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Review

3,4-Dihydro-2(1H)-Pyridones as Building Blocks of Synthetic Relevance

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Abstract: 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**) and their derivatives are privileged structures present in natural products, which has been increased its relevance due to its biological activity in front of a broad range of targets, but especially for its importance as synthetic precursors of a variety of compounds with marked biological activity. Taking into account the large number of contributions published over the years regarding this kind of heterocycle, here we presented a current view of 3,4-dihydro-2(1*H*)-pyridones (**3,4-DHPo**), which include general aspects such as those related to nomenclature, synthesis, and biological activity; but also highlighting the importance of **DHPo** as building blocks of other relevance structures.

Keywords: 3,4-DHPo; 1,4-DHPs; multicomponent reaction; non-conventional synthesis; synthetic precursors

1. Introduction

The study of determinate structures like small molecules in drug discovery has increased, engaging most in medicinal chemistry. These structures, particularly those based on *N*-heterocycles, represent a class of molecules capable of binding to multiple receptors with high affinity, showing a broad range of biological activity.

In this regard, the 3,4-dihydro-2(1*H*)-pyridones (**3,4-DHPo**) are biologically active *N*-heterocycles analogs of the well-known 1,4-dihydropyridines (**1,4-DHPs**), and dihydropyrimidines (**DHPMs**)[1] with this heterocyclic scaffold, which has been introduced in the scientific landscape. In this context, **DHPo's** as the Milrinone and the Amrinone are drugs with cardiotonic activity successfully used to treat heart failure (Figure 1).[2] In addition, they and their derivatives have also been reported to possess antitumor[3], antibacterial[4] anti-HIV[5], and other biological activities[6–9]. These results encourage many research groups to search potentially active **DHPo's** analogs.

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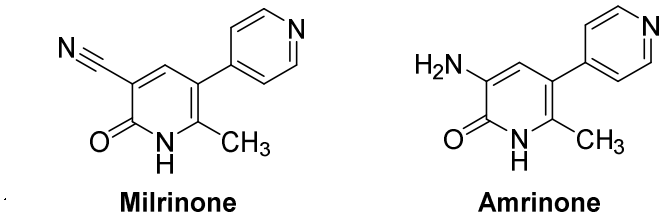


Figure 1. Milrinone and Amrinone structures which increase cardiac contractility vasodilators.

At the same time, the 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**) and its derivatives are extensively used as precursors in the synthesis of bioactive molecules such as (±)-Andranginine (Figure 2)[10], elective α1a adrenergic receptors,[11] Rho-kinase inhibitors[12] and $P2X_7$ receptor antagonists.[13]

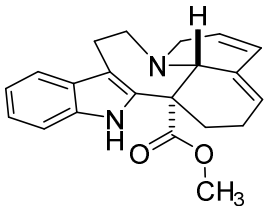
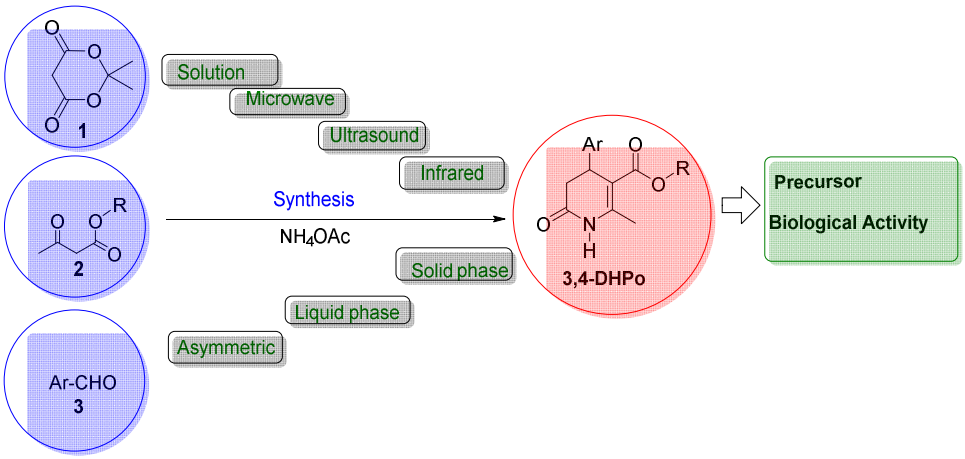


Figure 2. (±)-Andranginine structure.

The synthesis of **3,4-DHPo** derivatives has been important by the pass of time. Different synthetic procedures to synthesize its taking place in the last years, although the most reported use the multicomponent reaction (MCR-4CR) of Meldrum's acid (**1**), a β-ketoester derivative (**2**), and aromatic aldehydes (**3**) in the presence of ammonium acetate. Additionally, a broad range of techniques have been covered, from the conventional synthesis, through energy resources such as microwave, ultrasound and infrared assisted, until solid and liquid phase synthesis, and recently the chemoenzymatic assisted methodology applying to their asymmetric synthesis (Scheme 1).



Scheme 1. 3,4-Dihydro-2(1*H*)-pyridone (**3,4-DHPo**) synthesis procedures and applications, Meldrum's acid (**1**), β-keto-ester derivative (**2**), aldehyde derivative (**3**).

This overview presents the principal characteristics of the **3,4-DHPo** structures, the different procedures to synthesize them developed over time, the main biological application, and their crucial importance as precursors to molecules with high relevance in medicinal chemistry.

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2. Nomenclature, structure, and general synthesis

The heterocyclic 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**) (Figure 3), is commonly known 4-aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones (Figure 3a), although the correct IUPAC name is 4-arylsubstituted-2-methyl-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylates (Figure 3b). The calculated tridimensional structure (Figure 2c) shows the atoms' corroborated disposition present in the **DHPo**[14–16].

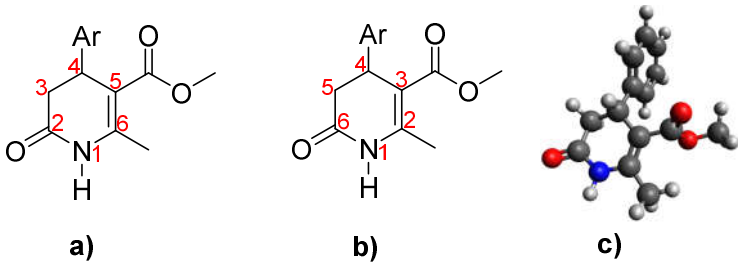
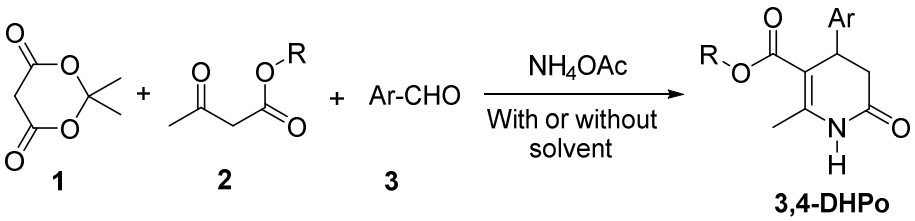


Figure 3. 3,4-DHPo structures. a) Common name: 4-aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones, b) IUPAC name: 4-arylsubstituted-2-methyl-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylates,and c) 3D structure model which substituent purple color represent the aryl (Ar) group.

The effort to synthesize **1,4-DHP** derivatives by modifying its ring gave rise to the first accidental synthesis of **3,4-DHPo**, as novel heterocycles that showed interesting biological activity.[17] The general synthesis of **3,4-DHPo** as a racemic mixture involves a multicomponent reaction (MCR 4-CR) of Meldrum's acid (**1**), a *β*-ketoester derivative (**2**), and an aromatic aldehyde (**3**) in the presence of ammonium acetate and with or without solvent (**Error! Reference source not found.**). The responsible for blocking the formation of the 1,4-dihydropyridines ring is the acidic character of Meldrum's acid (pKa = 9.97), which is higher than the *β*-ketoester (pKa =11.0) [18].



Scheme 2. General synthesis of 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**).

These kinds of molecules present a stereogenic center at C-4. Its absolute configuration (*R*- versus *S*-enantiomer) was a critical factor for the biological activity as an antagonist or agonist of calcium ions.[19] The mechanism reported in Scheme 3 has been demonstrated in the synthesis of intermediaries and their characterization.[20]

The general accepted mechanism follow a Hantzsch-like pathway with the previous formation of two intermediates; **4** from Knoevenagel condensation of Meldrum's acid (**1**) with the corresponding aromatic aldehyde (**3**), and **5** from the reaction involving β-ketoester (**2**) and ammonia. A Michael-type addition of the enamine **5** on ylidene compound **5** gives rise **DHPo's** (**Error! Reference source not found.**).[20]

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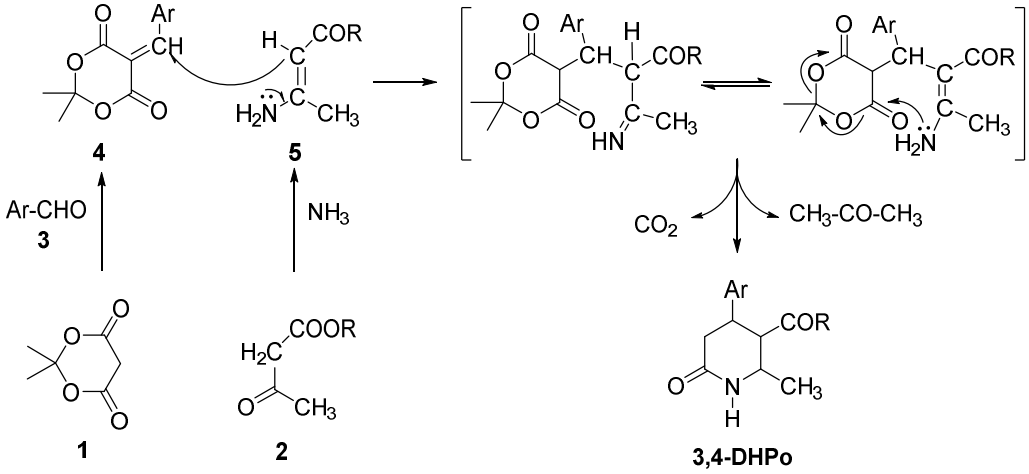


Scheme 3. Proposed reaction mechanism for **3,4-DHPo** synthesis.

