Polycyclic *N*-Heterocyclic Compounds, Part 71: Synthesis and Bronchodilator Evaluation of 5-Substituted 1,2-Dihydrofuro [3,2-*f*][1,7]naphthyridines and Related Compounds

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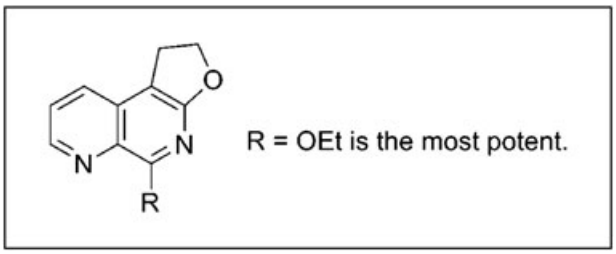

Several 5-substituted 1,2-dihydrofuro[3,2-*f*][1,7]naphthyridines were synthesized as part of our research to develop new effective bronchodilators. Amines, sulfanyls, and alcohols were used as substituents at the fifth position. Tetracyclic compounds were also obtained. Evaluation of the effects of the newly synthesized compounds on carbamoylcholine chloride-induced contractions of trachea revealed one promising bronchodilator candidate with potency comparable to that of 3-isobutyl-1-methylxanthine.

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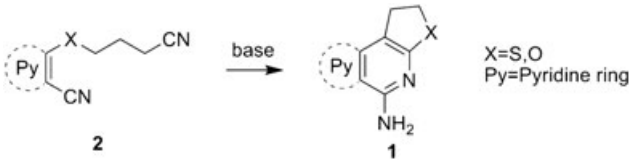
INTRODUCTION

We have previously reported the application of the Truce–Smiles rearrangement [1] for the one-step synthesis of dihydrofuro (or thieno) naphthyridines (**1**) from cyanopyridines having a 3-cyanopropoxy (or 3-cyanopropylsulfanyl) group adjacent to cyano group (**2**) (Scheme 1) [2–5]. Since current bronchodilator drugs are known to have certain detrimental side effects (*e.g.*, increased heart rate) and poor efficacy, we have tested these products and their chemically modified derivatives for bronchodilator activity in a random screening test. Some of the 8,9-dihyrothieno[2,3-*h*][1,6]naphthyridines (**3a**–**c**) and 3,4,7,8-tetrahydro-2*H*-thieno[2,3-*h*]pyrimido [2,1-*f*][1,6]naphthyridine hydrochloride (**4**) showed promising bronchodilator activity in a primary *in vitro* assay (Fig. 1) [6]. In the series of these synthetic studies, we have also reported the preparation of 5-amino-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (**5**) from 3-(3-cyanopropoxy)pyridine-2-carbonitrile (**6**) (Scheme 2) [4]. We now have extended these studies to include 5-substituted derivatives of **5**, which have structural similarity to **3**, to search for compounds with more potent bronchodilator activity. Here, we describe the preparation of 5-subsituted 1,2-dihydrofuro[3,2-*f*][1,7]naphthyridines as well as tetracyclic compounds. We also report the bronchodilator activity of these new analogs.

Scheme 1. One-step synthesis of dihydrofuro (or thieno) naphthyridines by Truce-Smiles rearrangement.



RESULTS AND DISCUSSION

To introduce nucleophiles at the fifth position of **5**, 5-chloro derivative (**7**) was prepared from **5** according to the procedure described in ref. [4]. First, **8** and **9** were prepared from **7** and respective aminoalcohols as analogs of **3b** and **3c** (Scheme 3). Other nucleophiles were also used

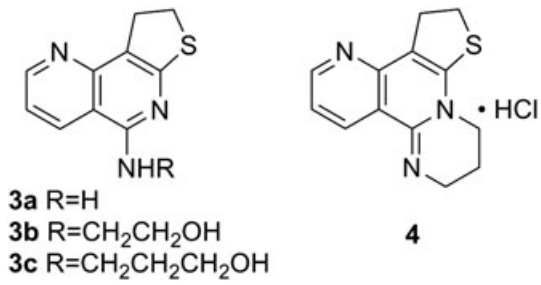
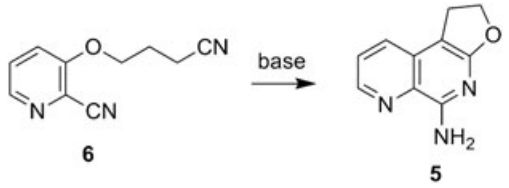


Figure 1. Previous hit compounds as bronchodilators.

