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Synthesis and Histamine H_2-Antagonist Activity of 4-Quinazolinone Derivatives[1)]

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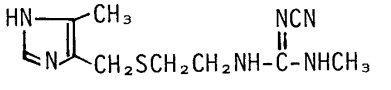
With the aim of developing new antiulcer agents, a series of 4-quinazolinone derivatives was synthesized and tested for histamine H_2-antagonist activity and gastric antisecretory activity. Thus, 2-alkylamino- (**8a**—**d**, **10a**—**s**), 2-alkylthio- (**15**), and 2-alkyl-4-quinazolinones (**18a**—**k**) were prepared by the condensation of alkylamines with 2-chloro- or 2-methylthio-4-quinazolinones, the condensation of alkyl bromides with 2-mercapto-4-quinazolinones, and the condensation of alkylcarboxylic acids with anthranilamides, respectively.

Several of the 4-quinazolinone derivatives thus synthesized showed potent H_2-antagonist activity, and one of them, 2-[3-[3-(1-piperidinylmethyl)phenoxy]propylamino]-4(3*H*)-quinazolinone (**8d**) showed the most potent antisecretory activity. The structure–activity relationships are discussed.

Keywords——4-quinazolinone derivative; antiulcer agent; histamine H_2-antagonist; H_2-antagonist activity; gastric antisecretory activity; structure–activity relationship

Cimetidine (**1**),[2)] the first antiulcer agent to exhibit histamine H_2-antagonist activity, has been widely used clinically. Subsequently many other H_2-antagonists, such as ranitidine (**2**), famotidine (**3**), and roxatidine acetate (**4a**), have been found.[3)] In these compounds, the imidazole ring of **1** has been replaced by a furan, thiazole, or benzene ring, and also the guanidine moiety of **1** has been modified so as to increase the activity and decrease the side



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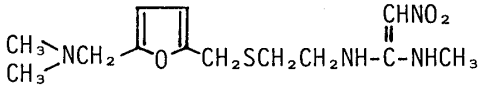

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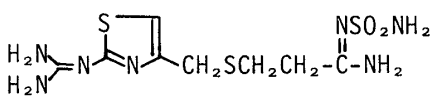

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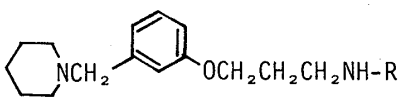
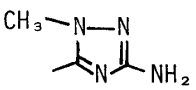
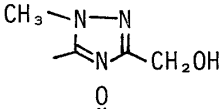
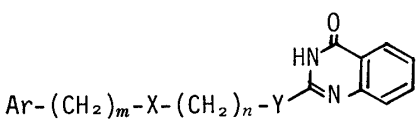


4a : R = $COCH_2OCOCH_3$

4b : R = 

4c : R = 



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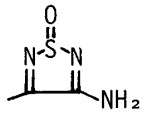
4d : R = 

Chart 1

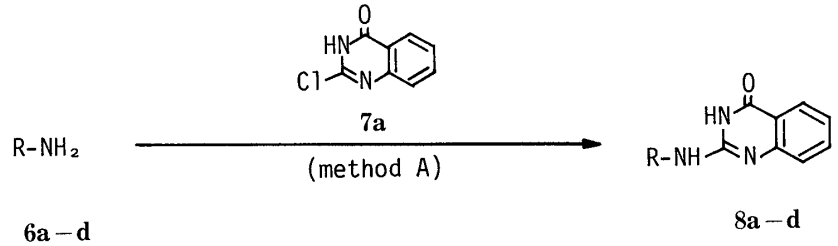
effects. Ganellin[4] has suggested that fixation of the conformation of the guanidine moiety and an increase in its lipophilicity may possibly enhance the H_2-antagonist activity. Indeed, lamtidine (**4b**), loxtidine (**4c**), L-643441 (**4d**), *etc.*, having a cyclic guanidine moiety (*e.g.* triazole or thiadiazole), exhibited potent H_2-antagonist activity.[3]

For the development of new antiulcer agents, we designed a general structure **5** containing a 4-quinazolinone ring as the new guanidine moiety. This paper describes the synthesis and pharmacological activity of **5**.

Chemistry

At first, we prepared **8a—d** (shown in Chart 2) to find the best basic structure for **5**. These compounds were obtained by the thermal condensation of amines (**6a—d**)[2,5] with 2-chloro-4(3*H*)-quinazolinone (**7a**)[6] in *n*-butanol (method A).

Next, we prepared the following analogues based on the active lead compound, **8d** (Charts 3 and 4): (1) compounds with a changed methylene chain length (**10a, b**); (2)



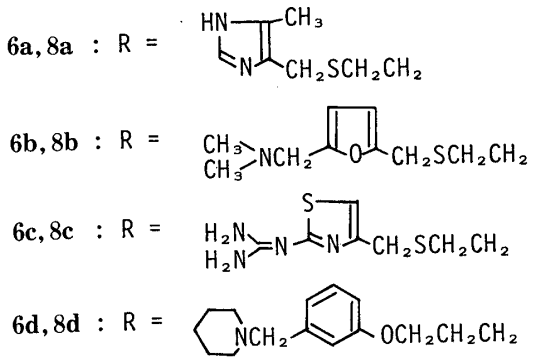


Chart 2

TABLE I. Physical and Pharmacological Data for 4-Quinazolinone Derivatives

Compd. No.	Method	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N	$-\log K_B$[a]
8a[b]	A	53.8	213—217 (aq. EtOH–ether)	$C_{15}H_{17}N_5OS \cdot 2HCl$	46.40 (46.17)	4.93 5.10	18.04 17.91)	5.18
8b	A	28.7	82—84 (AcOEt)	$C_{18}H_{22}N_4O_2S \cdot 1/2\,H_2O$	58.84 (58.61)	6.31 6.18	15.25 14.98)	6.17
8c[b]	A	20.2	193—197 (EtOH)	$C_{15}H_{17}N_7OS \cdot HCl \cdot 1/4\,H_2O$	43.26 (43.33)	4.48 4.75	23.54 23.68)	6.86
8d	A	67.2	157—158 (MeCOEt)	$C_{23}H_{28}N_4O_2$	70.38 (70.27)	7.19 7.27	14.27 14.09)	7.39
1 (Cimetidine)								6.31
2 (Ranitidine hydrochloride)								7.06

a) H_2-Antagonist activity in guinea-pig right atrium. *b*) Hydrochloride.

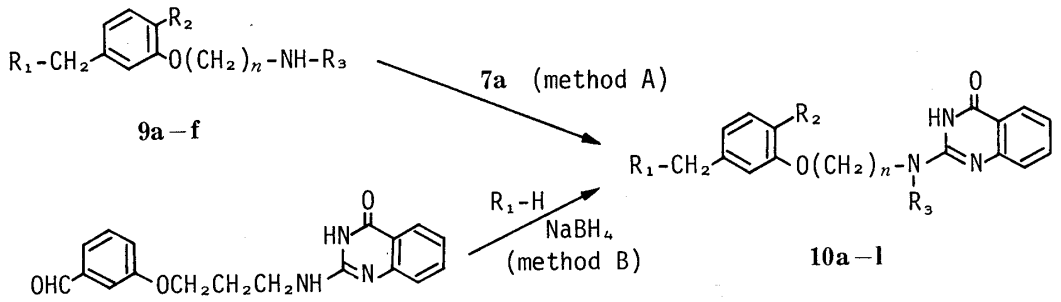
TABLE II. Physical and Pharmacological Data for 4-Quinazolinone Derivatives

