

Zinc Acetate-Catalyzed Efficient Synthesis of Hantzsch 1,4-Dihydropyridines

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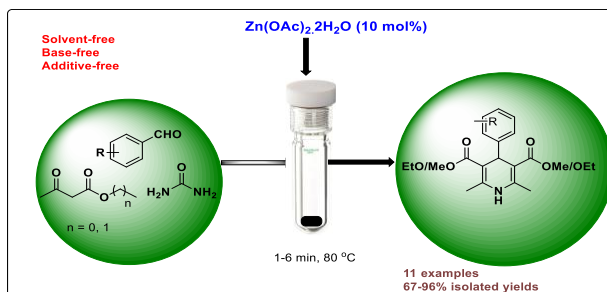
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Abstract

The Hantzsch multicomponent reaction is the classical synthetic approach toward 1,4-dihydropyridines (1,4-DHPs), compounds of great interest in medicinal chemistry and material science. We herein report a green and extremely efficient synthesis of Hantzsch ester derivatives catalyzed by inexpensive and easily available zinc acetate (10 mol%). The reaction was carried out in a sealed tube at 80 °C for 1-6 min under expedited and solvent-free conditions, yielding the required eleven dihydropyridine derivatives in good to excellent yields (67-96 %) and greatly decreased reaction time. The simple work-up and no solvent waste and recyclability of the catalyst (up to four cycles) make this technique as a better and environmentally sustainable alternative.



Keywords: Zinc acetate dihydrate ($\text{Zn(OAc)}_2 \cdot 2\text{H}_2\text{O}$); Sealed tube; Lewis acid; Catalyst, 1,4-Dihydropyridines; Hantzsch esters.

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1. Introduction

Heterocyclic compounds are of great interest in organic chemistry due to their various biological activity and medicinal uses [1-4]. Among them, nitrogen-containing compounds, in particular, are of interest due to their various biological activities and pharmacological properties [5-8]. Among these, 1,4-dihydropyridines (1,4-DHPs) are the most abundant and important scaffolds. Hantzsch was able to synthesize 1,4-DHPs successfully for the first

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time using a one pot multicomponent reaction (MCR) of aldehydes with two moles of ethyl acetoacetate and ammonia, which started the subsequent progress in the synthesis of 1,4-DHPs [9]. 1,4-DHPs are found in numerous natural and synthetic substances and are connected to molecules with striking pharmacological characteristics [10]. Natural derivatives, such as nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) (Fig. 1), highlight the importance of 1,4-DHPs in medicinal chemistry and therapeutic applications. 1,4-DHPs display diverse pharmacological activities, including antihypertensive, neuroprotective, antimicrobial, vasodilatory, anti-inflammatory, and antidiabetic effects.

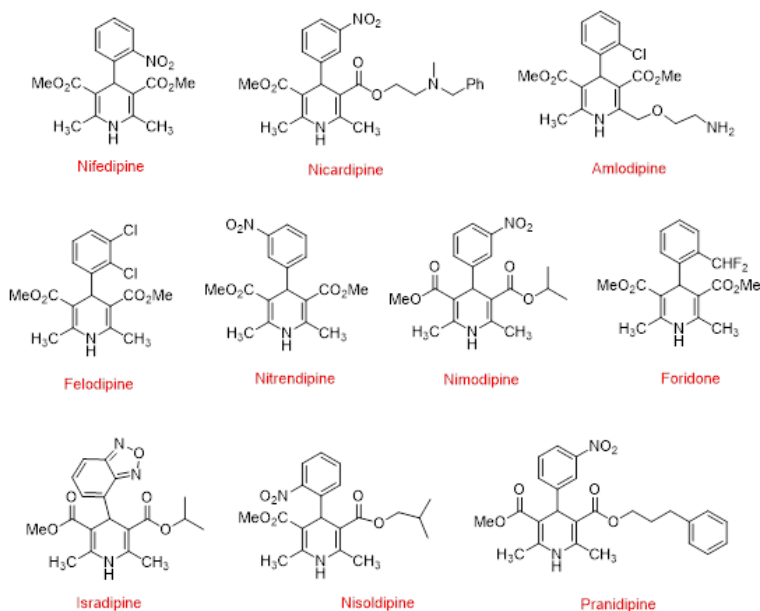


Fig. 1. Marketed antihypertensive 1,4-DHP containing drugs.

The great medicinal applications have stimulated the synthetic chemist to develop novel and green synthetic methods for the production of 1,4-dihydropyridine molecules employing Lewis's acid, Bronsted acid, biocatalysts, ionic liquids and organocatalysts [11–13]. Many studies focus on altering the Hantzsch process to increase the product yield and reduce the reaction time and by-product formation. The disadvantages of these transformations include the use of volatile organic solvents, long reaction times, high reaction temperatures, the use of environmentally toxic chemicals, low yield, limited scope and the use of hazardous solvents.

Multicomponent reactions (MCRs) are a special class of valuable synthetic organic reactions in which one or more diverse starting materials are reacted in one pot to create a final product [14]. These reactions have been judiciously used in some synthetic transformations where conventional procedures usually need a long process with many phases. The advantages of the MCR approach include high yields, atom-/step economy,

shorter reaction times and environmental friendliness. This technology is especially beneficial in the drug development process and a good tool for generating a library of new chemical entities (NCEs) [15-21]. Applications of solvent-free based synthetic techniques for the greener synthesis of pharmacologically important compounds have gained considerable impetus for decreasing the production costs and operational simplicity [22, 23].

So, this notion needs more diversity to obtain target libraries with defined building blocks for our diverse heterocyclic scaffolds. Previously, the title compounds were synthesized using the Zn-based complexes such as ZnO, bimetallic ZnFe_2O_4 nanopowder, Zn-VCO_3 hydrotalcite, $\text{Fe}_2\text{ZnAl}_2\text{O}_7$, ZnO/ZrO_2 , $\text{AlCl}_3@\text{ZnO}$ NPs, Zn-MOF microspheres, $\text{Zn}[(\text{L})\text{-proline}]_2$ etc. [24-33]. After an extensive literature search, we found $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ has not been used for the target reaction. One of the several zinc complexes that is stable in air and moisture under ambient settings and is easily available is zinc acetate ($\text{Zn}(\text{OAc})_2$) [34]. Several papers showing the catalytic effectiveness of $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ led us to execute the processes to synthesis 1,4-dihydropyridines (1,4-DHPs) [35-42].

