One-Pot Synthesis of 1,4-Dihydropyridine and Polyhydroquinoline Derivatives via *L*-Proline Catalyzed Hantzsch Multicomponent Reaction under Ultrasound Irradiation

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L-Proline efficiently catalyzed the multi-component Hantzsch reaction in EtOH at 60 ℃ under ultrasound irradiation to afford the corresponding 1,4-dihydropyridine and polyhydroquinoline derivatives in high yields. This method offers the advantages of neutral and mild reaction conditions, high to excellent yields of the products and simple workup.

Keywords multi-component Hantzsch reaction, 1,4-dihydropyridines, polyhydroquinoline, *L*-proline

Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are analogues of nicotinamide adenine nucleotide (NADH) coenzymes and an important class of drugs.[1] Current literature reveals that these compounds possess a variety of biological activities.[2] Furthermore, hydrogenation methods for the conversion of these compounds to pyridines have been investigated intensively.[3] These examples indicate clearly the remarkable potential of novel 1,4-dihydropyridine derivatives as a source of valuable drug candidates and useful intermediates in organic chemistry. Thus, the synthesis of this heterocyclic nucleus is of much importance.

Classical methods for the synthesis of 1,4-dihydropyridines are one-pot condensation of an aldehyde with ethyl acetoacetate and ammonium acetate, either in acetic acid or under reflux in alcohols.[4] However, these methods suffer from several drawbacks such as long reaction time, an excess of organic solvent, lower product yields, and harsh refluxing conditions. Therefore, it is necessary to develop more efficient and versatile methods for the preparation of 1,4-DHPs and the progress in this area is remarkable, including the recent use of microwaves,[5] ionic liquids,[6] refluxing at high temperature,[7] SiO_2-$HClO_4$,[8] silica sulfuric acid,[9] ZnO,[10] $Yb(OTf)_3$,[11] Ceric ammonium nitrate,[12] $ZrCl_4$[13] and solid-phase organic synthesis (SPOS) techniques.[14] Although some reactions are satisfactory in terms of yield, however, most of these methods employ expensive or poisonous catalysts, not commercially available catalysts, and suffer from long reaction times. Thus, it is clearly evident that the development of more flexible and effective protocols is required.

The catalytic property of small organic molecules like cinchona alkaloids and amino acids is well known,[15-16] small organic molecules have been shown as quite promising and highly efficient organocatalysts for multi-component reactions.[17] The amino acid *L*-proline is an abundant bifunctional chiral molecule that is inexpensive, the two functional groups can both act as acid or base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis. As the mechanism of multi-component Hantzsch reaction originally involves aldol related reactions such as Knoevenagel condensation and Michael addition, the use of *L*-proline for the same reaction will be an useful and attractive modification. Kumar[17] and Karade[18] reported the use of *L*-proline as an organocatalyst for the multi-component Hantzsch reaction and get excellent yields.

Herein, we would like to report the studies of a facile Hantzsch condensation in the presence of amino acid organocatalyst at 60 ℃ using substituted aldehyde (**1**), acetoacetate ester (**2**), and ammonium acetate to produce 1,4-dihydropyridine derivatives (**3**) in high yields. We examined this reaction under three different sets of reaction conditions: (I) organic solvents, and (II) water under ultrasonic irradiation.

Results and discussion

Firstly, we followed the typical experimental procedure, a solution of substituted aldehyde, acetoacetate ester, and ammonium acetate in ethanol was stirred in the presence of catalytic amount of 10 mol% *L*-proline for a certain period of time required to complete the reaction (TLC), resulting in the formation of 1,4-dihydropyridine derivatives **3** (Scheme 1). After the reaction was completed, cooling the reaction mixture to 0 ℃,

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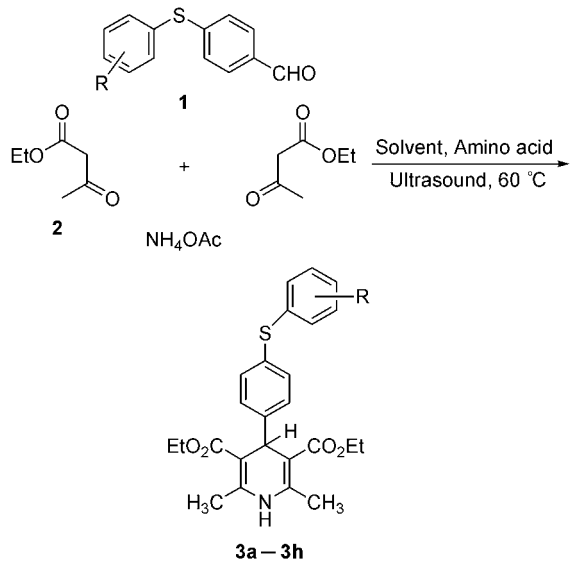
Scheme 1



