-dihydropyridines (1,4-DHPs) are pharmacologically active compounds and are an important class of L-type calcium channel blockers utilized in the treatment of cardiovascular disorders, including hypertension, angina, and other spastic muscle disorders. As a result, 1,4-dihydropyridines (DHPs) serve as privileged pharmacophores and are attractive synthetic targets in organic chemistry. This review aims to describe various methodologies employed in the synthesis of this class of compounds.

**Keywords:** 1,4-Dihydropyridines, Calcium Channel Blockers, Hantzsch reaction

## Introduction

Dihydropyridines (DHPs) are heterocyclic organic compounds based on the pyridine structure. This group of organic compounds can exist in five isomeric forms, and the most common forms are the 1,2-dihydro- and 1,4-dihydropyridine (1,2-DHP, 1,4-DHP) structures (Scheme 1) [1].



Scheme 1. The structures of the most common isomeric forms of DHPs.

Among compounds with six-membered heterocyclic scaffolds, 1,4-Dihydropyridines (1,4-DHP) are important constituents that are found in biologically active natural products and medicinal compounds [2]. 1,4-DHP derivatives as calcium channel blockers are widely used in treating cardiovascular diseases [3-6]. Apart from their cardiovascular benefits [7], they used anti-convulsant [8,9], anti-inflammatory [10, 11], anti-depressive [12], anti-cancer [13, 14], anti-tubercular [15], antiparasitic and antibacterial [10, 16] and anti-diabetic [17] agents.

## Marketed Drugs based on 1,4-Dihydropyridine

### Cardiovascular Diseases

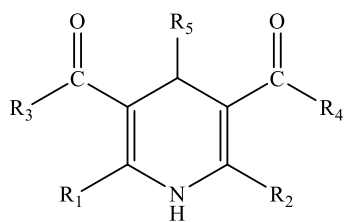
An important class of hypertension drugs is the calcium channel blockers (CCBs) or calcium channel antagonists [4, 18]. The

currently marketed 1,4-DHP-based drugs as calcium channel antagonists are used for the treatment of hypertension. The early ones include Nifedipine and Nicardipine, known for their rapid action due to limited half-life. The second generation, with improved bioavailability and longer duration of action, has been introduced after over 40 years [19].

The DHP CCBs act as antagonists of the nonindependent, T-type calcium channel [20]. DHP CCBs exhibits pharmacological effects on peripheral, coronary, and cerebral vasodilation; negative inotropic effect; and atrioventricular nodes and inhibition of excitation of sinoatrial [21]. plays a crucial role in their Ca<sup>2+</sup> channel-blocking activity. It can be summarized as follows:

C-4 serves as a chiral center in unsymmetrical 1,4-DHPs, with its absolute configuration playing a crucial role in calcium channel modulation. The nature and position of the substituents on the ring at C-4 are vital for optimizing activity. Substitutions at the N-1 position have a deterrent role; they can decrease or abolish activity. The 1,4-DHP is necessary for activity due to its ability to create hydrogen bonding. Substituents in C-3 and C-5 influence activity and tissue selectivity. The DHP receptor can tolerate different changes at the C-2 and C-6 positions [18].

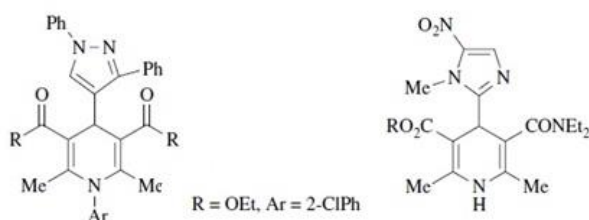
The general structure of these compounds is depicted in Scheme 2.



Scheme 2. The general structure of 1,4-DHP marketed calcium channel antagonist drugs.

## Infectious Diseases

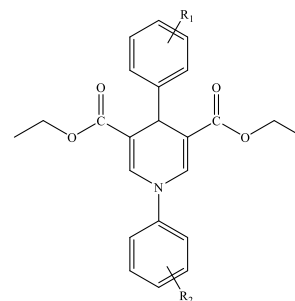
Tuberculosis is caused by a human pathogen, *Mycobacterium tuberculosis*, affecting a significant portion of the world's population [22-24]. 1,4-DHP with lipophilic groups exhibit anti-tubercular activity against *M. tuberculosis*. For example, 4-(4-pyrazol)-1,4-dihydropyridine derivatives [25] and 4-(2-imidazolyl)-1,4-dihydropyridine analogs [26] are anti-tubercular agents. In 2001 and 2002, 4-rayl-2,6-dimethyl-3,5-bis-N(rayl)carbamoyl-1,4-Dihydropyridines were synthesized as anti-tubercular agents (Scheme 3) [27, 28].



Scheme 3. The structure of 4-(4-pyrazolo)-1,4-dihydropyridine derivatives and 4-(2-imidazolyl)-1,4-dihydropyridine analogs.

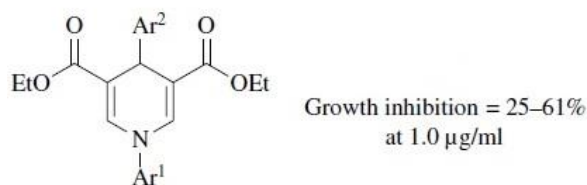
In cancer cells, classical 1,4-DHPs act as inhibitors of the transmembrane efflux pump ABCB1. In 2019, F. Lent, et al. investigated non-classical 1,4-DHP derivatives used to enhance the antitubercular drug efficacy of the second-line antitubercular drug clofazimine. Clofazimine is a known substrate of ABCB1, potentially inhibiting a

corresponding efflux pump in *Mycobacterium tuberculosis* (Mt). Discovering new enhancers of clofazimine toxicity may help prevent the development of clofazimine resistance through efflux pump activity (Scheme 4) [29].



Scheme 4. The structure of nonclassical 1,4-DHPs without a substitution in both the 2 and the 6-position.

In 2012, Y.L.N. Murthy, et al. synthesized thirteen derivatives of 4-aryl-1,4-DHP compounds, and their effectiveness as antibacterials against 27 ESBL isolates of *Klebsiella pneumoniae* and *Escherichia coli* were evaluated [30]. The growth inhibition of 1,4-diaryl-1,4-DHP against *M. tuberculosis* was evaluated in Germany in 2016 (Scheme 5) [31].

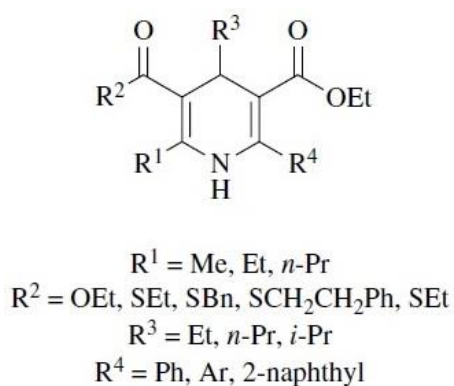


Scheme 5. The structure of 1,4-diaryl-1,4-DHPs.

## Inflammatory diseases

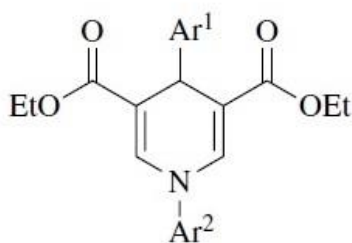
Capsaicin is an agonist that transduces painful chemical or thermal stimuli to peripheral nerve endings in skin or deep tissues by activating ion flux through the TRPV1 channel, a heat and

ganglionated cation channel [32, 33]. Researchers from the National Institutes of Diabetes and Digestive and Kidney Diseases have identified 1,4-DHP derivatives as novel "enhancers" of TRPV1 activity. These enhancers have been shown to increase the effect of capsaicin on  $\text{Ca}^{2+}$  uptake two to threefold compared to when capsaicin is used alone in Scheme 6.



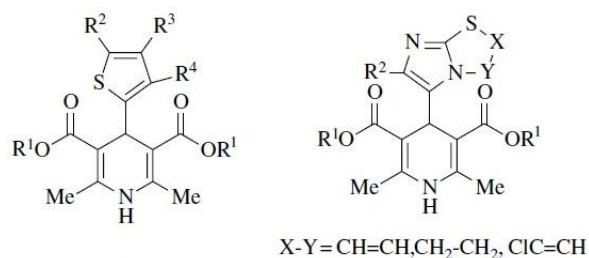
Scheme 6. The structure of novel "enhancers" of TRPV1-based 1,4-DHP derivatives.

2,6-Unsubstituted-1,4-diaryl-1,4-DHPs are selective inhibitors of phosphodiesterase type (PDE4) and could be beneficial in treating inflammatory diseases like asthma and chronic obstructive pulmonary disease (COPD). (Scheme 7) [34, 35].



Scheme 7. The structure of 2,6-Unsubstituted-1,4-diaryl-1,4-DHPs.

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene lead to Cystic fibrosis (CF), an autosomal recessive disease [36]. The deletion of phenylalanine in the CFTR chloride channel is the most common cause of CF. Antihypertensive 1,4-DHPs like Felodipine and Nifedipine inhibit T-type  $\text{Ca}^{2+}$  channels and also enhance CFTR gating [37]. Italian researchers have reported that 4-thiophenyl-2'-yl and 4-imidazole-[2,1-b]thiazole-1,4-DHPs act as potentiators of the CFTR chloride channel (Scheme 8) [38, 39].



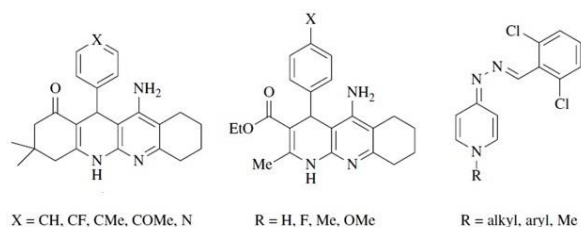
Scheme 8. The structure of 4-thiophenyl-2'-yl- and 4-imidazol[2,1-b]thiazole-1,4-DHPs and as potentiators of the CFTR chloride channel.

