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# Novel Synthesis of 1,4-Dihydropyridine and Quinoline Derivatives under Microwave Irradiation in Solvent-free Conditions

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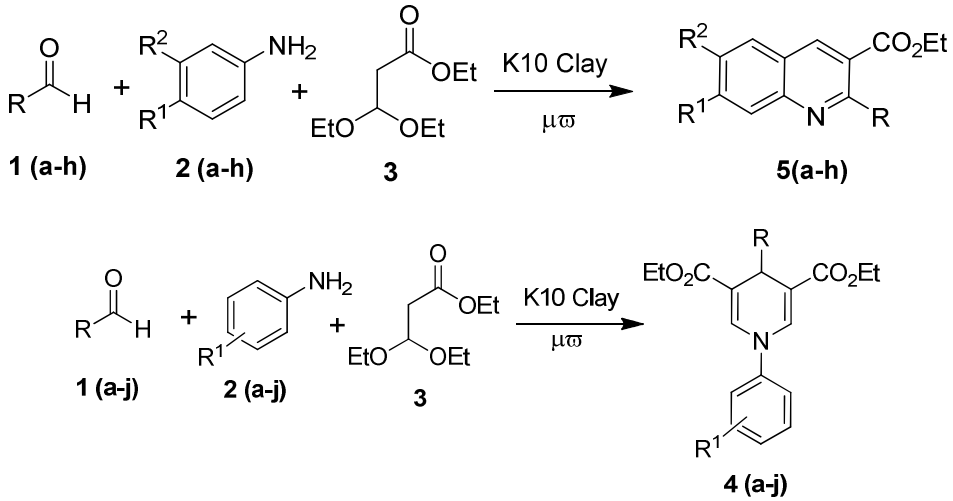
**ABSTRACT**

*An environmentally benign protocol has been described for the one-pot synthesis of novel 1,4-dihydropyridine and quinoline derivatives from aldehyde, aniline, and ethyl 3,3-diethoxy propionate. The use of montmorillonite K10 clay under microwave irradiation in solvent-free conditions makes it simple, convenient and greener approach.*




**Key words:** Microwave irradiation, k10 clay, 1,4-Dihydropyridine, Quinoline

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## INTRODUCTION

Quinolines are widely used in pharmaceutical industry,[1,2] because of their inherent biological activities. Consequently, a large number of methods have been developed for the construction of a quinoline ring, which include Skraup, Friedlander, Doebner–Miller, Combes or Pfitzinger syntheses.[2] Indeed, quinoline containing compounds display a wide range of biological activities.[3-7] On the other hand, 1,4-dihydropyridine (1,4-DHP) framework is considered as a privileged structure in drug discovery. In particular, 1,4-DHPs are used as calcium channel blockers (Nifedipine, Felodipine and Nicardipine) for the treatment of hypertension and related

cardiovascular diseases.[8-11] In addition, the pyridine nucleus is found to be an integral part of several phosphodiesterase-4 inhibitors (PDE4) such as piclamilast, roflumilast etc that are used for the treatment of asthma and chronic obstructive pulmonary disease (COPD).[12] As a result, several methods have been developed for the synthesis of 1,4-dihydropyridines.[13-16] A similar type of pyridine derivatives are prepared using a basic ionic liquid, which acts as a catalyst and reaction medium.[17] A plethora of reagents catalysts such as $AlCl_3$, $ZnCl_2$ and $FeCl_3$[18], InCl,[19] NaOH[20] and *p*-TSA[21] are reported for this conversion. However, many of these methods suffer from several disadvantages such as longer reaction time, excess of organic solvent, lower conversions, poor selectivity and harsh reaction conditions.

There is a great demand for the development of green approaches due to the reduction of by-products, reaction waste and reduction of energy. In view of environmental benefits, one-pot multi-component reactions (MCRs) have been reported for the synthesis of these heterocycles. MCRs are those reactions in which three or more reactants react together to give the product in a single step under suitable reaction conditions.[22] This method offers the advantage of simplicity and synthetic efficiency over conventional reactions. The MCRs have the additional advantage of high selectivity, synthetic convergence and atom economy.[23] Therefore, we envisioned that the similar strategy for the construction of DHP or quinoline ring would not only be benaficial for the development of a simpler and straight-forward method[24] but also might increase chances of achieving a greener synthetic route by combining microwave irradiation under solvent-free conditions. Therefore, the MCRs that are carried out in solvent free conditions under microwave irradiation offer better environmental perception.

In addition, the use of microwave irradiation and solvent-free conditions provide another advancement in green chemical synthesis because the microwave assisted organic reactions are accelerated as a consequence of three dimensional heating of the reaction mass, which cannot be attained by classical heating. Moreover, improved selectivity and clean reaction pathways are additional advantages. Indeed, the reactions that do not occur by conventional heating can be effectively performed using microwaves conditions. In the present study, the reaction is carried out using Montmorillonite K10 as a solid acidic catalyst in solvent-free conditions under microwave irradiation. The novelty of this method lies in its eco-friendly operation, formation of structurally unique molecules, short reaction time and higher yields.

