Synthesis of Selected Novel Covalently Linked Flavooquinolones

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Abstract: The synthesis of novel covalently linked flavoquinolones via amide bond is described using mixed anhydride method and their spectroscopic studies have been done by UV/Vis and 1H NMR spectroscopic data.

Key words: flavin, quinolone, flavoquinolone, spectroscopic studies

Quinolones are broad-spectrum antibiotics which act by inhibiting bacterial deoxyribonucleic acid (DNA) gyrase required for the initiation and propagation of DNA synthesis.1–4 The DNA gyrase is composed of A and B subunit, the inhibitory effect of quinolones is mediated via the catalytic A subunit. Quinolones develop their pharmacological action via specific inhibition of subunit A of the bacterial gyrase. The hydrophobic, electronic and steric parameters of quinolones play important roles in their biologic activity.

Flavins substituted at position 10 are found to possess antimalarial activity both in vivo against rodent malarials and in vitro against Plasmodium falciparum.5 The antimalarial effects of riboflavin are due to its effect on the change in the structural and/or functional integrity of red blood cell membranes.6 The riboflavin deficiency reduces the level of polyunsaturated fatty acids in membrane phospholipids and this influences fluidity, permeability and binding properties in membranes. These agents are potent inhibitors of both human and plasmodium glutathione reductase7, inhibition of the later may account for the anti-malarial properties of these agents.8 The substitution at the 10-position of the flavin nucleus accounts for the difference in the antimalarial properties.

The combination therapy is very useful for treatment of selected diseases; hence to study the biological activities of flavin linked quinolones, selected novel covalently linked flavoquinoline heterocycles have been synthesized for the first time. Their further studies are in progress.

Syntheses

Synthesis of Flavins

Synthesis of 10-substituted flavins by acidic cyclocondensation of 2-substituted aminoanilines with alloxan monohydrate is an important and widely used method.9–12 The reaction of diamino compound 2 with 1-chloro-2-nitrobenzene (1) gives a mixture of two compounds, N-(1′-aminoalkyl)-2-nitroanilines 3 and N,N-alkylbis(2-nitroanilines) 4. The required N-(1′-aminoalkyl)-2-nitroanilines 3 have been separated by column chromatography over silica gel (60–120 mesh) using chloroform–methanol as the eluent in 45–51% yields. Synthesis of 10-(1′-aminoalkyl)flavins 6 have been done by the acidic cyclocondensation of 2-(1′-aminoalkyl)aminoanilines, generated in situ by the reduction of 3 with Pd/C-H2, with alloxan monohydrate (5) in 32–40% yields (Scheme 1). The structures of the flavins have been confirmed by different spectroscopic data including UV/Vis, IR, 1H NMR and mass spectroscopy.

Scheme 1 Synthesis of flavin
Synthesis of Quinolones

Nalidixic acid (1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid) and related quinolones \( \text{12} \) have been synthesized by the modification of Gold–Jacob method\(^\text{13}\) by the reaction of appropriate aniline \( \text{7a} \) or aminopyridine \( \text{7b} \) with diethyl ethoxymethyleneamalonate \( \text{8} \) and subsequent cyclization (Scheme 2). The reaction of 3-methylaniline \( \text{7a} \) with \( \text{8} \) in refluxing ethanol gives diethyl 2-[(3-methylphenyl)amino]methylene propane-1,3-dioate \( \text{9a} \) in 85% yield.

The cyclization of substituted propane-1,3-dioate \( \text{9a} \) in diphenyl ether gives ethyl 4-hydroxy-7-methylquinoline-3-carboxylate \( \text{10a} \) in 81% yields. The reaction of \( \text{10a} \) with ethyl bromide in the presence of potassium carbonate in DMF gives ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate \( \text{11a} \), that on alkaline hydrolysis affords 1-ethyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid \( \text{12a} \). Similarly, nalidixic acid \( \text{12b} \) has also been synthesized. The structures of the quinolones have been confirmed by different spectroscopic data including UV-visible, IR, \(^1\)H NMR and mass spectroscopy (Experimental section).

