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An efficient, catalyst- and solvent-free, four-component, and one-pot synthesis of polyhydroquinolines on grinding

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Abstract

An efficient synthesis of polyhydroquinolines is achieved via a four-component reaction of aldehydes, dimedone, active methylene compounds, and ammonium acetate in one-pot under solvent-free conditions at room temperature on grinding. The present method does not involve any hazardous organic solvent or catalyst. The key advantages are the short reaction time, high yields, simple workup, and purification of products by non-chromatographic methods, i.e., by simple recrystallization from ethanol.

Keywords: Hantzsch condensation; One-pot synthesis; Polyhydroquinolines; Grinding; Solvent-free; Catalyst-free

1. Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) constitute an important class of Ca^{2+} channel blockers and have proved valuable as one of the most important class of drugs for the treatment of cardiovascular diseases, including hypertension.[1] 1,4-Dihydropyridines possess a variety of biological activities,[2] such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic agents. Recent studies have revealed that 1,4-DHPs exhibit several medicinal applications,[3] which include neuroprotectant and platelet anti-aggregatory activity, in addition to cerebral antiischemic activity in the treatment of Alzheimer's disease and as chemo sensitizer in tumor therapy. Quinolines having a 1,4-dihydropyridine nucleus are very important compounds because of their pharmacological properties. Members of this family are being used as antimalarial, antiinflammatory, antiasthamatic, antibacterial, and tyrosine kinase inhibiting agents.[4]

In view of the biological importance of polyhydroquinolines, several methods for their synthesis have been reported. The classical method involves the three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or refluxing alcohol.[5–7] However, these methods suffer from drawbacks of a long reaction time, usage of an excess of organic solvent, and lower yields of the products. Several alternate and more efficient methods have been developed for the synthesis of polyhydroquinoline derivatives by using microwaves,[8] ionic liquids,[9] TMSCl–NaI,[10] metal triflates,[11] I_2,[12] ceric ammonium nitrate,[13] polymers,[14] and organo-catalyst.[15] However, the use of high temperatures, expensive metal precursors, catalysts that are harmful to environment, and longer reaction times limit the use of these methods. Therefore, the search for a better method for the synthesis of polyhydroquinoline derivatives is still the need of the day.

In recent times, the progress in the field of solvent-free reactions is gaining significance because of their high efficiency, operational simplicity and environmentally benign processes. Solventless organic reactions based on grinding of two macroscopic particles together[16] mostly involve the formation of a liquid phase prior to reaction, i.e., formation of a eutectic melt of uniform distribution where the reacting components

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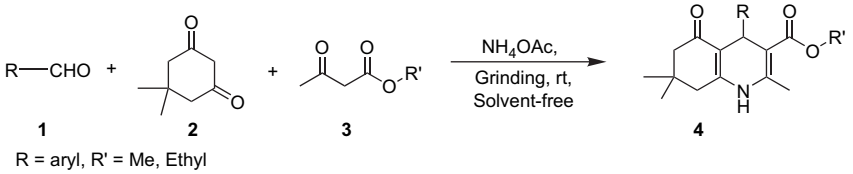
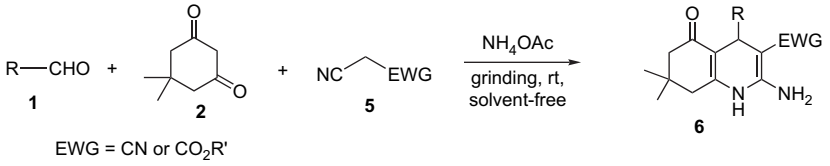


Scheme 1. Synthesis of hexahydroquinoline derivatives from aldehyde, dimedone, β-ketoesters, and ammonium acetate on grinding.



Scheme 2. Synthesis of 2-amino-hexahydroquinoline derivatives from aldehyde, dimedone, malononitrile/α-cyanoesters, and ammonium acetate on grinding.

being in close proximity are poised to react in a controlled way. The grinding mode for the solid-state reactions has earlier been reported for Grignard reaction,[17] Reformatsky reaction,[18] Aldol condensation,[19] Dieckmann condensation,[20] Knoevenagel condensation,[21] reduction,[22] and others.[23] Most of these reactions are carried out at room temperature in absolutely solvent-free environment using only a mortar and pestle. All these facts have strengthened our resolve to find newer eco-friendly methods[24,25] and prompted us to employ grinding at room temperature for the multicomponent synthesis of polyhydroquinoline in solvent-free environment (Schemes 1 and 2).