2. Experimental

2.1. Materials and Methods

$\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ was purchased from BLD Pharma. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F₂₅₄ MERCK (20 x 20 cm). Visualization was achieved by exposure to UV light. Organic solutions were concentrated by rotary evaporation on BUCHI-Switzerland; R-120 rotary evaporator and vacuum pump V-710. Column chromatography was performed on Merck silica gel 230-400 mesh size. ^1H and ^{13}C NMR spectra were recorded with Bruker 400 MHz NMR instruments. Mass spectra were recorded with Agilent LC-MS instrument. FTIR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27 spectrometer.

2.2. General procedure for synthesis of 1,4-DHPs

A mixture of the substituted benzaldehyde (1 mmol), methyl/ethyl acetoacetate (2 mmol), NH_4OAc (1.5 mmol) and $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (10 mol%) was put in a sealed tube. The mixture was heated at 80 °C for the time shown in Fig. 2. Upon completion of the reaction, the reaction mixture was cooled to room temperature when the TLC indicated the desired outcome, $\text{Zn}(\text{OAc})_2$ was precipitated and then filtered out. Diluted the reaction mixture with ethyl acetate and washed with brine and water to remove ionic salts or water-soluble contaminants. The organic phase was dried over a drying agent, filtered and the solvent evaporated in a rotary evaporator. The crude product was refined by short column chromatography using EtOAc:n-hexane (1:5) to provide pure 1,4-DHP. *Caution:* Before using glassware, check for damage and destroy any damaged containers. Do not over tighten the caps as this will apply pressure on the glass. Reaction containers

should be handled or opened after cooling to rt. When doing a reaction in a sealed vessel, make sure there are no excess flammable/reactive solvents/materials in the fume cupboard.

2.3. Spectral data for 4a (representative example)

Dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Table 2, entry 1): IR (NaCl): 3342, 2948, 1699, 1648, 1488, 1431, 1375, 1343, 1302, 1220, 1181, 1145, 1120, 1100, 1051 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.20-7.21 (m 4H), 5.62 (s, 1H, NH), 4.96 (s, 1H), 3.68 (s, 6H, COOCH_3), 2.34 (s, 6H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 168.18, 147.53, 144.53, 128.16, 127.76, 126.34, 104.04 51.13, 39.40, 19.73. LCMS: Exact Mass: 301.23; observed Mass: M-1=300.23

3. Results and Discussion

In continuing our previous work on the development of new methodologies for the construction of biologically active small heterocyclic molecules [43–45], initially, the three-component condensation reaction was screened for substituted benzaldehyde (1 mmol), methyl acetoacetate (2 mmol), NH_4OAc (15 mmol) as substrates for the model reaction and toluene as solvent in the presence of $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (10 mol%) at ambient temperature (Table 1). The reaction mixture was stirred at room temperature for 48 h and trace amount of matching imidazole production was noticed on basis of TLC and further purification (entry 1, Table 1). The reaction temperature is an important aspect for evaluating the feasibility of chemical processes. Thus, we performed a cyclocondensation reaction at a temperature of 60 $^\circ\text{C}$ –100 $^\circ\text{C}$, and the maximum yield of 84 % was achieved at 80 $^\circ\text{C}$, while the temperature above 80 $^\circ\text{C}$ had no obvious effect on the product yield (entry 5, Table 1).

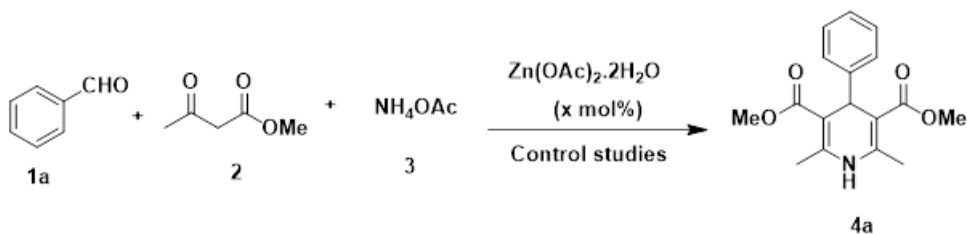


Table 1. $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ -catalyzed synthesis of 4a-Temperature studies

Entry	Temp ($^\circ\text{C}$)	Time (h)	Yield (%) ^a
1	r.t	48	trace
2	60	1	19
3	70	1	28
4	80	0.5	84
5	100	1	82

^aIsolated yields

The influence of solvent was studied by running the reaction at 80 °C using $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ as catalyst in different solvents such as toluene, acetonitrile, ethyl acetate and neat conditions (Table 2). It is observed that, compared with the reaction in selected solvents (entries 1–3, Table 2), the corresponding product was obtained in excellent yield under solvent-free conditions in sealed tube (entry 6, Table 2). Further, it was determined that 10 mol% of the catalyst was sufficient to push on the reaction to offer maximum isolated yield.

Table 2. Study of solvent and catalyst loading.

Entry	Solvent	Yield ^a (%)
1	Toluene	64
2	Acetonitrile	32
3	Ethyl acetate	27
4	Neat ($\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 5 mol%)	58
5	Neat ($\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 10 mol%)	84
6	Neat, sealed tube ($\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 10 mol%)	95

^aIsolated yields

To prove the efficiency of $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ as catalyst, we have used some commercially available zinc salts for the cyclocondensation reaction of benzaldehyde, methyl acetoacetate and ammonium acetate under solvent-free conditions in sealed tube and the obtained results were summarized in Table 3. It is noticed that for all other zinc salts utilized as catalysts, a poor conversion of 4a is obtained. The catalytic ability of $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ was found to be superior to other examined zinc salts (entry 6, Table 3). The catalyst is reusable upto four cycles without appreciable loss of its catalytic activity on the control reaction on 4a. The results revealed that from 1 to 4 cycles (95 %, 95 %, 94 %, 91 %, and 78 % respectively) the amount of Zn^{2+} ion might have marginally decreased and drastically decreased in the 5th cycle.

