MICROWAVE-IRRADIATED SYNTHESIS OF 1,2-DIHYDROPYRIDINES FROM N-FUNCTIONALIZED ENAMINONES AND ENALS THROUGH DOMINO CONDENSATION AND 6π-AZA-ELECTROCYCLIZATION

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Abstract – N-Amino-substituted 1,2-dihydropyridine motifs are constructed using cyclohexane-1,3-diones via the Knoevenagel condensation with enals followed by 6π-electrocyclization using ethylenediammonium diacetate as a catalyst under MW irradiation. A survey of substituents on the N atom of the enaminoes indicated that the phenylamino and benzoylamino groups are favorable for the reaction, while phenyl, benzyl, and no-substituent are not. The substituent at C2 of enals is crucial for smooth formation of the corresponding adducts and slightly higher yields are obtained with enals bearing an electron-withdrawing aromatic at C3.

Recently, 1,4-dihydropyridine-based systems have attracted considerable attention due to their wide spectra of biological activities. For example, cardiovascular agents such as nifedipine (I), used for the treatment of hypertension, contain the dihydropyridyl motif (Figure 1). NADH coenzymes are comprised of 1,4-dihydropyridine units, which have been explored for their calcium channel activity. Accordingly, numerous methods have been reported for the synthesis and biological evaluation of 1,4-dihydropyridine derivatives, i.e. IIa, however, most of them have relied on the three-component coupling of 1,3-dicarbonyls (2 equiv.), aldehydes (1 equiv.), and amines (1 equiv.) by the Hantzsch reaction or its
modification. Furthermore, the N-aminated derivatives IIb were recently prepared using enaminones derived from arylhydrazines for one component of the Hantzsch reaction, and their biological activities were evaluated.

In contrast to the intensive synthetic and biological studies of 1,4-dihydropyridines, little attention has been paid to the synthesis and biological evaluation of their double bond regioisomer, i.e., the 1,2-dihydropyridines IIIa. Until now, some synthetic access to the 1,2-dihydropyridines has been explored. The 6π-electron electrocyclic ring closures of the 1-azatriene systems are considered one of the most promising and useful means to form the 1,2-dihydropyridines. Key step to this strategy is the preparation of the functionalized 1-azatriene units. Currently, these units are assembled in situ and directly used to construct the nitrogen heterocycles. For example, the Knoevenagel condensation of iminium ions with enaminones has proven to be a successful strategy for the construction of the 1,2-dihydropyridines. A more direct access to the 1-azatrienes has relied on the reaction of primary amines and 2,4-dienals. Although the use of such cyclic enaminones in a formal [3+3] cycloaddition had already been described by Hsung et al., the reaction conditions were more severe (150 °C in a sealed tube) and the moisture sensitive α,β-unsaturated imminium salts have to be handled. Besides these procedures, Bronsted acid catalyzed procedures were developed for the formal [3+3] annulation to the cyclohexane-1,3-diones. Therefore, an improved procedure to the 1,2-dihydropyridine structures with the increased choice of substituents and structural diversity by examination of the kind of amine component is still in needed.

In this paper, we report the MW-assisted tandem Knoevenagel condensation of enaminone and enals followed by 6π-azaelectrocyclization, which is affected by kind of substituent on the N atom of the enamines and the substituent on the iminium intermediate from the enals.

The Knoevenagel condensation of enaminones was performed under the iminium conditions using ethylenediammonium diacetate (EDDA) as a catalyst. Microwave irradiation was used to enhance the
sequential condensation and 6π-electron electrocyclization in a short period. The effect of the substituent Y on the enaminones 1 was first examined using the enaminones 1a–1e, prepared by the reaction of cyclohexane-1,3-dione 8a and the respective phenylhydrazine (9a), benzoxydrazide (9b), aniline, benzylamine, and ammonia.

Results of the condensation and cyclization of these enaminones 1a–1e with the enal 2g are shown in Table 1. The reaction of the enaminone 1a with 2g smoothly proceeds to produce the corresponding 3g in moderate yield (entry 1). Similarly, the enaminone 1b reacts with 2g under the same conditions in a slightly lesser yield (entry 2). On the other hand, the enaminones 1c and 1d lack the N-N group in the nucleophilic unit result in a decreased reactivity, and produce none of the desired products 5g and 6g (entries 3 and 4). The enamine 1e formed the adduct 7g in a small quantity by the reaction with 2g, which changed to the starting enaminone 1e and the enal 2g during chromatographic purification.

