SYNTHESIS OF SUBSTITUTED 1,8-NAPHTHYRIDINE DERIVATIVES

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Abstract- A variety of substituted 1,8-napthyridines were synthesized from 2-alkoxy-6-amino-3-cyano-5-formyl-4-phenylpyridine (**1**) by Friedländer condensation with aldehydes, aliphatic, cyclic or aromatic ketones and other active methylene compounds. Reactions of **1** with other compounds, were also studied.

Annelation reactions involving suitable aromatic hydrocarbon compounds carrying aminoaldehyde moiety provide synthetic entry into heterocyclic systems;[1] also, the formation of ring structures from substituted heterocyclic aminoaldehydes is often the method of choice for preparation of polycondensed heterocycles.[2-7]

1,8-Naphthyridine derivatives are an important class of pharmaceutically active compounds. Their antibacterial, antiallergic, antihypertensive and anti-inflammatory properties have been reported.[8-14] The actual resurgence of interest in quinolones, naphthyridones and related compounds has resulted in an enormous account of research on new structural modifications to improve the overall spectrum of antibacterial activity, bioavailability and safety. Detailed structure-activity relationships have been reviewed.[15]

Within this respect, the present work is aimed to examine the chemistry of 2-alkoxy-6-amino-3-cyano-5-formyl-4-phenylpyridine (**1**) to be used as a starting material for the synthesis of some 1,8-naphthyridines. The heterocyclic aminoaldehyde (**1**), prepared by $LiAlH_4$ reduction[16] of 2-alkoxy-6-amino-3,5-dicyano-4-phenylpyridine, which is readily accessible from malononitrile and benzaldehyde,[17] opens a direct route for preparation of condensed heterocycles of pyridine series. Friedländer condensation of this compound with aliphatic aldehydes and ketones under a catalytic alkaline conditions (ethanolic or methanolic potassium hydroxide) leads to 7-,6- or 6,7-substituted 1,8-naphthyridines (**2a-f**) as shown in Scheme 1. Similarly, treatment of **1** with benzylideneacetone gives the expected compound (**2k**). Reactions with

aromatic ketones are also feasible. Thus, condensation of **1** with aryl ketones yielded the expected Friedländer products (**2h-j**) in moderate yields.

Besides, similar base-catalysed reactions of aminoaldehyde (**1**) with cyclic ketones provide access to fused heterocyclic systems (**3a-d**).

It should be noted that condensation of **1** with unsymmetric aliphatic ketones occurred in only one direction on ring closure, although it may principally give two different products depending on which α-carbon is used for bond formation. Thus, ring closure in the same base-catalyzed condensation of **1** with ethyl methyl ketone or methyl phenethyl ketone was found to occur preferentially at the α-methylene carbon. The absence of an isomeric product in the former was confirmed by nmr spectroscopy of the reaction product. If, however, piperidine is used for cyclization instead of ethanolic potassium hydroxide, the reaction of **1** with benzylacetone or 2-butanone takes a different course and the **2f** and **2g** are obtained. The compounds (**2d**) and (**2f**) or (**2e**) and (**2g**), whose structures were supported by analytical and spectroscopic data on Tables 1 and 2, were formed *via* the opposite regioselective annelation reaction each other. This indicates that the regioselectivity for the annelation reaction of benzylacetone and 2-butanone with the aminoaldehyde (**1**) were strikingly reversed, depending on the reaction conditions used. This result may provide an efficient regiocontrolled synthetic method for the reactions of unsymmetrical dialkyl ketones with **1**.

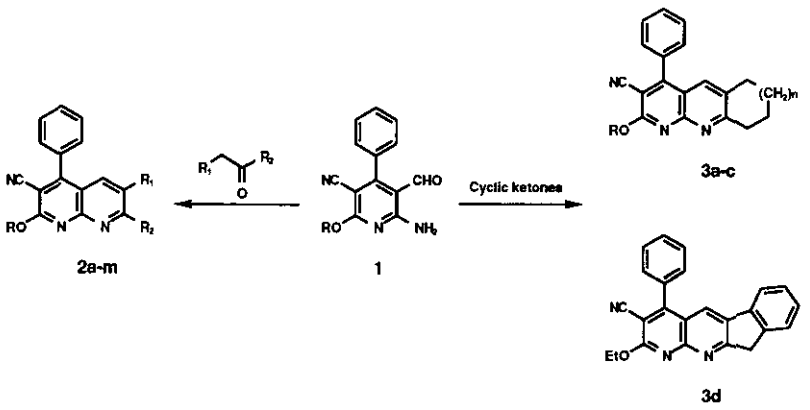
Annelation reactions of β-diketones with **1** are greatly facilitated by the presence of a doubly activated α-methylene group, and as expected, only one directed ring closure is observed. Thus, the reaction of **1** with 2,4-pentanedione affords 3-acetyl-1,8-naphthyridine (**2m**) in a good (cf. 80% yield) yield. Similarly, condensation of aminoaldehyde (**1**) and 1,3-cyclohexandione gives the tricyclic ketone (**4**). On the contrary, the reaction of 2,4-pentanedione with **1** in a 1:2 molar ratio in ethanol containing a few drops of 10% ethanolic KOH gives dimeric naphthyridine (**5**). Formation of **5** was confirmed by using an alternative way involving Friedländer condensation of 6-acetyl-7-methyl-1,8-naphthyridine (**2m**) with **1** under the same reaction conditions. Further unambiguous identification for **5** was obtained from ^{1}H nmr, ^{13}C nmr and mass spectra. In another type of reaction of β-diketones with **1**, condensation of **1** with benzoylacetone in the presence of methanolic KOH yielded 7-phenyl-1,8-naphthyridine (**2l**), which was identical with the compound prepared by the usual condensation of **1** with acetophenone. The formation of **2l** from benzoylacetone may be rationalized as follows: benzoylacetone is unstable in alkaline alcoholic solutions and gives rise to acetophenone by cleavage, then the ketone reacts with **1** to give naphthyridine (**2l**).

