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Inhibition of Gastric Acid Secretion by 1,8-Naphthyridin-2(1*H*)-ones

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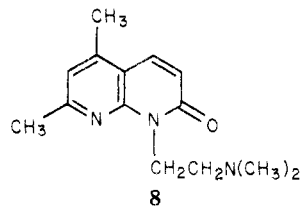
A number of 1-[(dialkylamino)alkyl]-1,8-naphthyridin-2(1*H*)-ones were prepared and evaluated in vivo for inhibition of gastric acid secretion evoked by gastrin tetrapeptide and also in vitro for antagonism of the rat uterine histamine H_2 receptor. The effect on activity of structural variation in the dialkylaminoalkyl group and the position and nature of naphthyridine ring substituents was examined. In this series, structural requirements for in vitro activity were found to be quite different from those required for maximal in vivo potency, and a positive correlation between histamine H_2-receptor antagonism and inhibition of gastrin tetrapeptide induced secretion could not be established. In addition, none of the compounds inhibited histamine-stimulated gastric secretion. 1-[2-(Dimethylamino)-ethyl]-1,8-naphthyridin-2(1*H*)-one and its 5- and 6-methyl analogues were the most potent in vivo inhibitors of gastrin tetrapeptide induced acid secretion, causing a 55–60% decrease in acid concentration at an oral dose of 20 mg/kg. However, they were only weakly active in vitro. On the other hand, 7-alkyl analogues, such as those with a 7-ethyl, 7-isopropyl, or 7-isobutyl substituent, had low in vivo potency but were excellent inhibitors, equivalent to metiamide, in the H_2-receptor assay.

Competitive antagonism of histamine H_2 receptors as a means of inhibiting gastric acid secretion has been established as an acceptable ulcer treatment.[1] The clinically effective antagonists metiamide (*N*-methyl-*N'*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]thiourea) and cimetidine (*N*-cyano-*N'*-methyl-*N''*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]guanidine) represent structural modifications of the physiological agonist histamine in which the imidazole nucleus was retained and major changes were made in the aminoethyl side chain.[2] In our approach to the inhibition of gastric acid secretion, the development of new structural types for H_2-receptor antagonism has been a major objective. As a working hypothesis, binding-site similarities were assumed for H_1- and H_2-histamine receptors, so that structural elements responsible for H_1-receptor antagonism could also be expected to interact with an H_2 receptor. Specifically, the presence on H_2 receptors of reactive sites for an alkylaminoalkyl group, a structure common to many antihistamine drugs, was postulated as a basis for an initial investigation.

Recent reports of the effects of dialkylaminoalkyl compounds on H_2 receptors or their dependent actions support the validity of these assumptions. Tripelennamine (*N*,*N*-dimethyl-*N'*-(phenylmethyl)-*N'*-2-pyridinyl-1,2-ethanediamine), an H_1 antagonist, has been shown to inhibit histamine-evoked gastric acid secretion in the dog stomach with an ED_{50} approximately tenfold that of metiamide,[3] while dimaprit (*S*-[3-(dimethylamino)-propyl]isothiourea) is a specific agonist for the H_2 receptor.[4a] Mepyramine (*N*-[(4-methoxyphenyl)methyl]-*N'*,*N'*-dimethyl-*N*-2-pyridinyl-1,2-ethanediamine) has been shown to inhibit both histamine- and dimaprit-induced activation of hippocampal adenylate cyclase,[4b] an H_2-receptor mediated response.

A variety of unique compounds having dialkylaminoalkyl substituents were tested in vitro in rat uterine tissue for antagonism of the H_2-receptor mediated response to histamine. Among the structures evaluated, an ethylenediamine analogue, 1-[2-(dimethylamino)ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one hydrochloride (**8**),



8

was reasonably active and also inhibited gastric acid secretion in the dog. These findings prompted the synthesis of a number of analogues for evaluation in vitro as inhibitors of the histamine H_2 receptor and in vivo for inhibition of gastrin tetrapeptide evoked gastric secretion.

Chemistry. The majority of the compounds listed in Tables I and II were synthesized directly from the appropriate 1,8-naphthyridin-2(1*H*)-one by forming the alkali metal salt with sodium ethoxide in EtOH (method 1) or NaH in DMF (method 2), which was then allowed to react with a dialkylaminoalkyl halide. Two compounds containing a primary amino group in the side chain, **17** and the intermediate required for the preparation of **26**, were generated from the corresponding phthalimides. The monomethylamino derivative **18** was prepared by de-