Table 3. Effect of zinc catalyst on synthesis of 4a.

Entry	Zinc salt	Reaction Time (h/min)	Yield ^a (%)
1	$\text{Zn}(\text{NO}_3)_2$	24 h	21
2	ZnBr_2	1.5 h	45
3	ZnCl_2	1 h	47
4	$\text{Zn}(\text{OTf})_2$	2 h	75
5	Zinc dust	2.5 h	42
6	$\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$	2 min	95

^aIsolated yields

The catalytic activity of $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ with other reported zinc catalysts (mono and bimetallic) from the literature is provided in Table 4.

Table 4. Comparison of catalytic activity of 4a.

Entry	Zinc catalyst and reaction conditions	Reaction Time (min/h)	Yield (%) ^a [ref]
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1	Heterogeneous bimetallic ZnFe ₂ O ₄ nanopowder (40 mg), H ₂ O, RT	30 min	95 [24]
2	Nano-ZnO (0.5 mol%), Microwave (P = 10 W), H ₂ O	1.5 min	96 [27]
3	ZnO@SnO ₂ mixed metal oxide nanoparticle (10 mol%), 80 °C, solvent-free	17 min	96 [26]
4	AlCl ₃ -loaded ZnO nanoparticles (20 mol%), RT, solvent-free	2 h	92 [30]
5	Zn[(L)proline] ₂ complex (0.04 mmol), 70 °C (thermal); microwave (P = 200 W) solvent-free	2.5 h 3 min	83 (T) 90 (MW) [32]
6	Present work	2 min	95

^aIsolated yields

After optimization of the conditions, a series of 1,4-DHP derivatives were synthesized utilizing different aromatic aldehydes containing both electron-donating and electron-withdrawing groups to examine the scope of the reaction (Fig. 2). The aldehydes bearing both electron-donating and electron-withdrawing groups reacted very well, affording the desired products in good yields within short reaction times (entries 4a–k, 1–6 min). As expected, aldehydes with electron withdrawing substituents reacted faster than those with electron donating substituents. The presence of electron-withdrawing substituents on aldehydes increases the electrophilicity of the carbonyl carbon atom and therefore, allows for a faster nucleophilic assault during the process of condensation. On the other hand, electron donating groups lessen the electrophilicity of the carbonyl and hence correspond to relatively longer reaction periods and slightly decreased reaction rates. This electronic factor accounts for the observed trend in yields and reaction times.

Because aliphatic aldehydes such as acetaldehyde and isobutyraldehyde did not react under ideal conditions to give any desirable product, only aromatic aldehydes were studied. Aliphatic aldehydes are often less electrophilic and have no conjugative stabilization of the reaction intermediates, which is important for the effective cyclocondensation. Their increased inclination to enolization and side reactions under the reaction circumstances may also hinder the targeted transformation and therefore resulting in poor or no product formation. Methyl (4a–f) and ethyl acetoacetates (4g–k) were employed in the present protocol. Either of the β -keto esters worked well in the optimized protocol.

IR spectrum of the product exhibits characteristic signal $\sim 3342\text{ cm}^{-1}$ (N–H stretching), $\sim 1698\text{ cm}^{-1}$ and 1648 cm^{-1} signal (carbonyl group and C=C bond stretching respectively) suggests the cyclic ring synthesis of 1,4-DHP 4a. Two key indications of ¹H NMR 1 and 4 dihydro carbon proton singlet at δ 4.96 validated the structure. Further confirmation of the structure was obtained by ¹³C-NMR and HRMS analysis.

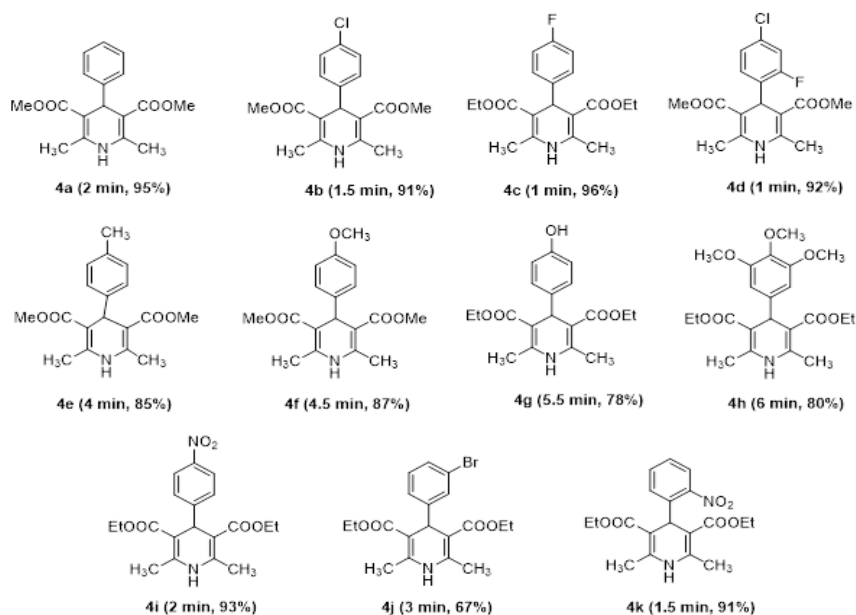


Fig. 2. $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ -catalyzed synthesis of divergent dihydropyridines.

The proposed mechanism highlights the role of the zinc acetate as Lewis acid, which facilitates carbonyl activation (1 and 2), intermediate formation (A/B), and subsequent cyclocondensation leading to the final product (4) (Fig. 3).

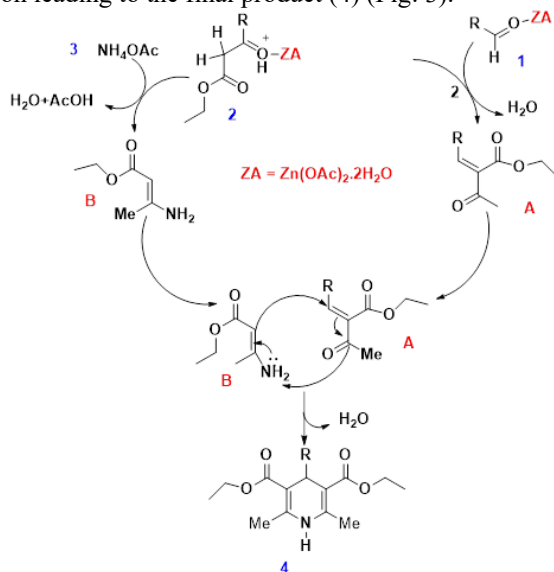


Fig. 3. Plausible reaction mechanism for the $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ -catalyzed synthesis of 1,4-dihydropyridines.