In the case of bifunctional compounds (XCH_2Y; X, Y= keto, cyano, alkoxycarbonyl and carbamoyl group) the amino group on **1** attacks the more electrophilic group to form functionalized naphthyridines (**6**) as shown in Scheme 2.

Thus, aminonicotinaldehyde (**1**) condenses with ethyl acetoacetate or ethyl benzoacetate in the presence of piperidine to give 6-ethoxycarbonyl-7-methyl(or phenyl)-1,8-naphthyridine

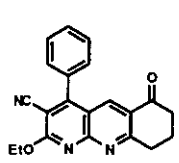
(**6a**) or (**6b**), whereas its condensation with acetoacetamide and diethyl malonate affords **6c** and **6d**, respectively. Similar condensations with acetonitrile or phenylacetonitrile lead to the corresponding 7-amino-1,8-naphthyridines (**6e**) and (**6f**), respectively, and cyclization reaction with malononitrile takes place *via* intramolecular addition of the amino groups to the cyano function on the intermediate produced by initial intermolecular condensation to give 7-amino-3,6-dicyano-1,8-naphthyridine (**6g**). The reaction product of **1** with ethyl cyanoacetate is dependent on the reaction conditions. Thus, while piperidine-catalyzed condensation of **1** with the cyanoacetate affords 7-hydroxy-1,8-naphthyridine (**7**) rather than compound (**6h**), which was observed only at high temperature in the absence of catalyst.

Scheme1

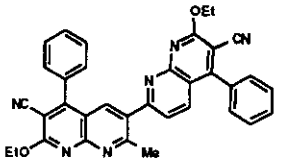


	R_1	R_2	R	Yield (%)
2a	Me	H	Me	30
2b	Ph	H	Me	40
2c	H	Me	Et	93
2d	CH_2Ph	Me	Et	75
2e	Me	Me	Et	92
2f	H	$(CH_2)_2Ph$	Me	65
2g	H	Et	Et	44
2h	Me	Ph	Et	81
2i	H	p-NO_2-C_6H_4	Me	51
2j	H	o-OH-C_6H_4	Me	65
2k	H	CH=CHPh	Et	81
2l	H	Ph	Me	60
2m	COMe	Me	Et	80

	n	R	Yield (%)
3a	0	Me	60
3b	1	Me	76
3c	2	Et	70



4



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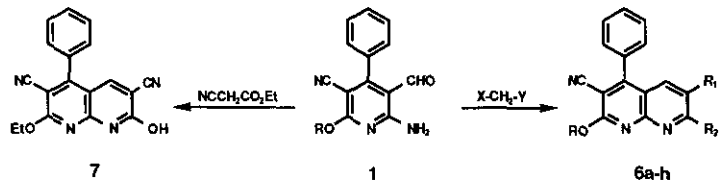
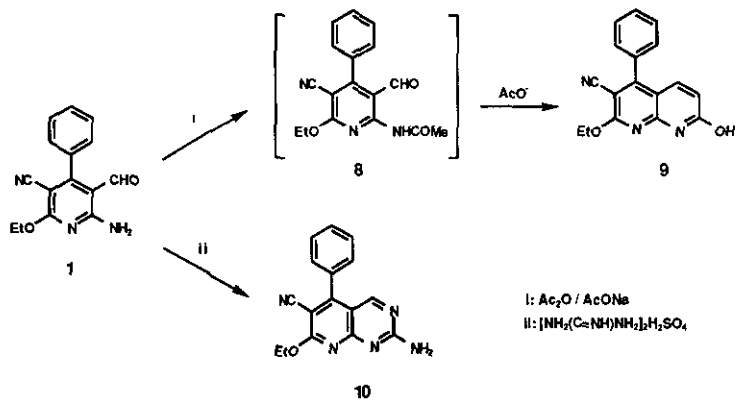
Scheme 2



X	Y
CO_2Et	COMe
CO_2Et	COPh
$CONH_2$	COMe
CO_2Et	CO_2Et
H	CN
Ph	CN
CN	CN
CO_2Et	CN

δ	R_1	R_2	R	Yield (%)
a	CO_2Et	Me	Et	72
b	CO_2Et	Ph	Et	70
c	$CONH_2$	Me	Et	65
d	CO_2Et	OH	Et	50
e	H	NH_2	Et	53
f	Ph	NH_2	Me	60
g	CN	NH_2	Et	95
h	CO_2Et	NH_2	Et	90

Scheme 3



In addition, treatment of heterocyclic aminoaldehyde (**1**) with acetic anhydride/sodium acetate led to an acylated derivative structurally analogous to the proposed intermediate (**8**),[18] which then cyclized to afford the corresponding 7-(1H)-naphthyridone (**9**). Finally, reaction of **1** with guanidine sulfate in boiling ethanol gave the corresponding pyrido[2,3-*d*]pyrimidine compound (**10**) *in moderate yield.*

The structures assigned to these compounds were fully confirmed by elemental analyses, as well as ir, mass, and nmr spectral data. Tables **1-4** show the *yields and spectral and the* physical data for the compounds prepared as described in the experimental section.