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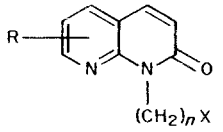
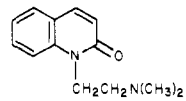
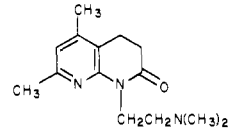
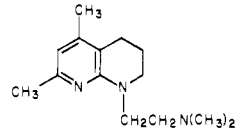
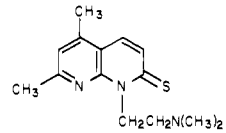
Table I. Inhibition of Gastric Acid Secretion and Histamine H_2 Receptors by 1,8-Naphthyridin-2(1*H*)-ones



no.	R	*n*	X	mp, °C	recrystn solvent[a]	formula[b]	in vitro H_2 recept inhibn (rat uterus): EC_{50}, μg/mL[c]	gastric secret.: % reduct acid concn[d] mean ± SE[e]	gastric secret.: % reduct acid concn[d] no. of animals
1	H	2	$N(CH_3)_2$	202–203.5	MeOH/Et_2O	$C_{12}H_{15}N_3O$·HCl	*	59 ± 4	4
2	5-CH$_3$	2	$N(CH_3)_2$	229–231.5	MeCN	$C_{13}H_{17}N_3O$·HCl	*	58 ± 9	4
3	6-CH$_3$	2	$N(CH_3)_2$	207–210	EtOH/Et_2O	$C_{13}H_{17}N_3O$·HCl·0.5H_2O	*	58 ± 21	5
4	7-CH$_3$	2	$N(CH_3)_2$	201–204	EtOH/Et_2O	$C_{13}H_{17}N_3O$·HCl·H_2O	2.18 (0.68, 7.04)	†	2
5	7-CH_2CH_3	2	$N(CH_3)_2$	146–149	MEK	$C_{14}H_{19}N_3O$·HCl·0.5H_2O	0.79 (0.22, 28.0)	†	4
6	7-$CH(CH_3)_2$	2	$N(CH_3)_2$	209–211	EtOH/Et_2O	$C_{15}H_{21}N_3O$·HCl	0.60 (0.16, 22.2)	†	2
7	7-$CH_2CH(CH_3)_2$	2	$N(CH_3)_2$	189–191	*i*-PrOH	$C_{16}H_{23}N_3O$·HCl	0.16 (0.08, 0.30)	†	2
8	5,7-$(CH_3)_2$	2	$N(CH_3)_2$	231–233	*i*-PrOH	$C_{14}H_{19}N_3O$·HCl	3.93 (0.94, 18.5)	40 ± 9	4
9	5,7-$(CH_2CH_3)_2$	2	$N(CH_3)_2$	59.5–61	hexane	$C_{16}H_{23}N_3O$	5.19 (3.51, 7.67)	†	2
10	5,7-$(CF_3)_2$	2	$N(CH_3)_2$	203.5–206.5	EtOH/Et_2O	$C_{14}H_{13}F_6N_3O$·HCl·H_2O	*	32 ± 11	4
11	5-CF_3, 7-CH_3	2	$N(CH_3)_2$	102.5–103.5	pet. ether	$C_{14}H_{16}F_3N_3O$	*	52 ± 10	4
12	5-CH_3, 7-CF_3	2	$N(CH_3)_2$	86–87.5	hexane	$C_{14}H_{16}F_3N_3O$	1.60 (0.91, 2.32)	34 ± 18	4
13	5-CH_3, 7-OCH_3	2	$N(CH_3)_2$	98.5–101.5	hexane	$C_{14}H_{19}N_3O_2$	7.01 (3.96, 12.4)	27 ± 10	3
14	5-CH_3, 7-Cl	2	$N(CH_3)_2$	110.5–111.5	*n*-BuCl/hexane	$C_{13}H_{16}ClN_3O$	9.23 (5.20, 16.4)	†	4
15	5,6,7-$(CH_3)_3$	2	$N(CH_3)_2$	180–185	EtOH/Et_2O	$C_{15}H_{21}N_3O$·HCl·H_2O	12.50 (7.83, 20.1)	61 ± 7	4
16	5,7-$(CH_3)_2$	2	H	90–92	hexane	$C_{12}H_{14}N_2O$	*	†	2
17	5,7-$(CH_3)_2$	2	NH_2	253.5–254.3	*i*-PrOH	$C_{12}H_{15}N_3O$·HCl	33.8 (7.02, 163.0)	†	2
18	5,7-$(CH_3)_2$	2	$NHCH_3$	106–109	*i*-PrOH	$C_{13}H_{17}N_3O$·HCl·0.5H_2O	21.1 (8.79, 50.8)	†	2
19	5,7-$(CH_3)_2$	2	$N(CH_2CH_3)_2$	226.5–228	*i*-PrOH	$C_{16}H_{23}N_3O$·HCl	1.12 (0.42, 3.03)	†	2
20	5,7-$(CH_3)_2$	2	c-NC_5H_{10}	216.5–217.5	*i*-PrOH/Et_2O	$C_{16}H_{21}N_3O$·HCl	3.05 (1.83, 5.10)	40	2
21	5,7-$(CH_3)_2$	2	$N(C_4H_9)_2$	195–197	*i*-PrOH/Et_2O	$C_{20}H_{31}N_3O$·HCl·0.5H_2O	1.80 (0.65, 4.99)	33	2
22	5,7-$(CH_3)_2$	2	$N[CH(CH_3)_2]_2$	262.5–263.5	*i*-PrOH	$C_{18}H_{27}N_3O$·HCl	1.44 (1.04, 1.98)	57 ± 15	6
23	5,7-$(CH_3)_2$	2	$N(c\text{-}C_6H_{11})_2$	259–260.5	*i*-PrOH/Et_2O	$C_{24}H_{35}N_3O$·HCl	*	†	3
24	5,7-$(CH_3)_2$	2		169–171	Et_2O	$C_{21}H_{31}N_3O$	*	†	2
25	5,7-$(CH_3)_2$	3	$N(CH_3)_2$	232.5–234	*i*-PrOH	$C_{15}H_{21}N_3O$·HCl	*	31	2
26	5,7-$(CH_3)_2$	4	$N(CH_3)_2$	222–225	EtOH/Et_2O	$C_{16}H_{23}N_3O$·2HBr	*	†	2
27	5,7-$(CH_3)_2$	1	$C(CH_3)_2N(CH_3)_2$	109–111	*n*-BuCl	$C_{16}H_{23}N_3O$	10.4 (1.97, 54.6)	38 ± 14	4
28	5,7-$(CH_3)_2$	2	$^+N(CH_3)_3I^-$	219–220	MeOH/Et_2O	$C_{15}H_{22}IN_3O$	*	†	2
29	H	2	$N[CH(CH_3)_2]_2$	241–242.5	*i*-PrOH	$C_{16}H_{23}N_3O$·HCl	20.9 (5.29, 82.6)	51 ± 6	4

