Studies on Antiulcer Drugs. II.[1] Synthesis and Antiulcer Activities of Imidazo[1,2-*a*]pyridinyl-2-alkylaminobenzoxazoles and 5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridinyl Derivatives

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A series of imidazo[1,2-*a*]pyridinylbenzoxazoles (4) and 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridinylbenzoxazoles (5) were synthesized and tested for anti-stress ulcer activity in rats. Several compounds were found to be more active than the reference compounds, sucralfate, cimetidine and ranitidine. Some of them 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 gastric lesion; cytoprotective activity; imidazo[1,2-*a*]pyridinylbenzoxazole; 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridinylbenzoxazole; sucralfate; cimetidine; ranitidine; structure–activity relationship

In a previous paper[1] we reported the synthesis and pharmacological activities of a series of imidazo[1,2-*a*]-pyridinyl-2-oxobenz(o)-azolidines (**1**), imidazo[1,2-*a*]pyridinyl-3-oxo-2*H*-1,4-benz(o)-azines (**2**) and 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine analogues (**3**) as a novel class (*i.e.*, two bicyclic hetero-ring system) of antiulcer agents. Some derivatives of these compounds showed good antiulcer activities in restraint and water-immersion stressed rats and cytoprotective activities against ethanol-induced gastric lesion in rats, and the potencies were superior to that of the prototype compound, zolimidine.

A previously obtained result in which annulation with heterocycles onto the phenyl ring improved the pharmacological activities prompted us to investigate a different type of benzo-fused heterocyclic moiety instead of the oxobenz(o)-azolidines and oxobenz(o)-azines.

In this paper, we describe the synthesis and pharmacological evaluation of imidazo[1,2-*a*]pyridinyl-2-alkylaminobenzoxazoles and 5,6,7,8-tetrahydroimidazo[1,2-*a*]-pyridinyl analogues.

Chemistry The desired benzoxazoles (**4** and **5**) listed in Tables I and II were synthesized by the routes outlined in Charts 2—7.

The imidazo[1,2-*a*]pyridinylbenzoxazoles (**4**) were prepared by three different pathways. The first pathway is shown in Chart 2. Reduction of **6b**, followed by treatment with alkylisocyanate gave *o*-hydroxyphenylureas (**8**). Cyclization of **8** with polyphosphate ester (PPE)[2] as the

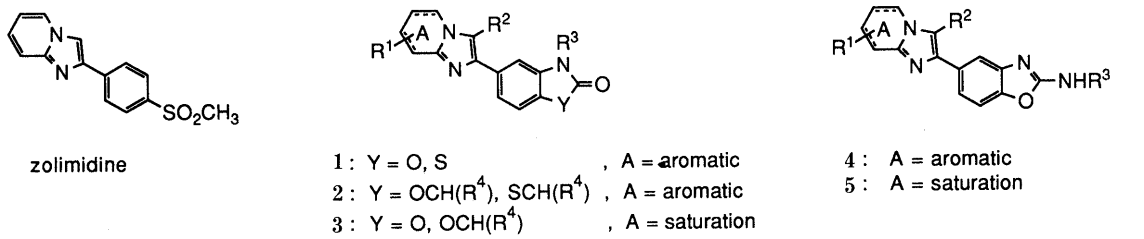


Chart 1

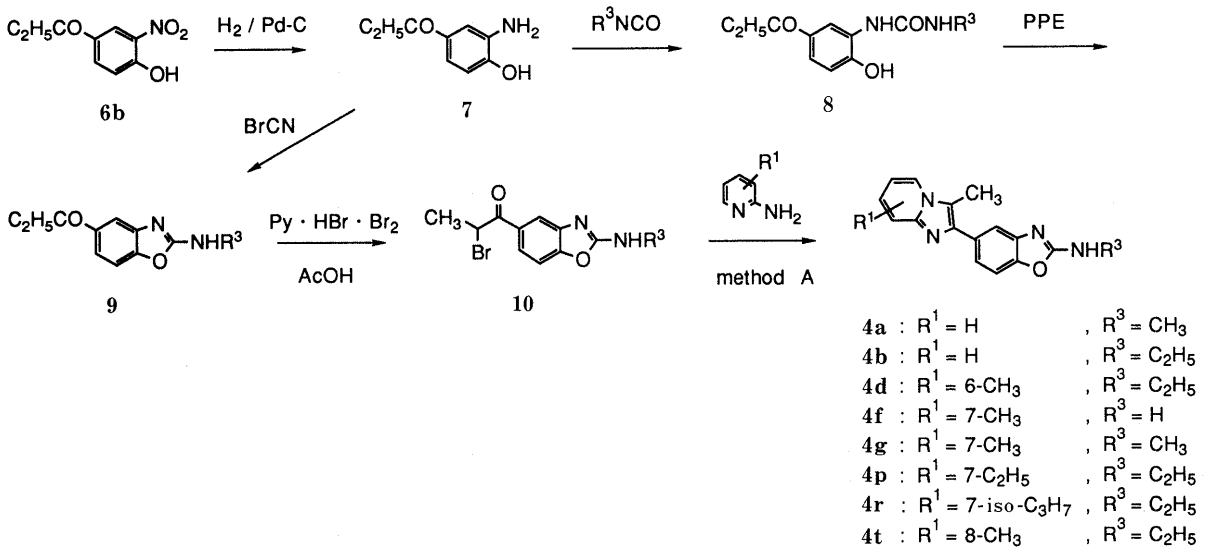
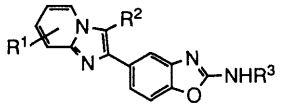


Chart 2

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



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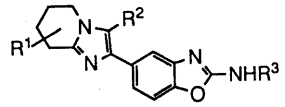
Compd. No.	R^1	R^2	R^3	Method	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
								C	H	N
4a	H	CH_3	CH_3	A	22	217—219 (A–H)	$C_{16}H_{14}N_4O$	69.05 (68.84)	5.07 4.99	20.13 20.00)
4b	H	CH_3	C_2H_5	A	24	198—200 (C–E)	$C_{17}H_{16}N_4O$	69.85 (69.60)	5.52 5.50	19.16 18.99)
4c	6-CH_3	H	C_2H_5	B_2	56	150—151 (AN)	$C_{17}H_{15}N_4O$	69.85 (69.74)	5.52 5.71	19.16 19.05)
4d	6-CH_3	CH_3	C_2H_5	A	34	238—241 (M–I)	$C_{18}H_{18}N_4O$	70.57 (70.61)	5.92 5.92	18.29 18.17)
4e	7-CH_3	H	C_2H_5	B_1	38	234—236 (EA–M–T)	$C_{17}H_{16}N_4O$	69.85 (69.72)	5.52 5.61	19.16 18.95)
4f	7-CH_3	CH_3	H	A	41	260—261 (EA)	$C_{16}H_{16}N_4O$	69.05 (68.77)	5.07 5.02	20.13 20.13)
4g	7-CH_3	CH_3	CH_3	A	49	245—246 (M–I)	$C_{17}H_{16}N_4O$	69.85 (69.61)	5.52 5.51	19.16 19.50)
4h	7-CH_3	CH_3	C_2H_5	B_1	50	215—217 (C)	$C_{18}H_{18}N_4O$	70.57 (70.32)	5.92 5.93	18.29 18.09)
4i	7-CH_3	CH_3	*n*-C_3H_7	B_1	44	203—204 (A–H)	$C_{19}H_{20}N_4O$	71.23 (71.30)	6.29 6.28	17.49 17.20)
4j	7-CH_3	CH_3	iso-C_3H_7	B_1	31	192—194 (EA)	$C_{19}H_{20}N_4O$	71.23 (70.84)	6.29 6.39	17.49 17.23)
4k	7-CH_3	CH_3	$CH_2CH=CH_2$	B_1	23	168—169 (A–I)	$C_{19}H_{18}N_4O$ ·1/5H_2O	70.87 (70.98)	5.76 5.82	17.40 17.22)
4l	7-CH_3	CH_3	c-C_6H_{11}	B_1	31	209—212 (I–M)	$C_{22}H_{24}N_4O$	73.31 (73.53)	6.71 6.62	15.54 15.37)
4m	7-CH_3	Br	C_2H_5	C	79	230—231 (I–M–T)	$C_{17}H_{15}BrN_4O$	55.00 (54.77)	4.07 4.04	15.10 14.79)
4n	7-CH_3	CHO	C_2H_5	B_3	36	220—221 (I–M–T)	$C_{18}H_{16}N_4O_2$	67.49 (67.33)	5.03 4.95	17.49 17.29)
4o	7-C_2H_5	H	C_2H_5	B_2	30	234—236 (A–EA)	$C_{18}H_{18}N_4O$	70.57 (70.42)	5.92 6.08	18.29 18.21)
4p	7-C_2H_5	CH_3	C_2H_5	A	47	162—164 (A–EA)	$C_{19}H_{20}N_4O$	71.23 (70.98)	6.29 6.25	17.49 17.73)
4q	7-iso-C_3H_7	H	C_2H_5	B_2	35	232—234 (I–M)	$C_{19}H_{20}N_4O$	71.23 (71.15)	6.29 6.41	17.49 17.78)
4r	7-iso-C_3H_7	CH_3	C_2H_5	A	68	193—195 (I–M)	$C_{20}H_{22}N_4O$	71.83 (71.55)	6.63 6.74	16.75 16.58)
4s	8-CH_3	H	C_2H_5	B_2	71	173—175 (AN)	$C_{17}H_{16}N_4O$	69.85 (69.73)	5.52 5.62	19.16 19.04)
4t	8-CH_3	CH_3	C_2H_5	A	69	212—214 (A–EA)	$C_{18}H_{18}N_4O$	70.57 (70.81)	5.92 5.97	18.29 18.36)