## Nervous diseases

Alzheimer's disease (AD) is a type of progressive neurodegenerative disorder that can lead to memory loss and dementia in elderly people [40-42]. It is caused by the buildup of abnormal extracellular amyloid-beta peptide ( $\text{A}\beta$ ) deposits, protein aggregation, disruptions in biometals like Cu, Fe, and Zn, oxidative stress (OS), intracellular neurofibrillary tangles, widespread neuronal death, and reduced levels of the neurotransmitter acetylcholine (ACh) [43-45]. One approach to treating AD involves boosting ACh levels in the brain, which can be achieved through the use of acetylcholinesterase inhibitors (AChEIs) [46]. The only administered drugs for AD

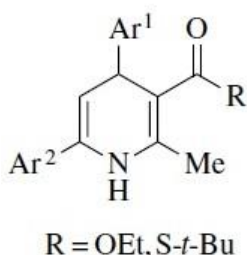
therapy include Donepezil, Rivastigmine, Galantamine, and the N-methyl-D-aspartate receptor antagonist Memantine, all of which act as acetylcholinesterase inhibitors. However, their effectiveness is limited [47].

Tacrine-1,4-DHPs in Spain and (benzylidene-hydrazono)-1,4-DHPs in Germany as AChEis were synthesized (Scheme 9) [48, 49].



Scheme 9. The structure of Tacrine-1,4-DHPs and (benzylidene-hydrazono)-1,4-DHPs as AChEis.

4,6-Diaryl-1,4-DHPs were synthesized by Spanish researchers. These compounds were found to prevent calcium overload and act as neuroprotective agents (Scheme 10) [50].

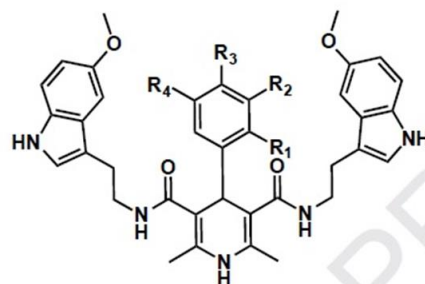


Scheme 10. The structure of 4,6-diaryl-1,4-DHPs.

The multitarget small molecule (MTSM) approach is a novel therapeutic strategy. In this method, drugs are designed to bind simultaneously to various enzymatic systems or receptors involved in AD pathology. R. Malek, et al. synthesized  $\text{Ca}^{+2}$  channel blockade capacity and investigated the

antioxidant power of N3, N5-bis(2-(5-methoxy-1H-indol-3-yl)ethyl)-2,6-dimethyl-4-aryl-1,4-DHP-3,5-dicarboxamides as several new MTSM by using multicomponent reactions

(Scheme 11) [51].

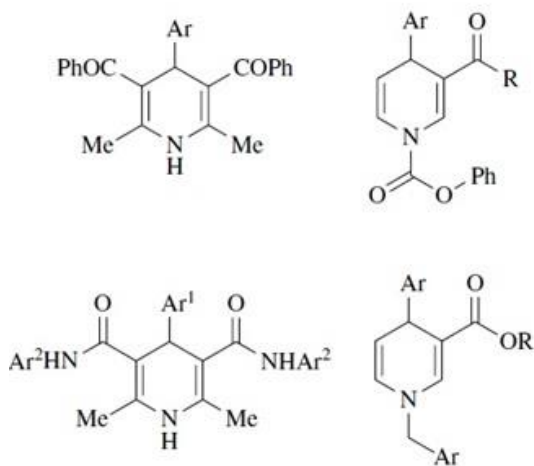


Scheme 11. The structure of N3, N5-bis(2-(5-methoxy-1H-indol-3-yl)ethyl)-2,6-dimethyl-4-aryl-1,4-DHP-3,5-dicarboxamides.

## Cancer

Multidrug resistance (MDR) in cancer cells refers to their resistance to multiple classes of chemotherapy drugs, posing a significant challenge in cancer treatment [52]. This resistance is primarily driven by the efflux of drugs through transmembrane activity, leading to insufficient intracellular drug levels for effective therapy. It is commonly associated with the overexpression of various proteins, such as ATP-dependent extrusion pumps like P-glycoprotein (Pgp) and multidrug resistance protein (MRP1), which belongs to the ABC superfamily of transporters [52- 54]. Inhibition of Pgp is an effective method for combating MDR [55, 56]. The cytotoxicity of several compounds

of the 1,4-DHP towards cancer cells is more than towards non-cancer cells and they kill cells by inhibiting the P-glycoprotein pump and reversing multidrug resistance [57]. Some 1,4-DHPs which used as inhibitors of Pgp and MRP1 include 3,5-dibenzoyl-1,4-DHPs [58], N-arylmethyl-1,4-DHPs [59], 3,5-bis(amido)-1,4-DHPs [60] cage dimeric 1,4-DHPs [61], N-acyloxy-1,4-DHPs [62], 3-pyridin-2-yl methyl 5alkyle 2,6-dimethyl-4-(aryl)-1,4-dihydropyridine-3,5-dicarboxylate [63], VdiE-2N ((isobutyryloxy)methyl 6-chloro-5-formyl-1,4-dihydro-2-methyl-4-(2-nitrophenyl)pyridine-3-carboxylate))(Scheme 12) [64].



Scheme 12. The structure of some 1,4-DHPs which used as inhibitors of Pgp and MRP1.

### Synthesis of 1,4-DHPs

For the first time, the synthesis of 1,4-DHP via the condensation of aldehyde, ethyl acetoacetate with ammonia refluxing to 6-72 h in a lower alcohol or acetic acid was reported by Arthur Hantzsch in 1882 (Figure

1) [65]. The reaction time in this procedure is long, and the yields of 1,4-DHP obtained by this method are generally low, especially with aliphatic and unsaturated aldehydes. However, the most common method for the synthesis of a wide variety of 1,4-DHP is the Schantz synthesis. To date, numerous literature citations have reported novel synthetic strategies for improving the classical methods by using alternative catalysts and greener methods [66-72].

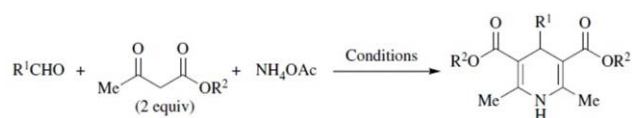


Figure 1. The Hantzsch reaction.

In recent years, various studies have documented different approaches to enhance the Hantzsch reaction, including the use of catalysts [73], fermenting baker's yeast [74], molecular iodine [75], ionic liquids [76], orientalist [77]. However, many of these methods rely on toxic and costly reagents, long reaction times, low yields, strong acidic environments, harsh conditions, and tedious workup, resulting in the production of significant amounts of hazardous waste. Consequently, researchers have endeavored to modify and optimize the Hantzsch reaction to maximize conversion rates, improve efficiency, reduce reaction times, and ensure the high purity of 1,4-DHPs. As a result, there is a growing inclination towards adopting environmentally friendly reactions [73].

Up to now, several more environmentally friendly methods have been documented, including solvent-free [78], catalyst-free [79], ultrasound irradiation [80], and aqueous media [81].

Here, we provide a review of various methods for synthesizing 1,4-DHPs. These reactions are categorized into different sections based on the methods used.

Due to issues with the Hantzsch reaction, various effective methods have been devised for the production of 1,4-DHPs.

### Using Catalyst

The one-pot multicomponent reactions (MCRs), in which three or more reactants combine in a single process to yield a sole product, are significant in synthetic organic chemistry due to their unique characteristics such as simple procedures, atomic economy, environmental friendliness, straightforward reaction design, high selectivity, and enhancing the yield of a reaction where consecutive chemical reactions are performed on a reactant in a single vessel. Compared to traditional methods for synthesizing complex molecules, MCRs involve two or more synthetic steps. They are conducted without isolating any intermediates, thereby saving time, energy, and raw materials [82-86]. Hantzsch is a notable one-pot MCR that enables the synthesis of a wide range of heterocyclic compounds 1,4-DHPs [65].

One efficient method developed for synthesizing 1,4-DHPs involves the use of catalysts. Catalysts are components that can improve reaction rates and product yield. They hold significant technological importance because of their excellent selectivity and stability [87]. Catalysts are divided into two categories: homogeneous [88-90] and heterogeneous catalysts [91-93].

Molecular iodine is a non-toxic, inexpensive, and readily available catalyst for a variety of

organic reactions. It has been utilized as a mild Lewis acid at room temperature, resulting in high yields in the production of symmetrical, unsymmetrical, and N-substituted 1,4-DHPs [75]. See Figure 2, as well as Spiro-dihydropyridine derivatives (Figure 3,4).

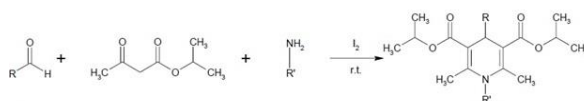


Figure 2. Synthesis of N-substituted 1,4-DHPs.

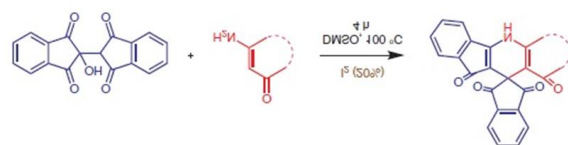


Figure 3. Synthesis spiro-dihydropyridines.

