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Antivertigo Agents. IV.[1] Synthesis and Antivertigo Activity of 6-[ω-(4-Aryl-1-piperazinyl)alkyl]-5,6,7,8-tetrahydro-1,6-naphthyridines

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A series of novel 6-[ω-(4-aryl-1-piperazinyl)alkyl]-5,6,7,8-tetrahydro-1,6-naphthyridines was synthesized and evaluated for antivertigo activity by testing their ability to inhibit spontaneous nystagmus in cats. Structure–activity relationships are discussed. Many of the compounds having the 4-(2-alkoxyphenyl)piperazine group as the 4-arylpiperazine moiety showed more potent antivertigo activity than diphenidol. Among them, 2-{2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethyl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (NK 422, **41**) was selected as a promising antivertigo agent. NK 422 also exhibited a more potent inhibitory effect on apomorphine-induced vomiting in dogs than diphenidol.

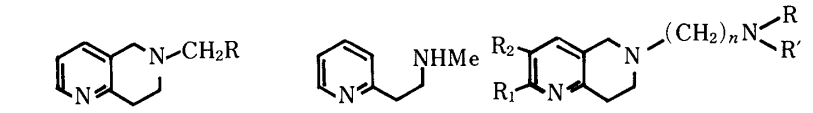
Keywords——antivertigo action; structure–activity relationship; 5,6,7,8-tetrahydro-1,6-naphthyridine; 1-(2-alkoxyphenyl)piperazine; 1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine; Michael addition

Previously, we have reported[2] that some simple tetrahydronaphtyridine derivatives such as 6-allyl- (**1a**), 6-isobutenyl- (**1b**), and 6-cyclopropylmethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**1c**) have potent antivertigo activity. The pharmacological characteristics of these compounds were judged to be more favorable than those of the lead compound, betahistine (**2**),[3] because they showed more potent antivertigo activity and less hypotensive activity. Thus, our next investigation was focussed on compounds having a skeleton like **3**, where the π-electrons in the substituents of **1a**—**c** are replaced with lone pair electrons of the nitrogen atom. Accordingly, several dialkylamino-, piperidino-, and morpholino-ethyl or propyl derivatives of **3** were synthesized, but their antivertigo activities were still unsatisfactory. After several trials, the introduction of a 4-(2-alkoxyphenyl)-1-piperazinyl group in place of the dialkylamino group of **3** was found to give a satisfactory result.

The present paper describes the synthesis and antivertigo activity of 6-[ω-(4-aryl-1-piperazinyl)alkyl]-5,6,7,8-tetrahydro-1,6-naphthyridines.

Chemistry

The synthesis of the 5,6,7,8-tetrahydro-1,6-naphthyridine ring (**4a**—**g**) was described in our previous paper.[1a] Charts 2, 3, and 4 illustrate the synthetic route used for the introduction of an amine-containing side chain into the 6-position of the 5,6,7,8-tetrahydro-1,6-naphthyridine ring. In the case of the normal side chain (Chart 2), this nitrogen was easily alkylated with 2-hydroxyethyl bromide or 3-hydroxypropyl bromide to give the corresponding N-(ω-hydroxyalkyl) derivatives (**5a**, **b** and **6a**, **b**) which were converted into the corresponding N-(ω-chloroalkyl) derivatives (**7a**, **b** and **8a**, **b**) as key intermediates by



1a–c **2** **3** ($n=2$ or 3)

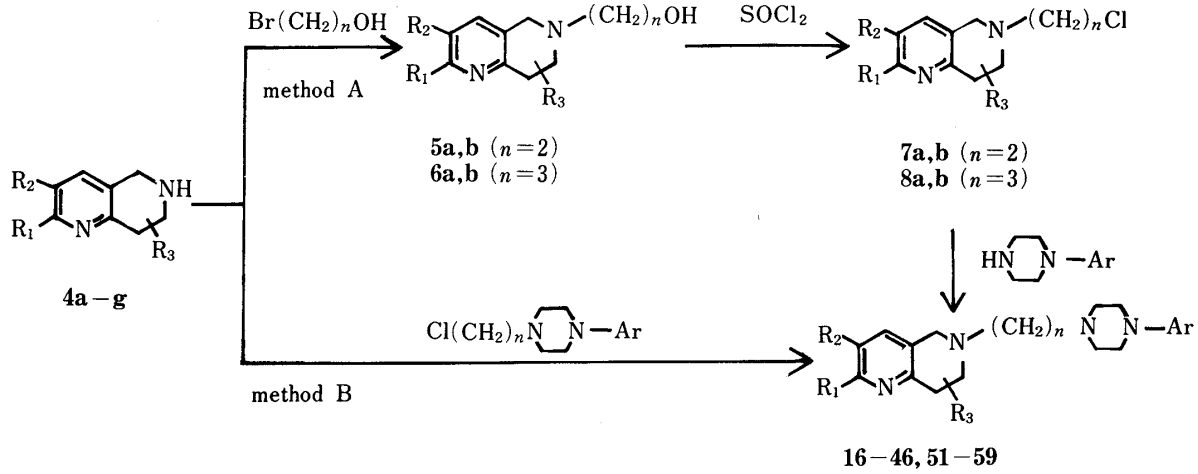
1a : R = $-CH=CH_2$

2b : R = $-\underset{\underset{Me}{|}}{CH}=CH_2$

3c : R =

Chart 1

treatment with thionyl chloride. Nucleophilic displacement of the chloro group in these intermediates by a variety of 1-arylpiperazines afforded the desired N-[ω-(4-aryl-1-piperazinyl)alkyl] compounds (**16**—**41** and **51**—**59**) in good yields (method A). An alternative N-alkylation of 5,6,7,8-tetrahydro-1,6-naphthyridines (**4c**—**g**) with ω-(4-aryl-1-piperazinyl)alkyl chloride directly gave the desired N-[ω-(4-aryl-1-piperazinyl)alkyl] compounds (**42**—**46**) in good yields (method B).



a: $R_1=R_2=R_3=H$, **b**: $R_1+R_2=(CH_2)_4$, $R_3=H$, **c**: $R_1=Me$, $R_2=R_3=H$,
d: $R_1=R_3=H$, $R_2=Me$, **e**: $R_1=R_2=H$, $R_3=5$-Me, **f**: $R_1=R_2=H$, $R_3=7$-Me,
g: $R_1=R_2=H$, $R_3=8$-Me

Chart 2

The synthesis of the derivatives with a methyl branched side chain is outlined in Charts 3 and 4 (method C). When **4a**, **b** were treated with 4-(2-methoxyphenyl)- and with 4-(2-ethoxyphenyl)-1-(2-chloropropionyl)piperazine, respectively, the corresponding amide derivatives (**9a**, **b**) were obtained. The products (**9a**, **b**) were converted to the α-branched compounds (**47** and **48**) by lithium aluminum hydride ($LiAlH_4$) reduction, as expected. The same starting compounds (**4a**, **b**) were treated with 2-chloropropionyl chloride to give the chloropropionyl compounds (**10a**, **b**). The reaction of **10a** with 1-(2-methoxyphenyl)-piperazine and the reaction of **10b** with 1-(2-ethoxyphenyl)piperazine afforded the 4-(2-methoxyphenyl)-1-piperazinyl (**11a**) and 4-(2-ethoxyphenyl)-1-piperazinyl (**11b**) compounds, respectively. Like **9a**, **b**, these products were smoothly reduced with $LiAlH_4$ to give β-branched compounds (**49** and **50**).