Compd. No.	Method	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found)			$-\log K_B$[a]
					C	H	N	
10a	A	86.1	156—157 (AcOEt)	$C_{22}H_{26}N_4O_2$	69.82 (69.82	6.92 6.97	14.80 14.76)	5.90
10b	A	87.3	107—109 (AcOEt)	$C_{24}H_{30}N_4O_2 \cdot 1/2\,H_2O$	69.37 (69.19	7.52 7.40	13.48 13.41)	6.67
10c	A	72.9	133—135 (AcOEt)	$C_{24}H_{30}N_4O_3$	68.22 (68.00	7.16 7.28	13.26 13.21)	6.17
10d	A	90.5	153—154 (MeCOEt)	$C_{24}H_{30}N_4O_2$	70.91 (70.99	7.44 7.47	13.78 13.71)	5.19
10e	A	32.8	139—140 (AcOEt)	$C_{22}H_{26}N_4O_2$	69.82 (69.75	6.92 6.91	14.80 14.65)	7.55
10f	A	83.6	170—171 (MeOH)	$C_{18}H_{19}N_3O_2$	69.88 (69.70	6.19 6.13	13.58 13.48)	<5
10g	B	83.3	169—170 (EtOH)	$C_{18}H_{19}N_3O_3$	66.45 (66.44	5.89 5.92	12.91 12.71)	<5
10h	B	39.2	142—143 (AcOEt)	$C_{20}H_{24}N_4O_2$	68.16 (68.16	6.86 6.96	15.90 15.78)	6.47
10i	B	61.5	164.5—165.5 (MeCOEt)	$C_{24}H_{30}N_4O_2$	70.91 (70.85	7.44 7.52	13.78 13.53)	6.91
10j	B	78.7	152—153 (MeCOEt)	$C_{24}H_{30}N_4O_2$	70.91 (70.97	7.44 7.40	13.78 13.70)	7.31
10k	B	68.4	149—150 (AcOEt)	$C_{22}H_{26}N_4O_3$	66.99 (66.98	6.64 6.63	14.20 14.27)	6.91
10l	B	66.3	144—145 (AcOEt)	$C_{23}H_{29}N_5O_2$	67.79 (67.71	7.17 7.26	17.19 16.98)	5.66
10m	A	55.7	106—108 (AcOEt)	$C_{24}H_{30}N_4O_2$	70.91 (70.84	7.44 7.69	13.78 13.70)	7.15
10n	A	55.6	159—161 (AcOEt)	$C_{23}H_{27}ClN_4O_2$	64.70 (64.42	6.37 6.58	13.12 12.95)	6.48
10o	A	42.5	168—169 (AcOEt)	$C_{23}H_{27}ClN_4O_2$	64.70 (64.46	6.37 6.58	13.12 13.05)	6.96
10p	A	54.8	139—140 (AcOEt)	$C_{25}H_{32}N_4O_4$	66.35 (66.46	7.13 7.28	12.38 12.26)	6.46
10q	A	75.6	189—191 (AcOEt)	$C_{25}H_{31}N_3O_4$	68.63 (68.71	7.14 7.23	9.60 9.62)	6.43
10r	C	22.0	169—170 (EtOH)	$C_{24}H_{30}N_4O_2$	70.91 (70.90	7.44 7.28	13.78 13.62)	6.26
10s[b]	C	20.6	142—143 (H_2O)	$C_{24}H_{30}N_4O_2 \cdot 1/2\,C_4H_4O_4 \cdot H_2O$	64.71 (64.86	7.10 7.06	11.61 11.38)	5.86
15[c]	D	9.7	145—147 (EtOH)	$C_{23}H_{27}N_3O_2S \cdot HCl \cdot 2H_2O$	57.31 (57.23	6.69 6.39	9.06 8.79)	6.39
18a	E	41.1	144—145 (AcOEt)	$C_{23}H_{27}N_3O_2$	73.18 (73.06	7.21 7.26	11.13 11.02)	7.04
18b	F	45.0	160.5—162 (AcOEt)	$C_{24}H_{29}N_3O_2$	73.63 (73.58	7.47 7.50	10.73 10.67)	6.64
18c	F	28.1	121.5—122.5 (MeOH)	$C_{24}H_{29}N_3O_2$	73.63 (73.68	7.47 7.54	10.73 10.73)	5.96
18d	F	30.0	165—166 (AcOEt)	$C_{23}H_{26}ClN_3O_2$	67.06 (67.04	6.36 6.37	10.20 10.22)	6.54
18e	F	35.9	143—143.5 (MeOH)	$C_{23}H_{26}ClN_3O_2$	67.06 (67.17	6.36 6.55	10.20 10.18)	5.81
18f	F	30.8	149—150 (AcOEt)	$C_{23}H_{26}FN_3O_2$	69.85 (70.01	6.63 6.79	10.63 10.67)	6.43

TABLE II. (continued)

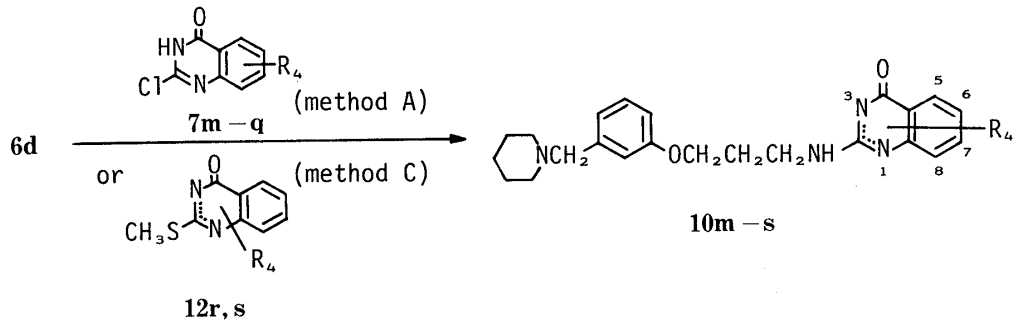
Compd. No.	Method	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N	$-\log K_B$[a)]
18g	F	56.2	174—175 (AcOEt)	$C_{24}H_{29}N_3O_2S$	68.06 (67.88	6.90 7.06	9.92 9.98)	6.03
18h	F	52.6	177—178 (MeOH)	$C_{25}H_{31}N_3O_4$	68.63 (68.71	7.14 7.23	9.60 9.62)	<5
18i	F	49.8	165—168 (EtOH)	$C_{24}H_{27}N_3O_4$	68.39 (68.65	6.46 6.53	9.97 10.01)	6.45
18j[d)]	F	44.5	162—163 (EtOH)	$C_{24}H_{29}N_3O_2 \cdot C_4H_4O_4$	66.26 (66.07	6.55 6.73	8.28 8.02)	6.32
18k	F	73.4	120—121, 136—137 (AcOEt)	$C_{24}H_{29}N_3O_2$	73.63 (73.76	7.47 7.54	10.73 10.62)	7.52

a) H_2-Antagonist activity in guinea-pig right atrium. *b*) Fumarate. *c*) Hydrochloride. *d*) Maleate.



