Studies on Antiulcer Drugs. I. Synthesis and Antiulcer Activities of Imidazo[1,2-*a*]pyridinyl-2-oxobenzoxazolidines-3-oxo-2*H*-1,4-benzoxazines and Related Compounds

Yousuke KATSURA,* Shigetaka NISHINO and Hisashi TAKASUGI

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan. *Received May 17, 1991*

A series of imidazo[1,2-*a*]pyridinyl-2-oxobenzoxazolidines (4a—i), -3-oxo-2*H*-1,4-benzoxazines (5a—q), their thio-analogues (4j—p and 5r—t) and 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridinyl derivatives (8 and 9) were synthesized and tested for anti-stress ulcer activity in rats. Several compounds were found to be more active than the reference compounds, zolimidine, cimetidine and sucralfate. Among them, compound 4e, 5i and 5l also exhibited potent protective activity against ethanol-induced gastric lesion. The synthesis and structure–activity relationships of these compounds are discussed.

Keywords anti-stress ulcer activity; ethanol-induced gastic lesion; cytoprotective activity; imidazo[1,2-*a*]pyridinyl-2-oxobenzoxazolidine; imidazo[1,2-*a*]pyridinyl-3-oxo-2*H*-1,4-benzoxazine; zolimidine; cimetidine; sucralfate; structure–activity relationship

It is well known that peptic ulcers are the outcome of an imbalance between the defensive factors (forces of mucosal resistance) and the aggressive factors (gastric acid and pepsin secretion).[1] In the last two decades, research of many antisecretory agents has been carried out in an effort to inhibit the latter factors, and as a result, a number of anti-cholinergic drugs, histamine H_2-receptor antagonists and recently proton potassium adenosine triphosphatase (ATPase) inhibitor (omeprazole)[2] have been marketed. These drugs are very useful in the treatment of gastric and duodenal ulcers, but it has been pointed out that the relapse of these ulcers occurs in a high ratio following the cessation of treatment with such antiacids. Although no clear cause for this has yet been proven, it has been empirically considered that the protection of the stomach against various injuries is advantageous to maintenance therapy for peptic ulcers. Therefore, numerous efforts have been continued to find a novel class of antiulcer agent which strengthens defensive mechanisms.

Some derivatives incorporating an imidazo[1,2-*a*]pyridine ring have been described as exhibiting cytoprotective activity.[3-5]

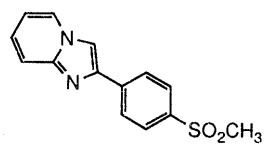
As a start for our studies on antiulcer durgs, we focused our attention on the activity of zolimidine (**1**), which was reported to protect against experimentally-induced lesions of the gastric mucosa in various animal species[3a] and to indicate its therapeutic benefit in peptic ulcer patients without marked side effects.[3b-d]

Oxobenz(o)-azolidine and -azine groups have been extensively introduced into various drugs, for example, anti-inflammatory,[6] antihypertensive,[7] cardiotonic,[8] and central nervous system affecting agents.[9] Thus, we wanted to combine this versatile pharmacophore with the imidazo-[1,2-*a*]pyridine nuclei.

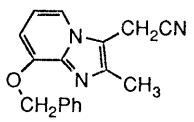
To our knowledge, no compound consisting of a two bicyclic hetero-ring system has been reported in the field of antiulcer drug treatment. In this paper, we describe the synthesis and pharmacological activities of a series of imidazo[1,2-*a*]pyridinyl-2-oxobenzoxazolidines, imidazo-[1,2-*a*]pyridinyl-3-oxo-2*H*-1,4-benzoxazines and related compounds.

Chemistry The desired compounds listed in Tables I and II were synthesized by the routes as shown in Charts 2—5.

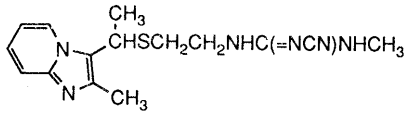
The 2-oxobenzoxazolidine and thiazolidine derivatives (**4**) were prepared according to methods similar to those described in the literature. Friedel–Crafts acylation[7-10] of 2-oxobenz(o)-azolidines (**6**) with α-bromoacylbromide in the presence of aluminum chloride gave the corresponding α-bromoketones (**7**). Condensation[11] of these haloketones (**7**) with the appropriate substituted 2-aminopyridines afforded the desired imidazo[1,2-*a*]pyridine derivatives (**4**) (Chart 2). The *N*-alkylated derivatives on the benzoxazolidine and thiazolidine group (**4g** and **4n**) were prepared by alkylation of **4d** and **4l** with the corresponding alkyl halides in the presence of sodium hydride in *N*,*N*-di-



zolimidine (1)



SCH-28080 (2)



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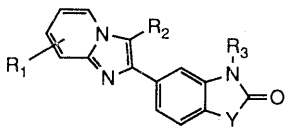
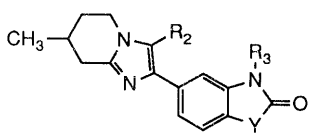


4 : Y = O, S
5 : Y = -O-CH-, -S-CH-
(R_4) (R_4)



8 : Y = O
9 : Y = -O-CH-
(CH_3)