4. Conclusion

Using inexpensive and easily available $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (10 mol%), we have effectively performed one-pot multi component synthesis of dihydropyridine molecules using Hantzsch multicomponent reaction under solvent free conditions in a sealed tube at 80 °C for 1-6 min in good to excellent yields (67-96 %) and greatly decreased reaction time. Aliphatic aldehydes such as acetaldehyde and isobutyraldehyde did not react under ideal conditions to give any desirable product thus limiting this study to only aromatic aldehydes. Aldehydes with electron withdrawing substituents reacted faster than those with electron donating substituents. Methyl and ethyl acetoacetates were employed in the present protocol. Either of the β -keto esters worked well in the optimized protocol. This method has many benefits over the old methods such as quick workup, broad scope of the substrate, shorter reaction time, high yield, use of environmentally benign catalyst and recyclability of the catalyst (up to four cycles).

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Supporting information

Spectral data of synthesized compounds

Dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Figure 2, 4a): IR (NaCl): 3342, 2948, 1699, 1648, 1488, 1431, 1375, 1343, 1302, 1220, 1181, 1145, 1120, 1100, 1051 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ in ppm 7.20-7.21 (m, 4H), 5.62 (s, 1H, NH), 4.96 (s, 1H), 3.68 (s, 6H, COOCH_3), 2.34 (s, 6H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ in ppm 168.18, 147.53, 144.53, 128.16, 127.76, 126.34, 104.04, 51.13, 39.40, 19.73. LCMS: Exact Mass: 301.23; observed Mass: $\text{M}-1=300.23$

Dimethyl 4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (Fig. 2, 4b): IR (NaCl): 3312, 2947, 1696, 1648, 1487, 1431, 1379, 1339, 1307, 1213, 1184, 1119, 1093, 1015, 840 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ in ppm 7.20-7.54 (m, 4H, -Ar), 5.88 (brs, 1H, -NH), 4.98 (s, 1H, -CH), 3.69 (s, 6H, - CH_3), 2.40 (s, 6H, - OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ in ppm 19.65, 39.58, 52.71, 103.61, 128.81, 129.68, 131.87, 144.57, 155.20, 167.99. LCMS: Exact Mass: 335.09; observed Mass: $\text{M}+1=336.23$.

Dimethyl-4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4c): IR (NaCl): 3307, 3257, 3100, 2923, 2853, 1694, 1648, 1495, 1430, 1380, 1339, 1305, 1242, 1211, 1156; ^1H NMR (400 MHz, CDCl_3): δ in ppm 7.22-7.20 (m, 2H), δ 6.90-6.86 (m, 2H), 4.96 (s, 1H), 3.64 (s, 6H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ in ppm 168.04, 162.52, 160.58, 144.21, 143.44, 129.29, 129.22, 104.12, 146.10, 144.37, 104.12, 51.16, 38.87, 29.84, 19.77. LCMS: Exact Mass: 319.12 observed Mass: $\text{M}-1=318.27$

Dimethyl-4-(4-chloro-2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4d): IR (NaCl): 3307, 3257, 3100, 2923, 2853, 1694, 1648, 1495, 1430, 1380, 1339, 1305, 1242, 1211, 1156 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ in ppm 7.32-7.20 (m, 1H), 7.01-6.95 (m, 2H), 4.96 (s, 1H), 3.68 (s, 6H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ in ppm 167.84, 160.95, 158.94, 144.73, 133.56, 133.44, 132.56, 131.88, 124.66, 128.28, 116.11, 102.59, 51.11, 34.44, 19.64. LCMS: Exact Mass: 353.08; observed Mass: $\text{M}+\text{H}_2\text{O}=370.23$

Dimethyl 1,4-dihydro-4-(4-methylphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (Fig. 2, 4e): ^1H NMR (CDCl_3 , 400 MHz): δ in ppm 6.93-7.18 (m, 4H, -Ar), 5.60 (brs, 1H, -NH), 4.88 (s, 1H, -CH), 3.56 (s, 6H, - CH_3), 2.25 (s, 6H, - OCH_3), 2.20 (s, 3H, - CH_3); ^{13}C NMR (CDCl_3): δ in ppm 19.46, 21.41, 38.80, 51.04, 103.76, 127.52, 129.26, 135.67, 144.70, 168.26

Dimethyl 4-(4-methoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (Fig. 2, 4f): ^1H NMR (CDCl_3 , 400 MHz): δ in ppm 6.66-7.48 (d, 4H, -Ar), 5.63 (brs, 1H, -NH), 4.86 (s, 1H, -CH), 3.69 (s, 3H, - OCH_3), 3.57 (s, 6H, - CH_3), 2.25 (s, 6H, - OCH_3); ^{13}C NMR (CDCl_3): δ in ppm 19.49, 38.61, 50.97, 55.16, 103.69, 113.80, 128.57, 140.11, 144.56, 157.88, 168.87