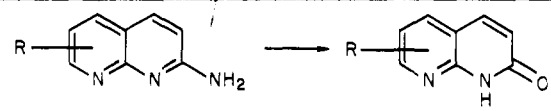
[a] MEK = methyl ethyl ketone. [b] All new compounds had analyses within 0.4% for C, H, and N, except 15 (C: calcd, 57.41, found, 57.96) and 18 (C: calcd, 56.42; found, 56.89). [c] EC_{50} is the concentration of test compound required to antagonize the histamine effect by 50%; 95% confidence limits are included in parentheses; an asterisk indicates less than 30% reduction in histamine response in the presence of 20 μg/mL of the test compound. [d] Compounds tested at 20 mg/kg base wt against gastrin tetrapeptide induced secretion; a dagger indicates less than 25% reduction in acid concentration. [e] Standard error (SE) determined where number of animals was greater than two.

Table II. Biological Activity of Compounds Related to 1,8-Naphthyridin-2(1*H*)-ones

no.	structure	in vitro H_2 recept inhibn (rat uterus):[a] EC_{50}, μg/mL	gastric secret % reduct acid concn:[b] mean ± SE[c]	no. of animals
30		*	†	2
31		4.8 (4.01, 5.78)	†	2
32		1.01 (0.47, 2.80)	inact[d]	4
33		3.65 (1.76, 7.89)	41	2
34	metiamide[e]	0.28 (0.20, 0.43)	76 ± 8	6

[a] EC_{50} is the concentration of test compound required to antagonize the histamine effect by 50%; 95% confidence limits are included in parentheses; an asterisk indicates less than 30% reduction in histamine response in the presence of 20 μg/mL of the test compound. [b] Compounds tested at 20 mg/kg base wt against gastrin tetrapeptide induced secretion; a dagger indicates less than 25% reduction in acid concentration. [c] Standard error (SE) determined where number of animals was greater than two. [d] Compound tested at 40 mg/kg. [e] Prepared in these laboratories.

Table III. New Substituted 1,8-Naphthyridin-2(1*H*)-ones



i ii

	compd i				compd ii			
R	mp, °C	recrystn solvent	formula[a]	yield, %	mp, °C	recrystn solvent	formula[a]	yield, %
7-$CH(CH_3)_2$	158-160.5	EtOAc	$C_{11}H_{13}N_3$	35	131.5-133	*n*-BuCl	$C_{11}H_{12}N_2O \cdot CF_3CO_2H$	84
5,7-$(CH_2CH_3)_2$	187-189.5	EtOAc	$C_{12}H_{15}N_3$	88	159-161	EtOAc	$C_{12}H_{14}N_2O$	83
7-$CH_2CH(CH_3)_2$	125-127	*n*-BuCl	$C_{12}H_{15}N_3$	69	135-137	*n*-BuCl	$C_{12}H_{14}N_2O$	88
5,6,7-$(CH_3)_3$			$C_{11}H_{13}N_3$[b]	50			$C_{11}H_{12}N_2O$[b]	58

[a] All compounds had analyses within 0.4%, unless otherwise indicated. [b] Crystalline product not obtained; structure confirmed by NMR.

benzylation of the benzylmethylamino precursor. Catalytic reduction of the pyridinone ring of 8 progressed only to the dihydro compound **31**. To obtain the tetrahydro derivative **32**, the alkali metal salt of 2,4-dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine was alkylated with dimethylaminoethyl chloride. Treatment of 8 with P_2S_5 gave thione **33** and treatment with CH_3I gave the methiodide **28**.

