SYNTHESES AND ANTIULCER ACTIVITIES OF NOVEL 2-[(6,7,8,9-TETRAHYDRO-5*H*-CYCLOHEPTA[*b*]PYRIDIN-9-YL)SULFINYL]-1*H*-BENZIMIDAZOLE ANALOGUES

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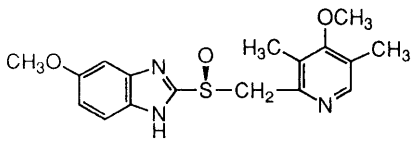
A synthetic study on a series of benzimidazole derivatives including cycloalka[*b*]pyridine moiety has been carried out. Among these compounds synthesized, a novel antipeptic agent with 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine moiety (TY-11345) was found to be superior to omeprazole in (H^++K^+)-ATPase inhibitory activity and antisecretory potencies.

KEYWORDS (H^++K^+)-ATPase inhibitor ; TY-11345 ; diastereoisomeric mixture isomerization ; antisecretory activity ; 2-[(cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole

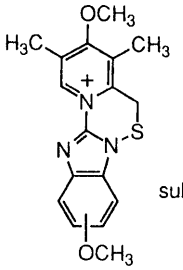
The clinical success of the histamine H_2 antagonist demonstrates that inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle in the treatment of acid-related gastrointestinal disorders. Accordingly, the gastric mucosal (H^++K^+)-ATPase, which is located in the apical membrane of the parietal cell and plays a major role in acid secretion,[1] has become the target for numerous investigations. Among synthetic studies on exploring (H^++K^+)-ATPase inhibitor, the substituted benzimidazoles have been found to have superior properties responsible for complete suppression of gastric acid secretion,[2] and one of these compounds, omeprazole (**1**),[3] has been introduced recently as a clinically useful agent. Our interest in inhibitors of gastric acid secretion led us to explore structural modifications of substituted benzimidazole derivatives by the introduction of cycloalka[*b*]pyridine moiety because an introduction of a rigid ring system is expected to influence a process of chemical transformation in acidic medium to biologically active sulfenamide (**2**)[4] from the parent compound, the mechanism of which is already verified by chemical and biological investigations.

In the present study, we have found novel compounds with 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine moiety which have extremely potent activities in antisecretion and antipeptic effect, overcoming those of omeprazole. Therefore, we wish herein to report the syntheses of benzimidazole derivatives modified by the introduction of cycloalka[*b*]pyridine moiety and preliminary biological activities of these compounds.

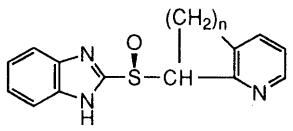
Among a series of synthesized cycloalka[*b*]pyridine derivatives (**3a-d**) and α-methyl compound (**4**)[5] (Table I), a novel compound (**3c**) was found to exhibit the most potent antisecretory activity. Therefore, we have carried out further chemical modifications of **3c** in order to reinforce (H^++K)$^+$-ATPase inhibitory activity and antiulcer activity by introduction of an appropriate substituent into either R^1 or R^2 in compound (**5**).



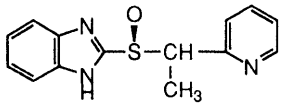
omeprazole (**1**)



sulfenamide (**2**)



3a n=2
3b n=3
3c n=4
3d n=5



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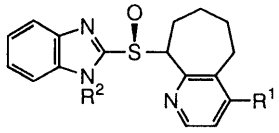

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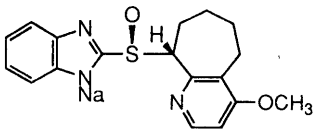


TY-11345 (**6**)