## MATERIALS AND METHODS

### General

Melting points were measured on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were recorded on FTIR spectrometer (KBr) and reported in reciprocal centimeters (cm-1). NMR spectra were recorded for $^1$H NMR at 300MHz, 500MHZ and for $^{13}$C NMR at 75MHz. For $^1$H NMR, tetramethylsilane (TMS) served as internal standard ($\delta = 0$) and data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t= triplet, q =quartet, m = multiplet, br = broad) and the coupling constant J in Hz. For $^{13}$C NMR, $CDCl_3$ ($\delta = 77.27$) was used as internal standard and the spectra were obtained with complete proton decoupling. HRMS data were obtained using Electrospray ionization (ESI). Microwave irradiation was performed by using a mono-mode discover microwave reactor (CEM Corp., Matthews, NC).

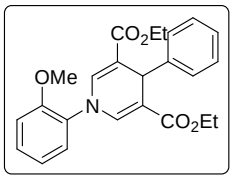
1.

### Preparation of 1,4-dihydropyridine and quinoline derivatives

An equiv molar ratio of **1a** (1 mmol), **2a** (1 mmol), and **3**(1 mmol) was mixed with montmorillonite K10 clay (50% w/w with respect to aldehyde).in a test tube. It was placed in a beaker and irradiated in a microwave oven for 2 min at 250 W and the heating was continued for 10-25 min to complete the reaction (monitored by TLC). After completion, the reaction mixture was cooled to room temperature, filtered through a celite bed and the bed was washed with dichloromethane (5.0 mL). The filtrates were collected, combined and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexanes (0-15%) to give the desired product **4a**. The same procedure was used for the synthesis of **4(b-j**) and **5(a-h).**

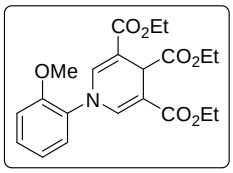
**Spectral data for the 1,4- dihydropyridine and quinoline derivatives:**

***Diethyl 1-(2-methoxyphenyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a):***



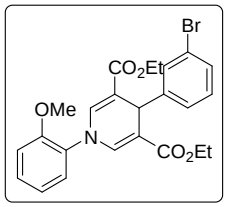

Off white solid; **mp:** 165-167 °C; **IR** (KBr) 2980, 1704, 1665, 1599, 1505, 1454, 1371, 1349, 1275, 1260, 1123, 1080 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.17 (t, *J* = 7.2 Hz, 6H), 3.92 (s, 3H), 4.02-4.12 (m, 4H), 4.94 (s, 1H), 7.01-7.24 (m, 4H), 7.29-7.40 (m, 5H), 7.43-7.54 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.1, 37.4, 55.9, 60.0, 109.2, 112.2, 121.0, 126.0, 126.3, 127.8, 128.5, 128.9, 137.9, 146.7, 154.0, 167.0; **HRMS**: *m/z* calcd for $C_{24}H_{26}NO_5$ $(M+H)^+$ 408.1811; found 408.1803.

***Triethyl 1-(2-methoxyphenyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (4b):***



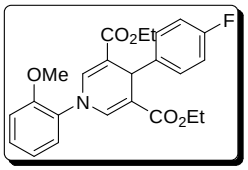

Brown liqiud; **IR** (KBr) 2985, 1709, 1665, 1573, 1465, 1373, 1263, 1126, 1073 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 300 MHz) δ 1.16-1.25 (t, *J* = 6.8 Hz, 9H), 3.90-4.14 (s, 9H), 4.90 (s, 1H), 7.01- 7.06 (d, 1H), 7.32-7.41 (m, 5H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.1, 37.0, 55.8, 60.1, 108.5, 112.1, 120.2, 121.1, 126.0, 129.1, 130.2, 130.9, 131.9, 138.1, 145.7, 154.0, 166.7; **HRMS**: *m/z* calcd for $C_{21}H_{26}NO_7$ $(M+H)^+$ 404.1689; found 404.1683.

***Diethyl 4-(3-bromophenyl)-1-(2-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c):***




Pale yellow solid; **mp:** 203-205 °C; **IR** (KBr) 2978, 1709, 1698, 1600, 1587, 1506, 1472, 1350, 1272, 1260, 1123, 1080 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.20-1.25 (t, *J* = 7.2 Hz, 6H), 3.95 (d, 3H), 4.03-4.16 (m, 4H), 4.91 (s, 1H), 7.01-7.15 (m, 3H), 7.27-7.41 (m, 6H), 7.63 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.1, 37.2, 55.9, 60.1, 108.5, 112.1, 121.0, 126.0, 127.2, 129.2, 131.7, 131.9, 138.3, 149.0, 154.3, 166.7; **HRMS**: *m/z* calcd for $C_{24}H_{25}BrNO_5$ $(M+H)^+$ 486.0916; found 486.0923.