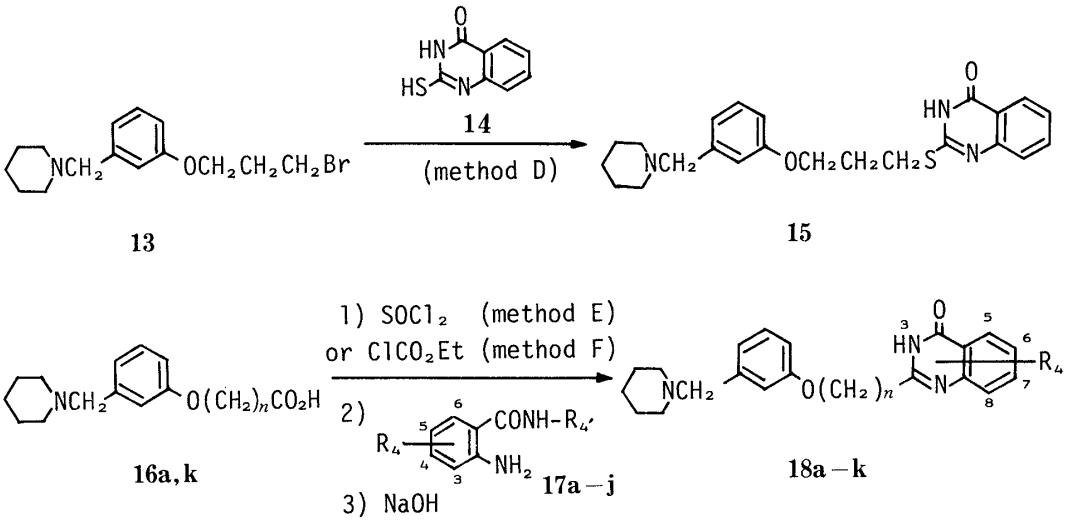
9a, 10a : R_1= pyridyl, R_2=R_3= H, n=2
9b, 10b : R_1= pyridyl, R_2=R_3= H, n=4
9c, 10c : R_1= pyridyl, R_2=OCH_3, R_3= H, n=3
9d, 10d : R_1= pyridyl, R_2= H, R_3=CH_3, n=3
9e, 10e : R_1= pyrrolidinyl, R_2=R_3= H, n=3
9f, 10f : R_1= H, R_2=R_3= H, n=3

10g : R_1=OH, R_2=R_3= H, n=3
10h : R_1=$N(CH_3)_2$, R_2=R_3= H, n=3
10i : R_1=CH_3-pyridyl, R_2=R_3= H, n=3
10j : R_1=CH_3-pyrrolidinyl, R_2=R_3= H, n=3
10k : R_1= morpholinyl, R_2=R_3= H, n=3
10l : R_1=CH_3N-piperazinyl, R_2=R_3= H, n=3



7m, 10m: R_4=6-CH_3
7n, 10n : R_4=6-Cl
7o, 10o : R_4=7-Cl
7p, 10p : R_4=6,7-di-OCH_3
7q, 10q : R_4=6,7-OCH_2O-
12r, 10r : R_4=1-CH_3
12s, 10s : R_4=3-CH_3

Chart 3



16a : n=3
16k : n=4

17a: $R_4=R_{4'}=H$
17b: R_4=5-CH_3, $R_{4'}=H$
17c: R_4=3-CH_3, $R_{4'}=H$
17d: R_4=5-Cl, $R_{4'}=H$
17e: R_4=4-Cl, $R_{4'}=H$
17f: R_4=4-F, $R_{4'}=H$
17g: R_4=5-SCH_3, $R_{4'}=H$
17h: R_4=4,5-di-OCH_3, $R_{4'}=H$
17i: R_4=4,5-OCH_2O–, $R_{4'}=H$
17j: $R_4=H$, $R_{4'}=CH_3$

18a: $n=3$, $R_4=H$
18b: $n=3$, R_4=6-CH_3
18c: $n=3$, R_4=8-CH_3
18d: $n=3$, R_4=6-Cl
18e: $n=3$, R_4=7-Cl
18f: $n=3$, R_4=7-F
18g: $n=3$, R_4=6-SCH_3
18h: $n=3$, R_4=6,7-di-OCH_3
18i: $n=3$, R_4=6,7-OCH_2O–
18j: $n=3$, R_4=3-CH_3
18k: $n=4$, $R_4=H$

Chart 4

compounds with substituents on the benzene ring or the chain NH of **8d** (**10c, d**); (3) compounds in which the piperidino group of **8d** is replaced by other groups (**10e—l**); (4) compounds with substituents on the quinazolinone ring of **8d** (**10m—s**); (5) compounds in which the chain NH group of **8d** is replaced by a thioether group (**15**); (6) compounds lacking the chain NH group of **8d**, and analogues (**18a—k**).

Compounds **10a—f** were obtained by the condensation of the corresponding amines (**9a—f**) with **7a** in a manner similar to that used for **8a—d** (method A). Compounds **10g—l** were obtained by the reduction of the aldehyde (**11**) with sodium borohydride in the presence or absence of appropriate amines in methanol (method B). Compounds **10m—s** were synthesized by the condensation of **6d** with the corresponding 2-chloro-4-quinazolinones (**7m—q**)[7] (method A) or 2-methylthio-4-quinazolinones (**12r, s**)[8] (method C). Further, **15** was obtained by the condensation of the bromide (**13**) with 2-mercapto-4(3*H*)-quinazolinone (**14**)[9] in methanol in low yield (method D). Compounds **18a—k** were obtained by the condensation of the anthranilamides (**7a—j**) with carboxylic acids (**16a, k**) pretreated with thionyl chloride (method E) or ethyl chloroformate (method F).

Among the starting materials, **9c**, **9d**, **11**, **16a**, **16k**, **17f**, and **17g** were new compounds and were synthesized as shown in Chart 5. That is, **9c** was obtained from isovanillin (**19**) *via* **20** and **21** in the usual manner. Compound **9d** was obtained by the reduction of the carbamate (**22**) derived from **6d**, with lithium aluminum hydride. For the synthesis of **11**, a key intermediate in method B, the condensation of the amine (**23**)[10] with **7a** in *n*-butanol gave **24**, which was deketalized in methanolic hydrochloric acid to give **11**. Compound **13** was obtained by reaction of **25** with excess 1,3-dibromopropane. The etherification of **25** with ethyl 4-