the soid products were precipitated from the mixture, filtered to get most of the products. The filtrate liquor was then poured into crushed ice to get residue solid product. The two parts of solid products were put together and recrystallized from ethanol to get straw yellow colored crystalline 1,4-dihydropyridine **3a** in 95% yield. The results of *L*-proline catalyzed synthesis of 1,4-dihydropyridine derivatives using ultrasound irradiations are given in Table 1 (I[a], I[b]). Using *L*-proline as promoter for the synthesis of 1,4-dihydropyridine derivatives does not only represent a dramatic improvement at 60 ℃ with regard to yield (83%—96%) over conventional thermal heating or reflux, and the reaction time also considerably decreased (0.5—2.50 h) compared to classical synthesis (6—8 h).

Table 1 One-pot synthesis of 1,4-dihydropyridines **3a**—**3h** catalyzed by *L*-proline in ethanol under classical conditions and using ultrasound irradiation at 60 ℃

Product	R	Yield[c]/% (Time/h)			m.p./℃
		I[a]	I[b]	II[a]	
3a	H	95 (1.5) 65[d] (0.5)	85 (6.0) 53[d](3.0)	79 (3.5) 45[d](1.5)	95—96
3b	4-F	89 (1.0)	82 (8.5)	78 (4.0)	167—168
3c	3-F	87 (1.5)	80 (6.6)	81 (3.5)	160—163
3d	4-CH_3	92 (1.0)	88 (5.0)	82 (3.5)	135—137
3e	4-CH_3O	90 (1.0)	82 (7.0)	78 (3.5)	164—166
3f	2-Cl, 6-CH_3	96 (0.5)	90 (3.5)	86 (3.5)	171—172
3g	3-CH_3, 4-F	86 (0.5)	82 (6.0)	76 (4.5)	153—155
3h	2-F, 5-F	83 (2.5)	78 (7.5)	80 (3.5)	175—177

[a] Reagents and conditions: **1** (3 mmol), **2** (6.1 mmol), NH_4OAc (6 mmol), *L*-proline (10 mol%) under ultrasound irradiation at 60 ℃. [b] Catalyzed by *L*-proline without ultrasound irradiation. [c] Isolated yields. [d] Refluxing.

Secondly, to avoid the use of ecologically suspected organic solvents, we carried out the reaction in aqueous medium. Indeed, water is recognized as an attractive medium for many organic reactions. The reaction was carried out successfully at 60 ℃ leading to moderate yields of the products using 10 mol% of *L*-proline in water (Table 1 II[a]). Upon refluxing in ethanol the reaction rate was increased and the reaction was completed within 1 h, but the yield was somewhat decreased.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields of 1,4-dihydropyridine derivatives. We further studied the catalytic efficiency of other organocatalysts on the Hantzsch reaction. In all cases the catalyst was taken as 10 mol% and reaction was done at 60 ℃ under ultrasonic irradiation for 2 h. The results of this study are shown in Table 2. Initially, we tried this reaction with simple secondary amines (diethylamine or piperidine) as catalyst in the absence of *L*-proline (Entries 1, 2), the product was isolated in low yield, instead, the Knoevenagel condensation was observed. We further screened a number of amino acids to optimize the reaction conditions. It was observed that basic amino acids like *L*-histidine and *L*-lysine resulted in poor conversion of **3a** (Entries 3, 4) and the acidic amino acids were found somewhat better (Entries 5, 6), but best result of 95% yield was obtained with neutral amino acids like *L*-proline (Entry 7). The use of 10 mol% of *L*-proline is sufficient to push the reaction forward. Lower or higher amounts of *L*-proline did not lead to significant improvement in the yield of 1,4-dihydropyridine. For example, using *L*-proline (5 mol%) as catalyst, the reaction gave yellow solid product in 78% yield. By changing the amount of the catalyst such as 7.5 mol% and 20 mol%, the reaction resulted in the formation of **3a** in 80% and 90% yield respectively (Table 2). Lastly, we also carried out reactions without any catalyst, but the 1,4-dihydropyridine derivatives were isolated in poor 25% yield and the major product isolated was a dimedone aldehyde adduct.