a) A, EtOH; AN, MeCN; C, CH_2Cl_2; EA, AcOEt; H, *n*-hexane; I, diisopropyl ether; M, MeOH; T, tetrahydrofuran.

dehydrating reagent furnished 2-alkylaminobenzoxazoles (**9**). Bromination of **9** with pyridinium bromide perbromide and subsequent condensation with the appropriate substituted 2-aminopyridines in the usual way[3] gave the desired compounds (**4**). The 2-unsubstituted aminobenzoxazole moiety was constructed from *o*-aminophenol derivative (**7**) by cyclization with cyanogen bromide (BrCN).[4] The resulting 2-aminobenzoxazole (**9a**) was brominated and condensed with 2-amino-4-methylpyridine to afford **4f** (method A). The second pathway is shown in Chart 3. The 4-(substituted imidazo[1,2-*a*]pyridin-2-yl)-2-aminophenols (**13**), obtained by the manner described in the previous paper,[1] were allowed to react with alkyl isocyanate to give the corresponding ureas (**14**). Cyclization of the ureas (**14**) with PPE provided the final products (**4**) (method B_1). In the third pathway, shown in Chart 4, the urea derivatives (**14**) were also formed by the reaction of the acetophenone (**15**) with pyridinium bromide perbromide and subsequent condensation with 2-aminopyridines. The *o*-hydroxyphenylureas were similarly cyclized with PPE to afford the required products (**4**) (method B_2). Introduction of formyl group at the 3-position on the imidazo[1,2-*a*]pyridine ring was performed through the route given in Chart 5. Formylation of **19**, prepared by the condensation of **18**[5] with 2-amino-4-methylpyridine, with phosphorous oxychloride in *N*,*N*-dimethylformamide (DMF) produced 3-formylimidazo[1,2-*a*]pyridine derivative (**20**). Reduction of the nitro group and simultaneous debenzylation by catalytic hydrogenation over Pd–C at room temperature under atmospheric pressure of hydrogen

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



5

Compd. No.	R^1	R^2	R^3	Method	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
								C	H	N
5a	H	H	C_2H_5	E	16	176—179 (AN)	$C_{16}H_{18}N_4O$	68.07 (67.76	6.43 6.38	19.84 19.75)
5b	H	CH_3	C_2H_5	D_1	73	217—218 (AN)	$C_{17}H_{20}N_4O$	68.90 (69.13	6.80 6.82	18.90 18.65)
5c	6-CH_3	H	C_2H_5	D_1	33	194—195 (I–M)	$C_{17}H_{20}N_4O$	68.90 (69.28	6.80 7.01	18.90 18.88)
5d	6-CH_3	CH_3	C_2H_5	D_1	24	228—231 (I–M)	$C_{18}H_{22}N_4O$	69.65 (69.47	7.14 7.28	18.05 17.83)
5e	7-CH_3	H	H	F	55	248—250 (A–I)	$C_{15}H_{16}N_4O$	64.96 (64.90	6.18 6.10	20.20 19.87)
5f	7-CH_3	H	CH_3	E	24	221—222 (AN)	$C_{16}H_{18}N_4O \cdot 1/3H_2O$	66.65 (66.91	6.52 6.56	19.43 19.59)
5g	7-CH_3	H	C_2H_5	E	18	184—186 (A–EA)	$C_{17}H_{20}N_4O$	68.90 (68.98	6.80 6.94	18.90 18.91)
5h	7-CH_3	H	*n*-C_3H_7	E	39	169—171 (AN)	$C_{18}H_{22}N_4O$	69.65 (69.50	7.14 7.12	18.05 17.96)
5i	7-CH_3	H	iso-C_3H_7	E	34	188—192 (A–AN)	$C_{18}H_{22}N_4O$	69.65 (69.35	7.14 7.42	18.05 18.02)
5j	7-CH_3	H	*n*-C_4H_9	E	36	169—172 (I–M)	$C_{19}H_{24}N_4O$	70.34 (70.17	7.46 7.53	17.27 17.21)
5k	7-CH_3	H	$CH_2CH=CH_2$	E	19	186—190 (I–M)	$C_{18}H_{20}N_4O$	70.11 (70.32	6.54 6.61	18.17 18.14)
5l	7-CH_3	CH_3	H	D_2	55	270—272	$C_{16}H_{18}N_4O$	68.07	6.43	19.84
				F	23	(EA–T)		(67.79	6.60	19.98)
5m	7-CH_3	CH_3	CH_3	D_2	68	250—252	$C_{17}H_{20}N_4O$	68.90	6.80	18.90
				E	15	(EA)		(68.69	6.82	18.57)
5n	7-CH_3	CH_3	C_2H_5	E	24	224—227 (A–I)	$C_{18}H_{22}N_4O_2$	69.65 (69.52	7.14 7.31	18.05 17.85)
5o	7-CH_3	CH_3	*n*-C_3H_7	D_1	62	191—193 (EA–T)	$C_{19}H_{24}N_4O$	70.34 (70.26	7.46 7.54	17.27 17.28)
5p	7-CH_3	CH_3	iso-C_3H_7	E	40	221—224 (A–I)	$C_{19}H_{24}N_4O$	70.34 (70.47	7.46 7.58	17.27 17.08)
5q	7-CH_3	CH_3	*n*-C_4H_9	E	40	137—138 (A–H)	$C_{20}H_{26}N_4O$	70.98 (70.63	7.74 8.06	16.55 16.39)
5r	7-CH_3	CH_3	$CH_2CH=CH_2$	E	32	213—216 (A–AN)	$C_{19}H_{22}N_4O$	70.78 (71.05	6.88 6.95	17.38 17.35)
5s	7-CH_3	Br	C_2H_5	C	62	226—229 (A)	$C_{17}H_{19}BrN_4O$	54.41 (54.66	5.10 5.08	14.93 14.76)
5t	7-C_2H_5	H	C_2H_5	D_2	35	222—223 (I–M)	$C_{18}H_{22}N_4O$	69.65 (69.37	7.14 7.24	18.05 17.79)
5u	7-C_2H_5	CH_3	C_2H_5	D_2	66	218—222 (EA–C)	$C_{19}H_{24}N_4O$	70.34 (70.56	7.46 7.38	17.27 17.52)
5v	7-iso-C_3H_7	H	C_2H_5	D_2	37	168—170 (EA–C)	$C_{19}H_{24}N_4O$	70.34 (70.08	7.46 7.48	17.27 17.31)
5w	7-iso-C_3H_7	CH_3	C_2H_5	D_2	25	229—230 (EA–C)	$C_{20}H_{26}N_4O$	70.98 (70.72	7.74 7.88	16.55 16.39)
5x	8-CH_3	H	C_2H_5	D_1	23	186—189 (A–H)	$C_{17}H_{20}N_4O$	68.90 (69.05	6.80 6.97	18.90 19.16)
5y	8-CH_3	CH_3	C_2H_5	D_2	25	185—186 (I–M)	$C_{18}H_{22}N_4O$	69.65 (69.41	7.14 7.32	18.05 17.92)

a) A, EtOH; AN, MeCN; C, CH_2Cl_2; EA, AcOEt; H, *n*-hexane; I, diisopropyl ether; M, MeOH; T, tetrahydrofuran.

gave *o*-aminophenol derivative (**21**). Treatment of **21** with ethyl isocyanate afforded urea derivative (**14h**), which was cyclized with PPE to provide **4n** (method B_3). The 3-bromo derivative (**4m**) of the imidazo[1,2-*a*]pyridine ring was obtained by the treatment of **4e** with pyridinium bromide perbromide (Chart 6) (method C).