**Table 1.** MW-Assisted tandem condensation and 6π-azaelectrocyclization by reaction of 1a–1e with 2g using ethylenediammonium diacetate (EDDA)^a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminone</th>
<th>Product</th>
<th>Yield^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>3g</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>4g</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>5g</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>6g</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>7g</td>
<td>--</td>
</tr>
</tbody>
</table>

^a) Carried out using the enaminones 1a–g (1 mmol) and 2g (1 mmol) in DMF (3 mL) with EDDA (5 mol%) at 115 °C under MW irradiation for 5 min. ^b) Yield based on isolated products.

We then applied this domino condensation-cyclization sequence to the reaction of 1a and 1b with various α-substituted enals 2, and the results are listed in Tables 2 and 3, respectively.
Table 2. Synthesis of 1-(phenylamino)-1,2-dihydropyridines 3 from enaminones 1a and enals 2^{a)}

\[
\begin{align*}
\text{8a} + \text{9a} & \rightarrow \text{1a} \quad \text{(i)} \\
\text{1a} & \rightarrow \text{3a} \quad \text{Yield, %}^{b)} 50
\end{align*}
\]

Reagents: (i) H\textsubscript{2}O-AcOH (cat), reflux, 2 h. (ii) DMF, ethylenediammonium diacetate (EDDA, 5 mol%), MW irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminone</th>
<th>Enaminone</th>
<th>2</th>
<th>Product</th>
<th>Yield, %^{b)}</th>
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<tbody>
<tr>
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<td>1a</td>
<td>a</td>
<td>Me</td>
<td>H</td>
<td>3a</td>
</tr>
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<td>1a</td>
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<td>Me</td>
<td>NO\textsubscript{2}</td>
<td>3g</td>
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<tr>
<td>5</td>
<td>1a</td>
<td>h</td>
<td>H</td>
<td>H</td>
<td>3h</td>
</tr>
</tbody>
</table>

^{a)} Carried out using the enaminones 1a (1 mmol) and 2 (1 mmol) in DMF (3 mL) with EDDA (5 mol%) at 115 °C under MW irradiation for 5 min. ^{b)} Yield based on isolated products.

Table 3. Synthesis of 1-(benzoylamino)-1,2-dihydropyridines 4, 11 from enaminones 1b, 10 and enals 2^{a)}

\[
\begin{align*}
\text{8a, R}^2 = \text{H} + \text{9b} & \rightarrow \text{1b, R}^2 = \text{H} \quad \text{(i)} \\
\text{1b, R}^2 = \text{H} & \rightarrow \text{4a} \quad \text{Yield, %}^{b)} 22
\end{align*}
\]

Reagents: (i) H\textsubscript{2}O-AcOH (cat), reflux, 2 h. (ii) DMF, EDDA (5 mol%), MW irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminone</th>
<th>Enaminone</th>
<th>2</th>
<th>R\textsuperscript{2}</th>
<th>Product</th>
<th>Yield, %^{b)}</th>
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<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>a</td>
<td>H</td>
<td>H</td>
<td>4a</td>
<td>22</td>
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<tr>
<td>2</td>
<td>1b</td>
<td>b</td>
<td>MeO</td>
<td>H</td>
<td>4b</td>
<td>33</td>
</tr>
</tbody>
</table>
Carried out using the enaminones 1b, 10 (1 mmol) and 2 (1 mmol) in DMF (3 mL) with EDDA (5 mol%) at 115 °C under MW irradiation for 5 min. b) Yield based on isolated products.

The effect of the kinds of aromatic rings at the \( \beta \)-carbon of the \( \alpha,\beta \)-unsaturated aldehydes 2 was observed. Thus, slightly higher yields are obtained using the aromatic R\(^2\) bearing electron-withdrawing groups (entries 3, 4 for 1a in Table 2, and entries 3–7, 9–13 for 1b in Table 3), compared to that of the donating group (entry 2 for 1a in Table 2, and entry 2 for 1b in Table 3).