Scheme 2. Synthesis of 5-amino-1,2-dihydrofuro[3,2-*f*][1,7] naphthyridine.



to give **10**–**17**, respectively, for further derivatization. All these derivatives have linear 5-subtitutions.

Next, we focused on cyclic type of 5-subtituents. Compound **7** was treated with cyclic aliphatic amines (pyrrolidine, piperidine, morpholine, piperazines) and aromatic amines (imidazoles, pyrazole) to produce 5-substituted products **18**–**25** (Scheme 4).

Finally, the tetracyclic ring product **26**, an analog of **4**, was prepared from **9** and phosphoryl chloride through a ring closure reaction in refluxing chloroform (Scheme 5). We also treated 5-hydrazino derivative **27** [4] with triethyl orthoformate to give a similar type of tetracyclic ring product **28**.

With these compounds in hand, the bronchodilator activities were evaluated. The primary *in vitro* assay was based on the ability of test compounds to relax tracheal contraction induced by carbamylcholine. For this test, the inhibition of carbamylcholine chloride-induced contraction in trachea isolated from guinea pigs was used. Compounds which produced more than 30% relaxation at 10.0 μg/mL, a value calculated from the percent of maximum relaxation by papaverine, were regarded as active. Their IC_{30} values then were obtained by a cumulative method. 3-Isobutyl-1-methylxanthine (IBMX) [7,8] was used as a reference compound. Data from these assays are shown in Table 1. Compounds that are analogs of biologically active **3a** and **4**, that is, **5** and **26**, also showed moderate bronchodilator activity, while **8** and **9**, which are analogs of modestly active compounds **3b** and **3c**, did not have significant activity. Of the compounds tested, ethoxy-substituted compound **17** showed the best activity, with potency comparable to that of IBMX. The activity of the methoxy-substituted analog **16** was one-half that of IBMX.

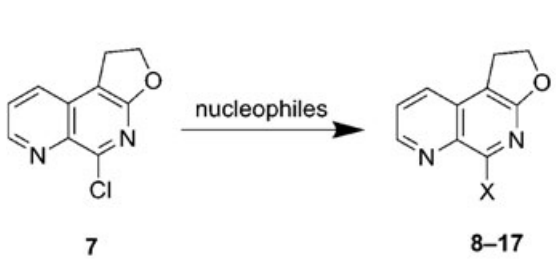
EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN corder elemental analyzer. The FAB-mass spectra were obtained on a VG 70 mass spectrometer, and *m*-nitrobenzyl alcohol was used as the matrix. The IR spectra were recorded on a JASCO A-102 diffraction grating spectrometer or a JASCO FT/IR-200 spectrophotometer, and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ), *J* values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; quin, quintet; br, broad; and m, multiplet. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). Thin layer chromatography was carried out on Kieselgel 60F254 (Merck) or silica gel 70FM (Wako).

5-(2-Hydroxyethylamino)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (8). A mixture of **7** [4] (1.00 g, 4.84 mmol) and 2-aminoethanol (5.90 g, 96.6 mmol) was heated at 120 °C for 1 h under stirring. After addition of ice water (100 mL) to the reaction mixture, the precipitated solid was collected on a filter and recrystallized from ethyl acetate to give **8** (760 mg, 68%) as yellow prisms, mp 171–173 °C; IR (potassium bromide): 3400, 3250 (OH and NH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 3.28 (t, 2H, *J* = 8.7 Hz, H1), 3.75–3.94 (m, 5H, changed to four protons multiplet after addition of deuterium oxide, H1′, 2′, OH), 4.72 (t, 2H, *J* = 8.7 Hz, H2), 7.32 (br, 1H, deuterium oxide exchangeable, NH), 7.42 (dd, 1H, *J* = 8.4, 4.1 Hz, H8), 7.69 (dd, 1H, *J* = 8.4, 1.8 Hz, H9), 8.45 (dd, 1H, *J* = 4.1, 1.8 Hz, H7); FAB-ms: *m/z* 232 (MH^+). *Anal*. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.04; H, 5.59; N, 18.32.