Synthesis of Covalently Linked Flavoquinolones

Mixed anhydride method is an important method for amide bond formation by the reaction of substituted acids to amines/anilines\(^\text{9,14}\). The reaction of 3-carboxy group of quinolone \( \text{12} \) with ethyl chloroformate forms a mixed anhydride, which on subsequent reaction with \( \text{6} \) gives the covalently linked flavoquinolones \( \text{13–15} \) in 29–37% yields (Scheme 3).

Spectroscopic Properties of Flavin-Linked Quinolones (Flavoquinolones)

**UV/Vis Spectra of Flavoquinolones**

The UV/Vis spectra of the flavins, quinolones and flavoquinolones are listed in Table 1. These data indicate that the UV/Visible spectra of flavoquinolones \( \text{13–15} \) are very similar to that of flavins \( \text{6} \) except for a band at 330–335 nm whose absorbance is larger than that of flavins. The shape of the absorption bands at 260 nm is slightly broadened. These broadening of the absorption bands of flavoquinolones may be due to the close proximity of the two chromophores. Similar results have also been observed in the case of flavin-linked porphyrins\(^\text{15}\) and quinone-linked porphyrins.\(^\text{16}\)

**\(^1\)H NMR Spectra of Flavoquinolones**

In contrast to the UV-Visible spectra, \(^1\)H NMR data provide information about the geometry of the flavoquinolones. \(^1\)H NMR data for the flavoquinolones are listed in Tables 2 and 3. These data show a significant upfield shift of the 7-methyl, 1-ethyl and H-2 signals by a shielding effect of the ring current of the closely linked flavin ring system. The shielding effect of flavin nucleus has already been studied in the case of flavin linked porphyrins.\(^\text{15}\) The ring current of quinolones is not so effective in changing the signal positions of flavin protons. The \(^1\)H NMR spectra of the flavoquinolone provide inconclusive but suggestive data about the stereochemical nature of these compounds. Due to the upfield shift of the quinolone protons, the flavin ring system seems to be located closely above the quinolone ring system.
The synthesis of selected novel covalently linked flavin linked quinolones has been achieved by the condensation of the quinolone-3-carboxylic acid and 10-(1′-aminoalkyl)flavin via mixed anhydride method. The spectroscopic data of flavoquinolones revealed that the flavin and quinolone moieties are in close proximity. The ring current of flavin strongly affects the position of quinolone protons when n = 2 in comparison to n = 6 or 12. Further, the ring current of quinolones is not strong enough to give a change in flavin protons.

Melting points were determined on a Thomas Hoover Unimelt capillary melting apparatus and are uncorrected. Electronic spectra were recorded on a Shimadzu UV-260 spectrophotometer and absorption maxima have been expressed in nanometers. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrophotometer and the \( \nu_{\text{max}} \) are expressed in cm\(^{-1}\). 1H NMR was recorded on a Bruker Avance 300 spectrophotometer (300 MHz) and Perkin-Elmer spectrophotometer (60 MHz) and the chemical shifts were expressed in ppm. EIMS spectra were recorded on a Joel SX 102/DA-6000 (6 kV, 10 mA) spectrophotometer.

Alloxan monohydrate was obtained from Acros (Belgium), 2-amino-6-methylpyridine, diethyl ethoxymethylenemalonate and 3-methylaniline was obtained from Fluka and used without further purification. The diamino compounds were obtained from s.d. Fine Chemicals, India. All the solvents were obtained from s.d. Fine Chemicals and were used after simple distillation.