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridinylbenzoxazoles (**5**) were prepared from imidazo[1,2-*a*]pyridine derivatives (**4**) by catalytic reduction over Pd–C or PtO_2[3d] at 3—9 atmospheric pressure of hydrogen (method D_1 or D_2). Alternatively, **5** could be obtained starting from the 4-(substituted imidazo[1,2-*a*]pyridin-2-yl)-2-nitrophenols (**12**). Catalytic reduction of **12** over Pd–C (3—5 atm), followed by treatment with alkyl isocyanate, and finally,

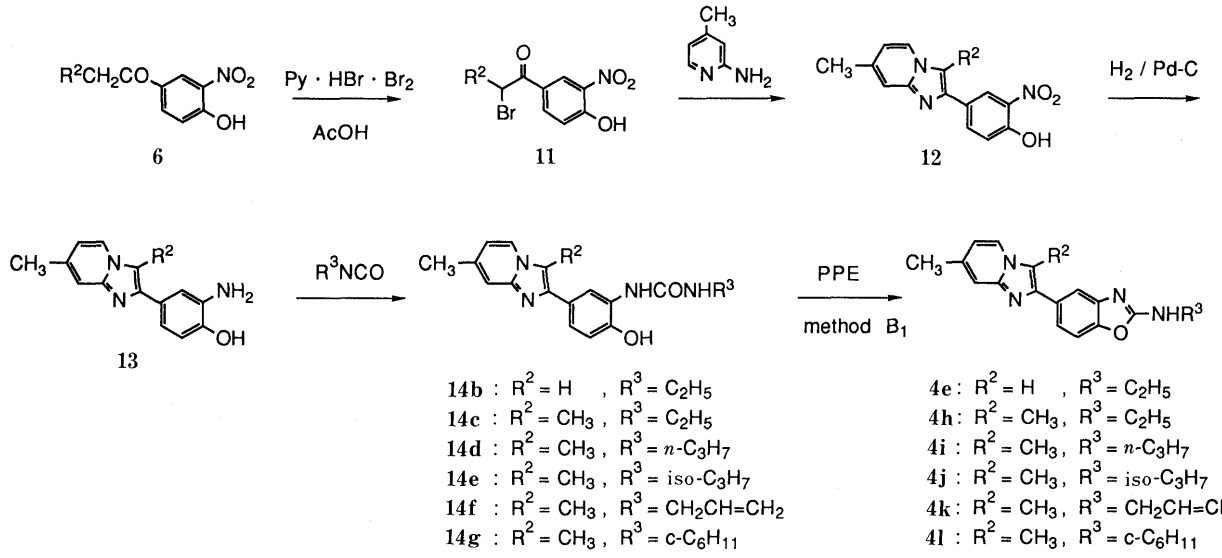


Chart 3

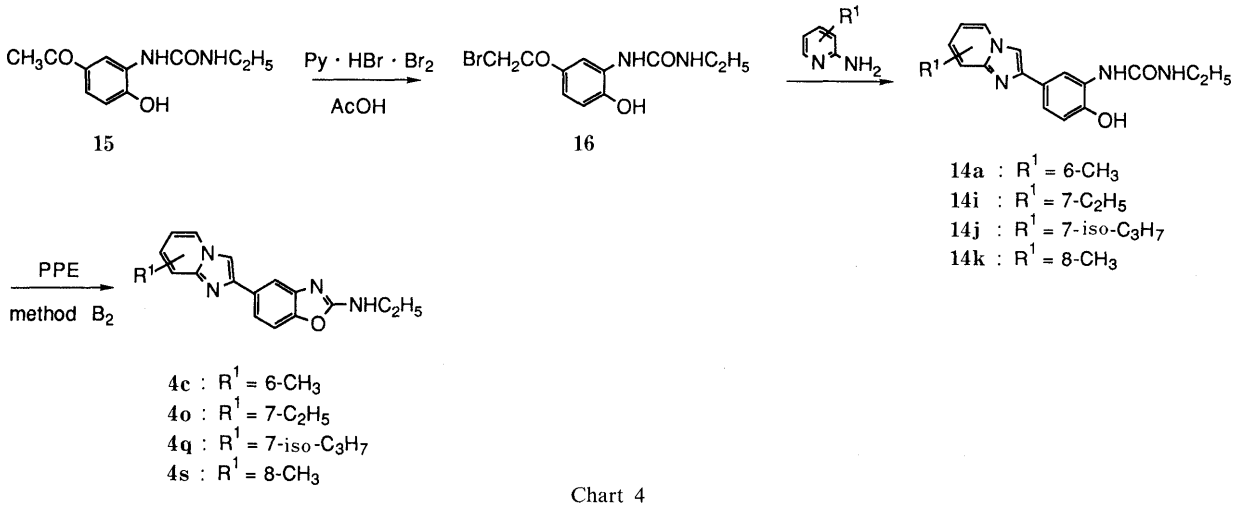


Chart 4

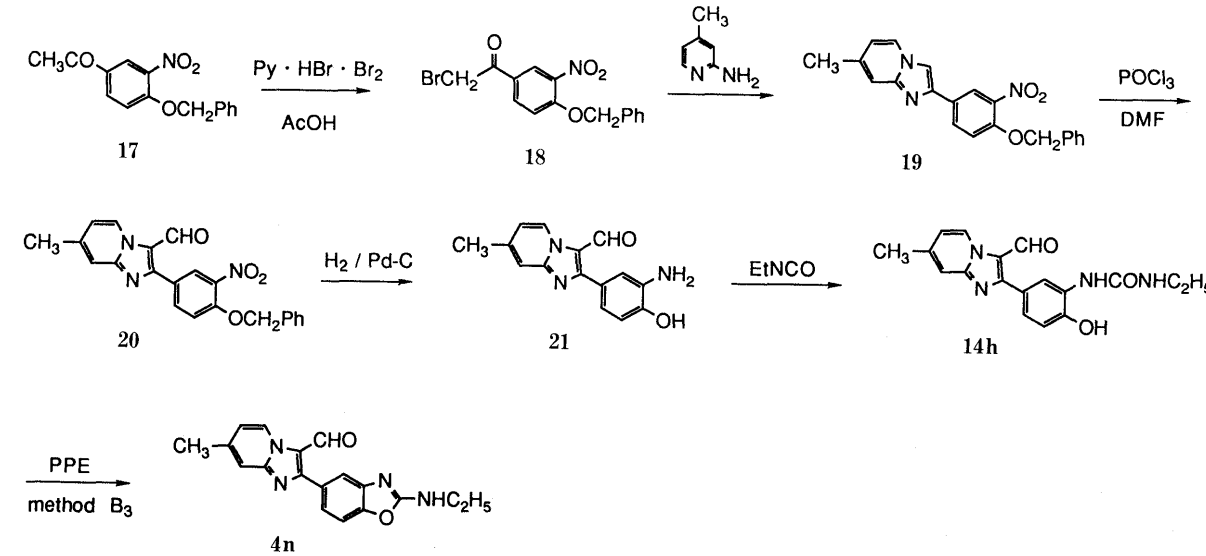


Chart 5

cyclization in the presence of PPE gave the desired products (**5**) (method E). Cyclization of *o*-aminophenols (**22b**, $R^1=7\text{-}CH_3$ $R^2=H$ and **22c**, $R^1=7\text{-}CH_3$ $R^2=CH_3$) with BrCN afforded 2-aminobenzoxazole derivatives (**5e** and **5l**), respectively (method F) (Chart 7).