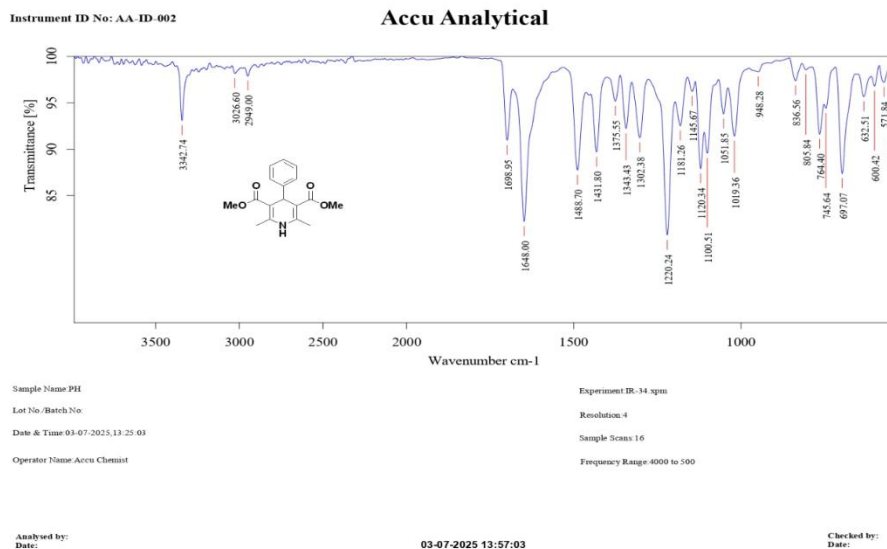
Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4g): off-white crystalline solid, mp. 228–229 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ in ppm 8.81 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.4 Hz, 2H), 7.09 (t, *J* = 7.1 Hz, 1H), 4.86 (s, 1H), 3.98 (dd, *J* = 9.1, 7.2 Hz, 4H), 2.25 (s, 6H), 1.12 (t, *J* = 7.1 Hz, 6H)

Diethyl-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyrimidine-3,5-dicarboxylate (Fig. 2, 4h): IR (KBr): ν 3357, 2928, 2853, 1696, 1636, 1593, 1497, 1460, 1378, 1317, 1273, 1205, 1127, 1092, 1001, 864, 803, 748, 627 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆) δ in ppm 1.28 (t, 6H, *J* = 6.0 Hz), 2.35 (s, 6H), 3.78 (s, 6H), 3.80 (s, 3H), 4.12 (q, 4H, *J* = 6.0 Hz), 4.90 (s, 1H), 5.52 (brs, 1H, NH), 6.45 (s, 2H).

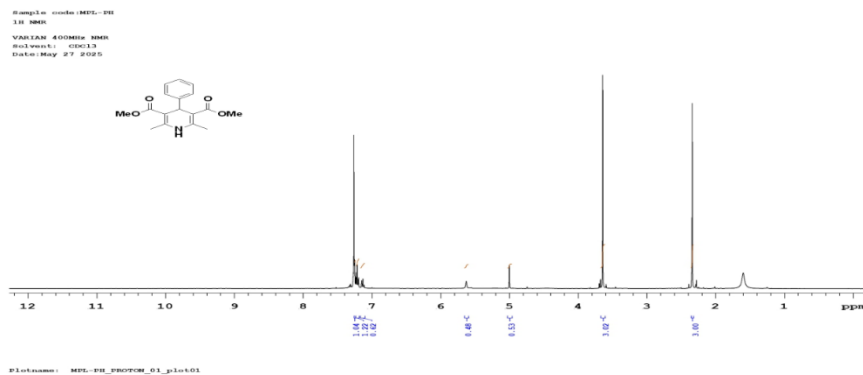
Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4i): mp 125–127 °C. FT-IR (KBr): ν in cm⁻¹ = 3320, 3249, 3101, 2978, 2933, 2902, 1701, 1682, 1648, 1517, 1488, 1372, 1347, 1301, 1252, 1213, 1119, 1094, 1050, 1020, 863, 837, 824, 758, 747, 707, 603, 499. ¹H NMR (400 MHz, DMSO-*d*₆): δ in ppm 9.00 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 1H), 4.09–3.92 (m, 4H), 2.30 (s, 6H), 1.14 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (76 MHz, DMSO-*d*₆): δ in ppm 167.00, 155.98, 146.81, 146.28, 129.10, 123.77, 101.31, 59.70, 18.73, 14.59.

Diethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4j): Dark-yellow crystalline solid, mp. 123–125 °C. IR (NaCl): 3336, 2919, 2341, 1701, 1642, 1478, 1430, 1380, 1340, 1293, 1260 1211, 1094, 1016 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ in ppm 8.89 (s, 1H), 7.32–7.27 (m, 2H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 4.82 (s, 1H), 4.06–3.92 (m, 4H), 2.26 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 6H). LCMS: Exact Mass: 379.01; observed Mass: M+1=380.23

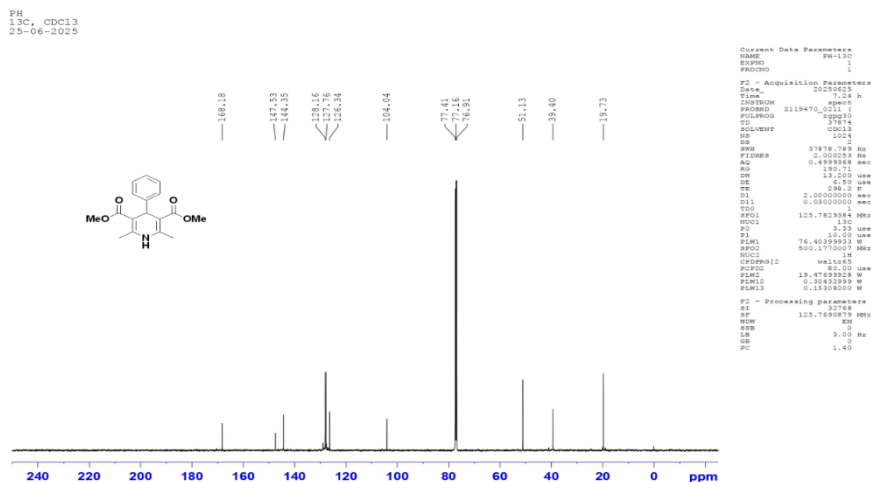
Diethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4k): ¹H NMR (400 MHz, CDCl₃) δ in ppm 7.67 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.26–7.22 (m, 1H), 5.72 (s, 1H), 5.65 (s, 1H), 3.59 (s, 6H), 2.34 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ in ppm 167.50, 144.70, 142.10, 132.68, 131.07, 127.04, 123.92, 103.83, 77.26, 77.01, 76.75, 51.01, 34.64, 19.54.