Most of the intermediate 1,8-naphthyridin-2(1*H*)-ones were either commercially available or obtainable by published synthetic procedures. Except for 7-methoxy-5-methyl-1,8-naphthyridin-2(1*H*)-one, previously undescribed intermediates including those tabulated in Table III were prepared by an efficient two-step route involving condensation of the appropriate 1,3-diketone or 3-oxoacetal with 2,6-diaminopyridine in 85% phosphoric acid, followed by conversion of the resulting 2-amino-1,8-naphthyridine to the 1,8-naphthyridin-2(1*H*)-one with $NaNO_2$ in trifluoroacetic acid.[5]

Structure–Activity Correlation. Rat Uterus. Results obtained in the in vitro test for antagonism of histamine inhibition of electrically stimulated uterine tissue contraction (an H_2-receptor mediated response) are shown in Tables I and II. In this assay, 8 has an EC_{50} = 3.93 μg/mL, about 0.07 the activity of the established H_2-receptor inhibitor metiamide (**34**).[6]

The importance of the ring alkyl substituents and their positions was made apparent by the low inhibitory activity of the demethyl (**1**), 5-methyl (**2**), and 6-methyl (**3**) analogues in contrast to the 7-methyl analogue (**4**) which is almost twice as active as **8**. As size and lipophilicity of the 7-alkyl substituent are increased, activity is enhanced and compounds equipotent with metiamide, such as **7**, result. The activity of 5,7-dialkyl compounds is lower than that of the corresponding 7-alkyl substituted compounds, as shown by a comparison of **8** (5,7-dimethyl) with **4** (7-methyl) and **9** (5,7-diethyl) with **5** (7-ethyl). A 6-methyl substituent (**15**) enhances the deactivating effect of the 5-methyl group in **8**. Thus, to generalize, 7-alkyl substituents have an activating effect while 5- and 6-alkyl substituents have an inactivating effect on the series.

Among other types of substituents examined, the 7-methoxy (**13**) and 7-chloro (**14**) have a weaker activating effect than a 7-methyl (**8**). Comparison of the trifluoro-

Table IV. Guinea Pig Atrium Test

compd	histamine ratio[a]
metiamide	0.003
22	0.011
31	0.013
8	0.18
7	0.21
1	0.54

[a] The ratio of the histamine concentration required in control trials to that required in the presence of 10 μg/mL of inhibitor to increase atrium rate by 50 beats/min.

methyl analogues 10–12 with each other and with 8 indicated that the effect of a trifluoromethyl group is significantly greater than that of a corresponding methyl group and is deactivating in the 5 position and activating in the 7 position.

The lack of activity of 16 shows that the presence of an amino group on the side chain is essential. As the lipophilicity of substituents on the amino group of the basic side chain increases, beginning with the unsubstituted compound 17, inhibitory activity increases to a maximum with the diethylamino (19), diisopropylamino (22), and dibutylamino (21) analogues. Larger and bulkier substitution on the nitrogen atom, such as in the dicyclohexylamino (23) and the 2,2,6,6-tetramethylpiperidyl (24) analogues, markedly decreases activity. It appears that a cyclic amino derivative, such as 20, is less active than its acyclic counterpart, 19. In the side chain, branching (27), extension to three or four methylene units (25 and 26), or quaternization of the amino group (28) reduces activity.

The thione 33 is equivalent to its oxo counterpart 8. Saturation of the 3,4 double bond of 8 to give 31 causes little change in activity; however, further reduction to the tetrahydro analogue 32 more than doubles the activity. The quinoline analogue 30 is inactive.

Guinea Pig Atrium. Five representative naphthyridines were evaluated in the guinea pig atrium for inhibition of the histamine-induced chronotropic response, an H_2-receptor mediated effect. The compounds are arranged in Table IV in order of decreasing activity as histamine antagonists. Except for 7, the compounds have essentially the same relative order of activity as in the rat uterine assay.