Chart 1

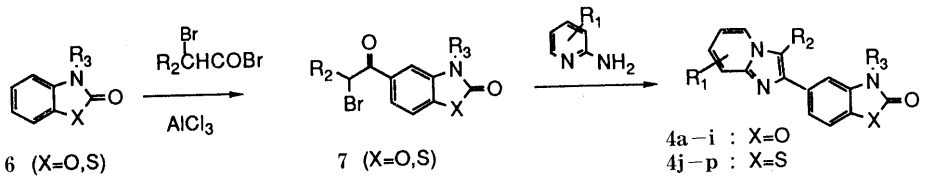


Chart 2

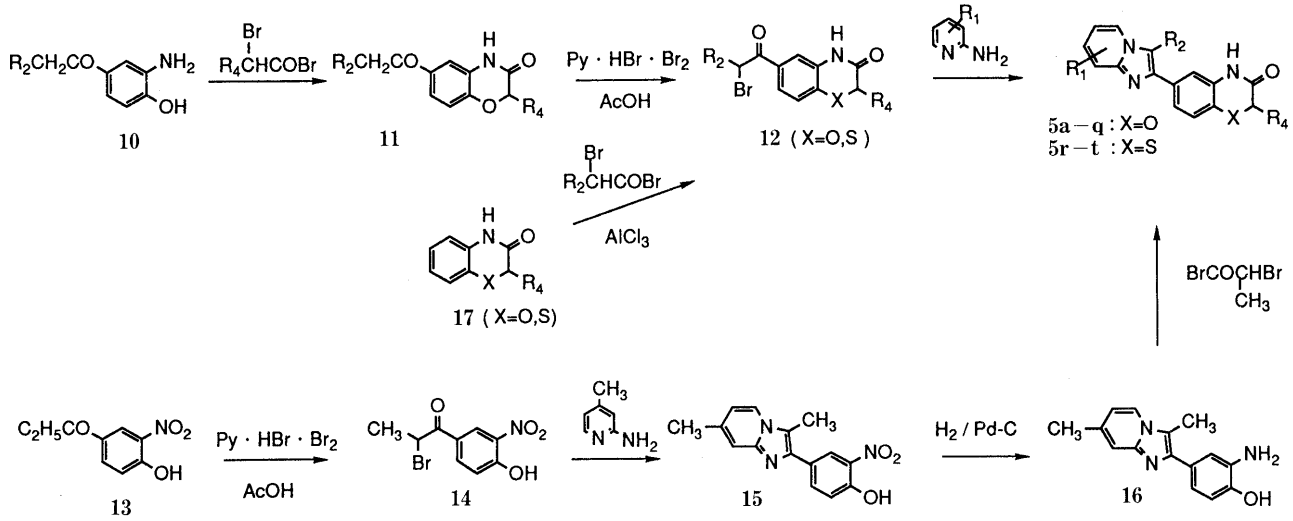


Chart 3

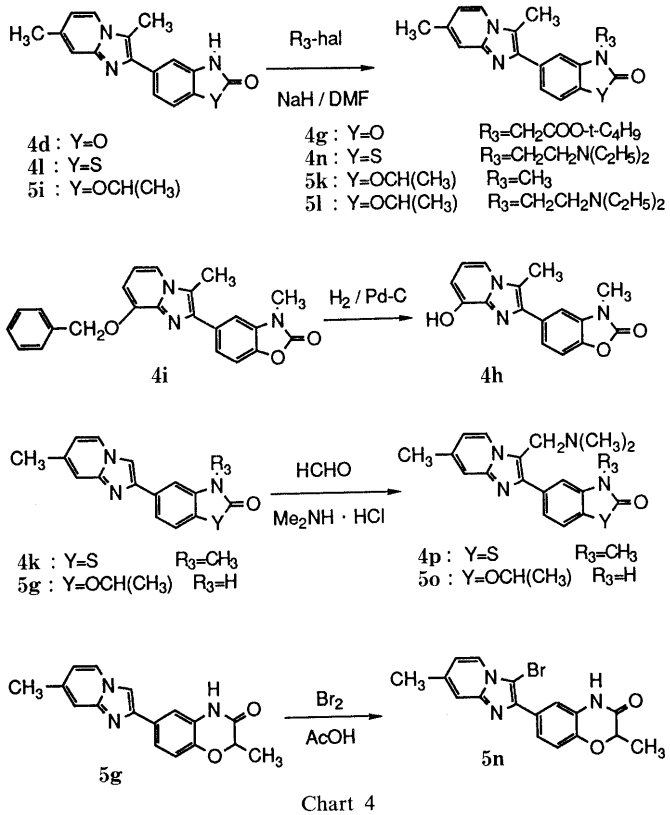


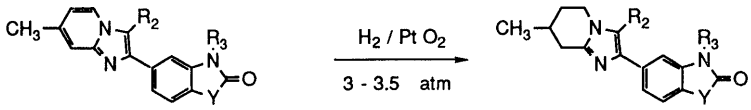
Chart 4

methylformamide (DMF). The 8-hydroxy derivative (**4h**) was obtained by debenzylation of **4i** using 10% palladium on carbon under hydrogen (1 atm) at room temperature. The Mannich base **4p** was prepared by the treatment of **4k** with formaline and dimethylamine hydrochloride in acetic acid[11a,b] (Chart 4). Hydrogenation of **4e** and **4f** by using platinum dioxide as a catalyst at 3 to 3.5 atm at room temperature afforded 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine derivatives (**8a** and **8b**)[11d] (Chart 5).

