Synthesis of Selected Novel Covalently Linked Flavoquinolones

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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 ^{1}H 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 biological activity.

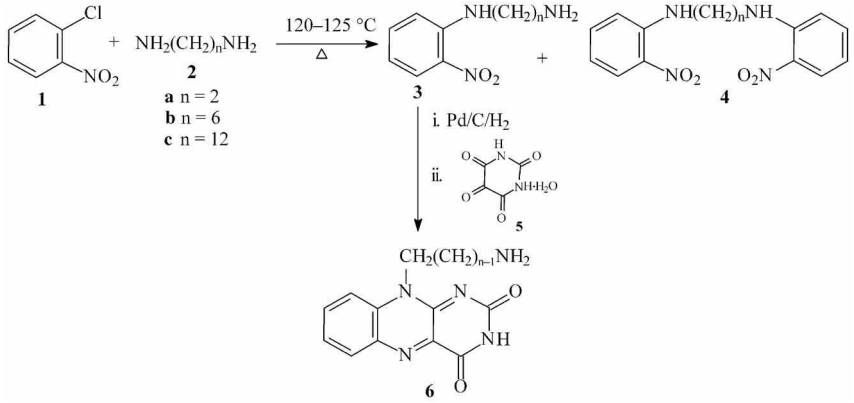
Flavins substituted at position 10 are found to possess antimalarial activity both in vivo against rodent malarials and in vitro against *Plasmodium falciparum*.[5] The antimalarial effects of riboflavin are due to its effect on the change in the structural and/or functional integrity of red blood cell 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 reductase[7], 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 flavoquinolone 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-H_2, 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, ^{1}H NMR and mass spectroscopy.



Scheme 1 Synthesis of flavin

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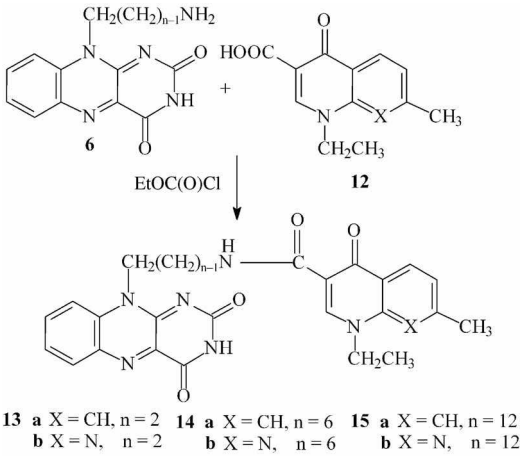
Synthesis of Quinolones

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

The cyclization of substituted propane-1,3-dioate **9a** in diphenyl ether gives ethyl 4-hydroxy-7-methylquinoline-3-carboxylate (**10a**) in 81% yields. The reaction of **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 (**11a**), that on alkaline hydrolysis affords 1-ethyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**12a**). Similarly, nalidixic acid (**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.[9,14] The reaction of 3-carboxy group of quinolone **12** with ethyl chloroformate forms a mixed anhydride, which on subsequent reaction with **6** gives the covalently linked flavoquinolones **13**–**15** in 29–37% yields (Scheme 3).



Scheme 3 Synthesis of flavoquinolones

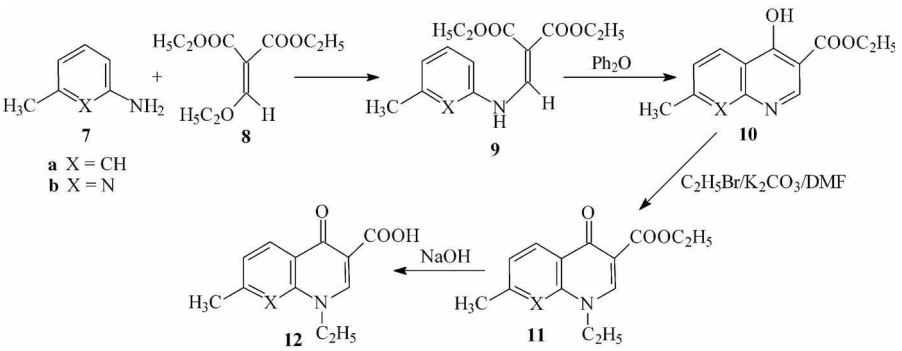
Spectroscopic Properties of Flavin-Linked Quinolones (Flavoquinolones)

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 **13**–**15** are very similar to that of flavins **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[15] and quinone-linked porphyrins.[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.[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.