3. Synthetic strategies

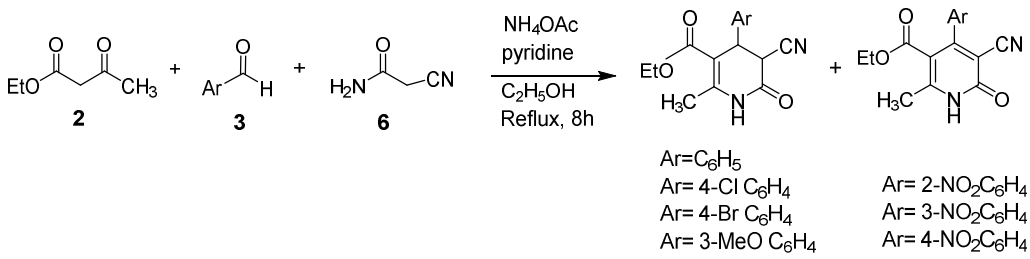
Different strategies have been reported to obtain **3,4-DHPo**, conventional synthesis with or without solvent, using different energy resources such as microwave, ultrasound, and infrared, to improve the yield and develop green chemistry reactions. Additionally, solid-phase organic synthesis (SPOS) and liquid phase synthesis (LPS) on soluble polymers as supports have been developed. Finally, chemoenzymatic to asymmetric synthesis has also been established.

3.1. Conventional Synthesis

The first strategy used to obtain the **3,4-DHPo** involved the Multicomponent Reaction (MCR) using equimolecular amounts of starting compounds under ethanol reflux for six hours, allowing the synthesis of 3,4-DHPo derivatives with a 15-26% yield[21]. One year later, Zayed et al.[22] reported the synthesis of two **3-CN-DHPo** with 51-70% yield from pyran derivatives previously synthesized.

The Suárez group has improved the efficiency of this MCR procedure, replaced the ethanol with acetic acid, allowed moderate to high yields (**Error! Reference source not found.**)[17–19],[23–30]. The best results are due to the catalytic effect and the higher boiling point of acetic acid, which improve the decarboxylation step and increase the yields compared to those previously reported[21].

An efficient one-pot synthesis of polysubstituted dihydropyridones derivatives was reported by Khazaei & Anary-Abbasinejad.[31] The reaction was done using cyanoacetamide (**6**), aryl aldehydes derivatives (**3**), ethyl acetoacetate (**2**), and ammonium acetate (**4**) and using pyridine in ethanol as solvent, and under reflux, conditions obtaining 54-68 % of yields (**Error! Reference source not found.**). The advantage of this method is the use of neutral conditions and the facility of mixing reagents without any previous activation or modification.



Scheme 4. Synthesis of polysubstituted dihydropyridones derivatives.

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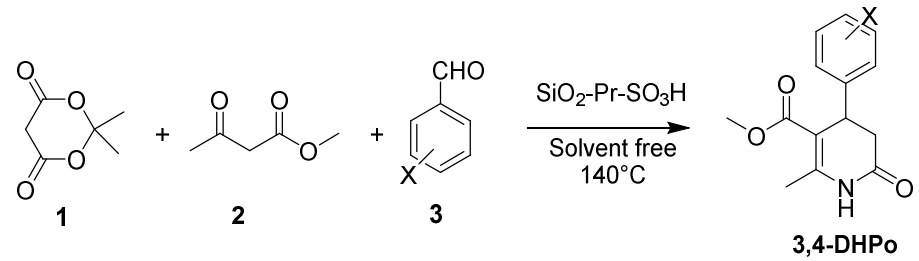
An improvement of this method was reported by Dehghan *et al.* They used similar general conditions, introducing some variations.[32] The researchers changed ammonium acetate to ammonium carbonate and did not use pyridine. Additionally, they also used and compared ethanol and water as reaction solvents. A significant yield improvement was obtained in water (90-96%) compared with ethanol (55-75%).

Furthermore, a new one-pot four-component synthesis of 3,4-dihydro-2-pyridone derivatives (**3,4-DHPo**) was reported by Hakimi *et al*. The reaction of Meldrum's acid (**1**), methyl acetoacetate (**2**), benzaldehyde derivatives (**3**), and ammonium acetate and using SiO_2-Pr-SO_3H as an efficient catalyst under solvent-free conditions was reported (Scheme 5).[33] The advantages of this methodology are high product yields (78-93%), environmentally benign, short reaction times, and easy handling.



X = H, 3-NO_2, 4-OMe, 2-OMe, 4-Cl, 2,4-$(OMe)_2$, 2,4-Cl_2

Scheme 5. Synthesis of 3,4-DHPo derivatives using SiO_2-Pr-SO_3H as the catalyst.

Moreover, the synthesis of 3,4-dihydro-2H-chromeno[4,3-b]pyridine-2,5(1*H*)-dione derivatives using 4-hydroxycoumarin, an aromatic aldehyde, ammonia, and Meldrum's acid under refluxing with 1-propanol has also been published.[34]

Li *et al.* reported the synthesis of **1,4 DHPs** derivatives with the precursor ethyl 4,4,4-trifluoro-3-oxobutanoate and a short report with the brominating of **3,4 DHPo** using *N*-bromosuccinimide.[35],[36] The reaction of α-hydroxyketene-(*S, S*)-acetals and active methylenes to obtain 3,4 DHPo derivatives was also reported.[37] Razdan *et al*. reported the synthesis of 3,4-dihydro-2-pyridones, using Bi(III) nitrate immobilized on neutral alumina as the catalyst, in the presence of co-catalyst of Zn (II) chloride with 79-88% yield.[38]

On the other hand, fluorinated **DHPo** derivatives synthesis has also been developed. For example, Song *et al*. reported the synthesis of 3-aryl-4-unsubstituted-6-CF_3-pyridin-2-ones and ethyl 2-hydroxy-6-oxo-4-aryl-2-(trifluoromethyl)piperidine-3-carboxylate as essential building blocks for the construction of trifluoromethylated heterocycles, and study the effect of base and solvents in the reaction obtained 0-93% of yields.[39,40]Also, Smits *et al*. published the formation of fluorous 3,4-dihydro-2(1*H*)-pyridone-5-carboxylate as a cationic amphiphile. **3,4-DHPo** moiety plays a key role as a scaffold for attaching cationic head groups.[9]

Instead, Dostanic *et al*. published about the synthesis of (substituted phenylazo)-pyridones in the presence of KOH and acetone to obtain 11-61% yield. [41] These were used dyeing polyester fabrics as yellow dyes. Another report described the synthesis of 3,4-dihydropyridones derivatives in the presence of Cs_2CO_3 and toluene with 53-66% yield.[42] The synthesis of aza- analogs of **3,4-DHPo** with anticancer activity was reported by Bariwal *et al*. using benzoylacetone, substituted aldehyde, urea, or thiourea with HCl and ethanol as a solvent with 55-77% yield.[43]

Besides, the conventional reaction has been improved by using different catalysts. Zhiqiang *et al*. reported a three-component cascade reaction to achieve **3,4-DHPo** derivatives using imidazole as a catalyst with ethylene glycol as solvent.[44] Bhattacharyya *et al*. reported a greener method to obtain **3,4-DHPo** derivatives using a one-pot multicomponent reaction in aqueous media catalyzed by nanostructured ZnO. [45] Also, Khazaei *et al*. used ZnO nanoparticles to give **3,4-DHPo** derivatives under ethanol as solvent.[43] Ziarani *et al*. published the synthesis of **3,4-DHPo** derivatives by sulphonic acid-

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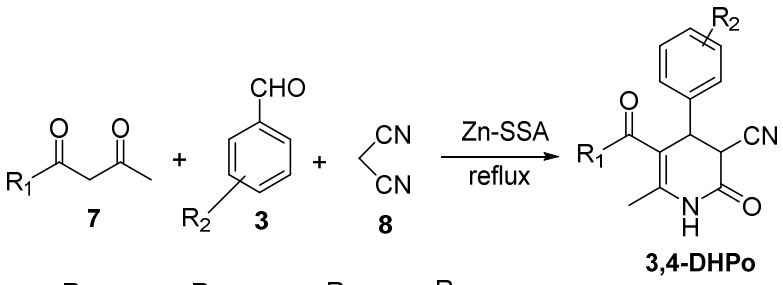
functionalized ordered nanoporous SBA-15 as a nano heterogeneous catalyst via one-pot four-component reaction under solvent-free conditions.[46] Also, Pradhan *et al*. presented green protocols to achieve 3,4-DHPo derivatives using two catalysts such as the vitamin B1or PEG–SO_3H in water as solvent.[47] All these described reactions showed moderate to good yields. Besides, those reactions where a catalyst attached to solid or polymeric supports show better results due to the possibility of the most efficient purification procedures.

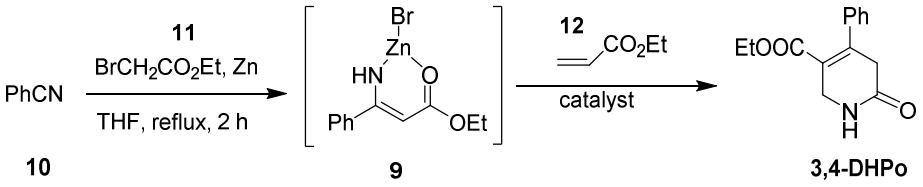
Zhang *et al*. reported the synthesis of 5-cyano-2-pyridinone catalyzed by Zn-SSA. The silica sulfuric acid (SSA) was modified with zinc chloride to form the novel catalyst (Zn-SSA), which improved the chemo-selectivity in the reaction.[48] The synthesis was developed using 3-dicarbonyl compounds (**7**), malononitrile (**8**) and arylaldehyde (**3**), and solvent-free conditions (Scheme 6).



R_1	R_2	R_1	R_2
OEt	4-OMe	OEt	3-NO_2
OMe	4-OMe	OEt	4-NO_2
OEt	H	Me	H
OMe	H	Me	2-NO_2
OMe	3-NO2	Me	4-NO_2
		Me	4-Cl

Scheme 6. Synthesis of 5-cyano-2-pyridinone using Zn-SSA as catalyst.