2. Results and discussion

In an initial endeavor, 1 equiv each of benzaldehyde **1**a, dimedone **2**, ethyl acetoacetate **3**, and ammonium acetate were heated under reflux in ethanol. After 4 h, only 55% of the expected product **4a** was obtained after workup and recrystallization from ethanol. In an attempt to improve the yields of the reaction and acknowledging the benefits of grinding,[17–23] the same reaction was performed in solvent-free conditions at room temperature. All the ingredients of the reaction were taken in a mortar, mixed thoroughly and ground well at room temperature. It was observed that the mixture which was initially in a partial liquid state, solidified during the process of grinding to a light yellow solid mass and thin layer chromatography (TLC), at this moment, indicated the complete conversion to the desired product. The solid mass was washed with cold water to remove any unreacted ammonium acetate, dried and recrystallized from ethanol to give 3-carbethoxy-1,4,5,6,7,8-hexahydro-4-phenyl-2,7,7-trimethyl-5-oxoquinoline, **4a** (95% yield). A possible explanation for the better yield in solvent-free conditions is that the eutectic mixture having uniform distribution of the reactants, brings the reacting species in close proximity to react than in solvent.

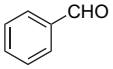
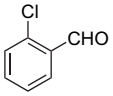
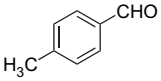
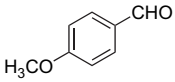
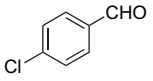
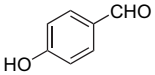
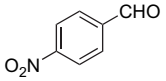
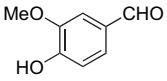
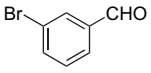
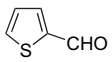
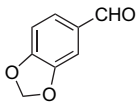
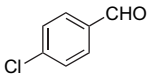
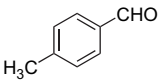
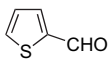
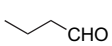
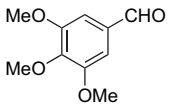
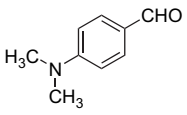
A variety of substrates were submitted to this reaction condition and the desired products were obtained in good to excellent yields (Table 1). It is evident that electron rich and electron deficient aldehydes as well as heterocyclic systems such as thiophene-2-carboxaldehyde, reacted smoothly with β-ketoesters (methyl and ethyl acetoacetate) to produce high yields of products. However, with aliphatic aldehydes, lower yields of the products were witnessed (entry 16). All the products were characterized by comparison of their analytical data (IR, NMR, and MS) with those of authentic samples. The structure of product **4q** (entry 17) was further confirmed by the crystal structure analysis. The structure solution reveals that both the six membered rings of the polyhydroquinoline derivative **4q** adopt half chair conformation. Figure 1 shows the ORTEP diagram of **4q**. The structure is stabilized by one intermolecular H-bonding interaction with neighboring translation equivalent ($x-1$, y, z) molecule (Fig. 2). The proton attached to nitrogen N1 forms a H-bond with the oxygen O6 such that the N1—H1···O6 distance is 2.057(2) Å. The molecule linked through H-bonds thus form a linear chain parallel to the 'a' axis of the unit cell.

In order to check the versatility of the procedure, β-ketoesters were replaced with other active methylene compounds such as malononitrile and ethyl cyanoacetate and the reactions were observed to follow the expected routes to yield 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolines and 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester, respectively, in good to excellent yields (Scheme 2). The results with different aldehydes are depicted in Table 2.

3. Conclusions

In conclusion, we have developed a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation under grinding the four reactants at room temperature in solvent-free conditions. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, efficient yields, short reaction times, and the easy workup procedure, makes this procedure attractive to synthesize a variety of these derivatives.