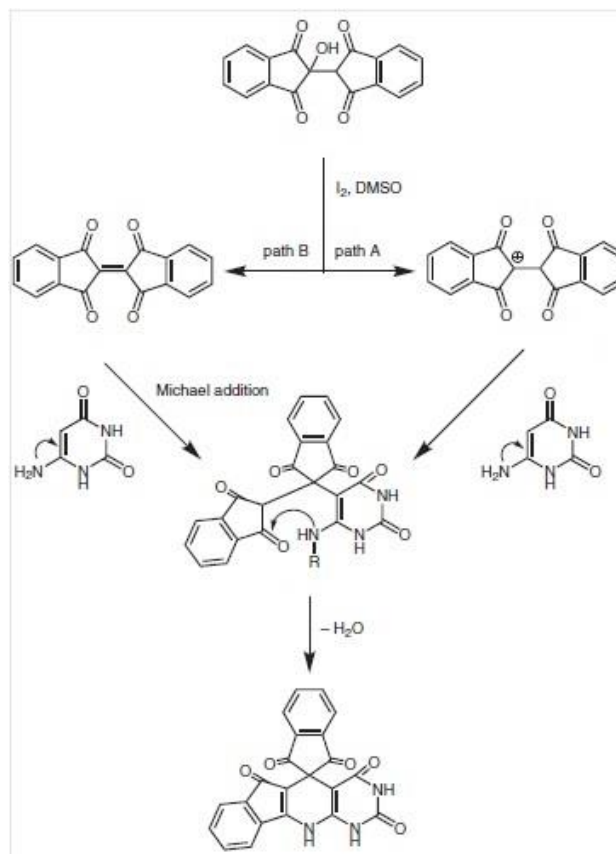


Figure 4. Proposed mechanism of formation of spiro-dihydropyridans.



Graphene oxide nanoparticles were reported as a metal-free heterogeneous catalyst for the synthesis of spirooxindole dihydropyridine derivatives (Figure 5) [95].

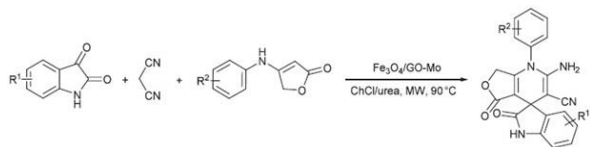


Figure 5. Synthesis of spirooxindole dihydropyridine derivatives.

Today, in organic synthesis, nano-catalysts are highly intriguing due to their large surface area, easy accessibility, cost-effectiveness, ease of product separation, catalyst recovery, high catalytic activity, potential for repeated recycling, and excellent stability.  $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ , as a novel Lewis acid catalyst, is one such catalyst used in the one-pot synthesis of 1,4-DHPs (Figure 6) [96].

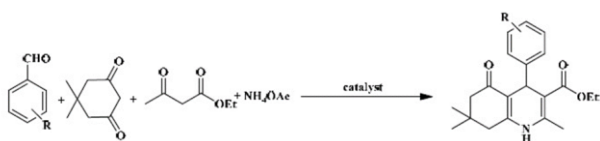


Figure 6. Synthesis of 1,4-DHPs in the presence of  $\text{TiCl}_2/\text{Nano-}\gamma\text{-Al}_2\text{O}_3$  as a novel Lewis acid catalyst.

Metal-organic frameworks (MOFs) are hybrid materials combining organic and inorganic components, known for their significant surface area, high porosity, and adjustable chemical properties utilized in heterogeneous catalysis.

Due to the coordinatively unsaturated metal sites and functional groups on the organic linkers, MOFs are well known for their

Lewis and Brønsted acidity/basicity [97-100]. The potential of MOFs has been explored as a Lewis acid catalyst in the synthesis of bioactive heterocycles. Functionalized sulfonic acid-containing MOFs are used in heterocycle synthesis, such as pre-sulfonic acid-functionalized MIL-101-SO<sub>3</sub>H MOF, which serves as a solid Brønsted acid catalyst for the synthesis of 1,4-DHPs (Figure 7) [101].

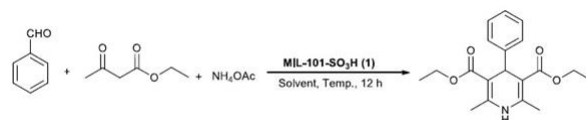


Figure 7. One-Pot Synthesis of 1,4-DHPs in the presence of MIL-101-SO<sub>3</sub>H MOF.

HKUST-1 is another example of MOF which is used as an efficient and reusable heterogeneous catalyst for the synthesis of 1,4-DHPs at room temperature (Figure 8) [102].

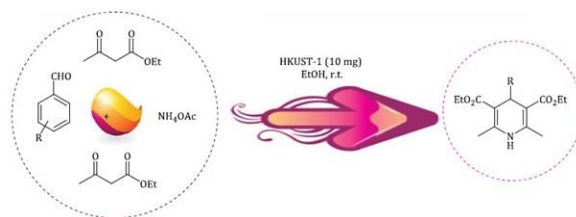


Figure 8. Synthesis of the 1,4-DHPs in the presence of HKUST-1

To enhance the efficiency of Hantzsch DHPs synthesis, various catalysts have been utilized, including  $\text{Fe}_3\text{O}_4$  nanoparticles [103], multiwalled carbon nanotubes [104], montmorillonite K10 [105-107], mesoporous vanadium ion doped titania nanoparticles [108, 109], nanomagnetic-supported sulfonic acid [110, 111], silica boron sulfonic acid [112], benzyl trimethylammonium fluoride



hydrate (BTMAFH) [113], Fe<sub>3</sub>O<sub>4</sub>@silica sulfonic acid nanocomposite [114], tin dioxide nanoparticles [115, 116], and others.

### Green methods

Our environment must be safeguarded from the increasing production of large amounts of waste and toxic by-products, which in turn leads to chemical pollution. Synthetic chemists are therefore working on developing safer technologies that are crucial in the field of green chemistry. Key green principles to be considered in new chemical processes include: the use of eco-friendly mediums, non-toxicity, non-flammability, and the ability to separate and recycle catalysts. As a result, significant efforts have been put into designing and synthesizing environmentally friendly methods that involve reagents, catalysts, and solvents that can easily biodegrade [117, 118].

### Hantzsch reaction in water and solvent-free conditions

The advancement of eco-friendly chemical protocols and technologies is a key objective of green chemistry. In green chemistry, significant emphasis is placed on selecting an environmentally friendly solvent [119, 120]. A new trend in organic synthesis has sparked increasing interest in replacing organic reactions in solvent-free conditions or aqueous media [121, 122]. Water, being an affordable, non-toxic, and non-flammable medium, has garnered significant attention as a solvent for organic transformations.

Moshtaghi Zonouz, et al., described the synthesis of 1,4-DHP derivatives through a three-component reaction involving aldehydes, ethyl acetoacetate, and ammonia in refluxing water (Figure 9).

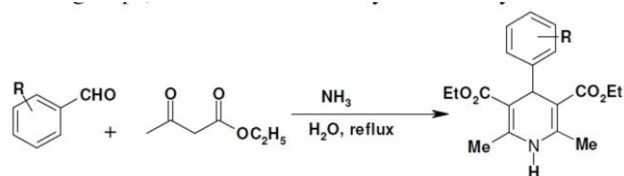


Figure 9. Synthesis of the 1,4-dihydropyridine under aqueous media.

In 2012, they also conducted the MCR between malononitrile, dimedone, aniline, and 3-nitro benzaldehyde in refluxing ethanol but obtained the 4H-chromene derivative instead of quinoline derivative (Figure 10, 11).

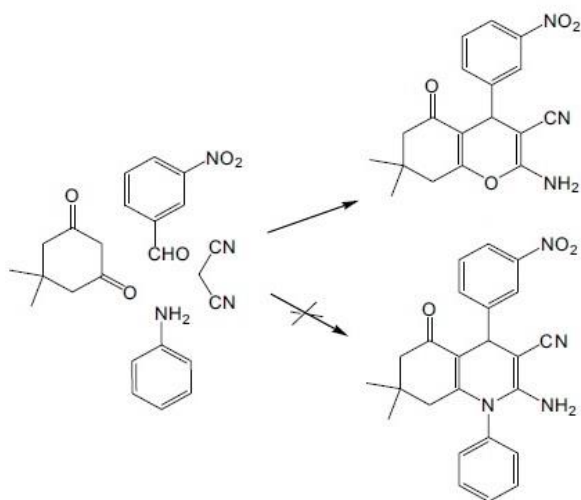


Figure 10. The multicomponent reaction of dimedone, aniline, malononitrile and 3-nitrobenzaldehyde.

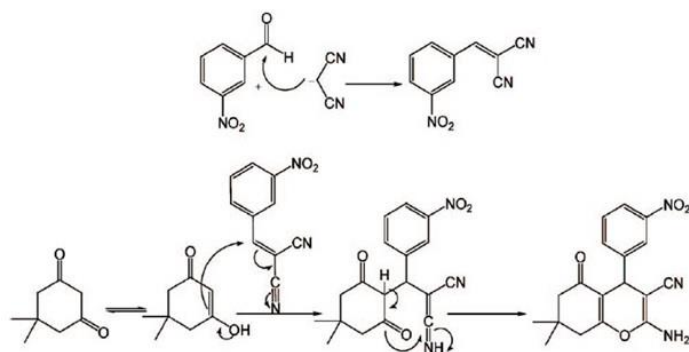


Figure 11. Proposed mechanism for the synthesis of chromene derivative.

So, they employed a one-pot, two-stage approach. By altering the sequence of adding the materials, they managed to synthesize the intended products. Initially, dimedone and aniline were refluxed in ethanol to obtain phenylaminocyclohex-2-enone. Then, arylaldehyde and malononitrile were introduced into the same vessel. The mixture was refluxed until the reaction was complete (2-72 h) (Figure 12). The proposed mechanism is depicted in figure 13 [123].

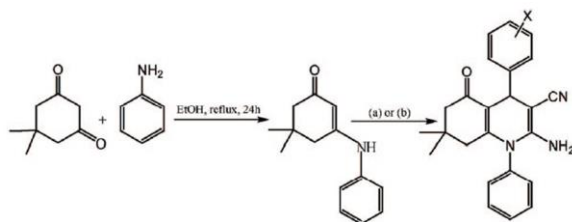


Figure 12. Synthesis of N-arylquinoline derivatives.