The synthesis of 3,4-dihydropyridine-2(1*H*)-ones catalyzed by $ZnBr_2$, $FeCl_3$, $AlCl_3$, BF_3, $Cu(OTf)_2$, $In(OTf)_2$, and BF_3 OEt_2 was reported by Meng *et al.*[49] This method was developed via Blaise reaction forming a cyclic intermediate (**9**) from benzonitrile (**10**) and Reformatsky reagents, which was generated *in situ* from ethyl bromoacetate (**11)** and zinc power in ethyl acrylate (**12**) and tetrahydrofuran with 0-81% yield (Scheme 7).



Scheme 7. Synthesis of 3,4-dihydropyridin-2-ones catalyzed by $ZnBr_2$, $FeCl_3$, $AlCl_3$, BF_3, $Cu(OTf)_2$, $In(OTf)_2$, and BF_3 OEt_2.

Paravidino *et al*.[50] developed a novel four-multicomponent reaction (4CR) of phosphonate (**13)**, aldehydes derivatives (**14),** nitriles (**15)**, and α-acidic isonitriles (**16)** to obtain **3,4-DHPo** derivatives in 53–88% of yield and with complete diastereoselectivity in favor of the cis-diastereomer (Scheme 8).[50],[51]

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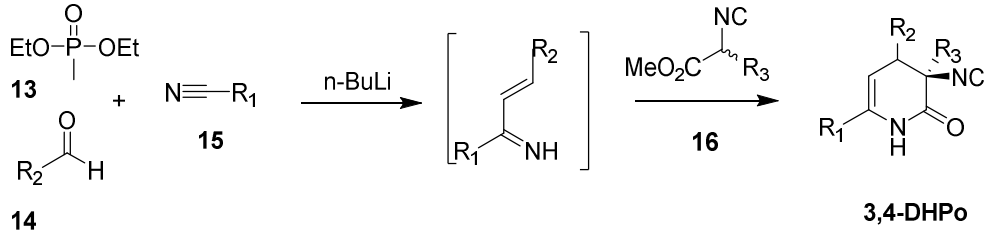
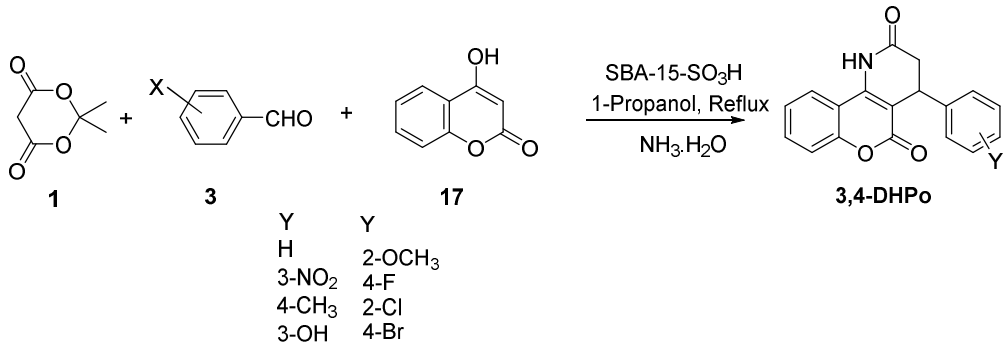


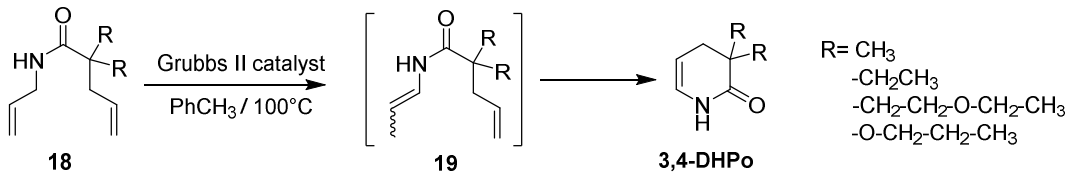
Scheme 8. Multicomponent Reaction (4CR) of phosphonate (**13**), aldehydes derivatives (**14**), nitriles (**15**), and α-acidic isonitriles (**16**) to obtain **3,4-DHPo**.

A novel four-component synthesis of 1-phenyl-1,4-dihydro-2*H*-9-oxa-4-aza-phenanthrene-3,10-dione was reported. The synthesis is done using Meldrum's acid (**1**), aromatic aldehydes (**2**), 4-hydroxycoumarin (**17**), ammonia solution, and three catalysts p-toluenesulfonic acid, Amberlyst-15, and SBA-15-SO_3H, which is the best catalyst giving 78-88% yield. The advantages of this method are the short periods and high yield (Scheme 9).[52]



Scheme 9. Multicomponent Reaction (4CR) of Meldrum's acid (**1**) and aromatic aldehydes (**3**), 4-hydroxycoumarin (**17**) and ammonia solution to obtain 3,4-DHPo.

Another report showed the synthesis of **3,4-DHPo** derivatives via tandem olefins isomerization-RCM reaction, through the *in situ* generated intermediate **19** from readily available N-Allyl amines type **18** as dienes catalyzed by second-generation Grubbs catalyst (ruthenium catalysts) and heated to obtain **3,4-DHPo** derivatives with 57-85% yield. [53]



Scheme 10. Tandem olefins isomerization-RCM to obtain 3,4-DHPo.

The conventional synthesis has been offered a broad possibility to obtain the desired product; however non-conventional energy sources as microwave, infrared, and ultraviolet have also been incorporated to improve the efficiency of this MCR.

3.2. Non-conventional Synthesis

-Microwave-Assisted Synthesis

In the last decades, microwave-assisted organic synthesis has been used as the energy source for many known and new organic reactions. In general, its application allowed to

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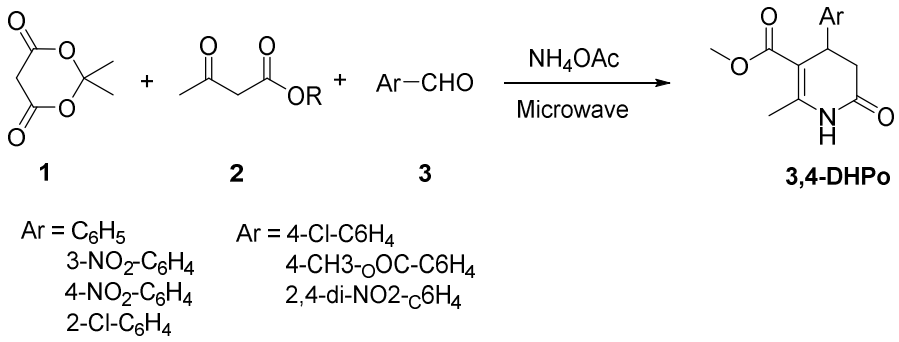
reduce reaction times, increase efficiency and in some cases, avoid or minimize the use of solvents, contributing to green procedures development.[54]

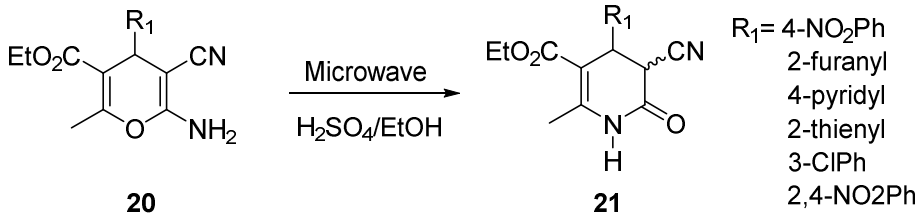
In 2003, our group reported the first solvent-free and accessible one-pot condensation reaction of Meldrum's acid (**1)** in the presence of methyl acetoate **(2)**, aldehyde derivatives (**3),** and ammonium acetate to obtained 4-aryl substituted 5-alkoxycarbonyl- 6-methyl-3,4-dihydropyridones (**3,4-DHPo**).[20] The mixtures were irradiated at controlled temperatures and times in continuous mechanical stirring, which provided a good homogeneity of materials and 81-91% yields (Scheme 11).



Scheme 11. Microwave-Assisted Multicomponent preparation (4CR) of 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**).

Afterward, another author reported the synthesis of **3,4-DHPos** derivatives with a similar technique and 70-92% yields.[55] Jaques *et al.* reported the quantitative MW-assisted synthesis of 3,4-dihydro-2(1*H*)-pyridones without solvents but in the presence of solid support as a catalyst.[56]

Besides, Hernandez *et al*. published the oxidation reaction of 4*H*-pyrans derivatives (**20)** to obtain 3-cyano-2-pyridones (**21**) in ethanol, using H_2SO_4 catalyst source and MW irradiation (Scheme 12).[57] These compounds are hybrid milrinone-enifedipine analogs.



Scheme 12. Microwave-Assisted oxidation of 4*H*-pyrans derivatives (**20**) to 3,4-Dihydro-2(1*H*)-pyridones (**21**).

This research group compared the different energy sources for oxidation, carried out the reaction at room temperature, at ethanol reflux, under infrared and microwave irradiation, obtained; 8, 72, 80, and 86% yields, respectively. Furthermore, the reaction times decreased from seven hours at room temperature until seven and five minutes for IR and MW irradiation, respectively.[57] These comparisons showed the importance of using different energy resources and their potential. Besides, ultrasound has been the other non-conventional energy source used to efficiently synthesize **3,4-DHPo**.

