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A SYNTHETIC ROUTE TO PYRIDAZINO[4,5-*b*]-1,8-NAPHTHYRIDINES, A NEW TETRAAZAHETEROCYCLIC SYSTEM

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Abstract – A synthesis of the substituted pyridazino[4,5-*b*]-1,8-naphthyridin-6(*7H*)-ones (**6**) based on the reaction of ethyl 2-(dibromomethyl)-6-cyano-7-ethoxy-5-phenyl-1,8-naphthyridine-3-carboxylate (**3**) with hydrazone or substituted hydrazones is described.

The structural diversity and biological importance of nitrogen-containing heterocycles have made them attractive targets for synthesis over many years. Nitrogen-containing heterocycles are of broad pharmaceutical interest and this justifies continuing efforts in the development of structure-activity relationship in this series and of new synthetic strategies.[1] The recent discovery that showed antitumor activity in a wide range of polyheterocyclic compounds isolated from marine organisms,[2] promoted the interest in the synthesis of new heterocyclic rings and in the study of their interaction with biomolecules. In the search for new effective antitumor agents, polycondensed nitrogen heterocycles having a planar structure are effective moieties for drugs endowed with antineoplastic activities. Their mechanism of action is correlated with the capacity to intercalate with the macromolecule of DNA, and to interfere with the activity of Topoisomerases I and II, two enzymes capable of modifying the topological state of DNA.[3] In many cases, biochemical studies have to rely on synthetic materials because the isolation of aza-polynuclear aromatic compounds from natural/environmental sources is sometimes very difficult. In the course of our studies directed toward the discovery and development of synthesis of new heterocyclic systems, we have previously reported on the synthesis of novel tri- and tetracyclic nitrogen-containing ring systems with anti-inflammatory and antihistaminic activity.[4]

Unlike linear carbocyclic “acene” homologous series, very little information on their analogues compounds, containing the pyridine ring as building unit is available.[5] As part of our research programs on the synthesis of new azaheterocyclic systems,[6] we reported the first example of the formation of the 1,7,10-anthyridine system. A literature scan revealed no mention to the synthesis of 8-aza-1,7,10-anthyridine ring. We report here the first preparation and isolation of a series of hitherto

unknown pyridazino[4,5-*b*]-1,8- naphthyridine system. The substituted annelated triheterocyclic poliaza compounds (**5a**,**e**), (**6a-d**) and (**7**) were conveniently obtained as outlined in Scheme 1. Ethyl 3-cyano-2-ethoxy-7-methyl-4-phenyl-1,8-naphthyridine-6-carboxylate (**1**), readily obtained by condensation of a suitably substituted 2-aminonicotinaldehyde with ethyl acetoacetate in ethanol using piperidine as catalyst,[7] is a versatile starting material for tetraazaanthracene derivatives.

