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Ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**1**), precursor of nalidixic acid, has been converted in two steps through ([1,8]naphthyridin-3-yl)carbonylguanidine derivatives into substituted pyrimido[4,5-*b*] and [5,4-*c*][1,8]naphthyridines.

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Quinolones such as nalidixic acid (**3**) have been used for the treatment of wide variety of infectious diseases.

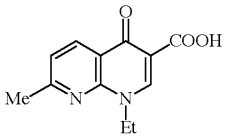

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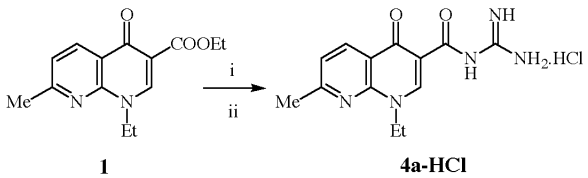
Figure 1

In the course of our work on the chemistry of [1,8]naphthyridine derivatives with potential biological activity [1], we have investigated the synthesis of pyrimido[1,8]naphthyridines which represent a new heterocyclic ring structure. The key step for the synthesis of these new compounds is the intramolecular cyclization of the carbonylguanidine chain.

In order to synthesize tricyclic compounds with the pyrimido[1,8]naphthyridine ring moiety, we have envisaged the preparation of naphthyridinoylguanidine which could be subsequently cyclized to afford the expected products. The synthesis of bicyclic aroylguanidines has been reported in 1997 [2]. These compounds were synthesized either from 2-naphthoyl chloride and excess guanidine by stirring at room temperature or from methyl bicyclic arylcarboxylates and excess guanidine by refluxing in methanol.

In our hands, naphthyridinoylguanidine **4a** was prepared, at room temperature, by condensation of commercially available guanidine carbonate, previously liberated by sodium methylate in dry ethanol at 50°, on ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**1**). The adduct was recristallized from a mixture of aqueous hydrochloric acid (10%) and methanol to give the corresponding hydrochloride **4a-HCl** that is more soluble in nmr solvents such as dimethylsulfoxide-d_6.

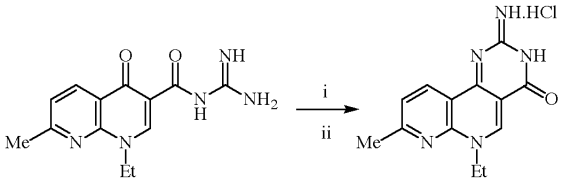


1 **4a-HCl**

i: guanidine, EtOH, RT. ii: HCl 10%.

Figure 2

Intramolecular cyclization of the carbonylguanidine chain can occur at the carbonyl group or by 1,4 addition on the conjugated ketone. Thus, compound **4a-HCl**, previously neutralized with aqueous sodium hydroxide (10%), was easily cyclized by refluxing in ethanol for 1 hour to afford the angular tricyclic ring system 6-ethyl-2-imino-8-methyl-2,6-dihydropyrimido[5,4-*c*][1,8]naphthyridin-4(3*H*)-one isolated as **5a-HCl** in 82% yield. The thermal cyclization mechanism seemed to proceed by an addition-elimination mechanism, which leads to the formation of a stable Schiff base. This compound, as all pyrimidonaphthyridine derivatives, can existed under different prototropic forms.

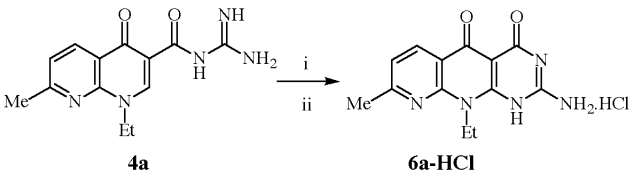


4a **5a-HCl**

i: EtOH, reflux. ii: HCl 10%.

Figure 3

The case of ring closure onto C-2 of the naphthyridine nucleus to prepare linear tricyclic heterocycles was particularly interesting. This method of cyclization of carbonylguanidine chain is based upon the known reactivity of 4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylates towards 1,4 addition. Indeed, 2,3-conjugated double bonds are known to react with nucleophiles, such as Grignard reagents [3] or cyanide [4], in a Michael fashion.