Table 2 Screening of organocatalysts for synthesis of **3a** under different conditions[a]

Entry	Organocatalyst	Catalyst/mol%	Time/h	Yield[b]/%
1	Diethylamine	10	24	21
2	Piperidine	10	8	32
3	*L*-Lysine	10	2.0	51
4	*L*-Histidine	10	2.0	85
5	*L*-Glutamic acid	10	2.0	88
6	*L*-Asparatic acid	10	2.0	91
7	*L*-Proline	10	1.5	95
8	*L*-Proline	5	1.5	78
9	*L*-Proline	7.5	1.5	80
10	*L*-Proline	20	1.5	90
11	*L*-Proline	0	3.5	25

[a] Reagents and conditions: **1** (3 mmol), **2** (6 mmol), NH_4OAc (4 mmol), organocatalyst, under ultrasound irradiation at 60 ℃. [b] Isolated yields.

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In the majority of instances, the crude product was so pure that it was directly subjected to NMR analysis. All yields are those of isolated products after purification and the structures of the products were confirmed from melting point and spectroscopic data, the structure of **3c** was unambiguously confirmed by an X-ray crystallographic analysis (Figure 1, Table 3), and it shows that the target product 1,4-dihydropyridine was fully formed.

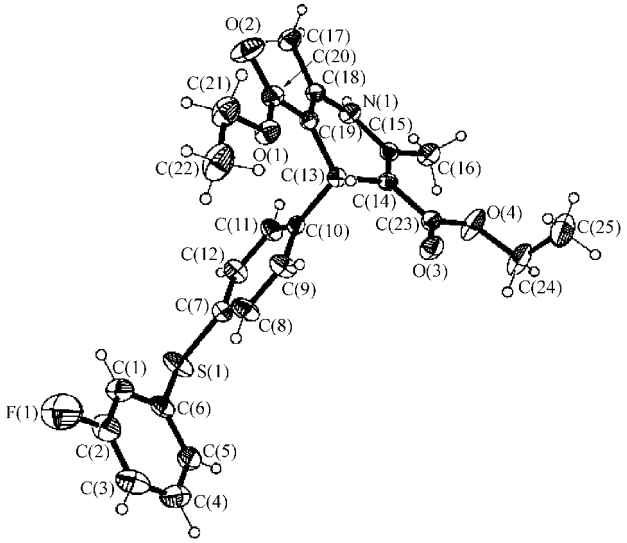


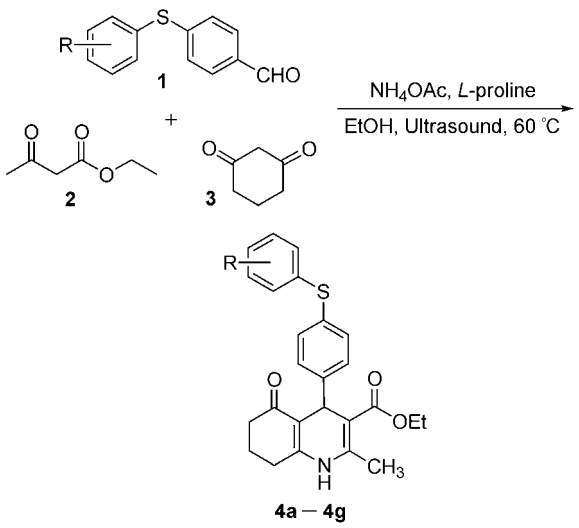
Figure 1 The crystal structure of **3c**.

To determine whether the ultrasound irradiation was another essential factor to realize the high conversions of this condensation, the same reaction was carried out in same conditions without using ultrasound irradiation. When the reaction mixture was irradiated with ultrasound, almost quantitative conversion was observed (TLC). As a result (Table 1) the reaction time was decreased by about 4—6 h. It is important to note that in the absence of catalysis and without using ultrasound irradiation, the yield of the reactions decreased to 5%—10%.

After successfully synthesizing a series of Hantzsch esters in excellent yields under ultrasonic irradiation, we turned our attention towards the synthesis of polydydroquionoline derivatives via unsymmetrical Hantzsch reaction using *L*-proline as catalyst under ultrasonic irradiation conditions (Scheme 2). We carried out the four-component coupling reaction of 4-arylsulfanylbenzaldehyde, ethyl acetoacetate, 1,3-cyclohexanedione and ammonium acetate in EtOH at 60 ℃ catalyzed by *L*-proline with ultrasonic irradiation for 1—3 h.