The 3-oxo-2*H*-1,4-benzoxazine derivatives were obtained by three different pathways as outlined in Chart 3. 4-Acyl-2-aminophenol (**10**) was treated with α-bromoacyl bromide to afford 6-acyl-3-oxo-2*H*-1,4-benzoxazine (**11**), which was brominated with pyridinium bromide perbromide in the presence of hydrogen bromide in acetic acid to yield the corresponding α-bromoketones (**12**). In the second method, starting from 4′-hydroxy-3′-nitropropiophenone (**13**), bromination of **13** with pyridinium bromide perbromide, followed by treatment with 4-methyl-2-aminopyridine, gave 4-imidazo[1,2-*a*]pyridinyl-2-nitrophenol (**15**). Catalytic reduction of the nitro group over 10% palladium on carbon at room temperature gave *o*-aminophenol (**16**), followed by cyclization with α-bromopropionyl bromide afforded the desired product (**5i**). The third method was performed according to a synthetic route similar to that of azolidines (**4**). The bromo derivative at the 3-position on the imidazo[1,2-*a*]pyridine nuclei (**5n**) was obtained by the bromination of **5g** with bromine.[11a,c] The preparation of *N*-alkylated derivatives (**5k** and **5l**), Mannich base (**5o**) and 5,6,7,8-tetrahydro-derivatives (**9a—c**) were carried out in a manner similar to that of **4g**, **4p** and **8**. The 3-oxo-2*H*-1,4-benzothiazines (**5r—t**) were also obtained in a manner similar to that of benzothiazolidines (**4j—n**) from substituted benzothiazines (**17**) as the starting materials.

Pharmacological Results and Discussion

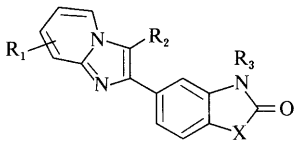
The imidazo[1,2-*a*]pyridine derivatives (**4** and **5**) and their 5,6,7,8-tetrahydro-analogues (**8** and **9**) obtained in this study were evaluated for antiulcer activity at a dose of 32 mg/kg



4e	Y=O	R_2=CH_3	R_3=CH_3	8a	Y=O	R_2=CH_3	R_3=CH_3
4f	Y=O	R_2=CH_3	R_3=iso-C_3H_7	8b	Y=O	R_2=CH_3	R_3=iso-C_3H_7
5g	Y=OCH(CH_3)	R_2=H	R_3=H	9a	Y=OCH(CH_3)	R_2=H	R_3=H
5i	Y=OCH(CH_3)	R_2=CH_3	R_3=H	9b	Y=OCH(CH_3)	R_2=CH_3	R_3=H
5k	Y=OCH(CH_3)	R_2=CH_3	R_3=CH_3	9c	Y=OCH(CH_3)	R_2=CH_3	R_3=CH_3

Chart 5

TABLE I. Physical Data of Imidazo[1,2-*a*]pyridines (**4** and **5**)



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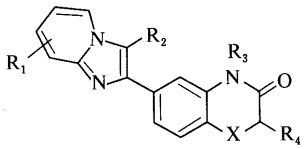