-Ultrasound-Assisted Synthesis

The ultrasonic activation is based on cavitation effects allowing this technique to improve the mass transfer in several organic reactions reported. In 2011, our group published the synthesis of 4-aryl 3,4-dihydropyridone derivatives (**3,4-DHPo**) by ultrasound-assisted technique, through the one-step condensation of Meldrum's acid (**1**), alkyl

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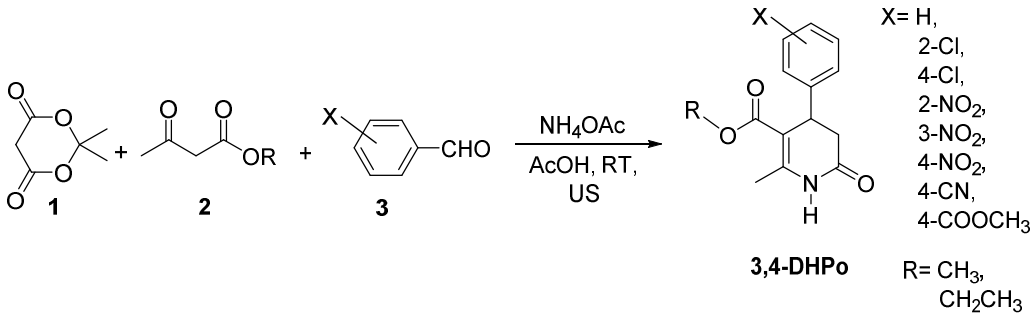
acetoacetates (**2**), aromatic aldehydes (**3**), and ammonium acetate, using glacial acetic acid as solvent, and at room temperature, obtaining high yields (Scheme 13).[58]

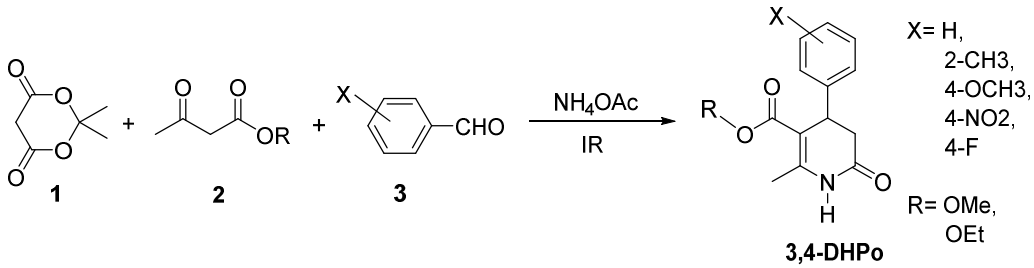


Scheme 13. Ultrasound-Assisted Multicomponent preparation (4CR) of 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**).

The main advantages of ultrasound-assisted synthesis compared to conventional synthesis are the milder conditions, the shorter reaction times, and the higher yields improve the efficiency of the organic synthesis of these heterocycles. In addition, another energy source such as the infrared assisted technique has also been explored.

-Infrared-Assisted Synthesis

Parallel to the MW-assisted synthesis design of **3,4-DHPo** derivatives, our group also reported the synthesis of 3,4-Dihydro-2(1*H*)-pyridones derivatives (**3,4-DHPo**) by infrared assisted synthesis of the same multicomponent reaction under solvent-free conditions and similar reagents with moderate yields (Scheme 14). [59]



Scheme 14. Infrared-Assisted Multicomponent preparation (4CR) of 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**).

To summarize, different energy sources have been used in the **3,4-DHPo** synthesis, allowing to obtain a broad range of products with different substituent patterns. Particularly non-conventional techniques such as MW and IR lead to high yields, short reaction times, and safe and straightforward work-up, constituting a notable improvement and involving green chemistry to synthesize these organic molecules. The support (insoluble or soluble)-assisted synthesis of **3,4-DHPo** has also been a successful development.

3.3. Solid Phase Organic Synthesis (SPOS)

One of the most commonly used techniques in combinatorial chemistry is Solid-Phase Organic Synthesis (SPOS), because it allows the rapid synthesis of many structurally diverse molecules in a short time. In 2006, our group published the first SPOS of **3,4-DHPo** derivatives following a solid-support assisted synthetic strategy (Scheme 15). [60] The immobilized acetoacetate (**22**) was obtained by reaction of 2,2,6-trimethyl-1,3-dioxin-4-one (**1**), and Wang resin (0.92 mmol OH/g), the further reaction of **22** in the presence of NH_4OAc and HOAc led to the corresponding immobilized enamine (**23**), which reacted with the Knovenagel derivatives (**24**) to afford the expected immobilized **3,4-DHPo** (**25**). The heterocycle was cleaved from the resin with 71-85% overall yield (Scheme 15).[60]

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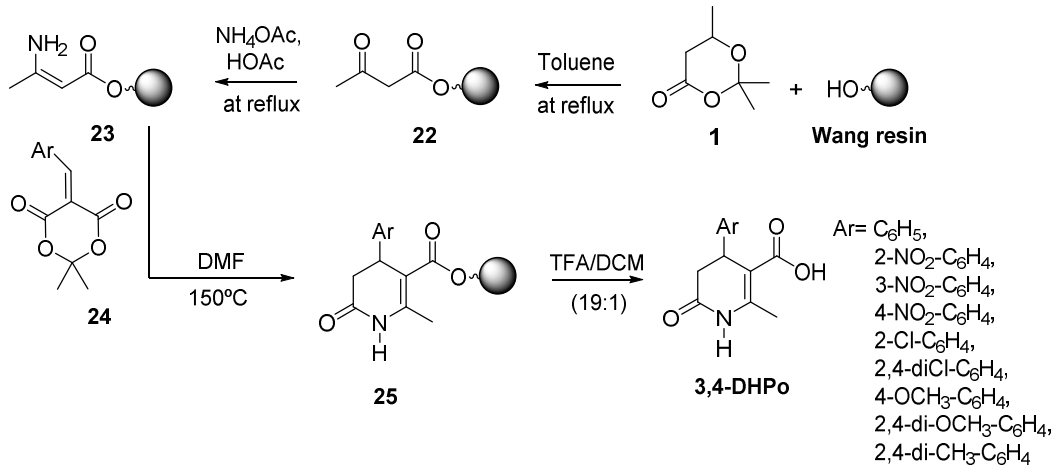
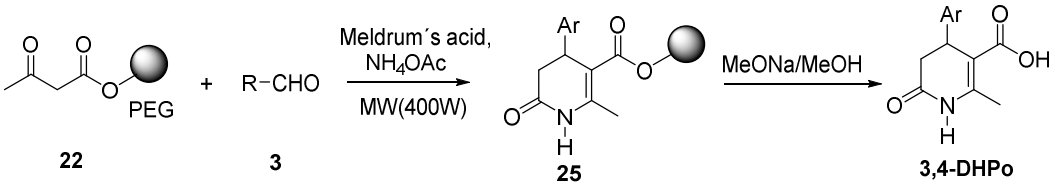


Scheme 15. SPOS of 3,4-Dihydro-2(1*H*)-pyridones derivatives (**3,4-DHPo**).

This technique has been used in response to the increment of target molecules synthesis to combinatorial chemistry. SPOS of **3,4-DHPo** derivatives synthesis presents good results and opens the way to synthesize other molecules with biological activity. Additionally, the synthesis of **3,4-DHPo** derivatives using soluble polymers as support has also been studied.[61]

3.4. Liquid Phase Organic Synthesis (LPOS)

The employ of soluble polymers as supports in organic synthesis is known as liquid-phase synthesis. In 2008, Fu *et al*.[62] reported the liquid-phase synthesis of 4-substituted-5-methoxycarbonyl-6-methyl-3,4-dihydropyridones on polyethylene glycol (PEG) 4000 assisted by MW irradiation (Scheme 16). First, the acetoacetylation of PEG was realized to obtain the immobilized acetoacetate (**22**), further condensation of PEG bound acetoate with aldehyde derivative (**3**), Meldrum's acid in the presence of ammonium acetate and solvent-free by microwave irradiation was obtained the immobilized 3,4-DHPo (**25**), the target compound **3,4-DHPo** was obtained after cleavage using NaOMe in MeOH with 88-95% yield.



Scheme 16. LP-MW assisted of 3,4-Dihydro-2(1*H*)-pyridones derivatives (**3,4-DHPo**).

The LPS of **3,4-DHPo** derivatives showed excellent results and improved the overall results with the solid phase, allowing the one-step condensation, which was not possible in the SPOS procedure. On the other hand, all synthesized **3,4-DHPo** showed at least one chiral center at C4, and all previously reported procedures allowed to obtain the corresponding racemic mixtures. Hence, efforts have been made to search for the chemo-selective synthesis of these derivatives.

3.5. Asymmetric Synthesis

The **3,4-DHPo** structure is closely related to the configuration of its chiral center at C4, and it brings biological activity. The chemoenzymatic synthesis can search the specific chiral center configuration, and at the same time, use an eco-friendly procedure. Torres et al.[63] reported the chemoenzymatic preparation of a series of racemic 4-aryl-5-(tert-butoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridones (**26**) using several combinations

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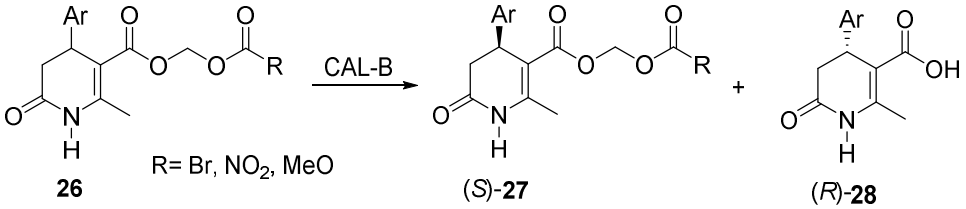
of lipases (PSL, CRL, CAL-A, and CAL-B) and organic solvents such as 1,4-dioxane, DIPE, TMBE. The authors improved the enzymatic hydrolysis of *R*-diesters (**28**) derivatives, making subsequent S-enantiomer (**27**) separation viable by acid-base extraction procedures (Scheme 17). An improvement of this methodology was made by the chemoenzymatic preparation of optically active phenolic 3,4-dihydropyridin-2-ones [64]

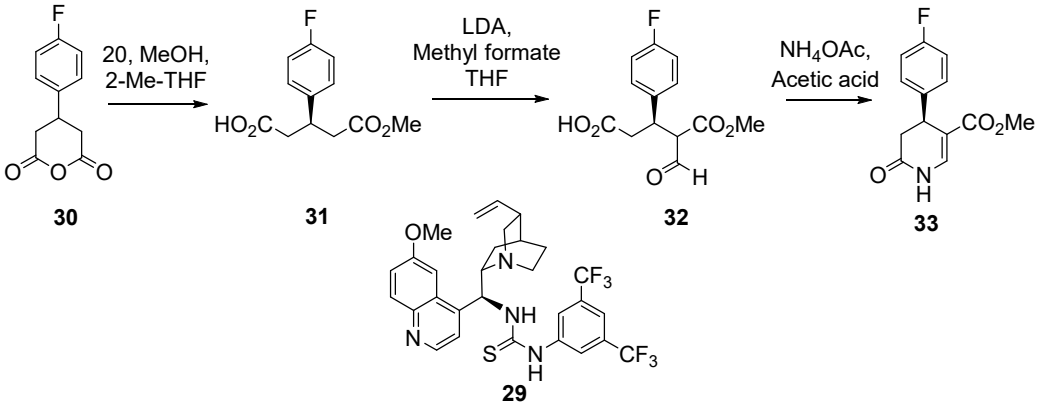


Scheme 17. Chemoenzymatic preparation of optically active phenolic 3,4-dihydropyridin-2-ones (**3,4-DHPo**) through hydrolysis of diesters.