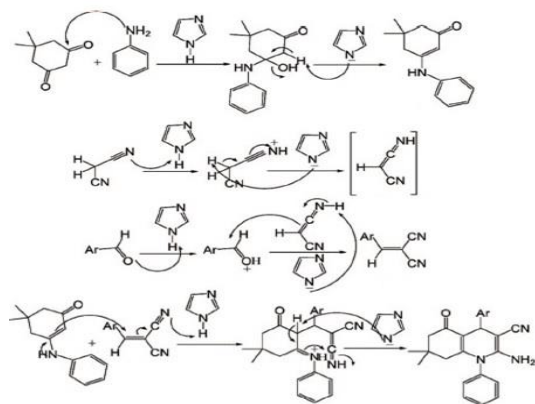


Figure 13. Proposed mechanism for the synthesis of N-arylquinoline derivatives.

Other examples include the synthesis of 4-alkyl/aryl-1,4-DHP through the Hantzsch three-component reaction of an aromatic/aliphatic aldehyde, alkyl acetoacetate, and ammonium carbonate in water (Figure 14) [124, 125].

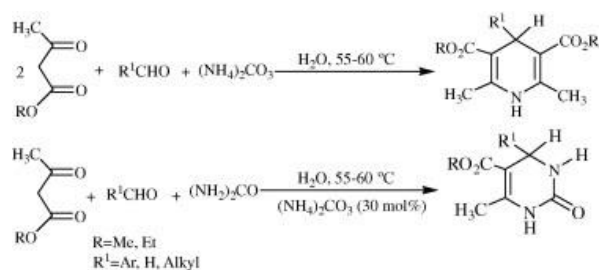


Figure 14. Synthesis of 1,4-dihydropyridines using ammonium carbonate in water.

Yang et al. utilized a sealed system for the Hantzsch reaction, as shown in Figure 15.

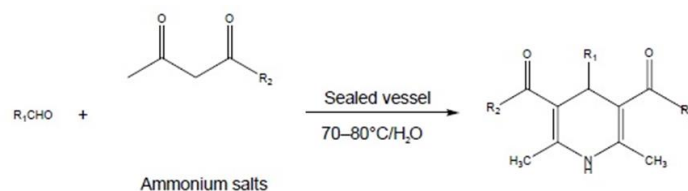
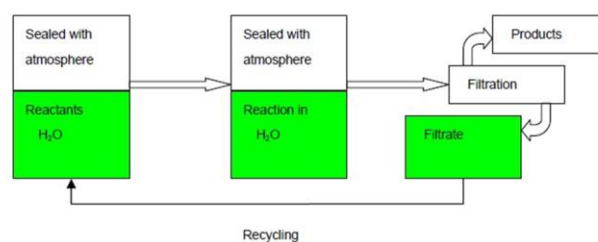


Figure 15. Synthesis of 1,4-DHPs via Hantzsch reaction in water [83].

An important aspect of organic reactions conducted in water is the low solubility of the reactants in aqueous solutions. Consequently, many organic transformations in aqueous environments have limited applicability. To address this issue, micelle-promoted reactions involving surfactants that can be carried out in water have been developed. Heterocyclic compounds such as furans, indoles, pyridines, pyrazolines, dihydropyridines, etc., have been successfully synthesized in aqueous media (Figure 16) [88, 126].

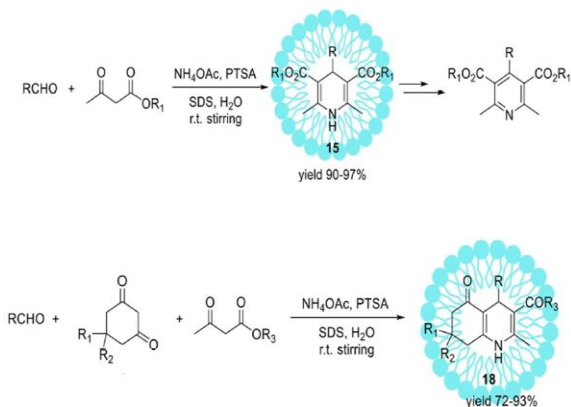


Figure 16. Micelles promoted the synthesis of dihydropyridines and polyhydroquinoline derivatives via the Hantzsch reaction.

Some enhanced techniques for the production of 1,4-DHPs through the Hantzsch reaction involve solvent-free conditions. M. G. Sharma et al. documented the creation of thiophene-based 1,4-DHP derivatives at room temperature and without solvents by employing ceric ammonium nitrate (CAN) as the catalyst, resulting 1,4-DHPs in high yields in short reaction times (Figure 17).

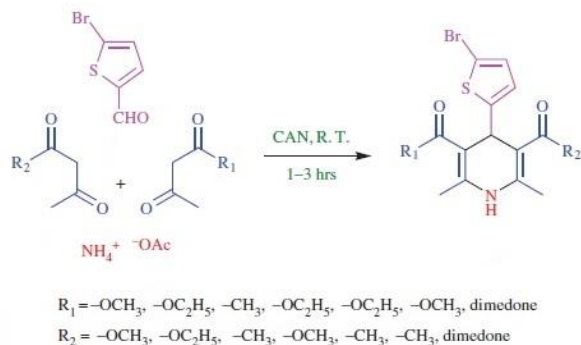


Figure 17. Solvent-free condition for the Hantzsch.

$\beta$ -Cyclodextrin ( $\beta$ -CD) is an oligomer of D-glucose that can bind with organic molecules through interactions between the charged part

of the guest molecule and  $\beta$ -cyclodextrin via van der Waals interaction, hydrophobic interactions, hydrogen bonding, and electrostatic interactions.  $\beta$ -CD is non-toxic to the environment, readily available, and cost-effective compared to other cyclodextrins. It is commonly used as a catalyst under solvent-free conditions in the Hantzsch reaction for the synthesis of 1,4-DHPs (Figure 18, 19) [73].

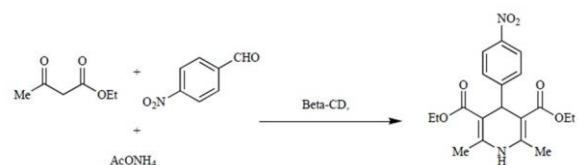


Figure 18. Solvent-free synthesis of the Hantzsch 1,4-DHPs.

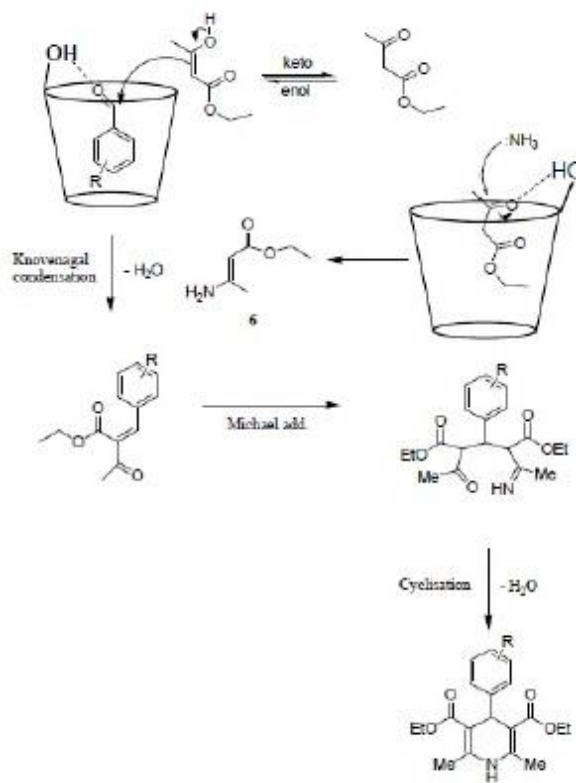


Figure 19. Proposed mechanism for synthesis of 1,4-DHPs.

Pramanik et al. described an ammonium acetate-mediated catalyst-free "on-water"

method for synthesizing the Hantzsch dihydropyridines (Figure 20).

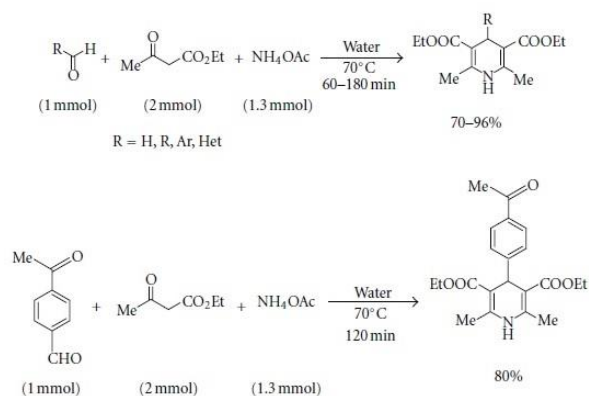


Figure 20. Ammonium acetate-mediated "on-water" synthesis of the Hantzsch 1,4-DHPs.

For the preservation of natural resources for future generations, it is essential to protect our environment. Chemists and chemical engineers are working on developing safe, sustainable, and eco-friendly processes. Among the green aspects of sustainable chemical transformations, such as atom economy, catalysis, and energy efficiency, the reaction media plays a central role. The solvent used in the manufacturing process of the active pharmaceutical ingredient (API) accounts for the maximum amount of total material mass in the process. As a result, major pharmaceutical companies like Pfizer, GSK, and Sanofi have recently created solvent selection guides for chemical processes in drug synthesis [129-133].

The solvent in the reaction plays a crucial role in modifying reactants, facilitating mass and heat transfer phenomena, stabilizing transition states, and influencing catalyst and product reactivity. Solvents are also utilized in various other applications during reactions, such as washing, purification, recrystallization, chromatography, and

extraction. Due to their extensive use in multiple steps of the process, solvents have a significant impact on the environmental aspects of the reaction. Typically, solvents are volatile organic compounds (VOCs) with low molecular weight, commonly derived from petrochemicals and alcohols, which possess drawbacks like high flammability, volatility, toxicity, and often non-biodegradability.