### Table 1 UV/Vis Spectral Data of Flavins 6, Quinolones 12 and Flavoquinolones 13–15

<table>
<thead>
<tr>
<th>Product</th>
<th>( \lambda_{\text{max}}, \text{nm} (\epsilon, \text{mM}) ) (MeOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>217 (16.12) 260 (18.02) 332.5 (1.98) 432 (5.12)</td>
</tr>
<tr>
<td>6b</td>
<td>217 (16.02) 259 (19.12) 331 (3.12) 432 (6.41)</td>
</tr>
<tr>
<td>6c</td>
<td>217 (15.91) 265 (18.02) 332 (2.42) 431 (4.45)</td>
</tr>
<tr>
<td>12a</td>
<td>– 255 (17.12) 328 (8.12) –</td>
</tr>
<tr>
<td>12b</td>
<td>– 260 (22.87) 330 (10.11) –</td>
</tr>
<tr>
<td>13a</td>
<td>216 (16.00) 260 (22.02) 331 (7.15) 433 (5.13)</td>
</tr>
<tr>
<td>13b</td>
<td>218 (12.21) 265 (19.32) 329 (5.12) 436 (5.66)</td>
</tr>
<tr>
<td>14a</td>
<td>216 (15.99) 259 (19.01) 332 (3.98) 434 (4.18)</td>
</tr>
<tr>
<td>14b</td>
<td>217 (14.12) 259 (21.12) 331 (8.21) 432 (6.11)</td>
</tr>
<tr>
<td>15a</td>
<td>217 (14.14) 263 (16.62) 333 (7.12) 431 (5.18)</td>
</tr>
<tr>
<td>15b</td>
<td>217 (15.00) 261 (17.42) 334 (8.31) 432 (7.65)</td>
</tr>
</tbody>
</table>

### Table 2 Comparison of 1H NMR Chemical Shifts of Flavoquinolones 13a–15a and Quinolone 12a

<table>
<thead>
<tr>
<th>Product</th>
<th>1-CH₂</th>
<th>CH₂CH₃</th>
<th>7-CH₃</th>
<th>H-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>4.45 (q)</td>
<td>1.37 (t)</td>
<td>2.63 (s)</td>
<td>8.88 (s)</td>
</tr>
<tr>
<td>13a</td>
<td>3.99 (q)</td>
<td>1.13 (t)</td>
<td>2.58 (s)</td>
<td>8.63 (s)</td>
</tr>
<tr>
<td>14a</td>
<td>4.19 (q)</td>
<td>1.20 (t)</td>
<td>2.59 (s)</td>
<td>8.73 (s)</td>
</tr>
<tr>
<td>15a</td>
<td>4.39 (q)</td>
<td>1.37 (t)</td>
<td>2.60 (s)</td>
<td>8.74 (s)</td>
</tr>
</tbody>
</table>

### Table 3 Comparison of 1H NMR Chemical Shifts for Flavoquinolones 13b–15b and Quinolone 12b

<table>
<thead>
<tr>
<th>Product</th>
<th>1-CH₂</th>
<th>CH₂CH₃</th>
<th>7-CH₃</th>
<th>H-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>12b</td>
<td>4.61 (q)</td>
<td>1.55 (t)</td>
<td>2.74 (s)</td>
<td>8.90 (s)</td>
</tr>
<tr>
<td>13b</td>
<td>4.17 (q)</td>
<td>1.25 (t)</td>
<td>2.66 (s)</td>
<td>–</td>
</tr>
<tr>
<td>14b</td>
<td>4.48 (q)</td>
<td>1.25 (t)</td>
<td>2.66 (s)</td>
<td>8.87 (s)</td>
</tr>
<tr>
<td>15b</td>
<td>4.50 (q)</td>
<td>1.28 (t)</td>
<td>2.69 (s)</td>
<td>8.75 (s)</td>
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</table>

The synthesis of selected novel covalently linked flavin linked quinolones has been achieved by the condensation of the quinolone-3-carboxylic acid and 10-(1′-aminoalkyl)flavin via mixed anhydride method. The spectroscopic data of flavoquinolones revealed that the flavin and quinolone moieties are in close proximity. The ring current of flavin strongly affects the position of quinolone protons when n = 2 in comparison to n = 6 or 12. Further, the ring current of quinolones is not strong enough to give a change in flavin protons.

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**N-(1′-Aminoalkyl)-2-nitroanilines 3; General Procedure**

A mixture consisting of 1-chloro-2-nitrobenzene (1; 0.425 g, 2.7 mmol) and diaminoalkane 2 (17.3 mmol) was heated at 120 °C for 24 h and cooled to r.t. The brown syrup was dissolved in CHCl₃ (250 mL) and washed with H₂O (2 × 100 mL). The CHCl₃ layer was dried (Na₂SO₄) and the solvent was evaporated. The residue was chromatographed on silica gel (60–120 mesh). The column was eluted successively with a mixture of CHCl₃ and MeOH (60:120 mesh). The fraction from the second large red band was collected.