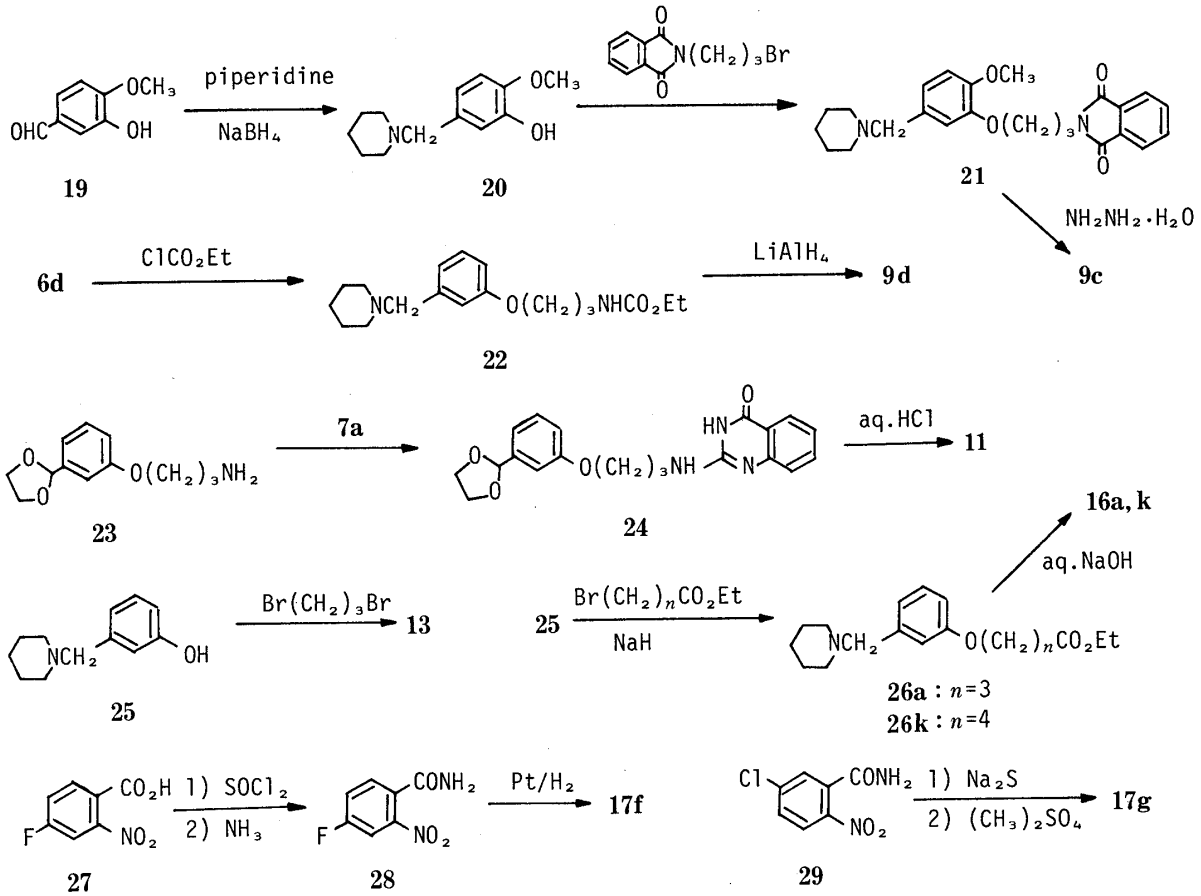


Chart 5

bromobutyrate or ethyl 5-bromovalerate in the presence of sodium hydride gave **26a**[11] or **26k**. Both were hydrolyzed with aqueous sodium hydroxide to give **16a** and **16k**, respectively. Compound **17f** was obtained by the amidation of **27**, followed by catalytic hydrogenation of the resulting **28**. Compound **17g** was obtained by treatment of **29** with sodium sulfide, followed by S-methylation with dimethyl sulfate.

Pharmacological Results and Discussion

The histamine H_2-antagonist activity of the compounds prepared was examined using excised atria from guinea-pigs, and the results are shown in Tables I and II.

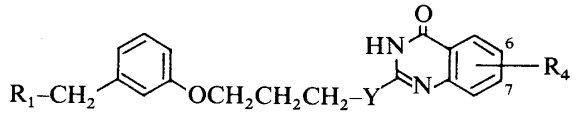
Among the four basic compounds (**8a—d**), **8d** having a benzene ring showed the highest $-\log K_B$ value (7.39), which was higher than that of ranitidine (7.06). Secondly, **8c** with a thiazole ring showed a high $-\log K_B$ value, but **8b** having a furan ring and **8a**, a imidazole ring showed low activity. From this result, it appears that the benzene ring is suitable to be used in combination with the quinazolinone moiety to bring about H_2-antagonist action. Thus, modification of **8d** was carried out.

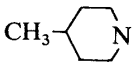
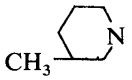
Compounds **10a, b**, in which the number of methylene groups of **8d** is changed from 3 to 2 or 4, showed lower activity than **8d**. This result indicates that three methylenes is the most suitable.

Among **10e—l**, in which the piperidino group of **8d** was changed, the activities of **10e** and **10j** having a pyrrolidinyl group and a 3-methylpiperidino group, respectively, were equal to that of **8d**, and the activities of other compounds tended to decrease with variation in amino group structure from the piperidino group. In particular, **10f** and **10g** without amino functions showed hardly any activity.

Among **10c, d, m—s**, containing various substituent groups on the structure of **8d**, the

TABLE III. Gastric Antisecretory Activity of 4-Quinazolinone Derivatives



Compd. No.	R_1	Y	R_4	$-\log K_B$[a]	Antisecretory activity[b]	
					Dose (mg/kg)	Inhibition (%)
8d		NH	H	7.39	5	82.5
					2.5	72.0
					1.25	51.1
10e		NH	H	7.55	5	71.5
					2.5	30.1
10i		NH	H	6.91	5	37.4
					2.5	29.8
10j		NH	H	7.31	5	74.7
					2.5	39.2
10k		NH	H	6.91	10	24.7
10m		NH	6-CH_3	7.15	5	68.2
					2.5	17.0
10o		NH	7-Cl	6.96	5	14.4
					2.5	−7.9
18a		—	H	7.04	10	37.2
18k		CH_2	H	7.52	10	37.2
2 (Ranitidine hydrochloride)				7.06	20	65.8
					10	42.7
					5	24.3

a) H_2-Antagonist activity in guinea-pig right atrium. *b*) Gastric antisecretory activity with intraduodenal administration in pylorus-ligated rat.

activity of **10c**, having a methoxy group on the benzene ring, and those of **10d, r, s**, each having a methyl group on the nitrogen atom of the guanidine moiety, were much less than that of **8d**. Compounds **10m—q**, with substituents at the 6 or 7 position on the quinazolinone ring, also showed less activity than **8d**, but the 6-methyl-substituted (**10m**) and 7-chloro-substituted (**10o**) compounds had relatively high activity.

Compound **15**, in which the chain NH group of **8d** is replaced by a thioether group, showed a fairly low $-\log K_B$ value.

Compound **18a**, an amidine-type compound lacking a chain NH group, showed a good $-\log K_B$ value, which was slightly less than that of **8d**. Further, the activities of **18b—j**, having substituents on the quinazolinone ring of **18a**, were lower than that of **18a**. Compound **18k**, in which the number of methylene groups is increased from 3 in **18a** to 4 showed a good $-\log K_B$ value, which was higher than that of **18a** and equal to that of **8d**.

Compounds having relatively high H_2-antagonist activity in this study were further tested for gastric antisecretory activity in pylorus-ligated rats by intraduodenal administration (Table III).

The results indicated that the compounds **8d**, **10e**, **10i**, **10j**, and **10m** had more potent antisecretory activity than ranitidine. It is particularly interesting that the most potent compound **8d** has the same benzene ring moiety as lamtidine (**4b**) has. On the other hand, **18a** and **18k** lacking a chain NH group failed to show potent antisecretory activity in spite of their high H_2-antagonist activity. This is probably due to factors such as differences in absorption rates from the intestinal canal, metabolic rates, and affinity for organs.

Thus, in this study, some 4-quinazolinone derivatives exhibiting high H_2-antagonist activity and potent gastric antisecretory activity were found. Among them, **8d** (ED_{50}: 0.9 mg/kg) was the most potent antisecretory compound, being 10 times more potent than ranitidine (ED_{50}: 12.3 mg/kg). Evaluation of **8d** (code name: NO-794) as an antiulcer agent is in progress.[12]

Experimental

All melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-202, mass spectra (MS) with a Hitachi RMU-6M, and proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL FX-90Q, using tetramethylsilane as an internal standard.

Preparation by Method A: 2-[3-[3-(1-Piperidinylmethyl)phenoxy]propylamino]-4(3*H*)-quinazolinone (8d)——A solution of 3-[3-(1-piperidinylmethyl)phenoxy]propylamine (**6d**,[5c] 2.48 g) and 2-chloro-4(3*H*)-quinazolinone (**7a**,[6] 1.99 g) in *n*-BuOH (15 ml) was refluxed for 3 h and then evaporated. The residue was acidified with aqueous (aq.) HCl and washed with $CHCl_3$. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was recrystallized from MeCOEt to give **8d** (2.64 g, 67.2%) as pale yellow crystals.