The syntheses of α-branched, β-branched, and γ-branched analogs (**60**—**65**) were

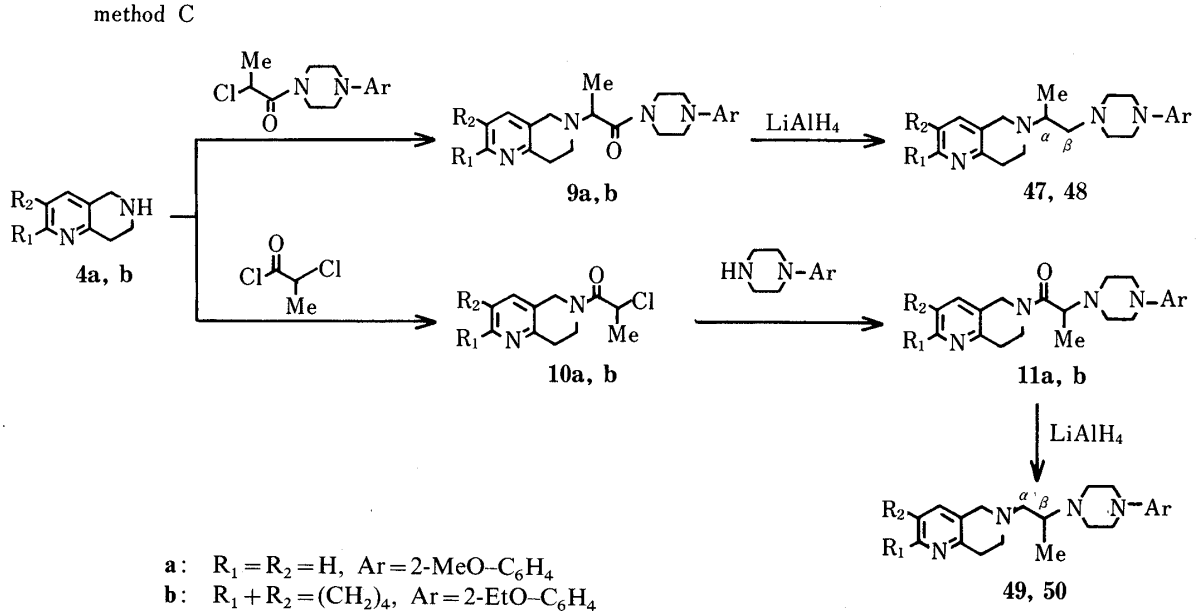


Chart 3

accomplished by means of the Michael-type addition of the secondary amines to appropriate unsaturated amides. As illustrated in Chart 4, the reaction of **4a**, **b** with 4-aryl-1-crotonoylpiperazine or with 4-aryl-1-methacryloylpiperazine afforded the corresponding methylamides (**12a**, **b** and **13a**, **b**), respectively. On treatment with $LiAlH_4$, these amides (**12a**, **b** and **13a**, **b**) were reduced to the desired α-methyl (**60** and **61**) and β-methyl compounds (**62** and **63**). When **4a**, **b** were acylated with crotonoyl chloride, the 6-crotonoyltetrahydronaphthyridines (**14a**, **b**) were obtained. The crotonoylamide smoothly underwent the Michael reaction with 1-(2-methoxyphenyl)piperazine or 1-(2-ethoxyphenyl)piperazine to give the corresponding adducts (**15a**, **b**). The $LiAlH_4$ reduction of **15a**, **b** gave the γ-methyl products (**64** and **65**).

All the products thus obtained were transformed into the fumarates, for which the melting points, recrystallization solvents, and results of elementary analysis are listed in Table IV.

Pharmacological Results and Discussion

The antivertigo activities of all compounds synthesized in the present study were evaluated by measuring the ability to inhibit spontaneous nystagmus induced by unilateral destruction of the labyrinth in cats.[4] The activities were expressed as ID_{30} (μmol/kg, *i.v.*) and compared with those of betahistine (**2**) and diphenidol. The results obtained in this animal model are shown in Table I.

It can be seen that the most critical structure element for activity in this series is the nature of the amine moiety. The compounds with amine moieties such as diethylamino, piperidino, and morpholino groups exhibited no activity ($ID_{30} > 100$), regardless of the alkyl substituents on the 5,6,7,8-tetrahydro-1,6-napthyridine and of the length of carbon chain and the type of carbon chain between the naphthyridine ring and the amine moiety.

On the other hand, most of the compounds with 4-aryl-1-piperazinyl groups showed potent activities (Table I). Among the compounds with a normal two-carbon chain, the 2-methoxyphenyl analog (**24**) was about 25 times more potent than the unsubstituted phenyl analog (**16**), whereas the 3-methoxy- (**25**) and 4-methoxyphenyl analogs (**26**) with the same lipophilicity (π) as the 2-methoxyphenyl analog (**24**) showed about 5 times less activity than **24**. Similarly, the activity of the 2-chlorophenyl analog (**18**) was more potent than those of the

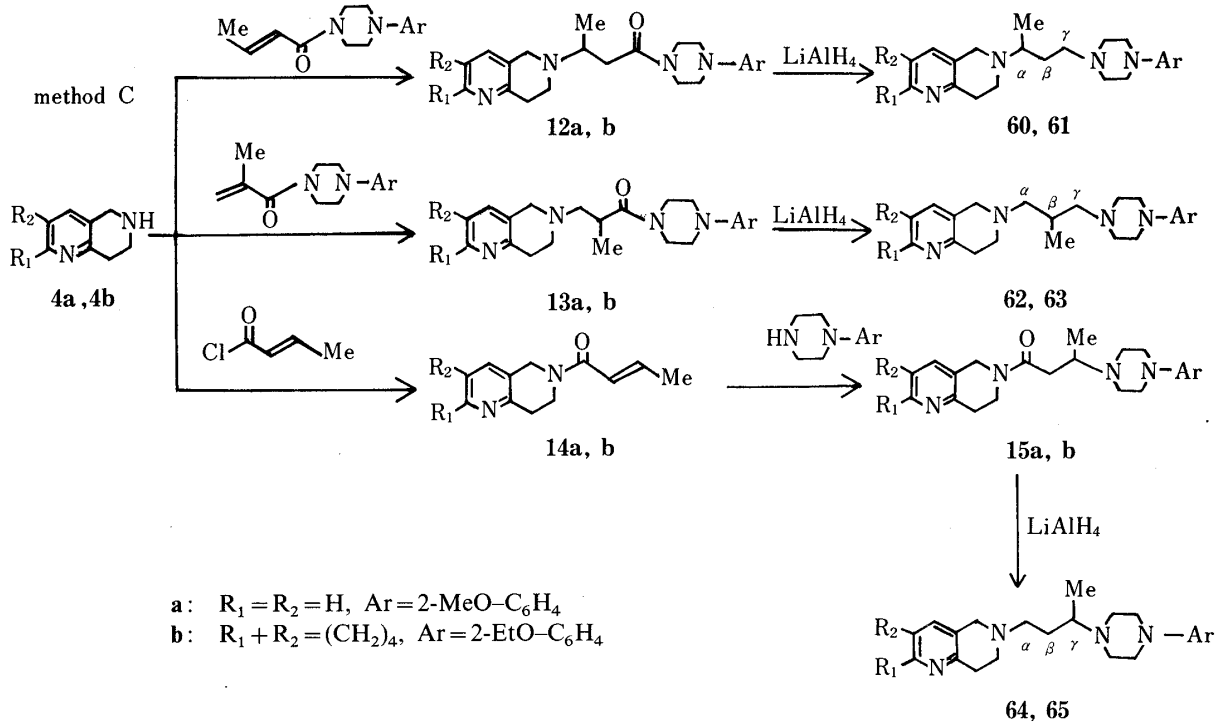
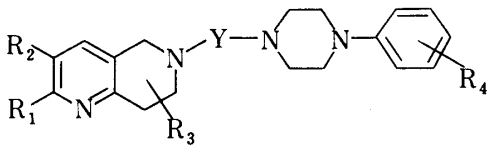