5

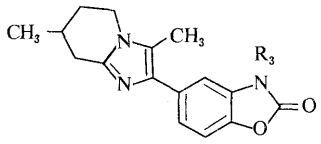
Compd. No.	R_1	R_2	R_3	R_4	X	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
4a	H	CH_3	CH_3		O	69.2	231—232 (D–W)	$C_{16}H_{13}N_3O_2$	68.81 (68.89	4.69 4.61	15.04 15.01)
4b	H	CH_3	iso-C_3H_7		O	61.9	195—197 (A–T)	$C_{18}H_{17}N_3O_2$	70.34 (70.49	5.57 5.57	13.67 13.63)
4c	6-CH_3	CH_3	CH_3		O	77.7	247—249 (A–T)	$C_{17}H_{15}N_3O_2$	69.61 (69.71	5.15 5.10	14.33 14.43)
4d	7-CH_3	CH_3	H		O	25.1	276—278 (T–W)	$C_{16}H_{13}N_3O_2 \cdot H_2O$	64.63 (64.72	5.41 5.03	14.13 14.14)
4e	7-CH_3	CH_3	CH_3		O	58.6	240 (EA–T)	$C_{17}H_{15}N_3O_2$	69.61 (69.55	5.15 5.23	14.33 14.21)
4f	7-CH_3	CH_3	iso-C_3H_7		O	65.6	179—180 (EA–I)	$C_{19}H_{19}N_3O_2$	71.01 (70.68	5.96 5.91	13.07 13.37)
4g	7-CH_3	CH_3	CH_2COO-*tert*-C_4H_9		O	71.1	198—200 (EA)	$C_{22}H_{23}N_3O_4$	67.16 (67.22	5.89 5.86	10.68 10.59)
4h	8-OH	CH_3	CH_3		O	63.4	>280 (A–T)	$C_{16}H_{13}N_3O_3$	65.08 (65.07	4.44 4.32	14.23 14.26)
4i	8-OCH_2Ph	CH_3	CH_3		O	54.5	210 (AN)	$C_{23}H_{19}N_3O_3$	71.68 (71.45	4.97 4.93	10.90 11.06)
4j	H	CH_3	CH_3		S	50.8	206—208 (EA)	$C_{16}H_{13}N_3OS$	65.10 (65.14	4.44 4.38	14.23 14.08)
4k	7-CH_3	H	CH_3		S	72.1	264—265 (EA)	$C_{16}H_{13}N_3OS$	65.10 (65.28	4.44 4.41	14.23 14.15)
4l	7-CH_3	CH_3	H		S	42.3	252—254 (A–EA)	$C_{16}H_{13}N_3OS$	65.10 (64.82	4.44 4.55	14.23 14.08)
4m	7-CH_3	CH_3	CH_3		S	63.4	204—206 (EA–T)	$C_{17}H_{15}N_3OS$	66.00 (65.73	4.89 4.80	13.58 13.42)
4n	7-CH_3	CH_3	$CH_2CH_2N(C_2H_5)_2$		S	26.4	272 (I–M)	$C_{22}H_{26}N_4OS \cdot 2HCl \cdot 3H_2O$	50.67 (50.26	6.57 6.61	10.74 10.64)
4o	7-CH_3	C_2H_5	CH_3		S	49.5	276—281 (A)	$C_{18}H_{17}N_3OS \cdot HCl \cdot 3/2H_2O$	55.88 (55.96	5.47 5.42	10.88 10.63)
4p	7-CH_3	$CH_2N(CH_3)_2$	CH_3		S	69.0	167—168 (EA)	$C_{19}H_{20}N_4OS$	64.75 (64.73	5.72 5.71	15.90 15.70)
5a	H	H	H	CH_3	O	50.2	241—243 (C)	$C_{16}H_{13}N_3O_2$	68.81 (68.53	4.69 4.55	15.04 14.98)
5b	H	CH_3	H	H	O	38.1	280—282 (A–EA)	$C_{16}H_{13}N_3O_2$	68.81 (68.65	4.69 4.58	15.04 14.83)
5c	H	CH_3	H	CH_3	O	48.6	216—217 (A–E)	$C_{17}H_{15}N_3O_2 \cdot H_2O$	65.58 (65.96	5.50 5.22	13.50 13.36)
5d	H	CH_3	H	C_2H_5	O	49.3	197—198 (C–E)	$C_{18}H_{17}N_3O_2 \cdot H_2O$	66.45 (66.09	5.89 5.87	12.91 13.03)
5e	H	C_2H_5	H	CH_3	O	55.4	237—239 (A)	$C_{18}H_{17}N_3O_2$	70.34 (69.96	5.57 5.56	13.67 13.50)
5f	6-CH_3	CH_3	H	CH_3	O	72.9	232 (D–W)	$C_{18}H_{17}N_3O_2 \cdot 7/5H_2O$	65.36 (65.15	5.97 5.95	12.70 12.43)
5g	7-CH_3	H	H	CH_3	O	79.5	255—256 (C)	$C_{17}H_{15}N_3O_2 \cdot 2/3H_2O$	66.87 (67.00	5.17 5.26	13.76 13.80)

TABLE I. (continued)

Compd. No.	R_1	R_2	R_3	R_4	X	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
5h	7-CH_3	CH_3	H	H	O	48.5	239—241 (C–E)	$C_{17}H_{15}N_3O_2 \cdot H_2O$	65.58 (65.21	5.50 5.35	13.50 13.33)
5i	7-CH_3	CH_3	H	CH_3	O	32.5	254—256 (EA)	$C_{18}H_{17}N_3O_2$	70.34 (70.38	5.57 5.59	13.67 13.67)
5j	7-CH_3	CH_3	H	C_2H_5	O	25.5	194—195 (EA)	$C_{19}H_{19}N_3O_2 \cdot H_2O$	67.24 (67.20	6.24 6.18	12.38 12.20)
5k	7-CH_3	CH_3	CH_3	CH_3	O	43.0	180—182 (EA)	$C_{19}H_{19}N_3O_2$	71.01 (70.79	5.96 6.01	13.07 12.98)
5l	7-CH_3	CH_3	$CH_2CH_2N(C_2H_5)_2$	CH_3	O	45.8	135—136 (EA–I)	$C_{24}H_{30}N_4O_2$	70.91 (70.74	7.44 7.43	13.78 14.03)
5m	7-CH_3	C_2H_5	H	CH_3	O	53.9	223—225 (C–E)	$C_{19}H_{19}N_3O_2$	71.01 (70.82	5.96 5.94	13.07 13.00)
5n	7-CH_3	Br	H	CH_3	O	72.0	229—230 (T)	$C_{17}H_{14}BrN_3O_2$	54.86 (55.17	3.79 3.76	11.29 10.94)
5o	7-CH_3	$CH_2N(CH_3)_2$	H	CH_3	O	66.5	183—184 (A–H)	$C_{20}H_{22}N_4O_2 \cdot H_2O$	65.20 (65.59	6.57 6.62	15.21 14.86)
5p	8-CH_3	CH_3	H	CH_3	O	62.8	249—250 (D–W)	$C_{18}H_{17}N_3O_2 \cdot 1/5H_2O$	69.53 (69.55	5.64 5.59	13.51 13.43)
5q	8-C_2H_5O	CH_3	H	CH_3	O	46.0	180—181 (D–W)	$C_{19}H_{19}N_3O_3 \cdot H_2O$	64.21 (64.33	5.96 6.03	11.82 11.73)
5r	H	CH_3	H	CH_3	S	45.3	229—231 (C–E)	$C_{17}H_{15}N_3OS \cdot 1/5H_2O$	65.24 (65.21	4.95 4.83	13.43 13.34)
5s	H	CH_3	CH_3	H	S	68.0	191 (E–EA)	$C_{17}H_{15}N_3OS$	66.00 (66.01	4.89 4.82	13.58 13.93)
5t	7-CH_3	CH_3	H	CH_3	S	68.1	259—261 (D–W)	$C_{18}H_{17}N_3OS$	66.85 (67.10	5.30 5.27	12.99 12.61)