Dog Gastric Fistula. In this model, compounds were evaluated primarily for effectiveness in reducing the concentration of gastric acid, since the volume of secretion is affected minimally by the naphthyridinones. The unsubstituted (1), the 5-methyl- (2), and the 6-methylnaphthyridinone (3) analogues have a high inhibitory effect on gastrin tetrapeptide stimulated gastric acid secretion. The 7-methyl (4) and other 7-alkyl (5–7) substituted analogues are less active than 1. Likewise, the potency of 2 is decreased by the introduction of a 7-methyl group to give compound 8. Activity induced by 5- and 6-methyl substituents appears to be additive, resulting in 15 being more potent than 8.

A 7-methoxy (13) or 7-chloro (14) substituent has a slightly greater inactivating effect than a 7-methyl (8) group. Comparison of the trifluoromethyl analogues 11 and 12 with 8 indicates that the 7-(trifluoromethyl) group has a greater inactivating effect than a 7-methyl group. However, a 5-(trifluoromethyl) group is more potent than a 5-methyl in overcoming deactivating effects of 7-alkyl substituents.

Removal of the dimethylamino group or one or both substituents from the amino nitrogen atom of the side chain of 8 decreases antisecretory potency, as shown by compounds 16–18. In general, the dialkylamino moiety is required for compounds to have maximal activity. Replacement of the dimethylamino group of 8 by diisopropylamino to give 22 increases activity; however, the same change on compound 1 to give 29 has little effect. Branching (27) or lengthening (25 or 26) of the methylene chain causes a decrease in potency. Quaternization of the amino group (28) or reduction of the 3,4 double bond (31) has a deactivating effect. The thione 33 has the same potency as the corresponding carbonyl derivative 8, while the decarbonyl derivative 32 and a quinoline analogue 30 are inactive.

When gastric secretion in this model is evoked by histamine instead of gastrin tetrapeptide, representative naphthyridinones are not inhibitory when tested at 40 mg/kg orally, whereas metiamide effects a 46% reduction of acid concentration when administered at 20 mg/kg orally.

Conclusion. The effects of the naphthyridinone analogues in the in vitro rat uterine and guinea pig atrium assays suggest that these compounds are histamine H_2-receptor inhibitors. In the dog, the naphthyridinones inhibit gastric acid secretion induced by gastrin tetrapeptide as does the H_2-receptor inhibitor, metiamide. However, unlike the latter, they do not inhibit histamine-induced gastric acid secretion nor do they reduce secretory volume. Moreover, the structure–activity relationships for inhibition of gastric secretion do not parallel those for in vitro activity and, in fact, are quite different.

The data for these compounds suggest that histamine H_2-receptor inhibitory activity may not be involved in their inhibition of gastric secretion, and the mode of inhibitory action in vivo is unknown. Thus, any underlying pharmacologic relationship between the in vitro and in vivo tests leading to the development of antisecretory compounds from the rat uterine test in this research remains obscure.

Although the naphthyridinone series has limited practical application because of the lack of inhibition of histamine-induced secretion, it has served as a structural base for the development of other potent, broadly active inhibitors of gastric secretion to be described in later reports.

Experimental Section

Chemistry. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results obtained are within ±0.40% of the theoretical values. Routine NMR spectra, obtained on the Varian Associates spectrometer, Model T-60, are consistent with the structures indicated. No effort was made to optimize yields.

Preparation of 1,8-Naphthyridin-2(1*H*)-ones. 5,7-Dimethyl-1,8-naphthyridin-2(1*H*)-one is commercially available. The following 1,8-naphthridin-2(1*H*)-ones were prepared according to the references cited: 5-methyl-,[7] 6-methyl-,[7] 7-methyl-,[8] 5,7-bis(trifluoromethyl)-,[5] 5-(trifluoromethyl)-7-methyl-,[5] 5-methyl-7-(trifluoromethyl)-,[5] 5-methyl-7-chloro,[9] and the unsubstituted 1,8-naphthyridin-2(1*H*)-one.[10]

New 1,8-naphthyridin-2(1*H*)-ones and their 2-amino-1,8-naphthyridine precursors shown in Table III were prepared by the procedure described for 7-ethyl-1,8-naphthyridin-2(1*H*)-one.

2-Amino-7-ethyl-1,8-naphthyridine. To cold 85% H_3PO_4 (75 mL) was added with stirring 2,6-diaminopyridine (16.4 g, 0.15 mol), followed by 1,1-dimethoxy-3-oxopentane (21.9 g, 0.15 mol). The mixture was warmed on a steam bath for 6 h, then poured onto crushed ice, and neutralized with NH_4OH. The product was extracted into chloroform, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated. The crude product was recrystallized from EtOAc to give 15.3 g (59%), mp 169.5–172.5 °C. Anal. ($C_{10}H_{11}N_3$) C, H, N.