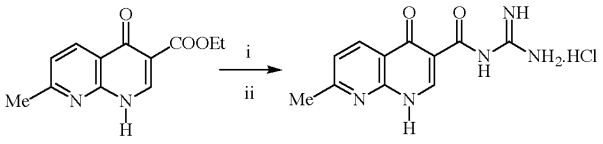
4a **6a-HCl**

i: NaH, DMF, RT. ii: HCl 10%.

Figure 4

Treatment of naphthyridinoylguanidine **4a** with excess sodium hydride in dry *N*,*N*-dimethylformamide at room temperature afforded 2-amino-10-ethyl-8-methyl-1,4,5,10-tetrahydropyrimido[4,5-*b*][1,8]naphthyridine-4,5(1*H*,10*H*)-dione isolated as **6a-HCl** in 89% yield. This result suggests that the saturated intermediate rearomatizes leading to a compound thermodynamically more stable.

Different behaviour was observed for ethyl 7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**2**). In this case, reaction with guanidine involves heating at 80° in *N*,*N*-dimethylformamide. Moreover, attempts to



i: guanidine, DMF, 80°. ii: HCl 10%.

Figure 5

obtain the angular or linear tricyclic compounds, after neutralization of compound **4b-HCl**, were unsuccessful. This result may be due to existence of the unreactive prototropic form **4b'**.

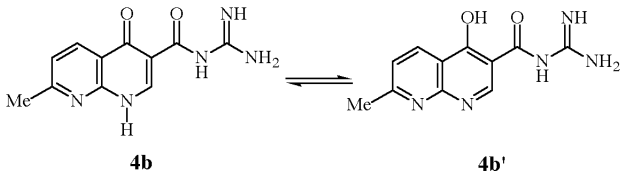
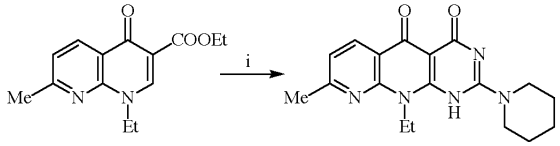


Figure 6

In order to introduce different amino groups in the 2 position of the pyrimido[4,5-*b*][1,8]naphthyridine ring, other guanidine derivatives were condensed and cyclized to give linear tricyclic compounds. These reagents were prepared by condensation of a suitable amine and 1*H*-pyrazole-1-carboxamidine as described in the literature [5].

The reaction of ester **1** with cyclohexylamine-*N*-carboxamidine hydrochloride, previously neutralized as described above, was carried out to give compound **4c** which was converted into 2-(cyclohexylamino)-10-ethyl-8-methyl-pyrimido[4,5-*b*][1,8]naphthyridine-4,5[1*H*,10*H*]-dione (**6c**) by treatment with sodium hydride in *N*,*N*-dimethylformamide at ambient temperature in good yield.

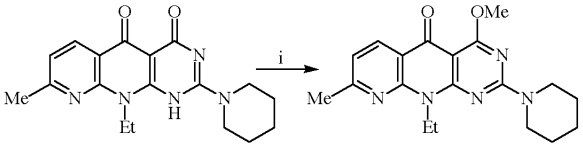
For the preparation of the 2-piperidino derivative **6d**, the intermediate was not isolated, because reaction between ester **1** and piperidine-1-carboxamidine [5] in *N*,*N*-dimethylformamide at ambient temperature led to a mixture, determinated by nmr and mass spectroscopy, of the expected linear and angular tricyclic products, which have not been isolated. In order to obtain only 10-ethyl-8-methyl-2-(1-piperidinyl)pyrimido[4,5-*b*][1,8]naphthyridine-4,5[1*H*,10*H*]-dione (**6d**), the base sodium hydride was added and the mixture was allowed to stir for 24 hours.



i: piperidine-1-carboxamidine hydrochloride, NaH, DMF, RT.

Figure 8

On compound **6d**, which possess only one labile hydrogen, we were able to *O*-alkylate **6d** regioselectively by treatment with sodium hydride and methyl iodide in *N*,*N*-dimethylformamide to obtain compound **7**. The structure of **7** was confirmed by the presence of singlet at δ 54.7 in the ^{13}C nmr spectrum, which was assigned based on a heteronuclear correlation between the methoxy group in position 4.



i: NaH, MeI DMF, RT.