**N-(1′-Aminooethyl)-2-nitroaniline (3a)**

Yield: 0.22 g (45%); mp 98 °C.

**IR (KBr):** 3402, 3312, 2928, 2856, 1623, 1575, 1520, 1444, 1410, 1346, 1310, 1262, 1220, 1140, 1062, 1030, 740 cm\(^{-1}\).

**1H NMR (CDCl₃, 300 MHz):**

\( \delta = 1.35 \text{ (br s, 2 H, NH₂)}, 2.55–2.65 \text{ (m, 2 H, CH₂)}, 2.75–2.95 \text{ (m, 2 H, CH₂)}, 6.65–6.95 \text{ (m, 2 H, H-4, H-6)}, 7.35–7.45 \text{ (m, 1 H, H-5)}, 8.13 \text{ (d, 1 H, H-3, } J = 8.12 \text{ Hz}).

**N-(1′-Aminoheptyl)-2-nitroaniline (3b)**

Yield: 0.326 g (51%); mp 92 °C.

**IR (KBr):** 3400, 3316, 2930, 2855, 1620, 1560, 1500, 1480, 1400, 1345, 1252, 1140, 1060, 720 cm\(^{-1}\).

**1H NMR (CDCl₃, 300 MHz):**

\( \delta = 1.35–1.76 \text{ (m, 10 H, NH₂, (CH₂)₄)}, 3.24–3.33 \text{ (m, 4 H, CH₂NH₂, CH₂NH), 6.64 (dt, 1 H, H-4, } J = 8.21, 1.30 \text{ Hz)}, 6.84 (d, 1 H, H-6, } J = 8.60 \text{ Hz)}, 7.43 (dt, 1 H, H-5, } J = 8.20, 1.32 \text{ Hz)}, 8.17 (dd, 1 H, H-3, } J = 8.6, 1.5 \text{ Hz}).
N-(1'-Aminododecyl)-2-nitroaniline (3c)

Yield: 0.42 g (49%); mp 73 °C.

IR (KBr): 3387, 3313, 2925, 2853, 1526, 1573, 1514, 1470, 1356, 1263, 1230, 1158, 1036, 735, 601, 514 cm⁻¹.

1H NMR (DMSO-d₆, 60 MHz): δ = 1.10–1.86 [m, 22 H, CH₂], 3.07–3.14 (m, 2 H, CH₂NH₂), 4.67 (t, 2 H, N=CH₂, J = 6.4 Hz), 7.65 (t, 1 H, CH=, J = 7.79 Hz), 7.72 (br s, 1 H, N=H), 7.86 (d, 1 H, H-9, J = 8.55 Hz), 7.96 (t, 1 H, H-8, J = 7.81 Hz), 8.18 (d, 1 H, H-6, J = 7.6 Hz).

10-(1'-Aminoalkyl)flavins 6; General Procedure

A mixture of amino compound (20 mmol) and diester (9a) (25 mmol) was heated to reflux and maintained at reflux for 30 min. After cooling the mixture to r.t., it was diluted with an equal volume of n-hexane. The precipitate was collected, washed with n-hexane and dried.

Diethyl 2-[[6-Methyl-2-pyridyl]amino]methylene)propane-1,3-dioate (9b)

Yield: 5.00 g (90%); mp 109–111 °C (Lit. 19 mp 113–114 °C).

IR (KBr): 3270, 3082, 2981, 2925, 2852, 1689, 1664, 1612, 1560, 1464, 1425, 1374, 1324, 1231, 1158, 1097, 1035, 794 cm⁻¹.

Yield: 4.10 g (71%); mp 279–280 °C (Lit. 19 mp 278–279 °C).

Ethyl 4-Hydroxy-1-ethyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (10b)

Yield: 4.12 g (80%); mp 150 °C (Lit. 18 mp 150 °C).

IR (KBr): 3450, 3144, 3021, 2910, 1720, 1688, 1604, 1545, 1454, 1391, 1355, 1329, 1202, 1181, 1146, 1098, 1026, 933, 857, 799 cm⁻¹.