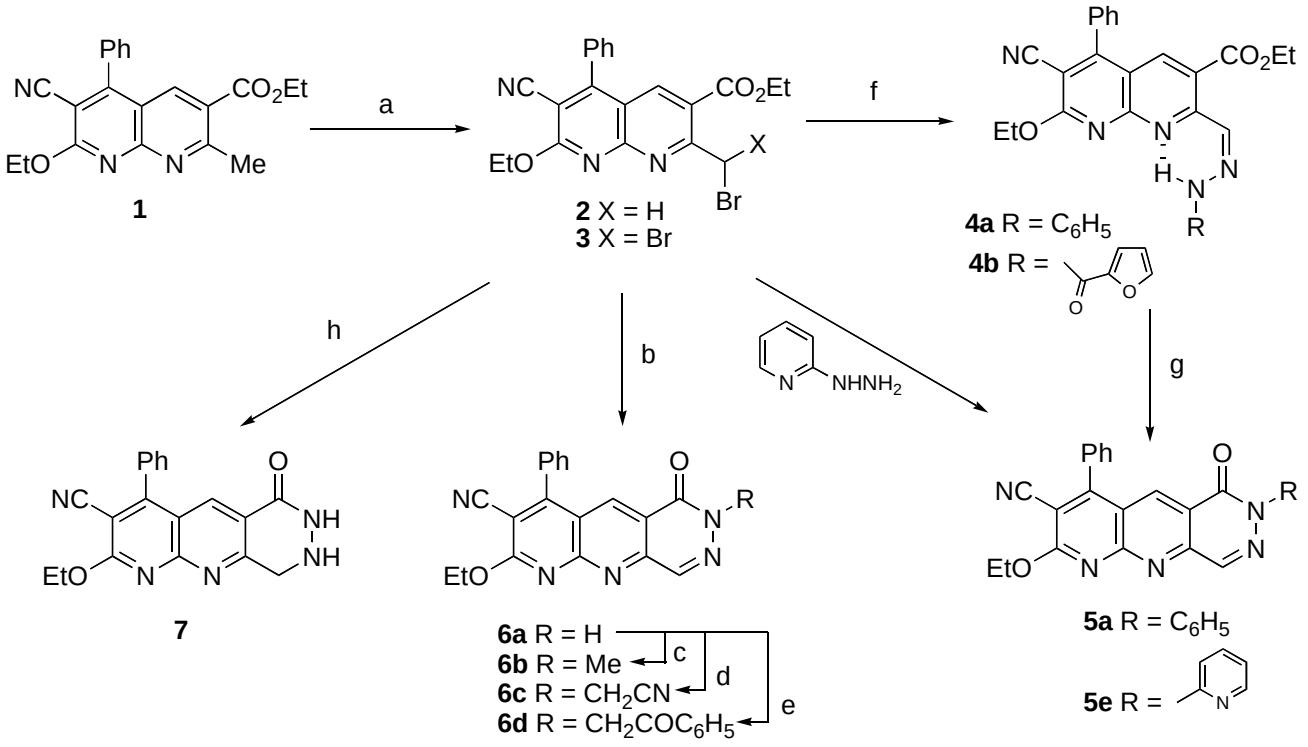
In order to prepare the key intermediate (**3**), when the naphthyridinecarboxylate (**1**) and pyridinium tribromide[8] in dichloromethane were stirred at room temperature for 20 h a one to one mixture of two brominated compounds were obtained in 84% yield, which were readily separated by silica gel column chromatography affording the bromo (**2**) and dibromo (**3**) derivatives, respectively. However, when **1** and pyridinium tribromide in dichloromethane were stirred at room temperature for 12 h and then refluxed for 4 h only the dibrominated naphthyridine (**3**) was obtained in 84% yield. The structures (**2**) and (**3**) are derivable from MS, IR and NMR spectral data. For example, the ^{1}H NMR spectrum of 2-bromomethyl-1,8-napthyridine (**2**) showed a methylene proton signal at δ = 5.18 (s, 2H) and the methine proton signal of dibromomethyl derivative (**3**) appears as a singlet at δ = 8.01 ppm. The MS spectra of **2** and **3** showed molecule ion peaks at *m/z* = 441 and 439 for **2**, and *m/z* = 519, 518 and 517 for **3**. Also, the ^{1}H and ^{13}C NMR spectra showed characteristic signals due to the ethoxy groups.

When ethyl 2-dibromomethyl-6-cyano-7-ethoxy-5-phenyl-1,8-naphthyridine-3-carboxylate (**3**) was allowed to reflux with hydrazine hydrate in ethanol, pyridazino[4,5-*b*][1,8]naphthyridin-6(*7H*)-one (**6**a) was afforded in 70% yield. The reaction of **3** with 2-hydrazinopyridine in reflux ethanol yielded directly the compound (**5e**). As shown in Scheme 1, the intermediate hydrazone compounds (**4**) could be isolated by treatment of **3** with substituted hydrazines in reflux ethanol. Only one isomer, *Z*-configuration (chelated *via* an intramolecular hydrogen-bond between the 8-nitrogen of the 1,8-naphthyridine ring and the hydrogen of the NH hydrazone) of these hydrazones was observed. This *Z*-configuration is consistent with ^{1}H NMR spectral evidence as the NH proton (15.32-16.14 ppm). Ring closure of the hydrazone derivative (**4a**) with sodium ethoxide in ethanol at room temperature yielded the annelated pyridazinonaphthyridone (**5a**). Several attempts to ring closure of **4b** were uniformly unsuccessful under a variety of conditions by the instability of the furan moiety. On the other hand, the reaction of **6a** with electrophilic reagents such as methyl iodide, chloroacetonitrile, and 2-bromoacetophenone in THF or toluene and sodium hydride afforded the 7-substituted pyridazinonaphthyridones (**6b-d**) in moderate yields.