Chart 4

TABLE I. Inhibitory Activities[a] of 6-[ω-(4-Aryl-1-piperazinyl)-alkyl]-5,6,7,8-tetrahydro-1,6-naphthyridines against Spontaneous Nystagmus in Cats



Compd. No.	R_1	R_2	R_3	Y	R_4	ID_{30}[b] (μmol/kg, *i.v.*)
16	H	H	H	$(CH_2)_2$	H	79.3
17	H	H	H	$(CH_2)_2$	4-F	76.8
18	H	H	H	$(CH_2)_2$	2-Cl	5.6
19	H	H	H	$(CH_2)_2$	3-Cl	41.6
20	H	H	H	$(CH_2)_2$	4-Cl	22.4
21	H	H	H	$(CH_2)_2$	2-Me	82.7
22	H	H	H	$(CH_2)_2$	3-Me	97.8
23	H	H	H	$(CH_2)_2$	4-Me	91.4
24	H	H	H	$(CH_2)_2$	2-MeO	3.1
25	H	H	H	$(CH_2)_2$	3-MeO	15.2
26	H	H	H	$(CH_2)_2$	4-MeO	17.4
27	H	H	H	$(CH_2)_2$	2-EtO	2.2
28	H	H	H	$(CH_2)_2$	2-PrO	1.4
29	H	H	H	$(CH_2)_2$	2-BuO	1.8
30	H	H	H	$(CH_2)_2$	2-Me-4-Cl	90.5
31	H	H	H	$(CH_2)_2$	2-Me-5-Cl	44.8
32	H	H	H	$(CH_2)_2$	2,5-di-Me	54.9
33	H	H	H	$(CH_2)_2$	2,6-di-Me	59.2
34	H	H	H	$(CH_2)_2$	2,5-di-MeO	8.5
35	$(CH_2)_4$		H	$(CH_2)_2$	H	70.6
36	$(CH_2)_4$		H	$(CH_2)_2$	3-Cl	73.9

TABLE I. (continued)

Compd. No.	R_1	R_2	R_3	Y	R_4	ID_{30}[b] (μmol/kg, *i.v.*)
37	$(CH_2)_4$		H	$(CH_2)_2$	4-Cl	74.6
38	$(CH_2)_4$		H	$(CH_2)_2$	2-Me	61.8
39	$(CH_2)_4$		H	$(CH_2)_2$	2-MeO	2.0
40	$(CH_2)_4$		H	$(CH_2)_2$	4-MeO	15.3
41	$(CH_2)_4$		H	$(CH_2)_2$	2-EtO	1.4
42	Me	H	H	$(CH_2)_2$	2-EtO	2.0
43	H	Me	H	$(CH_2)_2$	2-EtO	2.6
44	H	H	5-Me	$(CH_2)_2$	2-EtO	2.8
45	H	H	7-Me	$(CH_2)_2$	2-EtO	2.8
46	H	H	8-Me	$(CH_2)_2$	2-EtO	1.9
47	H	H	H	$CH(Me)CH_2$	2-MeO	12.6
48	$(CH_2)_4$		H	$CH(Me)CH_2$	2-EtO	9.4
49	H	H	H	$CH_2CH(Me)$	2-MeO	13.0
50	$(CH_2)_4$		H	$CH_2CH(Me)$	2-EtO	9.4
51	H	H	H	$(CH_2)_3$	4-F	76.8
52	H	H	H	$(CH_2)_3$	2-Cl	24.0
53	H	H	H	$(CH_2)_3$	3-Cl	89.5
54	H	H	H	$(CH_2)_3$	4-Cl	54.7
55	H	H	H	$(CH_2)_3$	2-Me	103.0
56	H	H	H	$(CH_2)_3$	2-MeO	2.9
57	H	H	H	$(CH_2)_3$	2-EtO	7.6
58	$(CH_2)_4$		H	$(CH_2)_3$	2-MeO	2.8
59	$(CH_2)_4$		H	$(CH_2)_3$	2-EtO	3.6
60	H	H	H	$CH(Me)CH_2CH_2$	2-MeO	5.3
61	$(CH_2)_4$		H	$CH(Me)CH_2CH_2$	2-EtO	4.7
62	H	H	H	$CH_2CH(Me)CH_2$	2-MeO	6.8
63	$(CH_2)_4$		H	$CH_2CH(Me)CH_2$	2-EtO	8.5
64	H	H	H	$CH_2CH_2CH(Me)$	2-MeO	5.6
65	$(CH_2)_4$		H	$CH_2CH_2CH(Me)$	2-EtO	9.4
Betahistine						417.2
Diphenidol						4.6

a) Each compound was injected as its salt (see Table IV).
b) See Experimental.

isomeric 3-chloro- (**19**) and 4-chlorophenyl analogs (**20**). Contrary to our expectation, the activity of the 2-methylphenyl analog (**21**) was almost equal to that of the 3-methyl- (**22**) or 4-methylphenyl analog (**23**), although the bulkiness (MR = 5.65[5]) of the methyl group is very close to that of the chloro (MR = 6.03[5]) group.

The introduction of the 2-methyl group into the phenyl ring resulted in no improvement in the activity. The introduction of *ortho* substituents on the phenyl ring decreased the activity in the order of methoxyl > chloro > hydrogen > methyl groups. Accordingly, these findings suggest that the effect of the *ortho* substituents is attributable not only to a steric factor but also to other factors, such as electronic factors, *etc.* Among 4-(disubstituted phenyl)piperazinyl derivatives (**30**—**34**) with the methyl or methoxyl group at the *ortho* position of the phenyl ring, compounds **31**—**33** showed moderately enhanced activities in comparison with the 2-methyl compound **21**, while compound **30** showed activity approximately equal to that of **21**. Furthermore, **34** was less active than the 2-methoxy compound **24**. The relationships between physicochemical parameters of the substituents on the phenyl ring and the activity seems not to be simple. Further investigation is required to clarify this relationship.

Thus, the 1-(2-methoxyphenyl)piperazinyl group was found to be the most favorable amine moiety for appearance of activity. Then, a series of analogs with other alkoxyl groups was synthesized and the antivertigo activities were examined: the 2-ethoxy- (**27**), 2-propoxy- (**28**), or 2-butoxy-phenyl analog (**29**) showed potent antivertigo activity almost equal to that of **24**. Accordingly, the 4-(2-alkoxyphenyl)-1-piperazinyl group was found to be the best amine moiety.

The length of normal carbon chain between the naphthyridine ring and the amine moiety was investigated. Many of the compounds with the two-carbon chain were more potent than those with the three-carbon chain, as compared to the compounds with the same amine moiety (**18** *vs.* **52**, **19** *vs.* **53**, **20** *vs.* **54**, **21** *vs.* **55**, and **27** *vs.* **57**).

In addition, the effect of a methyl-branched carbon chain was examined. The compounds (**47** and **49**) with a methyl-branched two-carbon chain showed lower activities than compound (**24**) having a normal two-carbon chain. The methyl-branched compounds (**60**, **62**, and **64**) having a methyl-branched three-carbon chain also showed similar activities. The activities of **60**, **62**, and **64** were more potent than those of compounds with a methyl-branched two-carbon chain. However, the activities of **60**, **62**, and **64** were less potent than those of the compound with a normal two-carbon chain (**24**). Therefore, the normal two-carbon chain between the naphthyridine ring and the amine moiety was found to be the best structure for enhancing the activity.