a) A, EtOH; AN, MeCN; C, CH_2Cl_2; D, DMF; E, Et_2O; EA, EtOAc; H, hexane; I, diisopropyl ether; M, MeOH; T, THF; W, H_2O.

TABLE II. Physical Data of 5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridines (**8** and **9**)



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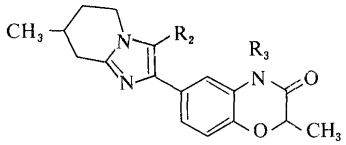

9

Compd. No.	R_2	R_3	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
8a		CH_3	49.0	213—215 (I–M)	$C_{17}H_{19}N_3O_2$	68.67	6.44	14.13	68.71	6.42	14.29
8b		iso-C_3H_7	52.7	164—166 (A–I)	$C_{19}H_{23}N_3O_2$	70.13	7.12	12.91	69.80	7.05	13.06
9a	H	H	82.9	215—218 (A–I)	$C_{17}H_{19}N_3O_2 \cdot 1/2H_2O$	66.65	6.58	13.72	66.52	6.61	13.55
9b	CH_3	H	74.7	221—222 (E–EA)	$C_{18}H_{21}N_3O_2 \cdot 6/5H_2O$	64.92	7.08	12.62	64.87	6.94	12.60
9c	CH_3	CH_3	66.5	112—115 (EA–I)	$C_{19}H_{23}N_3O_2 \cdot H_2O$	66.45	7.34	12.24	66.21	7.24	12.33

a) A, EtOH; E, Et_2O; EA, EtOAc; I, diisopropyl ether; M, MeOH.

p.o. in restraint and water-immersion stressed rats (stress ulcer). The results were compared with those of reference compounds, zolimidine (**1**), cimetidine and sucralfate, and are summarized in Table III.

In the series of 2-oxobenzoxazolidines, **4a** and **4e** exhibited excellent anti-stress ulcer activity. 6- and 8-substitution on the imidazo[1,2-*a*]pyridine ring (**4c** and **4h**) resulted in diminished activity. Introduction of a bulky substituent at the *N*-position of the benzoxazolidine ring (**4b**, **4f** and **4g**) tended to decrease activity. The activity of **4d**, the *N*-demethylated derivative of **4e**, was also relatively low. Among the 2-oxobenzothiazolidines, **4m**, which is the thio-isostere of **4e**, had high activity. Replacement of the 3-methyl group on the imidazo[1,2-*a*]pyridine ring of **4m** with a *N*,*N*-dimethylaminomethyl group (**4p**) showed lower activity, and the derivative with an ethyl group (**4o**) showed total disappearence of the activity. Compound **4j** without substitution on the pyridine component was less active than **4m**, but the degree of activity was comparable to that of cimetidine.

Next, the activities of 3-oxo-2*H*-1,4-benzoxazines and 3-oxo-2*H*-1,4-benzothiazines were examined. In this series, the most active compound was **5i**, which revealed complete inhibition of stress ulcers at the test dose. 6-Methyl (**5f**) and

TABLE III. Anti-ulcer Activity of Imidazo[1,2-*a*]pyridine Derivatives against Restraint and Water-Immersion Stressed Rats ($n=5$)

Compd. No.	Anti-stress ulcer activity (% inhibition) 32 mg/kg *p.o.*	Compd. No.	Anti-stress ulcer activity (% inhibition) 32 mg/kg *p.o.*
4a	88.1[a]	**5i**	98.8[a]
4b	45.0	**5j**	24.4
4c	44.9	**5k**	61.5
4d	52.2	**5l**	90.7[a]
4e	92.5[a]	**5m**	74.7
4f	60.5	**5n**	30.1
4g	−162.5	**5o**	19.1
4h	12.0	**5p**	59.7
4j	69.2	**5q**	−183.1
4m	80.5[a]	**5r**	54.5
4n	51.8	**5s**	31.0
4o	5.1	**5t**	66.7
4p	56.4	**8a**	74.7[a]
5a	2.2	**8b**	76.8[a]
5b	20.7	**9a**	62.2
5c	23.7	**9b**	74.2
5d	80.8[a]	**9c**	63.8
5e	48.9	Zolimidine	48.2
5f	57.5	Cimetidine	69.4[a]
5g	32.2	Sucralfate	45.6[b]
5h	58.3		

a) $p<0.01$. *b*) 100 mg/kg *p.o.*

TABLE IV. Gastric Cytoprotective Activity of **4e**, **5i** and **5l** in Rats ($n=5$)

Compd. No.	Dose (mg/kg *p.o.*)	Ethanol-induced gastric lesion (% inhibition)
4e	32	80.7[b]
	10	69.6[b]
	3.2	57.5[c]
5i	32	86.0[b]
	10	52.3[c]
	3.2	−20.6
5l	32	95.0[a]
	10	75.2[c]
	3.2	19.8
Zolimidine	32	64.9[c]
Cimetidine	100	40.3
Sucralfate	100	50.3

a) $p<0.001$. *b*) $p<0.01$. *c*) $p<0.05$.