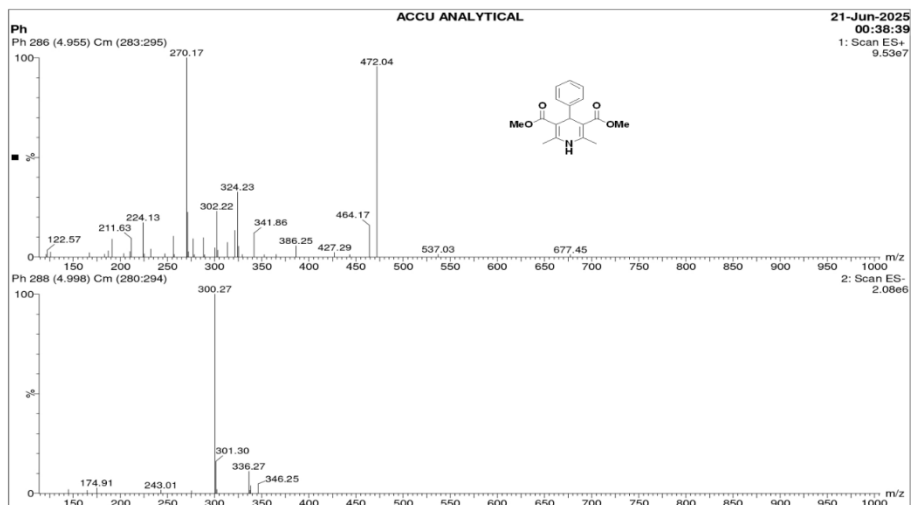
IR spectrum for dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4a)

¹H NMR for dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl₃ (Fig. 2, 4a)

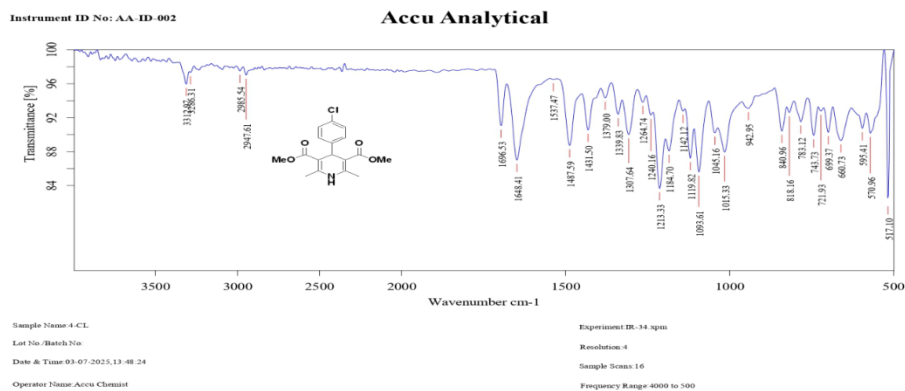
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¹³C NMR for dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl₃ (Fig. 2, 4a)



LCMS for dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4a)



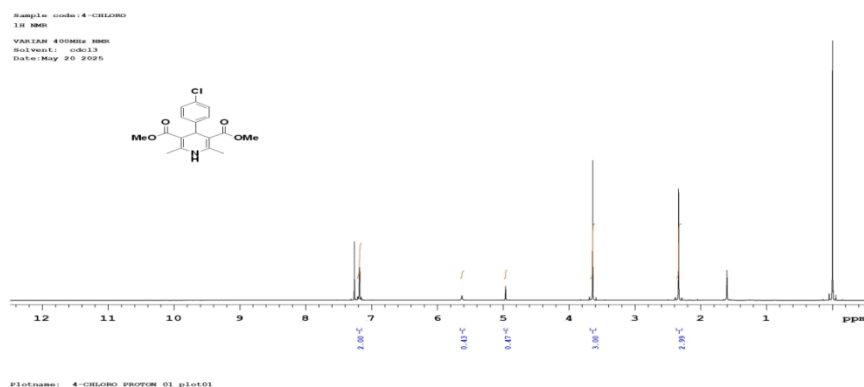
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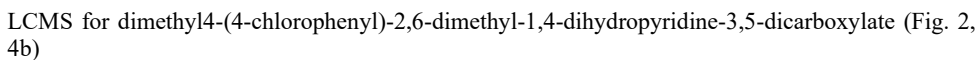
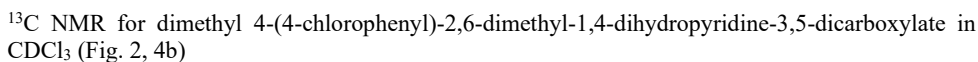
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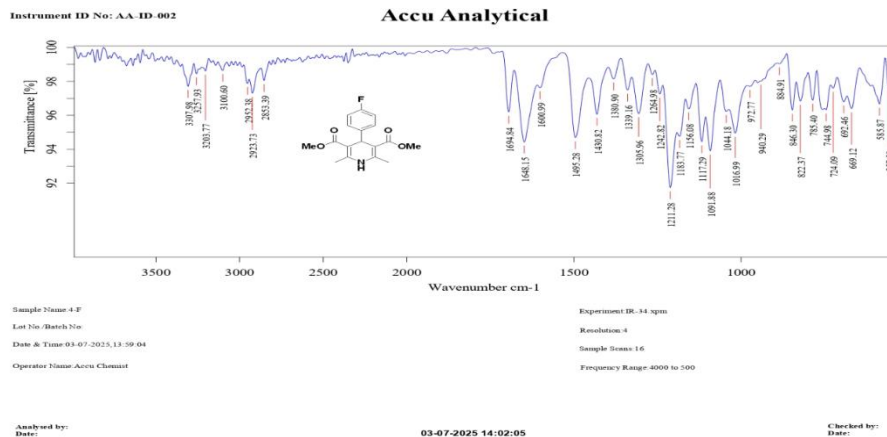
Date:

IR spectrum for dimethyl-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4b)