It has already been mentioned above that the 5,6,7,8-tetrahydro-1,6-naphthyridine drivatives bearing 2-[4-(2-alkoxyphenyl)-1-piperazinyl]ethyl groups showed potent antivertigo activities. Chemical modification of the 5,6,7,8-tetrahydro-1,6-naphthyridine ring was attempted with the aim of enhancing the activity: 2-methyl (**42**), 3-methyl- (**43**), 5-methyl- (**44**), 7-methyl- (**45**), or 8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**46**), with the 2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethyl group on the 6-position, showed activities equipotent to the unsubstituted compound (**27**).

On the other hand, compounds having a 1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]-naphthyridine ring were investigated. The activities of the compounds with 2-[4-(3-chlorophenyl)-1-piperazinyl]- (**36**) and 2-[4-(4chlorophenyl)-1-piperazinyl]ethyl (**37**) groups were considerably lower than those of the corresponding 5,6,7,8-tetrahydro-1,6-naphthyridine

TABLE II. Inhibitory Effects of **41** (NK 422), Diphenidol (DPD), and Chlorpromazine (CPZ) on Emesis Induced by Apomorphine[a] in Dogs

Compd. No.	Dose mg/kg, *s.c.*	Number vomited / number tested	Latency (s)[b] Mean ± S.E.	Frequency for 60 min[b] Mean ± S.E.	Duration (s)[b] Mean ± S.E.
Control		6/6	162.5 ± 10.1	12.3 ± 1.4	1317.7 ± 149.3
NK 422	1.00	6/6	328.7 ± 34.0	4.0 ± 0.6	180.8 ± 57.8
	1.73	4/6	378.8 ± 50.1	2.0 ± 0.4	120.3 ± 80.4
	3.00	0/6			
DPD	1.00	6/6	230.2 ± 14.4	7.7 ± 0.8	779.5 ± 63.9
	1.73	6/6	235.7 ± 20.3	5.5 ± 0.6	550.2 ± 139.4
	3.00	6/6	379.5 ± 53.3	4.3 ± 1.1	325.7 ± 30.9
CPZ	1.00	6/6	287.8 ± 29.0	4.5 ± 0.8	197.2 ± 45.2
	1.73	6/6	266.2 ± 23.5	3.2 ± 0.4	127.7 ± 40.4
	3.00	6/6	350.8 ± 25.9	2.5 ± 0.3	102.5 ± 26.8

a) Apomorphine·HCl 0.3 mg/kg, *s.c.*
b) See Experimental.

analogs (**19** and **20**), respectively. However, the activities of the benzo[*b*][1,6]naphthyridine analogs with 2-methyl- (**38**), 2-methoxy- (**39**), and 2-ethoxyphenyl groups (**41**) were moderately higher than those of the corresponding 1,6-naphthyridine analogs (**21**, **24**, and **27**, respectively). The modification of these alkyl substituents on the 5,6,7,8-tetrahydro-1,6-naphthyridine ring did not greatly improve the activity in comparison with the effect of changing the amine moieties. The effects of the length and type of carbon chain in these tricyclic analogs were examined. The elongation of carbon chain from two to three carbons resulted in a decrease of the activities, as seen in the bicyclics. Introduction of a methyl-branched carbon chain also decreased the activities (**48** and **50** *vs.* **41**, and **61**, **63**, and **65** *vs.* **59**).

Accordingly, the 2-[4-(2-alkoxyphenyl)-1-piperazinyl]ethyl derivatives exhibited the strongest activities in this series. After additional pharmacological and safety evaluation studies of these compounds, compound **41** (NK 422) was selected for clinical evaluation as a candidate antivertigo agent.

In addition, the antiemetic action of compound **41** (NK 422) was examined in comparison with those of diphenidol (DPD) and chlorpromazine (CPZ), because vertigo is known to be closely related to vomiting.[6] As shown in Table II, NK 422 was found to be more potent than DPD or CPZ.

Experimental

Chemistry

All melting points and boiling points are uncorrected. The structures of all compounds were consistent with the infrared (IR), proton magnetic resonance (^{1}H-NMR), and mass spectra (MS). IR spectra were measured on a JASCO IR-G spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer using Me_4Si as an internal standard. MS were determined with a Shimadzu GCMS-7000 spectrometer.

Synthesis of the 1,6-naphthyridines (**4a**—**g**) was described in our previous paper.[1a] Most of the 1-arylpiperazines used in this study were commercial products, with the exception of the following compounds which were prepared according to the literature: 1-(2-ethoxyphenyl)piperazine·HCl,[7] mp 207—209 °C; 1-(2-propoxyphenyl)piperazine,[8] bp 132—135 °C (1.5 mmHg); 1-(butoxyphenyl)piperazine·HCl,[7] mp 144—146 °C; 1-(2,5-dimethoxyphenyl)-piperazine,[8] bp 127—132 °C (0.5 mmHg).

1-(2-Chloroethyl)-4-(2-ethoxyphenyl)piperazine——A solution of 1-(2-ethoxyphenyl)piperazine·HCl (5.5 g, 23 mmol), 1-bromo-2-chloroethane (9.9 g, 69 mmol), and Et_3N (4.7 g, 47 mmol) in dimethylformamide (11 ml) was stirred at 5—10 °C for 20 h. The reaction mixture was poured into water and the pH was adjusted to pH 1.0 by addition of 3 N HCl, then the mixture was washed with ether. The aqueous layer was further neutralized to pH 5.5 by addition of 30% NaOH under ice-cooling. The precipitated crystals were collected by filtration and the crude crystals were recrystallized from petr. ether to give 1-(2-chloroethyl)-4-(2-ethoxyphenyl)piperazine (4.9 g, 80%) as colorless needles, mp 69—70 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=8.0 Hz, $OCH_2C\underline{H}_3$), 2.5—3.3 (10H, m, $=NC\underline{H}_2CH_2Cl$ and piperazinyl H), 3.56 (2H, t, J=7.0 Hz, $=NCH_2C\underline{H}_2Cl$), 4.02 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.82 (4H, s, phenyl H). *Anal.* Calcd for $C_{14}H_{21}ClN_2O$: C, 62.57; H, 7.87; N, 10.42. Found: C, 62.31; H, 7.80; N, 10.19.

6-(ω-Hydroxyalkyl)-5,6,7,8-tetrahydro-1,6-naphthyridines (5a, b and 6a, b)

Typical Example: 6-(2-Hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (5a)——A solution of 5,6,7,8-tetrahydro-1,6-naphthyridine (**4a**) (63.9 g, 0.48 mol), 2-bromoethanol (90.0 g, 0.72 mol), and Et_3N (96.4 g, 0.95 mol) in EtOH (650 ml) was refluxed for 9.5 h. The reaction mixture was evaporated *in vacuo* to give the residue. This residue was adjusted to pH 1.0 by addition of 6 N HCl and water, and then washed with toluene. The aqueous layer was made alkaline with 30% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3 and then evaporated *in vacuo* to give the residue, which was distilled to give **5a** (58.9 g, 69%) as an oil, bp 136—144 °C (0.3 mmHg). IR (neat) cm^{-1}: 3200 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.3—3.2 (6H, m, C_7–H, C_8–H, and $=NC\underline{H}_2CH_2OH$), 3.67 (2H, s, C_5–H), 3.75 (2H, t, J=5.0 Hz, $=NCH_2C\underline{H}_2OH$), 4.29 (1H, s, OH, exchangeable by adding D_2O), 7.00 (1H, dd, J=8.0 and 5.0 Hz, C_3–H), 7.30 (1H, dd, J=8.0 and 2.0 Hz, C_4–H), 8.33 (1H, dd, J=5.0 and 2.0 Hz, C_2–H). This compound was used in the next step without elementary analysis.

The following compounds were prepared by similar procedures and used in the next step without elementary analysis.

2-(2-Hydroxyethyl)-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (**5b**): oil, bp 181—183 °C (0.35 mmHg). Yield 87%.

