Studies on Antiulcer Agents. IV.[1] Antiulcer Effects of 2-Benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones and Related Compounds

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Received May 8, 1995; accepted August 11, 1995

With a view to finding more effective antiulcer agents, a series of 2-benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones and related compounds were synthesized and evaluated in a histamine-stimulated gastric secretion model. The sodium salt of the 2-(dimethylamino)benzylthio derivative (8) showed gastric mucosal protection and gastric antisecretion activities, and was also effective against experimental gastric and duodenal ulcers induced by some ulcerogenic agents. Based on a comparison of the antiulcer properties of 8 with those of the lead compounds (1 and 2) and cimetidine, it appears that, for improvement of antiulcer activity, the reduction of gastric acidity is a more important factor than the reduction of gastric volume output or gastric total acid output.

Key words antiulcer agent; 5,6,7,8-tetrahydro-4(3*H*)-quinazolinone; gastric mucosal protection; gastric antisecretion; structure–activity relationship; gastric acidity

We are seeking to develop a new type of antiulcer agent possessing both gastric mucosal protection and gastric antisecretion activities. In preceding papers, we have reported the antiulcer properties of 1,6-dihydro-2-[2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylic acid[2] (**1**) and ethyl 2-[(1*H*-benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidinecarboxylate[3] (**2**). These agents, although significantly active against ethanol-induced gastric lesions and water-immersion stress-induced gastric ulcer in rats, lacked satisfactory activities against indomethacin-induced gastric ulcer and mepirizole-induced duodenal ulcer in rats. Therefore, we are searching for superior antiulcer agent.

Generally, it has been thought that the reduction of gastric acid is the most important factor for the treatment of peptic ulcers, and potent antisecretory drugs such as histamine H_2-antagonists and H^+/K^+-ATPase inhibitors are frequently employed in clinical practice. Antisecretory activity is usually estimated in terms of inhibition of total acid output (TAO) calculated from the reduction of acidity and that of volume output of gastric juice secreted. Compounds **1** and **2** potently suppressed TAO in basal and histamine-stimulated secretion in rats, respectively, mainly through a marcked reduction of gastric volume output. Thus, we were interested in a new type of antiulcer agent which would inhibit gastric acidity more predominantly than gastric volume output, because such an agent should be more effective for increasing the pH value of gastric juice. We focused on compounds with the general formula **3**, lacking the electron-withdrawing functions (carboxylic acid and ester groups) incorporated in **1** and **2**, respectively.

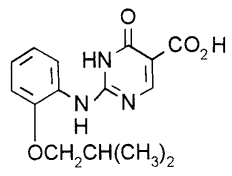
In this paper, we describe the structure–activity relationships of 2-benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones and the antiulcer effects of the sodium salt of the selected 2-(dimethylamino)benzylthio derivative (**8**).

Chemistry

Most of the 2-benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones (**4**, **5**, **7**, **10**, **11** and **13**—**18**) were prepared by coupling reaction between the 2-mercapto derivative[4] and the appropriate benzyl chlorides in the presence of a phase-transfer catalyst, tetrabutylammonium bromide, in a mixture of an aqueous potassium hydroxide solution and chloroform. Similarly, 6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-4(3*H*)-one and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*d*]pyrimidine-4(3*H*)-one (**6** and **9**) were obtained. The 2-(dimethylamino)benzylamino derivative (**12**) was synthesized by substitution of the 2-nitroamino derivative[5] with 2-(dimethylamino)benzylamine neat at 150 °C.

Results and Discussion

The compounds were evaluated for antisecretory activity against histamine-stimulated secretion in rats at the dose of 30 mg/kg after oral administration. As can be seen in Table 1, active compounds **7**, **8** and **10**, but not **15**, had the desirable property of suppressing the acidity of gastric juice more potently than the volume output. As regards structure–activity relationships, the effect of substituents at the 2 position of the phenyl ring was initially investigated. High activity was observed for the



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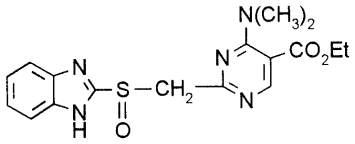

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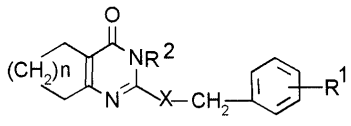

