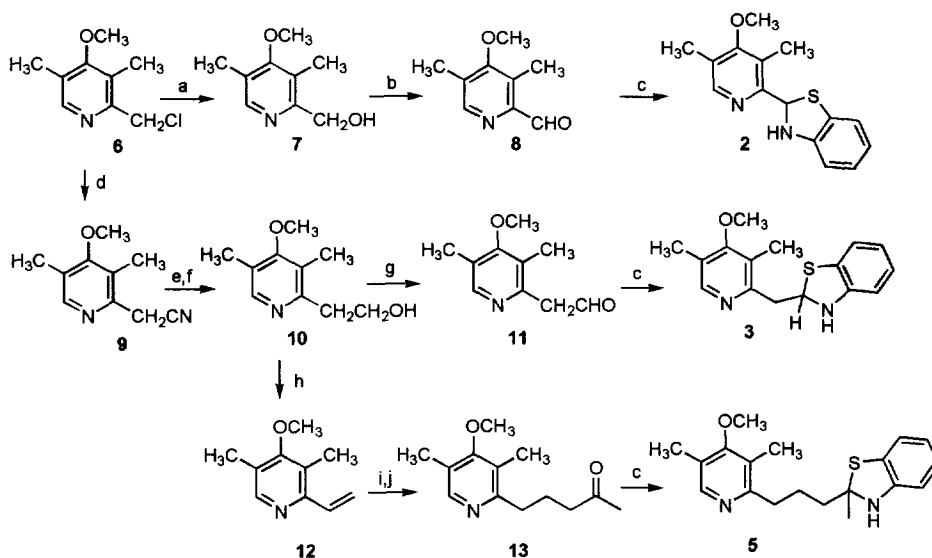


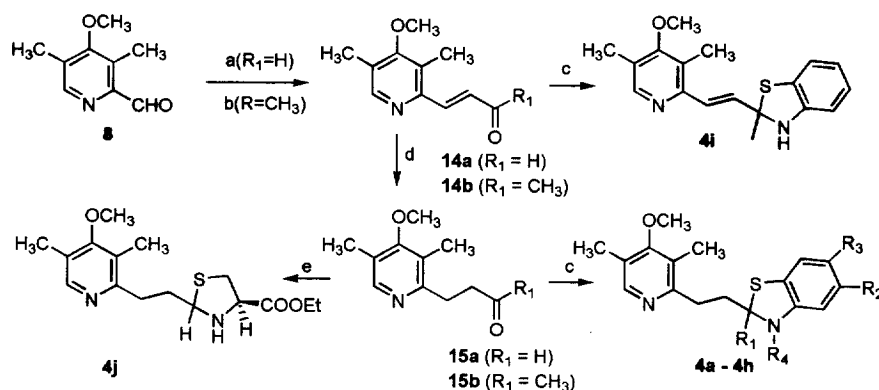
2 - 5 ($n = 0, 1, 2, 3$)

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 MnO₂ 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, H₂O-THF (1:1), 40°C, 5 hr, (68 %); b) SeO₂, pyridine, reflux, 2.5 hr, (91 %); c) 2-Aminothiophenol, benzene, *p*-TsOH, reflux, 6 hr, (30 - 66 %); d) NaCN, MeOH-H₂O (3:1), 30°C, 20 hr, (50 %); e) EtOH, c-HCl, reflux, 6 hr, (63 %); f) LiAlH₄ (1.2 eq.), THF, -15°C, 1 hr, (71 %); g) MnO₂, CH₂Cl₂, rt, 24 hr, (10 %); h) SeO₂, 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.

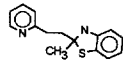
A variety of substitutions at the 5- or 6- position in the benzothiazolidine ring were made. The trifluoromethyl (**4d**) and fluoro (**4c**) derivatives which have the electron withdrawing group at the 5- position showed higher potency than parent compound (**4a**) with $IC_{50} = 24 \mu M$ and $33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

Table 1. Inhibition of (H⁺/K⁺)-ATPase activity.

Compd.	n	R ₁	R ₂	R ₃	R ₄	Inhibition(%) ^b	IC ₅₀ (μM)
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

- Part of this work presented as a poster in the 213th National Meeting of American Chemical Society, San Francisco, CA, USA, April 1997; paper MEDI 133.
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