We observed that the yield in Table 2 is better than that in Table 3. Thus, the electron-donating group (NH–NHPh) in the enaminones is more favorable for the formation of the corresponding 1,2-dihydropyridines than the enaminones with the NH–NHCOPh group bearing an electron-withdrawing group.

In spite of the smooth formation of the 2,3-disubstituted 1,2-dihydropyridine ring onto the cyclic 1,3-diketone monoimines 1a and 1b by the condensation-6\(\pi\)-electrocyclization sequence, the limitation of this method was encountered in the reaction of 1a with cinnamaldehyde (2h) which lacks an \( \alpha \)-substituent.

The reaction of 1a and cinnamaldehyde (2h) under the iminium conditions described above resulted in a decreased yield of the corresponding annulated adduct 3h (about 22% yield) (Table 2, entry 5).

The reaction mechanism for the formation of 3 can be rationalized as described in Scheme 1 by taking the steric effect of R\(^1\) substituent at the C2 of the enals 2 in account. The Knoevenagel condensation through the iminium A and enaminone 1a would lead to the 1-azatrienes B–E, the stereochemical and conformational isomers at equilibrium. The equilibration between B–E would be catalyzed by the employed EDDA. Among them, E (E, s-cis), a sterically favorable configuration for the ensuing cyclization would lead to the desired 3 via spontaneous 6\(\pi\)-electrocyclization. On the other hand, in all our attempts, the 2H-pyran structure F, which can be available by the 6\(\pi\)-electrocyclization of the
favorable configuration B (Z, s-cis), was not detected. This preferable cyclization at the 1-azatriene moiety rather than the 1-oxatriene in the same molecule is good agreement with the results reported by Hsung.9

Scheme 1. Rationale for favorable formation of 3 by the condensation of 1 and 2 catalyzed by EDDA followed by 6π-electrocyclization

In conclusion, we described the convergent access to the poly-substituted 1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-ones 3 and N-(5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamides 4 and 11 by the reaction of the corresponding enaminones 1a and 1b with 2-enals 2. This protocol involves the tandem Knoevenagel condensation, which was readily catalyzed using ethylenediammonium diacetate, and the subsequent 6π-electrocyclization. The reaction feasibility was dependent on the kind of N-substituents and the presence of a C2 substituent on the enals 2. The enaminones 1a from phenylhydrazine showed a slightly higher reactivity than the benzoyl analogues 1b obtained from benzoxydrazide. A further study of the biological activities of these products is currently underway.

EXPERIMENTAL
The 1H NMR, 13C NMR spectra were measured on the Varian INOVA-600 or Varian INOVA-400 spectrometer, using CDCl3 or DMSO-d6 as solvent and tetramethylsilane (TMS) as internal standard.
MW reaction was performed with μReactor EX, Shikoku Instrumentation Co. Ltd, operated at 2.46 GHz. 2-(4-Chlorophenyl)-3-methyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-one, a general procedure for 3c. In a side-armed tube flask (10 mm diameter) were introduced N′-(3-oxocyclohex-1-etyl)benzohydrazide (1a, 202 mg, 1 mmol) and 3-(4-chlorophenyl)-2-methylacryladehyde (2c, 180 mg, 1 mmol) and EDDA (9 mg, 5% mole) in DMF (2 mL) and the tube was placed into the microwave cavity. The mixture was irradiated under constant microwave for about 5 min at controlled temperature of 115 °C. Heating was continued for 3 min under TLC monitoring. The mixture was diluted with cold water and extracted with EtOAc (20 mL, 3 times). Combined organic layer was dried (MgSO₄), and concentrated in vacuum. The crude products were purified by flash column chromatography on SiO₂ using a mixture of hexane and AcOEt with a gradient from 4:1 to 1:4 to obtain the pure product.