Replacing toxic and volatile organic solvents with environmentally friendly alternatives is a key objective of green chemistry. This shift involves utilizing green solvents that are safe, non-toxic, recyclable, and biodegradable. Various alternative solvents, including ionic liquids (ILs), supercritical fluids (such as carbon dioxide and water), perfluorinated compounds, deep eutectic solvents (DESs), glycerol, and other solvents derived from biomass, are being explored.

### Ionic liquids (ILs)

In the late 20th century, Ionic liquids (ILs) have established a strong presence in technology and research. Compared to conventional molecular organic solvents (MOSs), the main advantage of ILs is the ability to tailor their structures to specific application requirements [134, 135]. ILs possess unique characteristics like low vapor pressure (eliminating volatility), recyclability, exceptional thermal stability, and effective solvating properties (the capacity to dissolve a wide range of substances) [136].

ILs consist entirely of mobile ions, such as an organic cation (mainly imidazolium, pyrrolidinium, pyridinium, ammonium, or

phosphonium) and typically a halide anion (usually Cl<sup>-</sup> or Br<sup>-</sup>) or a weakly basic non-coordinating anion like [PF<sub>6</sub>]<sup>-</sup>, [BF<sub>4</sub>]<sup>-</sup>, or [NTf<sub>2</sub>]<sup>-</sup> [136]. These low-temperature molten salts offer a wide range of possible combinations of anions and cations, allowing for adjustable physical and chemical properties. The environmentally friendly nature of this category of compounds makes them suitable as alternative solvents and catalysts in organic synthesis [137-140].

MCRs are conducted in ionic liquid solutions. Ionic environments create internal pressure and facilitate the interaction of reactants in solvent pockets, making them ideal environments for various bond-forming reactions. Due to their high solvating capacity and broad liquid range, they are suitable solvents for multicomponent processes [141]. X. Liu, et al. described a sustainable Hantzsch reaction for producing 1,4-DHPs. They used alcohols instead of aldehydes in the Hantzsch reaction and utilized the Brønsted acidic ionic liquid 3-(N,N-dimethyldodecylammonium) propane sulfonic acid hydrogen sulphate ([DDPA][HSO<sub>4</sub>]) as a catalyst. This catalyst facilitated the stepwise oxidation of aromatic alcohols with NaNO<sub>3</sub>, followed by their condensation with a dicarbonyl compound and ammonium acetate. The formation of 1,4-DHP occurred when ethyl acetoacetate and ammonium acetate were introduced into the reaction after the alcohol had been completely oxidized to the aldehyde (Figure 21).

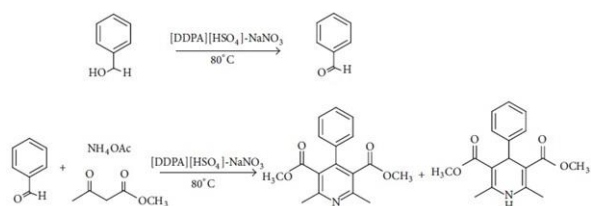


Figure 21. Hantzsch reaction directly from benzyl alcohol in [DDPA][HSO<sub>4</sub>].

Different ionic liquids were tested for the same model reaction. In [Hmim]NO<sub>3</sub> and [bmin]BF<sub>4</sub>, the absence of acidic hydrogen in the two ionic liquids led to an unsuccessful reaction. However, when [Hmim][H<sub>2</sub>PO<sub>4</sub>] and [DDPA][HSO<sub>4</sub>] were used, the reaction was successfully completed. The lower yields of the product in [Hmim][H<sub>2</sub>PO<sub>4</sub>] can be attributed to the reduced Brønsted acidity associated with [H<sub>2</sub>PO<sub>4</sub>]. [DDPA][HSO<sub>4</sub>] serves a dual purpose as an acid catalyst and a solvent for both the oxidation of alcohol and the subsequent condensation [142].

The sulfamic acid-supported functionalized mesoporous SBA-15/NHSO<sub>3</sub>H is a heterogeneous catalyst and an ionic liquid type, which can be easily separated from reaction products and recycled. It demonstrates superiority over homogeneous catalysts and was utilized in the synthesis of polyhydroquinolines and dihydropyridines under solvent-free conditions as investigated (Figure 22) [143].

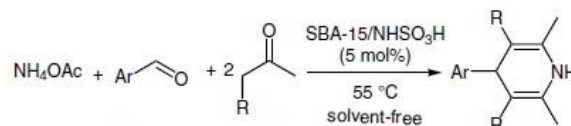


Figure 22. Solvent-Free Synthesis of DHPs Using SBA-15/NHSO<sub>3</sub>H Catalyst.

Crown ether complex cation ionic liquids (CECILs) chelated with sodium benzenesulfonates (alkali metal cations) are utilized as a green and environmentally friendly catalyst for the synthesis of 1,4-DHP derivatives. This is achieved through the three-component reaction of aromatic aldehydes and malononitrile with cyclic β-



dicarbonyls, or cyclic  $\beta$ -enaminoketone, in H<sub>2</sub>O/EtOH (1:1) under reflux conditions (Figure 23) [144].

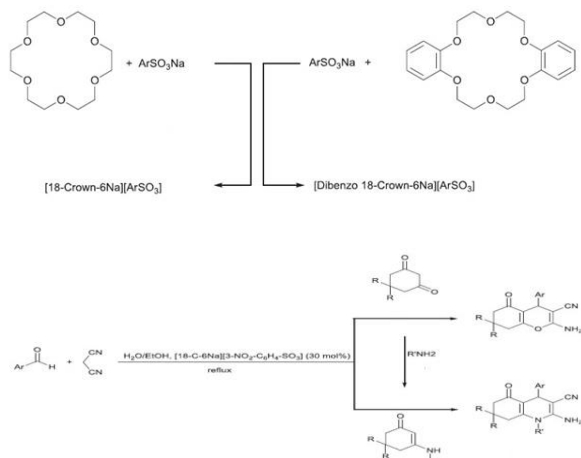


Figure 23. a) Synthesis of CECILs. b) Synthesis of tetrahydro-4H-chromene and 1,4-DHP derivatives.

1-Methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride ([MSEI]Cl) is a novel heterogeneous and environmentally friendly acidic ionic liquid catalyst utilized in one-pot multi-component reactions, such as the synthesis of 1,4-DHPs through the one-pot multi-component condensation of 1,3-dicarbonyl compounds (2 equiv.), NH<sub>4</sub>OAc (1.5 equiv.), and aldehydes (1 equiv.) under solvent-free conditions at a moderate temperature of 90 °C. This catalyst is reusable and unlike other acids, it does not require special precautions for storage and handling. It can be stored on the benchtop for weeks without losing its catalytic activity (Figure 24) [145].

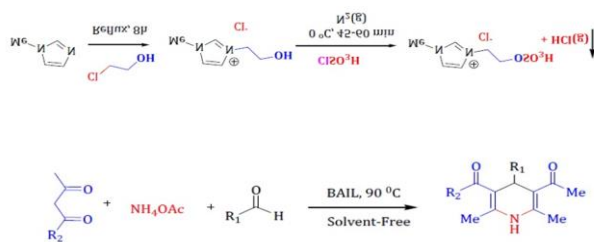


Figure 24. a) Preparation of 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-iumchloride. b) Synthesis of 1,4-DHPs using [MSEI]Cl.

The Dabco-base ILs as highly efficient catalysts used for the synthesis of spiro 1,4-DHP derivatives in moderate to good yields. (Figure 25) [146].

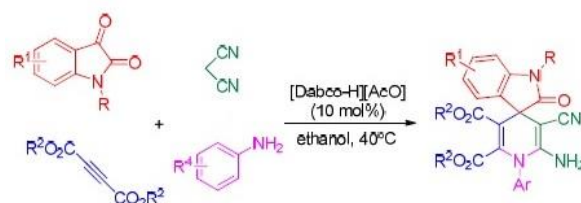


Figure 25. One-pot synthesis of derivatives spiro 1,4-DHPs.

## Deep Eutectic Solvents (DESs)

Some significant drawbacks of ILs, such as environmental toxicity [147] and high cost [148], as well as their occasional requirement for high purity that could alter the physical properties of ILs [149], have hindered their widespread industrial use. To address these issues, alternative solvents made from inexpensive, non-toxic, and biodegradable components have been developed. One such alternative to ILs is deep eutectic solvents (DESs), which were first synthesized by Abbott, et al., based on choline chloride (ChCl) [150]. Other types of DES include low-melting mixtures (LMMs) of sugar, urea, and inorganic salts described by König and colleagues [151, 152], low-transition temperature mixtures (LTTMs) recommended by Kroon and colleagues [153], natural deep eutectic solvents (NADESs) proposed by Choi and colleagues [154], and deep eutectic ionic liquids (DEILs) described by Hillman's group as low-cost eutectic mixtures with physical



properties and phase behavior similar to ILs [155]. These solvents are created from combinations of two or three safe and affordable components (a hydrogen acceptor and a hydrogen-bond donor) that can self-associate through hydrogen bond interactions. Consequently, the charge delocalization is responsible for reducing the melting point of the mixture compared to the melting points of the raw materials [117, 156].

These liquids have melting points below 100 °C, lower than those of their individual components. Due to the special properties of deep eutectic solvents (DES) such as low toxicity, a wide liquid range, low vapor pressure, water compatibility, biodegradability, non-flammability, and cost-effectiveness (cheaper production due to lower raw material costs), they have been utilized in various research fields including biodiesel synthesis, polymerizations, carbon dioxide adsorption, nanotechnology, and organic synthesis [117, 157-160].

DESs are also employed in the Hantzsch reaction. In 2013, Pednekar et al. documented the utilization of ChCl/urea as a deep eutectic solvent in the production of polyhydroacridines (PHA) with outstanding yields (Figure 26) [161].