Scheme 2 Synthesis of quinolones

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

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

Table 2 Comparison of ^{1}H NMR Chemical Shifts of Flavoquinolones **13a**–**15a** and Quinolone **12a**

Product	1-CH_2	CH_2CH_3	7-CH_3	H-2
12a	4.45 (q)	1.37 (t)	2.63 (s)	8.88 (s)
13a	3.99 (q)	1.13 (t)	2.58 (s)	8.63 (s)
14a	4.19 (q)	1.20 (t)	2.59 (s)	8.73 (s)
15a	4.39 (q)	1.37 (t)	2.60 (s)	8.74 (s)

Table 3 Comparison of ^{1}H NMR Chemical Shifts for Flavoquinolones **13b**–**15b** and Quinolone **12b**

Product	1-CH_2	CH_2CH_3	7-CH_3	H-2
12b	4.61 (q)	1.55 (t)	2.74 (s)	8.90 (s)
13b	4.17 (q)	1.25 (t)	2.66 (s)	–
14b	4.48 (q)	1.25 (t)	2.66 (s)	8.87 (s)
15b	4.50 (q)	1.28 (t)	2.69 (s)	8.75 (s)

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 ν_{max} are expressed in cm^{-1}. ^{1}H 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.

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 $CHCl_3$ (250 mL) and washed with H_2O (2 × 100 mL). The $CHCl_3$ layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed on silica gel (60–120 mesh). The column was eluted successively with a mixture of $CHCl_3$ and MeOH (4:1). The fraction from the second large red band was collected.

N-(1′-Aminoethyl)-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}.

^{1}H NMR ($CDCl_3$, 60 MHz): δ = 1.35 (br s, 2 H, NH_2), 2.55–2.65 (m, 2 H, CH_2), 2.75–2.95 (m, 2 H, CH_2), 6.65–6.95 (m, 2 H, H-4, H-6), 7.35–7.45 (m, 1 H, H-5), 8.13 (d, 1 H, H-3, *J* = 8.12 Hz).

N-(1′-Aminohexyl)-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}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.25–1.76 [m, 10 H, NH_2, $(CH_2)_4$], 3.24–3.33 (m, 4 H, CH_2NH_2, CH_2NH), 6.64 (dt, 1 H, H-4, *J* = 8.21, 1.30 Hz), 6.84 (d, 1 H, H-6, *J* = 8.60 Hz), 7.43 (dt, 1 H, H-5, *J* = 8.20, 1.32 Hz), 8.17 (dd, 1 H, H-3, *J* = 8.6, 1.5 Hz).

***N*-(1′-Aminododecyl)-2-nitroaniline (3c)**
Yield: 0.425 g (49%); mp 73 °C.

IR (KBr): 3387, 3313, 2925, 2853, 1626, 1573, 1514, 1470, 1418, 1356, 1263, 1230, 1158, 1036, 735, 601, 514 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.12–2.01 [m, 22 H, NH_2, $(CH_2)_{10}$], 3.24–3.35 (m, 4H, CH_2NH_2, CH_2NH), 6.64 (t, 1 H, H-4, *J* = 8.31 Hz), 6.86 (d, 1 H, H-6, *J* = 8.60 Hz), 7.43 (t, 1 H, H-5, *J* = 8.35 Hz), 8.12 (dd, 1 H, H-3, *J* = 8.4, 2.1 Hz).