Using the optimized reaction conditions, we synthesized a number of polyhydroquinoline derivatives and the results are shown in Table 4. The results of Table 4 indicate clearly the feasibility of four-component unsymmetrical Hantzsch reaction in ethanol catalyzed by amino acid *L*-proline. The products were synthesized in excellent yields under ultrasonic irradiation. Indeed, we found 91% of isolated yield with 24% *ee* of **4a**. This *ee* value is slightly higher than that obtained under proline/DMF system (21% *ee*) and comparable with other amino acid observed in alcohol. Unfortunately, all the amino acid examined demonstrated low enantioselectivities in the reaction.

Scheme 2



In summary, the use of inexpensive *L*-proline in a catalytic quantity is a general practical alternative to existing procedures for multicomponent Hantzsch synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives. The procedure offers several advantages including increased variations of substituent in the product with high yields, operational simplicity, minimum environmental effects and above all, the ease in

Table 3 Selected bond lengths (Å) and angles (°) for **3c**

S(1)—C(6)	1.766(3)	S(1)—C(7)	1.776(3)	N(1)—C(15)	1.371(4)
C(13)—C(14)	1.521(4)	C(13)—C(19)	1.526(4)	C(14)—C(15)	1.359(4)
C(14)—C(23)	1.456(4)	C(18)—C(19)	1.347(4)	N(1)—H(1A)	0.8600
N(1)—C(18)	1.379(4)				
C(6)-S(1)-C(7)	103.30(14)	C(10)-C(13)-C(14)	111.2(2)	C(10)-C(13)-C(19)	111.9(2)
C(14)-C(13)-C(19)	110.6(2)	C(15)-C(14)-C(13)	120.5(3)	C(23)-C(14)-C(13)	114.9(2)
C(14)-C(15)-N(1)	118.6(3)	C(14)-C(15)-C(16)	128.6(3)	N(1)-C(15)-C(16)	112.8(3)
C(19)-C(18)-N(1)	119.5(3)	C(19)-C(18)-C(17)	127.3(3)	N(1)-C(18)-C(17)	113.2(3)
C(18)-C(19)-C(20)	120.5(3)	C(18)-C(19)-C(13)	120.0(3)	C(20)-C(19)-C(13)	119.4(3)

Table 4 One-pot synthesis of polyhydroquinoline **4a**—**4g** catalyzed by *L*-proline in ethanol under classical conditions and using ultrasound irradiation at 60 ℃

Product	R	Yield[c]/%	Time/h	*ee*[d]/%	m.p./℃
4a	H	91	1.50	24, 21[e], 22[f], 19[g]	251—253
4b	4-F	87	1.00	19	227—229
4c	3-CH_3	89	1.50	14	268—271
4d	3-OCH_3, 4-OCH_3	87	0.75	18	276—278
4e	3-F, 4-OCH_3	85	0.75	9	195—197
4f	2-Cl, 6-CH_3	92	0.50	23, 17[f],15[g]	207—209
4g	2-F, 5-F	85	0.50	7	250—253

[a] Reagents and conditions: **1** (3 mmol), **2** (3 mmol), **3** (3 mmol), NH_4OAc (5 mmol), *L*-proline (10 mol%) and using ultrasound irradiation at 60 ℃. [b] Catalyzed by *L*-proline without using ultrasound irradiation. [c] Isolated yields. [d] Determined by chiral HPLC analysis using a Chiralcel OB column. [e] DMF as solvent. [f] *L*-Glutamic acid as catalyst. [g] *L*-Lysine as catalyst.

purification of products simply by crystallization.

Experimental

Melting points are uncorrected; infrared (IR) spectra were run on a Bruker spectrometer and expressed in cm^{-1} (KBr); ^1H NMR spectra were recorded on a Bruker AVANCE-300 MHz in $CDCl_3$ or DMSO solutions; mass spectra were determined using a Finigan 8230 mass spectrometer. Elemental analyses were conducted using a Yanaco MT-5CHN elemental analyzer; thin-layer chromatography (TLC) was GF254 with petroleum ether and ethyl acetate as eluent.

General procedure for the synthesis of 1,4-dihydropyridines

A mixture of 4-arylsulfanyl-benzaldehyde (3 mmol), ethylacetoacetate (6 mmol), ammonium acetate (4 mmol) and *L*-proline (10 mol%) was heated in ethanol (15 mL) at 60 ℃ under ultrasonic irradiation for the time as mentioned in Table 1. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into crushed ice and the solid product, which separated was filtered and recrystallized from ethanol to get pure yellow coloured crystalline polyhydroquinoline derivative **3a**—**3h**.