3 n=1,2 and 3

Chart 1

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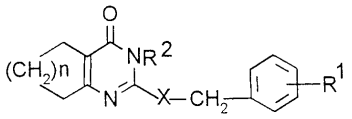
Table 1. 2-Benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones and Related Compounds



Compd. No.	R^1	R^2	X	*n*	Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Gastric secretion[a] Inhibition (%), 30 mg/kg, *p.o.* Volume	Acidity	TAO[c]
4	H	H	S	2	88	212—215 A–E	$C_{15}H_{16}N_2OS$	66.15 (65.98	5.92 5.73	10.29 10.14)	14.2	−0.5	10.2
5	2-CH_3	H	S	2	84	218—220 A–E	$C_{16}H_{18}N_2OS$	67.10 (66.87	6.33 6.15	9.78 9.83)	0	−4.1	−4.2
6	2-$N(CH_3)_2$	H	S	1	86	193—195 G–E	$C_{16}H_{19}N_3OS$	63.76 (63.97	6.35 6.68	13.94 13.85)	30.3	44.3*	59.0*
7	2-$N(CH_3)_2$	H	S	2	87	161—163 G–E	$C_{17}H_{21}N_3OS$	64.73 (64.95	6.71 6.74	13.32 13.33)	65.2*	88.8*	96.8*
8[d]	2-$N(CH_3)_2$	H	S	2	89	262—264 E	$C_{17}H_{20}NaN_3OS \cdot H_2O$	57.45 (57.15	6.24 6.35	11.82 11.66)	67.2* (56.4*	94.1* 66.8*	97.7* 84.1*)[e]
9	2-$N(CH_3)_2$	H	S	3	88	176—178 G–E	$C_{18}H_{23}N_3OS$	65.62 (65.65	7.04 7.13	12.75 12.77)	13.0	23.0	27.9
10	2-$N(CH_3)_2$	CH_3	S	2	85	82—83 D–H	$C_{18}H_{23}N_3OS$	65.62 (65.43	7.04 7.27	12.75 12.96)	23.0	73.1*	79.6*
11	2-$N(CH_3)_2$	C_6H_5	S	2	88	154—156 E–F	$C_{23}H_{25}N_3OS$	70.56 (70.39	6.44 6.39	10.73 10.79)	3.7	29.3	32.9
12	2-$N(CH_3)_2$	H	NH	2	42	164—165 B	$C_{17}H_{22}N_4O$	68.43 (68.21	7.43 7.51	18.78 18.71)	14.2	0.6	13.7
13	3-$N(CH_3)_2$	H	S	2	64	188—189 E–G	$C_{17}H_{21}N_3OS$	64.73 (64.55	6.71 6.80	13.32 13.18)	18.3	1.1	19.3
14	4-$N(CH_3)_2$	H	S	2	86	198—201 E–G	$C_{17}H_{21}N_3OS$	64.73 (64.63	6.71 6.55	13.32 13.70)	−14.0	8.0	−5.3
15	2-$N(CH_2CH_3)_2$	H	S	2	76	136–138 E–G	$C_{19}H_{25}N_3OS$	66.44 (66.36	7.34 7.15	12.23 12.58)	60.6*	45.8*	77.0*
16	2-N⟨⟩	H	S	2	68	169—170 E–G	$C_{20}H_{25}N_3OS$	67.57 (67.48	7.09 6.99	11.82 11.77)	12.1	23.2	29.8
17	2-OCH_3	H	S	2	86	187—188 A–E	$C_{16}H_{18}N_2O_2S$	63.55 (63.28	6.00 5.92	9.26 8.99)	−17.5	−12.6	−32.3
18	2-SCH_3	H	S	2	88	176—178 A–E	$C_{16}H_{18}N_2OS$	60.34 (60.09	5.70 5.50	8.80 8.64)	10.0	−4.6	4.3

a) Histamine-stimulated secretion in rats. * Significantly different from control value, $p<0.05$. *b*) A = chloroform, B = *N*,*N*-dimethylformamide, C = ethyl acetate, D = diethyl ether, E = EtOH, F = isopropyl ether, G = methylene chloride, H = petroleum ether. *c*) TAO = total acid output. *d*) Sodium salt of **7**. *e*) Test compound was given by intraduodenal administration.