Table 1
Synthesis of polyhydroquinolines **4** on grinding the four components **1**, **2**, **3**, and ammonium acetate at room temperature in solvent-free conditions (Scheme 1)

Entry	R	R′	Product	Time (min)	Yield (%)	Melting point (°C)	
						Observed	Reported
1		Et	**4a**	15	95	203–204	202–203[11]
2		Et	**4b**	15	93	209–211	208–210[9a]
3		Et	**4c**	15	92	258–259	260–261[11]
4		Et	**4d**	15	93	255–257	257–259[11]
5		Et	**4e**	15	95	250–251	245–246[9a]
6		Et	**4f**	30	83	228–230	232–234[11]
7		Et	**4g**	12	88	245–246	242–244[9a]
8		Et	**4h**	20	80	231–233	235–237[9a]
9		Et	**4i**	15	90	234–236	235[11]
10		Et	**4j**	25	80	241–244	238–240[11]
11		Et	**4k**	25	83	252–255	248–250[11]
12		Et	**4l**	20	92	243–245	251–253[9a]
13		Me	**4m**	15	95	221–222	222–223
14		Me	**4n**	15	87	283–285	>280[15]
15		Me	**4o**	30	81	213–215	216–217
16		Et	**4p**	45	56	144–146	147–148[11]
17		Me	**4q**	20	88	203–206	198–199[5a]
18		Me	**4r**	20	85	256–258	257–258[5a]

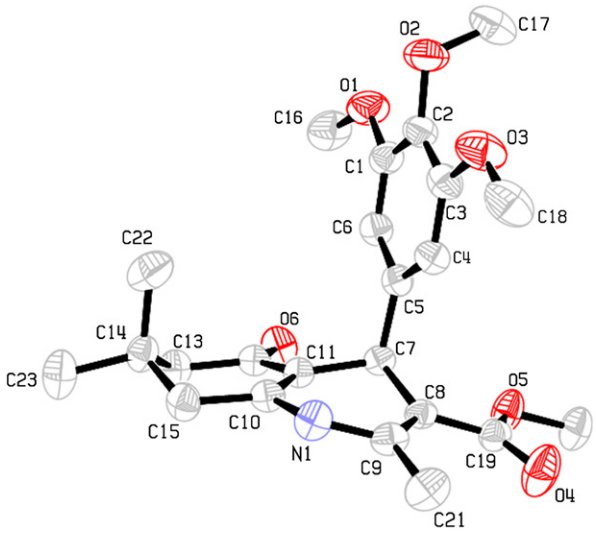


Figure 1. Showing the ORTEP diagram of **4q**. The H atoms have been omitted for clarity.

4. Experimental section

4.1. General procedures

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded in KBr discs on Perkin–Elmer FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on BrukerAC-200 (200 and 50 MHz, respectively) spectrometer. Mass spectra (ESI) were recorded on JEOL SX-102 spectrometer. Elemental analysis was performed on Leco CHNS-932 Analyzer. TLC was performed on 0.5 mm thick plates using BDH silica gel G as adsorbent.

*4.2. General procedure for the synthesis of 1,4,7,8-tetrahydro-2,7,7-trimethyl-4-aryl-5(6H)-oxoquinolin-3-carboxylic acid alkyl ester (**4a–k**)*

A mixture of aldehyde **1** (2 mmol), dimedone **2** (2 mmol), β-ketoester **3** (2 mmol), and ammonium acetate (3 mmol) was thoroughly mixed in a mortar followed by grinding till the completion of reaction as indicated by TLC (10–20 min). The resultant material was washed with water to remove any unreacted ammonium acetate and was air-dried to afford the crude product. The pure product was obtained by recrystallization from ethyl alcohol. The spectroscopic and analytical data for selected compounds are presented below.

*4.2.1. Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(2-chlorolphenyl)-5(6H)-oxoquinolin-3-carboxylate (**4b**)*

Yellow solid, mp 207–208 °C. IR (KBr) ν_{max}/cm^{-1}: 3063, 2956, 1721, 1640, 1611, 1467, 1384,1227, 1021, 745; ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.20 (t, J=7.2 Hz, 3H, CH_3), 2.01–2.21 (m, 4H, 2×CH_2), 2.40 (s, 3H, CH_3), 4.05 (q, J=7.2 Hz, 2H, CH_2), 4.60 (s, 1H, CH), 7.10–7.30 (m, 4H, ArH), 7.60 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 26.5, 29.1, 31.2, 32.3, 42.4, 46.8, 48.9, 50.5, 52.9, 55.1, 101.3, 109.2, 114.2, 125.9, 127.1, 128.7, 131.1, 132.3, 141.0, 167.5, 195.7; MS (ESI): *m/z* 374.1 (M+H)$^{+}$. Anal. Calcd for $C_{21}H_{24}NO_3Cl$: C, 67.56; H, 6.43; N, 3.75. Found: C, 67.52; H, 6.48; N, 3.72.