Figure 9

Attempts to synthesize naphthyridinoylguanidines by reaction between ester **1** and aryl-*N*-carboxamidine failed. However, a carboxamidine with a deactivating moiety could be introduced by peptide coupling. Thus, nalidixic acid (**3**) reacted with 1*H*-pyrazole-1-carboxamidine in the presence of hydroxybenzotriazole monohydrate (HOBT), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), diisopropylethylamine (DIPEA) in *N*,*N*-dimethylformamide to give compound **4e** in 49%

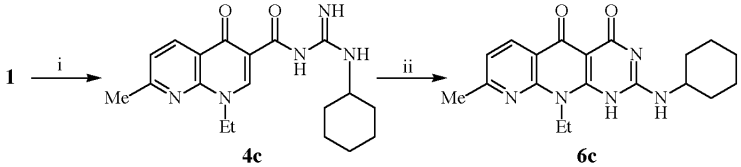
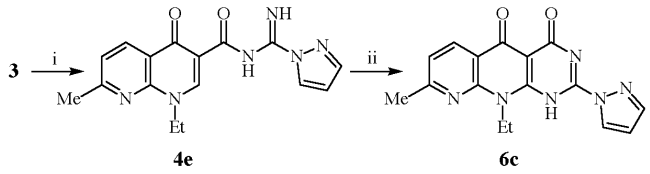


Figure 7

yield. The slow reaction rate can explain this relatively low yield because the 1*H*-pyrazole-1-carboxamidine can undergo a self-condensation reaction [5].



i: 1*H*-pyrazole-*N*-carboxamide hydrochloride, HOBT, EDCI, DIPEA, DMF.
ii: NaH, DMF, RT.

Figure 10

The 1-ethyl-*N*-[imino(1*H*-pyrazol-1-yl)methyl]-7-methyl-4-oxo-1,4-dihydro [1,8]naphthyridine-3-carboxamide (**4e**) was converted into the corresponding tricyclic compound **6e** under the same conditions.

In conclusion, it was found that naphthyridinoylguanidine derivatives are very useful synthons for synthesis of pyrimido-fused [1,8]naphthyridines. Moreover, for the purpose of extending the scope of this reaction, we have begun the study of pyrazole substitution of compound **6e** by nucleophilic reagents.

EXPERIMENTAL

Melting points (uncorrected) were determined on a köfler apparatus. Infrared (ir) spectra were recorded on a Perkin-Elmer Paragon FT-IR 1000 spectrophotometer with 4 cm^{-1} resolution, only the most significant ir absorptions are given. ^1H nmr spectra were recorded at 250 MHz and ^{13}C nmr spectra were recorded at 62.89 MHz on a Brucker AM-250 instrument. Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer (ion spray).

Starting Materials.

Literature procedures were used for the synthesis of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**1**) [6], 7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**2**) [6] and 1-ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (nalidixic acid (**3**)) [6,7].

N-[(1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)carbonyl] guanidine Hydrochloride (**4a-HCl**).

To a solution of 7.0 g (0.027 mole) of compound **1** dissolved in 60 ml of ethanol was added 6.35 g (0.107 mole) of guanidine. The mixture was stirred for 1 hour at room temperature, then poured into water. The precipitate was collected by filtration and recrystallized from a mixture of hydrochloric acid and methanol to give 6.65 g (80%) of **4a-HCl**, mp > 260°; ir (KBr): 3300-2900, 1696, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.37 (t, 3H, J = 7.0 Hz, CH_3), 2.66 (s, 3H, CH_3), 4.61 (q, 2H, J = 7.0 Hz, CH_2), 7.57 (d, 1H, J = 8.0 Hz, H_6), 8.53 (d, 1H, J = 8.0 Hz, H_5), 8.63 (br s, 2H, NH_2), 9.01 (br s, 2H, NH_2), 9.14 (s, 1H, H_2), 13.00 (s, 1H, NH); ms: m/z 274 (100).

Anal. Calcd. for $C_{13}H_{15}N_5O_2$.HCl: C, 50.41; H, 5.21; N, 22.61. Found: C, 50.39; H, 5.23; N, 22.60.

N-[(7-Methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)-carbonyl]guanidine Hydrochloride (**4b-HCl**).