Spectroscopic data of 3a—3h

Diethyl 2,6-dimethyl-4-(4-(phenylthio)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3a**) White solid, m.p. 95—96 ℃; ^1H NMR ($CDC1_3$, 300 MHz) δ: 1.23 (t, J=7.1 Hz, 6H), 2.34 (s, 6H), 4.07—4.11 (m, J=7.1 Hz, 4H), 4.99 (s, 1H), 5.90 (s, br, 1H, NH), 7.21—7.28 (m, 9H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.27, 19.58, 39.43, 59.76, 103.99, 126.55, 129.01, 130.31, 131.23, 132.28, 136.64, 143.90, 147.22, 167.49; IR (KBr) v: 3368, 3098, 3003, 2950, 2828, 1680, 1653, 1613, 1502, 1466, 1431, 1377, 1333, 1128, 843, 817, 805, 787, 745, 665, 587, 525 cm^{-1}; MS (EI, 70 eV) m/z (%): 436 (M−1, 14.53), 435 (M−2, 87.59), 408, 376, 363, 291, 182, 111, 77, 45. Anal. calcd for $C_{25}H_{27}NO_4S$: C 68.62, H 6.22, N 3.20; found C 68.36, H 6.28, N 3.31.

Diethyl 4-(4-(4-fluorophenylthio)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3b) White solid, m.p. 167—168 ℃; ^1H NMR ($CDC1_3$, 300 MHz) δ: 1.22 (t, J = 7.1 Hz, 6H), 2.32 (s, 6H), 4.09—4.14 (m, J=7.1 Hz, 4H), 4.95 (s, 1H), 5.60 (s, br, 1H, NH), 6.98—7.01 (m, 2H), 7.14—7.19 (m, 4H), 7.27—7.30 (m, 2H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.25, 19.57, 39.39, 59.75, 104.00, 116.04, 116.33, 128.96, 130.14, 133.21, 133.30, 133.41, 143.84, 146.94, 167.46; IR (KBr) v: 3348, 3066, 3030, 2807, 1686, 1657, 1610, 1508, 1464, 1431, 1128, 1092, 1049, 853, 818, 789, 745, 668, 588, 525 cm^{-1}; MS (EI, 70 eV) m/z (%): 455 (M^+, 32.13), 454 (M−1, 67.75), 453 (M−2, 78.70), 381, 309, 310, 183, 127, 96, 77, 45, 29. Anal. calcd for $C_{25}H_{26}FNO_4S$: C 65.91, H 5.75, N 3.07; found C 65.96, H 5.88, N 3.11.

Diethyl 4-(4-(3-fluorophenylthio)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3c) White solid, m.p. 154—155 ℃; ^1H NMR ($CDC1_3$, 300 MHz) δ: 1.22 (t, J = 7.1 Hz, 6H), 2.34 (s, 6H), 4.11—4.16 (m, J=7.1 Hz, 4H), 4.98 (s, 1H), 5.63 (s, br, 1H, NH), 6.97—7.02 (m, 2H), 7.10—7.12 (m, 1H), 7.25—7.33 (m, 5H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.26, 19.65, 39.56, 59.79, 103.94, 112.81, 112.90, 115.51, 115.83, 124.45, 129.129, 130.15, 132.66, 140.11, 143.84, 148.23, 167.42; IR (KBr) v: 3286, 3035, 2869, 1680, 1656, 1618, 1507, 1469, 1127, 1112, 1049, 858, 668, 588 cm^{-1}; MS (EI, 70 eV) m/z (%): 455 (M^+, 45.19), 454 (M−1, 27.09), 453 (M−2, 80.08), 408, 381, 309, 310, 183, 127, 96, 77, 45, 29. Anal. calcd for $C_{25}H_{26}FNO_4S$: C 65.91, H 5.75, N 3.07; found C 65.52, H 5.18, N 3.21.

Diethyl 2,6-dimethyl-4-(4-(*p*-tolylthio)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3d) White solid, m.p. 135—137 ℃; ^1H NMR (CD_3COCD_3, 300 MHz) δ: 1.18 (t, J=7.2 Hz, 6H), 2.32 (s, 6H), 2.35 (s, 3H), 4.05—4.12 (m, J = 7.1 Hz, 4H), 5.02 (s, 1H), 6.92—7.02 (m, 4H), 7.18—7.35 (m, 4H), 7.90 (s, br, 1H, NH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 14.23, 17.89, 19.55, 39.40, 59.05, 103.00, 115.89, 128.32, 128.86, 134.14, 135.21, 135.90, 145.21, 146.67, 160.32, 167.16; IR (KBr) v: 3218, 3006, 2887, 1716, 1665, 1508, 1464, 1431, 857, 788, 745, 668 cm^{-1}; MS (EI, 70 eV) m/z (%):

451 (M^+, 49.10), 450 (M－1, 78.01), 449 (M－2, 58.09), 422, 349, 305, 109, 91, 69, 43. Anal. calcd for $C_{26}H_{29}NO_4S$: C 69.15, H 6.47, N 3.10; found C 68.97, H 6.58, N 3.19.