Another enzymatic multicomponent reaction (EMCR) was reported using benzaldehyde, cyanoacetamide, ketone, and Acylaze Amano (AA)- catalyzed. This single enzymatic catalyzed reaction is attractive due to its high atom economy, easy workup process, the tolerance of a wide range of substituted reagents (benzaldehyde and ketones), and about all mild conditions.[65]

The best result was shown in the enzymatic hydrolysis of 4-aryl-5-(tert-butoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridones with CAL-B enzyme and TMBE as a solvent to obtain high ee(93-95%) and moderate yields (30-31%) of (S)-derivative (**27)**.

On the other side, Huang *et al*. reported the first asymmetric synthesis of **3,4-DHPo** derivatives (Scheme 18).[66] The formation of monoacid (*R*)-**31** was carried out by desymmetrization or asymmetric methanolysis of prochiral anhydride (**30)** using the organocatalyst **29**, 2-Me-THF, and MeOH as solvents gave. The conversion was 100%, and the best-observed ee 80%. The next step was the selective formylation to obtain the intermediate **32,** and finally, the cyclization of **32** with ammonium acetate using acetic acid achieve the final product (R)-**33**, with an overall yield of three steps 48% and >95% *ee* (Scheme 18).[66] The same group also reported the pilot-scale enantioselective synthesis of **33** and kilogram-scale production of *N*-methyl derivative of **33** in an excellent overall yield ~22% and excellent stereochemical purity (97% *ee*).[13]



Scheme 18. Asymmetric synthesis of (*R*)-3,4-DHPo derivatives (**3,4-DHPo, 33**).

Wanner *et al*. published the enantioselective synthesis of (*R*)-**3,4-DHPo** through *N*-Heterocyclic carbene (NHC)-catalyzed aza-Claisen reaction of enal (**36)** and enamine (**37)** in the presence of N-mesityl catalyst (**34)** and oxidant (**35)**, the better bases were DBU, NMM, and i-Pr2Net showed higher enantioselectivity with 60% to quantitative yields, and 79-96% of enantiomeric excess (Scheme 19).

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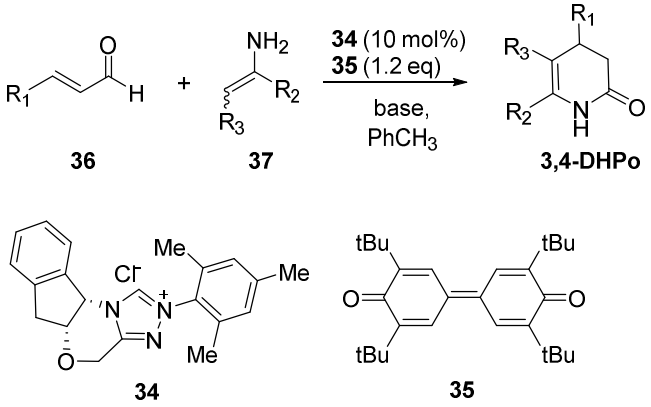
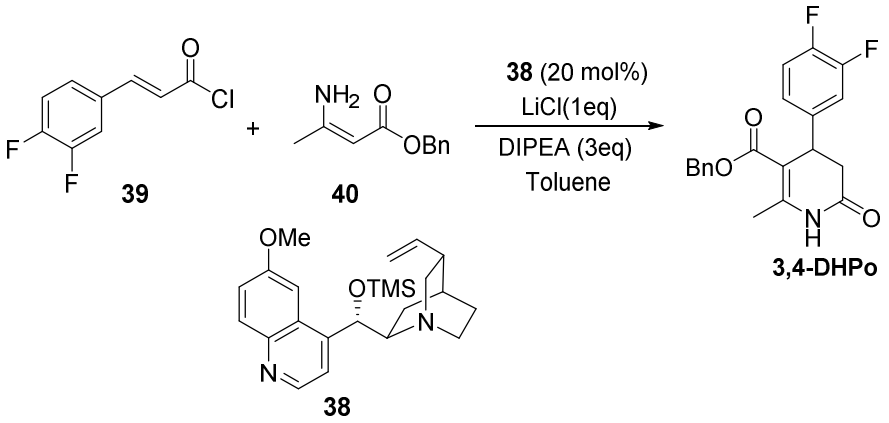


Scheme 19. Asymmetric synthesis of optically active 3,4-dihydropyridin-2-ones ((R)-**3,4-DHPo**) through *N*-Heterocyclic carbene (NHC)-catalyzed aza-Claisen reaction.

Vellalath *et al*. described the enantioselective nucleophile catalyzed Michael/proton transfer/lactamization cascade with 3,4-difluorocinnamoyl chloride (**39)** and the enamine (**40)** in the presence of **38** as a catalyst with a nonpolar solvent and LiCl as an additive which affected enantioselectivity, this mild process delivered 3,4-DHPo derivative in 78% yield and 92% *ee* (Scheme 20).[67]



Scheme 20. Asymmetric synthesis of optically active 3,4-dihydropyridin-2-ones ((R)-**3,4-DHPo**) through Michael/proton transfer/lactamization cascade.

As time went on, different strategies have been developed to obtain **3,4-DHPo** derivatives in higher yields. Nevertheless, a broad range of methodologies described shows the importance of these heterocycles, not only because of their biological activity but also because they are crucial starting materials for synthesizing other more complex entities.

4. Structural Characterization

The structure of 3,4-Dihydro-2(1*H*)-pyridones has been determined for physical and analytical techniques such as melting point (Table 1), ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry (electron impact (EI), and electrospray ionization (ESI)), and X-ray. These techniques allowed to obtain a broad range of databases of physical properties to synthesized **3,4-DHPo**. [20,28,59,68].

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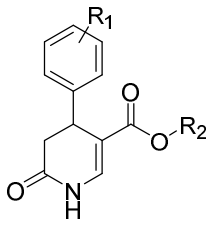
Table 1. This is a table. Tables should be placed in the main text near to the first time they are cited.



3,4-DHPo

R_1	R_2	MP (ºC)	Ref.	R_1	R_2	MP (ºC)	Ref.
4-Cl	Me	202-203	[16]	4-CN	Me	259-260	[50]
4-CH_3	Me	186-187		4-$COOCH_3$	Me	186-187	
2,4-di-NO_2	Me	212-213		4-Cl	Et	178-179	
				4-CN	Et	169-170	
				4-$COOCH_3$	Et	189-190	
H	Me	181-182	[24]	H	OMe	197-198	[51]
2-NO_2	Me	178-180		H	OEt	168-171	
3-NO_2	Me	212-214		4-F	OMe	206-208	
4-NO_2	Me	190-192		4-F	OEt	184-486	
2-Cl	Me	196-198		4-NO_2	OMe	200-202	
3-pyridyl	Me	199-201		4-NO_2	OEt	130-133	
H	Et	201-202		2-CH_3	OMe	Oil	
2-NO_2	Et	198-200		2-CH_3	OEt	Oil	
3-NO_2	Et	225-227		4-OCH_3	OMe	180-183	
4-NO_2	Et	251-253		4-OCH_3	OEt	185-188	
2-Cl	Et	210-212		p-CHO	OMe	Oil	
3-pyridyl	Et	217-219		m-CHO	OEt	Oil	

The technique most used in the characterization of **3,4-DHPo** derivatives has been ^{1}H-NMR spectroscopy, allowing us to corroborate the ring formation through the ABX pattern, as was explained by our group,[69] which showed the protons H1, H3a, H3b, and H4 of heterocycle ring (Table 2, Figure 4).

Electron impact (EI) and electrospray ionization (ESI) have been also used to characterized the **3,4-DHPo**. Our group reported the fragmentation patterns of the even-electron ions formed under ESI conditions and the odd-electron ions generated under EI conditions from substituted **3,4-DHPo**. [20] The characteristic pattern of fragmentation under EI conditions was also established (Scheme 21). [65]

Under ESI conditions, molecular ions $[M+H]^+$ and $[M-H]^-$ were observed, corresponding with the positive and negative modes. Additionally, some structures were proposed to explain the fragment ions found in the spectra (Scheme 22 and 23).

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Table 2. ^{1}H-NMR spectroscopy, ABX pattern of **3,4-DHPo** derivatives (δ, ppm; *J*, Hz).