To a solution of 10.0 g (0.043 mole) of compound **2** dissolved in 90 ml of *N*,*N*-dimethylformamide (DMF) was added 10.2 g (0.176 mole) of guanidine. The solution was heated at 80° for 2 hours. Evaporation of DMF *in vacuo* gives a residue, which was stirred in 400 ml of water. The precipitate was collected by filtration and recrystallized from a mixture of hydrochloric acid and ethanol to give 10.43 g (86%) of **4b-HCl**, mp > 260°; ir (KBr): 3367, 3200-2900, 1698, 1638, 1608 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 7.50 (d, 1H, J = 8.0 Hz, H_6), 8.48 (d, 1H, J = 8.0 Hz, H_5), 8.62 (br s, 2H, NH_2), 8.72 (s, 1H, H_2), 9.02 (br s, 2H, NH_2), 13.01 (s, 1H, NH), 13.79 (br s, 1H, NH); ms: m/z 246 (100).

Anal. Calcd. for $C_{11}H_{11}N_5O_2$.HCl: C, 46.90; H, 4.29; N, 24.86. Found: C, 46.94; H, 4.30; N, 24.83.

N-Cyclohexyl-*N*'-[(1-ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridin-3-yl)carbonyl]guanidine (**4c**).

To a solution of 3.0 g (0.011 mole) of compound **1** dissolved in 25 ml of DMF was added 3.0 g (0.021 mole) de *N*-cyclohexylguanidine. The mixture was stirred for 18 hours at room temperature, then poured into water. The precipitate was collected by filtration to give 3.65 g (89%) of **4c**, mp >260°; ir (KBr): 3343, 2928, 1643, 1622, 1610 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.21-1.98 (m, 13H, NCH_2CH_3 and CH_2 of cyclohexyl), 2.67 (s, 3H, CH_3), 3.61 (m, 1H, NHCH), 4.53 (q, 2H, J = 7.0 Hz, NCH_2), 7.29 (d, 1H, J = 8.0 Hz, H_6), 8.62 (d, 1H, J = 8.0 Hz, H_5), 8.81 (s, 1H, H_2); ms: m/z 356 (100).

Anal. Calcd. for $C_{19}H_{25}N_5O_2$: C, 64.20; H, 7.09; N, 19.70. Found: C, 63.95; H, 7.11; N, 19.63.

1-Ethyl-*N*-[imino(1*H*-pyrazol-1-yl)methyl]-7-methyl-4-oxo-1,4-dihydro[1,8] naphthyridine-3-carboxamide (**4e**).

To a suspension of 2.5 g (0.011 mole) of nalidixic acid (**3**) in 60 ml of DMF were added successively 1.89 g (0.013 mole) of 1*H*-pyrazole-1-carboxamidine hydrochloride, 2.48 g (0.013 mole) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.74 g (0.013 mole) of 1-hydroxybenzotriazole hydrate, and 4.47 ml (0.026 mole) of diisopropylethylamine. The mixture was stirred for 48 hours at room temperature. The solvent was evaporated *in vacuo* and the residue was diluted with 10% aqueous hydrochloric acid and dichloromethane. The organic layer was separated and washed with 10% aqueous sodium carbonate, then with water. The organic layer was dried over $MgSO_4$ and evaporated to give 1.70 g (49%) of **4e**, mp > 260°; ir (KBr): 3292, 1694, 1609 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.50 (t, 3H, J = 7.0 Hz, CH_3), 2.68 (s, 3H, CH_3), 4.55 (q, 2H, J = 7.0 Hz, CH_2), 6.41 (m, 1H, $H_{4'}$), 7.29 (d, 1H, J = 8.0 Hz, H_6), 7.77 (m, 1H, $H_{5'}$), 8.42 (m, 1H, $H_{3'}$), 8.73 (d, 1H, J = 8.0 Hz, H_5), 8.88 (s, 1H, H_2), 9.55 (s, 1H, NH), 13.71 (s, 1H, NH); ms: m/z 325 (100).

Anal. Calcd. for $C_{16}H_{16}N_6O_2$: C, 59.25; H, 4.97; N, 25.91. Found: C, 59.28; H, 4.97; N, 25.93.