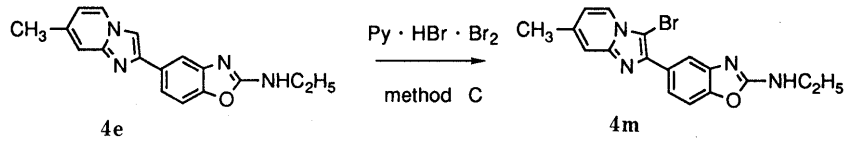


Chart 6

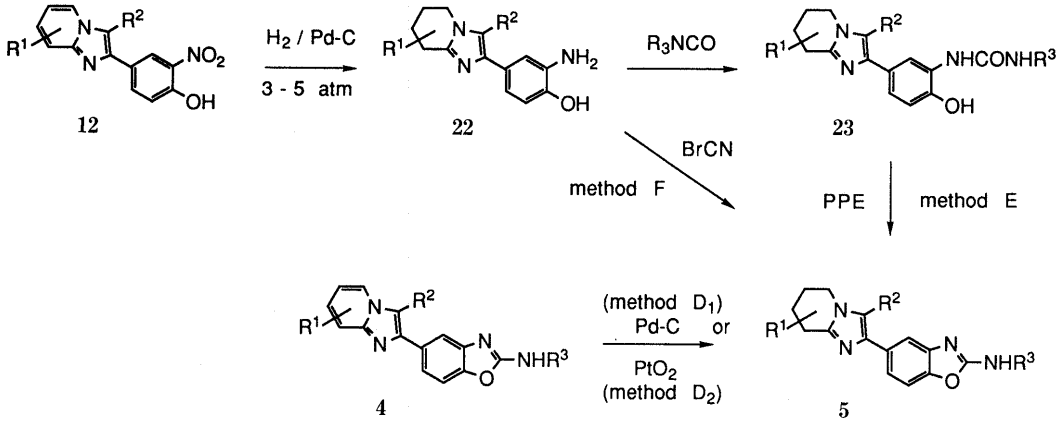


Chart 7

Pharmacological Results and Discussion

The imidazo[1,2-*a*]pyridinylbenzoxazoles (**4**) and 5,6,7,8-tetrahydro derivatives (**5**) obtained in this study were evaluated for antiulcer activity at a dose of 32 mg/kg *p.o.* in restraint and water-immersion stressed rats (stress ulcer). The results were compared with those of reference compounds, sucralfate, cimetidine and ranitidine, and are summarized in Table III.

In the series of the imidazo[1,2-*a*]pyridines (**4**), it could be seen that 3-methyl, 3,7-dimethyl and 3,8-dimethyl groups on this nucleus produced enhanced activity. Of these, the compounds **4b**, **4h** and **4t** possessing an ethyl group and **4k** containing an allyl group at the 2-position on the benzoxazole moiety exhibited remarkable antiulcer activity. Compounds **4a**, **4g**, **4i** and **4j**, produced by replacing the ethylamino group in **4b** and **4h** with a methyl- or a propylamino group, showed fairly good activity. Introduction of a more bulky substituent as in **4l**, however, caused disappearance of activity. Less potent activity was observed for the compound **4f** without substitution at the amino group. Concerning the substitution effect on the imidazo[1,2-*a*]pyridine ring, conversion of the 7-methyl group of **4h** to an ethyl group (**4p**) showed moderate activity which was comparable to that of cimetidine. On the other hand, 3-bromo (**4m**), 3-formyl (**4n**) and 3-unsubstituted (**4e**) derivatives on the imidazo-[1,2-*a*]pyridine nucleus resulted in a marked fall in activity. Compound **4d**, a positional isomer of the methyl group on the pyridine ring of **4h**, also had weak activity.

In the series of 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines (**5**), substitution at the 7-position on the tetrahydropyridine ring was advantageous for the expression of good activity. 7-Methyl (**5e**—**g**), 7-ethyl (**5t** and **5u**), 7-isopropyl (**5v**) and 3,7-dimethyl (**5l**—**p** and **5r**) derivatives revealed excellent potency. The activities of unsubstituted (**5b**) and 8-methyl (**5y**) derivatives on the tetrahydropyridine ring were relatively low. In particular, compounds **5a** and **5x**, which lack the methyl group on the 3-position, revealed completely loss of the activity. Replacement of the 3-methyl group in **5n** with a bromo group (**5s**) caused a reduction of the activity. As a substituent on the 2-amino group of benzoxazole moiety, introduction of a bulky group (**5i**, **5j** and **5q**) resulted in a reduced activity like the former series (**4**), while unsubstituted amino derivatives (**5e** and **5l**) showed good activity, contrary to **4**. These results appear to suggest that the activity of tetrahydro derivatives (**5**) were generally equivalent or superior to that of the corresponding unsaturated compounds (**4**) except

TABLE III. Anti-ulcer Activity of Benzoxazoles (**4** and **5**) 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	75.7[c]	**5e**	98.8[a]
4b	95.8[b]	**5f**	98.1[a]
4c	NT	**5g**	97.9[a]
4d	24.3	**5h**	69.8[b]
4e	14.6	**5i**	42.9
4f	46.0	**5j**	56.3[b]
4g	72.6	**5k**	67.6[b]
4h	97.1[a]	**5l**	91.8[b]
4i	79.7[a]	**5m**	100[a]
4j	80.9[a]	**5n**	97.8[b]
4k	89.4[a]	**5o**	97.1[b]
4l	2.2	**5p**	96.6[a]
4m	8.9	**5q**	59.3
4n	39.6	**5r**	95.7[a]
4o	NT	**5s**	59.2[b]
4p	68.2	**5t**	96.2[a]
4q	NT	**5u**	100[a]
4r	NT	**5v**	92.0[a]
4s	NT	**5w**	76.1
4t	86.0	**5x**	−6.0
5a	−12.5	**5y**	64.4[b]
5b	65.8[b]	Sucralfate	45.6[d]
5c	61.5[c]	Cimetidine	69.4[b]
5d	19.1	Ranitidine	81.8

a) $p<0.001$. *b*) $p<0.01$. *c*) $p<0.05$. *d*) 100 mg/kg. NT = Not tested.

in the cases of **5b** and **5y** *versus* **4b** and **4t**, respectively.

Next, dose–response activities of several compounds were examined on stress ulcer and cytoprotection against ethanol-induced gastric lesion (ethanol ulcer). The ED_{50} values and 95% confidence limits calculated in each test are shown in Table IV. All of the listed compounds were more efficacious than the reference compounds sucralfate, cimetidine and ranitidine on ethanol ulcer, and the activities of most of their derivatives on stress ulcer were superior to that of sucralfate and cimetidine.

In conclusion, we obtained several 2-aminobenzoxazole derivatives as novel structural antiulcer drugs. Although the reference drugs demonstrated a difference in their degree of activities on two ulcer models (stress ulcer and ethanol ulcer), these compounds synthesized showed strong inhibitory potency on both of the ulcer models.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were taken with a Hitachi 260-10 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a JNM-PMX 60 or a Varian EM-390 spectrometer using tetramethylsilane as an internal standard. Mass spectral measurements (MS) were made on a Hitachi M-80 or a JEOL JMS D-300 mass spectrometer.

3′-(3-Ethylureido)-4′-hydroxypropiophenone (8b) A solution of 3′-amino-4′-hydroxypropiophenone (**7**) (16.5 g, 100 mmol) and ethyl isocyanate (8.5 g, 120 mmol) in EtOH (80 ml)–THF (100 ml) was refluxed for 8 h with stirring. After the mixture was cooled, the resulting precipitate was isolated by filtration to afford **8b** (8.6 g, 36%). The filtrate was concentrated to a half volume *in vacuo* and the precipitate formed was collected by filtration to recover a second crop of **8b** (9.1 g, 39%). An analytical sample was obtained by recrystallization from MeOH–THF, mp 194—195 °C. *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.39; H, 7.08; N, 11.79. IR (Nujol): 3400, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (6H, t, J=7 Hz), 2.90 (2H, q, J=7 Hz), 2.83—3.47 (2H, m), 6.83 (1H, t, J=5 Hz), 6.87 (1H, d, J=8 Hz), 7.45 (1H, dd, J=2, 8 Hz), 7.93 (1H, s), 8.58 (1H, d, J=2 Hz), 10.70 (1H, s). MS m/z: 236 (M^+).

2-Amino-5-propionylbenzoxazole (9a) A solution of **7** (12.4 g, 75 mmol) and BrCN (8.8 g, 83 mmol) in EtOH (150 ml) was stirred for 2 h at room temperature. The resulting precipitate was collected by filtration and dissolved in H_2O (120 ml). After being adjusted to pH 8 with 20% aqueous K_2CO_3, the aqueous solution was extracted with AcOEt. The extract was washed H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was triturated with Et_2O to afford **9a** (5.7 g, 40%). An analytical sample was obtained by recrystallization from MeOH. *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.18; H, 5.30; N, 14.69. IR (Nujol): 3375, 3300, 1690, 1670 cm^{-1}. MS m/z: 190 (M^+).