8-methyl (**5p**) derivatives, positional isomers of the methyl group at the pyridine ring of **5i**, showed relatively low activities. The 8-ethoxy derivative (**5q**) exhibited an adverse effect. The activity of the 3-ethyl-7-methyl derivative (**5m**) was more potent than that of reference compounds. However, replacement of the substituent at the 3-position with a bromo (**5n**) or an *N*,*N*-dimethylaminomethyl group (**5o**) reduced the activities markedly. Introduction of an *N*,*N*-diethylaminoethyl group onto the *N*-position of the benzoxazine ring (**5l**) maintained high activity, but the activity of the *N*-methylated derivative (**5k**) was moderate. Conversion of the methyl group at the 2′-position on the benzoxazine ring (R_4) of **5i** into a hydrogen (**5h**) or an ethyl group (**5j**) tended to decrease activity. The activities of unsubstituted derivatives on the pyridine ring (**5a**—**c**, **5e**, **5r** and **5s**) were markedly reduced in comparison to that of the 7-methyl derivatives (**5i** and **5t**) except for the case of **5d** *versus* **5j**.

With regard to structure–activity relationships, these results indicate that the 3,7-dimethyl group is more favorable as a substituent on the imidazo[1,2-*a*]pyridine nuclei. On the other hand, the introduction of a bulky group at the *N*-position of the benz(o)-azolidine ring tends to cause the decrease of activity. As further study on the substitution at the *N*-position on the benz(o)-azine moiety is not yet complete, the influence in the case is still unclear.

Next, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridinyl derivatives (**8** and **9**) were evaluated. These compounds revealed good activities which were equipotent with that of cimetidine. No clear structure–activity relationship was apparent between these compounds and the parent compounds (**4e**, **4f**, **5g**, **5i** and **5k**).

Finally, the cytoprotective activities of three compounds (**4e**, **5i** and **5l**) were examined on the ethanol-induced gastric lesion (ethanol ulcer) in rats. The tested compounds were administered orally at a dose range from 3.2 to 32 mg/kg. The results were compared with those of reference compounds, zolimidine (32 mg/kg), cimetidine (100 mg/kg) and sucralfate (100 mg/kg), and are listed in Table IV. These evaluated compounds showed good activities, and the potencies at 32 mg/kg were superior to that of reference compounds.

In conclusion, we obtained several imidazo[1,2-*a*]pyridine derivatives having potent anti-stress ulcer activities (**4a**, **4e**, **4m**, **5d**, **5i** and **5l**). As an additional pharmacological profile, **4e**, **5i** and **5l** revealed cytoprotective activity against ethanol ulcer. The potencies of antiulcer activities of these compounds were superior to that of the prototype compound zolimidine and the therapeutic agents cimetidine and sucralfate.

Experimental

The melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared (IR) spectra were taken with Hitachi 260-10 spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with JNM-PMX 60 spectrometer using tetramethylsilane as an internal standard.

5-(3,7-Dimethylimidazo[1,2-*a*]pyridin-2-yl)-2-oxobenzoxazolidine (4d) A solution of 5-(2-bromopropionyl)-2-oxobenzoxazolidine (**7b**) (5.4 g, 20 mmol) and 2-amino-4-methylpyridine (6.5 g, 60 mmol) in MeCN (100 ml) was refluxed with stirring for 1 h. After the solvent was evaporated *in vacuo*, the residue was mixed with H_2O and AcOEt. The mixture was adjusted to pH 0.8 with 10% HCl and the resulting precipitate was collected by filtration. The obtained solid was suspended in a mixture of H_2O and AcOEt, and brought to pH 8.0 with 20% aqueous K_2CO_3. The crystals which separated were recrystallized from aqueous tetrahydrofuran (THF) to afford **4d** (1.4 g, 25.1%). IR (Nujol): 3500, 1760 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.37 (3H, s), 2.61 (3H, s), 6.79 (1H, dd, $J=2$, 7 Hz), 7.17 (1H, d, $J=8$ Hz), 7.33 (1H, d, $J=2$ Hz), 7.59 (1H, dd, $J=2$,8 Hz), 7.64 (1H, d, $J=2$ Hz), 8.21 (1H, d, $J=7$ Hz).

5-(8-Hydroxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)-3-methyl-2-oxobenzoxazolidine (4h) A solution of **4i** (1.6 g, 4.2 mmol) in a mixture of EtOH (200 ml) and THF (100 ml) was treated with 10% Pd–C (50% wet, 0.5 g) under atmospheric pressure of H_2 at room temperature. After the catalyst was filtered off, the solvent was evaporated *in vacuo*. The residue was recrystallized from a mixture of EtOH and THF to afford **4h** (0.78 g, 63.4%). IR (Nujol): 1770, 1615, 1550 cm^{-1}. ^{1}H-NMR (CF_3COOH) δ: 2.76 (3H, s), 3.63 (3H, s), 7.33—7.90 (5H, m), 8.10 (1H, t, $J=7$ Hz).