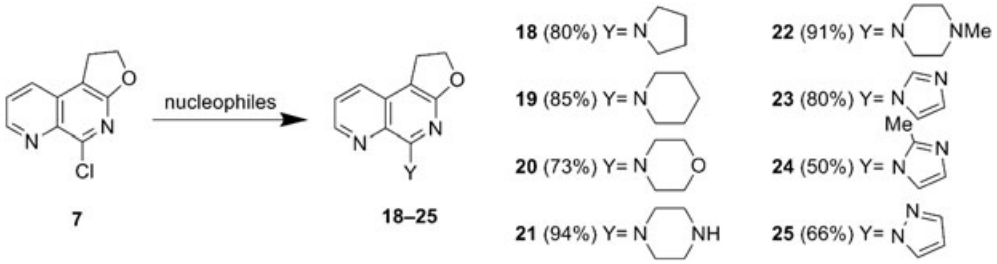
5-(3-Hydroxypropylamino)-1,2-dihydro[3,2-*f*][1,7]naphthyridine (9). A mixture of **7** (200 mg, 0.968 mmol) and 3-amino-1-propanol (1.10 g, 14.6 mmol) was heated at 70 °C for 1 h under stirring. After addition of ice water (80 mL), the precipitated solid was collected on a filter and recrystallized from ethyl acetate to give **9** (152 mg, 64%) as yellow prisms, mp 158–159°C; IR (potassium bromide): 3400, 3350 (OH and NH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.84 (br quin, 2H, *J* = 5.7 Hz, H2′), 3.27 (t, 2H, *J* = 8.5 Hz, H1), 3.62–3.83 (m,

Scheme 3. Preparation of **8**–**17**.



8 (68%) X=$NHCH_2CH_2OH$
9 (64%) X=$NHCH_2CH_2CH_2OH$
10 (97%) X=NHMe
11 (95%) X=NMe_2
12 (42%) X=$SCH_2CH_2CH_2OH$
13 (82%) X=SCH_2CO_2Et
14 (80%) X=$SCH_2CH_2CO_2Et$
15 (67%) X=OCH_2CH_2OH
16 (89%) X=OMe
17 (86%) X=OEt

Scheme 4. Preparation of **18–25**.



4H, H1′ and 3′), 4.46 (br, 1H, deuterium oxide exchangeable, OH), 4.72 (t, 2H, J = 8.5 Hz, H2), 7.16 (br, 1H, deuterium oxide exchangeable, NH), 7.42 (dd, 1H, J = 8.4, 4.1 Hz, H8), 7.69 (dd, 1H, J = 8.4, 1.6 Hz, H9), 8.44 (dd, 1H, J = 4.1, 1.6 Hz, H7); FAB-ms: *m/z* 246 (MH^+). *Anal*. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.40; H, 6.22; N, 17.12.

5-Methylamino-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (10). To a solution of **7** (300 mg, 1.45 mmol) in dioxane (10 mL), aqueous 40% methylamine (1.13 g, 14.6 mmol) was added and the mixture was heated at 100 °C for 2 h in a sealed flask. After evaporation of the reaction mixture *in vacuo*, the residue was recrystallized from diethyl ether to give **10** (283 mg, 97%) as yellow prisms, mp 125–126 °C; IR (potassium bromide): 3400 (NH) cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 3.16 (d, 3H, J = 5.1 Hz, changed to singlet with addition of deuterium oxide, NMe), 3.27 (t, 2H, J = 8.7 Hz, H1), 4.72 (t, 2H, J = 8.7 Hz, H2), 6.95 (br, 1H, deuterium oxide exchangeable, NH), 7.40 (dd, 1H, J = 8.3, 4.2 Hz, H8), 7.68 (dd, 1H, J = 8.3, 1.6 Hz, H9), 8.42 (dd, 1H, J = 4.2, 1.6 Hz, H7); FAB-ms: *m/z* 202 (MH^+). *Anal*. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.37; H, 5.50; N, 20.67.

5-Dimethylamino-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (11). To a solution of **7** (300 mg, 1.45 mmol) in dioxane (10 mL), aqueous 50% dimethylamine (1.31 g, 14.5 mmol) was added and the mixture was heated at 100 °C for 2 h in a sealed flask. After evaporation of the reaction mixture, the residue was recrystallized from diethyl ether to give **11** (297 mg, 95%) as yellow prisms, mp 72–74°C; ^{1}H-NMR (deuterochloroform): δ 3.30 (t, 2H, J = 8.7 Hz, H1), 3.44 (s, 6H, 2 × Me), 4.73 (t, 2H, J = 8.7 Hz, H2), 7.35 (dd, 1H, J = 8.4, 4.1 Hz, H8), 7.69 (dd, 1H, J = 8.4, 1.7 Hz, H9), 8.53 (dd, 1H, J = 4.1, 1.7 Hz, H7); FAB-ms: *m/z* 216 (MH^+). *Anal*. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.83; H, 6.10; N, 19.27.