2-Ethylamino-5-propionylbenzoxazole (9c) A mixture of **8b** (8.4 g, 36 mmol) and PPE (67 g) was stirred at 120 °C for 30 min. The reaction mixture was poured into H_2O (70 ml)–AcOEt (70 ml), and the aqueous layer was separated. The aqueous solution was adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography eluting with AcOEt–diisopropyl ether (IPE) (2:8) to afford **9c** (3.6 g, 44%). An analytical sample was obtained by recrystallization from MeCN. *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.43; H, 6.48; N, 12.87. IR (Nujol): 3350, 1655 cm^{-1}. MS m/z: 218 (M^+).

5-(2-Bromopropionyl)-2-ethylaminobenzoxazole (10c) A solution of **9c** (1.6 g, 7.3 mmol), pyridinium bromide perbromide (2.8 g, 8.8 mmol) and 30% HBr–AcOH (5 ml) in AcOH (20 ml) was stirred at room temperature for 1 h. After the mixture was poured into H_2O, the solution was adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from AcOEt–IPE to afford **10c** (1.8 g, 83%). *Anal.* Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.43. Found: C, 48.56; H, 4.42; N, 9.32. IR (Nujol): 1700, 1675 cm^{-1}. MS m/z: 298 ($M^+ - 1$).

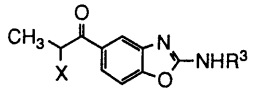
2-Ethylamino-5-(3-methylimidazo[1,2-*a*]pyridin-2-yl)benzoxazole (4b)

TABLE IV. ED_{50} Values of Some Benzoxazole Derivatives on Anti-stress Ulcer and Cytopotective Activity

Compound No.	ED_{50} value (mg/kg, *p.o.*) (95% confidence limits)	
	Anti-stress ulcer activity	Cytoprotective activity
4b	20.1 (5.3—76.7)	14.2 (9.9—20.3)
4h	10.6 (6.3—17.8)	0.05[b]
4j	15.1 (7.1—32.1)	0.10 (0.0063—2.17)
4k	16.2 (11.6—22.8)	4.4 (0.04—9.6)
5e	3.9 (1.3—11.7)	1.2 (0.18—8.5)
5f	7.6 (4.8—12.0)	1.6 (0.45—5.9)
5g	1.7 (0.32—8.8)	1.6 (0.51—5.0)
5l	9.1 (3.2—26.1)	6.3 (2.6—11.3)
5o	9.5 (6.7—13.5)	0.80 (0.20—3.5)
5p	0.13[a]	2.64 (1.67—4.17)
5r	9.4 (2.6—34.3)	9.5 (5.4—19.0)
5t	1.3 (0.27—6.4)	4.2 (0.84—7.4)
5u	7.3 (3.7—14.2)	12.5 (6.0—26.0)
5v	4.5 (1.2—16.7)	5.1 (2.5—10.8)
Sucralfate	156 (45.5—535)	55.7 (8.6—363)
Cimetidine	18.8 (5.1—69.1)	>320[c]
Ranitidine	1.5 (0.18—11.6)	29.6 (14.7—71.1)

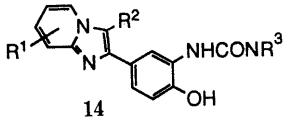
a) No dose-related response was observed. *b*) Inhibitory rate: 84.2% at 3.2 mg/kg, 85.0% at 10 mg/kg, 95.4% at 32 mg/kg. *c*) Inhibitory rate: 40.3% at 100 mg/kg, 23.7% at 320 mg/kg.

TABLE V. Physical Data of 2-Substituted Amino-5-acylbenzoxazoles (**9** and **10**)



Compd. No.	X	R^3	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
9a	H	H	40	225—227	1.09 (3H, t, J=7), 3.05 (2H, q, J=7), 7.43 (1H, d, J=8), 7.63 (2H, s), 7.67 (1H, dd, J=2, 8), 7.78 (1H, d, J=2)
9b	H	CH_3	45	153—155	1.10 (3H, t, J=7), 2.95 (3H, d, J=5), 3.05 (2H, q, J=7), 7.43 (1H, d, J=9), 7.72 (1H, dd, J=2, 9), 7.85 (1H, d, J=2), 8.00 (1H, q, J=5)
9c	H	C_2H_5	44	130—132	1.17 (3H, t, J=7), 1.25 (3H, t, J=7), 3.07 (2H, q, J=7), 3.13—3.67 (2H, m), 7.43 (1H, d, J=9), 7.70 (1H, dd, J=2, 9), 7.85 (1H, d, J=2), 8.10 (1H, t, J=5)
10a	Br	H	90	138—140	1.83 (3H, d, J=7), 5.87 (1H, q, J=7), 7.33—8.50 (5H, m)
10b	Br	CH_3	67	131—133	1.78 (3H, d, J=7), 2.93 (3H, d, J=5), 5.87 (1H, q, J=7), 7.50 (1H, d, J=9), 7.82 (1H, dd, J=2, 9), 7.97 (1H, d, J=2), 8.07 (1H, q, J=5)
10c	Br	C_2H_5	83	142—144	1.22 (3H, t, J=7), 1.79 (3H, t, J=7), 3.18—3.53 (2H, m), 5.84 (1H, q, J=7), 7.44 (1H, d, J=9), 7.73 (1H, dd, J=2, 9), 7.90 (1H, d, J=2), 8.13 (1H, t, J=5)

TABLE VI. Physical Data of 2-[3-(3-Alkylureido)-4-hydroxyphenyl]imidazo[1,2-*a*]pyridines (**14**)



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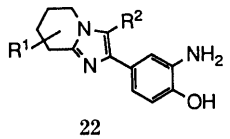
Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C)	IR (Nujol) cm^{-1} (C=O)	^{1}H-NHR	
							Solvent	δ (J=Hz)
14a	6-CH_3	H	C_2H_5	72	>300	1630	CF_3COOH	1.35 (3H, t, J=7), 2.57 (3H, s), 3.53 (2H, q, J=7), 7.23 (1H, d, J=9), 7.64 (1H, d, J=9), 7.80 (2H, s), 8.03 (2H, s), 8.35 (1H, s)
14b	7-CH_3	H	C_2H_5	84	>300	1630	CF_3COOH	1.37 (3H, t, J=7), 2.70 (3H, s), 3.57 (2H, q, J=7), 7.07—7.67 (4H, m), 8.00—8.07 (2H, m), 8.47 (1H, d, J=7)
14c	7-CH_3	CH_3	C_2H_5	77	>300	1660	CF_3COOH	1.37 (3H, t, J=7), 2.72 (3H, s), 2.75 (3H, s), 3.57 (2H, q, J=7), 7.20—8.23 (5H, m), 8.35 (1H, d, J=7)
14d	7-CH_3	CH_3	n-C_3H_7	91	233—236	1650	DMSO-d_6	0.90 (3H, t, J=7), 1.40—1.75 (2H, m), 2.36 (3H, s), 2.63 (3H, s), 3.21 (2H, t, J=7), 6.55—6.95 (2H, m), 7.05—7.31 (2H, m), 7.87 (1H, s), 8.10 (1H, d, J=7), 8.30 (1H, d, J=2)
14e	7-CH_3	CH_3	iso-C_3H_7	78	231	1640	DMSO-d_6	1.12 (6H, d, J=7), 2.36 (3H, s), 2.59 (3H, s), 3.47—3.86 (1H, m), 6.60—6.94 (2H, m), 7.08—7.35 (2H, m), 7.83 (1H, s), 8.13 (1H, d, J=6), 8.35 (1H, d, J=2), 9.94 (1H, br s)
14f	7-CH_3	CH_3	$CH_2CH=CH_2$	91	226—228	1630	DMSO-d_6	2.37 (3H, s), 2.61 (3H, s), 3.76 (2H, t, J=5), 4.94—5.39 (2H, m), 5.59—6.18 (1H, m), 6.73 (1H, d, J=7), 6.86 (1H, d, J=8), 7.21 (1H, dd, J=2, 8), 7.27 (1H, s), 8.07 (1H, s), 8.14 (1H, d, J=7), 8.40 (1H, d, J=2)
14g	7-CH_3	CH_3	c-C_6H_{11}	93	215—218	1655	DMSO-d_6	1.08—1.79 (10H, m), 2.36 (3H, s), 2.58 (3H, s), 3.41—3.56 (1H, m), 6.76 (1H, dd, J=2, 7), 6.82 (1H, d, J=6), 6.85 (1H, d, J=8)7.20 (1H, dd, J=2, 8), 7.28 (1H, d, J=2), 7.89 (1H, s), 8.16 (1H, d, J=7), 8.40 (1H, d, J=2), 10.02 (1H, br s)
14h	7-CH_3	CHO	C_2H_5	79	213—214	1635	DMSO-d_6	1.07 (3H, t, J=7), 2.50 (3H, s), 3.22 (2H, q, J=7), 6.97—7.08 (2H, m), 7.25 (1H, dd, J=2, 7), 7.63 (1H, s), 8.08 (1H, s), 8.50 (1H, d, J=2), 9.43 (1H, d, J=7), 10.01 (1H, s)
14i	7-C_2H_5	H	C_2H_5	59	168—169	1640	CF_3COOH	1.38 (3H, t, J=7), 1.48 (3H, t, J=7), 3.00 (2H, q, J=7), 3.57 (2H, q, J=7), 7.20—7.77 (3H, m), 7.73 (1H, s), 7.90—8.10 (2H, m), 8.46 (1H, d, J=7)
14j	7-iso-C_3H_7	H	C_2H_5	55	233	1635	DMSO-d_6	1.11 (3H, t, J=7), 1.28 (6H, d, J=7), 2.80—3.50 (3H, m), 6.70—7.00 (3H, m), 7.32 (1H, d, J=2), 7.39 (1H, dd, J=2, 7), 8.02 (1H, d, J=7), 8.06 (1H, s), 8.40 (1H, d, J=7), 8.51 (1H, d, J=2)
14k	8-CH_3	H	C_2H_5	71	216—218	1630	CF_3COOH	1.36 (3H, t, J=7), 2.78 (3H, s), 3.54 (2H, q, J=7), 7.24 (1H, d, J=8), 7.39—7.96 (3H, m), 8.02—8.23 (2H, m), 8.44 (1H, d, J=7)