3-Methyl-2-phenyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-one (3a): Yield 165 mg (50%), brown solids; mp 203–205 °C; IR (KBr) \( \nu_{\text{max}} = 3196, 3176, 3020, 2997, 2947, 1593, 1545, 1516, 1496, 1433, 1400, 1377, 1269, 1246, 1188, 1143, 1026, 875, 752, 696 \text{ cm}^{-1}; ^1\text{H NMR} (600MHz, CDCl₃) \delta 7.37 (m, 3H), 7.32 (t, \( J = 7.2 \text{ Hz} \), 2H), 7.25 (m, 2H), 6.98 (t, \( J = 7.20 \text{ Hz} \), 1H), 6.74 (d, \( J = 7.80 \text{ Hz} \), 2H), 6.59 (s, 1H), 5.49 (s, 1H), 4.99 (s, 1H), 2.63 (t, \( J = 6.6 \text{ Hz} \), 2H), 2.34 (t, \( J = 6.6 \text{ Hz} \), 2H), 1.92–1.96 (m, 2H), 1.47 (s, 3H); \(^{13}\text{C NMR} (151MHz, CDCl₃) \delta 193.6, 161, 4, 145.3, 139.5, 130.8 (2C), 130.1 (2C), 130.0, 128.9 (2C), 125.4, 122.7, 116.3, 114.4 (2C), 106.7, 68.2, 36.8, 25.9, 22.2, 21.0. Anal. Calcd for C₂₂H₂₂N₂O: C, 79.97; H, 6.71; N, 8.48%. Found: C, 79.29; H, 6.51; N, 8.44%.

2-(4-Methoxyphenyl)-3-methyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-one (3b): Yield 125 mg (35%), brown solids; mp 170–173 °C; IR (KBr) \( \nu_{\text{max}} = 3254, 2933, 1670, 1600, 1546, 1508, 1452, 1400, 1303, 1249, 1184, 1138, 1030, 835, 752, 696 \text{ cm}^{-1}; ^1\text{H NMR} (600 MHz, CDCl₃) \delta 7.32 (dd, \( J = 8.4, 7.5 \text{ Hz} \), 2H), 7.24–7.15 (m, 3H), 7.01 (s, 1H), 7.01–6.88 (m, 1H), 6.76 (d, \( J = 7.6 \text{ Hz} \), 2H), 6.60 (s, 1H), 5.46 (s, 1H), 4.96 (s, 1H), 3.81 (s, 3H), 2.65 (d, \( J = 4.0 \text{ Hz} \), 2H), 2.41 (t, \( J = 6.4 \text{ Hz} \), 2H), 1.93 (m, 2H), 1.49 (s, 3H); \(^{13}\text{C NMR} (151 MHz, CDCl₃) \delta 192.8, 160.7, 160.4, 144.7, 130.8, 130.1 (2C), 129.8, 129.4 (2C), 124.9, 121.9, 115.5, 114.7 (2C), 113.7 (2C), 106.7, 55.6, 36.0, 31.2, 25.2, 21.5. Anal. Calcd for C₂₃H₂₄N₂O₂: C, 76.64; H, 6.71; N, 7.77%. Found: C, 76.84; H, 6.19; N, 7.79%.

2-(4-Chlorophenyl)-3-methyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-one (3c): Yield 202 mg (55%), brown solids; mp 200–204 °C; IR (KBr) \( \nu_{\text{max}} = 3257, 2947, 1599, 1548, 1494, 1427, 1398, 1259, 1186, 1138, 1087, 1014, 879, 829, 754 \text{ cm}^{-1}; ^1\text{H NMR} (600 MHz, CDCl₃) \delta 7.39–7.27 (m, 4H), 7.25–7.15 (m, 2H), 6.99 (t, \( J = 7.4 \text{ Hz} \), 1H), 6.75 (d, \( J = 7.7 \text{ Hz} \), 2H), 6.60 (s, 1H), 5.49 (s, 1H), 5.00 (s, 1H), 2.63 (t, \( J = 6.2 \text{ Hz} \), 2H), 2.36 (t, \( J = 6.5 \text{ Hz} \), 2H), 2.09–1.89 (m, 2H), 1.49 (s, 3H); \(^{13}\text{C NMR} (151 MHz, CDCl₃) \delta 192.9, 160.5, 144.4, 137.4, 135.2, 130.1 (2C), 129.6 (2C), 129.5 (2C), 124.3, 122.0, 115.9, 113.5 (2C), 106.0, 66.8, 36.0, 25.2, 21.4, 20.2. Anal. Calcd for C₂₂H₂₁ClN₂O: C, 72.42; H, 5.80; N, 7.68%. Found: C, 71.82; H, 5.66; N, 7.73%. 