5-(3-Hydroxypropylsulfanyl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (12). To a solution of **7** (300 mg, 1.45 mmol) in dimethylformamide (5.0 mL), 3-sulfanyl-1-propanol (401 mg, 4.36 mmol) and potassium carbonate (301 mg, 2.18 mmol) were added and the reaction mixture was then stirred at room temperature for 2.5 h. After addition of ice water (200 mL) to the reaction mixture, the suspension was extracted with benzene (200 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from

Scheme 5. Preparation of **26** and **28**.

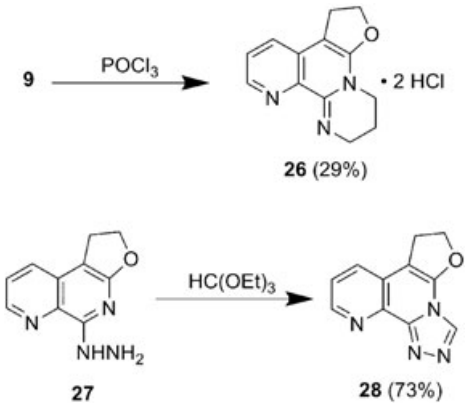


Table 1

IC_{30} value on carbamoylcholine chloride-induced tracheal response *in vitro*.

Compound	IC_{30} (μg/mL)	IC_{30} (μM)
5	2.19	11.7
8	>10.0	–
9	>10.0	–
10	2.96	14.7
11	3.48	16.2
12	7.68	25.7
13	>10.0	–
14	>10.0	–
15	>10.0	–
16	1.68	8.3
17	0.64	3.0
18	6.70	27.8
19	8.98	35.2
20	3.64	14.1
21	7.45	29.1
22	2.37	10.1
23	2.79	11.7
24	4.41	17.5
25	3.77	15.8
26	5.46	18.2
27	>10.0	–
28	>10.0	–
IBMX	0.75	3.4

IC_{30} value shows the concentration of each compound which gives 30% relaxation to tracheal contraction by carbamylcholine chloride (1.00 μM). It was calculated from the percent of maximum relaxation produced by 100 μM papaverine.

ethanol to give **12** (160 mg, 42%) as pale yellow needles, mp 133–135 °C; IR (potassium bromide): 3360 (OH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.03 (m, 2H, H2′), 3.44 (m, 4H, H1 and 1′), 3.56 (br, 1H, deuterium oxide exchangeable, OH), 3.72 (t, 2H, *J* = 5.5 Hz, H3′), 4.83 (t, 2H, *J* = 8.8 Hz, H2), 7.52 (dd, 1H, *J* = 8.5, 4.1 Hz, H8), 7.87 (dd, 1H, *J* = 8.5, 1.6 Hz, H9), 8.74 (dd, 1H, *J* = 4.1, 1.6 Hz, H7); FAB-ms *m/z* 263 (MH^+). *Anal*. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.67. Found: C, 59.32; H, 5.44; N, 10.62.

5-(Ethoxycarbonylmethylsulfanyl)-1,2-dihydro[3,2-*f*][1,7] naphthyridine (13). To a solution of **7** (300 mg, 1.45 mmol) in dimethylformamide (5.0 mL), ethyl sulfanylacetate (523 mg, 4.35 mmol) and potassium carbonate (300 mg, 2.17 mmol) were added and the mixture was then stirred at room temperature for 12 h. Ice water (50 mL) was poured into the reaction mixture and the precipitated solid was collected on a filter. The solid was recrystallized from ethanol to give **13** (345 mg, 82%) as pale yellow needles, mp 149–150 °C; IR (potassium bromide): 1730 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.30 (t, 3H, *J* = 7.1 Hz, Me), 3.43 (t, 2H, *J* = 8.8 Hz, H1), 4.08 (s, 2H, SCH_2), 4.24 (q, 2H, *J* = 7.1 Hz, C*H*$_2$Me), 4.80 (t, 2H, *J* = 8.8 Hz, H2), 7.51 (dd, 1H, *J* = 8.5, 4.1 Hz, H8), 7.86 (dd, 1H, *J* = 8.5, 1.5 Hz, H9), 8.73 (dd, 1H, *J* = 4.1, 1.5 Hz, H7); FAB-ms: *m/z* 291 (MH^+). *Anal*. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65. Found: C, 57.83; H, 4.91; N, 9.40.