Diethyl 4-(4-(4-methoxyphenylthio)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e) White solid, m.p. 164—166 ℃; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 1.16 (t, J=7.2 Hz, 6H), 2.29 (s, 6H), 3.79 (s, 3H), 4.02—4.06 (m, J=7.1 Hz, 4H), 4.96 (s, 1H), 6.92—6.96 (m, 2H), 7.01—7.07 (m, 2H), 7.19 (m, 2 H), 7.35—7.42 (m, 2H), 7.99 (s, br, 1H, NH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 13.75, 17.87, 39.08, 54.85, 59.03, 102.69, 115.01, 128.10, 128.65, 134.90, 135.13, 145.10, 146.82, 160.00, 167.06; IR (KBr) v: 3218, 3006, 2887, 1716, 1665, 1508, 1464, 1431, 857, 788, 745, 668 cm^{-1}. Anal. calcd for $C_{26}H_{29}NO_5S$: C 66.79, H 6.25, N 3.00; found C 66.84, H 6.31, N 3.05.

Diethyl 4-(4-(2-chloro-6-methylphenylthio)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3f) White solid, m.p. 171—172 ℃; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 1.16 (t, J=7.2 Hz, 6H), 2.29 (s, 3H), 2.31 (s, 6H), 4.01—4.08 (m, J=7.1 Hz, 4H), 5.02 (s, 1H), 6.89 (s, 1H), 7.10—7.13 (m, 1H), 7.20—7.24 (m, 3H), 7.33—7.36 (m, 2H), 8.02 (s, br, 1H, NH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 13.81, 17.81, 18.85, 39.52, 59.06, 102.54, 115.01, 126.34, 128.51, 129.54, 131.57, 131.68, 131.98, 132.04, 135.93, 138.46, 145.22, 145.35, 149.18, 166.99; IR (KBr) v: 3306, 3184, 1752, 1668, 1500, 1458, 857, 788, 665 cm^{-1}. Anal. calcd for $C_{26}H_{28}ClNO_4S$: C 64.25, H 5.81, N 2.88; found C 64.31, H 5.74, N 2.95.

Diethyl 4-(4-(4-fluoro-3-methylphenylthio)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3g) White solid, m.p. 153—155 ℃; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 1.19 (t, J=7.2 Hz, 6H), 2.25 (s, 3H), 2.29 (s, 6H), 4.03—4.09 (m, 4H), 5.05 (s, 1H), 6.80 (s, 1H), 7.10—7.14 (m, 1H), 7.21—7.28 (m, 3H), 7.31—7.39 (m, 2H), 7.96 (s, br, 1H, NH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 13.82, 17.79, 18.82, 39.55, 59.06, 102.51, 117.08, 127.36, 128.55, 129.89, 131.68, 132.94, 137.95, 137.76, 138.66, 145.28, 150.18, 166.90; IR (KBr) v: 3342, 3086, 1705, 1637, 1553, 1476, 1415, 855, 668 cm^{-1}. Anal. calcd. for $C_{26}H_{28}FNO_4S$: C 66.50, H 6.01, N 2.98; found C 66.57, H 6.07, N 2.95.

Diethyl 4-(4-(2,5-difluorophenylthio)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3h) White solid, m.p. 175—177 ℃; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 1.13 (t, J=7.2 Hz, 6H), 2.31 (s, 6H), 4.02—4.08 (m, 4H), 5.15 (s, 1H), 6.69 (s, 1H), 6.95—7.04 (m, 2H), 7.08—7.17 (m, 1H), 7.21—7.31 (m, 3H), 8.02 (s, br, 1H, NH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 14.54, 19.89, 39.53, 61.08, 104.52, 115.56, 117.39, 119.59, 120.79, 128.67, 129.98, 130.96, 136.76, 142.81, 158.20, 160.91, 167.20; IR (KBr) v: 3323, 3116, 1685, 1579, 1521, 1466, 877, 658 cm^{-1}. Anal. calcd for $C_{25}H_{25}F_2NO_4S$: C 63.41, H 5.32, N 2.96; found C 63.45, H 5.35, N 2.90.