The molecular structure of tetraazaheterocyclic compounds (**6a-d**) was supported by the general data (IR, ^{1}H NMR, ^{13}C NMR, and MS) and elemental analysis. In particular, the MS spectrum showed the expected molecular ion peak and the IR spectra showed strong absorptions at ν = 1660-1670 cm^{-1}, while in the ^{1}H NMR spectra, the H-5 and H-9 protons appear at δ = 8.03-8.78 and δ = 9.07-9.14, respectively. The most salient features of the ^{1}H NMR and ^{13}C NMR spectra are summarized in EXPERIMENTAL.

Finally, when ethyl 2-bromomethyl-6-cyano-7-ethoxy-5-phenyl-1,8-naphthyridine- 3-carboxylate (**2**) reacts with hydrazine hydrate in ethanol, ethoxy-6,7,8,9-tetrahydro- 6-oxo-4-phenylpyridazino[4,5-*b*]-1,8-naphthyridine-3-carbonitrile (**7**) is obtained in 77% yield. The structure of 6,7,8,9-tetrahydropyridazino[4,5-*b*][1,8]naphthyridine (**7**) was confirmed by their elemental analysis and spectroscopic data. The MS spectrum showed strong molecule ion peak at m/z = 345 with 100% abundance. The IR spectrum showed strong absorptions at ν = 3245 and 3200 cm^{-1} attributed to the NH group and ν = 1680 cm^{-1} due to the CO group. In the ^1H NMR spectrum, the CH_2N and NHCO protons appear at δ = 4.21 ppm and δ = 9.58 ppm (exchangeable with D_2O), respectively, in addition to the set of signals due to the ethoxy group and aromatic protons. Also, the ^{13}C NMR spectrum showed signals at δ = 14.2 and 64.0 ppm due to ethoxy group.

In conclusion, the present study clearly shows the usefulness of suitably *ortho*-substituted naphthyridines for the synthesis to tetracyclic pyridazine compounds (**5a**,**e**, **6a-d** and **7**) bearing various substituents on the pyridine and pyridazine rings. Because the starting materials are quite affordable and the experimental procedure is simple, the proposed synthetic approach provides a new, general entry to a variety of substituted derivatives of the pyridazino[4,5-*b*]-1,8-naphthyridine system. Tetraazaheterocyclic compounds (**5a**,**e**, **6a-d** and **7**) can be useful compounds in medicinal chemistry since polycondensed nitrogen heterocycles are effective moieties for drugs and have been widely used as pharmaceuticals.



Scheme 1

Reaction Conditions: a: pyridinium tribromide, CH_2Cl_2. b: NH_2NH_2, EtOH. c: MeI, NaH, THF. d: $ClCH_2CN$, NaH, THF. e: $BrCH_2COC_6H_5$, NaH, toluene. f: $RNHNH_2$, EtOH, reflux. g: NaOEt/EtOH, reflux. h: NH_2NH_2, EtOH, reflux.

EXPERIMENTAL

All reagents used were comercial grade chemicals from freshly opened containers. Mps were determinated on a Bibby SMP3 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Bruker vector 22 FT-IR. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. MS spectra were obtained on a VG-QUATTRO spectrometer. The silica gel 60F-254 used for analytical thin layer chromatography was purchased from Merck. Microanalyses for C, H, N, and S were performed by the elemental analyses general services of the University of La Coruña.

Ethyl 2-bromomethyl-6-cyano-7-ethoxy-5-phenyl-1,8-naphthyridine-3-carboxylate (**2**)

Pyridinium tribromide (2.22 g, 6.94 mmol) was added, in small portions, to a solution of **1** (1.0 g, 2.77 mmol) in dichloromethane (70 mL) at -25 °C. The reaction mixture was stirred for 5 h and then warmed to rt, stirring was continued for 20 h. The solvent was evaporated and the residue was purified by flash chromatography (99.5/0.5 dichloromethane/ethanol) to yield **2** (0.49 g, 40%) and **3** (0.59 g 41%).