5-(2-Ethoxycarbonylethylsulfanyl)-1,2-dihydrofuro[3,2-*f*] [1,7]naphthyridine (14). To a solution of **7** (300 mg, 1.45 mmol) in dimethylformamide (5.0 mL), ethyl 3-sulfanylpropionate (584 mg, 4.36 mmol) and potassium carbonate (300 mg, 2.17 mmol) were added and the mixture was stirred at room temperature for 12 h. Ice water (50 mL) was added to the reaction mixture and the precipitated solid was collected on a filter. The solid was recrystallized from ethanol to give **14** (354 mg, 80%) as pale yellow needles, mp 152–153 °C; IR (potassium bromide): 1730 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.27 (t, 3H, *J* = 7.1 Hz, Me), 2.87 (t, 2H, *J* = 7.1 Hz, H1′), 3.44 (t, 2H, *J* = 8.9 Hz, H1), 3.55 (t, 2H, *J* = 7.1 Hz, H2′), 4.17 (q, 2H, *J* = 7.1 Hz, C*H*$_2$Me), 4.82 (t, 2H, *J* = 8.9 Hz, H2), 7.50 (dd, 1H, *J* = 8.5, 4.2 Hz, H8), 7.86 (dd, 1H, *J* = 8.5, 1.7 Hz, H9), 8.72 (dd, 1H, *J* = 4.2, 1.7 Hz, H7); FAB-ms: *m/z* 305 (MH^+). *Anal*. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.24; H, 5.33; N, 9.10.

5-(2-Hydroxyethoxy)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (15). A mixture of **7** (300 mg, 1.45 mmol), 1,2-ethanediol (1.6 mL, 28.7 mmol), and potassium carbonate (300 mg, 2.17 mmol) was stirred at 80 °C for 4 h. Ice water (50 mL) was poured into the reaction mixture and the precipitated solid was collected on a filter. The solid was recrystallized from ethyl acetate to give **15** (225 mg, 67%) as colorless prisms, mp 189–191 °C; IR (potassium bromide): 3300 (OH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 3.39 (t, 2H, *J* = 8.8 Hz, H1), 3.95 (br, 1H, deuterium oxide exchangeable, OH), 4.11 (t, 2H, *J* = 4.5 Hz, H2′), 4.70–4.86 (m, 4H, H2 and 1′), 7.50 (dd, 1H, *J* = 8.5, 4.2 Hz, H8), 7.82 (dd, 1H, *J* =8.5, 1.6 Hz, H9), 8.73, (1H, dd, *J* = 4.2, 1.6 Hz, H7); FAB-ms: *m/z* 233 (MH^+). *Anal*. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.97; H, 5.33; N, 11.99.

5-Methoxy-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (16). To a solution of sodium (40.0 mg, 1.74 mmol) in methanol (20 mL), **7** (300 mg, 1.45 mmol) was added and the reaction was refluxed for 12 h. After evaporation of solvent *in vacuo*, ice water (300 mL) was poured into the residue which was then extracted with ethyl acetate (300 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from diethyl ether to give **16** (261 mg, 89%) as colorless needles, mp 131–132 °C; ^{1}H-NMR (deuterochloroform): δ 3.40 (t, 2H, *J* = 8.8 Hz, H1), 4.21 (s, 3H, Me), 4.81 (t, 2H, *J*= 8.8 Hz, H2), 7.50 (dd, 1H, *J* = 8.5, 4.0 Hz, H8), 7.83 (dd, 1H, *J* = 8.5, 1.6 Hz, H9), 8.73 (dd, 1H, *J* = 4.0, 1.6 Hz, H7); FAB-ms: *m/z* 203 (MH^+). *Anal*. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.08; H, 5.05; N, 13.76.

5-Ethoxy-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (17). To a solution of sodium (40.0 mg, 1.74 mmol) in ethanol (20 mL), **7** (300 mg, 1.45 mmol) was added and the solution was refluxed for 2.5 h. After evaporation of solvent *in vacuo*, ice water (300 mL) was poured into the residue which was then extracted with ethyl acetate (300 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from diethyl ether to give **17** (270 mg, 86%) as colorless needles, mp 143–145 °C; ^{1}H-NMR (deuterochloroform): δ 1.56 (t, 3H, *J* = 7.3 Hz, Me), 3.39 (t, 2H, *J* = 8.9 Hz, H1), 4.67 (q, 2H, *J* = 7.3 Hz, C*H*$_2$Me), 4.80 (t, 2H, *J* = 8.9 Hz, H2), 7.49 (dd, 1H, *J* = 8.5, 4.4 Hz, H8), 7.82 (dd, 1H, *J* = 8.5, 1.4 Hz, H9), 8.75 (dd, 1H, *J* = 4.4, 1.4 Hz, H7); FAB-ms: *m/z* 217 (MH^+). *Anal*. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.63; H, 5.61; N, 13.00.