1H NMR (CDCl₃, 60 MHz): δ = 1.25 (t, 3 H, CH₂CH₃, J = 7.11 Hz), 2.37 (s, 3 H, 7-CH₃), 4.13 (q, 2 H, CH₂CH₃, J = 7.11 Hz), 7.12 (d, 1 H, H-6, J = 8.08 Hz), 8.12 (d, 1 H, H-5, J = 8.21 Hz), 8.22 (s, 1 H, H-2).

Ethyl 1-Ethyl-7-methyl-4-oxo-1,4-dihydroquinoline/naphthyridine-3-carboxylates 11; General Procedure

A mixture of diphenyl ether (100 mL) and compound (20 mmol), ethyl bromide (100 mmol) and K₂CO₃ (6.90 g, 50 mmol) was suspended in DMF (100 mL) and heated at 90–100 °C for 20–22 h. The DMF was evaporated on the rotary evaporator under reduced pressure. The residue was partitioned between CHCl₃ and H₂O. The CHCl₃ extract was washed with H₂O and brine. The solution was dried (Na₂SO₄) and filtered.

Ethyl 1-Ethyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (11a)

Yield: 4.12 g (80%); mp 150 °C.

IR (KBr): 3044, 2985, 2885, 1677, 1634, 1612, 1547, 1471, 1367, 1311, 1246, 1192, 1099, 1023, 935, 796, 538 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 1.14 (t, 3 H, CH₂CH₃, J = 7.05 Hz), 1.54 (t, 3 H, 7-CH₃), 1.91 (s, 3 H, 1-H), 3.24 (q, 2 H, CH₂CH₃, J = 7.23 Hz), 4.39 (q, 2 H, CH₂CH₃, J = 7.23 Hz), 6.06 (d, 1 H, CH=C, J = 14 Hz).

Diethyl 2-[[[(3-Methylphenyl)amino]methylene]propane-1,3-dioate (9a)

Yield: 11.74 g (85%); mp 39–40 °C (Lit. 18 red brown oil).
added dropwise to the above mixture at 0 °C. The mixture was small portions to a solution of anhyd Et$_3$N (0.2 mL) and (d, 1 H, H-6, J = 8.25 Hz), 7.31 (d, 1 H, H-5, J = 8.25 Hz), 7.62 (s, 1 H, H-8), 8.88 (s, 1 H, H-2), 13.91 (s, 1 H, CO$_2$H).

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.37$ (t, 3 H, CH$_2$CH$_3$, $J = 7.10$ Hz), 2.65 (s, 3 H, 7-CH$_3$), 4.45 (q, 2 H, CH$_2$CH$_3$, $J = 7.11$ Hz), 5.59 (d, 1 H, H-6, $J = 8.25$ Hz), 7.31 (d, 1 H, H-5, $J = 8.25$ Hz), 7.62 (s, 1 H, H-8), 8.88 (s, 1 H, H-2), 13.91 (s, 1 H, CO$_2$H).

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.55$ (t, 3 H, CH$_2$CH$_3$, $J = 7.04$ Hz), 2.74 (s, 3 H, 7-CH$_3$), 4.61 (q, 2 H, CH$_2$CH$_3$, $J = 7.08$ Hz), 7.39 (d, 1 H, H-6, $J = 8.19$ Hz), 8.68 (d, 1 H, H-5, $J = 8.22$ Hz), 8.90 (s, 1 H, H-2), 14.67 (s, 1 H, CO$_2$H).

Flavonolines 13–15; General Procedure
Ethyl chloroformate (1.1 g, 96.1 ml, 10.1 mmol) was added in small portions to a solution of anhyd Et$_3$N (0.2 mL) and 12 (0.2 mmol) in anhyd CHCl$_3$ (50 ml) maintaining the temperature at 0 °C. The CH$_3$Cl-MeOH (1:1) solution of flavin 6 (0.2 mmol) was added dropwise to the above mixture at 0 °C. The mixture was stirred for 30 min at r.t. The solvent was removed under reduced pressure and the residue was redissolved in MeOH (15 ml) and purified by preparative TLC using MeOH as mobile phase.