10-(1′-Aminoalkyl)flavins 6; General Procedure
Pd/C (10%, 0.075 g) was added to a solution of **3** (0.024 mol) in abs EtOH (70 mL), and the mixture was hydrogenated with vigorous stirring at r.t. and at 60 psi pressure for a time period when a quantitative amount of H_2 had been absorbed and the mixture changed its color from yellow to colorless. When the solution became almost colorless, aq 1 N HCl (20 mL) was added to the mixture and the catalyst was removed by filtration. The alloxan monohydrate **5** (0.03 mol) was added to the filtrate and the mixture was refluxed for 1 h. The mixture was allowed to cool to r.t. and kept overnight in a refrigerator. The resulting brown precipitate was filtered and washed with cold EtOH (5 mL) to give a yellowish green solid that was recrystallized from EtOH. The filtrate on concentration gave a second crop of the product.

10-(2′-Aminoethyl)flavin (6a)
Yield: 2.34 g (38%); mp 294 °C (Lit.[17] mp 290–293 °C).

IR (KBr): 3437, 2932, 2885, 1729, 1682, 1642, 1584, 1546, 1500, 1460, 1406, 1385, 1288, 1222, 1184, 1107, 819, 769 cm^{-1}.

^1H NMR (DMSO-d_6, 300 MHz): δ = 2.57 (m, 2 H, CH_2NH_2), 4.88 (t, 2 H, N^{10}-CH_2, *J* = 6.9 Hz), 7.64 (t, 1 H, H-7, *J* = 8.15 Hz), 7.92 (t, 1 H, H-8, *J* = 8.21 Hz), 8.02 (d, 1 H, H-9, *J* = 7.72 Hz), 8.21 (d, 1 H, H-6, *J* = 7.59 Hz).

10-(6′-Aminohexyl)flavin (6b)
Yield: 2.40 g (32%); mp >290 °C.

IR (KBr): 3425, 2933, 2867, 1722, 1662, 1622, 1583, 1544, 1500, 1462, 1406, 1385, 1288, 1223, 1166, 1108, 820 and 776 cm^{-1}.

^1H NMR (DMSO-d_6, 300 MHz): δ = 1.10–1.86 [m, 10 H, NH_2, $(CH_2)_4$], 3.07–3.14 (m, 2 H, CH_2NH_2), 4.67 (t, 2 H, N^{10}-CH_2, *J* = 6.4 Hz), 7.65 (t, 1 H, H-7, *J* = 7.79 Hz), 7.72 (br s, 1 H, N^3H), 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-(12′-Aminododecyl)flavin (6c)
Yield: 3.81 g (40%); mp >290 °C.

IR (KBr): 3425, 2929, 2881, 1710, 1650, 1610, 1580, 1542, 1510, 1460, 1280, 1170, 1180, 1040, 940 cm^{-1}.

^1H NMR (DMSO-d_6, 300 MHz): δ = 0.97–1.89 [m, 22 H, NH_2, $(CH_2)_{10}$], 2.87–3.01 (m, 2 H, CH_2NH_2), 4.47 (t, 2 H, N^{10}-CH_2, *J* = 5.81 Hz), 7.63 (t, 1 H, H-7, *J* = 7.89 Hz), 7.76 (d, 1 H, H-9, *J* = 8.12 Hz), 7.91 (t, 1 H, H-8, *J* = 7.91 Hz), 8.01 (br s, 1 H, N^3H), 8.17 (d, 1 H, H-6, *J* = 7.6 Hz).

Diethyl 2-{[(Substituted)amino]methylene}propane-1,3-dioates 9; General Procedure
A mixture of amino compound **7** (20 mmol) and diester **8** (4.32 g, 4 mL, 20 mmol) were refluxed in EtOH (40 mL) for 16 hours. The EtOH was removed under reduced pressure and the residue was washed with cold H_2O. The product was dried and recrystallized from EtOH to give fine needle shaped white crystals.

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).