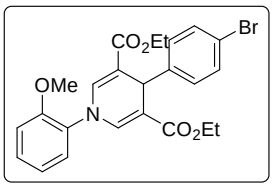
***Diethyl4-(4-fluorophenyl)-1-(2-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d):***




Off white solid; **mp:** 174-176 °C; **IR** (KBr) 2983, 1701, 1601, 1586, 1506, 1459, 1372, 1347, 1277, 1260, 1156, 1081 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.19 (t, *J* = 6.8 Hz, 6H), 3.91 (s, 3H), 4.02-4.18 (m, 4H), 4.93

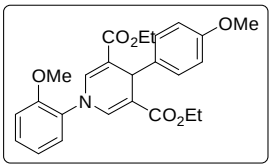
(s, 1H), 6.92-7.06 (m, 4H), 7.24-7.26 (m, 1H), 7.32-7.44 (m, 5H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.2, 36.7, 55.8, 60.0, 109.0, 112.2, 114.6, 121.1, 126.0, 129.1, 129.8, 129.9, 132.0, 137.9, 142.6, 154.0, 160.5, 162.4, 166.8; **HRMS**: *m/z* calcd for $C_{24}H_{25}FNO_5$ $(M+H)^+$ 426.1717; found 426.1708.

***Diethyl 4-(4-bromophenyl)-1-(2-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4e):***



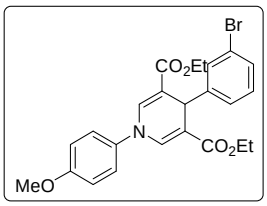

Yellow solid; **mp:** 211-213 °C; **IR** (KBr) 2975, 1706, 1693, 1590, 1505, 1485, 1371, 1345, 1259, 1202, 1121, 1076 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.18 (t, *J* = 6.8 Hz, 6H), 3.90 (s, 3H), 4.01-4.13 (m, 4H), 4.90 (s, 1H), 6.99-7.09 (m, 2H), 7.11-7.22 (m, 3H), 7.30-7.43 (m, 5H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.2, 37.0, 55.9, 60.1, 108.7, 112.1, 121.2, 126.0, 127.3, 129.1, 130.2, 130.9, 138.1, 145.8, 154.1, 166.7; **HRMS**: *m/z* calcd for $C_{24}H_{25}BrNO_5$ $(M+H)^+$ 486.0916; found 486.0914.

***Diethyl 1-(2-methoxyphenyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4f):***



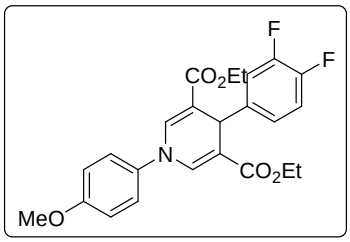

Reddish brown oil; **IR** (KBr) 2987, 1701, 1674, 1596, 1507, 1463, 1373, 1362, 1275, 1202, 1127, 1083 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.28 (t, *J* = 7.2 Hz, 6H), 3.77 (s, 3H), 3.85 (s, 3H), 4.02-4.14 (m, 4H), 4.88 (s, 1H), 6.79-6.83 (m, 1H), 6.96-7.21 (m, 4H), 7.30-7.42 (m, 5H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) 13.9, 29.2, 36.2, 55.5, 59.7, 106.4, 109.1, 112.0, 113.0, 120.8, 125.8, 128.8, 129.2, 137.5, 139.5, 153.3, 157.8, 166.6; **HRMS**: *m/z* calcd for $C_{25}H_{28}NO_6$ $(M+H)^+$ 438.1850; found 438.1854.

***Diethyl 4-(3-bromophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4g):***



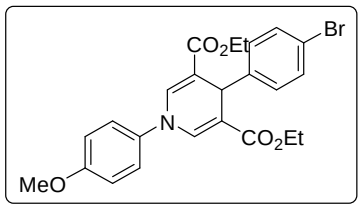

Yellow solid; **mp:** 189-191 °C; **IR** (KBr) 2962, 1707, 1694, 1663, 1578, 1512, 1460, 1348, 1276, 1228, 1116, 1060 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.19 (t, *J* = 7.2 Hz, 6H), 3.84 (s, 3H), 4.02-4.19 (m, 4H), 4.92 (s, 1H), 6.96-6.98 (m, 2H), 7.11-7.24 (m, 5H), 7.27-7.31 (m, 1H), 7.47-7.58 (m, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) **δ** 14.1, 37.5, 55.6, 60.2, 109.6, 114.9, 122.9, 127.1, 129.6, 131.5, 136.5, 148.5, 158.3, 166.6; HRMS: *m/z* calcd for $C_{24}H_{25}BrNO_5$ $(M+H)^+$ 486.0916; found 486.0932.