H_1	H_{3a}	H_{3b}	H_4
9.90 (s)	2.39 (d)	2.92 (dd)	4.12 (d)
	J =16.2	*J* =16.2, *J* =7.2	*J* =7.2

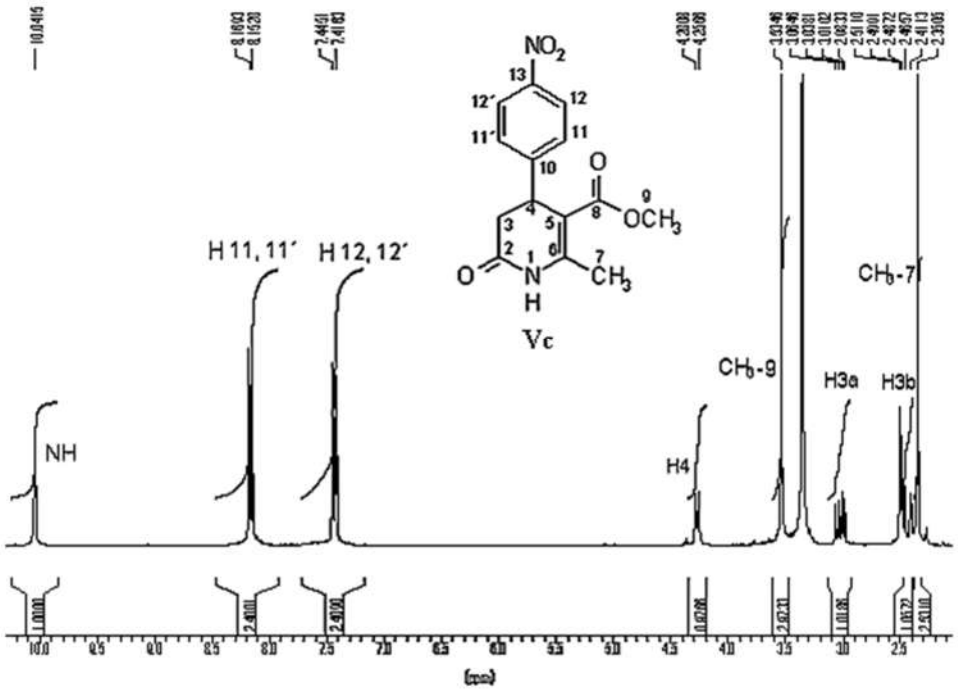
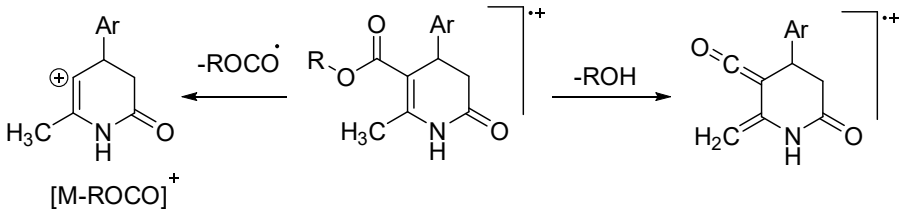


Figure 4. ^{1}H-NMR spectrum of 6-methyl-5-methoxycarbonyl-4-(4'-nitrophenyl)-3,4-dihydro-2(1H)-pyridone.



Scheme 21. Fragmentation pattern of 3,4-DHPo derivatives established under EI conditions.

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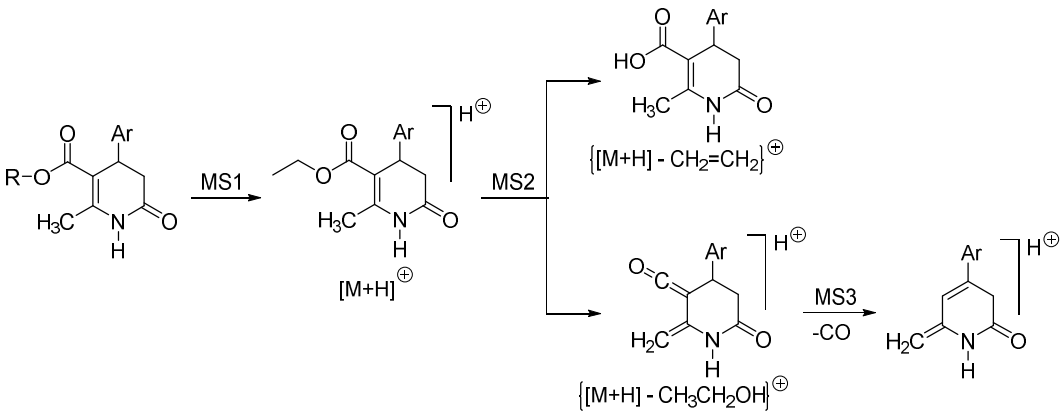
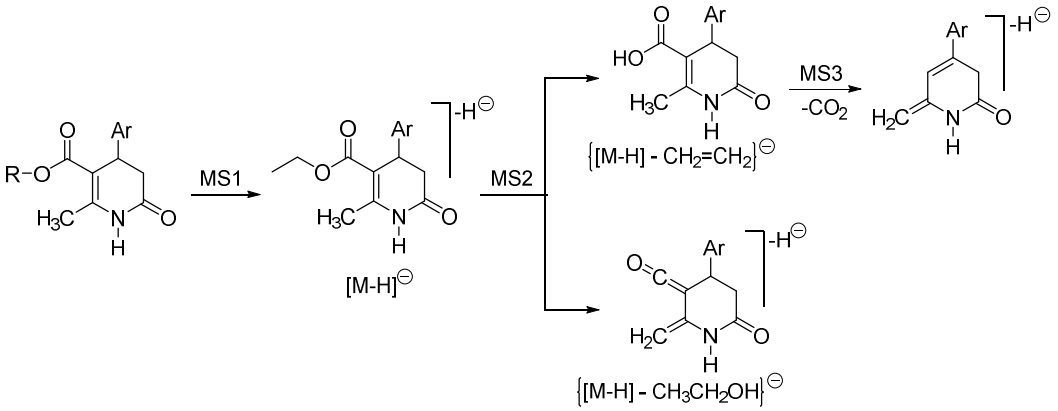


Scheme 22. Fragmentation pattern of **3,4-DHPo** derivatives established under ESI positive mode.



Scheme 23. Fragmentation pattern of **3,4-DHPo** derivatives established under ESI negative mode.

Different authors have confirmed the structure of **3,4-DHPo** with different substituents by X-ray diffraction,[17,29,30]·[70–74]semiempirical (AM1) calculations,[25] NMR spectroscopic including NOE experiments, and coupling constants to determinate the structural conformation in solution.[17]

There are some structural requirements to the **3,4-DHPo** derivatives conformation, such as the absolute configuration at C-4 (*R- versus S*-enantiomer) acting as a molecular switch, the substituted phenyl ring occupies an axial position perpendicularly bisecting the boat-like **DHPo** ring in a synperiplanar orientation, and the *cis-carbonyl* ester orientation concerning the olefinic double bond.[17] The semiempirical (AM1) calculations and NOE experiments defined two conformational structures; a first presents the aryl substituent at C-4 extended in a pseudoaxial position, and a second in which the aryl substituent is in a pseudoequatorial position, besides, the first conformation was 2-4 kcal/mol more stable than second structure. In both arrangements, the pyridone ring presented a twisted boat.[17,19,23,24] The X-ray studies confirmed the the pseudoaxial disposition (Figure 5), which was stable in a solid-state after the crystallization of ethanol.[17]

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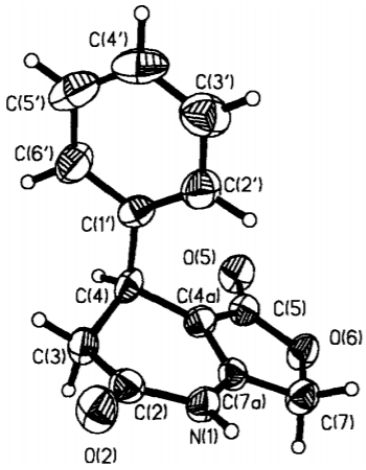

Figure 5. Crystallographic structure of 3,4-DHPo adapted from Ochoa et al. [17.]

5. 3,4-Dihydro-2(1H)-pyridones (3,4-DHPo) as synthetic precursors

Over time the **1,4-DHP** and **3,4-DHPo** cores have served as scaffolds for the relevant design of more complex entities with various biological activities.

The effort to improve the synthesis of **1,4-DHP** with a broad range of substitution patterns gave rise to 3,4-DHPo as crucial intermediaries. For example, **3,4-DHPo** were converted to the aromatics 4-(3-nitrophenyl) pyridines (Figure 6a),[75] and to alkyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate derivatives (Figure 6b) by reaction with the Vilsmeier–Haack reagent. **3,4-DHPo** and the 6-chloro-5-formyl-1,4-**DHPs** (Figure 6b) have become versatile intermediaries of other compounds (Figure 6).[26–28,76–82]

Starting from **b**, more complex structures have been synthesized. 1,5-benzodiazepine fused to a dihydropyridine moiety (Figure 6c) have been prepared, and one derivative (**JM-20**, Figure 6c) has shown promising neuroprotective and antioxidant properties.[83–86] Besides, [3,4-b]pyridines derivatives (Figure 6d) were obtained by treatment of **b** with hydrazine hydrate. Fulleropyrrolidines endowed with chlorine-containing biologically active 1,4-dihydropyridines (**1,4-DHPs**)(Figure 6e) were also prepared using Prato's procedure.[87,88] The chloro-formyl derivative b also allowed to obtain 1,4-dihydropyridines (1,4-DHPs) bearing a semicarbazone moiety on C5 (Figure 6f)[89] and iminium salts of dihydropyrido[3,2-e][1,3]thiazines (Figure 6g).[90]

The **3,4-DHPo** has been used as an intermediate for the formation of β-lactams derivatives through photochemical cycloaddition (Figure 6h).[91] Besides, this heterocycle has been incorporated in the diastereoselective synthesis of 3-Oxo-14,15-dihydroandranginine, a unique indole alkaloid with an unusual ring system that includes a tetrahydroazepine unit condensed with an hexahydroquinoline entity in a *trans-trans* fashion (Figure 6i).[33] The α_{1a} receptor antagonist from **3,4-DHPo** was also synthesized, and its efficacy was demonstrated in a screen of prostate contraction model in rats (Figure 6j).[11]

Indazole amide (Figure 6k)[11] was also prepared through saponification of the ester provided by **3,4-DHPo**, which smoothly underwent coupling with an indazole to give close pyridine analogs derivatives with different aryl groups. Thus, imidazole amide is an interesting structure with a selective ROCK1 inhibition. Moreover, a series of isoxazolo[5,4-b]pyridin-6(7H)-ones (Fig. 8l)[19] have been synthesized by the reaction of novel 3,4-dihydro-2(1*H*)-pyridones with hydroxylamine hydrochloride and following 5-endo-trig cyclization. Additionally, 3,4-DHPos is an intermediate for the synthesis of Furo[3,4-b]- 2(1H)-pyridones (Figure 8m)[17,25,92], which act as potential Calcium channel modulators.