5-(3-*N*,*N*-Dimethylaminomethyl-7-methylimidazo[1,2-*a*]pyridin-2-yl)-3-methyl-2-oxobenzothiazolidine (4p) A mixture of **4k** (1.9 g, 6.4 mmol), 36% aqueous HCHO (1.07 g, 12.8 mmol), 50% aqueous Me_2NH (1.16 g 12.8 mmol) and AcOH (770 mg, 12.8 mmol) in MeOH (10 ml) was stirred at 55—60 °C for 3 h. After the solvent was evaporated *in vacuo*, the residue was dissolved with 1 N HCl (10 ml), H_2O (10 ml) and AcOEt (30 ml). The aqueous layer was separated, adjusted to pH 7.0 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was dried over $MgSO_4$ and

evaporated *in vacuo*. The residue was recrystallized from AcOEt to afford **4p** (1.56 g, 69.0%). IR (Nujol): 1670, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.16 (6H, s), 2.38 (3H, s), 3.45 (3H, s), 3.88 (2H, s), 6.78 (1H, dd, J=2,7 Hz), 7.35 (1H, d, J=8 Hz), 7.40 (1H, d, J=2 Hz), 7.89 (1H, dd, J=2, 8 Hz), 8.12 (1H, d, J=2 Hz), 8.40 (1H, d, J=7 Hz).

2-Bromo-4′-hydroxy-3′-nitropropiophenone (14) Pyridinium bromide perbromide (19.2 g, 60 mmol) was added in portions to a solution of 4′-hydroxy-3′-nitropropiophenone (**13**) (10.8 g, 55 mmol) and 30% HBr–AcOH (10 ml) in AcOH (50 ml) at room temperature with stirring. After being stirred for 1 h, the mixture was poured into H_2O. The resulting precipitate was collected by filtration, washed with H_2O and recrystallized from a mixture of AcOEt and ether to afford **14** (14.3 g, 94.1%), mp 62—64 °C. IR (Nujol): 3150, 1690, 1620, 1535 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.80 (3H, d, J=7 Hz), 5.78 (1H, q, J=7 Hz), 7.30 (1H, d, J=9 Hz), 8.20 (1H, dd, J=2, 9 Hz), 8.55 (1H, d, J=2 Hz).

3,7-Dimethyl-2-(4-hydroxy-3-nitrophenyl)imidazo[1,2-*a*]pyridine (15) This compound was prepared from **14** in a manner similar to that described for **5i**. Yield 35.9%, mp 176—179 °C (from AcOEt–THF). IR (Nujol): 1630, 1530, 1350 cm^{-1}. ^{1}H-NMR (CF_3COOH) δ: 2.69 (3H, s), 2.74 (3H, s), 7.45 (1H, d, J=7 Hz), 7.46 (1H, d, J=9 Hz), 7.70 (1H, s), 7.92 (1H, dd, J=2, 9 Hz), 8.30 (1H, d, J=7 Hz), 8.46 (1H, d, J=2 Hz).

2-(3-Amino-4-hydroxyphenyl)-3,7-dimethylimidazo[1,2-*a*]pyridine (16) A solution of **15** (2.6 g, 9.2 mmol) in a mixture of EtOH (200 ml) and THF (100 ml) was hydrogenated under atmospheric pressure of H_2 over 10% Pd–C (50% wet, 2.0 g) at room temperature. After the catalyst was removed by filtration, the filtrate was evaporated *in vacuo*. The residue was recrystallized from a mixture of AcOEt and THF to afford **16** (1.25 g, 53.9%), mp 251—253 °C. IR (Nujol): 3370, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 2.55 (3H, s), 6.72 (1H, dd, J=2, 8 Hz), 6.75 (1H, d, J=8 Hz), 6.88 (1H, d, J=7 Hz), 7.13 (1H, d, J=2 Hz), 7.25 (1H, s), 8.17 (1H, d, J=7 Hz).

3,4-Dihydro-6-(3,7-dimethylimidazo[1,2-*a*]pyridin-2-yl)-2-methyl-3-oxo-2*H*-1,4-benzoxazine (5i) 2-Bromopropionyl bromide (1.30 g, 6.0 mmol) was added dropwise to a solution of **16** (1.27 g, 5.0 mmol) and Et_3N (1.0 g, 10.0 mmol) in THF (100 ml) at room temperature and the mixture was stirred for 2 h. After being stirred at 60—70 °C for an additional 2 h, the solvent was evaporated *in vacuo* and the residue was mixed with AcOEt and H_2O. The organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel by eluting with a mixture of $CHCl_3$ and MeOH (9 : 1) to give **5i** (0.5 g, 32.5%) after recrystallization from AcOEt. IR (Nujol): 1690, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.45 (3H, d, J=7 Hz), 2.37 (3H, s), 2.60 (3H, s), 4.71 (1H, q, J=7 Hz), 6.79 (1H, dd, J=2,7 Hz), 7.03 (1H, d, J=8 Hz), 7.31 (1H, d, J=2 Hz), 7.33 (1H, dd, J=2,8 Hz), 7.44 (1H, d, J=2 Hz), 8.20 (1H, d, J=7 Hz), 10.70 (1H, s).