Compound **(2)**. mp: 192-193 °C (hexane). IR (KBr, cm^{-1}): 2980, 2225 (CN), 1720 (CO), 1590, 1575, 1445, 1390, 1255, 1025, 815. ^{1}H NMR ($CDCl_3$): 1.38 (3H, t, J = 7.1 Hz, CH_3), 1.56 (3H, t, J = 7.1 Hz, CH_3), 4.40 (2H, q, J = 7.1 Hz, OCH_2), 4.71 (2H, q, J = 7.0 Hz, OCH_2), 5.18 (2H, s, CH_2Br), 7.47-7.66 (5H, m, C_6H_5), 8.58 (1H, s, H-4). ^{13}C NMR($CDCl_3$): 14.0, 14.3, 32.6, 62.2, 64.9, 100.6, 113.7, 116.6, 123.1, 129.2, 129.3, 130.7, 132.1, 141.3, 155.9, 159.0, 162.3, 163.9, 164.6. MS (EI, *m/z*, %): 441 (M^+, 9), 439 (M^+, 8), 413 (10), 411 (10), 361 (27), 360 (97), 304 (100). Anal. Calcd for $C_{21}H_{18}N_3O_3Br$: C, 57.29; H, 4.12; N, 9.54. Found C, 57.34; H, 4.14; N, 9.46.

Ethyl 2-dibromomethyl-6-cyano-7-ethoxy-5-phenyl-1,8-naphthyridine-3-carboxylate (**3**)

Pyridinium tribromide (0.56 g, 1.75 mmol) was added, in small portions, to a solution of **1** (0.25 g, 0.69 mmol) in dichloromethane (20 mL) at -25 °C. The reaction mixture was stirred for 5 h and then warmed to rt, stirring was continued for 20 h. The solution was refluxed for 4 h. The solvent was evaporated and the residue purified by flash chromatography (99.5/0.5 dichloromethane/ethanol) to yield **3** (0.30 g, 84%). mp: 150-151 °C (hexane). IR (KBr, cm^{-1}): 3060, 2980, 2225 (CN), 1720 (CO), 1585, 1330, 1260, 1020, 925, 815. ^{1}H NMR($CDCl_3$): 1.33 (3H, t, J = 7.1 Hz, CH_3), 1.49 (3H, t, J = 7.0 Hz, CH_3), 4.37 (2H, q, J = 7.1 Hz, OCH_2), 4.74 (2H, q, J = 7.0 Hz, OCH_2), 7.44-7.65 (5H, m, C_6H_5), 8.01 (1H, s, $CHBr_2$), 8.35 (1H, s, H-4). ^{13}C NMR($CDCl_3$): 14.0, 14.3, 39.3, 62.5, 65.2, 101.0, 113.6, 117.3, 119.1, 129.2, 129.3, 130.8, 132.1, 141.5, 156.5, 158.8, 161.3, 164.1. MS (EI, *m/z*, %): 521 (M^++4, 6), 519 (M^+, 11), 518 (M^+, 19), 517 (M^+, 5), 441 (24), 440 (99), 438 (100). Anal. Calcd for $C_{21}H_{17}N_3O_3Br_2$: C, 48.58; H, 3.30; N, 8.09. Found C, 48.42; H, 3.36; N, 8.12.

General procedure for the synthesis of hydrazones (**4a,b**).

A solution of dibromide (**3**) (0.1 g, 0.19 mmol) and the appropriate hydrazine (0.28 mmol) in ethanol (6 mL) was refluxed for 2 h. After cooling, the precipitate was filtered off and the solid recrystallized from ethanol.

Ethyl 6-cyano-7-ethoxy-5-phenyl-2-phenylhydrazonomethyl-1,8-naphthyridine-3- carboxylate (**4a**) yield: 78%. mp: 199-200 °C. IR (KBr, cm^{-1}): 3975, 2225 (CN), 1710 (CO), 1355, 1230, 1065, 850, 810. ^{1}H NMR(CDCl$_3$): 1.37 (3H, t, *J* = 7.0 Hz, CH_3), 1.63 (3H, t, *J* = 7.1 Hz, CH_3), 4.39 (2H, q, *J* = 7.0 Hz, OCH_2), 4.82 (2H, q, *J* = 7.0 Hz, OCH_2), 7.02-7.06 (2H, m, C_6H_5), 7.38-7.66 (8H, m, C_6H_5), 8.16 (1H, s, CH), 8.48 (1H, s, H-4), 15.32 (1H, s, NH). ^{13}C NMR(CDCl$_3$): 14.1, 14.3, 62.1, 64.5, 98.9, 113.5, 114.2, 114.3, 114.6, 122.5, 122.7, 123.6, 129.4, 130.6, 132.3, 140.1, 143.7, 154.9, 155.1, 158.3, 164.1, 165.1. MS (EI, *m/z*, %): 465 (M^+, 57), 437 (4), 436 (11), 364 (28). Anal. Calcd for $C_{27}H_{23}N_5O_3$: C, 69.66; H, 4.98; N, 15.04. Found C, 69.82; H, 4.91; N, 14.80.