Compounds **8a**—**c**, **10a**—**f** and **10m**—**q** were also prepared in the same manner. The results are shown in Tables I, II and IV.

Preparation by Method B: 2-[3-[3-(1,3-Dioxolan-2-yl)phenoxy]propylamino]-4(3*H*)-quinazolinone (24)——A solution of 3-[3-(1,3-dioxolan-2-yl)phenoxy]propylamine (**23**,[10] 2.50 g), **6d** (2.02 g) and NEt_3 (2.26 g) in *n*-BuOH was heated at 100 °C for 1 h with stirring and then evaporated. The residue was recrystallized from MeOH to give **24** (3.41 g, 79.1%) as colorless crystals, mp 194—196 °C. *Anal.* Calcd for $C_{20}H_{21}N_3O_4 \cdot H_2O$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.19; H, 5.75; N, 10.78. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO). MS *m/z*: 367 (M^+). ^{1}H-NMR (in CD_3OD) δ: 2.12 (2H, quintet, J=6.5 Hz, $OCH_2C\underline{H}_2CH_2N$), 3.63 (2H, t, J=6.5 Hz, $OCH_2CH_2C\underline{H}_2N$), 5.65 (1H, s, CH).

2-[3-(3-Formylphenoxy)propylamino]-4(3*H*)-quinazolinone (11)——A suspension of **24** (2.50 g) in MeOH (150 ml) was stirred with 10% aq. HCl (15 ml) at room temperature for 0.5 h and then evaporated. The residue was made alkaline with aq. NaOH and extracted with AcOEt. The extract was washed with H_2O, dried and evaporated. The residue was recrystallized from AcOEt to give **11** (1.58 g, 68.6%) as colorless crystals, mp 141—142 °C. *Anal.* Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.61; H, 5.30; N, 12.77. IR ν_{max}^{KBr} cm^{-1}: 1690 (CO). MS *m/z*: 323 (M^+). ^{1}H-NMR (in CD_3OD) δ: 2.15 (2H, quintet, J=6 Hz, $OCH_2C\underline{H}_2CH_2N$), 3.65 (2H, t, J=6 Hz, $OCH_2CH_2C\underline{H}_2N$), 4.17 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2N$), 9.86 (1H, s, CHO).

2-[3-[3-[(4-Methyl-1-piperidinyl)methyl]phenoxy]propylamino]-4(3*H*)-quinazolinone (10i)——A solution of **11** (646 mg) and 4-methylpiperidine (396 mg) in MeOH (15 ml) was heated at 50 °C for 1 h with stirring. The solution was cooled, $NaBH_4$ (151 mg) was added, and the reaction mixture was stirred at room temperature for 0.5 h and then evaporated. The residue was taken up in H_2O and the mixture was extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on Al_2O_3 with $CHCl_3$–MeOH (100 : 3) to give **10i** (500 mg, 61.5%), which was recrystallized from MeCOEt as colorless crystals.

Compounds **10g, h** and **10j**—**l** were also prepared in the same manner. The results are shown in Tables II and IV.

Preparation by Method C: 1-Methyl-2-[3-[3-(1-piperidinylmethyl)phenoxy]propylamino]-4(1*H*)-quinazolinone (10r)——A mixture of **6d** (2.00 g) and 1-methyl-2-methylthio-4(1*H*)-quinazolinone (**12r**,[8a] 2.50 g) was heated at 200—230 °C for 0.5 h with stirring. The reaction mixture was cooled, aq. HCl was added, and the whole was washed with $CHCl_3$. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (20 : 1) to give pale yellow crystals (**10r**), which were recrystallized from EtOH as pale yellow prisms (0.72 g, 22.0%). The physical properties are shown in Tables II and IV.

3-Methyl-2-[3-[3-(1-piperidinylmethyl)phenoxy]propylamino]-4(3*H*)-quinazolinone Fumarate (10s)——A mixture of **6d** (1.91 g) and 3-methyl-2-methylthio-4(3*H*)-quinazolinone (**12s**,[8b] 2.00 g) was treated according to the same procedure as that described for **10r** to give a pale yellow oil, which was converted to the fumarate in the usual way and recrystallized from H_2O as pale yellow prisms (**10s**, 0.75 g, 20.6%). The physical properties are shown in Tables II and IV.

TABLE IV. Spectral Data for 4-Quinazolinone Derivatives

Compd. No.	MS m/z	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR[a] δ	Solv.[b]
8a[c]	315 (M^+)	1712, 1680 (CO)	2.30 (3H, s, CH_3), 2.73 (2H, t, J=7 Hz, SCH_2CH_2N), 3.72 (2H, t, J=7 Hz, SCH_2CH_2N), 3.96 (2H, s, $ArCH_2S$), 7.94 (1H, dd, J=8, 1 Hz, Qu-H_5), 8.95 (1H, s, imidazole-H)	D
8b	358 (M^+)	1693 (CO)	2.31 (6H, s, $NCH_3\times2$), 2.87 (2H, t, J=6 Hz, SCH_2CH_2N), 3.44 (2H, s, NCH_2Ar), 3.75 (2H, s, $ArCH_2S$), 6.12 (2H, s, furan-H), 8.08 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
8c[c]	375 (M^+)	1700 (CO)	2.75 (2H, t, J=6.5 Hz, SCH_2CH_2N), 3.85 (2H, s, $ArCH_2S$), 7.90 (2H, d, J=8 Hz, Qu-H_5)	D
8d	392 (M^+)	1670 (CO)	3.39 (2H, s, NCH_2Ph), 4.11 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 7.99 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10a	378 (M^+)	1670 (CO)	3.39 (2H, s, NCH_2Ph), 4.22 (2H, t, J=5 Hz, OCH_2CH_2N), 8.06 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10b	406 (M^+)	1675 (CO)	3.43 (2H, s, NCH_2Ph), 4.00 (2H, t like, $OCH_2CH_2CH_2$), 8.05 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10c	422 (M^+)	1670 (CO)	3.36 (2H, s, NCH_2Ph), 3.88 (3H, s, OCH_3), 4.27 (2H, t, J= 6 Hz, $OCH_2CH_2CH_2N$), 8.04 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10d	406 (M^+)	1675 (CO)	3.26 (3H, s, CH_3), 3.42 (2H, NCH_2Ph), 3.85 (2H, t, J=7 Hz, $OCH_2CH_2CH_2N$), 4.11 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.01 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10e	378 (M^+)	1670 (CO)	2.16 (2H, quintet, J=6 Hz, $OCH_2CH_2CH_2N$), 3.55 (2H, s, NCH_2Ph), 4.12 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.00 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10f	309 (M^+)	1655 (CO)	2.16 (2H, quintet, J=6 Hz, $OCH_2CH_2CH_2N$), 2.29 (3H, s, CH_3), 3.66 (2H, t, J=6.5 Hz, $OCH_2CH_2CH_2N$), 4.11 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.03 (1H, dd, J=8, 1 Hz, Qu-H_5)	C+M
10g	325 (M^+)	1670 (CO)	2.15 (2H, quintet, J=6 Hz, $OCH_2CH_2CH_2N$), 3.65 (2H, t, J= 6.5 Hz, $OCH_2CH_2CH_2N$), 4.12 (2H, t, J=6 Hz, $OCH_2CH_2CH_2$-N), 4.59 (2H, s, $HOCH_2Ph$), 8.02 (1H, dd, J=8, 1 Hz, Qu-H_5)	C+M
10h	352 (M^+)	1670 (CO)	2.19 (6H, s, $NCH_3\times2$), 3.34 (2H, s, NCH_2Ph), 4.11 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 7.99 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10i	406 (M^+)	1670 (CO)	0.92 (3H, m, CH_3), 3.44 (2H, s, NCH_2Ph), 4.14 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.02 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10j	406 (M^+)	1670 (CO)	0.81 (3H, d, J=6 Hz, CH_3), 2.19 (2H, quintet, J=6 Hz, OCH_2-CH_2CH_2N), 3.44 (2H, s, NCH_2Ph), 4.15 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.02 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
10k	394 (M^+)	1670 (CO)	2.19 (2H, quintet, J=6 Hz, $OCH_2CH_2CH_2N$), 3.44 (2H, s, NCH_2Ph), 4.14 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.00 (1H, dd, J=8, 1.5 Hz, Qu-H_5)	C
10l	407 (M^+)	1670 (CO)	2.67 (3H, s, CH_3), 2.43 (8H, s, piperazine-H), 3.43 (2H, s, NCH_3), 4.13 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 8.00 (1H, dd, J=8, 1.5 Hz, Qu-H_5)	C
10m	406 (M^+)	1680 (CO)	2.27 (3H, s, CH_3), 3.39 (2H, s, NCH_2Ph), 4.13 (2H, t, J=5.5 Hz, $OCH_2CH_2CH_2N$), 7.81 (1H, s, Qu-H_5)	C
10n	428, 426 (1 : 3, M^+)	1680 (CO)	2.00 (2H, quintet, J=6.5 Hz, $OCH_2CH_2CH_2N$), 3.36 (2H, s, NCH_2Ph), 4.04 (2H, t, J=6.5 Hz, $OCH_2CH_2CH_2N$), 7.22 (1H, d, J=9 Hz, Qu-H_8), 7.54 (1H, dd, J=9, 2.5 Hz, Qu-H_7), 7.79 (1H, d, J=2.5 Hz, Qu-H_5)	D
10o	428, 426 (1 : 3, M^+)	1670 (CO)	2.00 (2H, quintet, J=6.5 Hz, $OCH_2CH_2CH_2N$), 3.37 (2H, s, NCH_2Ph), 4.05 (2H, t, J=6.5 Hz, $OCH_2CH_2CH_2N$), 7.07 (1H, dd, J=8.5, 2 Hz, Qu-H_6), 7.18 (1H, d, J=2 Hz, Qu-H_8), 7.85 (1H, d, J=8.5 Hz, Qu-H_5)	D
10p	452 (M^+)	1670 (CO)	3.37 (2H, s, NCH_2Ph), 3.86 (6H, s, $OCH_3\times2$), 4.14 (2H, t, J= 5.5 Hz, $OCH_2CH_2CH_2N$), 7.34 (2H, s, Qu-$H_{5,8}$)	C