General procedure for the synthesis of polyhydroquinoline

A mixture of 1,3-cyclohexanedione (3 mmol), 4-arylsulfanyl-benzaldehyde (3 mmol), ethylacetoacetate (3 mmol), ammonium acetate (4 mmol) and *L*-proline (10 mol%) was heated in ethanol (15 mL) at 60 ℃ under ultrasonic irradiation for the time as mentioned in Table 3. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into crushed ice and the solid product, which separated was filtered and recrystallized from ethanol to get pure yellow coloured crystalline polyhydroquinoline derivative **4a**—**4g**.

Spectroscopic data of 4a—4g

Ethyl 2-methyl-5-oxo-4-(4-(phenylthio)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a) Yellow crystal solid, m.p. 251—253 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.16 (t, J=6.9 Hz, 3H), 1.98 (t, J=4.9 Hz, 2H), 2.29—2.35 (m, 2H), 2.37 (s, 3H), 2.40 (t, J=4.9 Hz, 2H), 4.01—4.08 (m, 2H), 5.06 (s, 1H), 5.93 (br, 1H), 7.20—7.29 (m, 9H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.2, 19.4, 21.0, 27.5, 36.2, 37.0, 59.9, 105.9, 113.2, 126.6, 129.3, 129.6, 130.5, 131.2, 131.6, 131.9, 136.2, 137.8, 143.7, 147.1, 149.8, 167.3, 195.7. Anal. calcd for $C_{25}H_{23}F_2NO_3S$: C 65.92, H 5.09; found C 65.89, H 5.05.

Ethyl 4-(4-(4-fluorophenylthio)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4b) Yellow crystal solid, m.p. 227—229 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.20 (t, J=7.0 Hz, 3H), 1.90—1.98 (m, 2H), 2.31—2.36 (m, 2H), 2.38 (s, 3H), 2.41—2.45 (m, 2H), 4.03—4.11 (m, 2H), 5.07 (s, 1H), 6.04 (s, 1H), 6.97—7.02 (m, 2H), 7.11—7.28 (d, J=8.2 Hz, 2H), 7.29—7.35 (m, 4H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.2, 19.4, 21.0, 27.5, 36.2, 37.0, 59.9, 105.9, 113.2, 116.0, 116.3, 128.9, 130.1, 133.2, 133.4, 133.5, 143.4, 146.3, 149.6, 167.3, 195.7. Anal. calcd for $C_{25}H_{24}FNO_3S$: C 68.63, H 5.53; found C 68.70, H 5.58.

Ethyl 2-methyl-5-oxo-4-(4-(*m*-tolylthio)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4c) Yellow crystal solid, m.p. 268—271 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.19 (t, J = 7.0 Hz, 3H), 1.92—1.99 (m, 2H), 2. 25—2. 32 (m, 2H), 2.35 (s, 3H), 2.39 (s, 3H), 2.41—2.45 (m, 2H), 4.05 (q, J=7.0 Hz, 2H), 5.05 (s, 1H), 5.89 (s, 1H), 7.12 (t, J=8.3 Hz, 4H), 7.23 (t, J=8.3 Hz, 4H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.2, 19.4, 21.0, 21.1, 27.5, 36.0, 37.2, 59.9, 105.9, 113.3, 128.8, 129.9, 131.7, 133.6, 137.1, 143.3, 145.8, 149.4, 167.3, 196.0. Anal. calcd for $C_{26}H_{27}NO_3S$: C 72.03, H 6.28; found C 72.10, H 6.32.

Ethyl 4-(4-(3,4-dimethoxyphenylthio)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4d) Yellow crystal solid, m.p. 276—278 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.16 (t, J=7.0 Hz, 3H), 1.90—1.98 (m, 2H), 2.35 (s, 3H), 2.37—2.45 (m, 4H), 3.80 (s, 3H), 3.81 (s, 3H), 4.04 (q, J=7.0 Hz, 2H), 5.02 (s, 1H), 5.89 (s, 1H), 6.42—6.49 (m, 2H), 6.99 (d, J=

8.2 Hz, 2H), 7.16 (d, J=8.2 Hz, 2H), 7.23 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.2, 19.4, 21.0, 27.5, 35.9, 37.0, 55.5, 55.9, 59.8, 99.1, 105.9, 105.2, 113.1, 113.3, 128.2, 128.6, 134.1, 135.9, 143.3, 144.9, 149.4, 159.9, 161.4, 167.4, 195.9. Anal. calcd for $C_{27}H_{29}NO_5S$: C 67.62, H 6.09; found C 67.52, H 6.13.

