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SYNTHESES OF 2-[(3,5-DIMETHYL-4-METHOXYPYRIDYL)ALKYL]-BENZOTHIAZOLIDINE DERIVATIVES AS A POTENTIAL GASTRIC H^+/K^+-ATPASE INHIBITOR[1]

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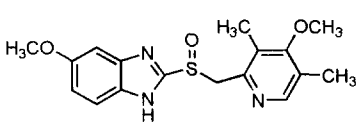
Abstract: A series of 2-[(3,5-dimethyl-4-methoxypyridyl)alkyl]benzothiazolidine derivatives were synthesized and tested their inhibitory effects on gastric H^+/K^+-ATPase. Compound **4d** exhibited potent *in vitro* inhibitory activity.

Since the inhibitory effect of omeprazole (**1**) on gastric H^+/K^+-ATPase results from the formation of S-S bond between the highly thiophilic intermediates and the thiol groups in gastric H^+/K^+-ATPase,[2] there have been efforts to develop a new class of gastric H^+/K^+-ATPase inhibitors by fine-tuning the nuclephilic/electrophilic properties of thiophile which could afford an enzyme-inhibitor complex with good stability in neutral condition.[3]

During an investigation of a new class of gastric H^+/K^+-ATPase inhibitors which is more stable under neutral and weakly acidic conditions, we recently observed that disulfide bond was formed from the reaction of benzothiazolidine analogue with 2-mercaptoethanol under the acidic condition.[1,4] Based on this observation, we assumed that the benzothiazolidine analogue could inhibit H^+/K^+-ATPase, because the opening of a thiazolidine ring in the acidic media generates an iminium intermediate, which can react with a thiol group to form the disulfide bond.[5] In modifying the structure of omeprazole, we replaced the benzimidazole moiety with a structurally similar benzothiazolidine ring and maintained the pharmacological effect of the pyridine ring moiety. Here, we report the syntheses and biological activities of benzothiazolidine derivatives (**2** - **5**) in which the benzothiazolidine ring moiety is connected with the pyridine moiety of omeprazole having different chain lengths.



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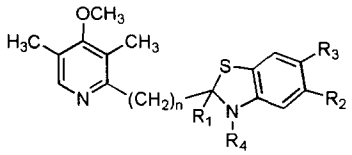

2 - **5** (n = 0, 1, 2, 3)

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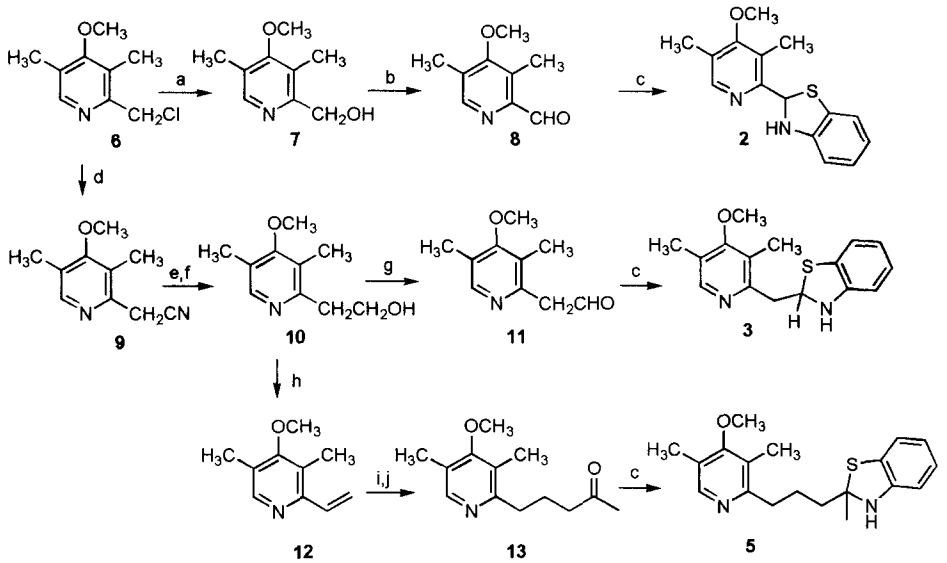
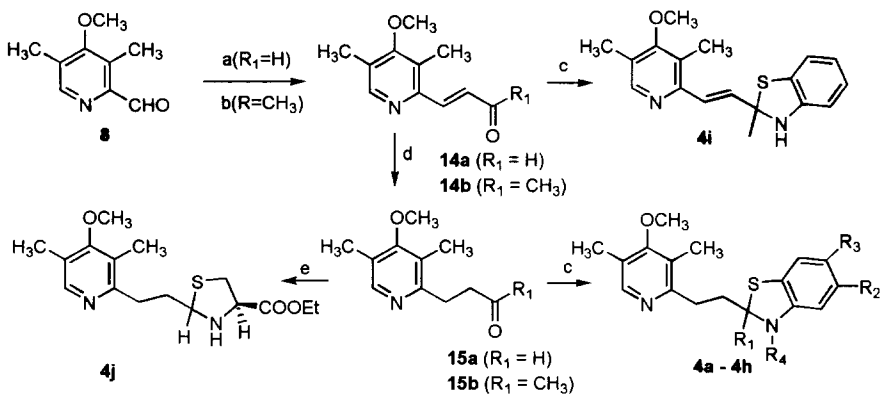
Chemistry. The desired benzothiazolidine derivatives **2** - **5** were prepared by condensation of oxo compounds (**8**, **11**, **12**, **13**, **15**) either with the corresponding substituted 2-aminothiophenols or with *L*-cysteine ethyl ester hydrochloride (Scheme 1, 2). Oxo compounds were prepared as follows: 3,5-Dimethyl-4-methoxy-2-formylpyridine (**8**) was readily prepared from **6**[6] via substitution of the chloro group by treatment of aqueous NaOH solution, followed by partial oxidation with selenium oxide (Scheme 1). For the synthesis of **11**, reaction of **6** with sodium cyanide, followed by acid catalyzed esterification with methanol, gave **9**, which was then reduced with LAH to give **10**. Partial oxidation of **10** with activated MnO_2 afforded **11** (Scheme 1). For the synthesis of **13**, the vinylpyridine **12** was first prepared by reduction of **10** with LAH followed by dehydration of the resulting hydroxyethylpyridine intermediate with selenium oxide. It was then reacted with sodium ethyl acetoacetate and refluxed with 20 % HCl solution to give **13**. For the syntheses of **14** and **15**, the formylpyridine **8** was reacted with triphenylphosphonoranylidene-2-propanone to give **14**, which was then hydrogenated over 10% Pd-C to give **15** (Scheme 2). The corresponding substituted 2-aminothiophenols were prepared by the following classical procedures that were well described in heterocyclic chemistry literature.[7] *L*-Cysteine ethyl ester hydrochloride was purchased from Aldrich Chemical Company.