6-(3-Hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (**6a**): oil, bp 155—158 °C (0.8 mmHg). Yield 56%.

2-(3-Hydroxypropyl)-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (**6b**): colorless prisms, mp 102—103 °C (iso-Pr_2O). Yield 44%.

6-(ω-Chloroalkyl)-5,6,7,8-tetrahydro-1,6-naphthyridines (7a, b and 8a, b)

Typical Example: 2-(2-Chloroethyl)-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine Dihydrochloride (7b)——Compound **5b** (6.0 g, 26 mmol) was gradually added to $SOCl_2$ (9.2 g, 77 mmol) with stirring under ice-cooling, and then the mixture was stirred at room temperature for 2 h. The mixture was evaporated *in vacuo* to give the residue, which was washed with a small amount of ether. The residue was treated with active charcoal in hot EtOH, and then recrystallized from EtOH to give **7b** (5.8 g, 70%) as colorless prisms, mp 208—211 °C (dec.). ^{1}H-NMR (D_2O, $Me_3Si(CH_2)_3SO_3Na$ as an internal standard) δ: 1.6—2.3 (4H, m, C_7–H and C_8–H), 2.7—3.3 (4H, m, C_6–H and C_9–H), 3.4—4.4 (8H, m, C_3–H, C_4–H, and $=NCH_2CH_2Cl$), 3.80 (2H, s, C_1–H), 8.12 (1H, s, C_{10}–H).

Data for **7a**, **b** and **8a**, **b** prepared as described above are listed in Table III.

Reaction of 7a, b and 8a, b with 1-Arylpiperazines

Typical Example (Method A): 6-{2-[4-(2-Methylphenyl)-1-piperazinyl]ethyl}-5,6,7,8-tetrahydro-1,6-naphthyridine Difumarate (21)——A mixture of **7a** (2.70 g, 10 mmol), 1-(2-methylphenyl)piperazine·HCl (3.0 g, 12 mmol), and Et_3N (10 ml, 72 mmol) in EtOH (30 ml) was refluxed for 2 h. The reaction mixture was evaporated *in vacuo* to give the residue, which was partitioned between toluene and H_2O. The toluene layer was separated, dried over K_2CO_3, and then evaporated *in vacuo* to give the residue. This residue was recrystallized from iso-Pr_2O to afford the free base of **21** (2.0 g, 60%) as colorless prisms, mp 93—94 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s, CH_3), 2.5—2.8 (8H, m, aliphatic H), 2.8—3.3 (8H, m, aliphatic H), 3.67 (2H, s, C_5–H), 6.7—7.4 (6H, m, aromatic H), 8.44 (1H, dd, J= 5.0 and 2.0 Hz; C_2–H). MS *m/z* (relative intensity): 336 (M^+, 12.2), 189 (100), 159 (19.2), 147 (33.5), 70 (19.5). This free base was converted to the salt (**21**) by treatment with fumaric acid in acetone.

Melting points, recrystallization solvents, and elementary analyses of the salts are listed in Table IV.

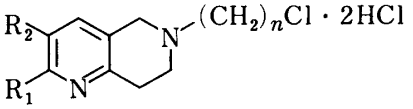
Reaction of 4c—g with 1-(2-Chloroethyl)-4-(2-ethoxyphenyl)piperazine

Typical Example (Method B): 6-{2-[4-(2-Ethoxyphenyl)-1-piperazinyl]ethyl}-5,6,7,8-tetrahydro-8-methyl-1,6-naphthyridine Difumarate (46)——A solution of **4g** (1.8 g, 12 mmol), 1-(2-chloroethyl)-4-(2-ethoxyphenyl)piperazine (3.9 g, 15 mmol), and Et_3N (2.5 g, 24 mmol) in EtOH (25 ml) was refluxed for 5 h. The mixture was evaporated *in vacuo* to give the residue, which was partitioned between toluene and H_2O. The toluene layer was separated, dried over K_2CO_3, and then evaporated *in vacuo* to give the free base of **46** (3.3 g, 72%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7.0 Hz, C_8–CH_3), 1.45 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.4—3.3 (14H, m, aliphatic H), 3.66 (2H, s, C_5–H), 4.05 (2H, q, J=7.0 Hz, $OC\underline{H_2}CH_3$), 6.7—7.4 (6H, m, C_3–H, C_4–H, and phenyl H), 8.40 (1H, dd, J=5.0 and 2.0 Hz, C_2–H). MS *m/z* (relative intensity): 380 (M^+, 8.8), 219 (100), 206 (11.5), 204 (9.4), 189 (9.4), 161 (9.4). This free base was converted to the salt (**46**) by treatment with fumaric acid in acetone.

Melting points, recrystallization solvents, and elementary analyses of the salts are listed in Table IV.

2-(2-Chloropropionyl)-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (10b)——A solution of 2-chloropropionyl chloride (3.0 g, 24 mmol) in $CHCl_3$ (20 ml) was added dropwise to a solution of **4b** (3.8 g, 20 mmol) and Et_3N (2.4 g, 24 mmol) in $CHCl_3$ (100 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h and evaporated *in vacuo* to give the residue, which was partitioned between 3 N HCl and toluene. the aque-

TABLE III. 6-(ω-Chloroalkyl)-5,6,7,8-tetrahydro-1,6-naphthyridines



Compd. No.	R_1	R_2	n	Yield (%)	mp[a] (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
7a	H	H	2	60	218—221	MeOH	$C_{10}H_{15}Cl_3N_2$	44.55 (44.16	5.61 5.93	10.39 10.08)
7b	$(CH_2)_4$		2	70	208—211	EtOH	$C_{14}H_{21}Cl_3N_2$	51.95 (52.24	6.54 6.81	8.65 8.97)
8a	H	H	3	74	197.5—200	EtOH	$C_{11}H_{17}Cl_3N_2$	46.58 (46.60	6.04 6.25	9.88 10.15)
8b	$(CH_2)_4$		3	54	233—235	MeOH–AcOEt	$C_{15}H_{23}Cl_3N_2$	53.35 (53.74	6.86 6.54	8.29 8.50)

a) All the compounds melt with decomposition.

TABLE IV. The Salts[a] of 6-[ω-(4-Aryl-1-piperazinyl)alkyl]-5,6,7,8-tetrahydro-1,6-naphthyridines