Ethyl 4-(4-(3-fluoro-4-methoxyphenylthio)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4e) Yellow crystal solid, m.p. 195—197 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.20 (t, J=7.0 Hz, 3H), 1.93—2.02 (m, 2H), 2.37 (s, 3H), 2.39—2.45 (m, 4H), 3.88 (s, 3H), 4.04—4.11 (m, 2H), 5.07 (s, 1H), 6.20 (s, 1H), 6.90 (t, J=8.4 Hz, 1H), 7.07—7.13 (m, 4H), 7.23 (d, J=8.2 Hz, 2H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.2, 19.4, 21.0, 27.4, 36.1, 37.0, 42.3, 56.3, 59.9, 105.7, 113.1, 113.8, 119.8, 120.0, 128.4, 128.9, 129.7, 133.4, 143.6, 146.1, 149.9, 167.3, 195.9. Anal. calcd for $C_{26}H_{26}FNO_4S$: C 66.79, H 5.61; found C 66.84, H 5.72.

Ethyl 4-(4-(2-chloro-6-methylphenylthio)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4f) Yellow crystal solid, m.p. 207—209 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.17 (t, J=7.0 Hz, 3H), 1.91—2.02 (m, 2H), 2.30 (s, 3H), 2.39 (s, 3H), 2.40—2.47 (m, 4H), 4.00—4.12 (m, 2H), 5.09 (s, 1H), 6.16 (s, 1H), 6.98 (d, J=1.5 Hz, 2H), 7.11—7.04 (m, 2H), 7.16 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.3, 19.4, 19.9, 20.9, 27.5, 36.3, 37.0, 59.9, 105.7, 113.1, 126.6, 129.3, 129.6, 130.5, 131.2, 131.6, 131.9, 136.2, 137.8, 143.7, 147.1, 149.8, 167.3, 195.8. Anal. calcd for $C_{26}H_{26}ClNO_3S$: C 66.73, H 5.60; found C 66.79, H 5.55.

Ethyl 4-(4-(2,5-difluorophenylthio)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4g) Yellow crystal solid, m.p. 250—253 ℃; ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 1.23 (t, J=7.0 Hz, 3H), 1.96—2.03 (m, 2H), 2.33—2.49 (m, 4H), 2.45 (s, 3H), 4.02—4.12 (m, 2H), 5.13 (s, 1H), 5.88 (s, 1H), 6.60—6.66 (m, 1H), 6.80—6.85 (m, 1H), 6.96—7.03 (m, 1H), 7.33—7.39 (m, 4H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 14.3, 19.9, 20.9, 27.5, 36.3, 37.0, 59.9, 109.8, 113.8, 128.9, 129.0, 129.9, 130.5, 131.8, 132.6, 133.6, 135.9, 137.8, 143.7, 147.1, 149.8, 166.5, 195.7. Anal. calcd for $C_{25}H_{23}F_2NO_3S$: C 65.92, H 5.09; found C 65.84, H 5.11.

X-ray diffraction study of crystal structure of 3c

Single crystals of **3c** suitable for X-ray diffraction study were obtained from hexane/ethyl acetate solution at r.t. The diffraction data were collected on a Brucker SMART APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.71073 Å). An empirical absorption correction was applied by using SADABS. The strucμture was solved by direct method and refined by full-matrix least-square on F^2 using SHELXTL. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located on calculated positions and refined as rigid groups. Refinement details: empirical formula, $C_{25}H_{26}FNO_4S$; M_r = 455.53; temperature 298(2) K; crystal system: triclinic; space group: P-1; a = 7.5539(16) Å, b=11.059(2) Å, c=14.841(3) Å, V= 1145.5(4) Å^3, Z=2, ρ_{calcd}=1.321 Mg/m^3, m=0.181 mm^{-1}, F(000)=480, crystal size=0.38×0.22×0.18 mm^3, θ range=1.98° to 23.32°; Index ranges: $-7 \leqslant h \leqslant 8$, $-12 \leqslant k \leqslant 12$, $-16 \leqslant l \leqslant 16$; reflections collected 5247, independent reflections 3307 [R(int)=0.0178], completeness to θ=23.32°, 99.3%; max/min transmission 0.9681/0.9344; data/restraints/parameters 3307/0/293; goodness-of-fit on F^2 1.090; final R indices [$I > 2\sigma(I)$]: R_1=0.0626, wR_2=0.1428; R indices (all data): R_1=0.0722, wR_2=0.1490 and the other details see Table 3. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least squares methods (SHELXL-97) with anisotropic temperature factors for the non-H atoms. All H atoms were placed at chemically acceptable positions and were refined with isotropic temperature factors.

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