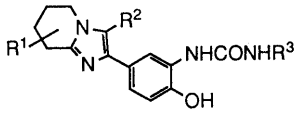
TABLE VII. Physical Data of 2-(3-Amino-4-hydroxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines (**22**)



22

Compd. No.	R^1	R^2	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
22a	H	H	72	182—187	1.58—2.05 (4H, m), 2.54—2.85 (2H, m), 3.73—3.96 (2H, m), 4.43 (2H, br s), 6.56 (1H, d, J=8), 6.74 (1H, dd, J=2, 8), 6.97 (1H, d, J=2), 7.04 (1H, s)
22b	7-CH_3	H	64	252—257	1.06 (3H, d, J=6), 1.47—2.41 (4H, m), 2.67—3.11 (1H, m), 3.75—4.33 (2H, m), 6.57 (1H, d, J=8), 6.79 (1H, dd, J=2, 8), 7.04 (1H, s), 7.08 (1H, d, J=2)
22c	7-CH_3	CH_3	82	238—242	1.07 (3H, d, J=7), 1.37—2.40 (4H, m), 2.26 (3H, s), 2.64—3.07 (1H, m), 3.56—4.04 (2H, m), 6.64 (2H, s), 6.91 (1H, s)

TABLE VIII. Physical Data of 2-[3-(3-Alkylureido)-4-hydroxyphenyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines (**23**)



23

Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C)	IR (Nujol) cm^{-1} (C=O)	^{1}H-NMR	
							Solvent	δ (J=Hz)
23a	H	H	C_2H_5	92	197—199	1660	DMSO-d_6	1.06 (3H, t, J=7), 1.63—2.10 (4H, m), 2.36—2.86 (2H, m), 2.94—3.45 (2H, m), 3.78—4.10 (2H, m), 6.60—6.93 (1H, m), 6.70 (1H, d, J=8), 7.07 (1H, dd, J=2, 8), 7.10 (1H, s), 7.83 (1H, s), 8.13 (1H, s)
23b	7-CH_3	H	CH_3	100	226—228	1630	CF_3COOH	1.91 (3H, d, J=5), 1.77—2.65 (4H, m), 2.70—3.00 (1H, m), 3.07 (3H, s), 4.13—4.51 (2H, m), 7.17 (1H, d, J=8), 7.35 (1H, s), 7.46 (1H, dd, J=2, 8), 7.70 (1H, d, J=2)
23c	7-CH_3	H	C_2H_5	97	209—211	1680	DMSO-d_6	1.07 (3H, t, J=7), 1.07 (3H, d, J=6), 1.46—2.60 (4H, m), 2.67—2.98 (1H, m), 2.94—3.41 (2H, m), 3.73—4.20 (2H, m), 6.56—6.86 (1H, m), 6.69 (1H, d, J=8), 7.08 (1H, dd, J=2, 8), 7.10 (1H, s), 7.81 (1H, s), 8.11 (1H, d, J=2), 9.73 (1H, s)
23d	7-CH_3	H	n-C_3H_7	85	224—226	1640	DMSO-d_6	0.92 (3H, t, J=7), 1.08 (3H, d, J=5), 1.25—2.40 (6H, m), 2.66—3.42 (3H, m), 3.72—4.38 (2H, m), 6.55—6.90 (1H, m), 6.72 (1H, d, J=8), 7.09 (1H, dd, J=2, 8), 7.13 (1H, s), 7.86 (1H, s), 8.17 (1H, d, J=2), 9.75 (1H, br s)
23e	7-CH_3	H	iso-C_3H_7	96	218—220	1670	DMSO-d_6	0.78—1.34 (9H, m), 1.55—2.66 (4H, m), 2.67—3.11 (1H, m), 3.57—4.30 (3H, m), 6.52—6.86 (2H, m), 7.08 (1H, dd, J=2, 8), 7.14 (1H, s), 7.75 (1H, s), 8.18 (1H, d, J=2), 9.73 (1H, br s)
23f	7-CH_3	H	n-C_4H_9	95	221—223	1640	CF_3COOH	1.10 (3H, t, J=7), 1.17—2.60 (8H, m), 1.31 (3H, d, J=5), 2.67—2.97 (1H, s), 3.30—3.67 (2H, m), 3.90—4.50 (2H, m), 7.16 (1H, d, J=9), 7.35 (1H, s), 7.45 (1H, dd, J=2, 9), 7.79 (1H, d, J=2)
23g	7-CH_3	H	$CH_2CH=CH_2$	97	221—223	1640	DMSO-d_6	1.06 (3H, d, J=6), 1.38—2.40 (4H, m), 2.70—3.06 (1H, m), 3.51—4.14 (4H, m), 4.96—5.37 (2H, m), 5.65—6.17 (1H, m), 6.73 (1H, d, J=8), 6.88 (1H, t, J=6), 7.10 (1H, dd, J=2, 8), 7.12 (1H, s), 8.95 (1H, s), 8.21 (1H, d, J=2), 9.74 (1H, s)
23h	7-CH_3	CH_3	CH_3	95	207—208	1640	CF_3COOH	1.31 (3H, d, J=5), 1.68—2.63 (4H, m), 2.47 (3H, s), 2.63—2.91 (1H, m), 3.08 (3H, s), 3.82—4.38 (2H, m), 7.20 (1H, d, J=8), 7.38 (1H, dd, J=2, 8), 7.60 (1H, d, J=2)
23i	7-CH_3	CH_3	C_2H_5	87	225—226	1635	DMSO-d_6	1.06 (3H, t, J=7), 1.07 (3H, d, J=6), 1.49—2.41 (4H, m), 2.26 (3H, s), 2.65—2.93 (1H, m), 2.93—3.44 (2H, m), 3.57—3.94 (2H, m), 6.56—6.88 (2H, m), 6.98 (1H, d, J=2, 8), 7.83 (1H, s), 8.04 (1H, d, J=2), 9.76 (1H, br s)
23j	7-CH_3	CH_3	iso-C_3H_7	78	204—206	1655	$CDCl_3$ + CD_3OD	1.17 (3H, d, J=6), 1.20 (6H, d, J=6), 1.56—2.70 (4H, m), 2.32 (3H, s), 2.86—3.16 (1H, m), 3.56—4.16 (3H, m), 6.92 (1H, d, J=8), 7.15 (1H, dd, J=2, 8), 7.37 (1H, d, J=2)
23k	7-CH_3	CH_3	n-C_4H_9	59	209—211	1680	CF_3COOH	1.00 (3H, t, J=6), 1.18—2.56 (8H, m), 1.31 (3H, d, J=5), 2.44 (3H, s), 2.63—2.93 (1H, m), 3.33—3.71 (2H, m), 3.90—4.39 (2H, m), 7.21 (1H, d, J=8), 7.39 (1H, d, J=8), 7.63 (1H, s)
23l	7-CH_3	CH_3	$CH_2CH=CH_2$	57	210—212	1630	$CDCl_3$ + CD_3OD	1.15 (3H, d, J=5), 1.46—2.71 (4H, m), 2.30 (3H, s), 2.87—3.17 (1H, s), 3.48—4.20 (4H, m), 5.04—5.40 (2H, m), 5.88—6.15 (1H, m), 6.90 (1H, d, J=9), 7.14 (1H, dd, J=2, 9), 7.46 (1H, d, J=2)