7-Ethyl-1,8-naphthyridin-2(1*H*)-one. To a stirred solution of 2-amino-7-ethyl-1,8-naphthyridine (13.9 g, 0.08 mol) in

CF_3COOH (80 mL) maintained at 0 °C was added sodium nitrite (6.55 g, 0.095 mol) in small portions. This mixture was stirred at 0 °C for 2 h and then warmed to room temperature. The reaction mixture was poured onto crushed ice and made slightly basic with NH_4OH. The precipitated product was extracted into chloroform and dried (Na_2SO_4), and the solvent was removed. Recrystallization of the residue from EtOAc yielded 13.5 g (97%) of product; mp 133–134.5 °C. Anal. ($C_{10}H_{10}N_2O$) C, H, N.

7-Methoxy-5-methyl-1,8-naphthridin-2(1*H*)-one. To 7-chloro-5-methyl-1,8-naphthyridin-2(1*H*)-one[9] (0.98 g, 5 mmol) in dimethoxyethane (10 mL) was added commercial NaOMe (0.54 g, 10 mmol). This mixture was stirred on a steam bath overnight, cooled, and neutralized with dilute HCl. The product was extracted into Et_2O, dried with Na_2SO_4, and evaporated to give 0.84 g (88%). An analytical sample was obtained by recrystallization from EtOH, mp 214–216.5 °C. Anal. ($C_{10}H_{10}N_2O_2$) C, H, N.

Preparation of 1-(Aminoalkyl)-1,8-naphthyridin-2(1*H*)-ones (Table I). Method 1. 1-[2-(Diethylamino)ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one Hydrochloride (19). 5,7-Dimethyl-1,8-naphthyridin-2(1*H*)-one (3.48 g, 20 mmol) was added to a solution of NaOEt prepared by dissolving Na pellets (1.0 g, 43 mmol) in absolute EtOH (50 mL). The mixture was heated to reflux and a solution of 2-(diethylamino)ethyl chloride hydrochloride (3.44 g, 20 mmol) in absolute EtOH (50 mL) was added dropwise. After heating an additional 6 h, the mixture was cooled, salts were removed by filtration, and the solvent was evaporated. The residue was dissolved in Et_2O, the product was extracted into dilute HCl and filtered through a pad of charcoal, and the solution was made basic with saturated Na_2CO_3. The product was extracted into Et_2O and precipated as the HCl salt by addition of ethanolic HCl. The collected salt was recrystallized from *i*-PrOH to give 3.56 g (57%) of **19**; mp 226.5–228 °C. Anal. ($C_{16}H_{23}N_3O$·HCl) C, H, N.

This method was also used to prepare compounds **8**, **20–25**, and **27** in 20–47% yields from the appropriate alkyl halides and naphthyridinones.

Method 2. 1-[2-(Dimethylamino)ethyl]-1,8-naphthyridin-2(1*H*)-one Hydrochloride (1). 1,8-Naphthyridin-2(1*H*)-one (2.9 g, 20 mmol) was added to a suspension of 57% NaH in mineral oil (1.7 g, 41 mmol) in dry DMF (50 mL) and the mixture gradually warmed to 90 °C. 2-(Dimethylamino)ethyl chloride hydrochloride (2.9 g, 20 mmol) was cautiously added in portions, and the mixture was heated for an additional 4 h. The cooled reaction mixture was poured into ice–H_2O cautiously, and the crude product was extracted into CH_2Cl_2. The product was then extracted into dilute HCl, filtered through a pad of charcoal, made basic with saturated Na_2CO_3, and reextracted into CH_2Cl_2. The dried solution (Na_2SO_4) was evaporated, the residue was dissolved in Et_2O and treated with ethanolic HCl, and the precipitate was collected and recrystallized from MeOH–Et_2O to give 4.6 g (91%) of **1**, mp 202–203.5 °C. Anal. ($C_{12}H_{15}N_3O$·HCl) C, H, N.

This method was also used to obtain compounds **2–7**, **9–16**, and **29** in 26–88% yields from the appropriate alkyl halides and naphthyridinones.

1-(2-Aminoethyl)-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one Hydrochloride (17). The reaction of 5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one with *N*-(2-chloroethyl)phthalimide was carried out by method 2 to give a 45% yield of crude **1-(2-phthalimidoethyl)-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one.** The unsubstituted amine was prepared from this compound by the method of Sheehan and Bolhofer,[11] converted to the salt by treatment with ethanolic HCl, and recrystallized from *i*-PrOH to give a 67% yield of 17, mp 253.5–254.5 °C. Anal. ($C_{12}H_{15}N_3O$·HCl) C, H, N.

1-[4-(Dimethylamino)butyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one Dihydrobromide (26). Starting from 5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one, in two steps, by the procedure analogous to that for the preparation of 17, **1-(4-aminobutyl)-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one hydrochloride**, mp 188–190 °C [Anal. ($C_{14}H_{19}N_3O$·HCl) C, H, N], was prepared in 40% overall yield. Under standard conditions (formic acid–formaldehyde[12]), this derivative was bismethylated to give, after treatment with HBr and recrystallization from EtOH–Et_2O, a 45% yield of **26**, mp 222–225 °C. Anal. ($C_{16}H_{23}N_3O$·2HBr) C, H, N.