In conclusion, we synthesized a number of 1,8-naphthyridine derivatives of potentially pharmaceutical or biological interest by use of Friedländer's approach.

EXPERIMENTAL SECTION

All melting points were measured by using a Büchi 510 instrument and are given uncorrected. Ir spectra (potassium bromide) were recorded on a Perkin-Elmer 383 spectrophotometer. ^{1}H and ^{13}C nmr (200 MHz and 50 MHz) were measured on a Bruker AC200F spectrometer. Chemical shifts are given on the scale δ and using tetramethylsilane as an internal standard. Mass spectra were obtained on a VG4 spectrometer. Microanalyses for C, H and N were performed by the Elemental Analyses General Service of the University of La Coruña. Silica gel HF $_{254+366}$ for thin layer chromatography and silica gel 60 (230-400 mesh) for medium-pressure chromatography (mplc) were used as purchased from Merck. All reagents used were commercial-grade chemicals from freshly opened containers.

2-Alkoxy-3-cyano-4-phenyl-1,8-naphthyridine (2a-e, 2h-m, 3a-d); General Procedure:
A solution of **1** (0.75 mmol), a suitable aldehyde or ketone (0.90 mmol) and a catalytic amount of 10% ethanolic or methanolic potassium hydroxide (KOH 0 05 g in alcohol 0.62 ml) in ethanol or methanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc. After cooling, the precipitates were collected by filtration and recrystallized from a suitable solvent or purified by medium-pressure chromatography. For the reaction conditions, and analytical, physical and spectroscopic data, see Tables **1** and **2**.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-phenyl-1,8-naphthyridines 2f and **2g**
A solution of **1**, (0.20 g, 0.75 mmol; R = Et), benzylacetone (3 ml, 20.02 mmol) or 2-butanone (3 ml, 33.49 mmol) and piperidine (0.2 ml, 2 02 mmol), was heated at 120°C and 60°C, respectively, until all starting material had disappeared as checked by tlc. After cooling, the precipitates were collected by filtration, washed with ethanol or water, and recrystallized from a suitable solvent. For the reaction conditions, analytical, physical and spectroscopic data, see Tables **1** and **2**

3-Cyano-2-ethoxy-4-phenyl-6-oxo-6,7,8,9-tetrahydrobenzo[3,2-*b*]1,8-naphthyridine (4)
A solution of **1** (0.40 g, 1.50 mmol; R = Et), 1,3-cyclohexanedione (0.19 g, 1.67 mmol) and a catalytic amount of 10% ethanolic potassium hydroxide (KOH 0.05 g in ethanol 0.62 ml) in ethanol (15 ml) was refluxed until all starting material had disappeared as checked by tlc (3 h). After cooling, the precipitates were collected by filtration and recrystallized from ethanol/acetone to obtain 0.41 g (80%), mp 281-283°C. ^{1}H-Nmr ($CDCl_3$) δ: 1 54 (3H, t, J = 7.1 Hz); 2.13-2.31 (2H, m); 2.74 (2H, t, J = 6.5 Hz); 3.36 (2H, t, J = 6.2 Hz); 4.79 (2H, q, J=7.1 Hz); 7.40-7.50 (2H, m), 7.55-7.65 (3H, m); 8.58 (1H, s). ^{13}C-Nmr ($CDCl_3$/TMS) δ: 14.3 (CH_3); 21.3 (CH_2); 33.5 (CH_2); 38.6 (CH_2); 64.7 (OCH_2); 113.8 (CN); 196.4 (CO). Ms (70ev) m/z(%): 343 (M^+, 39), 342 (100); 316 (18); 315 (79); 287 (47). Ir (KBr): 2220 (CN); 1690 (CO). Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99, N, 9.32. Found: C, 73.33; H, 5.12; N, 9.27.

3-Cyano-6-(3´-cyano-2´-methoxy-4´-phenyl-1,8-naphthyridin-7´yl)-2-methoxy-7-methyl-4-phenyl-1,8-naphthyridine (5)

Method A:

A solution of **1** (0.48 g, 1.80 mmol; R = Et), 2,4-pentanedione (0.09 ml, 0.90 mmol) and a catalytic amount of 10% ethanolic potassium hydroxide (KOH 0.10 g in ethanol 1.24 ml) in ethanol (15 ml) was refluxed until all starting material had disappeared as checked by tlc (24 h) After cooling, the precipitate was collected by filtration, purified by medium-pressure chromatography on silica gel 60 (6:1 dichloromethane-hexane) and recrystallized from ethanol/acetone to obtain 0.32 g (65%).