***Diethyl 4-(3,4-difluorophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4h):***



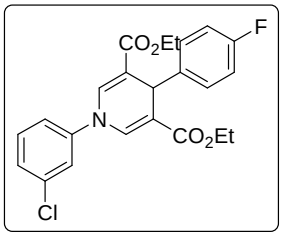

Off white solid; **mp:** 181-183 °C; **IR** (KBr) 2981, 1707, 1688, 1598, 1582, 1514, 1463, 1375, 1327, 1277, 1231, 1085 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 7.2 Hz, 6H), 3.85 (s, 3H), 4.05-4.22 (m, 4H), 4.93 (s, 1H), 6.95-7.24 (m, 7H), 7.54-7.56 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.2, 37.0, 55.6, 60.3, 109.5, 114.9, 116.4, 117.0, 122.9, 124.1, 127.6, 128.7, 136.5, 143.3, 158.3, 166.5; **HRMS**: *m/z* calcd for $C_{24}H_{24}F_2NO_5$ $(M+H)^+$ 444.1623; found 444.1661.

***Diethyl 4-(4-bromophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4i):***



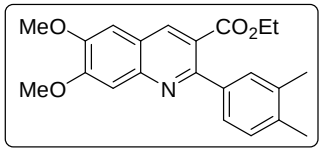

Yellow solid; **mp:** 207-209 °C; **IR** (KBr) 2981, 1707, 1687, 1583, 1512, 1473, 1368, 1337, 1263, 1202, 1117, 1085 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.20 (t, *J* = 6.8 Hz, 6H), 3.85 (s, 3H), 4.04-4.18 (m, 4H), 4.93 (s, 1H), 6.94-6.99 (m, 2H), 7.11-7.24 (m, 4H), 7.29-7.36 (m, 2H), 7.46-7.59 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.0, 29.2, 40.5, 55.5, 59.8, 106.3, 112.0, 120.8, 125.8, 127.5, 128.7, 131.6, 132.5, 139.5, 149.2, 153.3, 166.6; **HRMS***: m/z* calcd for $C_{24}H_{25}BrNO_5$ $(M+H)^+$ 486.0916; found 486.0938.

***Diethyl 1-(3-chlorophenyl)-4-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4j):***



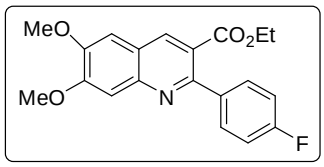

Yellow oil; **IR** (KBr) 2983, 1707, 1693, 1599, 1505, 1485, 1362, 1373, 1283, 1202, 1137, 1086 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.21-1.27 (t, *J* = 6.8 Hz, 6H), 4.05-4.20 (m, 4H), 4.94 (s, 1H), 6.71 (s, 1H), 6.91-6.99 (m, 2H), 7.04-7.17 (m, 3H), 7.35-7.63 (m, 4H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) 14.0, 40.5, 59.8, 106.3, 112.0, 120.8, 125.8, 128.7, 131.8, 132.5, 135.6, 139.5, 142.3, 144.2, 149.2, 153.3, 166.6; **HRMS**: *m/z* calcd for $C_{23}H_{22}ClFNO_4$ $(M+H)^+$ 430.1207; found 430.1201.

***Ethyl 2-(3,4-dimethylphenyl)-6,7-dimethoxyquinoline-3-carboxylate (5a):***



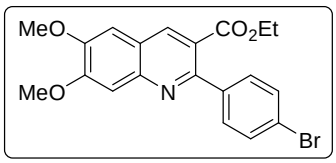
Yellow solid; **mp**: 147-148 °C; **IR** (KBr) 1715, 1619, 1596, 1516, 1443, 1431, 1336, 1267, 1232, 1156, 1071 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.12 (t, *J* = 6.8 Hz, 3H), 2.33 (s, 6H), 4.04 (s, 6H), 4.21 (q, *J* = 6.8 Hz, 2H), 7.11-7.23 (m, 2H), 7.27-7.29 (m, 1H), 7.36-7.53 (s, 2H), 8.48 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 13.8, 19.6, 19.8, 56.1, 56.3, 61.2, 105.2, 108.1, 121.3, 123.4, 126.0, 129.2, 129.6, 136.2, 136.6, 136.9, 138.4, 145.8, 150.1, 154.0, 156.6, 168.3; **HRMS***: m/z* calcd for $C_{22}H_{24}NO_4$ $(M+H)^+$ 366.1705; found 366.1728.