*4.2.2. Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxylphenyl)-5(6H)-oxoquinolin-3-carboxylate (**4d**)*

Yellow solid, mp 255–257 °C. IR (KBr) ν_{max}/cm^{-1}: 3276, 2956, 1703, 1648, 1606, 1496,1381, 1215, 1031, 765; ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.21 (t, J=7.2 Hz, 3H, CH_3), 2.01–2.10 (m, 4H, 2×CH_2), 2.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.00 (q, J=7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.65 (d, J=7.3 Hz, 2H, ArH), 7.10 (d, J=7.3 Hz, 2H, ArH), 8.65 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.1, 18.2, 26.4, 29.1, 32.1, 34.7, 50.2, 50.5, 54.8, 58.9, 103.2, 110.1, 113.0, 113.1, 128.2, 128.3, 139.8, 144.6, 149.1, 157.2, 166.9, 194.2; MS (ESI): *m/z* 370.2 (M+H)$^{+}$. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.54; H, 7.31; N, 3.79. Found: C, 71.59; H, 7.35; N, 3.84.

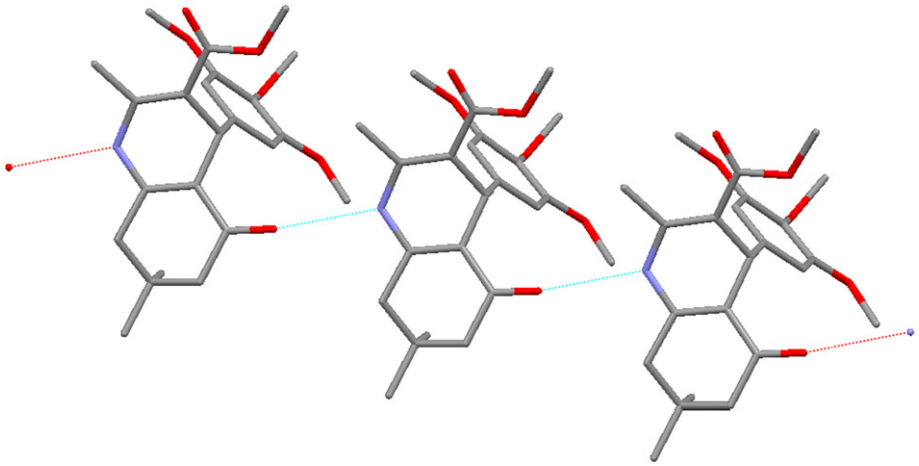
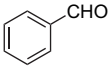
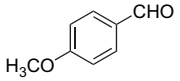
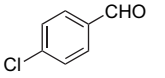
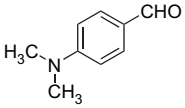
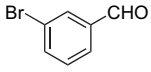
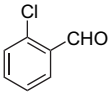
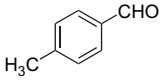
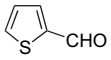
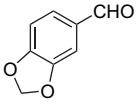
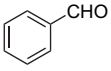
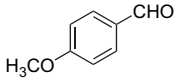
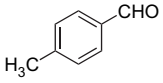
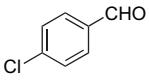
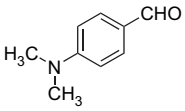


Figure 2. Showing the formation of a chain due to H-bonding interactions.

Table 2
Synthesis of polyhydroquinoline derivatives **6** on grinding the four components **1**, **2**, **5**, and ammonium acetate at room temperature in solvent-free conditions (Scheme 2)

Entry	R	EWG	Product	Time (min)	Yield (%)	Melting point (°C)	
						Observed	Reported[8c]
1		CN	**6a**	15	88	275–277	280–281
2		CN	**6b**	15	82	289–293	288–289
3		CN	**6c**	15	87	287–288	290–291
4		CN	**6d**	25	75	>300	>300
5		CN	**6e**	20	88	293–294	295–296
6		CN	**6f**	20	75	273–276	—
7		CN	**6g**	15	80	294–295	>300
8		CN	**6h**	20	74	253–255	256–257
9		CN	**6i**	25	77	265–267	269–270
10		CO_2Et	**6j**	20	72	150–155	—
11		CO_2Et	**6k**	25	70	122–125	—
12		CO_2Et	**6l**	18	65	135–137	—
13		CO_2Et	**6m**	15	75	174–176	—
14		CO_2Et	**6n**	25	77	115–120	—