Method B:

A solution of **1** (0.11 g, 0 40 mmol; R = Et) and 6-acetyl-3-cyano-2-ethoxy-7-methyl-4-phenyl-1,8-naphthyridine (**2m**, 0.15 g, 0.45 mmol), and a catalytic amount of 10% ethanolic potassium hydroxide (KOH 0.06 g in ethanol 0.74 ml) in ethanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc (16 h). After cooling, the precipitate was collected by filtration, purified by medium-pressure chromatography on silica gel 60 (6:1 dichloromethane-hexane) and recrystallized from ethanol/acetone to obtain 0 17 g (74%), mp >300°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.51-1 71 (6H, m); 2.86 (3H, s); 4.72-4.88 (4H, m); 7.41-7.65 (11H, m); 8.07 (2H, d, J = 10.1 Hz). ^{13}C-Nmr ($CDCl_3$) δ: 14.3 (CH_3); 14.4 (CH_3); 24.7 (CH_3); 64.5 (CH_2O), 114.1 (CN); 114.3 (CN). Ms (70ev) m/z(%): 562 (M^+, 91); *561 (100); 533 (32); 506 (27); 505 (68).* Ir (KBr). 2225 (CN). Anal. Calcd for $C_{35}H_{26}N_6O_2$. C, 74.72; H, 4.66; N, 14.94. Found: C, 74.80; H, 4.59; N, 14 87.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-phenyl-1,8-naphthyridines (6a) and (6b)

A solution of **1**, (0.20 g, 0 75 mmol; R = Et), ethyl acetoacetate(5 ml, 39.23 mmol) or benzoyl acetoacetate (5 ml, 28.87 mmol) and piperidine (0.3 ml, 3.03 mmol), was refluxed until all starting material had disappeared as checked by tlc. After cooling, the precipitates were collected by filtration, washed with ethanol and recrystallized from a *suitable solvent or purified by medium-pressure chromatography.* For the reaction conditions, analytical, physical and spectroscopic data, see Tables **3** and **4**.

3-Cyano-2-ethoxy-4-phenyl-1,8-naphthyridine (6c-e and 6h); General Procedure:

A solution of **1** (0.20 g, 0.75 mmol; R = Et), a suitable highly reactive α-methylene derivative (0.83 mmol) and a catalytic amount of 10% ethanolic potassium hydroxide (KOH 0.05 g in ethanol 0.62 ml) in ethanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc After cooling, the precipitates were collected *by filtration, washed with ethanol and recrystallized* from a suitable solvent or purified by medium-pressure chromatography. For reaction conditions, and analytical, physical and spectroscopic data, see Tables **3** and **4**.

7-Amino-3-cyano-4,6-diphenyl-2-methoxy-1,8-naphthyridine (6f)

A solution of **1** (0.15 g, 0.59 mmol; R = Me), benzyl cyanide (0.1 ml, 0.87 mmol) and a catalytic amount of 10% methanolic potassium hydroxide (KOH 0.05 g in methanol 0.63 ml) in methanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc (6 h). After cooling, the precipitate was collected by filtration and *recrystallized from ethanol/acetone to obtain* 0 12g (60%). For the reaction conditions, and analytical, physical and spectroscopic data, see Tables **3** and **4**.

7-Amino-3,6-dicyano-2-ethoxy-4-phenyl-1,8-naphthyridine (6g)

A solution of **1** (0.20 g, 0.75 mmol; R = Et), malononitrile (0.06 g, 0.9 mmol) and piperidine (0.3 ml, 3.03 mmol) in THF (10 ml) was stirred at room temperature for 3 h. After cooling, the precipitate was collected by filtration and recrystallized from acetone. For the reaction conditions, and analytical, physical and spectroscopic data, see Tables **3** and **4**.

3,6-Dicyano-2-ethoxy-7-hydroxy-4-phenyl-1,8-naphthyridine (7)

A solution of **1** (0.20 g, 0.75 mmol; R = Et) and piperidine (0.3 ml, 3.03 mmol) in ethyl cyanoacetate (5 ml, 46.99 mmol), was refluxed until all starting material had disappeared as checked by tlc (10 h). After cooling, the precipitate was filtered off, washed with ethanol and purified by medium-pressure chromatography on silica gel with 0.5% ethanol in dichloromethane For reaction conditions, and analytical, physical and spectroscopic data, see Tables **3** and **4**.

3-Cyano-2-ethoxy-7-hydroxy-4-phenyl-1,8-naphthyridine (9)

A mixture of **1** (0.20 g, 0.75 mmol; R = Et) and sodium acetate (0.2 g, 2.43 mmol) in acetic anhydride (6 ml) was refluxed until all starting material had disappeared as checked by tlc (10 h). After cooling, the mixture was stirred on an ice-cooled bath for 3 h and then allowed to stand at room temperature for 20 h. The mixture was then poured into water (30 ml), collected by filtration and recrystallized from ethanol to obtain 0.13 g (60%), mp 283-285°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.51 (3H, t, J =7.1 Hz); 4.62 (2H, q, J = 7.1 Hz), 6.54 (1H, d, J = 9.8 Hz); 7.40-7.61 (6H, m), 10.75 (1H, br s). ^{13}C-Nmr ($CDCl_3$) δ: 14 3 (CH_3); 64.5 (OCH_2); 114.4 (CN). Ms (70ev) m/z(%): 291 (M^+, 37); 264 (10); 263 (54); 262 (15). Ir (KBr): 2220 (CN). Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4 50; N, 14.42. Found: C, 70.15; H, 4.56; N, 14.33