TABLE IV. (continued)

Compd. No.	MS m/z	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR[a] δ	Solv.[b]
10q	436 (M^+)	1662 (CO)	2.13 (2H, quintet, J=6.5 Hz, $OCH_2C\underline{H}_2CH_2N$), 3.45 (2H, s, $NC\underline{H}_2Ph$), 3.62 (2H, t, J=6.5 Hz, $OCH_2CH_2C\underline{H}_2N$), 4.11 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2N$), 6.02 (2H, s, OCH_2O), 6.79 (1H, s, Qu-H_8), 7.36 (1H, s, Qu-H_5)	C+M
10r	406 (M^+)	1630 (CO)	2.14 (2H, quintet, J=5.5 Hz, $OCH_2C\underline{H}_2CH_2N$), 3.42 (2H, s, $NC\underline{H}_2Ph$), 3.59 (2H, s, NCH_3), 3.76 (2H, q, J=5.5 Hz, OCH_2-$CH_2C\underline{H}_2N$), 8.26 (1H, dd, J=7.5, 1.5 Hz, Qu-H_5)	C
10s[d]	406 (M^+)	1680 (CO)	2.12 (2H, quintet, J=6 Hz, $OCH_2C\underline{H}_2CH_2N$), 3.21 (2H, s, $NC\underline{H}_2Ph$), 3.44 (3H, s, NCH_3), 3.62 (2H, t, J=6 Hz, OCH_2-$CH_2C\underline{H}_2N$), 4.11 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2N$), 6.62 (1H, s, fumarate-H), 7.92 (1H, dd, J=8, 2 Hz, Qu-H_5)	D
15[c]	409 (M^+)	1710 (CO)	2.32 (2H, quintet, J=6 Hz, $OCH_2C\underline{H}_2CH_2S$), 3.66 (2H, t, J=6 Hz, $OCH_2CH_2C\underline{H}_2S$), 4.22 (2H, s, $NC\underline{H}_2Ph$), 4.22 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2S$), 8.15 (1H, dd, J=8, 1 Hz, Qu-H_5)	M
18a	377 (M^+)	1672 (CO)	3.00 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.41 (2H, s, $NC\underline{H}_2Ph$), 4.15 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 8.28 (1H, d, J=7.5 Hz, Qu-H_5)	C
18b	391 (M^+)	1675 (CO)	2.49 (3H, s, CH_3), 2.98 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.37 (2H, s, $NC\underline{H}_2Ph$), 4.14 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 8.08 (1H, s, Qu-$H_5$)	C
18c	391 (M^+)	1682, 1668 (CO)	2.61 (3H, s, CH_3), 3.00 (2H, t, J=7 Hz, $OC\underline{H}_2CH_2CH_2$), 3.38 (2H, s, $NC\underline{H}_2Ph$), 4.16 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 8.13 (1H, dd, J=8, 1 Hz, Qu-H_5)	C
18d	413, 411 (1:3, M^+)	1680 (CO)	2.98 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.36 (2H, s, $NC\underline{H}_2Ph$), 4.14 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 8.23 (1H, s, Qu-$H_5$)	C
18e	413, 411 (1:3, M^+)	1660 (CO)	2.98 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.37 (2H, s, $NC\underline{H}_2Ph$), 4.13 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 7.39 (1H, dd, J=8.5, 2 Hz, Qu-H_6), 7.69 (1H, d, J=2 Hz, Qu-H_8), 8.19 (1H, d, J=8.5 Hz, Qu-H_5)	C
18f	395 (M^+)	1680 (CO)	2.99 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.37 (2H, s, $NC\underline{H}_2Ph$), 4.13 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 8.28 (1H, dd, J=9, 6 Hz, Qu-H_5)	C
18g	423 (M^+)	1675 (CO)	2.56 (3H, s, SCH_3), 2.97 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.38 (2H, s, $NC\underline{H}_2Ph$), 4.13 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 8.05 (1H, s, Qu-$H_5$)	C
18h	437 (M^+)	1672 (CO)	2.98 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.38 (2H, s, $NC\underline{H}_2Ph$), 3.98, 4.00 (each 3H, s, OCH_3), 4.13 (2H, t, J=6 Hz, $OC\underline{H}_2$-CH_2CH_2), 7.11 (1H, s, Qu-H_8), 7.59 (1H, s, Qu-H_5)	C
18i	421 (M^+)	1660 (CO)	2.95 (2H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_2$), 3.38 (2H, s, $NC\underline{H}_2Ph$), 4.12 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2$), 6.10 (2H, s, OCH_2O), 7.05 (1H, s, Qu-H_8), 7.57 (1H, s, Qu-H_5)	C
18j[e]	391 (M^+)	1662 (CO)	2.36 (2H, quintet, J=7 Hz, $OCH_2C\underline{H}_2CH_2$), 3.65 (3H, s, NCH_3), 4.20 (2H, s, $NC\underline{H}_2Ph$), 4.20 (2H, t, J=6 Hz, $OC\underline{H}_2$-CH_2CH_2), 6.23 (2H, s, maleate-H), 8.15 (1H, dd, J=8, 1 Hz, Qu-H_5)	M
18k	391 (M^+)	1680 (CO)	2.89 (2H, t, J=7 Hz, $OCH_2CH_2CH_2C\underline{H}_2$), 3.40 (3H, s, $NC\underline{H}_2Ph$), 4.05 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2CH_2CH_2$), 8.26 (1H, d, J=8 Hz, Qu-H_5)	C

a) Ph, benzene ring; Qu, quinazolinone ring. *b*) D, DMSO-d_6; C, $CDCl_3$; M, CD_3OD. *c*) Hydrochloride. *d*) Fumarate. *e*) Maleate.