Compd. No.	Yield[b] (%)	Method[c]	mp[d] (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
16	85	A	189—190	EtOH	$C_{20}H_{26}N_4 \cdot 2C_4H_4O_4$	60.64	6.18	10.10
						(60.80	6.21	9.94)
17	65	A	182—183	EtOH	$C_{20}H_{25}FN_4 \cdot 2C_4H_4O_4$	58.73	5.81	9.78
						(58.96	5.77	9.92)
18	64	A	189—190	EtOH	$C_{20}H_{25}ClN_4 \cdot 2C_4H_4O_4$	57.09	5.65	9.51
						(56.73	5.72	9.35)
19	52	A	191—193	EtOH	$C_{20}H_{25}ClN_4 \cdot 2C_4H_4O_4$	57.09	5.65	9.51
						(56.80	5.48	9.76)
20	69	A	190—193	EtOH	$C_{20}H_{25}ClN_4 \cdot 2C_4H_4O_4$	57.09	5.65	9.51
						(57.23	5.82	9.58)
21	70	A	198—202	EtOH	$C_{21}H_{28}N_4 \cdot 2C_4H_4O_4$	61.26	6.38	9.85
						(61.09	6.41	9.90)
22	54	A	194—196	EtOH–iso-PrOH	$C_{21}H_{28}N_4 \cdot 2C_4H_4O_4$	61.26	6.38	9.85
						(60.98	6.33	9.75)
23	60	A	182—186	EtOH	$C_{21}H_{28}N_4 \cdot 2C_4H_4O_4$	61.26	6.38	9.85
						(60.97	6.44	9.66)
24	57	A	168—169	iso-PrOH	$C_{21}H_{28}N_4O \cdot 2C_4H_4O_4$	59.58	6.21	9.58
						(59.87	6.04	9.76)
25	76	A	188—190	EtOH	$C_{21}H_{28}N_4O \cdot 2C_4H_4O_4$	59.58	6.21	9.58
						(59.78	6.43	9.71)
26	74	A	182—185	EtOH	$C_{21}H_{28}N_4O \cdot 2C_4H_4O_4$	59.58	6.21	9.58
						(59.30	6.36	9.84)
27	57	A	177—181	EtOH	$C_{22}H_{30}N_4O \cdot 2C_4H_4O_4$	60.19	6.40	9.36
						(59.88	6.68	9.49)
28	59	A	178—180	EtOH	$C_{23}H_{32}N_4O \cdot 2C_4H_4O_4$	60.78	6.58	9.14
						(61.02	6.35	9.37)
29	62	A	178—179	EtOH	$C_{24}H_{34}N_4O \cdot 2C_4H_4O_4$	61.33	6.75	8.94
						(61.07	6.45	9.26)
30	66	A	208—209	MeOH–EtOH	$C_{21}H_{27}ClN_4 \cdot 2C_4H_4O_4$	57.76	5.85	9.29
						(57.98	6.14	9.03)
31	72	A	204—207	EtOH	$C_{21}H_{27}ClN_4 \cdot 2C_4H_4O_4$	57.76	5.85	9.29
						(57.63	5.67	9.46)
32	64	A	204—207	EtOH	$C_{22}H_{30}N_4 \cdot 2C_4H_4O_4$	61.84	6.57	9.62
						(62.11	6.60	9.39)
33	54	A	198—201	EtOH	$C_{22}H_{30}N_4 \cdot 2C_4H_4O_4$	61.84	6.57	9.62
						(61.97	6.34	9.38)
34	36	A	164—167	EtOH	$C_{22}H_{30}N_4O_2 \cdot 2C_4H_4O_4$	58.62	6.23	9.12
						(58.34	6.51	8.82)
35	81	A	208—210	EtOH	$C_{24}H_{32}N_4 \cdot 2C_4H_4O_4$	63.15	6.62	9.20
						(62.40	6.38	9.06)
36	48	A	211—213	EtOH	$C_{24}H_{31}ClN_4 \cdot 2C_4H_4O_4$	59.77	6.11	8.71
						(60.02	6.34	8.57)
37	65	A	194—196	EtOH	$C_{24}H_{31}ClN_4 \cdot 2C_4H_4O_4$	59.77	6.11	8.71
						(59.69	6.20	8.66)
38	72	A	221—222	EtOH	$C_{25}H_{34}N_4 \cdot 2C_4H_4O_4$	63.65	6.80	9.00
						(63.47	6.93	8.94)
39	67	A	206—207	MeOH–iso-PrOH	$C_{25}H_{34}N_4O \cdot 2C_4H_4O_4$	62.06	6.63	8.77
						(62.34	6.78	8.59)
40	68	A	199—202	EtOH	$C_{25}H_{34}N_4O \cdot 2C_4H_4O_4$	62.06	6.63	8.77
						(61.83	6.73	8.90)
41	71	A	185—187	MeOH–EtOH	$C_{26}H_{36}N_4O \cdot 2C_4H_4O_4$	62.57	6.79	8.58
						(62.85	6.99	8.72)

TABLE IV. (continued)

Compd. No.	Yield[b] (%)	Method[c]	mp[d] (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
42	85	B	216—217	EtOH	$C_{23}H_{32}N_4O \cdot 2C_4H_4O_4$	60.78	6.58	9.14
						(60.54	6.43	9.25)
43	50	B	200—201	EtOH	$C_{23}H_{32}N_4O \cdot 2C_4H_4O_4$	60.78	6.58	9.14
						(61.03	6.72	9.40)
44	30	B	102—105	CH_3COCH_3	$C_{23}H_{32}N_4O \cdot 2C_4H_6O_6$[e]	54.70	6.51	8.23
						(55.06	6.79	8.42)
45	37	B	99—103	CH_3COCH_3	$C_{23}H_{32}N_4O \cdot 2C_4H_6O_6$[e]	54.70	6.51	8.23
						(54.98	6.81	8.17)
46	72	B	161—163	EtOH	$C_{23}H_{32}N_4O \cdot 2C_4H_4O_4$	60.78	6.58	9.14
						(60.95	6.48	9.38)
47	53	C	94—96	CH_3COCH_3	$C_{22}H_{30}N_4O \cdot 2C_4H_6O_6$[e]	54.05	6.35	8.40
						(54.30	6.57	8.25)
48	65	C	129—131	EtOH	$C_{27}H_{38}N_4O \cdot 2C_4H_4O_4$	63.05	6.95	8.40
						(62.74	7.02	8.26)
49	92	C	120—122	CH_3COCH_3	$C_{22}H_{30}N_4O \cdot 2C_4H_4O_4$	60.19	6.40	9.36
						(60.43	6.51	9.08)
50	60	C	91—94	CH_3COCH_3	$C_{27}H_{38}N_4O \cdot 2C_4H_6O_6$[e]	57.21	6.86	7.62
						(57.40	6.69	7.53)
51	34	A	204—207	EtOH	$C_{21}H_{27}FN_4 \cdot 2C_4H_4O_4$	59.38	6.01	9.55
						(59.16	5.97	9.41)
52	88	A	169—171	EtOH	$C_{21}H_{27}ClN_4 \cdot 2C_4H_4O_4$	57.76	5.85	9.29
						(57.74	5.76	9.47)
53	60	A	208—210	EtOH	$C_{21}H_{27}ClN_4 \cdot 2C_4H_4O_4$	57.76	5.85	9.29
						(57.91	5.98	9.40)
54	55	A	215—218	EtOH	$C_{21}H_{27}ClN_4 \cdot 2C_4H_4O_4$	57.76	5.85	9.29
						(57.45	6.12	9.44)
55	79	A	176—179	EtOH	$C_{22}H_{30}N_4 \cdot 2C_4H_4O_4$	61.84	6.57	9.62
						(62.03	6.87	9.47)
56	48	A	179—182	EtOH	$C_{22}H_{30}N_4O \cdot 2C_4H_4O_4$	60.19	6.40	9.36
						(60.41	6.40	9.75)
57	36	A	138—142	EtOH	$C_{23}H_{32}N_4O \cdot 2C_4H_4O_4$	60.78	6.58	9.14
						(60.49	6.63	9.46)
58	77	A	201—202	EtOH	$C_{26}H_{36}N_4O \cdot 2C_4H_4O_4$	62.57	6.79	8.58
						(62.25	7.02	8.73)
59	36	A	192—194	MeOH–EtOH	$C_{27}H_{38}N_4O \cdot 2C_4H_4O_4$	63.05	6.95	8.40
						(62.81	7.28	8.12)
60	85	C	108—112	CH_3COCH_3	$C_{23}H_{32}N_4O \cdot 2C_4H_6O_6$[e]	54.70	6.51	8.23
						(54.52	6.73	8.01)
61	86	C	116—119	CH_3COCH_3	$C_{28}H_{40}N_4O \cdot 2C_4H_6O_6$[e]	57.74	7.06	7.48
						(57.99	6.85	7.34)
62	88	C	92—95	CH_3COCH_3	$C_{23}H_{32}N_4O \cdot 2C_4H_6O_6$[e]	54.70	6.51	8.23
						(54.56	6.41	8.50)
63	91	C	99—102	CH_3COCH_3	$C_{28}H_{40}N_4O \cdot 2C_4H_6O_6$[e]	57.74	7.00	7.48
						(57.46	6.87	7.72)
64	82	C	106—109	CH_3COCH_3	$C_{23}H_{32}N_4O \cdot 2C_4H_6O_6$[e]	54.70	6.51	8.23
						(54.91	6.72	8.04)
65	90	C	117—120	CH_3COCH_3	$C_{28}H_{40}N_4O \cdot 2C_4H_6O_6$[e]	57.74	7.00	7.48
						(57.59	7.27	7.19)

a) Fumarate unless othewise noted. *b*) Yield refers to the last step in each synthetic sequence and is given for free base. *c*) See Experimental. *d*) All the fumarates except for *dl*-tartrates melt with decomposition. *e*) *dl*-Tartrate.