1-[2-(Methylamino)ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one Hydrochloride Hemihydrate (18). The reaction of 5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one with 2-[(benzylmethyl)amino]ethyl chloride hydrochloride was carried out by method 1 to give, after treatment with ethanolic HCl and recrystallization from *i*-PrOH, a 47% yield of **1-[2-[(benzylmethyl)amino]ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one hydrochloride**, mp 208–210 °C. Anal. ($C_{20}H_{23}N_3$·HCl) C, H, N.

This salt was debenzylated in absolute EtOH with 5% Pd/C under H_2 atmosphere and, after recrystallization from *i*-PrOH, gave a 98% yield of **18**, mp 106–109 °C. Anal. ($C_{13}H_{12}N_3O$·HCl·0.5H_2O) C, H, N.

Methiodide Salt of 1-[2-(Dimethylamino)ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one (28). Methyl iodide (1.7 g, 12 mmol) was added to a solution of **8** (2.45 g, 10 mmol) in absolute EtOH (10 mL) and stirred at room temperature for 20 min. The product precipitated upon dilution with Et_2O. Recrystallization from MeOH–Et_2O gave 2.6 g (67%) of **28**, mp 219–220 °C. Anal. ($C_{15}H_{22}IN_3O$) C, H, N.

1-[2-(Dimethylamino)ethyl]-5,7-dimethyl-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one Dihydrobromide (31). A solution of **8** (2.82 g, 10 mmol) in glacial HOAc (35 mL) containing PtO_2 (0.3 g) was hydrogenated in a Parr apparatus (24 h). After removal of the catalyst by filtration and evaporation of the solvent, the residue was treated with saturated Na_2CO_3, and the product was extracted into CH_2Cl_2 and dried (Na_2SO_4). This solution was evaporated, and the residue was taken up in Et_2O, filtered, and treated with ethanolic HBr. The collected precipitate was recrystallized from MeOH–Et_2O to give 1.2 g (30%) of **31**, mp 225–228 °C. Anal. ($C_{14}H_{21}N_3O$·2HBr) C, H, N.

1-[2-(Dimethylamino)ethyl]-5,7-dimethyl-1,8-naphthyridin-2(1*H*)-thione Hydrochloride (33). A mixture of **8** (2.5 g, 10 mmol) and P_2S_5 (2.0 g, 9 mmol) in CH_2Cl_2 (60 mL) was refluxed for 4 h. The reaction mixture was cooled and diluted with H_2O, and solid Na_2CO_3 was added. The organic layer was separated, dried (Na_2SO_4), and filtered through a pad of charcoal, and the solvent was evaporated. The residue was dissolved in Et_2O and treated with ethanolic HCl, and the collected precipitate was recrystallized from *i*-PrOH to give 1.5 g (50%) of **33**, mp 209–211 °C. Anal. ($C_{14}H_{12}N_3S$·HCl) C, H, N.

1-[2-(Dimethylamino)ethyl]-5,7-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine Dihydrochloride (32). A mixture of 2,4-dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine[13] (6.3 g, 39 mmol) and 57% NaH in mineral oil (2.4 g, 57 mmol) in dry dioxane (75 mL) was heated at reflux for 3 h. Dimethylaminoethyl chloride (7.0 g, 65 mmol) in dioxane (30 mL) was added dropwise and the reaction mixture heated for an additional 4 h. It was then cooled and cautiously quenched with H_2O. The crude product was extracted into Et_2O and then into dilute HCl. This aqueous extract was filtered through a pad of charcoal and the solution made basic with NaOH. The product was extracted into Et_2O and dried (Na_2SO_4) and the solution was concentrated to a small volume. Upon cooling the solution in an ice bath, starting material precipitated and was removed by filtration. This ethereal filtrate was treated with ethanolic HCl, and the precipitate was collected and recrystallized from MeOH–Et_2O to give 2.8 g (25%) of **32**, mp 232–234 °C. Anal. ($C_{14}H_{23}N_3$·2HCl) C, H, N.

1-[2-(Dimethylamino)ethyl]quinolin-2(1*H*)-one Hydrochloride (30). The reaction of 2-hydroxyquinoline with 2-(dimethylamino)ethyl chloride hydrochloride was carried out by method 1 to give a 28% yield of **30**, mp 240–241 °C, after recrystallization from MeOH–Et_2O. Anal. ($C_{13}H_{16}N_2O$·HCl) C, H, N.