Ethyl 6-cyano-7-ethoxy-5-phenyl-2-(2-furoylhydrazonomethyl)-1,8-naphthyridine-3- carboxylate (**4b**) yield: 67%. mp: 288-289 °C. IR (KBr, cm^{-1}): 2929, 2225 (CN), 1715 (CO), 1700 (CO), 1590, 1560, 1430, 1265, 1160, 1025, 775. ^{1}H NMR(CDCl$_3$): 1.38 (3H, t, *J* = 7.1 Hz, CH_3), 1.66 (3H, t, *J* = 7.1 Hz, CH_3), 4.42 (2H, q, *J* = 7.1 Hz, OCH_2), 4.88 (2H, q, *J* = 7.1 Hz, OCH_2), 6.61-6.62 (1H, m, C_4H_3O), 7.51-7.69 (7H, m, C_6H_5, C_4H_3O), 8.64-8.69 (2H, m, CH, H-5), 16.14 (1H, s, NH). ^{13}C NMR(CDCl$_3$): 14.1, 14.4, 62.7, 64.6, 101.1, 112.2, 113.6, 116.0, 116.3, 124.1, 129.4, 131.0, 131.7, 134.0, 141.8, 145.4, 147.2, 154.0, 154.4, 155.9, 158.8, 164.3. MS (FAB, *m/z*, %): 484 [$(MH)^+$, 100)], 438 (5), 387 (11), 375 (15). Anal. Calcd for $C_{26}H_{21}N_5O_5$: C, 64.59; H, 4.38; N, 14.48. Found C, 64.41; H, 4.49; N, 14.53.

2-Ethoxy-6,7-dihydro-6-oxo-4,7-diphenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile (**5a**)

A suspension of **4a** (0.1 g, 0.21 mmol) and sodium ethoxide (0.05 g, 0.71 mmol) in ethanol (8 mL) was refluxed for 0.5 h. After cooling, the precipitate was filtered off and the solid recrystallized from ethanol to yield **5a** (0.07 g, 81%). mp: > 300 °C. IR (KBr, cm^{-1}): 3500, 2225 (CN), 1660 (CO), 1585, 1415, 1330, 1120, 760. ^{1}H NMR(CDCl$_3$): 1.61 (3H, t, *J* = 7.1 Hz, CH_3), 4.89 (2H, q, *J* = 7.1 Hz, OCH_2), 7.41-7.68 (10H, m, $2C_6H_5$), 8.73 (1H, s, H-5), 9.14 (1H, s, H-9). ^{13}C NMR (CDCl$_3$): 14.3, 65.4, 102.1, 113.5, 120.0, 121.6, 125.3, 128.2, 128.9, 129.3, 129.5, 131.1, 131.9, 139.7, 141.1, 148.7, 157.9, 158.2, 160.0, 164.1. MS (EI, *m/z*, %): 419 (M^+, 82), 418 (63), 391 (43), 390 (45). Anal. Calcd for $C_{25}H_{17}N_5O_2$: C, 71.59; H, 4.08; N, 16.70. Found C, 71.63; H, 4.04, N; 16.75.

2-Ethoxy-6,7-dihydro-6-oxo-4-phenyl-7-(pyridin-2-yl)pyridazino[4,5-*b*][1,8]naphthyridine-3- carbonitrile (**5e**).