***Ethyl 2-(4-fluorophenyl)-6,7-dimethoxyquinoline-3-carboxylate (5b):***



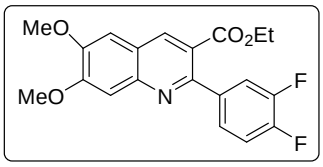

Pale yellow solid; **mp**: 165-166 °C; **IR** (KBr) 1714, 1618, 1498, 1454, 1431, 1393, 1351, 1269, 1237, 1158, 1029 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.14 (t, *J* = 7.2 Hz, 3H), 4.04 (s, 6H), 4.18-4.25 (q, 2H), 7.14-7.17 (m, 3H), 7.49 (s, 1H), 7.55-7.59 (m, 2H), 8.55 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 13.8, 56.1, 56.3, 61.3, 105.2, 107.8, 114.9, 115.1, 121.6, 122.9, 130.3, 130.4, 137.5, 150.5, 154.4, 155.3, 161.9, 163.3, 167.7***;*** **HRMS:** *m/z* calcd for $C_{20}H_{19}FNO_4$ $(M+H)^+$ 356.1298; found 356.1281.

***Ethyl 2-(4-bromophenyl)-6,7-dimethoxyquinoline-3-carboxylate (5c):***



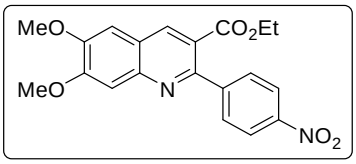

Off white solid; **mp**: 200-201 °C; **IR** (KBr) 1703, 1617, 1590, 1495, 1465, 1419, 1345, 1270, 1237, 1177, 1071 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.15 (t, *J* = 6.8 Hz, 3H), 4.05 (s, 6H), 4.18-4.25 (q, 2H), 7.15 (s, 1H), 7.44-7.50 (m, 3H), 7.57-7.61 (m, 2H), 8.55 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 13.8, 56.1, 56.3, 61.3, 105.1, 107.9, 121.6, 122.5, 122.7, 130.2, 131.1, 137.4, 140.1, 145.8, 150.5, 154.4, 155.3, 167.6; **HRMS:** *m/z* calcd for $C_{20}H_{19}BrNO_4$ $(M+H)^+$ 416.0497; found 416.0511.

***Ethyl 2-(3,4-difluorophenyl)-6,7-dimethoxyquinoline-3-carboxylate (5d):***



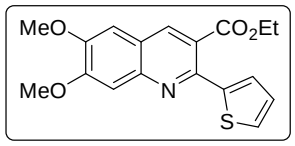

Off white solid; **mp**: 164-166 °C; **IR** (KBr) 1722, 1619, 1589, 1522, 1500, 1463, 1343, 1269, 1203, 1158, 1096 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.18 (t, *J* = 6.8 Hz, 3H), 4.06 (s, 6H), 4.21-4.27 (q, *J* = 6.8 Hz, 2H), 7.13-7.25 (m, 2H), 7.27-7.31 (m, 1H), 7.42-7.49 (m, 2H), 8.57 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 13.8, 56.2, 56.3, 61.4, 105.2, 107.9, 116.7, 116.8, 117.8, 118.0, 121.7, 122.6, 124.9, 137.6, 145.8, 150.6, 154.2, 154.5, 167.4; **HRMS***: m/z* calcd for $C_{20}H_{18}F_2NO_4$ $(M+H)^+$ 374.1204; found 374.1206.

***Ethyl 6,7-dimethoxy-2-(4-nitrophenyl)quinoline-3-carboxylate (5e):***



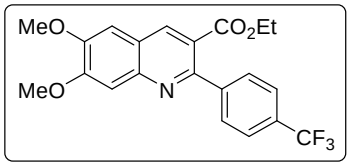

Light yellow solid; **mp**: 173-174 °C; **IR** (KBr) 1720, 1619, 1598, 1511, 1462, 1435, 1352, 1269, 1228, 1160, 1094 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 4.06 (s, 6H), 4.20-4.26 (q, *J* = 7.2 Hz, 2H), 7.18 (s, 1H), 7.49 (s, 1H), 7.72-7.75 (m, 2H), 8.30-8.37 (m, 2H), 8.65 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 14.0, 56.4, 56.6, 61.6, 105.4, 108.1, 115.1, 115.3, 121.8, 123.2, 130.6, 137.8, 150.7, 154.7, 155.6, 162.2, 163.6, 168.0; **HRMS: *m/z*** calcd for $C_{20}H_{19}N_2O_6$ $(M+H)^+$ 383.1243; found 383.1253.