2-Amino-6-cyano-7-ethoxy-5-phenyl-1,3,8-triazanaphthalene (10)

A mixture of **1** (0.20 g, 0.75 mmol; R = Et), guanidine sulfate (0.18 g, 0.82 mmol) and potassium carbonate (0.12 g, 0.87 mmol), was refluxed in ethanol (8 ml) until all starting material had disappeared as checked by tlc (3 h). The hot suspension was collected by filtration, thus leaving out excess salt. The solution was evaporated in vacuum and the solid was purified by medium-pressure chromatography (elution with 2% ethanol, and 2% acetone in dichloromethane) and recrystallized from ethanol/acetone to obtain 0.17 g (80%), mp 270-271°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.36 (3H, t, J = 7.0 Hz); 4.51 (2H, q, J = 7.0 Hz); 7.54-7.66 (5H, m); 8.41 (1H, s). ^{13}C-Nmr ($CDCl_3$) δ: 14.2 (CH_3); 63.5 (OCH_2); 114.8 (CN). Ms (70ev) m/z(%): 291 (M^+, 20); 290 (33), 264 (9); 263 (41). Ir (KBr). 3480 (NH); 2225 (CN). Anal. Calcd for $C_{16}H_{13}N_5O$: C, 65.97; H, 4 50; N, 24.04. Found: C, 65.91; H, 4.57; N, 24.00.

Table 1. 1,8-Naphthyridine derivatives (2a-m, and 3a-d)

No	Reaction time (h)	Yield (%)	mp (°C)	Molecular formula	Analysis (%) Calcd/Found C	H	N
2a	25	30[a]	239-241	$C_{17}H_{13}N_3O$	74 17 74 28	4 76 4 64	15.26 15 13
2b	25	40[a]	227-229	$C_{22}H_{15}N_3O$	78.32 78 20	4 48 4 59	12 46 12 36
2c	1	93[a]	244-246	$C_{18}H_{15}N_3O$	74 72 74 61	5 22 5 29	14.52 14 39
2d	4	75[a]	184-185	$C_{25}H_{21}N_3O$	79.13 79 02	5.09 5.25	11 07 11.19
2e	10	92[a]	221-222	$C_{19}H_{17}N_3O$	75 23 75.13	5 57 5.63	13.85 13 81
2f	24	65[a]	214-216	$C_{24}H_{19}N_3O$	78.88 78 74	5.24 5 32	11.50 11.41
2g	24	44[a]	192-193	$C_{19}H_{17}N_3O$	75 23 75 20	5.65 5.60	13 85 13.89
2h	24	81[a]	159-160	$C_{24}H_{19}N_3O$	78.88 78.99	5 24 5 16	11 50 11 61
2i	19	51[a]	259-261	$C_{22}H_{14}N_4O_3$	69 11 69 23	3 69 3.53	14.65 14.59
2j	4	65 [a]	259-261	$C_{22}H_{15}N_3O_2$	74.78 74 63	4.28 4 35	11 89 11 80
2k	1	81[a]	233-235	$C_{25}H_{19}N_3O$	79.56 79 43	5.07 5 19	11 13 11.01
2l	7	60[a]	235-237	$C_{22}H_{15}N_3O$	78.32 78 20	4 48 4 59	12.46 12 53
2m	6	80[a]	180-182	$C_{20}H_{17}N_3O_2$	72 49 72 57	5 17 5 23	12.68 12 56
3a	6	80[b]	>295	$C_{19}H_{15}N_3O$	75 73 75 62	5 02 5 09	17.94 17 83
3b	6	76[a]	244-245	$C_{20}H_{17}N_3O$	76 17 76 30	5 43 5 31	13 32 13 25
3c	7	70[b]	262-264	$C_{22}H_{21}N_3O$	76 94 76 82	6 16 6 30	12 24 12 10
3d	30	50[a]	296-298	$C_{24}H_{17}N_3O$	79 32 79 23	4 72 4 84	11 56 11 63

[a] Recrystallized from ethanol/acetone.
[b] Purified by column chromatography on silica gel with 0 5 % ethanol in dichloromethane

Table 3. 1,8-Naphthyridine derivatives (6a-h, and 7)

No	Reaction time (h)	Yield (%)	mp (°C)	Molecular formula	Analysis (%) Calcd/Found C	H	N
6a	24	72[a]	224-225	$C_{21}H_{19}N_3O_3$	69 79 69.88	5 30 5.18	11.63 11 84
6b	20	70[b]	243-245	$C_{26}H_{21}N_3O_3$	73 74 73.67	5 00 5.08	9 92 9.87
6c	24	65[b]	294-295	$C_{19}H_{16}N_4O_2$	68 66 68 60	4 85 4 91	16.86 16 81
6d	48	50[a]	290-291	$C_{20}H_{17}N_3O_4$	66 11 66 27	4.72 4 80	11 56 11 37
6e	30	53[a]	268-270	$C_{17}H_{14}N_4O$	70 33 70 26	4 86 4.92	19 30 19 38
6f	6	60[a]	291-293	$C_{22}H_{16}N_4O$	74 98 75.10	4.58 4 42	15.90 15 81
6g	3	95[a]	293-295	$C_{18}H_{13}N_5O$	68.56 68 69	4.16 4 07	22.21 22 37
6h	24	90[a]	293-295	$C_{20}H_{18}N_4O_3$	66 29 66 17	5 01 5 02	15.46 15.50
7	10	98[b]	>300	$C_{18}H_{12}N_4O_2$	68.35 68 43	3.82 3 76	17 71 17 69