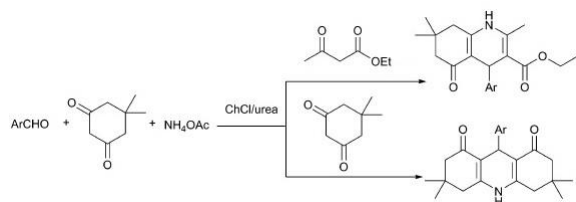


Figure 26. Synthesis of 1,4-DHP derivatives in ChCl/urea.

Wang, et al. have developed an efficient and green procedure for the one-pot synthesis of PHA and PHQ derivatives using ChCl/urea as a reaction medium. This deep eutectic solvent could be recycled and reused for several runs. It was environmentally benign and easily available (Figure 27) [162].

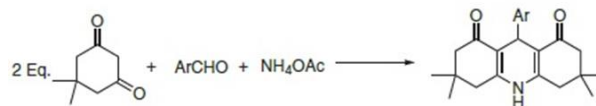


Figure 27. Synthesis of PHA derivatives in ChCl/urea.

Synthesis of 1,4-DHP esters using different low-melting mixtures (LMMs) under catalyst-free conditions was reported in 2016 by J. A. Kumara and colleagues. Various LMMs were prepared by utilizing different hydrogen bond donors (HBD). The use of sugar, urea, and CeCl<sub>3</sub> was explored, with the sugar/HBD/CeCl<sub>3</sub> ratio fixed at 5:4:1 as a novel solvent medium. They tested 14 aldehydes with five LMMs IA–VA. They achieved moderate to good yields for all desired products (Figure 28) [163].

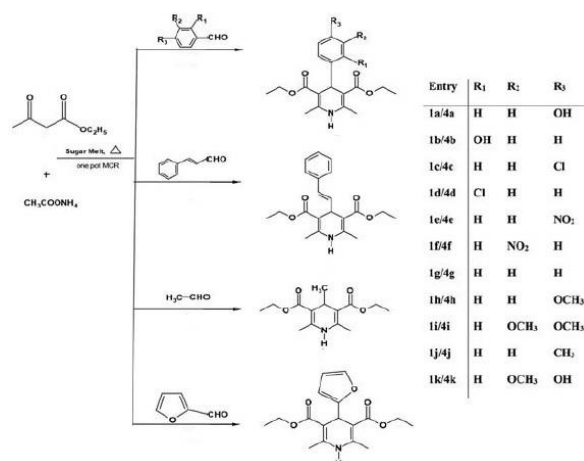


Figure 28. Synthesis of 1,4-DHP esters.

They introduced a more gentle and highly effective protocol that can readily substitute current methods. They utilized DESs, which can be reused without compromising their efficacy for up to 5 cycles, offering a more environmentally friendly option [161].

## Ultrasound

One of the most environmentally friendly and efficient methods in producing various bulk and nanomaterials is sonochemistry. When ultrasonic irradiation used in synthesis, the amount of solvents and catalysts is reduced, leading to cost savings. It enables unique pathways for initiating high-energy reactions. Sonochemistry's foundation demonstrates significant potential in accelerating reaction rates, achieved through the mechanical impact of sound waves (for heterogeneous processes) and chemical activation (for homogeneous processes) in an energy-efficient way.

Cavitation is the predominant phenomenon induced by ultrasound in the liquid medium. When a liquid is subjected to a periodic pressure wave, the creation, growth, and then implosion (collapse) of bubbles happen. The result of the implosion of the bubble is the release of a large amount of thermal energy and mechanical energy without any significant change in the whole medium. Therefore, the cavitation bubble collapse is the driving force, which moves the reactions toward completion in a very short time [164, 165]. Due to the unusual properties like simplicity, controllable reaction conditions, rapid reaction rate, enhanced catalyst efficiency, and high purity of the product, this technique has been extensively used [166].

Solvent- and catalyst-free one-pot multicomponent reactions (MCRs) for the synthesis of 1,4-DHPs are the focus of interest for chemists. The synthesis of symmetric 4-(3-bromo-4-hydroxy-5-methoxyphenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-DHP (4a) and 4-(3-bromo-4-hydroxy-5-methoxyphenyl)-2,6-dimethyl-3,5-dicarbomethoxy-(4-nitrophenyl)-1,4-DHP (4b) was achieved in high yield using solvent- and catalyst-free microwave-assisted multicomponent Hantzsch reaction by Maru et al. (Figure 29).

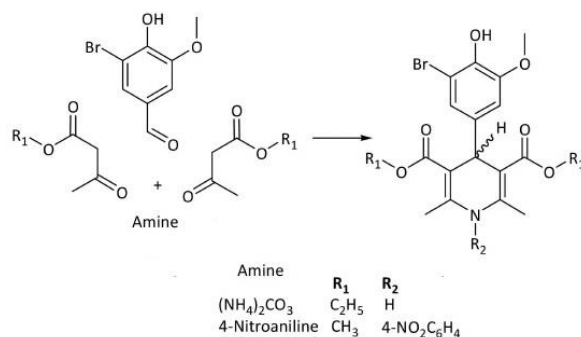


Figure 29. Reaction scheme for the synthesis of compounds (4 a) and (4 b).

The core/shell Fe<sub>3</sub>O<sub>4</sub>@GA@IG bio nanocatalyst has been prepared and evaluated for the first time in the synthesis of 1,4-DHPs under sonication in ethanol. In this method, ultrasound waves as an alternative green source of energy have been used. Other advantages of this method are omitting toxic solvents or catalysts, good yields, short reaction times, very simple workup, and magnetically separable, recyclable, and green catalysts obtained from a natural source. This catalyst is recyclable with no significant yield decrease after six runs (Figure 30) [167].

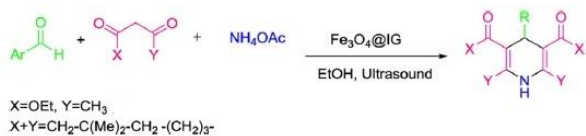


Figure 30. Synthesis of 1,4-DHP derivatives in ethanol under ultrasound irradiation.

the Fe<sub>3</sub>O<sub>4</sub>@GA@IG nanocomposite has been compared as a catalyst for the synthesis of 1,4-DHP and polyhydroquinoline derivatives with other catalysts and procedures [168-170].

Moradi et al. presented a novel synthetic method for producing 1,4-DHP derivatives using MWCNTs@meglumine as a highly efficient and recyclable catalyst. The approach followed green chemistry principles to create a practical heterogeneous catalyst by attaching meglumine onto CNT surfaces. The optimal use of ultrasonic irradiation was determined. The reaction was carried out in EtOH with varying power levels. The best yield (95%) was achieved after 15 minutes at 70 W, with no significant impact on reaction time and yield observed at higher power (75 W) (Figure 31) [171].

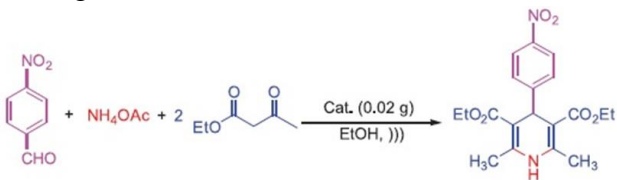


Figure 31. Synthesis of 1,4-DHPs MWCNTs@meglumine as catalyst, under ultrasonic irradiation.

In 2015, Tabassum et al. reported a one-pot four-component cyclocondensation reaction for the synthesis of polysubstituted 1,4-DHPs. The reaction was catalyzed by copper (I) iodide in an aqueous medium under ultrasound irradiation (Figure 32)

[172].

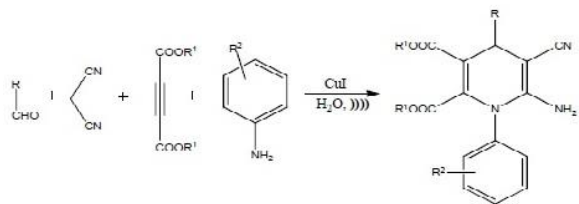


Figure 32. Preparation of polysubstituted 1,4-DHPs.

This experiment was conducted under solvent-free conditions, resulting in a maximum yield (45%) of product. Unsatisfactory yields were obtained under different conditions, even after an extended period. Other examples of ultrasound application in the synthesis of 1,4-DHPs can be found in references [80, 173, 174].

## Mechanochemistry

The significance of green chemistry techniques is increasing. Alternative processes can help conserve resources and reduce costs [175]. Mechanochemistry is a method within green chemistry as it allows for solvent-free conditions. Chemical transformations occur through the application of mechanical energy (e.g. compression, shear, or friction). In solvent-free conditions, the reaction rate speeds up due to the absence of solvation phenomena and the high reagent concentrations resulting from the lack of solvents. Reactions involving insoluble reactants enable efficient solvent-free synthetic procedures with high yields and shorter reaction times, achievable at a rapid pace through mechanochemistry. Mechanochemical reactions involve the direct absorption of mechanical energy, often from grinding or milling processes [176, 177].

A mechanochemical version of the Hantzsch dihydropyridine synthesis was developed by Hunda et al. They ground mixtures of aldehydes, dimedone, acyclic active methylene compounds, and ammonium acetate at room temperature in a mortar in the absence of solvent. When aromatic aldehydes were used, the reaction yielded good to excellent results (Figure 33) [178].

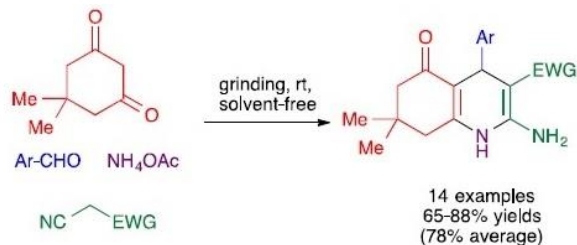


Figure 33. The preparation of polyhydroquinolines under mechanochemical conditions.