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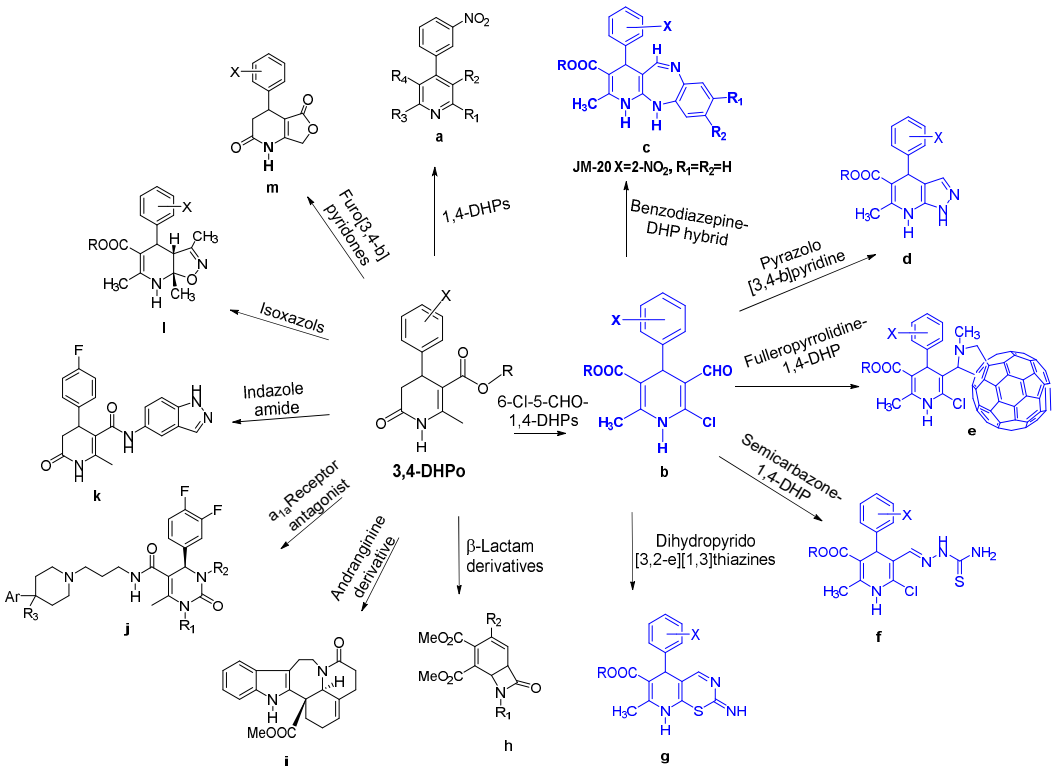
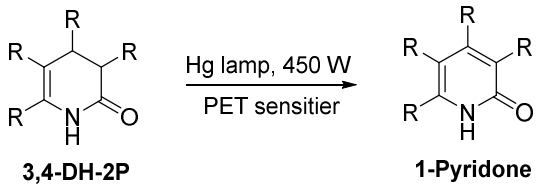


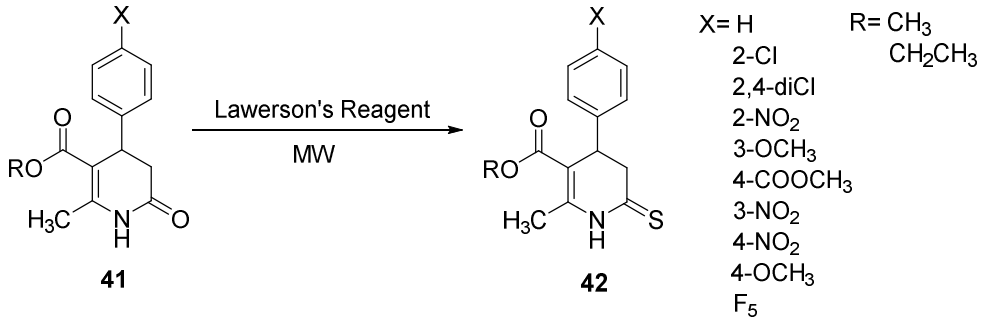
Figure 6. 3,4-Dihydro-2(1*H*)-pyridones (**3,4-DHPo**) as synthetic precursors.

Sadhu *et al*. report an efficient way for the photochemical dehydrogenation of various substituted **3,4-DHPo** to get 2-Pyridone derivatives in excellent yields (83-97%) using different photoinduced electron transfer (PET) sensitizers (Scheme 24).[93]



Scheme 24. Photochemical dehydrogenation of substituted **3,4-DHPo**.

Lawesson's reagent has been widely used as a powerful, mild, and versatile reagent for transforming carbonyl functionalities into their thio analogs. Our group reported the synthesis of 4-aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates (**41**) with a 29-93% yield. The thionation of **3,4-DHPo** was carried out in a one-step procedure of the **3,4-DHPo** derivatives (**42**) by exposure to microwave irradiation under solvent and free-solvent conditions (Scheme 25). [94]



Scheme 25. Transforming of **3,4-DHPo** carbonyl group into their thio-analogs by MW irradiation.

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In 2011 our group reported the preparation of *N*-Heterocycles using non-conventional synthesis as an eco-friendly approach to producing heterocyclic nitrogen compounds starting with **DHPo**. MW-assisted synthesis (MWAS) of alkyl 4-arylsubstituted-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylates (**44)** and 4-arylsubstituted-4,7-dihydrofuro[3,4-*b*]pyridine-2,5(1*H*,3*H*)-diones (**45)** from **3,4-DHPo's** (**43**) were reported **(**Figure 7).[95] US-assisted synthesis (USAS) was also used to obtain chloroformyl derivatives from **3,4-DHPo's** as starting materials (Figure. 7). [27] MWAS and USAS showed higher yields in shorter reaction times and milder conditions.

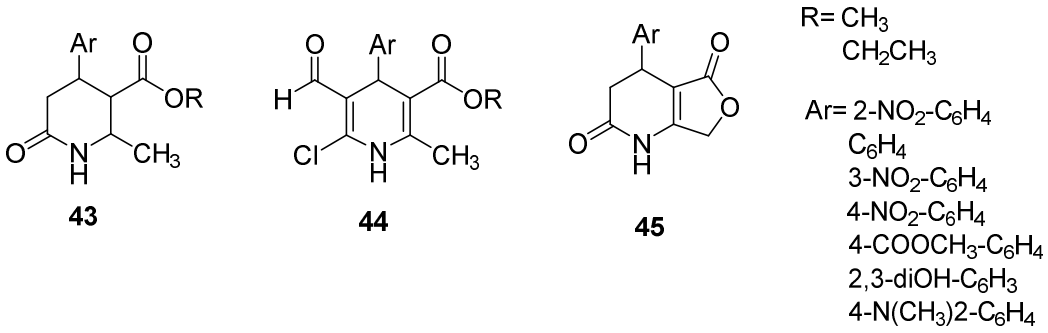


Figure 7. N-Heterocycles prepared using non-conventional synthesis, MWAS and USAS.

Ueyama *et al*. identified the **3,4-DHPo** derivative **46** as a degradation product of Azelnidipine (**47**) after radical initiator-based oxidative conditions (Figure 8).[96]

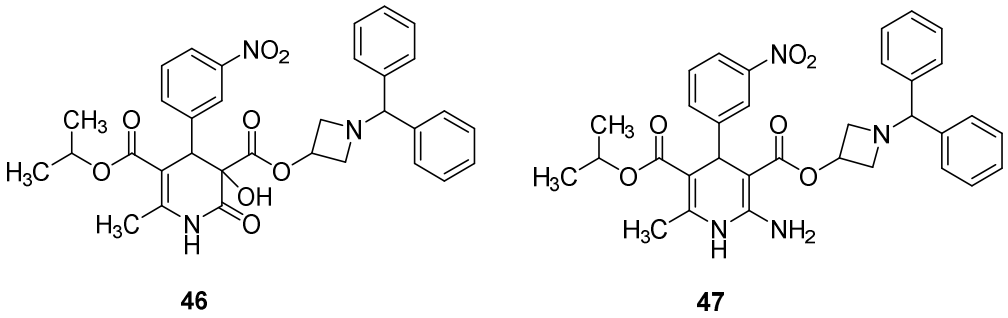
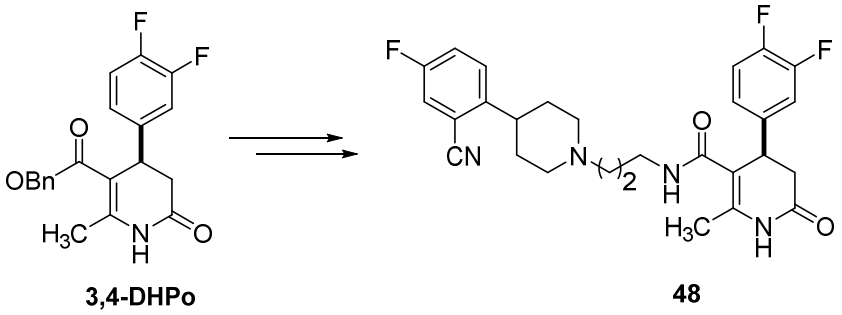


Figure 8. 3,4-DHPo derivative (**46**) obtained from the degradation of Azelnidipine (**47**).

3,4-DHPo has been used as an enamine precursor to obtaining nitrogen heterocycles like dihydropyridinones by applying the nucleophile-catalyzed Michael/proton transfer/lactamization (NCMPL) cascade, allowing the total synthesis of α_{1a} adrenergic receptor antagonist (**48**) (Scheme 26). [67]



Scheme 26. 3,4-DHPo as the synthetic precursor of dihydropyridinone (**48**).