Reagents: a) NaOH, H_2O-THF (1;1), 40°C, 5 hr, (68 %); b) SeO_2, pyridine, reflux, 2.5 hr, (91 %) c) 2-Aminothiophenol, benzene, p-TsOH, reflux, 6 hr, (30 - 66 %); d) NaCN, MeOH-H_2O (3:1), 30°C, 20 hr, (50 %); e) EtOH, c-HCl, reflux, 6 hr, (63 %); f) $LiAlH_4$ (1.2 eq.), THF, -15°C, 1 hr, (71 %); g) MnO_2, CH_2Cl_2, rt, 24 hr, (10 %); h) SeO_2, pyridine, 100°C, 2 hr, (64 %); i) ethyl acetoacetate, Na, 110°C, 6 hr, (47 %); j) 20 % HCl, reflux, 6 hr, (66 %).

Scheme 1



Reagents: a) CH_3CHO (6.0 eq.), 10 % NaOH, 0°C, 2 min, (26 %); b) Triphenylphosphoranylidene-2-propanone, THF, 40°C, 5 hr (18 %); c) Substituted-2-aminothiophenol, benzene, p-TsOH, reflux, 6 hr, (30 - 66 %); d) H_2/Pd-C, MeOH, 14psi, rt, 1 hr, (90 %); e) *L*-Cysteine ethyl ester.HCl, benzene, reflux, 6 hr, (69 %).

Scheme 2

Results and Discussion

All compounds were tested for *in vitro* inhibitory activities of gastric H^+/K^+-ATPase by using a previously reported method,[8] and the results are summarized in Table 1.

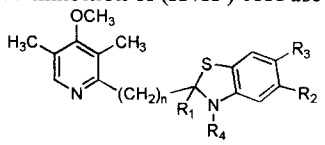
We initially examined the effects of the chain length connecting the benzothiazolidine ring and pyridine moiety on structure-activity relationships and found that the ethylene unit's compound (n = 2) exhibited a high inhibitory activity compared to other compounds (n = 0, 1, 3). Therefore, we prepared the extended set of 2-[(3,5-dimethyl-4-methoxypyridyl)ethyl]benzothiazolidine derivatives for further investigation. Either the replacement of benzothiazolidine ring with a cysteine ring (**4j**) or of 3,5-dimethyl-4-methoxypyridyl moiety with pyridyl one (**4k**) reduced the activity significantly, whereas the addition of a double bond in the ethylene unit (**4i**) resulted in a modest reduction of activity. In addition, the methylation of nitrogen in the benzothiazolidine ring (**4h**) also reduced the activity.

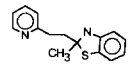
A variety of substitutions at the 5- or 6- position in the benzothiazolidine ring were made. The trifluoromethyl (**4d**) and fluoro (**4c**) derivatives which have the electron withdrawing group at the 5- position showed higher potency than parent compound (**4a**) with IC_{50} = 24 μM and 33 μM, respectively, while the substitution at the 6- position rendered the compound (**4g**) inactive.

The trifluoromethyl derivative (**4d**) was further investigated for its *in vivo* inhibitory activity by measuring the gastric secretion and acidity in rats.[8] The volume of gastric juice was decreased by 21% and the acid output was decreased by 38 % at the dose of 30 mg/Kg of **4d** (n = 8, po administration). This result indicated that a benzothiazolidine derivative could be used as a novel (H^+/K^+)-ATPase inhibitor.

Mechanistic and further *in vivo* studies are currently underway.

Table 1: *In vitro* inhibition of (H^+/K^+)-ATPase activity.[a]



Compd.	n	R_1	R_2	R_3	R_4	Inhibition(%)[b]	$IC_{50}(\mu M)$
2	0	H	H	H	H	0	
3	1	H	H	H	H	58.5	
4a	2	H	H	H	H	24.6	
4b	2	CH_3	H	H	H	96.4	98
4c	2	CH_3	F	H	H	81.0	33
4d	2	CH_3	CF_3	H	H	84.4	24
4e	2	CH_3	CH_3	H	H	0	
4f	2	CH_3	Cl	H	H	20.0	>100
4g	2	CH_3	H	Cl	H	0	
4h	2	CH_3	H	H	CH_3	17.0	
4i	(CH=CH)	CH_3	H	H	H	61.1	>100
4j	2	H	(L-Cysteine ethylester)			19.8	
4k						0	
5	3	CH_3	H	H	H	0	
Omeprazole						95	3.8

a: performed at pH = 7.4 buffer solution. b: measured at the concentration of 400 μM.

References and Notes

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