3-Methyl-2-(4-nitrophenyl)-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-one (3g): Yield 245 mg (65%), brown solids; mp 106–108 °C; IR (KBr) \( \nu_{\text{max}} = 3240, 2945, 1670, 1599, 1548, 1519, 1398, 1346, 1271, 1247, 1188, 1139 \text{ cm}^{-1} \);
\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 8.24 (d, \( \nu = 8.6 \) Hz, 2H), 7.01 (t, \( \nu = 7.4 \) Hz, 1H), 6.75 (d, \( \nu = 7.7 \) Hz, 2H), 6.66 (s, 1H), 5.46 (s, 1H), 5.17 (s, 1H), 2.66 (t, \( \nu = 6.2 \) Hz, 2H), 2.41 (t, \( \nu = 6.5 \) Hz, 2H), 1.99–1.92 (m, 2H), 1.51 (s, 3H);
\(^{13}\)C NMR (151 MHz CDCl\(_3\)) 194.5, 162.0, 150.0, 147.5, 145.6, 131.8 (2C), 131.7, 130.5 (2C), 126.1 (2C), 123.7, 118.1, 114.9 (2C), 107.9, 68.5, 37.5, 26.7, 19.7, 18.7. Anal. Calcd for C\(_{22}\)H\(_{21}\)N\(_3\)O\(_3\): C, 70.38; H, 5.64; N, 11.19%. Found: C, 69.87; H, 5.19; N, 10.82%.

2-Phenyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6H)-one (3h): Yield 70 mg (22%), brown solids; mp 180–183 °C; IR (KBr) \( \nu_{\text{max}} = 3211, 3176, 3024, 2945, 1735, 1643, 1593, 1531, 1494, 1433, 1348, 1278, 1190, 1028, 904 \text{ cm}^{-1} \);
\(^1\)H NMR (600 MHz, CDCl\(_3\)) 7.38–7.30 (m, 2H), 7.29–7.25 (m, 5H), 6.99 (t, \( \nu = 12.1 \), 1H), 6.97 (m, 3H), 5.58 (s, 1H), 5.33 (m, 1H), 5.28 (d, \( \nu = 4.8 \) Hz, 1H), 2.86–2.62 (m, 2H), 2.36 (t, \( \nu = 6.6 \) Hz, 2H), 1.96–1.88 (m, 2H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) 192.5, 162.7, 144.2, 139.9, 129.8 (2C), 129.2 (2C), 129.0, 127.7 (2C), 121.7, 119.0, 116.6, 113.4 (2C), 105.4, 63.4, 35.7, 21.1. Anal. Calcd for C\(_{21}\)H\(_{20}\)N\(_2\)O: C, 79.72; H, 6.37; N, 8.85%. Found: C, 78.97; H, 6.09; N, 9.01%.

N-(3-Methyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (4a): Yield 72.5 mg (22%), yellow solids; mp 130–133 °C; IR (KBr) \( \nu_{\text{max}} = 3176, 2947, 1683, 1591, 1543, 1523, 1491, 1433, 1396, 1375, 1352, 1265, 1193, 1166, 1139, 1089, 1028, 896, 806, 738, 698 \text{ cm}^{-1} \);
\(^1\)H NMR (600 MHz, CDCl\(_3\)) 7.62 (d, \( \nu = 7.4 \) Hz, 2H), 7.54 (dd, \( \nu = 13.0, 4.3 \) Hz, 1H), 7.42 (t, \( \nu = 7.6 \) Hz, 3H), 7.34–7.28 (m, 5H), 6.51 (s, 1H), 5.26 (m, 1H), 2.49 (m, 2H), 2.28 (m, 2H), 1.88–1.79 (m, 2H), 1.45 (s, 3H). Anal. Calcd for C\(_{23}\)H\(_{22}\)N\(_2\)O\(_2\): C, 77.07; H, 6.19; N, 7.82%. Found: C, 76.89; H, 5.76; N, 7.86%.