1-Ethyl-(10-ethylalloxazinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 13a

Yield: 0.055 g (30%); mp 198 °C.

IR (KBr): $\delta = 3449$, 2926, 1710, 1657, 1614, 1580, 1546, 1549, 1504, 1406, 1281, 1244, 1092, 774 cm$^{-1}$.

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.25$ (t, 3 H, CH$_2$CH$_3$, $J = 6.91$ Hz), 2.66 (s, 3 H, 7-CH$_3$), 3.66 (q, 2 H, CH$_2$CH$_3$NH, J = 6.71 Hz), 7.28 (t, 1 H, H-7', $J = 8.11$ Hz), 7.28 (d, 1 H, H-6, $J = 8.65$ Hz), 7.42 (s, 1 H, H-8), 7.63 (t, 1 H, H-8’, $J = 8.11$ Hz), 8.04 (d, 1 H, H-6, $J = 8.95$ Hz), 8.19 (d, 1 H, H-5, $J = 8.35$ Hz), 8.28 (d, 1 H, H-9’, $J = 7.43$ Hz), 8.63 (s, 1 H, H-2).

MS: $m/z$ (%) = 470 (M$^+$, 28), 283 (23), 228 (100), 215 (11), 187 (55).

Anal. Calcd for C$_{32}$H$_{25}$N$_2$O$_4$: C, 63.82; H, 4.71; N, 17.86. Found: C, 63.79; H, 4.59; N, 17.89.

1-Ethyl-N-(10-hexylalloxaizinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 13b

Yield: 0.062 g (33%); mp 230 °C.

IR (KBr): $\delta = 3449$, 2926, 2885, 1712, 1675, 1645, 1614, 1580, 1547, 1500, 1421, 1285, 1248, 1093, 957, 778 cm$^{-1}$.

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.37$ (t, 3 H, CH$_2$CH$_3$, $J = 7.04$ Hz), 1.40–1.65 (m, 20 H, (CH$_2$)$_{10}$), 2.60 (s, 3 H, CH$_3$), 3.17 (q, 2 H, CH$_2$CH$_3$NH, J = 6.71 Hz), 4.39 (q, 2 H, 1-CH$_2$, J = 6.96 Hz), 4.69 (t, 2 H, N$_2$CH$_2$J, J = 6.79 Hz), 7.25 (t, 1 H, H-7’, $J = 8.09$ Hz), 7.29 (d, 1 H, H-9’, $J = 8.75$ Hz), 7.38 (s, 1 H, H-8), 7.62 (t, 1 H, H-8’, $J = 8.09$ Hz), 8.19 (d, 1 H, H-6, $J = 8.15$ Hz), 8.20 (d, 1 H, H-5, $J = 8.36$ Hz), 8.29 (d, 1 H, H-6’, $J = 7.44$ Hz), 8.74 (s, 1 H, H-2).

MS: $m/z$ (%) = 610 (M$^+$, 38), 423 (18), 228 (18), 215 (55), 187 (100).

Anal. Calcd for C$_{37}$H$_{39}$N$_2$O$_4$: C, 68.83; H, 6.93; N, 13.76. Found: C, 68.81; H, 7.01; N, 13.89.

1-Ethyl-N-(10-ethylalloxaizinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 13c

Yield: 0.062 g (33%); mp 230 °C (dec.).

IR (KBr): $\delta = 3449$, 2926, 1710, 1657, 1614, 1580, 1546, 1549, 1504, 1406, 1281, 1244, 1092, 774 cm$^{-1}$.

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.25$ (t, 3 H, CH$_2$CH$_3$, $J = 6.91$ Hz), 2.66 (s, 3 H, 7-CH$_3$), 3.66 (q, 2 H, CH$_2$CH$_3$NH, J = 6.71 Hz), 4.17 (q, 2 H, 1-CH$_2$, J = 6.91 Hz), 4.88 (t, 2 H, N$_2$CH$_2$J, J = 6.73 Hz), 5.17 (br s, 1 H, NH), 7.68 (t, 1 H, H-7’, $J = 8.14$ Hz), 7.99 (t, 1 H, H-8’, $J = 8.15$ Hz), 8.17 (d, 1 H, H-7, $J = 7.44$ Hz), 8.33 (d, 1 H, H-9, $J = 7.91$ Hz), 8.48 (br s, 1 H, N$_2$H), 8.65 (d, 1 H, $J = 7.93$ Hz), 8.90 (s, 1 H, H-2).