*4.2.3. Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-hydroxy-3-methoxylphenyl)-5(6H)-oxoquinolin-3-carboxylate (**4h**)*

Yellow solid, mp 231–233 °C. IR (KBr) ν_{max}/cm^{-1}: 3388, 2953, 1700, 1643, 1589, 1482, 1385, 1218, 1029, 782; ^1H NMR (200 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.25 (t, J=7.2 Hz, 3H, CH_3), 2.02–2.20 (m, 4H, 2×CH_2), 2.30 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.05 (q, J=7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.60 (s 2H, ArH), 6.82 (s, 1H, ArH), 7.69 (s, OH), 8.49 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.2, 18.2, 26.3, 29.2, 32.1, 35.0, 50.2, 55.4, 58.9, 104.0, 110.1, 112.0, 114.9, 119.3, 119.5, 139.0, 144.3, 144.5, 146.7, 149.2, 167.0, 194.3; MS (ESI): *m/z* 386.2 $(M+H)^+$. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.57; H, 7.06; N, 3.64. Found: C, 68.52; H, 7.10; N, 3.68.

4.2.4. Methyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(3,4,5-trimethoxylphenyl)-5(6H)-oxoquinolin-3-carboxylate (**4q**)

Yellow solid, mp 223–226 °C. IR (KBr) ν_{max}/cm^{-1}: 3280, 3185, 3058, 2931, 1686, 1644, 1603, 1490, 1382, 1333, 1227, 1114, 1004, 787; ^1H NMR (200 MHz, DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.00–2.51 (m, 4H, 2×CH_2), 2.27 (s, 3H, CH_3), 3.47 (s, 3H, CO_2Me), 3.59 (s, 3H, OMe), 3.67 (s, 6H, two OMe), 4.83 (s, 1H, CH), 6.41 (s, 2H, ArH), 8.39 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 18.6, 26.7, 29.6, 32.5, 35.9, 50.6, 55.9, 60.2, 103.0, 104.7, 110.0, 136.1, 143.5, 145.4, 150.3, 152.7, 167.8, 194.9; MS (ESI): *m/z* 416.0 $(M+H)^+$. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.57; H, 7.11; N, 3.46.

4.3. X-ray crystallography[26]

The data were collected on a Siemens P4 single crystal diffractometer using graphite monochromatized Mo Kα radiation (λ=0.71073 Å). Table 3 shows the unit cell parameters and other crystallographic details. Data collection and cell refinement were done with XSCANS.[26a] The data was corrected for Lorentz and polarization effects. Structure was solved by direct methods and refined anisotropically by full-matrix least-squares method. All the hydrogens were fixed geometrically as riding atoms with a displacement parameter equal to 1.2 (CH, CH_2) or 1.5 (CH_3) times that of the parent atoms. Data reduction, structure solutions, refinement and molecular graphics were performed using SHELXLTL-PC[26b] and WINGX.[26c] Torsion angles and least-square planes were calculated by using PARST.[25d] CCDC number for compounds **4**q is CCDC 656035.

Table 3
Showing the crystal data and refinement details for **4q**

Identification code	**4q**
Empirical formula	$C_{23}H_{29}NO_6$
Formula weight	415.47
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a=7.167(1) Å b=20.095(1) Å c=15.157(1) Å β=90.66(1)°
Volume	2182.8(4) $Å^3$
Z, Calculated density	4, 1.264 mg/m^3
Absorption coefficient	0.091 mm^{-1}
$F(000)$	888
Theta range for data collection	1.68–27.50
Limiting indices	$0\le h\le 9$, $0\le k\le 26$, $-19\le l\le 19$
Reflections collected/unique	5395/5009 [R(int)=0.0244]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5009/0/271
Goodness-of-fit on F^2	1.069
Final R indices [$I>2\sigma(I)$]	R_1=0.0700, wR_2=0.1750
R indices (all data)	R_1=0.1470, wR_2=0.2201
CCDC number	656035

4.4. General procedure for the synthesis of 2-amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**6a–i**)

A mixture of aldehyde **1** (2 mmol), dimedone **2** (2 mmol), malononitrile or ethyl cyanoacetate **5** (2 mmol), and ammonium acetate (3 mmol) was mixed thoroughly in a mortar with pestle followed by grinding till the completion of reaction as indicated by TLC (10–20 min). The resultant material was washed with water to remove any unreacted ammonium acetate and was air-dried to afford the crude product. The pure product was obtained by recrystallization from ethyl alcohol. The spectroscopic and analytical data for selected compounds are presented below.