Bazgir et al. utilized a reactive cyclic ketone through manual grinding in solvent-free conditions and with toluene sulfonic acid as a catalyst to produce spiro compounds using Hantzsch-like chemistry (Figure 34) [179].

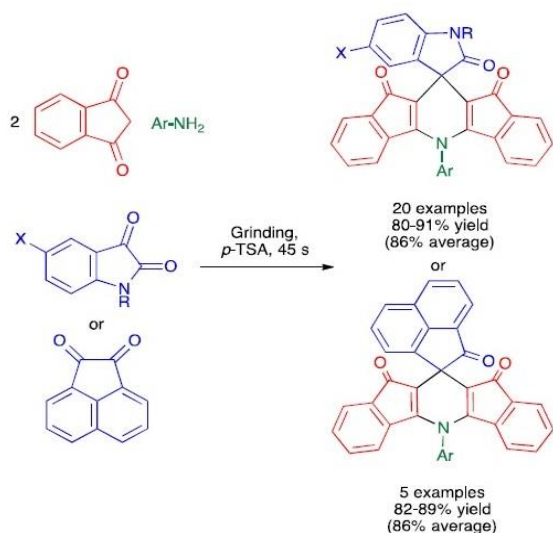


Figure 34. Synthesis of spiro compounds under manual grinding conditions.

Another mechanochemical multicomponent reaction was described by Kamur and Sharma. It involved grinding of aldehydes, amines, diethyl acetylenedicarboxylate (DEAD), and malononitrile/ethyl cyanoacetate in a porcelain mortar for 5-20 minutes to produce the desired compounds (Figure 35) [180].

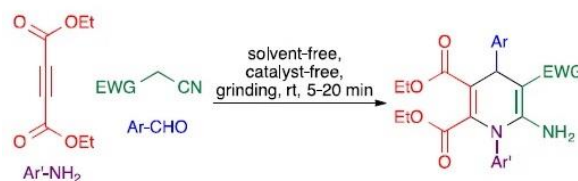


Figure 35. Mechanochemical four-component synthesis of DHPs from an acetylenedicarboxylate.

Synthesis of 1,4-DHP calcium antagonists and their derivatives through a new mechanochemical enzymatic protocol under ball milling conditions was studied by Jiang et al. In mechanochemical reactions, the grinding frequency plays a crucial role. Increasing the grinding frequency from 15 to 25 Hz resulted in a rise in the reaction yield from 39.7 to 68.8% (Figure 36) [181].

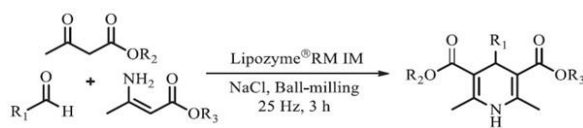


Figure 36. Lipozyme®RMIM-catalyzed rapid synthesis of 1,4-DHP derivatives under ball milling conditions.

In 2016, Moshtaghi Z. et al. reacted aromatic aldehydes, dimedone, and malononitrile with ammonium acetate. Surprisingly, they discovered that tetrahydrobenzo[b]pyrans were formed instead of polyhydroquinolines under both grinding and reflux conditions. The researchers observed that in this transformation, ammonium acetate acts as a

catalyst rather than a reactant (Figure 37) [182].

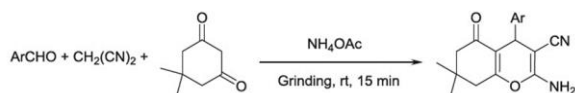


Figure 37. Ammonium acetate-mediated reaction of aromatic aldehydes, dimedone, and malononitrile at room temperature under grinding.

Then, they modified the reaction conditions. The reaction was carried out with the presence of ammonium acetate and imidazole as catalysts. The reaction acceleration and reduction of reaction time occurred upon the addition of either ammonium acetate or imidazole. The two-step synthesis of polyhydroquinoline derivatives in refluxing ethanol was conducted with a catalytic amount of imidazole (20 mol %) and refluxing in ethanol (Figure 38).

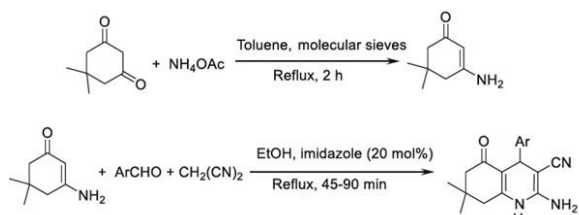


Figure 38. The two-stage synthesis of polyhydroquinoline derivatives in refluxing ethanol in the presence of the catalytic amount of imidazole.

Zhang et al. conducted a mechanochemical reaction by ball milling  $\beta$ -enaminones and chalcones with  $\text{AlCl}_3$ . This method included the in situ formation of enaminones through Michael's addition of anilines to acetylene dicarboxylates (Figure 39) [183].

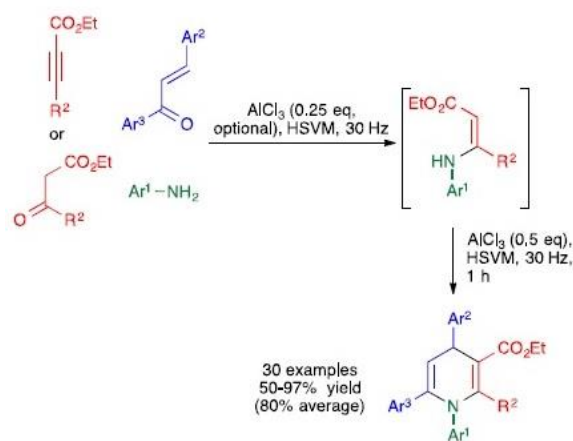


Figure 39. Mechanochemical four-component synthesis of DHPs from chalcones

In a different study, the researchers acquired dihydropyridines through a similar process starting from in situ-generated Knoevenagel adducts. However, they observed that by using 1,3-cyclohexanedione derivatives under the same conditions, instead of the anticipated fused dihydropyridines, they produced fused pyran derivatives (Figure 40).

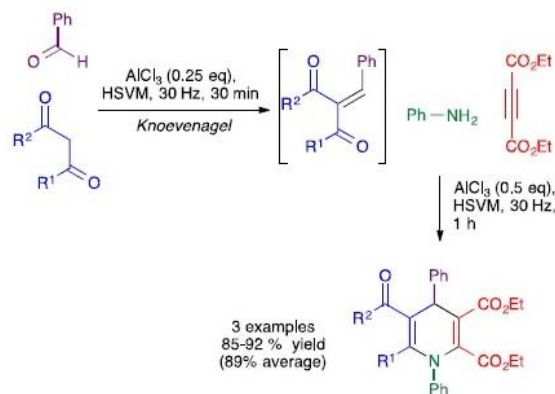


Figure 40. Knoevenagel-initiated mechanochemical four-component synthesis of DHPs.

### Stereochemistry investigations (Synthesis of enantiopure 1,4-DHPs)

The Hantzsch procedure is mostly used in the synthesis of the 1,4-DHPs. Although this procedure is simple, and isolation of the



product is generally straightforward the yield of the desired products is well for symmetrical dihydropyridines [184]. Later many efforts were made to synthesize the unsymmetrically substituted 1,4-DHP with high efficiency, and in some cases, the crystal structure was investigated [185, 186].

Nifedipine is a symmetrically substituted dihydropyridine, which is an achiral compound. The second-generation such as Amlodipine, Nitrendipine, and Nicardipine, are chiral derivatives and the pharmacological effects of their enantiomers are different from each other. The differences are quantitative in the case of the calcium antagonists. It means that the enantiomers exhibit opposite activities, one of them acting as an agonist, and the other as an antagonist. Moshtaghi et al. reported the synthesis of derivatives of unsymmetrically substituted 1,4-DHP and described the separation of the enantiomers of S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl) 1,4-dihydropyridin-2-yl)-methyl]-isothiouras. The C-4 carbon atom of 1,4-DHPs is prochiral (Figure 41) [187].

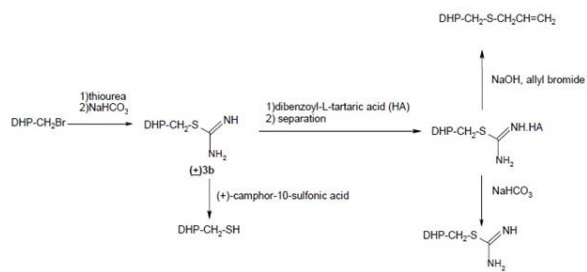


Figure 41. synthesis of DHPs derivatives and separation of the enantiomers of S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl) 1,4-dihydropyridin-2-yl)-methyl]-isothiouras.

Auria-Luna et al. used Takemoto's thiourea for the synthesis of 2-oxospiro-[indole-3,4-(1,4-dihydropyridine)] derivatives, which are

chiral, and have good reactivity and promising enantioselectivities (Figure 42, route a) [188]. In the next work, they used bis-cinchona derivative as an organocatalyst (Figure 42, route b) [189].

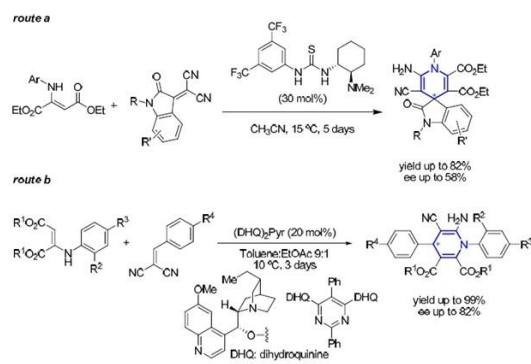


Figure 42. Synthesis of chiral 1,4-DHPs.

In 2018, the first organocatalytic asymmetric synthesis of chiral 1-Benzamido-1,4-dihydropyridine derivatives was investigated by them. In this method, they used chiral amine-based catalysts, hydrazones, and alkylidenemalononitriles. The catalyst could provide the first asymmetric version of 1,4-DHP derivatives (Figure 43) [77].