Nitration of *N*-oxide (**7**) with fuming HNO_3 at 80 °C gave the 4-nitro derivative (**8**),[6] which was converted to the methoxy compound (**9**) by treatment with methanolic NaOH in 84% overall yield from **7**. Treatment of **9** with acetic anhydride allowed smooth rearrangement to give secondary alcohol (**10**) in 65% yield after hydrolysis. Chlorination of **10** with $SOCl_2$ followed by reaction with 2-mercaptobenzimidazole in the presence of NaOH afforded the sulfide (**12**) in 77% overall yield from **10**. Oxidation of **12** with m-CPBA in CH_2Cl_2 proceeded at -15 °C without difficulty to give a diastereoisomeric mixture of the corresponding sulfoxides (**13**) and (**14**) in a ratio of 8 : 2 (89%). One diastereoisomer (**13**) was easily separated by recrystallization of the crude reaction product, whereas the other (**14**) could not be isolated by crystallization or chromatographic purification of the residue because of its inherent instability. Compound (**13**) was obtained in 68% yield as colorless crystals, mp 147-150°C (dec.) ; ^{1}H-NMR ($CDCl_3$) δ : 1.07-2.74 (6H, m), 2.95-3.40 (2H, m), 3.82 (3H, s), 4.73-4.98 (1H, m), 6.69 (1H, d, *J*=6.0Hz), 7.06-7.92 (4H, m), 8.30 (1H, d, *J*=6.0Hz) ; IR (KBr) : 3068, 2972, 2932, 2852, 1580, 1476, 1454, 1430, 1286, 1270, 1086, 1054, 996, 746 cm^{-1} ; MS (FAB) *m/z* : 342 (M^++1). *Anal.* Calcd for $C_{18}H_{19}N_3O_2S$: C. 63.32 ; H. 5.61 ; N. 12.31. Found : C. 63.32 ; H. 5.52 ; N. 12.19 (Chart 1).

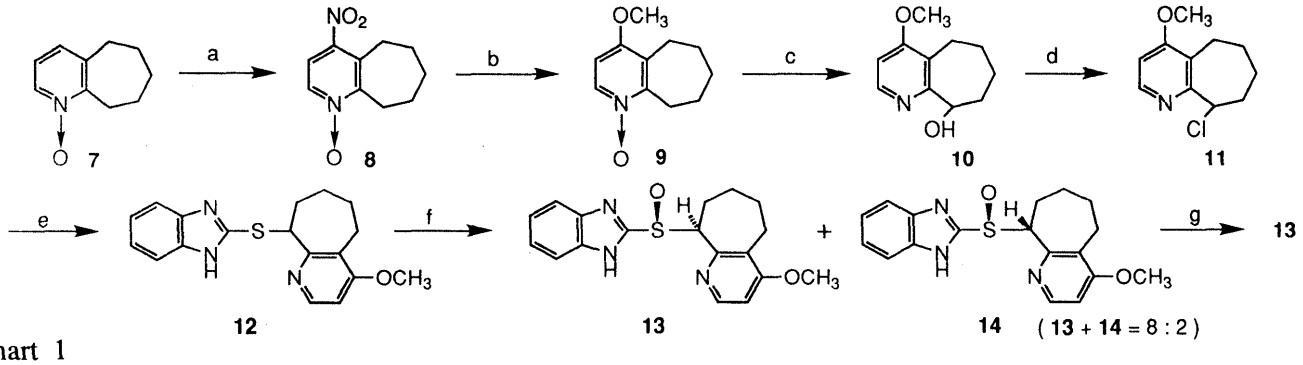
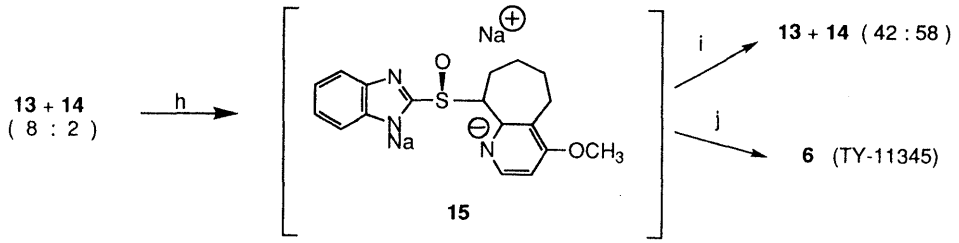


Chart 1

(a) fuming HNO_3, 80°C (b) MeOH, NaOH, r.t. (c) (i) $(CH_3CO)_2O$, 80°C (ii)10% NaOH, r.t.
(d) $SOCl_2$,$CHCl_3$, r.t. (e) 2-mercaptobenzimidazole, NaOH,EtOH,H_2O, reflux
(f) m-CPBA,CH_2Cl_2, -15°C (g) recrystallization from CH_2Cl_2-Et_2O