N-(2-(4-Methoxyphenyl)-3-methyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (4b): Yield 114 mg (33%), yellow solids; mp 116–118 °C; IR (KBr) \( \nu_{\text{max}} = 3198, 2951, 1681, 1668, 1608, 1510, 1404, 1354, 1251, 1174, 1139, 1028, 895, 835 \text{ cm}^{-1} \);
\(^1\)H NMR (600 MHz, CDCl\(_3\)) 7.65 (m, 2H), 7.53 (m, 1H), 7.37 (t, \( \nu = 7.6 \) Hz, 2H), 7.24 (m, 3H), 6.82 (d, \( \nu = 3.9 \) Hz, 2H), 6.43 (s, 1H), 5.18 (s, 1H), 3.75 (s, 3H), 2.47 (m, 2H), 2.17 (t, \( \nu = 6.5 \) Hz, 2H), 1.87–1.80 (m, 2H), 1.44 (s, 3H). HRMS (ESI) calcd for C\(_{24}\)H\(_{24}\)N\(_2\)O\(_3\) [M+H\(^+\)] Exact Mass: 388.18, found 388.18.

N-(2-(4-Chlorophenyl)-3-methyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (4c): Yield 158.5 mg (45%), yellow solids; mp 143–146 °C; IR (KBr) \( \nu_{\text{max}} = 3198, 2951, 2362, 1686, 1599, 1556, 1489, 1435, 1402, 1354, 1288, 1263, 1193, 1089, 1014, 895, 831 \text{ cm}^{-1} \);
\(^1\)H NMR (600 MHz, CDCl\(_3\)) 7.58 (d, \( \nu = 7.8 \) Hz, 2H), 7.50 (t, \( \nu = 7.2 \) Hz, 1H), 7.36 (t, \( \nu = 7.2 \) Hz, 2H), 7.28 (m, 3H), 7.28 (d, \( \nu = 8.4 \) Hz, 2H), 6.33 (s, 1H), 5.25 (s, 1H), 2.47 (t, \( \nu = 6.5 \) Hz, 2H), 2.03 (t, \( \nu = 10.6 \) Hz, 2H), 1.81 (m, 2H), 1.42 (s, 3H). HRMS (ESI) calcd for C\(_{23}\)H\(_{21}\)ClN\(_2\)O\(_2\) [M+H\(^+\)] Exact Mass: 392.13, found 392.13.

N-(2-(4-Fluorophenyl)-3-methyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (4d): Yield
206 mg (54%), yellow solids; mp 140–142 °C; IR (KBr) νmax = 3192, 2947, 1681, 1602, 1552, 1506, 1402, 1266, 1222, 1193, 1155, 1139, 1087, 1028, 896, 839, 694 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.67 (d, J = 7.3 Hz, 2H), 7.54 (m, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.33–7.26 (m, 3H), 7.01 (s, 2H), 6.43 (s, 1H), 5.25 (s, 1H), 2.50 (m, 2H), 2.26 (t, J = 4.8 Hz, 2H), 2.00–1.83 (m, 2H), 1.46 (s, 3H). Anal. Calcd for C₂₃H₂₁FN₂O₂: C, 73.39; H, 5.62; N, 7.44 %. Found: C, 73.53; H, 5.43; N, 7.24%.

Methyl 4-(1-benzamido-3-methyl-5-oxo-1,2,5,6,7,8-hexahydroquinolin-2-yl)benzoate (4e): Yield 186 mg (45%), yellow solid; mp 131–133 °C (decomp.); IR (KBr) νmax = 3192, 2947, 1681, 1670, 1602, 1552, 1506, 1437, 1354, 1265, 1222, 1139, 1087, 1028, 896, 839, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.44–7.35 (m, 4H), 6.49 (s, 1H), 5.35 (s, 1H), 3.86 (s, 3H), 2.52 (dd, J = 9.6, 5.8 Hz, 2H), 2.25 (s, 2H), 1.90 (d, J = 5.3 Hz, 2H), 1.46 (s, 3H). HRMS (ESI) calcd for C₂₅H₂₄N₂O₄ [M+H]+ Exact Mass: 416.17, found 416.17.

N-(3-Methyl-5-oxo-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (4f): Yield 241 mg (56%), yellow solids; mp 125–127 °C; IR (KBr) νmax = 3176, 2947, 1681, 1591, 1543, 1433, 1396, 1265, 1253, 1193, 1139, 1091, 1028, 896, 698 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.69–7.60 (d, J = 6 Hz, 2H), 7.54 (t, J = 8.0 Hz, 3H), 7.47 (d, J = 7.8 Hz, 2H), 7.40 (t, J = 6 Hz, 2H), 6.45 (s, 1H), 5.36 (s, 1H), 2.51 (dt, J = 15.3, 6.2 Hz, 2H), 2.16 (t, J = 6.5 Hz, 2H), 2.02–1.71 (m, 2H), 1.46 (s, 3H). Anal. Calcd for C₂₄H₂₁N₂O₂: C, 67.60; H, 4.96; N, 6.57%. Found: C, 66.98; H, 4.82; N, 6.49%.