IR (KBr): 3280, 3179, 2924, 2855, 1689, 1643, 1614, 1458, 1409, 1381, 1256, 1166, 1097, 1031, 805, 764, 570 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 1.33–1.40 (m, 6 H, 2 CH_3), 2.35 (s, 3 H, CH_3), 4.26–4.33 (m, 4 H, 2 OCH_2), 6.90–7.50 (m, 4 H, ArH), 8.60 (d, 1 H, CH=C, *J* = 14 Hz).

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, 1646, 1612, 1560, 1464, 1425, 1374, 1336, 1254, 1231, 1158, 1097, 1035, 794 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 1.37–1.43 (m, 6 H, 2 CH_3), 2.55 (s, 3 H, 6-CH_3), 4.39–4.44 (m, 4 H, 2 OCH_2), 6.65–7.60 (m, 3 H, ArH), 9.12 (d, 1 H, CH=C, *J* = 14 Hz).

MS: *m*/*z* (%) = 277 (M^+, 23), 232 (37), 204 (100), 177 (59), 158 (98), 132 (50), 92 (100), 65 (42), 53 (12), 43 (21).

Ethyl 4-Hydroxy-7-methylquinoline/naphthyridine-3-carboxylates 12; General Procedure
A mixture of diphenyl ether (100 mL) and compound **9** (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.

Ethyl 4-Hydroxy-7-methylquinoline-3-carboxylate (10a)
Yield: 4.66 g (81%); mp 270 °C (Lit.[20] mp 272–273 °C).

IR (KBr): 3133, 3056, 2924, 2854, 1699, 1615, 1553, 1465, 1377, 1292, 1201, 1096, 1027, 938, 894, 795 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.20 (t, 3 H, CH_2CH_3, *J* = 7.29 Hz), 2.17 (s, 3 H, 7-CH_3), 4.03 (q, 2 H, CH_2CH_3, *J* = 7.30 Hz), 6.89 (d, 1 H, H-6, *J* = 8.29 Hz), 6.93 (s, 1 H, H-8), 8.02 (d, 1 H, H-5, *J* = 8.18 Hz), 8.14 (s, 1 H, H-2).

Ethyl 4-Hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (10b)
Yield: 4.10 g (71%); mp 279 °C (Lit.[19] mp 278–280 °C).

IR (KBr): 3450, 3144, 3021, 2910, 1720, 1688, 1604, 1545, 1454, 1391, 1355, 1329, 1308, 1242, 1181, 1146, 1098, 1026, 933, 857, 799 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 1.25 (t, 3 H, CH_2CH_3, *J* = 7.11 Hz), 2.37 (s, 3 H, 7-CH_3), 4.13 (q, 2 H, CH_2CH_3, *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/1,4-dihydro[1,8]naphthyridine-3-carboxylates 11; General Procedure
A mixture of compound **10** (20 mmol), ethyl bromide (100 mmol) and K_2CO_3 (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 $CHCl_3$ and H_2O. The $CHCl_3$ extract was washed with H_2O and brine. The solution was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to afford product **11**.

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 ($CDCl_3$, 300 MHz): δ = 1.42 (t, 3 H, CH_2CH_3, *J* = 7.05 Hz), 1.54 (t, 3 H, CH_2CH_3, *J* = 7.22 Hz), 2.52 (s, 3 H, 7-CH_3), 4.24 (q, 2 H, CH_2CH_3, *J* = 7.08 Hz), 4.39 (q, 2 H, CH_2CH_3, *J* = 7.23 Hz),

7.21 (d, 1 H, H-6, *J* = 8.20 Hz), 7.27 (s, 1 H, H-8), 8.43 (d, 1 H, H-5, *J* = 8.23 Hz), 8.47 (s, 1 H, H-2).