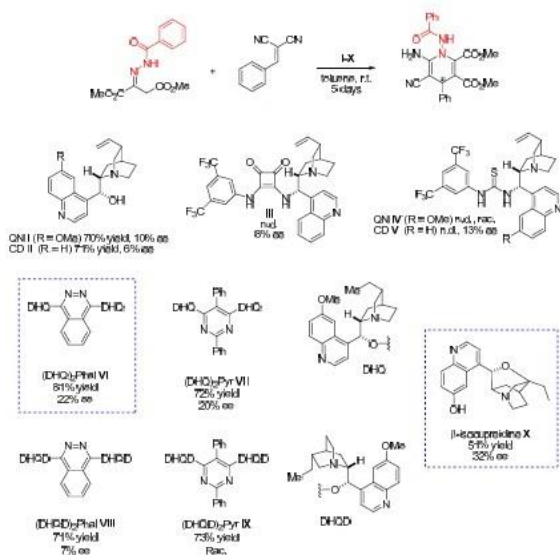


Figure 43. Chiral organocatalyst I-X is used for the synthesis of chiral derivatives of 1,4-DHPs.



For the synthesis of chiral 1-benzamido-1,4-DHP, the solvent, catalyst, and concentration of each reagent were analyzed.

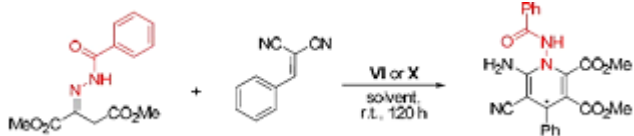


Figure 44. The synthesis of chiral 1-benzamido-1,4-DHP.

Another work in the enantioselective synthesis of 1,4-DHPs was reported, which was catalyzed by chiral Brønsted acids (Figure 44) [125].

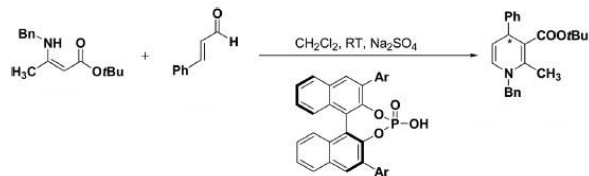


Figure 45. Enantioselective synthesis of 1,4-DHP catalyzed by chiral Brønsted acids.

### Using chiral auxiliary for separation of racemic 1,4 DHPs

In this approach for the production of optically active 1,4-DHPs, a chiral auxiliary was utilized. Subsequently, the resulting diastereomeric esters were isolated, and the chiral auxiliary can be selectively removed [125].

Lamm, et al., in the synthesis of pure enantiomers of felodipine, a calcium channel antagonist, utilized a chiral auxiliary (Figure 46)

[190].

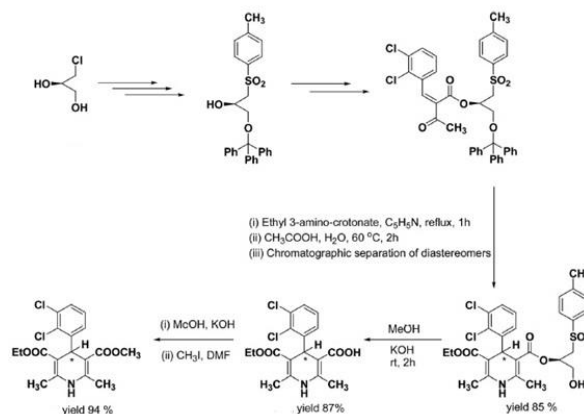


Figure 46. Enantiopure synthesis using chiral auxiliary.

Yamamoto et al. utilized the *t*-butyl ester of *L*-valine as a chiral auxiliary in synthesizing asymmetric 1,4-DHP derivatives, achieving a high enantiomeric excess (>95%) in a decent yield. The key aspect of this process is the stereoselective Michael addition (Figure 47) [191].

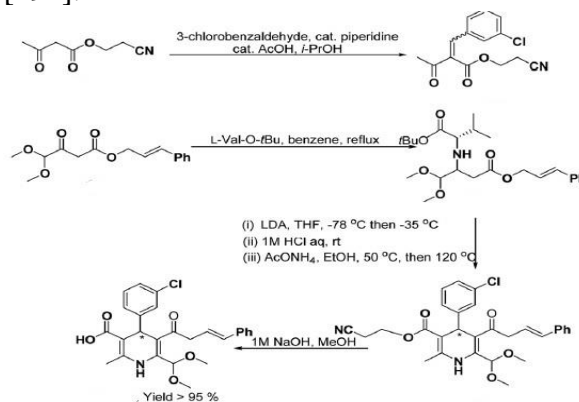


Figure 47. Stereoselective synthesis of 1,4-DHP.

### Organocatalytic asymmetric synthesis to form enantiomerically enriched dihydropyridines

Excellent e.e. up to 98% in the asymmetric synthesis of 1,4-DHPs has been achieved in the presence of chiral phosphonic acids (Figure 48) [192].

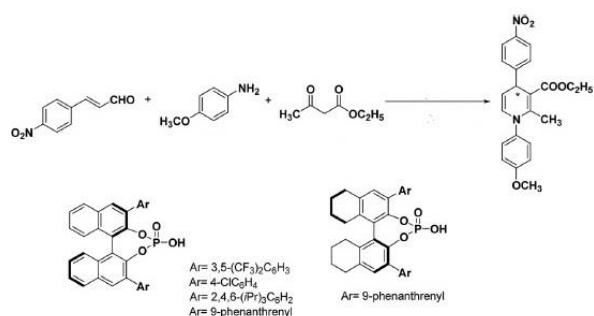


Figure 48. Chiral phosphonic acids catalyzed the synthesis of 1,4-DHP.

Synthesis of enantiomerically pure 1,4-DHPs has been done by utilizing chiral aldehydes. Michael addition of ethyl aminocrotonate to chiral  $\alpha$ -acetylacrylates produced enantiopure 1,4-DHPs (Figure 49) [125].

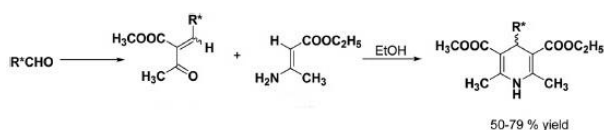


Figure 49. Synthesis of chiral 1,4-DHPs using chiral aldehydes.

Resolution of racemic 1,4-dihydropyridine carboxylic acids via diastereomeric salt formation has been reported [125]. Treating of racemic acid derivative of 1,4-DHP with chiral bases cinchonidine and quinidine, and then recrystallization to form diastereomeric salts. Next, treatment of each diastereomeric salt with hydrochloric acid gave each of enantiomers (Figure 50) [193].

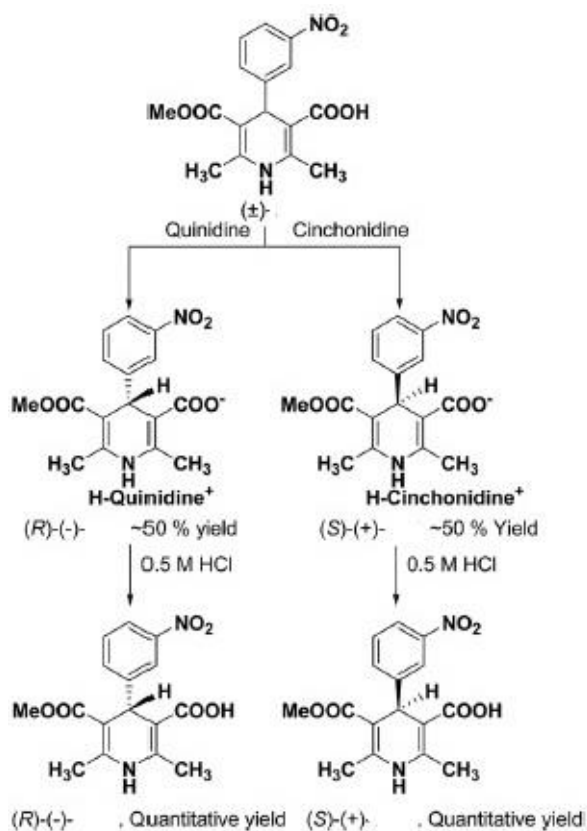


Figure 50. Synthesis of chiral 1,4-DHP via diastereomeric salt formation method

Also, R-(+) and S-(-) amlodipine enantiomers have been resolved via diastereomeric salt formation with L- or D-Tartaric acid, respectively. When L-tartaric acid is used with racemic amlodipine in DMSO, (R)-amlodipine tartrate crystallized out. When the solvent system was switched to DMF/H<sub>2</sub>O (85:15 ratio), the (S)-(-) amlodipine enantiomer crystallized with 99% purity (Figure 51).

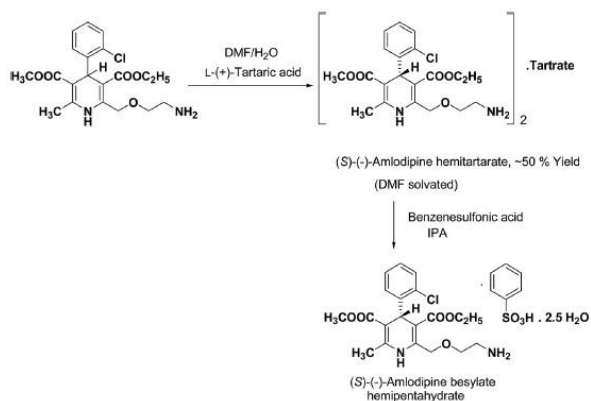


Figure 51. Resolution of R-(+) and S-(-) amlodipine via diastereomeric salt formation with L- or D-tartaric acid, respectively in DMSO.

### Conflict of Interest

No conflict of interest was declared by the authors.

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