N-(3-Methyl-2-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (4g): Yield 241 mg (58%), yellow solids; mp 125–127 °C; IR (KBr) νmax = 3182, 3026, 2945, 1645, 1595, 1552, 1516, 1491, 1437, 1244, 1290, 1193, 1149, 1107, 1084, 956, 920, 856 cm⁻¹; ¹H NMR (600 MHz, DMSO-d₆) δ 8.23 (d, J = 6 Hz, 2H), 7.88 (d, J = 6 Hz, 1H), 7.72 (d, J = 6.2 Hz, 2H), 7.60 (d, J = 6.2 Hz, 2H), 7.55–7.43 (m, 3H), 6.94 (s, 1H), 6.38 (s, 1H), 5.39 (s, 1H), 2.47 (m, 2H), 2.16 (s, 2H), 1.81 (m, 2H), 1.44 (m, 3H). HRMS (ESI) calcd for C₂₃H₂₁N₃O₄ [M+H]^+ Exact Mass: 403.15, found 403.17.

N-(3,7,7-Trimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (11a): Yield 172 mg (45%), yellow solids; mp 198–201 °C; IR (KBr) νmax = 3157, 2956, 2362, 1680, 1597, 1585, 1552, 1519, 1489, 1437, 1404, 1301, 1292, 1251, 1186, 1151, 1089, 1070, 1028, 1001, 966, 927, 910, 881, 806, 763, 694 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.70 (d, J = 6.0 Hz, 2H), 7.51 (d, J = 6 Hz, 1H), 7.39 (d, J = 6.1 Hz, 2H), 7.32 (s, 4H), 6.37 (s, 1H), 5.25 (s, 1H), 2.45 (dd, J = 18.0, 18.0 Hz, 2H), 1.94 (s, 2H), 1.45 (s, 3H), 0.97 (d, J = 6.0 Hz, 6H). Anal. Calcd for C₂₅H₂₆N₂O₂: C, 77.69; H, 6.78; N, 7.25%. Found: C, 77.55; H, 6.05; N, 6.82%.

N-(2-(4-Chlorophenyl)-3,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzamide (11b): Yield 255 mg (60%), yellow solid; mp 125–127 °C; IR (KBr) νmax = 3188, 2958, 2360, 1681, 1600, 1552, 1487, 1435, 1402, 1288, 1257, 1149, 1089, 1014, 883, 833, 694 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.71 (d, J = 6.0 Hz, 2H), 7.51 (d, J = 6 Hz, 1H), 7.38 (t, J = 12 Hz, 2H), 7.28–7.24 (m, 4H), 6.35 (s, 1H), 5.24
(s, 1H), 7 (dd, J = 18.0, 18.0 Hz, 2H), 1.93 (s, 2H), 1.43 (s, 3H), 0.95 (d, J = 4.2 Hz, 6H). Anal. Calcd for C25H25ClN2O2: C, 71.33; H, 5.99; N, 6.66%. Found: C, 70.93; H, 5.75; N, 6.67%.

\(N-(3,7,7-\text{Trimethyl}-2-(4\text{-nitrophenyl})-5\text{-oxo}-5,6,7,8\text{-tetrahydroquinolin-1(2H)-yl})\text{benzamide (11c):}\)

Yield 305 mg (70%), yellow solids; mp 158–160 °C; IR (KBr) \(\nu_{\text{max}} = 3192, 2958, 1685, 1600, 1554, 1519, 1437, 1346, 1247, 1182, 1149, 1070, 1028, 1014, 968, 922, 889, 812, 754, 694 \text{ cm}^{-1}; \) \(^1\text{H} \text{NMR} \text{(600 MHz, CDCl}_3\text{)} \delta 8.12 (d, J = 6.0 Hz, 2H), 7.77 (d, J = 6.0 Hz, 2H), 7.52 (m, 3H), 7.42 (t, J = 12.0 Hz, 2H), 6.38 (s, 1H), 5.37 (s, 1H), 27 (dd, J = 18.0, 18.0 Hz, 2H), 2.1 (s, 2H), 1.46 (s, 3H), 1.01 (d, J = 12.0 Hz, 6H). Anal. Calcd for C25H25N3O4: C, 69.59; H, 5.84; N, 9.74%. Found: C, 68.86; H, 5.64; N, 9.54%.