6-Ethyl-2-imino-8-methyl-2,6-dihydropyrimido[5,4-*c*]-[1,8]naphthyridin-4(3*H*)-one Hydrochloride (**5a-HCl**).

A solution of 5.0 g (0.018 mole) of compound **4a** in 60 ml of ethanol was refluxed for 1 hour, then poured into water. The precipitate was collected by filtration and recrystallized from a mixture of hydrochloric acid and methanol to give 4.38 g (82%)

of **5a-HCl**, mp > 260°; ir (KBr): 3336, 2998, 2920, 1711, 1654, 1621 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.46 (t, 3H, J = 7.0 Hz, CH_3), 2.76 (s, 3H, CH_3), 4.82 (q, 2H, J = 7.0 Hz, CH_2), 7.81 (d, 1H, J = 8.0 Hz, H_9), 8.36 (s, 1H, Hexch.), 8.85 (d, 1H, J = 8.0 Hz, H_{10}), 9.07 (s, 1H, Hexch.), 9.59 (s, 1H, H_5), 12.53 (s, 1H, Hexch.); ms: m/z 256 (100), 228 (40).

Anal. Calcd. for $C_{13}H_{13}N_5O$.HCl: C, 53.52; H, 4.84; N, 24.01. Found: C, 53.56; H, 4.83; N, 24.04.

2-Amino-10-ethyl-8-methylpyrimido[4,5-*b*][1,8]naphthyridine-4,5(1*H*,10*H*)-dione Hydrochloride (**6a-HCl**).

To a suspension of 6.0 g (0.022 mole) of compound **4a** in 60 ml of dry DMF was added 2.63 g (0.066 mole) of sodium hydride (60% in mineral oil). The reaction mixture was stirred at room temperature for 18 hours, then poured into water. The precipitate was collected by filtration and recrystallized from a mixture of hydrochloric acid and methanol to give 6.0 g (89%) of **6a-HCl**, mp > 260°; ir (KBr): 3170, 1703, 1650, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (t, 3H, J = 7.0 Hz, CH_3), 2.55 (s, 3H, CH_3), 4.65 (q, 2H, J = 7.0 Hz, CH_2), 7.20 (d, 1H, J = 8.0 Hz, H_7), 8.29 (d, 1H, J = 8.0 Hz, H_6), 6.60-7.60 (br s, 2H, Hexch.); ms: m/z 272 (100), 244 (40).

Anal. Calcd. for $C_{13}H_{13}N_5O_2$.HCl: C, 50.74; H, 4.59; N, 22.76. Found: C, 50.72; H, 4.60; N, 22.76.

2-(Cyclohexylamino)-10-ethyl-8-methylpyrimido[4,5-*b*][1,8]naphthyridine-4,5[1*H*,10*H*]-dione (**6c**).

To a solution of 2.0 g (0.0056 mole) of compound **4c** in 20 ml of dry DMF was added 0.67 g (0.017 mole) of sodium hydride (60% in mineral oil). The reaction mixture was stirred at room temperature for 18 hours, then poured into water. The precipitate was collected by filtration and washed with water to give 1.5 g (75%) of **6c**, mp > 260°; ir (KBr): 3328, 2924, 1690, 1623, 1601 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.23-2.20 (m, 13H, NCH_2CH_3 and CH_2 of cyclohexyl), 2.70 (s, 3H, CH_3), 4.02 (m, 1H, NHCH), 4.88 (q, 2H, J = 7.0 Hz, NCH_2), 5.52 (d, 2H, J = 6.8 Hz, NH), 7.19 (d, 1H, J = 8.0 Hz, H_7), 8.52 (d, 1H, J = 8.0 Hz, H_6); ms: m/z 354 (100).

Anal. Calcd. for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.80; H, 6.58; N, 19.89.

10-Ethyl-8-methyl-2-(1-piperidinyl)pyrimido[4,5-*b*][1,8]naphthyridine-4,5[1*H*,10*H*]-dione (**6d**).