Preparation by Method D: 1-[3-(3-Bromopropoxy)benzyl]piperidine (13)——A solution of 3-(1-piperidinylmethyl)phenol (**25**,[5c] 1.91 g) and 1,3-dibromopropane (8.08 g) in MeOH was refluxed with 20% aq. NaOH (4 ml) for 4 h and then evaporated. The residue was acidified with aq. HCl and washed with ether. The aqueous layer was

made alkaline with aq. NaOH and extracted with ether. The extract was washed with H_2O, dried, and evaporated to give **13** (1.55 g, 49.6%) as a colorless oil. MS *m/z*: 313, 311 (M^+, 1 : 1). ^{1}H-NMR (in $CDCl_3$) δ: 3.44 (2H, s, NCH_2), 3.60 (2H, t, J=6.5 Hz, $OCH_2CH_2\underline{CH_2}Br$), 4.90 (3H, t, J=6 Hz, $O\underline{CH_2}CH_2CH_2Br$).

This product (**13**) was used for the next reaction without further purification because of its instability.

2-[3-[3-(1-Piperidinylmethyl)phenoxy]propylthio]-4(3*H*)-quinazolinone Hydrochloride (15)——A mixture of **13** (2.00 g), 2-mercapto-4(3*H*)-quinazolinone (**14**,[9] 1.14 g), and K_2CO_3 (0.88 g) in MeOH (50 ml) was refluxed for 7 h and evaporated. The residue was acidified with aq. HCl and washed with AcOEt. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated to give a pale yellow oil, which was converted to the hydrochloride in the usual way and then recrystallized from EtOH as colorless crystals (**15**, 0.30 g, 9.7%). The physical properties are shown in Tables II and IV.

Preparation by Method E: 4-[3-(1-Piperidinylmethyl)phenoxy]butyric Acid (16a)——A solution of ethyl 4-[3-(1-piperidinylmethyl)phenoxy]butyrate (**26a**,[11] 15.4 g) in MeOH was refluxed with 20% aq. NaOH (20 ml) for 20 min. The reaction mixture was adjusted to pH 7 with aq. HCl and evaporated. The residue was dissolved in $CHCl_3$ and the solution was filtered. The filtrate was evaporated to give **16a** (15.0 g, quantitative) as a pale yellow viscous oil. MS *m/z*: 277 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 3.87 (2H, s, NCH_2), 4.04 (2H, t, J=6 Hz, $O\underline{CH_2}CH_2CH_2$).

2-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl-4(3*H*)-quinazolinone (18a)——A mixture of **16a** (2.00 g) and $SOCl_2$ (5 ml) was refluxed for 1 h and then evaporated. The residue was dissolved in benzene and evaporated again. A solution of the residue in CH_2Cl_2 (20 ml) was added dropwise to a solution of anthranilamide (**17a**, 0.98 g) and NEt_3 (1.45 g) in CH_2Cl_2 (20 ml). The reaction mixture was stirred for 0.5 h at room temperature and washed with aq. K_2CO_3. The organic layer was washed with H_2O, dried, and evaporated to give a brown viscous oil (2.78 g). A solution of the obtained oil in MeOH (40 ml) was refluxed with 10% aq. NaOH (2.9 ml) for 0.5 h and evaporated. The residue was dissolved in aq. HCl and the solution was washed with AcOEt. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated. The residue was recrystallized from AcOEt to give **18a** (1.12 g, 41.1%) as pale yellow plates. The physical properties are shown in Tables II and IV.

Preparation by Method F: 6-Methyl-2-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-4(3*H*)-quinazolinone (18b)——To a solution of **16a** (1.39 g) and NEt_3 (0.71 g) in dry tetrahydrofuran (THF, 25 ml) was added $ClCO_2Et$ (0.54 g), and the mixture was stirred at room temperature for 15 min. Next, 5-methylanthranilamide (**17b**, 0.75 g) was added, and the mixture was refluxed for 1 h. Further, MeOH (10 ml) and 10% aq. NaOH (4 ml) were added to the reaction mixture, and the whole was refluxed for 0.5 h and then evaporated. The residue was dissolved in aq. HCl and the solution was washed with AcOEt. The aqueous layer was made alkaline with K_2CO_3 to give a precipitate, which was recrystallized from AcOEt as colorless needles (**18b**, 0.88 g, 45.0%).

Compounds **18c**—**k** were also prepared in the same manner. The results are shown in Tables II and IV.

Preparation of Starting Material: 2-Methoxy-5-(1-piperidinylmethyl)phenol (20)——To a solution of isovanillin (**19**, 7.61 g) and piperidine (5.95 g) in MeOH (50 ml) was added $NaBH_4$ (2.84 g) in small portions under cooling, and the reaction mixture was stirred at room temperature for 1.5 h and then evaporated. To the residue was added a solution of NH_4Cl (5.35 g) in H_2O to give a precipitate, which was recrystallized from MeOH as colorless columns (**20**, 4.99 g, 45.1%), mp 119—121 °C. *Anal.* Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.37; H, 8.80; N, 6.20. MS *m/z*: 221 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 1.17—1.74 (6H,m, piperidine-$CH_2\times3$), 2.21—2.50 (4H, m, piperidine-$CH_2\times2$), 3.38 (2H, s, NCH_2), 3.86 (3H, s, OCH_3), 4.81 (1H, br, OH), 6.70—6.91 (3H, m, Ar-H).

N-**[3-[2-Methoxy-5-(1-piperidinylmethyl)phenoxy]propyl]phthalimide (21)**——A mixture of **20** (4.00 g), *N*-bromopropylphthalimide (6.27 g) and K_2CO_3 (3.23 g) in *N*,*N*-dimethylformamide (20 ml) was heated at 80 °C for 12 h with stirring. Water was added to the cooled reaction mixture, and the whole was extracted with AcOEt. The extract was further extracted with aq. HCl. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to give **21** (2.70 g, 36.7%) as a pale yellow viscous oil. IR ν_{max}^{liq} cm^{-1}: 1775, 1710 (CO). MS *m/z*: 408 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 3.38 (2H, s, NCH_2), 3.71 (3H, s, OCH_3), 3.91 (2H, t, J=7 Hz, $OCH_2CH_2\underline{CH_2}N$), 4.10 (2H, t, J=6.5 Hz, $O\underline{CH_2}CH_2CH_2N$).

3-[2-Methoxy-5-(1-piperidinylmethyl)phenoxy]propylamine (9c)——To a solution of **21** (2.50 g) in EtOH (20 ml) was added 90% $NH_2NH_2\cdot H_2O$ (4 ml), and the mixture was heated at 50 °C for 1 h. The precipitate was filtered off and the filtrate was evaporated. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O. The organic layer was dried and evaporated to give **9c** (1.51 g, 88.7%) as a colorless oil. MS *m/z*: 278 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 1.49 (2H, s, NH_2, disappeared on addition of D_2O), 1.97 (2H, quintet, J=6.5 Hz, $OCH_2\underline{CH_2}CH_2N$), 2.93 (2H, t, J=6.5 Hz, $OCH_2CH_2\underline{CH_2}N$), 3.39 (2H, s, NCH_2), 3.84 (3H, s, OCH_3), 4.12 (2H, t, J=6 Hz, $O\underline{CH_2}CH_2CH_2N$).