[a] Recrystallized from ethanol/acetone.
[b] Purified by column chromatography on silica gel with 0 5 % ethanol in dichloromethane

Table 2. 1,8-Naphthyridines (2a-m, and 3a-d)

No.	Ir (KBr) ν (cm^{-1})	Ms (70eV) m/z (%)	^{1}H-Nmr ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-Nmr ($CDCl_3$/TMS) δ
2a	2220 (CN)	275 (M^+, 47); 274 (100); 244 (21), 83 (48)	2.44 (3H, s); 4.28 (3H, s); 7.43-7.63 (6H, m); 8.90 (1H, d, J=2.5)	18.4; 55.2, 99.1; 114.4; 117 5, 129.0 129.2; 130.2; 133.0; 135.1; 154.1; 157.1 158,.2; 162.0
2b	2220 (CN)	337 (M^+, 12); 336 (15); 306 (8); 104 (39)	4.33 (3H, s); 7.43-7 65 (10H, m), 8.10 (1H, d, J=3.5); 9.30 (1H, d, J=3.5)	55.4, 99.6; 114.2; 117.6; 127.3; 128.5 129.1; 129.3; 130.4; 132.8; 133.5; 134.2 136.5; 154.7; 154.8; 158.8; 162.5
2c	2230 (CN)	289 (M^+, 35); 288 (100); 261 (75); 233 (41); 149 (71)	1.54 (3H, t, J=7.2); 2.80 (3H, s); 4.78 (2H, q, J=7.2); 7.24 (1H, d, J=8.5); 7.43-7.47 (2H, m); 7.58-7.62 (3H, m); 7.85 (1H, d, J=8.5)	14.4; 25.6; 64.1; 98.3; 114 5; 115.7 121.7; 129.0; 129.3; 130.1; 133.2; 136.6 155.6; 158.4; 162.5; 165.8
2d	2230 (CN)	379 (M^+, 57); 378 (100); 351 (55)	1.51 (3H, t, J=7.2); 2.65 (3H, s); 4.03 (2H, s); 4.75 (2H, q, J=7.2); 6.98-7.01 (2H, m); 7.19-7.41 (3H, m); 7.51-7 58 (6H, m)	14.3; 23.7; 38.7, 40.4; 63.9; 98.1; 114.6 116.1; 121.2; 126.1, 126.5; 128.3; 128.6 128.8; 129.2; 130.0; 132.6; 133.0; 136 1 136.4; 138.0; 154.3; 157.8; 162.2; 165.4
2e	2225 (CN)	303 (M^+, 33); 302 (71); 275 (62), 247 (39); 148 (100)	1.52 (3H, t, J=7.0); 2.34 (3H, s); 2.73 (3H, s); 4.74 (2H, q, J=7 0); 7.41-7.46 (2H, m); 7.57-7.60 (3H, m)	14.4; 19.2; 23.8; 63.8; 98.1; 114.6; 116.2 120 4; 128.9; 129.2; 129.9; 130.1, 133.3 135.1; 154 1; 157.6; 161.9; 165.4
2f	2220 (CN)	365 (M^+, 28); 364 (23); 350 (7), 288 (9); 85 (70); 83 (100)	3.25-3.52 (4H, m); 4.45 (3H, s); 7.31-7.74 (11H, m); 7.99 (1H, d, J=8.5)	35.8; 41 0; 55.4; 98.3, 114.5; 116.2 121 4; 126.2; 128.4; 128.5; 128.7; 129.0 129.3; 130.2; 133.1; 136.5; 140.9, 155.7 158.5; 162 8; 16.8.5
2g	2220 (CN)	365 (M^+, 59); 364 (98); 337 (56); 336 (100); 149 (25)	1.53 (3H, t, J=7.2); 2.38 (3H, s); 4.77 (2H, q, J=7.2), 7.46-7.64 (10H, m); 7.80 (1H, s)	14.4; 20 3; 64.0; 98.8, 114 6; 116.7 124.4; 128.2; 128.9; 129.0; 129.3; 133.3 137.2; 139.6, 150 3; 154.1; 157 7; 159.0 162.1; 165.6; 168 1; 175.8, 177.2; 179.6
2h	2225 (CN)	303 (M^+, 81), 302 (75), 275 (85); 274 (100)	1.40 (3H, t, J=7.6); 1.54 (3H, t, J=7.1), 3 06 (2H, q, J=7 7); 4.79 (2H, q, J=7.1); 7.26 (1H, d, J=8.6); 7.43-7.62 (5H, m); 7.89 (1H, d, J=8.6)	14.0; 14 4; 32.4; 64 2; 98.3, 114.5; 115.9 120.4, 129.0; 129.3; 130.1; 133.1; 136.7 155.5; 158.3; 162.5; 170.7