Biological Methods. Rat Uterus. Compounds were evaluated for their ability to block the response to histamine by the isolated rat uterus. Female Charles River rats (150–200 g) were injected with diethylstilbesterol (0.16 mg/rat) 16–20 h prior to sacrifice. Single uterine horns were placed in 20 mL of McEwen's solution[14] (34 °C, 95% O_2–5% CO_2) and were electrically stimulated every 50 s for 10 s using maximal current and pulse trains of 60 Hz (1-ms duration). A contractile response was obtained in the presence of placebo or test compound alone and after the addition of histamine (20 μg/mL). Results are expressed as the percent change in the response to histamine relative to a placebo–histamine trial. The concentration of test compound

required to block the effect of histamine by 50% (EC_{50}, in μg/mL) and confidence intervals were determined by regression analysis.

Guinea Pig Atrium. The atria from guinea pigs (Hartley strain) were dissected from other myocardial tissue, suspended in 20 mL of McEwen's solution,[14] and attached to a transducer. Spontaneous rate was counted from the recorded tracing. Chronotropic responses to increasing concentrations of histamine (0.05–3.2 μg/mL) were obtained in the presence of placebo or test compound. Results are expressed as the ratio of (a) the concentration of histamine required to increase the rate by 50 beats/min in a placebo trial to (b) the concentration required in the presence of a test compound.

Dog Gastric Fistula. Nonanesthetized female beagle dogs (7–10 kg) with a chronic gastric fistula were administered test compounds directly into the stomach via the gastric cannula (identified herein as oral administration). Placebo or test compounds were administered in 50 mL of a 1% methylcellulose solution 1 h prior to stimulation of gastric secretion. Secretion was stimulated with gastrin tetrapeptide (64 μg/kg sc from a 30% Me_2SO solution containing 640 μg/mL) or histamine (64 μg of base, wt/kg sc, from a solution of histamine diphosphate, 640 μg of base, wt/mL, in physiological saline). Gastric output was collected for three consecutive 30-min periods (90 min total) after administration of the stimulant. Volume was measured and the acid concentration (titratable acid) was determined on an aliquot by titration to pH 7 with 0.01 N NaOH using a glass–calomel electrode. Results are reported as the maximal percent reduction in acid concentration following treatment relative to a placebo trial in the same animal.

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Notes

An Attempt to Apply Lethal Synthesis to the Design of Chemotherapeutic Agents. Fluorinated 5β-(Hydroxyethyl)-4-methylthiazoles

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2-Fluoro-5β-(hydroxyethyl)-4-methylthiazole (V) was prepared from 5β-acetoxy-2-amino-4-methylthiazole (X), which was prepared from 5β-acetoxy-3-chloropentanone (IX) and thiourea. Diazotization with $NOBF_4$ followed by pyrolysis gave 5β-acetoxy-2-fluoro-4-methylthiazole (XII), which on hydrolysis with $KHCO_3$ gave V. (Trifluoroacetyl)-γ-butyrolactone (XIII) was chlorinated with SO_2Cl_2 to give 2-chloro-2-(trifluoroacetyl)-γ-butyrolactone (XIV), which on hydrolysis and decarboxylation gave 3-chloro-1,1,1-trifluoro-5-hydroxy-2-pentanone which exists as the hemiketal XV. Treatment with thiourea gave 2-amino-5β-(hydroxyethyl)-4-(trifluoromethyl)thiazole (XVI), but no thiazole formation was observed when XV was treated with thioformamide. Ethyl 2-(trifluoroacetyl)-γ-methoxybutyrate (XVIII), prepared from ethyl γ-methoxybutyrate and ethyl trifluoroacetate, gave after hydrolysis and decarboxylation 5-methoxy-1,1,1-trifluoro-2-pentanone (XIX), which on bromination followed by treatment with thioformamide gave 5β-(methoxyethyl)-4-(trifluoromethyl)thiazole (XXI). Treatment of XXI with BBr_3 gave 5β-(hydroxyethyl)-4-(trifluoromethyl)thiazole (VI). Neither V nor VI showed antibacterial action against two strains of *Escherichia coli*. A rationalization of this lack of activity is discussed.

Lethal synthesis may be defined as the conversion of substrate analogues by enzymes of a metabolic pathway to an antimetabolite of either the end product of a biosynthetic sequence or an intermediate thereof. An attractive feature of using this approach in the design of chemotherapeutic agents is that by the selection of appropriate biosynthetic pathways, preferably those that are present in the target organism and absent in the host, selective toxicity may be achieved. Gale et al.[1] pointed out that the concept of lethal synthesis has not been fully exploited. These authors cite the action of fluoroacetate as a classic example of this idea. Because of its chemical and structural similarity to acetate, fluoroacetate undergoes similar biochemical transformations as the natural substrate and eventually is converted to fluorocitrate, which is an irreversible inhibitor of aconitase, the enzyme

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