***Ethyl 6,7-dimethoxy-2-(thiophen-2-yl)quinoline-3-carboxylate (5f):***



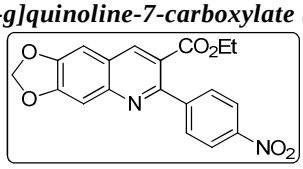

Light yellow solid; **mp**: 155-156 °C; **IR** (KBr) 1708, 1615, 1583, 1500, 1467, 1421, 1341, 1263, 1223, 1156, 1086 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 4.04 (s, 3H), 4.06 (s, 3H), 4.31-4.38 (q, *J* = 7.2 Hz, 2H), 7.04-7.16 (m, 2H), 7.35-7.37 (m, 1H), 7.44-7.46 (m, 2H), 8.34 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 13.9, 56.1, 56.3, 61.6, 105.0, 107.8, 121.3, 123.1, 127.3, 127.5, 136.4, 143.2, 145.6, 148.4, 150.4, 154.1, 168.4; **HRMS: *m/z*** calcd for $C_{18}H_{18}NO_4S$ $(M+H)^+$ 344.0957; found 344.0966.

***Ethyl 6,7-dimethoxy-2-(4-(trifluoromethyl)phenyl)quinoline-3-carboxylate (5g):***




Yellow solid; **mp**: 185-186 °C; IR (KBr) 1702, 1615, 1591, 1516, 1496, 1423, 1321, 1273, 1238, 1174, 1067 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.09 (t, *J* = 7.2 Hz, 3H), 4.05 (s, 6H), 4.17-4.22 (q, *J* = 7.2 Hz, 2H), 7.16 (s, 1H), 7.48 (s, 1H), 7.68- 7.74 (m, 4H), 8.61 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 13.6, 29.6, 56.2, 56.3, 61.4, 105.2, 107.9, 121.8, 122.6, 124.9, 128.9, 129.9, 130.2, 137.7, 144.8, 145.9, 150.7, 154.5, 155.2, 167.2; **HRMS*:*** *m/z* calcd for $C_{21}H_{19}F_3NO_4$ $(M+H)^+$ 406.1266; found 406.1292.

***Ethyl 6-(4-nitrophenyl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate (5h):***




Light yellow solid; **mp:** 212-214 °C; **IR** (KBr) 1722, 1599, 1587, 1512, 1462, 1435, 1349, 1258, 1231, 1175, 1083 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 500 MHz) δ 1.18 (t, *J* = 6.8 Hz, 3H), 4.20-4.27 (q, *J* = 6.8 Hz, 2H), 6.17 (s, 2H), 7.13 (s, 1H), 7.20-7.30 (m, 3H), 7.41-7.47 (m, 2H), 8.49 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 13.8, 61.5, 102.1, 102.8, 105.8, 116.7, 117.8, 118.0, 122.8, 123.2, 124.9, 138.0, 147.1, 148.7, 152.7, 154.1, 154.1, 167.4; **HRMS**: *m/z* calcd for $C_{19}H_{15}N2O_6$ $(M+H)^+$ 367.0930; found 367.0925.

## RESULTS AND DISCUSSION

Initially, the reactions were carried out under different conditions and the result are presented in Table 1. Of various acid catalysts, such as p-TSA, $AlCl_3$, $ZnCl_2$, $FeCl_3$ and $InCl_3$ studied, montmorillonite K10 gave the best result under

solvent free conditions. The reaction was also quite successful in water (entry e, Table 1). In the absence of clay, no reaction was observed in water (entry h, Table 1). Low yield was obtained in ethanol (entry i, Table 1). The best results were obtained when the reaction was performed using montmorillonite K10 50% w/w under microwave irradiation in solvent free conditions (entry j, Table 1). Under optimized conditions, the product was obtained in maximum yield of 93% with high selectivity (Scheme 1, entry j, Table 1). These results encouraged us to extend this approach for other substrates. Interestingly, several aldehydes and aryl amines participated well in this reaction (Table 2). Both mono-, and disubstituted aldehydes worked well for this reaction. In case of disubtituted anilines, the quinoline derivatives are formed exclusively (Scheme 2, Table 3).

We observed mainly three phenomenon in this work:

a) *Reaction time difference* :
Synthesis of 1,4-dihydroderivatives **4(a-j**): Three component reaction of aromatic aldehydes **1**(**a-j**) with aryl amines **2**(**a-j**) and ethyl-3,3-diethoxypropionate (**3**) in presence of montmorillonite K-10 was carried out as follows.
An equiv molar ratio of aldehyde (**1),** amine **(2),** ethyl diethoxy propionate (**3)** and catalyst (50% w/w with respect to aldehyde) was mixed thoroughly and then subjected to microwave irradiation for 2 min at 250 W. The irradiation was then continued for 10-25 min until complete disappearance of starting materials (as monitored by TLC). In case of electron deficient aldehydes, the products such as **4h, 4i, 5a, 5d and 5g** were formed within 10 min. It clearly indicates that the reactions are faster with electron deficient aldehydes.