5-(Pyrrolidin-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (18). To a solution of **7** (300 mg, 1.45 mmol) in ethanol (10 mL), pyrrolidine (1.03 g, 14.5 mmol) was added and then refluxed for 0.5 h. After evaporation of solvent *in vacuo*, ice water was poured into the residue and the precipitated solid was collected on a filter. The solid was recrystallized from *n*-hexane to give **18** (279 mg, 80%) as yellow prisms, mp 113–114 °C; ^{1}H-NMR (deuterochloroform): δ 1.94–2.01 (m, 4H, H3′ and 4′), 3.25 (t, 2H, *J* = 8.7 Hz, H1), 4.02–4.09 (m, 4H, H2′ and 5′), 4.70 (t, 2H, *J* = 8.7 Hz, H2), 7.30 (dd, 1H, *J* = 8.4, 4.1 Hz, H8), 7.61 (dd, 1H, *J* = 8.4, 1.7 Hz, H9), 8.45 (dd, 1H, *J* = 4.1, 1.7 Hz, H7); FAB-ms: *m/z* 242 (MH^+). *Anal*. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.69; H, 6.34; N, 17.37.

5-(Piperidin-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (19). To a solution of **7** (300 mg, 1.45 mmol) in ethanol (10 mL), piperidine (1.23 g, 14.4 mmol) was added and the mixture was then refluxed for 1.5 h. After evaporation of solvent *in vacuo*, ice water was poured into the residue and the precipitated solid was collected on a filter. The solid was recrystallized from *n*-hexane to give **19** (314 mg, 85%) as yellow prisms, mp 99–101 °C; ^{1}H-NMR (deuterochloroform): δ 1.68–1.83 (m, 6H, H3′, 4′, and 5′), 3.32 (t, 2H, *J* = 8.8 Hz, H1), 3.90–3.95 (m, 4H, H2′ and 6′), 4.73 (t, 2H, *J* = 8.8 Hz, H2), 7.36 (dd, 1H, *J* = 8.4, 4.1 Hz, H8), 7.72 (dd, 1H, *J* = 8.4, 1.8 Hz, H9), 8.56 (dd, 1H, *J* = 4.1, 1.8 Hz, H7); FAB-ms: *m/z* 256 (MH^+). *Anal*. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.70; H, 6.80; N, 16.40.

5-(Morpholin-4-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (20). To a solution of **7** (200 mg, 0.968 mmol) in ethanol (10 mL), morpholine (847 mg, 9.72 mmol) was added and the mixture was then refluxed for 11 h. Ice water (300 mL) was poured into the reaction mixture which was then extracted with benzene (300 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and

evaporated *in vacuo*. The residue was recrystallized from *n*-hexane to give **20** (181 mg, 73%) as yellow needles, mp 109–111 °C; ^{1}H-NMR (deuterochloroform): δ 3.35 (t, 2H, *J* = 8.8 Hz, H1), 3.91–4.05 (m, 8H, H2′, 3′, 5′, and 6′), 4.76 (t, 2H, *J* = 8.8 Hz, H2), 7.40 (dd, 1H, *J* = 8.4, 4.1 Hz, H8), 7.77 (dd, 1H, *J* = 8.4, 1.8 Hz, H9), 8.57 (dd, 1H, *J* = 4.1, 1.8 Hz, H7); FAB-ms: *m/z* 258 (MH^+). *Anal*. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.35; H, 5.93; N, 16.37.