Subsequently, we tried to examine reciprocal isomerization of these two compounds under various basic conditions. Treatment of a 8 : 2 diastereoisomeric mixture of **13** and **14** with $NaOCH_3$ in CH_2Cl_2 at room temperature followed by addition of H_2O gave a 1 : 1 mixture of **13** and **14**. Very fortunately, we found that sodium salt (**6**) of **14** could be precipitated selectively by gradual addition of Et_2O to the diastereoisomeric salt solution of CH_2Cl_2. As a result, **6** was obtained from **12** in 87% overall yield. This result was interpreted by assuming equilibration between **13** and **14** *via* the intermediate (**15**). The stereochemistry of **14** was determined by an X-ray analysis of its *N*-methyl derivative.[7] Compound (**6**) shows the following properties and spectral data. Colorless crystals, mp 167-175 °C (dec.) ; ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ : 1.00-2.67 (7H, m), 2.95-3.34 (1H, m), 3.82 (3H, s), 4.75 (1H, d, *J*=6.0Hz), 6.65 (1H, d, *J*=5.0Hz), 6.85-7.10 (2H, m), 7.40-7.65 (2H, m), 8.23 (1H, d, *J*=5.0Hz) ; IR (KBr) : 3372, 3048, 2972, 2928, 2856, 1580, 1474, 1298, 1270, 1090, 1052, 820, 800, 744 cm^{-1}; MS (FAB) *m/z* : 386 (M^++Na), 364 (M^++1). *Anal.* Calcd for $C_{18}H_{18}NaN_3O_2S \cdot H_2O$: C. 56.68 ; H. 5.29 ; N. 11.02. Found : C. 56.56 ; H. 5.03 ; N. 10.86 (Chart 2).



(h) 28% NaOMe, CH_2Cl_2, r.t. (i) H_2O
(j) Et_2O

Chart 2

Preliminary biological examinations indicated that **6** and **13** had potent activity both in the *in vitro* (H^++K^+)-ATPase inhibition assay [8] and in the *in vivo* antisecretory assay.[9] The results are summarized in Tables I, II and III.

It can be seen in Table II that **6** and **13** potently inhibited (H^++K^+)-ATPase activity in a concentration-dependent manner, with an IC_{50} values of 3.3μM, 3.5μM at pH6.0 and of 9.7μM, 5.7μM at pH7.4, respectively. The (H^++K^+)-ATPase inhibitory activity of **6** and **13** was about 3~35 fold higher than that of omeprazole.

Tables I and III show that the antisecretory activity of **3c**, **4**, **6** and **13** against pentagastrin-stimulated gastric acid secretion in rats is almost same as that of omeprazole at the maximal suppression. However, the introduction of methoxy group into R^1 in the 6,7,8,9-tertahydro-5*H*-cyclohepta[*b*]pyridine ring increased the duration of antisecretory activity. Namely, the antisecretory activities of **6** and **13** clearly became longer than that of omeprazole.

As a consequence, 2-[(4-methoxy-6,7,8,9-terahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole sodium salt, TY-11345 (**6**), was selected as a promising antiulcer agent after examining the pharmacological and toxicological properties and stability. Further development of TY-11345 is in progress.

Table I. Inhibitory Effect of **3** and **4** on Pentagastrin Stimulated Gastric Acid Secretion in Rats

Compound	% maximum inhibn. (at i.v. 3mg / kg)
3a	NE
3b	NE
3c	63.5
3d	44.7
4	47.9

NE, not effective.

Table II. Inhibitory Effect of **6** and **13** on Isolated (H^++K^+)-ATPase of Rabbit Gastric Mucosa

Compound	IC_{50}(μM) pH 6.0	pH 7.4
6	3.3	9.7
13	3.5	5.7
Omeprazole	11.0	200.0

Table III. Inhibitory Effect of **3**, **6** and **13** on Pentagastrin Stimulated Gastric Acid Secretion in Rats

Compound	% inhibn. (at i.v. dose, mg / kg) Maximum	3hours after dosing
3c [a]	63.5 (3)	29.5 (3)
6	67.1 (1)	54.9 (1)
13	86.2 (1)	44.7 (1)
Omeprazole	86.3 (1)	36.9 (1)

a) Diastereoisomer of type **13**.

ACKNOWLEDGMENT We thank Dr. K. Kogi and his co-workers, TOA EIYO Ltd., for examining biological activities.

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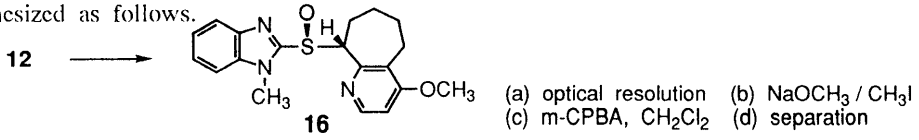
5) All new compounds were fully characterized by ^{1}H-NMR, IR and elemental analyses.

6) Nitration of **7** under standard conditions (HNO_3-H_2SO_4) afforded **8** in a poor yield (45%).

7) *N*-Methy derivative (**16**) was synthesized as follows.



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(Received December 17, 1993; accepted January 27, 1994)