A solution of dibromide (**3**) (0.1 g, 0.19 mmol) and 2-hydrazinopyridine (0.03 g, 0.28 mmol) in ethanol (6 mL) was refluxed for 3 h. After cooling, the precipitate was filtered off and the solid recrystallized from ethanol/dichloromethane to yield **5e** (0.07 g, 87%). mp: 266-267 °C. IR (KBr, cm^{-1}): 2230 (CN), 1670

(CO), 1590, 1470, 1305, 1125, 815. ^{1}H NMR(CDCl$_3$): 1.61 (3H, t, *J* = 7.1 Hz, CH$_3$), 4.89 (2H, q, *J* = 7.1 Hz, OCH$_2$), 7.37-7.74 (7H, m, C$_6$H$_5$, C$_5$H$_4$N), 7.87-7.95 (1H, m, C$_5$H$_4$N), 8.67-8.70 (1H, m, C$_5$H$_4$N), 8.78 (1H, s, H-5), 9.14 (1H, s, H-9). ^{13}C NMR(CDCl$_3$): 14.3, 65.4, 102.1, 113.4, 120.9, 121.6, 123.7, 129.4, 129.5, 131.1, 131.9, 138.1, 139.6, 140.3, 148.9, 149.4, 152.6, 158.0, 158.4, 158.6, 160.0, 164.2. MS (EI, *m/z*, %): 420 (M$^+$, 53), 392 (39), 365 (31), 364 (28). Anal. Calcd for C$_{24}$H$_{16}$N$_6$O$_2$: C, 68.56; H, 3.84; N, 19.99. Found C, 68.32; H, 3.98; N, 19.77.

2-Ethoxy-6,7-dihydro-6-oxo-4-phenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile (**6a**)

A solution of **3** (0.12 g, 0.23 mmol) in ethanol (10 mL) and 80% hydrazine monohydrate (0.1 mL, 2.0 mmol) was refluxed for 24 h. After cooling, the precipitate was filtered off and recrystallized from ethanol to yield **6a** (0.055 g,70%). mp: > 300 °C. IR (KBr, cm^{-1}): 3800, 2215 (CN), 1685 (CO), 1420, 1380, 1010, 815. ^{1}H NMR(DMSO-d$_6$): 1.49 (3H, t, *J* = 7.0 Hz, CH$_3$), 4.71 (2H, q, *J* = 7.0 Hz, OCH$_2$), 7.62-7.74 (5H, m, C$_6$H$_5$), 8.52 (1H, s, H-5), 8.60 (1H, s, H-9), 13.01 (1H, s, NHCO). ^{13}C NMR (DMSO-d$_6$): 14.1, 64.5, 100.9, 114.0, 119.5, 120.9, 129.1, 129.5, 130.7, 132.4, 137.3, 139.1, 149.1, 157.0, 159.2, 159.6, 163.1. MS (EI, *m/z*, %): 343 (M$^+$, 41), 342 (100), 316 (22), 315 (76). Anal. Calcd for C$_{19}$H$_{13}$N$_5$O$_2$: C, 66.47; H, 3.82; N, 20.40. Found C, 66.63; H, 3.65; N, 20.44.

2-Ethoxy-6,7-dihydro-7-substituted6-oxo-4-phenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile (**6b-d**). General procedure.

A suspension of naphthyridine (**6a**) (0.08 g, 0.23 mmol), sodium hydride (0.009 g, 0.40 mmol) and the appropriate electrophile (0.31 mmol) in dry THF (6 mL) (toluene was used for **6d**) was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (dichloromethane/ethanol 99:1) and recrystallized from dichloromethane/ethanol.

2-Ethoxy-6,7-dihydro-7-methyl-6-oxo-4-phenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile (**6b**) yield: 72%. mp: 224-226 °C. IR (KBr, cm^{-1}): 3040, 2220 (CN), 1665 (CO), 1590, 1260, 800. ^{1}H NMR (CDCl$_3$): 1.45 (3H, t, *J* = 7.1 Hz, CH$_3$), 3.85 (3H, s, CH$_3$), 4.72 (2H, q, *J* = 7.1 Hz, OCH$_2$), 7.43-7.69 (5H, m, C$_6$H$_5$), 8.40 (1H, s, H-5), 8.74 (1H, s, H-9). ^{13}C NMR(CDCl$_3$): 12.9, 38.2, 39.6, 109.6, 113.7, 117.8, 119.4, 128.7, 129.3, 129.5, 131.1, 131.6, 137.9, 138.6, 147.4, 152.1, 157.4, 158.5. MS (EI, *m/z*, %): 357 (M$^+$, 100), 356 (63), 342 (10), 329 (35), 314 (74), 301 (96). Anal. Calcd for C$_{20}$H$_{15}$N$_5$O$_2$: C, 67.22; H, 4.23; N, 19.60. Found C, 67.17; H, 4.06; N, 19.87.