5-(Piperadin-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (21). To a solution of piperazine (2.50 g, 29.0 mmol) in dioxane (10 mL) at 100 °C, **7** (300 mg, 1.45 mmol) in dioxane (30 mL) was added dropwise and the solution was then refluxed for 1 h. Ice water (300 mL) was poured into the reaction mixture and the precipitated solid was collected on a filter. The solid was recrystallized from diethyl ether to give **21** (350 mg, 94%) as yellow prisms, mp 123–126 °C; IR (potassium bromide): 3290 (NH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.72 (br, 1H, deuterium oxide exchangeable, NH), 3.15 (br t, 4H, *J* = 5.0 Hz, H3′ and 5′), 3.34 (t, 2H, *J* = 8.8 Hz, H1), 4.05 (br t, 4H, *J* = 5.0 Hz, H2′ and 6′), 4.75 (t, 2H, *J* = 8.8 Hz, H2), 7.39 (dd, 1H, *J* = 8.5, 4.1 Hz, H8), 7.75 (dd, 1H, *J* = 8.5, 1.7 Hz, H9), 8.57 (dd, 1H, *J* = 4.1, 1.7 Hz, H7); FAB-ms: *m/z* 257 (MH^+). *Anal*. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.64; H, 6.32; N, 21.59.

5-(4-Methylpiperadin-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7] naphthyridine (22). To a solution of **7** (300 mg, 1.45 mmol) in dioxane (10 mL), *N*-methylpiperazine (1.45 g, 14.5 mmol) was added and the solution was then refluxed for 1 h. After evaporation of solvent *in vacuo*, ice water (300 mL) was poured into the reaction mixture which was then extracted with ethyl acetate (300 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from diethyl ether to give **22** (357 mg, 91%) as colorless needles, mp 142–144 °C; ^{1}H-NMR (deuterochloroform): δ 2.39 (s, 3H, Me), 2.69 (br t, 4H, *J* = 5.0 Hz, H3′ and 5′), 3.33 (t, 2H, *J* = 8.9 Hz, H1), 4.09 (br t, 4H, *J* = 5.0 Hz, H2′ and 6′), 4.75 (t, 2H, *J* = 8.9 Hz, H2), 7.39 (dd, 1H, *J* = 8.5, 4.1 Hz, H8), 7.75 (dd, 1H, *J* = 8.5, 1.7 Hz, H9), 8.57 (dd, 1H, *J* = 4.1, 1.7 Hz, H7); FAB-ms: *m/z* 271 (MH^+). *Anal*. Calcd. for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.71; H, 6.73; N, 20.65.

5-(Imidazol-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (23). To a solution of **7** (300 mg, 1.45 mmol) in dioxane (10 mL), imidazole (988 mg, 14.5 mmol) and potassium carbonate (300 mg, 2.17 mmol) were added and then refluxed for 19 h. The reaction solution was condensed to half volume and ice water (100 mL) was added. The precipitated solid was filtered off and recrystallized from ethyl acetate to give **23** (277 mg, 80%) as colorless needles, mp 214–216 °C; ^{1}H-NMR (deuterochloroform): δ 3.52 (t, 2H, *J* = 8.9 Hz, H1), 4.89 (t, 2H, *J* = 8.9 Hz, H2), 7.19 (dd, 1H, *J* = 1.5, 1.2 Hz, H4′), 7.55 (dd, 1H, *J* = 8.6, 4.0 Hz, H8), 7.94 (dd, 1H, *J* = 8.6, 1.7 Hz, H9), 8.25 (dd, 1H, *J* = 1.5, 1.4 Hz, H5′), 8.83 (dd, 1H, *J* = 4.0, 1.7 Hz, H7), 9.11 (br s, 1H, H2′); FAB-ms: *m/z* 239 (MH^+). *Anal*. Calcd. for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.42; H, 4.30; N, 23.73.

5-(2-Methylimidazol-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (24). To a solution of **7** (300 mg, 1.45 mmol) in dioxane (10 mL), 2-methylimidazole (1.79 g, 21.8 mmol) and sodium hydride (70.0 mg, 2.92 mmol) were added and the mixture was then refluxed for 4 h. Ice water (300 mL) was poured into the reaction mixture which was then extracted with ethyl acetate (300 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of ethyl acetate–ethanol (9:1) was evaporated *in vacuo* and the residue was recrystallized from water to give **24** (183 mg, 50%) as colorless prisms, mp 216–217 C; ^{1}H-NMR (deuterochloroform): δ 2.45 (s, 3H, Me), 3.60 (t, 2H, *J* = 8.9 Hz, H1), 4.93 (t, 2H, *J* = 8.9 Hz, H2), 7.09 (d, 1H, *J* = 1.5 Hz, H4′), 7.43 (d, 1H, *J* = 1.5 Hz, H5′), 7.56 (dd, 1H, *J* = 8.6, 4.0 Hz, H8), 8.00 (dd, 1H, *J* = 8.6, 1.7 Hz, H9), 8.84 (dd, 1H, *J* = 4.0, 1.7 Hz, H7); FAB-ms: *m/z* 253 (MH^+). *Anal*. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.63; H, 4.95; N, 22.22.