Method A: A solution of **10c** (1.9 g, 6.4 mmol) and 2-aminopyridine (1.8 g, 19 mmol) in MeCN (40 ml) was refluxed for 7 h with stirring. The resulting precipitate was collected by filtration and dissolved in AcOEt (20 ml)–5% HCl (20 ml). The aqueous layer was separated out, adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to afford **4b** (0.45 g, 24%). IR (Nujol): 1675 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz), 2.63 (3H, s), 3.17—3.53 (2H, m), 6.90 (1H, dt, J=2, 7 Hz), 7.20—7.63 (5H, m), 7.90 (1H, t, J=5 Hz), 8.25 (1H, dd, J=2, 7 Hz).

2-Bromo-3′-(3-ethylureido)-4′-hydroxyacetophenone (16) Pyridinium bromide perbromide (114 g, 356 mmol) was added in portions to a solution of 3′-(3-ethylureido)-4′-hydroxyacetophenone (**15**) (72 g, 320 mmol) and 25% HBr–AcOH (140 ml) in AcOH (580 ml). After being stirred at room temperature for 4 h, the mixture was poured into H_2O. The resulting precipitate was collected by filtration and washed with water to afford **16** (69 g, 70%), which was not recrystallized because of its relative instability, mp 180—181 °C. *Anal.* Calcd for $C_{11}H_{13}BrN_2O_3$: C, 43.87; H, 4.35; N, 9.30. Found: C, 43.65; H, 4.22; N, 9.04. IR (Nujol): 3400, 1680, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.05 (3H, t,

$J=7$ Hz), 3.11 (2H, q, $J=7$ Hz), 4.72 (2H, s), 6.89 (1H, d, $J=8$ Hz), 7.51 (1H, dd, $J=2$, 8 Hz), 8.00 (1H, br s), 8.64 (1H, d, $J=2$ Hz).

2-[3-(3-Ethylureido)-4-hydroxyphenyl]-6-methylimidazo[1,2-*a*]pyridine (14a) A mixture of **16** (10.0 g, 33 mmol) and 2-amino-5-methylpyridine (9.0 g, 83 mmol) in EtOH (100 ml) was refluxed for 3.5 h with stirring. After cooling in an ice bath, the resulting precipitate was collected by filtration and added to H_2O (100 ml). The pH of the mixture was adjusted to 8 with 10% aqueous K_2CO_3 and the product separated out was collected by filtration to afford **14a** (7.4 g, 72%). An analytical sample was obtained by recrystallization from IPE–MeOH–THF. *Anal.* Calcd for $C_{17}H_{18}N_4O_2 \cdot 4/5H_2O$: C, 62.82; H, 6.07; N, 17.24. Found: C, 62.74; H, 6.02; N, 16.97. IR (Nujol): 3300, 1630 cm^{-1}. MS *m/z*: 310 (M^+).

2-[3-(3-Ethylureido)-4-hydroxyphenyl]-7-methylimidazo[1,2-*a*]pyridine (14b) A mixture of 2-(3-amino-4-hydroxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (**13b**)[1] (12.8 g, 49 mmol) and ethyl isocyanate (4.2 g, 59 mmol) in MeOH (50 ml)–THF (100 ml) was refluxed with stirring for 3 h. After the reaction mixture was cooled, the resulting precipitate was collected by filtration and washed with MeOH to afford **14b** (12.8 g, 84%). An analytical sample was obtained by recrystallization from IPE–MeOH–THF. *Anal.* Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.76; H, 5.93; N, 17.80. IR (Nujol): 3300, 1630 cm^{-1}. MS *m/z*: 310 (M^+).

2-Ethylamino-5-(7-methylimidazo[1,2-*a*]pyridin-2-yl)benzoxazole (4e) Methods B_1 and B_2: A mixture of **14b** (10.5 g, 34 mmol) and PPE (100 g) was stirred at 120 °C for 1.5 h and the reaction mixture was poured into H_2O (100 ml). The solution was washed with AcOEt (100 ml), adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was subjected to silica gel chromatography by eluting with $CHCl_3$–MeOH (20 : 1), and the product obtained was recrystallized from AcOEt–MeOH–THF to afford **4e** (3.7 g, 38%). IR (Nujol): 1695, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, $J=7$ Hz), 2.36 (3H, s), 3.18—3.55 (2H, m), 6.72 (1H, dd, $J=2$, 7 Hz), 7.32 (1H, d, $J=8$ Hz), 7.34 (1H, d, $J=2$ Hz), 7.57 (1H, dd, $J=2$, 8 Hz), 7.78 (1H, d, $J=2$ Hz), 7.90 (1H, t, $J=5$ Hz), 8.23 (1H, s), 8.34 (1H, d, $J=7$ Hz).

2-(4-Benzyloxy-3-nitrophenyl)-7-methylimidazo[1,2-*a*]pyridine (19) This compound was prepared from 4′-benzyloxy-3′-nitro-2-bromoacetophenone (**18**)[5] in the similar manner as described for **4b** from **10c**. Yield 65%, mp 162—164 °C (DMF–H_2O). *Anal.* Calcd for $C_{21}H_{17}N_3O_3$: C, 70.58; H, 4.77; N, 11.69. Found: C, 70.21; H, 4.92; N, 11.54. IR (Nujol): 1640, 1620, 1525, 1350 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 5.35 (2H, s), 6.75 (1H, dd, $J=2$, 7 Hz), 7.35—7.53 (7H, m), 8.18 (1H, s), 8.37 (1H, s), 8.41 (1H, d, $J=7$ Hz), 8.43 (1H, d, $J=2$ Hz). MS *m/z*: 359 (M^+).

2-(4-Benzyloxy-3-nitrophenyl)-3-formyl-7-methylimidazo[1,2-*a*]pyridine (20) $POCl_3$ (24.7 g, 161 mmol) was added dropwise to a solution of **19** (29 g, 81 mmol) in DMF (300 ml) at room temperature with stirring. After being stirred for 8 h at 65 °C, the mixture was poured into H_2O (1.2 l) and adjusted to pH 8 with 20% aqueous K_2CO_3. The resulting precipitate was collected by filtration and washed with H_2O to afford **20** (30 g, 95%). An analytical sample was obtained by recrystallization from DMF–H_2O, mp 162—164 °C. *Anal.* Calcd for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.42; N, 10.85. Found: C, 68.05; H, 4.51; N, 10.73. IR (Nujol): 1640, 1535, 1360 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.47 (3H, s), 5.41 (2H, s), 7.18 (1H, dd, $J=2$, 7 Hz), 7.33—7.68 (8H, m), 8.18 (1H, d, $J=2$ Hz), 9.40 (1H, d, $J=7$ Hz), 9.99 (1H, s).

2-(3-Amino-4-hydroxyphenyl)-3-formyl-7-methylimidazo[1,2-*a*]pyridine (21) A suspension of **20** (10.0 g, 26 mmol) in MeOH (200 ml)–THF (200 ml) was hydrogenated under atmospheric pressure of H_2 over 10% Pd–C (1.5 g) at room temperature. After the catalyst was filtered off, the filtrate was evaporated *in vacuo*. The residue was triturated with Et_2O to afford **21** (3.2 g, 47%). An analytical sample was obtained by recrystallization from MeOH–IPE, mp 265—270 °C. *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.51; H, 4.86; N, 15.68. IR (Nujol): 3450, 3360, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.46 (3H, s), 4.85 (1H, br s), 6.80 (1H, d, $J=8$ Hz), 6.97 (1H, dd, $J=2$, 8 Hz), 7.12 (1H, dd, $J=2$, 7 Hz), 7.20 (1H, d, $J=2$ Hz), 7.62 (1H, d, $J=2$ Hz), 9.41 (1H, d, $J=7$ Hz), 9.95 (1H, s). MS *m/z*: 267 (M^+).