2-Ethoxy-6,7-dihydro-7-cyanomethyl-6-oxo-4-phenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile (**6c**) yield: 72%. mp: 205-207. °C. IR (KBr, cm^{-1}): 2920, 2840, 2220 (CN), 1675 (CO), 1600, 1450, 1260, 1105, 800. ^{1}H NMR (CDCl$_3$): 1.44 (3H, t, *J* = 7.1 Hz, CH$_3$), 4.72 (2H, q, *J* = 7.1 Hz, OCH$_2$), 5.08 (2H, s, CH$_2$), 7.43-7.68 (5H, m, C$_6$H$_5$), 8.46 (1H, s, H-5), 8.71 (1H, s, H-9). ^{13}C NMR(CDCl$_3$): 12.8, 38.3, 38.9, 113.4, 113.7, 118.1, 119.0, 128.6, 129.6, 129.8, 130.1, 130.6, 131.3, 136.0, 137.0, 138.6, 139.9, 140.2,

157.1, 157.7. MS (EI, *m/z*, %): 382 (M^+, 88), 381 (54), 354 (17), 326 (54). Anal. Calcd for $C_{21}H_{14}N_6O_2$: C, 65.96; H, 3.69; N, 21.98. Found C, 66.15; H, 3.76; N, 21.73.

2-Ethoxy-6,7-dihydro-6-oxo-7-phenacyl-4-phenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile **(6d)** yield 40 %. mp: 234-236 °C. IR (KBr, cm^{-1}): 3045, 2220 (CN), 1690 (CO), 1655 (CO), 1585, 1410, 1325, 1010, 810. ^1H NMR($CDCl_3$): 1.60 (3H, t, J = 7.1 Hz, CH_3), 4.88 (2H, q, J = 7.1 Hz, OCH_2), 5.66 (2H, s, CH_2), 7.47-7.66 (8H, m, C_6H_5), 8.00-8.05 (2H, m, C_6H_5), 8.63 (1H, s, H-5), 9.07 (1H, s, H-9). ^{13}C NMR ($CDCl_3$): 14.3, 57.6, 65.3, 102.0, 113.5, 119.8, 120.8, 128.1, 128.9, 129.3, 129.4, 131.0, 132.0, 134.1, 134.6, 139.2, 139.8, 149.2, 157.8, 158.9, 160.0, 164.0, 191.7. MS (EI, *m/z*, %): 461 (M^+, 8). Anal. Calcd for $C_{27}H_{19}N_5O_3$: C, 70.27; H, 4.15, N; 15.18. Found C, 70.20; H, 4.19; N, 15.33.

2-Ethoxy-6,7,8,9-tetrahydro-6-oxo-4-phenylpyridazino[4,5-*b*][1,8]naphthyridine-3-carbonitrile (**7**)

A solution of **2** (0.10 g, 0.23 mmol) in ethanol (10 mL) and hydrazine monohydrate 80% (0.1 mL, 2.0 mmol) was refluxed for 24 h. After cooling, the precipitate was filtered off and recrystallized from ethanol to yield **7** (0.061 g, 77%). mp: > 300 °C. IR (KBr, cm^{-1}): 3245, 3200, 2900, 2225 (CN), 1680 (CO), 1330, 1200, 1015, 910, 710. ^1H NMR (DMSO-d_6): 1.46 (3H, t, J = 7.0 Hz, CH_3), 4.21 (2H, br s, CH_2N), 4.66 (2H, q, J = 7.0 Hz, OCH_2), 5.90 (1H, br s, CH_2NH) 7.55-7.92 (5H, m, C_6H_5), 8.20 (1H, s, H-5), 9.58 (1H, br s, NHCO). ^{13}C NMR (DMSO-d_6): 14.2, 50.6, 64.0, 98.7, 114.2, 116.8, 121.9, 129.0, 129.3, 130.4, 132.8, 135.2, 155.7, 159.3, 162.5, 163.4, 165.2. MS (EI, *m/z*, %): 345 (M^+, 100), 344 (76), 317 (25), 316 (77), 288 (21). Anal. Calcd for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found C, 66.23; H, 4.19; N, 20.41.

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