ous layer was separated, made alkaline with 30% NaOH under ice-cooling, and extracted with toluene. The toluene extract was dried over K_2CO_3 and evaporated *in vacuo* to give the residue. These crude crystals were recrystallized from iso-Pr_2O to give **10b** (4.2 g, 75%) as colorless needles, mp 113—115 °C. IR (KBr) cm^{-1}: 1644 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.1 (4H, m, C_7–H and C_8–H), 1.68 (3H, d, J=6.0 Hz, =NCOCHClC$\underline{H}_3$), 2.5—3.2 (6H, m, C_4–H, C_6–H, and C_9–H), 3.88 (2H, t, J=7.0 Hz, C_3–H), 4.60 (1H, q, J=6.0 Hz, =NCOC$\underline{H}$ClCH$_3$), 4.65 (2H, s, C_1–H), 7.10 (1H, s, C_{10}–H). *Anal.* Calcd for $C_{15}H_{19}ClN_2O$: C, 64.62; H, 6.87; N, 10.05. Found: C, 64.27; H, 6.98; N, 9.86.

6-(2-Chloropropionyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (**10a**) was similarly prepared from **4a** as an oil. Yield 89%. This compound was used in the next step without further purification.

1-Acyl-4-arylpiperazines were similarly prepared by the method described above.

1-(2-Chloropropionyl)-4-(2-methoxyphenyl)piperazine: oil. Yield 85%. This compound was used in the next step without further purification.

1-(2-Chloropropionyl)-4-(2-ethoxyphenyl)piperazine: colorless prisms (petr. ether), mp 68—68.5 °C. Yield 68%. *Anal.* Calcd for $C_{15}H_{21}ClN_2O_2$: C, 60.70; H, 7.13; N, 9.44. Found: C, 60.51; H, 7.02; N, 9.08.

2-{2-[4-(2-Ethoxyphenyl)-1-piperazinyl]propionyl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (11b)——A solution of **10b** (4.2 g, 15 mmol), 1-(2-ethoxyphenyl)piperazine·HCl (4.4 g, 18 mmol), and Et_3N (3.6 g, 36 mmol) in EtOH (80 ml) was refluxed for 76 h. Evaporation of the reaction mixture *in vacuo* gave the residue, which was partitioned between 3 N HCl and toluene. The aqueous layer was made alkaline with 30% NaOH and extracted with toluene. The toluene extract was dried over K_2CO_3, and evaporated *in vacuo* to give **11b** (5.7 g, 84%) as an oil. This compound was used in the next step without further purification. IR ($CHCl_3$) cm^{-1}: 1635 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7.0 Hz, =NCOCH(C$\underline{H}_3$)N=), 1.50 (3H, t, J=7.0 Hz, OCH$_2$C$\underline{H}_3$), 1.6—1.9 (4H, m, C_7–H and C_8–H), 2.5—3.2 (14H, m, C_4–H, C_6–H, C_9–H, and piperazinyl H), 3.3—4.3 (5H, m, C_3–H, OC$\underline{H}_2$CH$_3$, and =NCOC$\underline{H}$(CH$_3$)N=), 4.4—4.9 (2H, m, C_1–H), 6.85 (4H, s, phenyl H), 7.10 (1H, s, C_{10}–H).

6-{2-[4-(2-Methoxyphenyl)-1-piperazinyl]propionyl}-5,6,7,8-tetrahydro-1,6-naphthyridine (**11a**) was similarly prepared as colorless prisms (ether), mp 122—123 °C. Yield 79%. *Anal.* Calcd for $C_{22}H_{28}N_4O_2$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.71; H, 7.60; N, 14.53.

6-{2-[4-(2-Methoxyphenyl)-1-piperazinyl]-1-methyl-2-oxoethyl}-5,6,7,8-tetrahydro-1,6-naphthyridine (**9a**) was similarly prepared in 60% yield as an oil from **4a** and 1-(2-chloropropionyl)-4-(2-methoxyphenyl)piperazine. Further, 2-{2-[4-(2-ethoxyphenyl)-1-piperazinyl]-1-methyl-2-oxoethyl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (**9b**) was similarly prepared in 73% yield as an oil from **4b** and 1-(2-chloropropionyl)-4-(2-ethoxyphenyl)piperazine. These compounds (**9a, b**) were used in the next step without further purification.

6-Crotonoyl-5,6,7,8-tetrahydro-1,6-naphthyridine (14a)——A solution of crotonyl chloride (3.14 g, 30 mmol) in $CHCl_3$ (25 ml) was added dropwise to a solution of **4a** (3.35 g, 25 mmol) and pyridine (2.4 ml, 30 mmol) in $CHCl_3$ (125 ml) with stirring under ice-cooling. During the addition, the reaction temperature was kept below 10 °C. After the addition, the reaction mixture was stirred for 2 h at *ca.* 5 °C and then at room temperature overnight. After a small amount of hydroquinone had been added to the mixture, the whole was evaporated *in vacuo* to give the residue. This residue was partitioned between 1 N HCl and toluene. The aqueous layer was separated, made alkaline with 10% NaOH, and extracted with toluene. After the toluene layer had been dried over K_2CO_3, a small amount of hydroquinone was added to the toluene layer, which was then evaporated *in vacuo* below 30 °C to give the residue. Recrystallization of the residue from iso-Pr_2O gave **14a** (4.2 g, 84%) as colorless prisms, mp 58 °C. IR (Nujol) cm^{-1}: 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, dd, J=6.4 and 1.3 Hz, –CH=CHC$\underline{H}_3$), 3.06 (2H, t, J=5.8 Hz, C_8–H), 3.92 (2H, t, J=5.8 Hz, C_7–H), 4.79 (2H, s, C_5–H), 6.33 (1H, dd, J=15.2 and 1.3 Hz, –C$\underline{H}$=CHCH$_3$), 6.6—7.3 (2H, m, C_3–H and –CH=C$\underline{H}$CH$_3$), 7.43 (1H, dd, J=7.2 and 1.2 Hz, C_4–H), 8.42 (1H, dd, J=4.9 and 1.2 Hz, C_2–H). *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.45; H, 6.72; N, 13.96.

2-Crotonoyl-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (**14b**) was similarly prepared as colorless prisms (iso-Pr_2O), mp 82—85 °C. Yield 98%. *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.77; H, 7.69; N, 10.69.

The following 4-acyl-1-piperazines were prepared by a similar method using methacryloyl chloride and crotonoyl chloride from 1-(2-methoxyphenyl)- and 1-(2-ethoxyphenyl)piperazine.

4-Methacryloyl-1-(2-methoxyphenyl)piperazine: colorless needles (iso-Pr_2O), mp 89—90.5 °C. Yield 78%. *Anal.* Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 68.97; H, 7.69; N, 10.58.

1-(2-Ethoxyphenyl)-4-methacryloylpiperazine: colorless oil, bp 165—175 °C (0.8 mmHg). Yield 79%. This compound was used in the next step without elementary analysis.