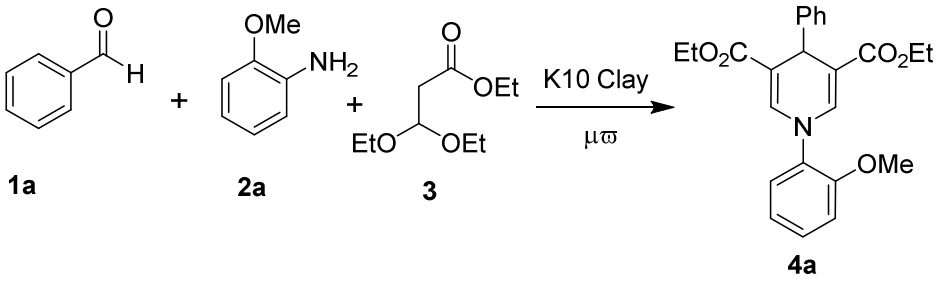
b)*Aliphatic and aromatic ring effect*:
Treatment of *p*-nitrobenzaldehyde (**1p**) with 3,4-dimethoxyaniline (**2p**) and ethyl diethoxy propionate **3** afforded the corresponding product **4p** in 93% yield. In case of *p*-$CF_3$-benzaldehyde (**1r**), the desired product **4r** was obtained in 90% yield. This is due to the presence of strong electron withdrawing effect of nitro group than $CF_3$. Furthermore, aromatic aldehyde gave the product in high yield with enhanced reaction rate than the aliphatic substrate. For example, treatment of aliphatic aldehyde **1b** with methoxyaniline and ethyl diethoxy propionate **3** gave the corresponding product **4b** in 62% after 25 min, which was higher than that of rest of the reactions. The above two facts exemplified that the electron withdrawing aromatic aldehydes possesses higher reactivity than the other compounds.

c) *Substitution effect* :
In case of anilines, there are two different phenomenons. Mono-substituted anilines gave entirely the different products than the disubstituted anilines, which afforded the quinolines and former one produced the pyridine derivatives. Irradiation of aldehydes **1(a-k), mono-substituted** anilines **2(a-k)**, and ethyl diethoxy propionate **3** furnished the pyridine derivatives **4(a-j)**. But the disubstituted anilines **2(l-s)** afforded the quinoline derivatives **5(a-h)** when treated with aldehydes **1(l-s)** and ethyl diethoxy propionate **3** (Table 2). All the new compounds **4(a-j**) and **5 (a-h)** were characterized by IR, $^1$HNMR, $^{13}$C NMR and mass analyses.

## CONCLUSION

In summary, we have demonstrated a novel synthesis of 1,4-dihydropyridine and quinoline derivatives using microwave irradiation under solvent-free conditions. The use of montmorillonite K10 catalyst has resulted high yields in short reaction time. We observed three phenomenons in this work a) reaction time difference, b) aliphatic and aromatic ring effect and c) substituent effect, which led to the difference in yield and product formation.

**Scheme:** Synthesis of 1,4-dihydropyridine and quinolines




**1a** **2a** **3** **4a**

**Table 1. Screening the catalysis in the formulation of 4a**

| Entry | Catalyst | Solvent | Yield (%)[a] |
|---|---|---|---|
| A | *P* -TSA (2.5 mol%) | $H_2O$ | 41 |
| B | $ZnCl_2$ (2.5 mol %) | $H_2O$ | 15 |
| C | $TiCl_4$ (2.5 mol %) | $H_2O$ | 30 |
| d | $SnCl_4$ (2.5 mol %) | $H_2O$ | 10 |
| e | K10 (50% w/w) | $H_2O$ | 68 |
| F | K10 (20% w/w) | $H_2O$ | 41 |
| G | K10 (0.5% w/w) | $H_2O$ | 28 |
| H | No catalyst | $H_2O$ | 0 |
| I | K10 (50% w/w) | EtOH | 35 |
| J | K10 (Microwave) | Neat | 72 |

[a]*Reactions were carried out using **1** (0.98 mmol), **2** (1.0 mmol) and **3** (2.4 mmol) of **4a***