To a solution of 0.5 g (0.0019 mole) of ester **1** in 7 ml of dry DMF were added 0.63 g (0.0038 mole) of piperidine-1-carboxamidine hydrochloride, 0.26 g (0.0058 mole) of sodium hydride (60% in mineral oil). The reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated *in vacuo* and the residue was diluted with water and dichloromethane. The organic layer was separated, dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on silica gel with dichloromethane:methanol 98/2 to give 0.27 g (41%) of **6d**, mp 233°; ir (KBr): 2928, 1685, 1647, 1633 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.32 (t, 3H, J = 7.0 Hz, CH_3), 1.66 (m, 6H, $CH_2CH_2CH_2$), 2.63 (s, 3H, CH_3), 3.92 (t, 4H, J = 5.0 Hz, $N(CH_2)_2$), 4.77 (q, 2H, J = 7.0 Hz, NCH_2), 7.10 (d, 1H, J = 8.0 Hz, H_7), 8.45 (d, 1H, J = 8.0 Hz, H_6); ms: m/z 340 (100).

Anal. Calcd. for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.73; H, 6.27; N, 20.59.

10-Ethyl-4-methoxy-8-methyl-2-(1-piperidinyl)pyrimido[4,5-*b*][1,8]naphthyridine-5(10*H*)-one (**7**).

To a solution of 0.2 g (0.0006 mole) of compound **6d** in 3 ml of DMF was added 29 mg (0.0007 mole) of sodium hydride (60% in mineral oil). The solution was stirred 30 minutes at room temperature, then 125 mg (0.0009 mole) of methyl iodide was added. The reaction mixture was stirred at 70° for 2 hours. The solvent was evaporated *in vacuo* and the residue was diluted with water and dichloromethane. The organic layer was separated, dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on silica gel with dichloromethane:methanol 98/2 to give 0.155 g (74%) of **7**, mp 202°; ir (KBr): 2936, 1635, 1602 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.32 (t, 3H, J = 7.0 Hz, CH_3), 1.62 (m, 6H, $CH_2CH_2CH_2$), 2.58 (s, 3H, CH_3), 3.87 (m, 4H, $N(CH_2)_2$), 4.07 (s, 3H, OCH_3), 4.78 (q, 2H, J = 7.0 Hz, NCH_2), 7.01 (d, 1H, J = 8.0 Hz, H_7), 8.51 (d, 1H, J = 8.0 Hz, H_6); ^{13}C nmr ($CDCl_3$): 13.59 ($NCH_2\mathbf{C}H_3$), 25.18 (2 $\mathbf{C}H_2$ piperidine), 25.56 (8-$\mathbf{C}H_3$), 26.25 ($\mathbf{C}H_2$ piperidine), 37.84 ($N\mathbf{C}H_2CH_3$), 45.43 (2 $\mathbf{C}H_2$ piperidine), 54.65 ($O\mathbf{C}H_3$), 96.24 (**C**), 117.95 (**C**), 118.51 (**C**H), 136.68 (**C**H), 150.46 (**C**), 159.53 (**C**), 159.96 (**C**), 162.52 (**C**), 170.76 (**C**), 175.09 (**C**); ms: m/z 354 (100).

Anal. Calcd. for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.80; H, 6.59; N, 19.81.

10-Ethyl-8-methyl-2-(1*H*-pyrazol-1-yl)pyrimido[4,5-*b*][1,8]naphthyridine-4,5[1*H*,10*H*]-dione (**6e**).

To a solution of 0.6 g (0.0018 mole) of compound **4e** in 12 ml of dry DMF was added 0.148 g (0.0037 mole) of sodium hydride (60% in mineral oil). The reaction mixture was stirred at room temperature for 4 hours, then poured into water. After concentration, the residue was taken up with water and isolated by filtration. The crude product was purified by recrystallization from DMF to 0.43 g (73%) of **6e**, mp > 260°; ir (KBr): 1654, 1603 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.25 (t, 3H, J = 7.0 Hz, CH_3), 2.55 (s, 3H, CH_3), 4.77 (q, 2H, J = 7.0 Hz, NCH_2), 6.45 (m, 1H, $H_{4'}$), 7.10 (d, 1H, J = 8.0 Hz, H_7), 7.71 (m, 1H, $H_{5'}$), 8.31 (d, 1H, J = 8.0 Hz, H_6), 8.56 (m, 1H, $H_{3'}$); ms: m/z 323 (100).

Anal. Calcd. for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.63; H, 4.40; N, 26.05.

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