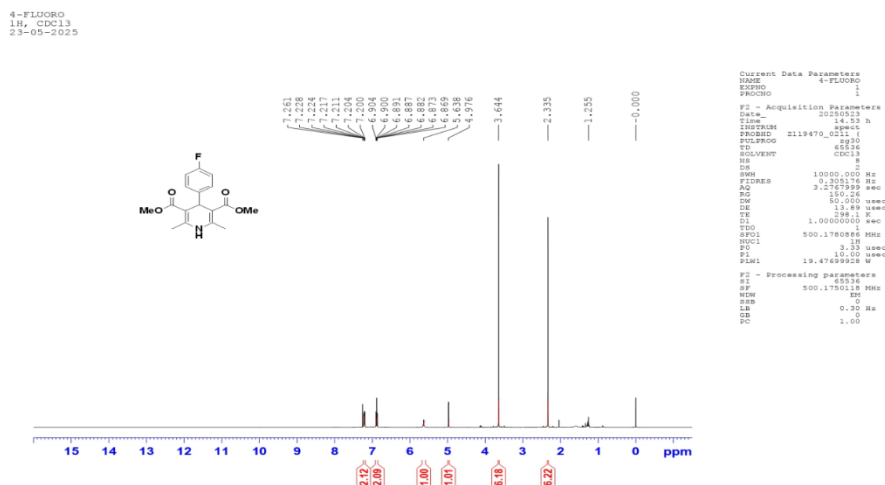


¹H NMR for dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl₃ (Fig. 2, 4b)





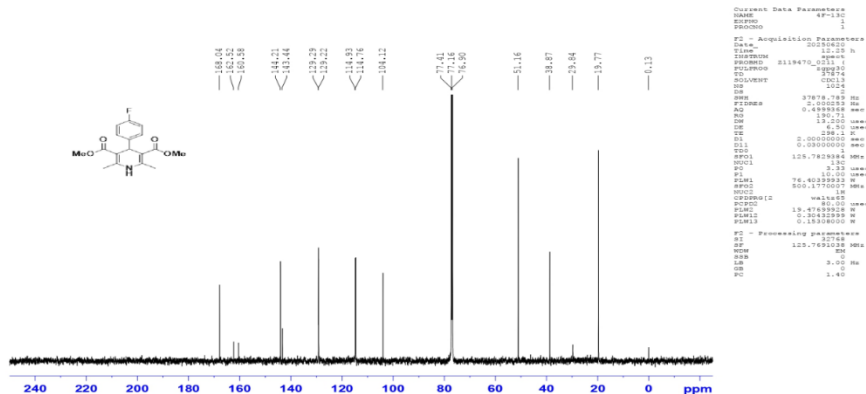
IR spectrum for dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4c)



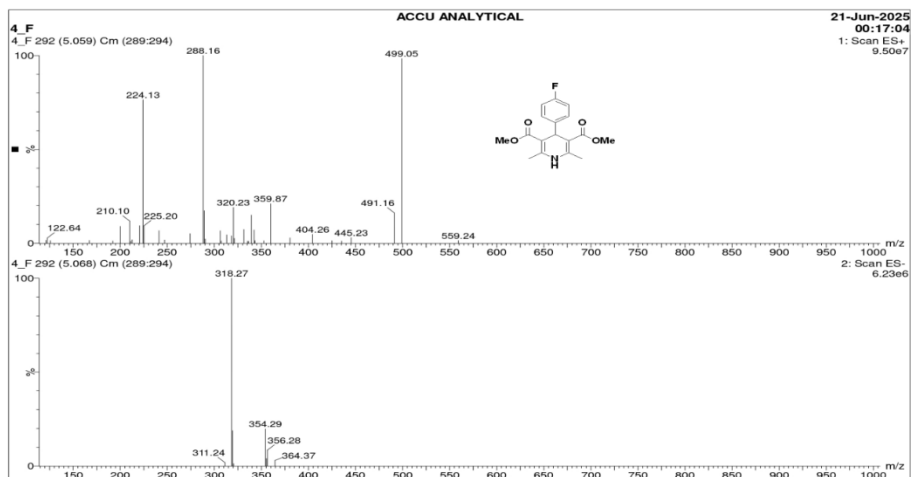
^1H NMR for dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl_3 (Fig. 2, 4c)

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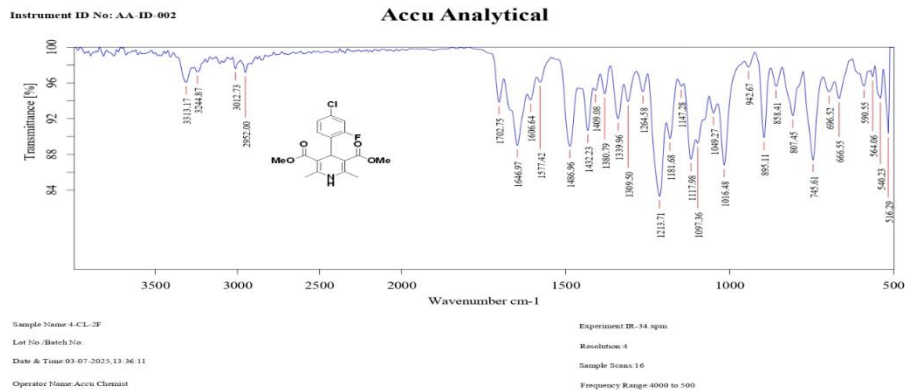
4F
13C, CDCl3
20-06-2025



¹³C NMR for dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl₃ (Fig. 2, 4c)



LCMS for dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4c)

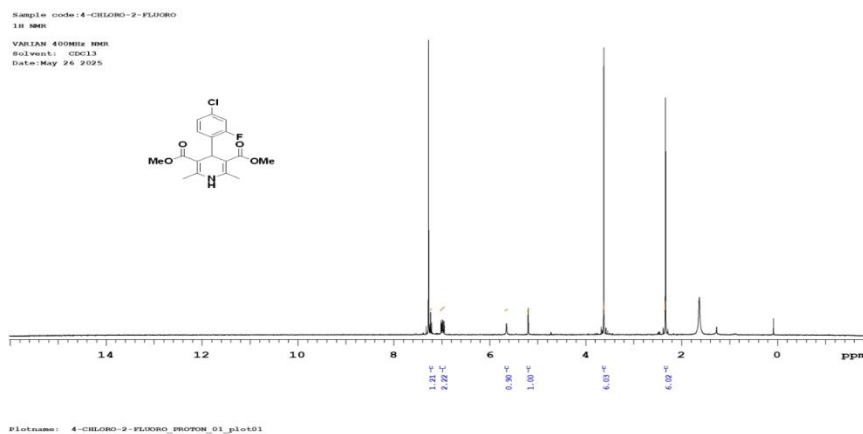


Analysed by:
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03-07-2025 13:55:16