Ethyl 1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (11b)
Yield: 3.74 g (72%); mp 122 °C (Lit.[21] mp 120.8–121.6 °C).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.45 (t, 3 H, CH_2CH_3, *J* = 7.20 Hz), 1.54 (t, 3 H, CH_2CH_3, *J* = 7.33 Hz), 2.68 (s, 3 H, 7-CH_3), 3.99 (q, 2 H, CH_2CH_3, *J* = 7.23 Hz), 4.08 (q, 2 H, CH_2CH_3, *J* = 7.33 Hz), 7.14 (d, 1 H, H-6, *J* = 8.20 Hz), 8.04 (d, 1 H, H-5, *J* = 8.12 Hz), 8.19 (s, 1 H, H-2).

1-Ethyl-7-methyl-4-oxo-1,4-dihydroquinoline/1,4-dihydro[1,8]naphthyridine-3-carboxylic Acids (12); General Procedure
A mixture of compound **11** (5 mmol) and aq 1 M NaOH (6 mL) in THF (60 mL) was heated to reflux and maintained at reflux for 8 h. The THF was removed on the rotary evaporator at reduced pressure. H_2O was added to the residue and the mixture was filtered. The filtrate was acidified with aq 6 M HCl and the precipitate was collected, washed and dried. The product was recrystallized from DMF.

1-Ethyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (12a)
Yield: 1.097 g (95%); mp 280 °C (Lit.[20] mp 280–282 °C).

IR (KBr): 3047, 2926, 1712, 1660, 1620, 1525, 1466, 1378, 1244, 976, 801, 685 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37 (t, 3 H, CH_2CH_3, *J* = 7.10 Hz), 2.63 (s, 3 H, 7-CH_3), 4.45 (q, 2 H, CH_2CH_3, *J* = 7.11 Hz), 6.59 (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_2H).

1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthylridine-3-carboxylic Acid (12b)
Yield: 1.055 g (91%); mp 232 °C (Lit.[17] mp 226.8–230.2 °C).

IR (KBr): 3045, 2924, 2362, 1714, 1627, 1519, 1474, 1442, 1353, 1295, 1228, 1130, 972, 805 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.55 (t, 3 H, CH_2CH_3, *J* = 7.04 Hz), 2.74 (s, 3 H, 7-CH_3), 4.61 (q, 2 H, CH_2CH_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_2H).

Flavoquinolones 13–15; General Procedure
Ethyl chloroformate (1.1 g, 0.96 mL, 10.1 mmol) was added in small portions to a solution of anhyd Et_3N (0.2 mL) and **12** (0.2 mmol) in anhyd $CHCl_3$ (50 mL) maintaining the temperature at 0 °C. The $CHCl_3$–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-*N*-(10-ethylisoalloxazinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (13a)
Yield: 0.055 g (30%); mp 198 °C.

IR (KBr): 3425, 2927, 1708, 1669, 1656, 1614, 1580, 1546, 1459, 1500, 1406, 1285, 1248, 1092, 957, 774 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.13 (t, 3 H, CH_2CH_3, *J* = 6.99 Hz), 2.58 (s, 3 H, CH_3), 3.57 (q, 2 H, CH_2CH_2NH, *J* = 6.71 Hz), 3.99 (q, 2 H, 1-CH_2, *J* = 7.01 Hz), 4.79 (t, 2 H, $N^{10}CH_2$, *J* = 6.73 Hz), 7.05 (t, 1 H, H-7′, *J* = 8.11 Hz), 7.28 (d, 1 H, H-9′, *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 $C_{25}H_{22}N_6O_4$: C, 63.82; H, 4.71; N, 17.86. Found: C, 63.79; H, 4.59; N, 17.89.

1-Ethyl-*N*-(10-hexylisoalloxazinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (14a)
Yield: 0.061 g (29%); mp 189 °C.