**Table 2.** 3CC reaction for the synthesis of 1,4-dihydropyridines

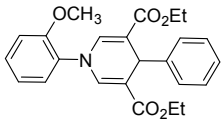
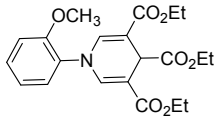
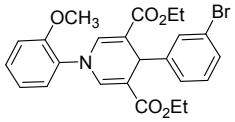
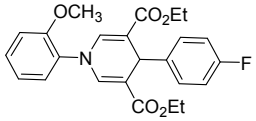
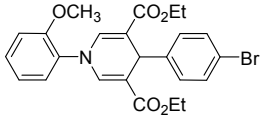
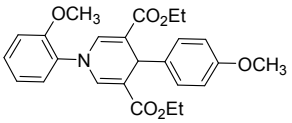
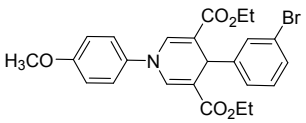
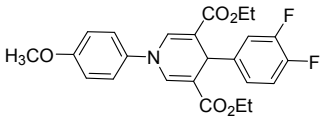
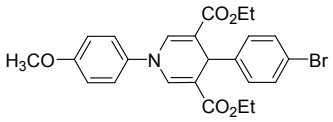
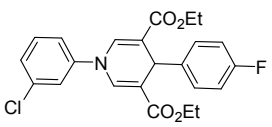
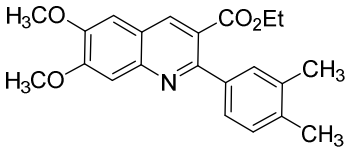
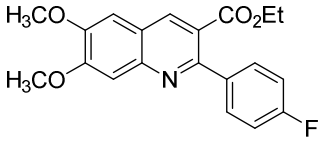
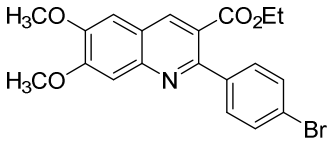
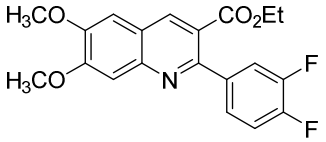
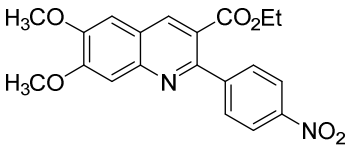
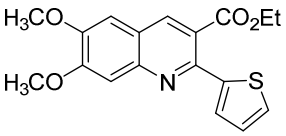
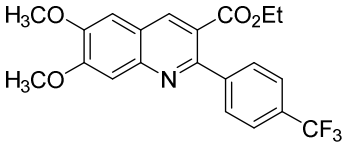
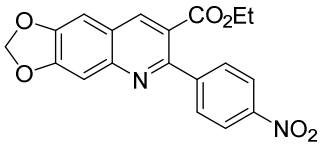
| Entry | Aldehyde(1) R | Aryl amine(2) $R^1$ | Product (4)[a] | Time (m) | Yield (%)[b] |
|---|---|---|---|---|---|
| a | $C_6H_5$ | 2-$OCH_3$ |  | 20 | 72 |
| b | $CO_2Et$ | 2-$OCH_3$ |  | 25 | 62 |
| c | 3-Br-$C_6H_4$ | 2-$OCH_3$ |  | 18 | 80 |
| d | 4-F-$C_6H_4$ | 2-$OCH_3$ |  | 20 | 83 |
| e | 4-Br-$C_6H_4$ | 2-$OCH_3$ |  | 15 | 84 |
| f | 4-$CH_3OC_6H_4$ | 2-$OCH_3$ |  | 20 | 78 |
| g | 3-Br-$C_6H_4$ | 4-$OCH_3$ |  | 15 | 85 |
| h | 3,4-Di-$FC_6H_3$ | 4-$OCH_3$ |  | 10 | 87 |
| i | 4-Br-$C_6H_4$ | 4-$OCH_3$ |  | 10 | 85 |
| j | 4-$FC_6H_4$ | 3-Cl |  | 15 | 82 |

**Table 3**. 3CC reaction for the synthesis of 2,3-disubstituted quinolines

| Entry | Aldehyde (1) $R^1$ | Aryl amine (2) $R^2$ | Product (5)[a] | Time (m) | Yield (%)[b] |
|---|---|---|---|---|---|
| a | 3,4-Di-$CH_3C_6H_3$ | 3,4-Di-$OCH_3$ |  | 20 | 75 |
| b | 4-$FC_6H_4$ | 3,4-Di-$OCH_3$ |  | 10 | 83 |
| c | 4-$BrC_6H_4$ | 3,4-Di-$OCH_3$ |  | 15 | 85 |
| d | 3,4-Di-$FC_6H_3$ | 3,4-Di-$OCH_3$ |  | 10 | 88 |
| e | 4-$NO_2C_6H_4$ | 3,4-Di-$OCH_3$ |  | 11 | 93 |
| f | 2-Thienyl | 3,4-Di-$OCH_3$ |  | 15 | 87 |
| g | 4-$CF_3C_6H_5$ | 3,4-Di-$OCH_3$ |  | 10 | 90 |
| h | 4-$NO_2C_6H_5$ | 3,4-Methylenedioxy |  | 20 | 85 |

[a]All products were characterized by NMR, IR and mass spectrometry.
[b]Isolated yields after column chromatography.

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