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 Date:

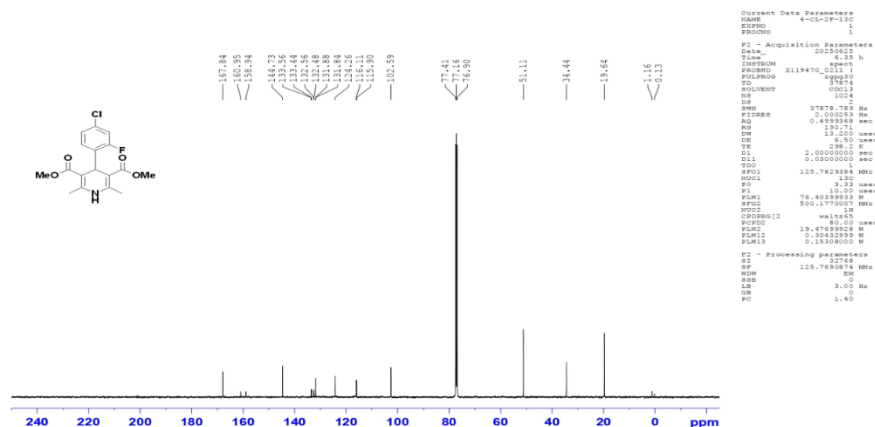
IR spectrum for dimethyl 4-(4-chloro-2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4d)



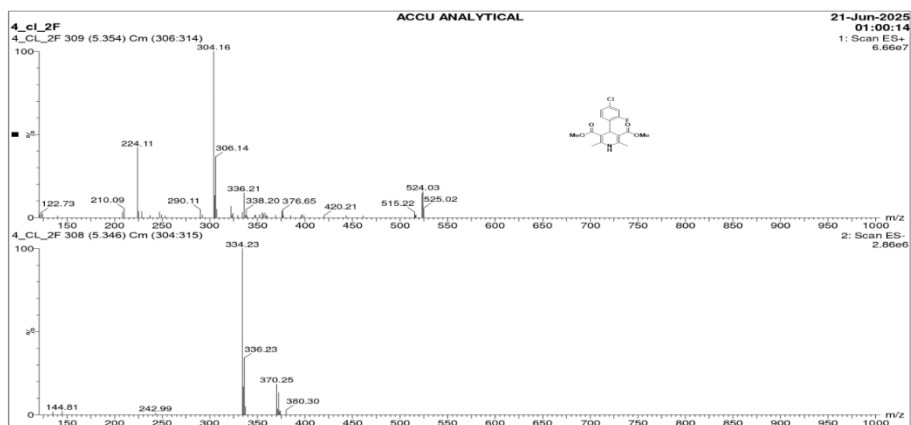
^1H NMR for dimethyl 4-(4-chloro-2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl_3 (Fig. 2, 4d)

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4-Cl-2F
13C, CDCl₃
23-06-2023



¹³C NMR for dimethyl 4-(4-chloro-2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl₃ (Fig. 2, 4d)

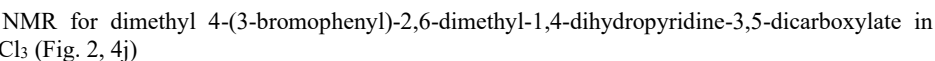


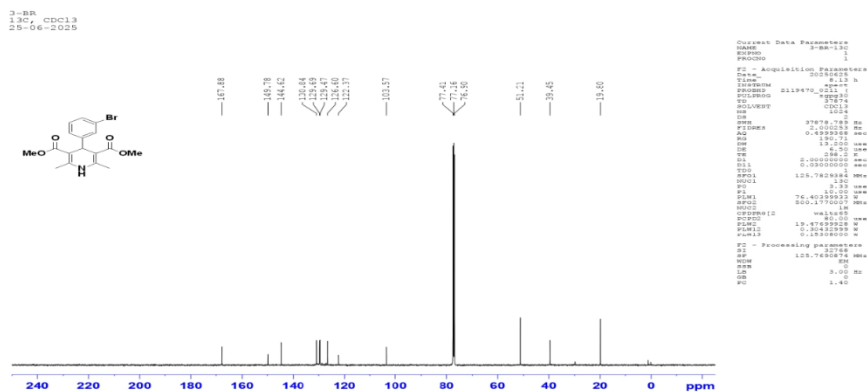
LCMS for dimethyl 4-(4-chloro-2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4d)

Accu Analytical

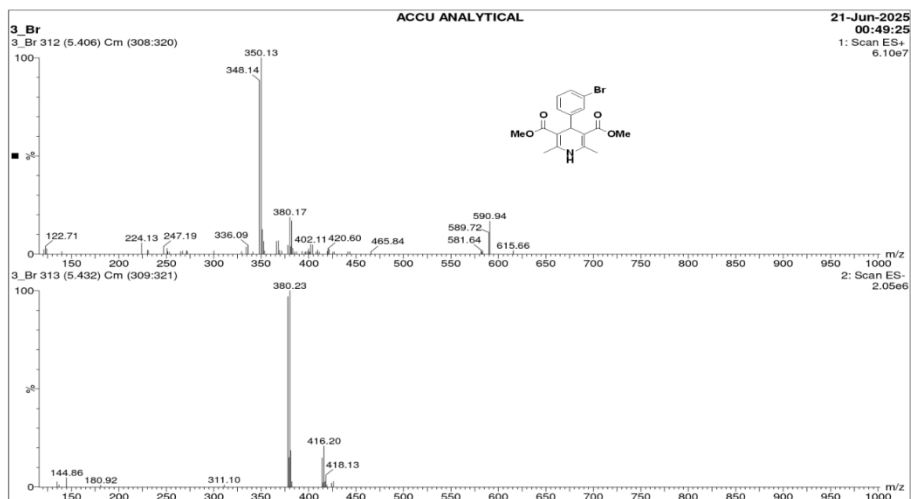
Checked by:
Date:

3-BROMO
1H, CDC13
26-05-2025





¹³C NMR for Dimethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in CDCl₃ (Fig. 2, 4j)



LCMS for dimethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 2, 4j)