MS: $m/z$ (%) = 471 (M$^+$, 28), 284 (20), 228 (12), 215 (49), 187 (100).

Anal. Calcd for C$_{36}$H$_{37}$N$_2$O$_4$: C, 61.14; H, 4.49; N, 20.80. Found: C, 61.21; H, 4.29; N, 20.89.

1-Ethyl-N-(10-ethylalloxaizinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 13d

Yield: 0.078 g (37%); mp 202–204 °C.

IR (KBr): $\delta = 3432$, 2926, 2918, 2362, 1714, 1670, 1550, 1458, 1102, 725, 669 cm$^{-1}$.
$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ = 1.25 (t, 3 H, CH$_2$CH$_3$, $J$ = 7.10 Hz), 1.48–1.85 [m, 8 H, (CH$_2$)$_4$], 2.66 (s, 3 H, 7-CH$_3$), 3.18 (q, 2 H, CH$_2$CH$_2$NH, $J$ = 6.85 Hz), 4.48 (q, 2 H, 1-CH$_2$, $J$ = 7.10 Hz), 4.70 (t, 2 H, N$_{10}$CH$_2$, $J$ = 6.83 Hz), 4.83 (br s, 1 H, NH), 7.24 (d, 1 H, H-$6$, $J$ = 8.21 Hz), 7.66 (t, 1 H, H-$7$, $J$ = 8.11 Hz), 7.94 (t, 1 H, H-$8'$, $J$ = 8.09 Hz), 8.34 (d, 1 H, H-$6'$, $J$ = 7.65 Hz), 8.65 (d, 1 H, H-$5$, $J$ = 7 Hz), 8.73 (br s, 1 H, N$_3$¢H), 8.87 (s, 1 H, H-2).

MS: $m/z$ (%) = 527 (M+, 28), 340 (52), 228 (12), 215 (83), 187 (21), 137 (100).

Anal. Calcd for C$_{28}$H$_{29}$N$_7$O$_4$: C, 63.74; H, 5.54; N, 18.58. Found: C, 63.81; H, 5.49; N, 18.89.

1-Ethyl-N-(10-dodecylisoalloxazinyl)-7-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (15b)

Yield: 0.078 g (32%); mp 196 °C.

IR (KBr): 3433, 2956, 2828, 1711, 1671, 1555, 1451, 1103, 998, 887, 725, 666 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta$ = 1.28 (t, 3 H, CH$_2$CH$_3$, $J$ = 6.91 Hz), 1.38–1.95 [m, 20 H, (CH$_2$)$_{10}$], 2.69 (s, 3 H, 7-CH$_3$), 3.37 (q, 2 H, CH$_2$CH$_2$NH, $J$ = 6.80 Hz), 4.50 (q, 2 H, 1-CH$_2$, $J$ = 6.91 Hz), 4.71 (t, 2 H, N$_{10}$CH$_2$, $J$ = 6.81 Hz), 4.84 (br s, 1 H, NH), 7.28 (d, 1 H, H-$6$, $J$ = 7.99 Hz), 7.56 (t, 1 H, H-$7$, $J$ = 8.21 Hz), 7.98 (t, 1 H, H-$8'$, $J$ = 8.22 Hz), 8.24 (d, 1 H, H-$6'$, $J$ = 7.65 Hz), 8.65 (d, 1 H, H-$5$, $J$ = 7 Hz), 8.75 (s, 1 H, H-$2$), 8.83 (br s, 1 H, N$_3$¢H).

MS: $m/z$ (%) = 611 (M +, 28), 424 (62), 228 (12), 215 (89), 187 (100).

Anal. Calcd for C$_{34}$H$_{41}$N$_7$O$_4$: C, 66.76; H, 6.76; N, 16.03. Found: C, 66.81; H, 6.69; N, 15.91.

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