IR (KBr): 3422, 2921, 2828, 1709, 1657, 1610, 1581, 1547, 1451, 1510, 1406, 1287, 1248, 1092, 957, 885, 774 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20 (t, 3 H, CH_2CH_3, *J* = 7.09 Hz), 1.34–1.75 [m, 8 H, $(CH_2)_4$], 2.59 (s, 3 H, CH_3), 3.27 (q, 2 H, CH_2CH_2NH, *J* = 6.89 Hz), 4.19 (q, 2 H, 1-CH_2, *J* = 7.10 Hz), 4.70 (t, 2 H, $N^{10}CH_2$, *J* = 6.73 Hz), 7.15 (t, 1 H, H-7′, *J* = 8.19 Hz), 7.28 (d, 1 H, H-9′, *J* = 8.65 Hz), 7.46 (s, 1 H, H-8), 7.73 (t, 1 H, H-8′, *J* = 8.20 Hz)), 8.12 (d, 1 H, H-6, *J* = 8.95 Hz), 8.21 (d, 1 H, H-5, *J* = 8.35 Hz), 8.38 (d, 1 H, H-9′, *J* = 7.43 Hz), 8.73 (s, 1 H, H-2).

MS: *m*/*z* (%) = 526 (M^+, 21), 339 (12), 228 (77), 215 (100), 187 (45).

Anal. Calcd for $C_{29}H_{30}N_6O_4$: C, 66.14; H, 5.74; N, 15.96. Found: C, 66.21; H, 5.69; N, 15.89.

1-Ethyl-*N*-(10-dodecylisoalloxazinyl)-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (15a)
Yield: 0.081 g (33%); mp 185 °C.

IR (KBr): 3425, 2958, 2885, 1712, 1675, 1645, 1614, 1580, 1547, 1500, 1421, 1285, 1248, 1093, 957, 778 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37 (t, 3 H, CH_2CH_3, *J* = 6.95 Hz), 1.40–1.65 [m, 20 H, $(CH_2)_{10}$], 2.60 (s, 3 H, CH_3), 3.17 (q, 2 H, CH_2CH_2NH, *J* = 7.00 Hz), 4.39 (q, 2 H, 1-CH_2, *J* = 6.96 Hz), 4.69 (t, 2 H, $N^{10}CH_2$, *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 $C_{35}H_{42}N_6O_4$: C, 68.83; H, 6.93; N, 13.76. Found: C, 68.81; H, 7.01; N, 13.89.

1-Ethyl-*N*-(10-ethylisoalloxazinyl)-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxamide (13b)
Yield: 0.062 g (33%); mp 230 °C (dec.).

IR (KBr): δ = 3449, 2926, 1710, 1657, 1614, 1580, 1546, 1459, 1504, 1406, 1281, 1244, 1092, 774 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.25 (t, 3 H, CH_2CH_3, *J* = 6.91 Hz), 2.66 (s, 3 H, 7-CH_3), 3.66 (q, 2 H, CH_2CH_2NH, *J* = 6.71 Hz), 4.17 (q, 2 H, 1-CH_2, *J* = 6.91 Hz), 4.88 (t, 2 H, $N^{10}CH_2$, *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, *J* = 7.44 Hz), 8.33 (d, 1 H, *J* = 7.91 Hz), 8.48 (br s, 1 H, $N^{3'}H$), 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 $C_{24}H_{21}N_7O_4$: C, 61.14; H, 4.49; N, 20.80. Found: C, 61.21; H, 4.29; N, 20.89.

1-Ethyl-*N*-(10-hexylisoalloxazinyl)-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-carboxamide (14b)
Yield: 0.078 g (37%); mp 202–204 °C.

IR (KBr): 3432, 2926, 2918, 2362, 1714, 1670, 1550, 1458, 1102, 725, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.25 (t, 3 H, CH_2CH_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_2CH_2NH, *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* = 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 $C_{28}H_{29}N_7O_4$: 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-dihydro[1,8]naphthyridine-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 ($CDCl_3$): δ = 1.28 (t, 3 H, CH_2CH_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_2CH_2NH, *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* = 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 $C_{34}H_{41}N_7O_4$: C, 66.76; H, 6.76; N, 16.03. Found: C, 66.81; H, 6.69; N, 15.91.

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