2i	2220 (CN)	382 (M^+, 62); 381 (100); 335 (34)	4.21 (3H, s); 7 47-7.64 (5H, m); 7.86 (1H, d, J=8.6); 8.13 (1H, d, J=8.6), 8.29-8.44 (2H, m)	55.4; 99.4, 114.1; 117.4; 118.6, 123 9 128.9; 129.1; 129.2; 130.4; 132.6; 137.9 143.6; 148.9; 155.6; 158.4; 159.8; 163.2
2j	2225 (CN)	353 (M^+, 100); 352 (47); 325 (9)	4.28 (3H, s); 6.88-7 27 (2H, m), 7.35-7.65 (6H, m); 7.82-7.94 (2H, m); 8.05 (1H, d, J=9.0); 14.80 (1H, s)	55.3, 98.2; 114.2; 115.8; 116.7; 117 9 118.9; 119.1; 127.3; 129 0; 129.3; 130 3 132.6; 133 4; 137.3; 157.7; 161.6; 162.6
2k	2220 (CN)	377 (M^+, 20); 376 (22); 350 (4); 349 (27); 348 (100); 149 (22)	1.55 (3H, t, J=7.1); 4.81 (2H, q, J=7.1); 7.27-7.63 (12H, m); 7.90 (1H, s), 7.94 (1H, d, J=6 9)	14.4; 64.1; 98.2; 114.6; 116.7; 119.2 127.6; 128.9; 129.0; 129.3, 129.4; 129.7 130.1, 133.2; 135.8; 136.6; 137.6, 156.0 158.0; 161.2; 169.7; 172.2; 174.4; 179.2
2l	2220 (CN)	337 (M^+, 18); 336 (25); 103 (25); 69 (49)	4.35 (3H, s); 7 27-7.65 (8H, m); 7.84 (1H, d, J=8 7); 8.06 (1H, d, J=8.6); 8.21-8 26 (2H, m)	55.4; 98.4; 114.5; 116.8; 118 7; 128.2 128.9; 129.0; 129.3; 130 2; 130.6; 133 1 137.2; 138.0; 155.9; 158.4, 162.9; 163 1
2m	2230 (CN); 1685 (CO)	331 (M^+, 41); 330 (93); 304 (10); 303 (42); 289 (26); 288 (100)	1 55 (3H, t, J=7.1); 2.49 (3H, s); 2.96 (3H, s); 4 80 (2H, q, J=7 1); 7.46-7.97 (5H, m); 8.23 (1H, s)	14.3; 25.9; 29 1; 64.7, 99.5; 114.0; 115.0 129.2; 130.6; 132.4; 137 8; 154.5; 155 8 158.8, 163.8; 164.7; 166 0; 198.6
3a	2220 (CN)	301 (M^+, 51); 300 (100); 149 (27)	2.21 (2H, m), 2.96-3.04 (2H, dt, J= 1.3, J=7.5); 3.22 (2H, t, J=7 7), 4 27 (3H, s); 7.41-7.68 (6H, m)	23.4; 30 3; 35.1; 55.1; 97.6; 114.6, 116 4 128.9; 129.2; 129.9; 130.2, 133 4; 135.8 155.4; 158.1; 174.5
3b	2230 (CN)	315 (M^+, 51); 314 (100); 149 (40)	1.85-2.00 (4H, m); 2.85 (2H, t, J=5.9); 3.38 (2H, t, J=6 4); 4.27 (3H, s), 7.42-7.61 (6H, m)	22.5; 22.6; 28.8; 33.8; 55.2; 97.9; 114 6 116.2; 128.9, 129.2; 130 0; 131.0, 131.2 133.3; 135.2; 157.9; 162.2, 165.8
3c	2220 (CN)	343 (M^+, 47); 342 (100); 315 (80); 149 (55)	1.52 (3H, t, J=7.1); 1.64-1 89 (6H, m); 2.17-2.85 (2H, m), 3.23-3.29 (2H, m); 4.75 (2H, q, J=7.1); 7 42-7.60 (6H, m)	14 4; 26.5, 28.4; 32.0; 34.9; 40 0; 63.8 98.1; 114.7; 116.0; 128.9, 129.2; 129.9 133.4; 134.4; 136.6; 154.0; 157.7; 162.0 171.0
3d	2220 (CN)	363 (M^+, 76); 362 (94); 335 (100); 319 (13); 318 (25)	1.57 (3H, t, J=7.0); 3.92 (2H, br s), 4.84 (2H, q, J=7.1); 7.48-7.66 (7H, m); 7.95 (1H, br s); 8.40-8.45 (1H, m)	14.4; 33.9; 64.0; 116.4; 123.4; 125.4 127.7; 129.0; 129.3; 131.0; 134.5; 146.1 166.7

Table 4. 1,8-Naphthyridines (6a-h, and 7)