Table 2. Antiulcer Properties of **1**, **2**, **8**, and Reference Compound

Compd. No.	Histamine-stimulated secretion ED_{50} (mg/kg), i.d. Volume	Acidity	TAO[a]	Ethanol-induced gastric lesion ED_{50} (mg/kg), *p.o.*	Acidified aspirin-induced gastric ulcer ED_{50} (mg/kg), *p.o.*	Indomethacin-induced gastric ulcer ED_{50} (mg/kg), *p.o.*	Mepirizole-induced duodenal ulcer ED_{50} (mg/kg), *p.o.*
1	>100	>100	>100	2.8[b]	35.6[b]	238.5[b]	>100
2	4.1	44.3	2.2	1.8	5.1	73.3	32.3
8	27.0 (16.0)[c]	15.7 (11.6)[c]	19.0 (9.9)[c]	4.6	2.9	11.2	3.15
Cimetidine	>100	61.4	10.2	>100	14.7	23.3	21.5

a) TAO = total acid output. *b*) Test compound was given 15 min before oral administration of ulcerogenic agents. *c*) Test compound was given by oral administration.

disubstituted amino derivatives (**7** and **15**), compared with non-substituted (**4**), methyl (**5**), methoxy (**17**) and methylthio (**18**) derivatives. However, replacement of the dimethylamino group attached to **7** with bulkier diethylamino (**15**) and piperidino (**16**) groups, or transfer the **3** or **4** position, as in **13** or **14**, resulted in loss of activity. With respect to the introduction of substituents into the pyrimidine moiety, good activity was maintained in the derivative with a small methyl group (**10**), but not that with a bulky phenyl group (**11**). In addition, the ring-contraction or ring-expansion derivative (**6** or **9**) of the alicyclic moiety was tested and proved to be obviously less active than **7**. Based on the structure–activity relationships, compound **7** was found as a promising compound, but it is somewhat unstable, yielding 5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione and 2-(dimethylamino)ben-

zylthiol under acidic conditions. In an attempt to overcome this disadvantage, derivatization to the 2-(dimethylamino)benzylamino compound (**12**), which is stable under acidic conditions, was tried, but it had weak activity. Consequently, the sodium salt (**8**) of **7** was selected for further evaluation. The ED_{50} values of **8** in histamine-stimulated gastric secretion in rats after oral and intraduodenal administrations are given in Table 2. When its mode of antisecretory action was compared with that of **2**, compound **8** was considerably less active in the reduction of gastric volume output and TAO, and was more active only in the reduction of gastric acidity. In the ethanol-induced gastric lesion model in rats, compound **8** possessed fairly good mucosal protection activity but was less active than **2**, suggesting that the reduction effect on gastric acidity did not contribute much to the prevention of gastric mucosal damage, which seems consistent with the fact that cimetidine had no effect. Compound **8** showed marked activities in acidified aspirin-induced and indomethacin-induced gastric ulcers and, in particular, in mepirizole-induced duodenal ulcer in rats, indicating that the reduction of gastric acidity was very closely associated with antiulcer activity.

In conclusion, chemical modification aimed at the reduction of gastric acidity provided a candidate antiulcer agent that was active in every ulcer model examined, without the remarkable lack of favorable mucosal protective action seen in the lead compounds **1** and **2**. The reduction of gastric acidity may be a more important factor for antiulcer activity than that of gastric volume output or TAO.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in a Nujol mull on a Hitachi 270-30 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a Bruker AC250 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a JEOL JMS-300 mass spectrometer using a direct inlet system.

Starting Materials 6,7-Dihydro-2-mercapto-5*H*-cyclopenta[*d*]pyrimidine-4(3*H*)-one was prepared by reaction of ethyl 2-oxocyclopentanecarboxylate with thiourea in the presence of sodium ethoxide in ethanol. mp >300 °C. Also, 6,7,8,9-tetrahydro-2-mercapto-5*H*-cyclohepta[*d*]-pyrimidine-4(3*H*)-one was obtained by similar procedure. mp 295—298 °C.