5-(Pyrazol-1-yl)-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine (25). To a solution of **7** (300 mg, 1.45 mmol) in dioxane (10 mL), pyrazole (1.48 g, 21.7 mmol) and sodium hydride (70.0 mg, 2.92 mmol) were added and the reaction was then refluxed for 0.5 h. Ice water (300 mL) was poured into the reaction mixture which was then extracted with ethyl acetate (300 mL × 3). The combined organic layer was washed with saturated brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of ethyl acetate was evaporated *in vacuo* and recrystallized from benzene–cyclohexane to give **25** (227 mg, 66%) as pale yellow needles, mp 155–156 °C; ^{1}H-NMR (deuterochloroform): δ 3.54 (t, 2H, *J* = 8.9 Hz, H1), 4.89 (t, 2H, *J* = 8.9 Hz, H2), 6.54 (dd, 1H, *J* = 3.0, 1.9 Hz, H4′), 7.53 (dd, 1H, *J* = 8.6, 4.0 Hz, H8), 7.92 (d, 1H, *J* = 1.9 Hz, H3′), 7.96 (dd, 1H, *J* =8.6, 1.7 Hz, H9), 8.78 (d, 1H, *J* = 3.0 Hz, H5′), 8.91 (dd, 1H, *J* = 4.0, 1.7 Hz, H7); FAB-ms: *m/z* 239 (MH^+). *Anal*. Calcd. for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.35; H, 4.34; N, 23.43.

3,4,7,8-Tetrahydro-2*H*-furo[3,2-*f*]pyrimido[1,2-*h*][1,7]naphthyridine dihydrochloride (26). To a solution of **9** (300 mg, 1.22 mmol) in chloroform (10 mL), phosphoryl chloride (562 mg, 3.67 mmol) was added and the mixture was refluxed for 0.5 h. After evaporation of the reaction mixture *in vacuo*, aqueous concentrated NH_3 was added to basify. The resulting mixture was evaporated *in vacuo* again and the residue was recrystallized from ethanol to give **26** (107 mg, 29%) as yellow fine crystals, mp 270–273 °C (dec.); IR (potassium bromide): 3500–2800 broad (NH^+) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.16 (br quin, 2H, *J* = 6.0 Hz, H3), 3.39 (t, 2H, *J* = 8.9 Hz, H8), 3.59 (br t, 2H, *J* = 6.0 Hz, H2), 4.20 (t, 2H, *J* = 6.0 Hz, H4), 5.00 (t, 2H, *J* = 8.9 Hz, H7), 7.87 (dd, 1H, *J* = 8.4, 4.2 Hz, H10), 8.09 (dd, 1H, *J* = 8.4, 1.5 Hz, H9), 8.75 (dd, 1H, *J* = 4.2, 1.5 Hz, H11), 10.35 (br s, 1H, deuterium oxide exchangeable, NH); FAB-ms: *m/z* 228 (MH^+-2HCl). *Anal*. Calcd. for $C_{13}H_{13}N_3O{\cdot}2HCl$: C, 52.01; H, 5.04; N, 14.00. Found: C, 52.29; H, 5.41; N, 13.87.

6,7-Dihydrofuro[3,2-*f*][1,2,4]triazolo[4,3-*h*][1,7]naphthyridine (28). To a solution of **27** [4] (300 mg, 1.48 mmol) in dioxane (10 mL), triethyl orthoformate (22 mL) was added and the mixture was refluxed for 1 h. After evaporation of the solvent *in vacuo*, the residue was recrystallized from ethanol to give **28** (230 mg, 73%) as colorless needles, mp 285–289 °C (dec.); ^{1}H-NMR (deuterochloroform): δ 3.48 (t, 2H, *J* = 8.9 Hz, H7), 5.11 (t, 2H, *J* = 8.9 Hz, H6), 7.56 (dd, 1H, *J* = 8.2, 4.5 Hz, H9), 7.78 (dd, 1H, *J* = 8.2, 1.5 Hz, H8), 8.81 (s, 1H, H3), 8.87 (dd, 1H, *J* = 4.5, 1.5 Hz, H10); FAB-ms: *m/z* 213 (MH^+). *Anal*. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.14; H, 3.89; N, 26.24.

Carbamoylcholine chloride-induced tracheal response *in vitro*. This assay was performed according to the procedure described in ref. 6.

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