No.	Ir (KBr) ν (cm^{-1})	Ms (70eV) m/z (%)	^{1}H-Nmr ($DCCl_3$/TMS) δ, J (Hz)	^{13}C-Nmr ($DCCl_3$/TMS) δ
6a	2230 (CN); 1725 (CO)	361 (M^+, 45); 360 (100); 333 (83); 332 (31); 288 (75)	1.33 (3H, t, J=7.0); 1.53 (3H, t, J=7.1); 3.02 (3H, s); 4.34 (2H, q, J=7.1); 4.78 (2H, q, J=7.1); 7.45-7.62 (5H, m); 8.47 (1H, s)	14 0; 14.2; 25.8; 61 6, 64.6; 99.5; 114.0; 115.3; 124.1; 129.1; 129.4; 130.5; 132 7, 139.8; 159.1; 163.9; 165.5; 165.7, 166.7
6b	2230 (CN); 1700 (CO)	423 (M^+, 76); 422 (78); 396 (23); 395 (79); 394 (94); 367 (66); 366 (100)	0.96 (3H, t, J=7.1); 1.54 (3H, t, J=7.1); 4.09 (2H, q, J=7.1); 4.81 (2H, q, J=7.1); 7.42-7.71 (10H, m); 8.39 (1H, s)	13.4; 14.2; 61.4; 64.6; 99.8; 1140; 115.6; 125.5; 128.1; 128.7; 129.1; 129.3; 129.4; 130.5; 132.5; 139.1; 155.7; 158.9; 163.6; 163.7; 167 2
6c	3300, 3110 (NH); 2220 (CN); 1670 (CO)	332 (M^+, 7), 331 (39); 330 (100); 313 (8); 312 (17); 303 (59)	1.54 (3H, t, J=7.1); 2.92 (3H, s); 4.78 (2H, q, J=7.1); 5.92 (2H, br s), 7 44-7.46 (2H, m); 7.60-7.61 (3H, m); 8 00 (1H, s)	14.3; 24.4; 64.6; 114.0; 115 0; 128.8; 129.2; 130.5; 132.6; 135.,1; 155.6; 158.6; 163.2; 163 3; 169.1
6d	3440 (OH); 2220 (CN); 1660 (CO)	363 (M^+, 31), 291 (53); 263 (32); 83 (100)	1 09 (3H, t, J=7.0), 1.32 (3H, t, J=7 0); 4.02 (2H, q, J=7 1); 4.40 (2H, q, J=7.0); 7.25-7.58 (6H, m)	14.2; 14.5; 59.6; 61.8; 84.8; 107.3; 116 7; 121 2; 128.6; 129.0; 129.1; 134.8, 136.1, 155.6; 161 4; 162 4; 167.6; 168.6
6e*	3480 (NH), 3100 (NH); 2220 (CN)	290 (M^+, 100); 275 (12); 262 (33); 245 (5), 234 (7)	1.39 (3H, t, J= 7.1); 4.52 (2H, q, J=7.0); 6.65 (1H, d, J= 8.8); 7.30-7.59 (8H, m)	14.3; 62.5; 90.4; 110.4; 111.6; 115.6; 128.4; 128.7; 129.1; 129 5; 133.9; 135.8; 156.3; 157.2; 162.1; 162.6
6f	3470 (NH); 2220 (CN)	352 (M^+, 7); 351 (9); 236 (11)	4.23 (3H, s); 5.46 (2H, br s); 7.38-7.58 (6H, m);	54.9; 93.6; 112.3; 115 3, 123.8; 128.7; 128.8; 129.1; 129.3; 129 7; 133.6, 136.1; 136 2; 156.4; 157.2; 159.3; 163.6
6g*	3420, 3340, 3230 (NH); 2220 (CN)	315 (M^+, 29); 314 (42); 300 (13); 287 (37); 69 (58)	1.36 (3H, t, J=7.1); 4.51 (2H, q, J=7.1); 7.46-7 60 (5H, m); 7.83 (2H, br s); 7.87 (1H, s)	14.2; 63.5; 93.3; 109.8; 114.8, 115 7; 128 9; 129.3; 130.1; 132.7; 144.4; 157.5; 157.8; 160.1; 163.8
6h	3340, 3230 (NH); 2225 (CN); 1650 (CO)	362 (M^+, 14); 361 (68); 334 (4); 333 (28)	1 29 (3H, t, J=7.1); 1.51 (3H, t, J=7.1); 4.30 (2H, q, J=7.1); 4.71 (2H, q, J=7.1); 6 15 (1H, br s); 7.42-7.61 (5H, m); 8.05 (1H, br s); 8.40 (1H, s)	14.0; 14.3; 61.5; 64.1; 94.7; 108.8; 110 9; 114.8; 128.8; 129.3; 130.2; 133.1; 142.1; 158 5; 158.8; 160.4. 164.8; 165.7
7	3000 (OH); 2225 (CN)	316 (M^+, 1); 315 (2); 314 (6); 288 (1); 287 (3); 286 (10)	1 54 (3H, t, J=7.1); 4.66 (2H, q, J=7.1); 7.37-7.66 (5H, m); 8.00 (1H, s); 10.09 (1H, br s)	14.2; 65.7; 95.0; 105.7; 106.6; 113.3; 114.1; 128.9; 129.5; 131.1; 131 5; 145.8; 151.4; 158 1; 159.2; 165.8

(*) ^{1}H-Nmr and ^{13}C-Nmr ($DMSO-d_6$)

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