2-[2-(Dimethylamino)benzylthio]-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone (7) A solution of 2-(dimethylamino)benzyl chloride HCl (2.1 g, 0.01 mol) in $CHCl_3$ (30 ml) was added to a stirred mixture of 2-mercapto-5,6,7,8-tetrahydro-3(4*H*)-quinazolinone[4] (1.8 g, 0.01 mol) and tetrabutylammonium bromide (0.5 g, 0.0015 mol) in a 0.1 N aqueous KOH solution (30 ml), and the mixture was adjusted to pH 7 by further addition of a 0.1 N aqueous KOH solution. The suspension was stirred at room temperature for 15 h. It was neutralized with 1 N HCl, then the organic layer was separated, washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting solid was recrystallized from EtOH–CH_2Cl_2 to give **7** (2.7 g, 87%) as prisms. mp 161—163 °C. IR cm^{-1}: 2780 (NH), 1640 (C=O). MS *m/z*: 315 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.50—1.80 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.29 (2H, m, $C\underline{H}_2(CH_2)_3$), 2.50 (2H, m, $(CH_2)_3C\underline{H}_2$), 2.65 (6H, s, $N(CH_3)_2$), 4.44 (2H, s, SCH_2), 7.02 (1H, m, Ar-H), 7.10—7.30 (2H, m, Ar-H), 7.39 (1H, m, Ar-H), 12.46 (1H, br s, NH). Compound **8**, the sodium salt of **7**, was prepared from **7** and sodium methoxide in a usual manner. Compounds **4**—**6**, **9**—**11** and **13**—**18** were obtained by a method similar to that described for the preparation of **7**.

2-[2-(Dimethylamino)benzylamino]-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone (12) A mixture of 2-nitroamino-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone[5] (1.5 g, 0.007 mol) and 2-(dimethylamino)benzylamine (1.2 g, 0.008 mol), was heated at 150 °C for 1 h. After cooling, the crude product was purified by column chromatography on silica gel with $CHCl_3$ and recrystallized from dimethylformamide to give **12** (0.9 g, 42%) as a white powder. mp 164—165 °C. IR cm^{-1}: 3250, 2730 (NH), 1670 (C=O). MS *m/z*: 298 (M^+). ^{1}H-NMR (DMSO-d_6): 1.50—1.80 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.20 (2H, m, $C\underline{H}_2(CH_2)_3$), 2.33 (2H, m, $(CH_2)_3C\underline{H}_2$), 2.65 (6H, s, $N(CH_3)_2$), 4.47 (2H, d, J=4.3 Hz, $NHCH_2$), 6.62 (1H, br s, NH), 7.03 (1H, m, Ar-H), 7.10—7.30 (3H, m, Ar-H), 10.73 (1H, br s, NH).

Animals Seven male Sprague-Dawley (SD) rats, weighing 200—260 g, were used per group. Rats were fasted for 24 h with access to water *ad libitum* until the test.

Histamine-Stimulated Secretion in Pylorus-Ligated Rats A suspension of a test compound in a 0.5% carboxymethyl cellulose (CMC) solution was administered orally. One h later, the animals were anesthetized and the pylorus was ligated. The abdomen was closed by suturing, and histamine (30 mg/kg) was injected subcutaneously. Two h later, the animals were killed with ether. The gastric contents were collected and analyzed for volume and acidity. The acidity was titrated with 0.1 N NaOH to pH 7 using an autoburette (Radiometer, Copenhagen, Denmark). In the case of the examination for intraduodenal activity, the test compound was given just after pylorus ligation.

Ethanol-Induced Gastric Lesions in Rats[6] A suspension of a test compound in a 0.5% CMC solution was administered orally and, 30 min later, absolute ethanol (5 ml/kg) was given orally. One h later, the animals were killed, and the stomachs were isolated and fixed by treatment with 1% formalin solution. The stomachs were cut open along the greater curvature and the length of lesions in the glandular portion was measured under a dissecting microscope (10×) with a square grid. The sum of the lengths of all lesions was employed as an ulcer index.

Acidified Aspirin-Induced Gastric Ulcers in Rats A suspension of a test compound in 0.5% CMC solution was given orally 30 min before the oral administration of a solution of aspirin (150 mg/kg) in 150 mM HCl, One h later, the rats were killed and the stomachs were removed. The isolated stomachs were examined for ulcers.

Indomethacin-Induced Gastric Ulcers in Rats The experiment was carried out according to the method reported by Kasuya *et al.*[7] A suspension of indomethacin (25 mg/kg) in physiological saline was injected subcutaneously. Seven h later, the animals were killed and the stomachs were removed. The isolated stomachs were examined for ulcers. A suspension of test compound in a 0.5% CMC solution was given orally 1 h before administration of indomethacin.

Mepirizole-Induced Duodenal Ulcers in Rats The experiment was performed according to the method of Okabe *et al.*[8] A suspension of mepirizole (200 mg/kg) in 0.5% CMC solution was given to rats orally. Twenty four h later, rats were killed and the duodenums were removed. The isolated duodenums were examined for ulcers. A suspension of test compound in 0.5% CMC solution was given orally twice, 1 h before and 8 h after administration of mepirizole.

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