3,4-Dihydro-2,4-dimethyl-6-(3,7-dimethylimidazo[1,2-*a*]pyridin-2-yl)-3-oxo-2*H*-1,4-benzoxazine (5k) NaH (50% dispersion in mineral oil, 0.6 g, 12.5 mmol) was added in portions to a solution of **5i** (2.5 g, 8.1 mmol) in DMF (25 ml) at room temperature and the mixture was stirred for 2 h. MeI (1.7 g, 12.0 mmol) was added and the resulting mixture was further stirred for 3 h. The solvent was evaporated *in vacuo*. The residue was suspended in H_2O and acidified with 10% aqueous HCl. The aqueous solution was washed with AcOEt, and then adjusted to pH 7.5 with aqueous K_2CO_3. The resulting precipitate was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from AcOEt to afford **5k** (1.1 g, 43.0%). IR (Nujol): 1680, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.47 (3H, d, J=7 Hz), 2.37 (3H, s), 2.60 (3H, s), 3.37 (3H, s), 4.75 (1H, q, J=7 Hz), 6.78 (1H, dd, J=2,7 Hz), 7.03 (1H, d, J=8 Hz), 7.32 (1H, d, J=2 Hz), 7.43 (1H, dd, J=2, 8 Hz), 7.52 (1H, d, J=2 Hz), 8.20 (1H, d, J=7 Hz).

6-(3-Bromo-7-methylimidazo[1,2-*a*]pyridin-2-yl)-3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine (5n) Pyridinium bromide perbromide (1.44 g, 4.5 mmol) was added in portions to a solution of **5g** (1.20 g, 4.1 mmol) in a mixture of AcOH (9 ml) and THF (7 ml) at room temperature with stirring. After being stirred for 2 h, the reaction mixture was poured into H_2O and neutralized to pH 7.0 with 20% aqueous K_2CO_3. The resulting precipitate was extracted with AcOEt and the extract was dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was recrystallized from THF to afford **5n** (1.10 g, 72.0%). IR (Nujol): 1685, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.46 (3H, d, J=7 Hz), 2.40 (3H, s), 4.74 (1H, q, J=7 Hz), 6.94 (1H, dd, J=2, 7 Hz), 7.08 (1H, d, J=8 Hz), 7.43 (1H, d, J=2 Hz), 7.68 (1H, dd, J=2,8 Hz), 7.70 (1H, d, J=2 Hz), 8.26 (1H, d, J=7 Hz), 10.81 (1H, s).

3,4-Dihydro-6-(3,7-dimethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl)-2-methyl-3-oxo-2*H*-1,4-benzoxazine (9b) A solution of **5i** (2.46 g, 8.0 mmol) in MeOH (200 ml) was hydrogenated over PtO_2 (0.35 g) at 3 to 3.5 atm pressure of H_2 for 6 h at room temperature. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give a residue. An aqueous solution of the residue was adjusted to pH 8.0 with 20% aqueous K_2CO_3 and extracted with AcOH. The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from a mixture of AcOEt and ether to afford **9b** (1.86 g, 74.7%). IR (KBr): 3400, 1680, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, d, J=6 Hz), 1.42 (3H, d, J=7 Hz), 1.52—1.64 (1H, m), 1.94—2.01 (2H, m), 2.18—2.36 (1H, m), 2.27 (3H, s), 2.83 (1H, dd, J=4, 16 Hz), 3.68 (1H, dt, J=5, 12 Hz), 3.88—3.95 (1H, m), 4.64 (1H, q, J=7 Hz), 6.78 (1H, d, J=8 Hz), 7.11 (1H, dd, J=2, 8 Hz), 7.23 (1H, d, J=2 Hz), 10.63 (1H, br s).

Restraint and Water-Immersed Stress Ulcer The stress ulcer was produced according to the method described by Takagi and Okabe.[12] 7 week old male SD rats, weighing 200 to 260 g, were fasted for 24 h before the experiment. A suspension of the test drug in 0.1% methylcellulose (MC) was administered orally to the group of five rats 30 min before stress initiation. The rats were immobilized in a stress cage and immersed vertically in a water bath at 22 °C to the height of the xiphoid process of the rats. 7 h later, the animals were sacrificed. The isolated stomachs were cut open along the greater curvature and examined for ulcers generated in the glandular portion. The ulcer index was calculated as the sum of the area (mm^2) of each ulcer in the stomach. The inhibitory ratio (%) was obtained by comparing the ulcer index with that of the control group.

Ethanol-Induced Gastric Lesion The cytoprotective effect against absolute ethanol was examined by the method of Robert *et al.*[13] 6 week old male SD rats, weighing 150 to 210 g, were fasted for 24 h before the experiment. A suspension of the test drug in 0.1% MC was administered orally to a group of five rats. After 30 min, absolute ethanol (1 ml) was given orally, and the animals were sacrificed 1 h later. The stomachs were isolated and cut open along the greater curvature. The ulcer index was calculated as the sum of the length (mm) of each lesion in the glandular portion. The inhibitory ratio (%) was obtained by comparing the ulcer index with that of the control group.

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