\(N-(3,7,7-\text{Trimethyl}-5\text{-oxo}-2-(4\text{-(trifluoromethyl)phenyl})-5,6,7,8\text{-tetrahydroquinolin-1(2H)-yl})\text{benzamide (11d):}\)

Yield 297 mg (65%), yellow solids; mp 128–130 °C; IR (KBr) \(\nu_{\text{max}} = 3201, 2960, 1681, 1600, 1556, 1435, 1325, 1249, 1165, 1126, 1066, 1018, 883, 844, 798, 761, 694 \text{ cm}^{-1}; \) \(^1\text{H} \text{NMR} \text{(600 MHz, CDCl}_3\text{)} \delta 7.69 (d, J = 7.6 Hz, 2H), 7.64–7.51 (m, 2H), 7.47–7.41(m, 5H), 6.44 (s, 1H), 5.34 (s, 1H), 2.37 (dd, J = 18.0, 18.0 Hz, 2H), 2.05 (s, 2H), 1.46 (s, 3H), 0.99 (m, 6H). Anal. Calcd for C26H25F3N2O2: C, 68.71; H, 5.54; N, 6.16%. Found: C, 68.76; H, 5.29; N, 5.86%.

\(N-(2-(4\text{-(Fluorophenyl)-3,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl})\text{benzamide (11e):}\)

Yield 252 mg (62%), yellow solids; mp 204–206 °C; IR (KBr) \(\nu_{\text{max}} = 3201, 2960, 1681, 1600, 1556, 1435, 1325, 1249, 1165, 1126, 1066, 1018, 883, 844, 798, 761, 694 \text{ cm}^{-1}; \) \(^1\text{H} \text{NMR} \text{(600 MHz, CDCl}_3\text{)} \delta 7.71 (d, J = 7.4 Hz, 2H), 7.53 (d, J = 7.4 Hz, 1H), 7.41 (dd, J = 12.0, 6.0 Hz, 2H), 7.31–7.25 (m, 2H), 7.01 (s, 2H), 6.40 (s, 1H), 5.25 (s, 1H), 2.46–2.23 (dd, J = 18.0, 18.0 Hz, 2H), 2.01 (d, J = 3.6 Hz, 2H), 1.45 (s, 3H), 0.97 (d, J = 30.0 Hz, 6H). HRMS (ESI) calcd for C25H25FN2O2 [M+H]^+ Exact Mass: 404.19, found 404.19.

\(\text{Methyl 4-(1-benzamido-3,7,7-trimethyl-5-oxo-1,2,5,6,7,8-hexahydroquinolin-2-yl)benzoate (11f):}\)

Yield 250 mg (57%), Yellow solids; mp 130–133 °C; IR (KBr) \(\nu_{\text{max}} = 3209, 2955, 1724, 1681, 1600, 1556, 1435, 1325, 1249, 1165, 1126, 1066, 1018, 883, 844, 798, 761, 694 \text{ cm}^{-1}; \) \(^1\text{H} \text{NMR} \text{(600 MHz, CDCl}_3\text{)} \delta 7.91 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 7.3 Hz, 2H), 7.42 (dt, J = 15.8, 8.2 Hz, 1H), 7.33–7.20 (m, 4H), 6.38 (s, 1H), 5.34 (s, 1H), 3.81 (d, J = 6.3 Hz, 3H), 2.33 (dd, J = 18.0, 18.0 Hz, 2H), 1.97 (t, J = 6.0 Hz, 2H), 1.42 (s, 3H), 0.96 (d, J = 5.8 Hz, 6H). Anal. Calcd for C27H28N2O4: C, 72.95; H, 6.35; N, 6.30%. Found: C, 72.93; H, 6.30; N, 6.06%.

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REFERENCES (AND NOTES)