4.4.1. 2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**6a**)

Light yellow solid, mp 275–277 °C. IR (KBr) ν_{max}/cm^{-1}: 3426, 3315, 3203, 2177, 1657, 1603, 1495; ^1H NMR (200 MHz, DMSO-d_6): δ 0.91 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.98–2.42 (m, 4H, 2×CH_2), 4.31 (s, 1H, CH), 5.73 (s, 2H, ArH), 7.15–7.24 (m, 5H, ArH), 8.86 (s, 1H, NH); MS (ESI): *m/z* 294.1 $(M+H)^+$. Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.73; H, 6.59; N, 14.35.

4.4.2. 2-Amino-4-(2′-thienyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**6h**)

Yellow solid, mp 254–255 °C. IR (KBr) ν_{max}/cm^{-1}: 3378, 3319, 3286, 2198, 1679, 1607; ^1H NMR (200 MHz, DMSO-d_6): δ 0.92 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.06–2.29 (m, 4H, 2×CH_2), 4.51 (s, 1H, CH), 5.85 (s, 2H, NH_2), 6.85–7.12 (m, 3H, ArH), 8.98 (s, 1H, NH); MS (ESI): *m/z* 300.2 $(M+H)^+$. Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.15; H, 5.68; N, 13.99.

4.4.3. 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**6j**)

Light yellow solid, mp 150–155 °C. IR (KBr) ν_{max}/cm^{-1}: 3426, 3315, 3203, 2177, 1657, 1603, 1495; ^1H NMR (200 MHz, DMSO-d_6): δ 0.88 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.07 (t, J=7.1 Hz, 3H, CH_3) 1.99–2.49 (m, 4H, 2×CH_2), 3.92 (q, J=7.1 Hz, 2H, CH_2), 4.48 (s, 1H, CH), 5.73 (s, 2H, ArH), 7.07–7.19 (m, 5H, ArH), 7.52 (s, 2H, NH_2). MS (ESI): *m/z* 341.2 $(M+H)^+$. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.48; H, 7.17; N, 8.18.

4.4.4. 2-Amino-7,7-dimethyl-5-oxo-4-(4′-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**6k**)

Light yellow solid, mp 122–125 °C, IR (KBr) ν_{max}/cm^{-1}: 3410, 3323, 3198, 2976, 1679, 1619, 1507; ^1H NMR (200 MHz, DMSO-d_6): δ 0.90 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.09 (t, 3H, J=7.1 Hz, CH_3), 2.07–2.54 (m, 4H, 2×CH_2), 3.76 (s, 3H, OMe), 3.98 (q, 2H, J=7.1 Hz, CH_2), 4.56 (s, 1H, CH), 6.82 (d, 2H, J=8.0 Hz, ArH), 7.06 (d, 2H, J=8.0 Hz, ArH), 7.55 (s, 2H, NH_2); MS (ESI): *m/z* 371.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.13; H, 7.02; N, 7.54.

*4.4.5. 2-Amino-7,7-dimethyl-5-oxo-4-(4′-chlorophenyl)-1,4,5, 6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**6k**)*

Light yellow solid, mp 174–176 °C. IR (KBr) ν_{max}/cm^{-1}: 3465, 3329, 2995, 1726, 1595, 1507, 1365, 1272, 1208, 1198, 1094, 1020, 816, 762; ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.15 (t, 3H, J=7.1 Hz, CH_3), 2.22 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 4.04 (q, 2H, J=7.1 Hz, CH_2), 4.66 (s, 1H, CH), 6.17 (s, 2H, NH_2), 7.23 (m, 4H, ArH), 7.26 (s, 1H, NH); MS (ESI): *m/z* 374.1 (100), 376.1 (30) $(M+H)^+$. Anal. Calcd for $C_{20}H_{23}ClN_2O_3$: C, 64.08; H, 6.18; N, 7.47. Found: C, 64.03; H, 6.12; N, 7.44.

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