2-[3-(3-Ethylureido)-4-hydroxyphenyl]-3-formyl-7-methylimidazo[1,2-*a*]pyridine (14h) This compound was prepared from **21** in the similar manner described for **14b** from **13b**. An analytical sample was obtained by recrystallization from DMF–H_2O. *Anal.* Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.60; H, 5.40; N, 16.32. IR (Nujol): 3330, 1635 cm^{-1}. MS *m/z*: 338 (M^+).

2-Ethylamino-5-(3-formyl-7-methylimidazo[1,2-*a*]pyridin-2-yl)benzoxazole (4n) Method B_3: A mixture of **14h** (2.9 g, 8.6 mmol) and PPE (20 g) was stirred for 1 h at 120 °C. The reaction mixture was poured into H_2O (30 ml), adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt–THF. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on alumina by eluting with $CHCl_3$–AcOEt (4 : 1), and the product obtained was recrystallized from IPE–MeOH–THF to afford **4n** (1.0 g, 36%). IR (Nujol): 3370, 1700, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, $J=7$ Hz), 2.47 (3H, s), 3.21—3.55 (2H, m), 7.14 (1H, dd, $J=2$, 7 Hz), 7.47 (2H, s), 7.66 (1H, s), 7.68 (1H, d, $J=2$ Hz), 8.03 (1H, t, $J=5$ Hz), 9.40 (1H, d, $J=7$ Hz), 9.93 (1H, s).

5-(3-Bromo-7-methylimidazo[1,2-*a*]pyridin-2-yl)-2-ethylaminobenzoxazole (4m) Method C: Pyridinium bromide perbromide (1.3 g, 4.1 mmol) was added in portions to a solution of **4e** (1.0 g, 3.4 mmol) and 25% HBr–AcOH (0.2 ml) in AcOH (10 ml) at room temperature with stirring. After being stirred for 1 h, the mixture was poured into H_2O (100 ml). The solution was adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from IPE–MeOH–THF to afford **4m** (1.0 g, 79%). IR (Nujol): 1675 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, $J=7$ Hz), 2.40 (3H, s), 3.20—3.56 (2H, m), 6.91 (1H, dd, $J=2$, 7 Hz), 7.41 (1H, d, $J=8$ Hz), 7.42 (1H, d, $J=2$ Hz), 7.71 (1H, dd, $J=2$, 8 Hz), 7.90 (1H, d, $J=2$ Hz), 7.95 (1H, t, $J=5$ Hz), 8.23 (1H, d, $J=7$ Hz).

5-(3,7-Dimethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl)-2-*n*-propylaminobenzoxazole (5o) Method D_1: A mixture of **4k** (0.65 g, 2.0 mmol) in EtOH (200 ml) was hydrogenated over 10% Pd–C (0.1 g) under 3—5 atmospheric pressure of H_2 for 3 h at 60—70 °C. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was recrystallized from AcOEt–THF to afford **5o** (0.41 g, 62%). IR (Nujol): 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, t, $J=7$ Hz), 1.07 (3H, d, $J=6$ Hz), 1.31—2.39 (6H, m), 2.29 (3H, s), 2.66—3.01 (1H, m), 3.03—3.42 (2H, m), 3.45—4.08 (2H, m), 7.16 (1H, d, $J=8$ Hz), 7.32 (1H, dd, $J=2$, 8 Hz), 7.48 (1H, d, $J=2$ Hz), 7.83 (1H, t, $J=6$ Hz).

5-(3,7-Dimethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl)-2-methylaminobenzoxazole (5m) Method D_2: A mixture of **4g** (1.4 g, 4.8 mmol) in MeOH (100 ml)–THF (40 ml)–AcOH (10 ml) was hydrogenated over PtO_2 (0.15 g) under 3—3.5 atmospheric pressure of H_2 for 8 h at room temperature. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in H_2O. The solution was adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from AcOEt to afford **5m** (0.97 g, 68%). IR (Nujol): 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, d, $J=7$ Hz), 1.47—2.63 (4H, m), 2.34 (3H, s), 2.90—3.23 (1H, m), 3.08 (3H, s), 3.50—4.16 (2H, m), 5.70 (1H, br s), 7.18 (1H, d, $J=8$ Hz), 7.38 (1H, dd, $J=2$, 8 Hz), 7.51 (1H, d, $J=2$ Hz).

2-(3-Amino-4-hydroxyphenyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (22b) A solution of 2-(4-hydroxy-3-nitrophenyl)-7-methylimidazo[1,2-*a*]pyridine (**12c**) (26 g, 97 mmol) in EtOH (500 ml) was hydrogenated over 10% Pd–C (2.5 g) under 3—5 atmospheric pressure of H_2 for 3 h at 60—70 °C. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was recrystallized from EtOH to afford **22b** (15 g, 64%). *Anal.* Calcd for $C_{14}H_{17}N_3O \cdot 1/5H_2O$: C, 68.10; H, 7.10; N, 17.02. Found: C, 68.24; N, 7.19; N, 16.83. IR (Nujol): 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, d, $J=6$ Hz), 1.47—2.41 (4H, m), 3.75—4.33 (2H, m), 6.57 (1H, d, $J=8$ Hz), 6.79 (1H, dd, $J=2$, 8 Hz), 7.04 (1H, d, $J=2$ Hz), 7.08 (1H, s). MS *m/z*: 243 (M^+).

2-[4-Hydroxy-3-(3-methylureido)phenyl]-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (23b) A mixture of **22b** (2.6 g, 11 mmol) and methyl isocyanate (0.8 ml, 14 mmol) in MeOH (13 ml)–THF (26 ml) was stirred for 2 h at room temperature. The reaction mixture was concentrated *in vacuo* to about half volume and the resulting precipitate was collected by filtration to afford **23b** (3.2 g, 100%). An analytical sample was obtained by recrystallization from DMF–H_2O. *Anal.* Calcd for $C_{16}H_{20}N_4O_2 \cdot 3/4H_2O$: C, 61.23; H, 6.90; N, 17.85. Found: C, 61.38; H, 7.06; N, 18.03. IR (Nujol): 3320, 1630 cm^{-1}. MS *m/z*: 300 (M^+).

5-(7-Methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl)-2-methylaminobenzoxazole (5f) Method E: A mixture of **23b** (3.0 g, 10 mmol) and PPE (30 g) was stirred at 120 °C for 30 min. The reaction mixture was dissolved in AcOEt (15 ml)–THF (15 ml)–H_2O (30 ml), and the resulting solution was adjusted to pH 8 with 20% aqueous K_2CO_3. The separated organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on alumina by eluting with $CHCl_3$–MeOH (39 : 1) to give crystals. Recrystallization from MeCN to afford **5f** (0.67 g, 24%). IR (Nujol): 1670, 1645 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6 Hz), 1.40—2.39 (4H, m), 2.70—3.04 (1H, m), 2.90 (3H, d, J=5 Hz), 3.65—4.19 (2H, m), 7.19 (1H, d, J=8 Hz), 7.33 (1H, s), 7.35 (1H, dd, J=2, 8 Hz), 7.51 (1H, d, J=2 Hz), 7.65 (1H, q, J=5 Hz).

2-Amino-5-(7-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl)benzoxazole (5e) Method F: A mixture of **22b** (3.0 g, 12 mmol) and BrCN (1.6 g, 15 mmol) in EtOH (30 ml) was stirred for 2 h at room temperature. The resulting precipitate was collected by filtration, and dissolved in AcOEt (30 ml)–H_2O (30 ml). The solution was adjusted to pH 8 with 20% aqueous K_2CO_3. A solid separated was collected, washed with AcOEt–H_2O and recrystallized from EtOH–IPE to afford **5e** (1.8 g, 55%). IR (Nujol): 1655, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.09 (3H, t, J=6 Hz), 1.24—2.44 (4H, m), 2.68—3.09 (1H, m), 3.68—4.25 (2H, m), 7.23 (1H, d, J=8 Hz), 7.33 (2H, s), 7.42 (1H, dd, J=2, 8 Hz), 7.54 (1H, d, J=2 Hz).

Biological Test Restraint and water-immersed stress ulcer (stress ulcer) and ethanol-induced gastric lesion (ethanol ulcer; cytoprotective activity) were evaluated by the methods described in the literature,[6,7] and in our previous paper.[1] The ED_{50} values, the dose required for 50% inhibition of the ulcer index, were estimated according to the method of Litchfield and Wilcoxon.[8]

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