1-Crotonoyl-4-(2-methoxyphenyl)piperazine: colorless needles (iso-Pr_2O), mp 65 °C. Yield 93%. *Anal.* Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 68.98; H, 7.60; N, 10.99.

1-Crotonoyl-4-(2-ethoxyphenyl)piperazine: colorless oil, bp 175—185 °C (1.3 mmHg). Yield 96%. This compound was used in the next step without elementary analysis.

The Michael Reaction of Unsaturated Amides with Amines

Typical Example: 2-{3-[4-(2-Ethoxyphenyl)-1-piperazinyl]-1-methyl-3-oxopropyl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (12b)——A solution of **4b** (3.4 g, 18 mmol), 1-crotonoyl-4-(2-ethoxyphenyl)piper-

azine (4.1 g, 15 mmol), and Triton B (2 ml) in EtOH (20 ml) was refluxed for 48 h. After evaporation of the reaction mixture *in vacuo*, the residue was made alkaline with 30% NaOH and then extracted with toluene. The toluene extract was dried over K_2CO_3 and evaporated *in vacuo* to give a viscous oil, which was purified by SiO_2 column chromatography using $CHCl_3$–EtOH (10 : 1, v/v) as an eluent to afford **12b** (5.0 g, 71%) as a gum. This compound was used in the next step without elementary analysis. IR ($CHCl_3$) cm^{-1}: 1625 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=6.0 Hz, $=CHC\underline{H}_3$), 1.45 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.6—2.1 (4H, m, C_7–H and C_8–H), 2.2—3.2 (15H, m, aliphatic H), 3.2—3.9 (6H, m, aliphatic H), 4.07 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.89 (4H, s, phenyl H), 6.99 (1H, s, C_{10}–H).

The following compounds were prepared by a similar method as gummy compounds and used in the next step without elementary analysis: 6-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-1-methyl-3-oxopropyl}-5,6,7,8-tetrahydro-1,6-naphthyridine (**12a**), 6-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-3-oxopropyl}-5,6,7,8-tetrahydro-1,6-naphthyridine (**13a**), 2-{3-[4-(2-ethoxyphenyl)-1-piperazinyl]-2-methyl-3-oxopropyl}-1,2,3,4,6,7,8,9-oxtahydrobenzo[*b*][1,6]naphthyridine (**13b**), 6-{3-[4-(2-methoxyphenyl)-1-piperazinyl]butyryl}-5,6,7,8-tetrahydro-1,6-naphthyridine (**15a**), 2-{3-[4-(2-ethoxyphenyl)-1-piperazinyl]butyryl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (**15b**).

Reaction of Amide Derivatives with $LiAlH_4$

Typical Example (Method C): 2-{2-[4-(2-Ethoxyphenyl)-1-piperazinyl]propyl}-1,2,3,4,6,7,8,9-octahydrobenzo-[*b*][1,6]naphthyridine Difumarate (50)——A solution of **11b** (5.4 g, 12 mmol) in dry ether (40 ml) was added dropwise to a suspension of $LiAlH_4$ (0.5 g, 12 mmol) in dry ether (80 ml) and the mixture was refluxed for 4 h. The mixture was cautiously quenched by treatment with H_2O (1 ml) below 10 °C. After the mixture had been stirred for an additional 2 h, the precipitate was filtered off, and then washed well with ether. Evaporation of the combined ethereal filtrate *in vacuo* gave the residue. This residue was purified by SiO_2 column chromatography using toluene–EtOH (5 : 1, v/v) as an eluent to afford the free base of **50** (3.10 g, 60%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7.0 Hz, $=CHC\underline{H}_3$), 1.43 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.6—2.0 (4H, m, C_7–H and C_8–H), 2.3—3.3 (19H, m, aliphatic H), 3.62 (2H, s, C_1–H), 4.05 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.6—7.1 (5H, m, aromatic H). MS *m/z* (relative intensity): 434 (M^+, 1.9), 234 (17.5), 233 (100), 231 (6.5).

This free base was converted to the salt (**50**) by treatment with *dl*-tartaric acid in acetone. Melting points, recrystallization solvents, and elementary analyses of the salts are listed in Table I.

Pharmacological Methods

Spontaneous Nystagmus——The methods described in this report were the same as those previously reported.[4b] The effect of each compound was expressed as inhibition percent, I (%), based on the following formula: I (%) $=(A-B)\times 100/A$ (%), where A and B are the values of total beat number of nystagmus for 60 min before and after the administration of the compounds, respectively. Mean I (%) at not less than 3 screening dose levels was obtained from at least three different preparations, and ID_{30} of each compound was determined graphically from the dose-response curves plotted on semilogarithmic paper.

Antagonism of Emesis——All experimental procedures were carried out according to Janssen's methods.[9] Six beagle dogs weighing 9.0—13.0 kg were previously selected based on sensitivity to apomorphine·HCl (0.3 mg/kg, *s.c.*). They were used at weekly intervals. After a fast of 12—18 h, they were fed 1 h prior to the experiment. Compound **41** (NK 422), diphenidol·HCl (DPD), chlorpromazine·HCl (CPZ), and saline (control) were given subcutaneously 30 min before the administration of apomorphine·HCl (0.3 mg/kg, *s.c.*). The following phenomena were recorded: a) onset of time of vomiting (latency), b) frequency of vomiting, and c) duration of vomiting (time interval between first and last emesis). These phenomena were observed for 1 h after the administration of apomorphine·HCl.

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References and Notes

1) *a*) Part III: A. Shiozawa, Y.-I. Ichikawa, C. Komuro, S. Kurashige, H. Miyazaki, H. Yamanaka, and T. Sakamoto, *Chem. Pharm. Bull.*, **32**, 2522 (1984); *b*) A part of this work was presented at the North American Medicinal Chemistry Symposium (Toronto, Canada, 1982): A. Shiozawa, Y.-I. Ichikawa, C. Komuro, M. Ishikawa, S. Kurashige, Y. Furuta, H. Miyazaki, H. Yamanaka, and T. Sakamoto, Abstracts of Papers, p. 76.
2) A. Shiozawa, Y.-I. Ichikawa, C. Komuro, M. Ishikawa, Y. Kogo, S. Kurashige, H. Miyazaki, H. Yamanaka, and T. Sakamoto, *Chem. Pharm. Bull.*, **32**, 995 (1984).
3) *a*) L. A. Walter, Wm. H. Hunt and R. J. Fosbinder, *J. Am. Chem. Soc.*, **63**, 2771 (1941); *b*) J. C. Elia, *J. Am. Med. Assoc.*, **196**, 187 (1966).
4) *a*) M. Ishikawa, K. Tanaka, Y. Furuta, and H. Miyazaki, Abstracts of Papers, the 8th International Congress of Pharmacology, Tokyo, July 1981, p. 608; *b*) A. Shiozawa, Y.-I. Ichikawa, C. Komuro, G.-I. Idzu, M. Ishikawa, S. Kurashige, H. Miyazaki, H. Yamanaka, and T. Sakamoto, *Chem. Pharm. Bull.*, **32**, 553 (1984).

5) C. Hansch, A. Leo, S. H. Unger, K.-H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
6) H. A. Bickerman, "Drugs of Choice," 1976—1977, ed. by W. Modell, C. V. Mosby Co., Saint Louis, 1976, Chapter 30.
7) P. T. Bysouth and R. W. Clarke, S. African Patent 6804082 (1969) [*Chem. Abstr.*, **71**, 91527*g* (1969)].
8) R. F. Parcell, U. S. Patent 2922788 (1960) [*Chem. Abstr.*, **54**, 9966*g* (1960)].
9) P. A. J. Janssen and C. J. E. Niemegeers, *Arzneim.-Forsch.*, **9**, 765 (1959).