Quinolizin-4-ones (**50)** have been prepared from 6-ciano-**3,4-DHPo's** derivatives (**49**) with low to high yields (20-90%) through allylation/intramolecular Heck reaction

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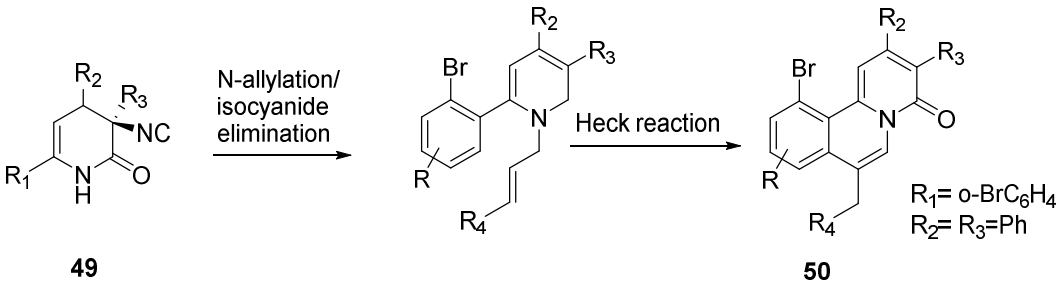
sequence (Scheme 27). Quinolizin-4-ones showed attractive biological activities related to CNS diseases, including Alzheimer's.[43]



49 50

Scheme 27. Quinolizin-4-ones prepared from 6-ciano-**3,4-DHPo's** derivatives.

6. Biological activity

DHPos and its derivatives possess a wide variety of biological activities such as vasorelaxant[57], reverse transcriptase inhibition of human immunodeficiency virus-1[5,97],84, Rho-kinase inhibitors[12], anticancer[3], antibacterial[4], human rhinovirus 3C protease inhibitors[6,7], urease inhibitors[99], antifungal activity[100], glycine/NMDA receptor inhibitor[8], and as cellular transport.[9]

-Vasorelaxant activity

The regulation of blood pressure depends on vascular tone. In addition, nitric oxide (NO) is an excellent vasodilator molecule, but a low production of endothelium-derived NO cause a diminish in vasodilator tone. This increases vascular resistance, which contributes to elevated blood pressure.[101] Therefore, various research groups are focused on finding compounds with vasorelaxant activity. A recent study demonstrates that 3-cyano-pyridin-2-ones (Figure 9) show a significant vasorelaxant. Three of them are the most potent and revealed an endothelium-independent effect.

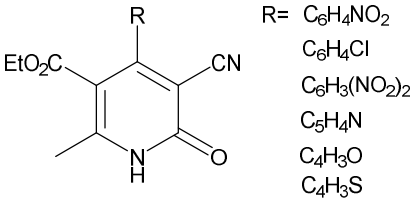


Figure 9. 5-cyano-pyridin-2-ones with vasorelaxant activity.

In addition, 3-cyano-2-pyridone derivatives were synthesized as calcium channel blockers and probable PD3 and PD4 inhibitors, taken as comparison; nifedipine for L-type calcium channel blocker, milrinone and amrinone for PD3 and PD4 inhibition. These compounds also have antihypertensive and vasorelaxant activity.[57]

- HIV-1 inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) play an essential role in treating HIV infections. They have been used as the main target in the attack against this virus, and most of them present butterfly-like conformation.[97,98] This conformation facilitates the intramolecular interactions between receptor and ligand. The NNRTI interacts specifically with the HIV reverse transcriptase (RT) substrate-binding site and inhibits its replication. Pyridone derivatives act in this way due to their favorable conformation. Hence they are highly active against HIV-1. Parreira et al. reported a series of 22 **DHPo** derivatives like **51** (Figure 10), which are inhibitors of HIV-1.[97] In 2001, it synthesized 32 **DHPo** and proved their HIV-1 inhibitor activity; one of these compounds (**52**) (Figure

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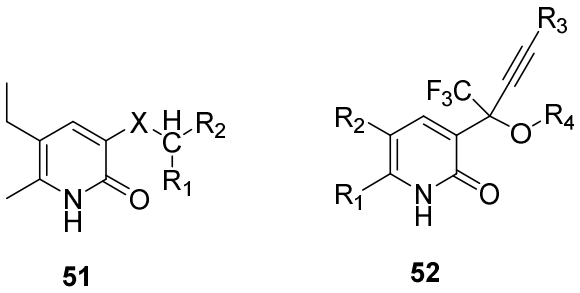
10) showed higher activity.[102] Additionally, another research group described the use of pyridines cocktails to attack viral variants that exhibit drug resistance.[97]

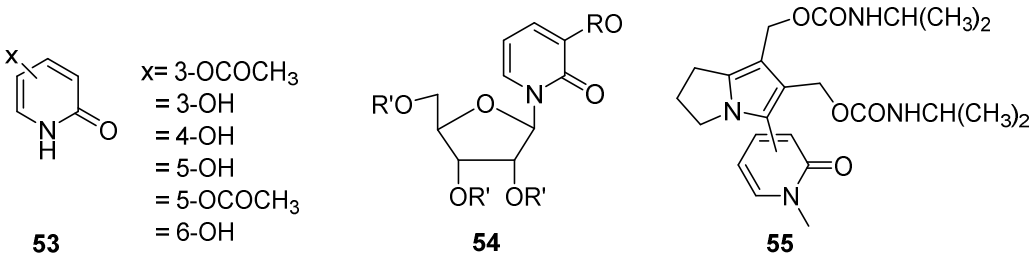


51 **52**

Figure 10. 3,4-DHPo with HIV-1 inhibitor activity.

- Antitumor activity

Several **DHPo** have emerged during the last twenty years with potent antitumor activity. They have been mainly tested against P388 lymphocytic leukemia cells demonstrating a potential antitumors.[103,104] Oxygen-containing functional groups play an essential role in P388 activity; at least two groups are required. Hwang and Driscoll reported a series of compounds (**53**) with high activity (Figure 11). [103] Additionally, 3-Hydroxy-2-pyridone Nucleosides (**54**),[104], and a series 2- pyridones (**55**) were reported (Figure 11).[3] These studies demonstrate the potential utility of 3,4-Dihydro-2(1*H*)-pyridones as building blocks in drug design.



53 **54** **55**

Figure 11. 3,4-DHPo with antitumor activity.

- Antibacterial and antifungal activity

DHPos derivatives present favorable properties as antibacterial agents against multidrug-resistant bacteria such as streptococci and anaerobic microorganisms.[4] In 2018, in vitro antimicrobial activity was reported in some 4-(biphenyl-4-yl)-1,4- dihydropyridine and 4-(biphenyl-4-yl)pyridine derivatives, followed by molecular docking and DFT studies.[105] Ahamed et al. have tested in *vitro* antibacterial activity of some 1,4- dihydropyridine derivatives against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus aureus, and Klebsiella pneumoniae*. Most of these compounds were highly active against *E. coli,* and some even showed antifungal activity.[106]

- Other biological activities

Although the **DHPos** have been exceptionally well explored as a vasorelaxant, they have a privileged structure or scaffold that could act as human rhinovirus 3C protease inhibitors, urease inhibitors, Rho-Kinase N-methyl-D-aspartate (NMDA) inhibitors. Recent studies reported a series of 3,4-dihydro-2-pyridone derivatives from which 4-(4-nitrophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**3,4-DHPo**) exhibited the most potent activity (IC_{50} = 29.12 μM). This inhibitory activity grows with the increase of the electron-withdrawing ability of the groups.[99]

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NMDA inhibitors are highly interesting in pharmaceutical research due to their application in treating moderate to severe Alzheimer's disease.[107] A series of **122 DHPos** derivatives have been proved their NMDA inhibitor through QSAR methodology.[8] Five of them, whose structures have a **DHPo** ring fused to a substituted aromatic ring (**56** to **60)**, showed the highest inhibitory capacity (Figure 12).

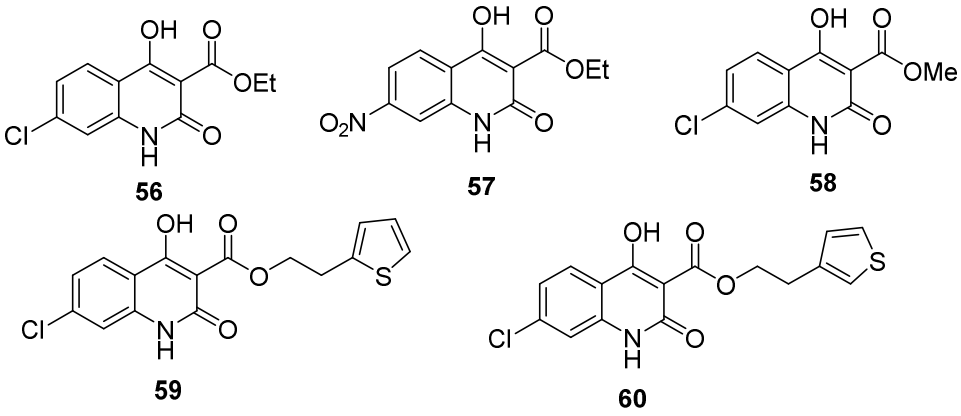

Figure 12. 3,4-DHPo with NMDA inhibitor activity.

Additionally, some dihydropyridines act as calcium channel blockers, potential candidates for schizophrenia and antihypertensive treatment.[108,109]

7. Conclusions

Since the first accidental **3,4-DHPo** synthesis, the most extensive method reported to obtain these derivatives proceeded via a multicomponent reaction (MCR-4CR) of Meldrum's acid, a β-ketoester**,** and an aromatic aldehyde in the presence of ammonium acetate. This experimental procedure is simple and allows a wealth of molecular diversity depending on substituents in the starting reagents. Besides, this base strategy has been extended to non-conventional methods such as Microwave-, Ultrasound- or Infrared- assisted reactions, allowed to increase the efficiency by reducing the reaction time, increasing the yields and, for some of them, eliminating the reaction solvents, as an important contribution to Green Chemistry. Besides, SPOS and LPOS have also been applied allowed to obtain a combinatorial library of these structures.

All **3,4-DHPo** synthesized showed a broad range of biological activity highlighted as vasorelaxants and antihypertensives due to its structural similarity with 1,4-DHPs. Many of them also showed activity as antitumors, HIV-inhibitors, or antibacterial and antifungal, among others. On the other hand, **3,4-DHPo** have become excellent synthetic precursors of many different complex structures with exciting applications.

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