Ethyl *N*-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]carbamate (22)——To a solution of **6d** (3.72 g) in EtOH (20 ml) was added 10% aq. NaOH (16 ml) and $ClCO_2Et$, and the mixture was stirred at room temperature for 1 h and then evaporated. The residue was dissolved in ether and the solution was washed with H_2O. The organic layer was dried and evaporated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to give **22** (4.78 g, 99.6%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 3350 (NH), 1700 (CO). MS *m/z*: 320 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 1.98 (2H, quintet, J=6 Hz, $OCH_2\underline{CH_2}CH_2N$), 3.38 (2H, q, J=6 Hz, $OCH_2CH_2\underline{CH_2}N$), 3.44 (2H, s,

NCH_2), 4.03 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 4.11 (2H, q, J=7 Hz, OCH_2CH_3), 4.97 (1H, br, NH), 7.21 (1H, t, J=8 Hz, Ar-H_5).

***N*-Methyl-3-[3-(1-piperidinylmethyl)phenoxy]propylamine (9d)**——To a suspension of $LiAlH_4$ (1.06 g) in dry THF was added dropwise a solution of **22** (4.50 g) in dry THF (50 ml), and the reaction mixture was refluxed for 5 h. The excess hydride was decomposed with H_2O, and the precipitate was filtered off. The filtrate was evaporated and the residue was distilled to give **9d** (3.10 g, 84.5%) as a colorless oil, bp 168—171 °C (2 mmHg). MS m/z: 262 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 1.93 (1H, s, NH, disappeared by addition of D_2O), 1.96 (2H, quintet, J=6 Hz, $OCH_2CH_2CH_2N$), 2.45 (3H, s, NCH_3), 2.77 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 3.43 (2H, s, NCH_2), 4.04 (2H, t, J=6 Hz, $OCH_2CH_2CH_2N$), 7.20 (1H, t, J=8 Hz, Ar-H_5).

Ethyl 5-[3-(1-Piperidinylmethyl)phenoxy]valerate (26k)——To a solution of 3-(1-piperidinylmethyl)phenol (**25**, 1.91 g) in dry dimethyl sulfoxide (12 ml) was added 60% NaH (0.52 g), and the mixture was stirred at room temperature for 0.5 h. Next, ethyl 5-bromovalerate (2.72 g) was added, and the mixture was stirred at room temperature for 1 h. Water was added, and the whole was extracted with AcOEt. The extract was further extracted with aq. HCl. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated to give **26k** (2.91 g, 91.2%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 1735 (CO). MS m/z: 319 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 3.43 (2H, s, NCH_2), 3.97 (2H, t, J=6 Hz, OCH_2CH_2), 4.13 (2H, q, J=7 Hz, OCH_2CH_3), 7.20 (1H, t, J=8 Hz, Ar-H_5).

5-[3-(1-Piperidinylmethyl)phenoxy]valeric Acid (16k)——A solution of **26k** (1.29 g) in MeOH (10 ml) was refluxed with 20% aq. NaOH (1.5 ml) for 20 min. The reaction mixture was neutralized with aq. HCl and evaporated. The residue was dissolved in $CHCl_3$ and the solution was filtered. The filtrate was evaporated to give **16k** (1.65 g, quantitative) as a pale yellow viscous oil. MS m/z: 291 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 3.94 (2H, NCH_2), 4.01 (2H, t, J=6.5 Hz, OCH_2CH_2).

4-Fluoro-2-nitrobenzamide (28)——To a suspension of 4-fluoro-2-nitrobenzoic acid (**27**, 2.00 g) in benzene (5 ml) was added dropwise $SOCl_2$ (2.6 ml), and the mixture was refluxed for 3.5 h and then evaporated. The residue was poured into 28% aq. NH_3 (10 ml) to give a precipitate, which was recrystallized from AcOEt–ether as colorless needles (**28**, 1.40 g, 64.3%), mp 152.5 °C. *Anal.* Calcd for $C_7H_5FN_2O_3$: C, 45.66; H, 2.74; N, 15.21. Found: C, 45.57; H, 2.96; N, 15.32. IR ν_{max}^{KBr} cm^{-1}: 3400, 3200 (NH_2), 1680 (CO). MS m/z: 184 (M^+).

2-Amino-4-fluorobenzamide (17f)——A solution of **28** (1.30 g) in MeOH was hydrogenated over PtO_2 (0.13 g) at atmospheric pressure and room temperature. The catalyst was filtered off, and the filtrate was evaporated to give **17f** (1.10 g, quantitative), which was recrystallized from benzene as colorless needles, mp 132 °C. *Anal.* Calcd for $C_7H_7FN_2O$: C, 54.54; H, 4.58; N, 18.17. Found: C, 54.45; H, 4.71; N, 18.16. IR ν_{max}^{KBr} cm^{-1}: 3400, 3350, 3190 (NH_2), 1665 (CO). MS m/z: 154 (M^+).

2-Amino-5-methylthiobenzamide (17g)——To a solution of 2-nitro-5-chlorobenzamide (**29**, 6.10 g), 20% aq. NaOH (7 ml), and H_2O (70 ml) in MeOH (90 ml) was added a solution of Na_2S (27.0 g) in H_2O (20 ml), and the mixture was heated at 50 °C for 5 min with stirring. Next, 20% aq. NaOH (6 ml) was added and $(CH_3)_2SO_4$ (6 ml) was added dropwise, then the reaction mixture was refluxed for 2 h. The MeOH was evaporated off to give a precipitate, which was recrystallized from AcOEt as colorless needles (**17g**, 2.20 g, 39.7%), mp 139—140.5 °C. *Anal.* Calcd for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.60; H, 5.70; N, 15.19. IR ν_{max}^{KBr} cm^{-1}: 3460, 3380 (NH_2), 1650 (CO). MS m/z: 182 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 2.38 (3H, s, CH_3), 6.70 (1H, d, J=8.5 Hz, Ar-H_3), 7.24 (1H, dd, J=8.5, 2 Hz, Ar-H_4), 7.57 (1H, d, J=2 Hz, Ar-H_6).

Pharmacological Test: Histamine H_2-Antagonist Activity——Right atria isolated from male Hartley guinea-pigs were suspended in a 10 ml bath containing Krebs–Henseleit solution at 31 °C gassed with 95% O_2–5% CO_2. A cumulative dose–response curve was determined for increases in spontaneous contraction frequency elicited by histamine alone or in the presence of test compounds. The test compounds were added to the bath at 10 min before the addition of histamine. Response curves were plotted as percent of maximal response against log concentration of histamine. Dose ratios were calculated at the level of the 50% response. Estimates of the dissociation constants (K_B) were made by the method of Furchgott[13] from the formula K_B = concentration of antagonist/dose ratio − 1. Parallel shifts in dose–response curves were obtained without depressing the maximal response at the antagonist concentrations utilized.

Gastric Antisecretory Activity——According to the method of Shay *et al.*,[14] pylorus-ligated rats were prepared from male Wistar rats (about 250 g) fasted for 24 h. The test compounds were administered intraduodenally immediately after ligation. At 4 h after ligation, the gastric juice was collected and its volume was measured. Acid concentration was determined by titrating the gastric juice to pH 7.0 with 0.05 N aq. NaOH. The results are expressed in terms of percent inhibition.

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